

ON THE ROLE OF ELECTROPHILIC CATALYSIS IN COMPETITIVE REDUCTION OF KETONES

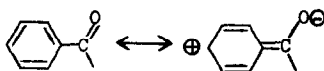
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Carbonyl addition reactions generally involve electrophilic catalysis, whether by classical protonic acids (as in oxime formation), hydrogen bonding solvents (as in sodium borohydride reductions in alcohol), or metal cations (as in organometallic addition reactions) (1). In most cases, when steric factors are relatively constant, the reactivity of aryl ketones is substantially less than that of alkyl ketones and this has been attributed essentially to ground-state resonance stabilization (2a,b) e.g.



which increases the activation energy, since this stabilization is largely wiped out in the transition state (3). Our observations on the reactivity of various ketones toward lithium tetrakis(N-dihydropyridyl)aluminate, which showed diaryl ketones to be most reactive (4), led us to seek an explanation which might be partly based on the apparent absence of electrophilic catalysis in this system, rather than on steric, inductive and conjugative arguments exclusively. For the present, we will confine our discussion to the borohydride reduction of ketones which is a mechanistically

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simple carbonyl addition reaction. The results of this reaction will then be used to rationalize the unusual results with the dihydropyridine reagent*.

Brown and Ichikawa have reported extensive data on the reduction of a variety of ketones with sodium borohydride in isopropyl alcohol (2) and also have examined acetone in a variety of solvents with both sodium and lithium borohydride (5). The reactivity of the various ketones (2a,b) could be qualitatively explained by the combined steric and polar effects of alkyl groups and the conjugative effect of aryl groups, when steric factors permitted the latter (2b). We have examined the reactivity of model ketones in pairs (diaryl ketone vs. dialkyl) and, by varying solvent and/or metal ion of the borohydride, can actually reverse the relative rates of reduction of the ketones present. We feel that these reversals of reactivity require the evaluation of electrophilic catalysis in these reactions under the various conditions, particularly the relative importance of ground-state resonance in aryl ketones in the presence or absence of electrophiles that interact with the carbonyl group.

Since sodium borohydride does not reduce either 2-octanone or benzophenone in anhydrous pyridine (6) or diglyme, we chose more active examples of each type for these reactions, namely cyclohexanone, which is unusually fast because of I-strain (2c), and p,p'-dichlorobenzophenone.

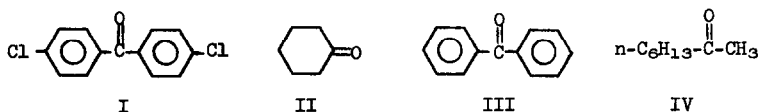
* In reactions with ketones containing enolizable α -hydrogens, e.g. acetophenone and 2-octanone, some enolization has been detected by noting the disappearance of ketone (by n.m.r. and/or I.R.) to be faster than the formation of alcohol. However, the combined rates of enolization and reduction of 2-octanone, for example, still are substantially smaller than the rate of reduction of benzophenone by lithium tetrakis-(N-dihydropyridyl)aluminate under comparable conditions (J. O. Peterson, unpublished results).

Lithium borohydride is sufficiently reactive so that both pairs of ketones were examined competitively in all solvents, namely methanol, pyridine and diglyme.

Methods and Results: The relative rates of lithium and sodium borohydride reductions in pyridine and diglyme could not be determined by the usual sampling techniques (2) because hydrolysis of aliquots results in much faster reduction during work-up than in the reaction proper (6). Therefore, solutions containing both ketones and the reducing agent were examined periodically by infrared spectroscopy at room temperature (ca. $25 \pm 2^\circ\text{C}$) in sodium chloride cells which were stored in a desiccator between readings. Relative rate ratios were obtained from the ratio of absorbances of the two carbonyl peaks at various times. In addition, one observes the decrease of the borohydride band at 2240 cm^{-1} and the appearance of pyridine-borane at 2380 cm^{-1} in reactions run in pyridine, where only the first hydride is used (6). The results of runs assayed by the infrared method are reported in Table 1; all results could be duplicated qualitatively but this requires extremely careful manipulations to avoid the entry of water into the reacting system. Also, several competitive reactions run in methanol were worked up in the usual manner and product composition (which in this case, as well as in diglyme, involves all four stages of reduction, utilizing alkoxyborohydrides) determined by gas chromatography and isolation. These studies parallel Brown's kinetic studies (2a), in that in all cases the dialkyl ketone was more completely reduced than the diaryl ketone (e.g. $k_{\text{acetone}}/k_{\text{benzophenone}}$ for sodium borohydride in isopropyl alcohol at 0° is ca. 8, whereas $k_{2\text{-octanone}}/k_{\text{benzophenone}}$ for lithium borohydride in methanol at 25° from our product studies is ca. 10).

