Kinetics and Mechanism of the Morpholine–Borane Reduction of Substituted Acetophenones and Benzaldehydes †

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Rates of reduction of substituted acetophenones and benzaldehydes by morpholine–borane in aqueous ethanol are enhanced by the introduction of electron-withdrawing groups in the carbonyl compound are are relatively independent of the water:ethanol ratio. Reduction by morpholine–[$^2H_3$]borane, is somewhat slower (k_H/k_D = 1·23 and 1·47 for acetophenone and benzaldehyde respectively) and a pronounced retardation of rate is observed for reduction by morpholine–cyanoborane. A four-centre transition state is proposed and it is suggested that hydride transfer from boron to the carbonyl carbon atom may be energetically important in forming the activated complex. No significant intramolecular catalysis occurs on substitution of a hydroxy-group *ortho* to the carbonyl carbon atom.

RESULTS obtained in the study of alkyl methyl ketone reduction by morpholine–borane in neutral, aqueous solution have been interpreted in terms of the formation of a four-centre transition state involving addition of boron and hydrogen across the carbonyl group.[1] Since an increase in *C*-alkyl substitution caused a moderate rate *increase* in a series of three ketones studied and since the substrate isotope effect for the reduction of acetone was small (k_H/k_D *ca.* 1·1), it was suggested that rupture of a boron–hydrogen bond might not have progressed very far at the transition state and, therefore, probably did not represent a very important contribution to the activation energy. Interpretation of such substituent effects is complicated, however, by the fact that increasing substitution at the α-carbon atom imposes an increase in the size of substituent near the site of reaction. It seemed desirable, therefore, to select a system for study wherein substituent effects could be interpreted solely in terms of the electronic contributions of groups, *i.e.* independent of possible steric interactions. For this reason, and in order to expand the scope of the reaction, an investigation of the morpholine–borane reduction of selected ring substituted aromatic ketones and aldehydes was undertaken.

RESULTS

For the reduction of a series of aromatic carbonyl compounds by morpholine–borane in neutral, aqueous ethanol, the rate of loss of soluble hydride is first-order both in amine–borane and the carbonyl compound [equation (1) where Ar = phenyl or ring substituted phenyl, R = Me, CH_2X, or H, and X = Br or Cl]. The form of the rate

$$-d[O(CH_2)_4NHBH_3]/dt = k[O(CH_2)_4NHBH_3][ArCOR] \quad (1)$$

equation is similar to that previously described for the uncatalysed reduction of aliphatic ketones.[2] For the aryl systems, however, the second-order rate constant is quite sensitive to substitution in the ring and at the α-carbon atom of the ketone, and pronounced rate enhancement upon introduction of electron-withdrawing groups is observed (Table 1). Correlation of kinetic data with the

TABLE 1

Rates of reduction of substituted acetophenones and benzaldehydes by morpholine–borane in 95% ethanol at 34·8°

$XC_6H_4COCH_2R$			XC_6H_4CHO	
X	R	10^5k/l mol^{-1} s^{-1}	X	10^3k/l mol^{-1} s^{-1}
p-NH_2	H	0·281	*p*-OH	0·156
p-OH	H	0·501	*p*-Me	1·12
p-OEt	H	0·701	*o*-OH	1·19
o-OH	H	0·985	H	2·21
m-NH_2	H	1·83	*p*-Cl	3·33
p-Me	H	2·27	*m*-Cl	6·02
m-OH	H	3·08	H	1·50 [a]
H	H	3·28		
p-Br	H	5·78		
H	Cl	21·7		
H	Br	130		
H	H	2·67 [a]		

[a] Reduction with $O(CH_2)_4NHBD_3$.

TABLE 2

Effect of solvent composition on the rate of reduction of acetophenone by morpholine–borane at 34·8°

EtOH–H_2O (V/V)	10^5k/l mol^{-1} s^{-1}	
100 : 0	3·75	3·71
95 : 5	3·28	
80 : 20	2·99	2·82
60 : 40	2·78	2·89
40 : 60	3·38	3·27

TABLE 3

Temperature dependence of the morpholine–borane reduction of acetophenone and benzaldehyde in 95% ethanol

	PhCOMe	PhCHO
t/°C	10^5k/l mol^{-1} s^{-1}	10^3k/l mol^{-1} s^{-1}
19·9	0·866	0·615
24·9	1·38	0·905
34·8	3·28	2·21
40·0	5·00	2·83
45·4	7·86	4·02
$\Delta H^‡$/kcal mol^{-1}	15·4	13·3
$\Delta S^‡$/cal mol^{-1} K^{-1}	−29	−27·5
r	0·999	0·995

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[2] H. C. Kelly, M. B. Giusto, and F. R. Marchelli, *J. Amer. Chem. Soc.*, 1964, **86**, 3882.