TABLE I

Competitive Reductions of Ketones Followed by Infrared Spectroscopy



Run	Ketones (M)	Reducing Agent (M)	Solvent ¹	Absorbance Ratios ² t_0	$t(\text{min})$	k_{Ar_2}/k_{Alk_2} ³
1	I (0.056) II (0.059)	NaBH ₄ (0.086)	A	1.02	0.348 (550)	4.4
2	I (0.065) II (0.069)	NaBH ₄ (0.067)	A	1.04	0.690 (340)	4.5
3	I (0.049) II (0.052)	LiBH ₄ (0.055)	A	1.02	0.380 (170)	3.7
4	III (0.135) IV (0.133)	LiBH ₄ (0.073)	A	1.18	0.870 (126)	2.0
5	III (0.081) IV (0.079)	LiBH ₄ (0.088)	A	1.23	0.667 (154)	2.4
6	I (0.091) II (0.100)	NaBH ₄ (0.062)	B ⁴	1.00	0.725 (375)	1.3
7	I (0.091) II (0.100)	LiBH ₄ (0.049)	B	1.00	1.84 (75)	0.32
8	III (0.062) IV (0.061)	LiBH ₄ (0.065)	B	1.20	1.97 (16)	0.49

¹ A=pyridine, B=diglyme (diethylene glycol dimethyl ether).

² Expressed in terms of A_{Ar_2}/A_{Alk_2} ; at time t , the most reactive ketone was generally ca. 40-75% consumed and the other, 15-40%.

³ Calculated from the expression $\frac{k_A}{k_B} = \frac{\log[A]_t/[A]_0}{\log[B]_t/[B]_0}$ where absorbances were used to express concentrations, since Beer's law plots for all ketones were linear.

⁴ The relative rates in diglyme are composites for all four stages of reduction involving alkoxyborohydrides.

Discussion: One basis upon which the observed reactivities of pairs of ketones can be explained is by assuming that contributions of dipolar resonance forms to the ground state structure of aryl ketones in non-polar solvents are relatively unimportant, but that complexing with electrophilic species can change the degree of stabilization and hence reactivity. The greater reactivity of p,p'-dichlorobenzophenone over cyclohexanone (I>II) is observed in those experiments where no electrophilic catalysis is available (Runs 1-6), that is aprotic solvents which do not have hydrogen-bonding ability are used, and in those runs where lithium ion is present it is effectively tied up by pyridine solvent. In these cases, dipolar resonance contributors to the ground state structures of the ketones are considered to be insignificant, thus making more prominent the inductive electron-withdrawing effect of aryl groups, which increases reactivity toward nucleophiles. Thus benzophenone is reduced more rapidly than 2-octanone by lithium borohydride in pyridine*, just as with lithium tetrakis(N-dihydropyridyl)aluminate (4). On the other hand, it can be seen that those competitive reductions run in alcohol solvent and those where lithium ion is available to coordinate with the carbonyl oxygen (7) (e.g. in diglyme, Runs 7 and 8) result in the dialkyl ketone being more reactive than the diaryl ketone (II>I). This is in complete accord with Brown's kinetic results for sodium borohydride reductions in isopropyl alcohol (2a). We feel that in these cases, one is dealing with a ketone:electrophile complex in which

* The fact that lithium borohydride reductions are faster than sodium borohydride reductions in pyridine does not require one to assume that lithium coordinates with the carbonyl group better than sodium ion in this solvent. Rather, the difference may result simply from the different reactivities of the metal borohydride ion pairs present in a non-polar solvent such as pyridine.

a lithium ion or an unspecifiable number of alcohol molecules is the electrophile, rather than the ketone itself. Although reactivity toward nucleophiles should increase for all ketones, charge delocalization (rather than separation) in the diaryl ketone complex results in less activation than in the dialkyl ketone complex, where the positive charge is less spread out (hyperconjugation). In this situation, aryl conjugation does reduce reactivity. Taft and coworkers have extensively studied the effect of solvent polarity and hydrogen-bonding ability on the importance of dipolar forms in ground state resonance hybrids by looking at F^{19} chemical shifts in p-substituted fluorobenzenes (8). Important consequences on reactivities, rotational barriers and infrared frequencies were cited (8).

At this point, it is worth noting that the use of ketones as models for carbonium ions by Brown (2) appears to be qualitatively valid for sodium borohydride reductions in alcohol solvents. Our present results clearly show that such a comparison would not hold in the absence of electrophilic catalysis.

In conclusion, we have attempted to rationalize the dependence of ketone reactivity toward borohydride reduction under various conditions on the basis of the important role of electrophilic catalysis. These ideas help one to understand the reactivity of lithium tetrakis(N-dihydropyridyl)aluminate (4). We wish to emphasize that other factors may be operative also and studies now underway in these laboratories will hopefully provide further insight into the problem.

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