Hammett σ parameter gave ρ = +1·64 and a correlation coefficient *r* of 0·96 for a study of eight *meta*- and *para*-substituted acetophenones, and ρ = +1·95 (*r* 0·94) for a series of five benzaldehydes. A comparison of rates of reduction with morpholine–borane and morpholine–[$^2H_3$]-borane in 95% ethanol leads to k_H/k_D values of 1·23 and 1·47 for acetophenone and benzaldehyde respectively. The rate of acetophenone reduction is relatively insensitive to changes in the proportion of components of the aqueous ethanol solvent (Table 2). The temperature dependence of rate is shown in Table 3.

For the morpholine–borane reduction of aliphatic ketones,[1b] relative rates in water at 25° were acetone, 1·0; ethyl methyl ketone, 1·7; methyl t-butyl ketone, 6·8. For acetone reduction at 25°, k_H/k_D = 1·1. Activation parameters determined for the range 10—40° were $\Delta H^{\ddagger}$ 11 kcal mol^{-1} and $\Delta S^{\ddagger}$ −40 cal mol^{-1} K^{-1}. In aqueous dioxan at 25°, the reduction of acetone was mildly accelerated by increasing the proportion of water.

No significant reduction of acetophenone or benzaldehyde in 95% aqueous ethanol at 34·8° was observed over a period of several days when morpholine–cyanoborane was employed as the reducing agent. Acetophenone remained unreactive towards morpholine–cyanoborane even in the presence of 0·005M-H^+ in both 50 and 95% aqueous ethanol.

DISCUSSION

Similarities in the form of the rate expression and in activation parameters (relatively low enthalpies and large negative entropies of activation) in this study and in the previously reported reduction of aliphatic ketones suggest similar mechanisms and a common feature is proposed, involving the addition, *via* a four-centre transition state, of boron and hydrogen to the oxygen and carbon atoms, respectively, of the corresponding carbonyl groups. For the reaction of the aromatic carbonyl compounds, however, the rate-accelerating influence of electron-withdrawing groups in the rings and at the α-carbon atom of the phenyl ketone suggests a transition state characterized by partial neutralization of the positive charge on the carbon atom of the polarized carbonyl group, implying that hydride transfer may be more important in the formation of the activated complex for reduction of these substrates than for the aliphatic ketones. This suggestion is somewhat supported by the slightly larger substrate isotope effect observed for the aromatic carbonyl compounds compared with that for acetone. The absence of a significant effect on rate of changes in composition of the solvent system also suggests an activated complex of polarity comparable with that of the reactants, and a transition state arising from bimolecular collision of two neutral molecules appears to be reasonable. The observation that, in aqueous dioxan, a slight acceleration of the rate of reduction of acetone accompanies an increase in water content of the solvent suggests that the polarity of the carbonyl group of the aliphatic ketone may be somewhat augmented in the activated complex, as might arise if hydride transfer were less important energetically than bond formation between boron and the carbonyl oxygen atom.[1b]

This solvent effect is small, however, and it should be emphasized that the implication that energetic aspects of hydride transfer are significantly different in degree for reduction of the alkyl and aryl substrates remains highly speculative.

Since amine–borane reduction of carbonyl compounds also occurs *via* an acid catalysed path, presumed to involve protonation of the carbonyl group in a rapid pre-equilibrium followed by a rate-limiting reduction of the protonate substrate,[1b,2] a study was made of the rates of the morpholine–borane reduction of *o*-hydroxyacetophenone and salicylaldehyde to determine whether some acceleration of rate might occur as a result of internal acid catalysis originating through intramolecular hydrogen bonding between the phenol hydrogen and carbonyl oxygen atoms. From Table 1 it can be seen that substrates containing *ortho*-hydroxy-groups react at somewhat greater rates than the corresponding *para*-derivatives (by a factor of *ca.* 2 for the acetophenones and 7—8 for the benzaldehydes) in spite of the fact that steric effects of the *ortho*-substituents might be expected to retard the attack of amine–borane. Nevertheless, since in both systems, the *o*-hydroxy-derivatives react 2—3 times slower than the unsubstituted carbonyl compounds, these accelerations are not sufficient to overcome the retarding effect produced by introducing the electron-releasing hydroxy-substituent into the ring. Thus, such internal catalysis cannot be very important under these conditions.

The greatly diminished rate of carbonyl reduction by morpholine–cyanoborane is attributed to destabilization of a transition state involving hydride transfer due to the electron-withdrawing inductive effect of the boron-bonded cyanide ligand. A decrease in reactivity of BH_3CN^- relative to BH_4^- toward selected organic functional groups also has been reported.[3] It is interesting that no acid catalysed pathway for reduction of acetophenone by morpholine–cyanoborane could be detected even in solutions containing 0·005M-H^+.

EXPERIMENTAL

Materials.—Aldehydes and ketones were obtained from Matheson, Coleman, and Bell (MCB) or Eastman. Most were of reagent grade and used without further purification. The *m*-amino- and -hydroxy-acetophenones were of technical and practical grade respectively and were recrystallized from ethanol. Reagent grade *p*-hydroxyacetophenone was also recrystallized from ethanol. Practical grade *p*-chlorobenzaldehyde was used without further purification. Morpholine–borane was used as obtained from Aldrich and was of a purity comparable with that prepared as previously described.[4] Inorganic salts were of reagent grade except for sodium cyanotrihydroborate which was obtained from

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[4] H. C. Kelly, F. R. Marchelli, and M. B. Giusto, *Inorg. Chem.* 1964, **3**, 431.

Alfa Inorganics and subjected to a Soxhlet extraction with tetrahydrofuran to obtain a crystalline product. Ethanol was obtained from U.S. Industrial Chemicals and diluted with dionized water to give the desired composition. Tetrahydrofuran (MCB) was purified by distillation from lithium tetrahydroaluminate.[5,6]

Morpholine–[$^2H_3$]borane was prepared by the procedure previously described for the synthesis of *p*-toluidine–[$^2H_3$]-borane, involving the addition of morpholine to a tetrahydrofuran solution of [$^2H_6$]diborane which had been prepared by the reaction of lithium tetradeuterioaluminate with the boron trifluoride–diethyl ether complex.[4] The product was recovered by evaporation of the solvent and then recrystallized from water. It was characterized by its i.r. spectrum (KBr wafer) which is distinguished from that of morpholine–borane by the absence of strong absorption in the B–H stretching region (2250—2350 cm^{-1}) and the presence of strong absorption attributed to the presence of the B–D linkage at 1770 cm^{-1}. A sharp band also is found at 1655, and a weaker band at 1700—1710 cm^{-1}. When the product is recrystallized from deuterium oxide, the sharp band normally present at 3180 cm^{-1} is replaced by strong absorption at *ca.* 2350 cm^{-1}, indicating substitution of the nitrogen-bonded proton by deuterium. This exchange is readily reversed by recrystallization of the *N*-deuterio-compound from water.

Morpholine–cyanoborane was prepared by the addition of the amine to a tetrahydrofuran solution of sodium cyanotrihydroborate which had been acidified with hydrogen chloride.[7,8] The product was recovered by evaporation of solvent and sublimed *in vacuo*.

Kinetic Studies.—For each run, *ca.* 0·08 g (8×10^{-4} mol) of morpholine–borane was dissolved in aqueous ethanol and the solution brought to temperature equilibrium in a Freas Precision constant temperature bath. This solution was then added to a sample of ketone or aldehyde which had been equilibrated at the same temperature to yield a solution of 0·050—0·250M-carbonyl compound and *ca.* 8mM-amine–borane. The reaction was followed by determining the rate of loss of amine–borane *via* analysis of the soluble hydride content of the solution using standard iodometric techniques.[9] Under these conditions, the reaction is pseudo-first order. The second-order rate constant is obtained from a knowledge of the concentration of carbonyl compound.

Studies using morpholine–cyanoborane as the reducing agent were carried out at 34·8° in aqueous ethanol solutions containing 8—12mM-morpholine–cyanoborane and 0·08—0·16M-acetophenone or 0·1—0·3M-benzaldehyde. Solutions containing 0·005M-H^+ in 50 and 95% ethanol were prepared from standard solutions of aqueous hydrochloric acid and absolute ethanol. Since the reaction of morpholine–cyanoborane with iodine in aqueous acid is much slower than that of morpholine–borane, a direct iodometric determination of soluble hydride could not be employed. Reduction by Br_2 by the cyanoborane is rapid, however, and a modified procedure was used involving this reagent.[10] Standard $KBrO_3$ was added to acidified samples of the hydrolysate followed by excess of KBr to generate bromine. The quantity of Br_2 remaining in excess of the amount required to oxidize the contained hydride was reduced to bromide by the addition of KI and the liberated I_2 was then determined by titration with standard $Na_2S_2O_3$.

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