

Mechanism of the Grignard Addition Reaction

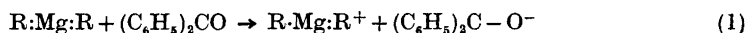
X. Kinetics and Deuterium Isotope Effects in the Reaction of Isobutylmagnesium Bromide with Benzophenone

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Direct rate measurements and product distribution data have been obtained for the reaction of isobutylmagnesium bromide and β -deuterioisobutylmagnesium bromide with benzophenone in diethyl ether. Interpretation of the results requires separation of a rate determining step and a product determining step if Grignard reagent is in excess, but a one step mechanism is indicated when benzophenone is in excess.

The separation of a rate determining and a product determining step in the reaction of benzophenone with *tert*-butylmagnesium chloride has been demonstrated by kinetic means.¹ Intervention of radical species in this type of reaction has been shown by product analysis² and by ESR spectroscopy.³ The reaction most probably takes place in accordance with the general scheme by Blicke and Powers.⁴ Thus the rate limiting initial step is the transfer of a single electron (SET) from the Grignard reagent to benzophenone. Since the majority of the reaction seems to occur *via* the dialkylmagnesium of the Schlenk equilibrium,⁵ the SET step may be written:



The various reaction products are produced in rapidly succeeding steps in which the radical ion pairs combine or disproportionate. A SET rate determining step was well documented¹ for the case of R = *tert*-butyl and evidence has been presented in favor of the operation of SET also with secondary and primary Grignard reagents.⁶ With these reagents some reduction to benzhydrol occurs by transfer of a β -hydrogen to the ketone. As suggested by Whitmore⁷ the reduction process has been assumed to occur *via* a synchronous shift of electrons in a cyclic arrangement of a complex of the reactants as shown in Fig 1 (I). This concerted one step mechanism requires a primary deuterium isotope effect, if the β -hydrogen is substituted with deuterium.

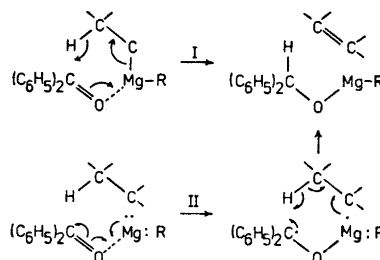


Fig. 1. I. Cyclic one step mechanism for the reduction of benzophenone with isobutylmagnesium bromide. II. Two step SET mechanism for the same process.

A SET mechanism would show only a secondary isotope effect in the rate limiting electron transfer step.

With isobutylmagnesium bromide the reaction with benzophenone yields more than 90 % benzhydrol. The β -deuteriated reagent was found to react almost as fast as the non-deuteriated, when the rate was measured directly,⁶ while a rather large isotope effect was observed in a competition experiment between deuterio and non-deuterio reagent.^{6,8} The results were explained by assuming a two step mechanism initiated by SET. The present work has included a repetition of the rate measurements with isobutylmagnesium bromide and benzophenone and measurements have been made at several concentrations and at various ratios of Grignard reagent to substrate. The reaction mixtures have been analysed to obtain the product distributions shown in Table 2.

The present work indicates that the earlier measurements with isobutylmagnesium bromide were somewhat in error. This was probably due to the formation of small amounts of *tert*-butyl bromide in the isobutyl bromide and the deuterioisobutyl bromide used. With the best obtainable reagents the deuterium isotope effect for β -deuterioisobutylmagnesium bromide reacting with pseudo first order concentrations of benzophenone is in the present work found to be $k_H/k_D=1.46$. If this value is compared with the isotope effects obtained with other Grignard reagents shown in Table 1, it follows that there is a clear correlation between the amount of benzhydrol formed in the reaction and the deuterium isotope effect for the over all reaction. $k_H/k_D=1.0$ for *tert*-butyl and ethyl Grignards. These derivatives yield none and very little

Table 1. Yield of benzhydrol in the reaction of non-deuteriated Grignard reagents with 0.02 M benzophenone at 20° in diethyl ether and kinetic isotope effect of the total reaction by β -deuteriation of the Grignard reagent to the extent shown.

	$\frac{k_H}{k_D}$	Benzhydrol %	$\frac{\beta-D}{\beta-(H+D)}$ %
0.50 M C ₂ H ₅ MgBr	1.01	6	95
0.20 M C ₄ H ₉ MgBr	1.28	55	97
0.50 M (CH ₃) ₂ CHMgBr	1.16	20	92
0.25 M iso-C ₄ H ₉ MgBr	1.46	91	95
0.26 M <i>t</i> -C ₄ H ₉ MgCl	1.0	0	64

reduction product. $k_H/k_D=1.28$ for butyl and isobutyl compounds which produce 55 % and 92 % reduction product, respectively.

This observed correlation would in itself indicate a primary isotope effect which is associated with the reduction and not the addition reaction. The value 1.46 should therefore be compared with the change in the ratio between reduction product and addition product observed by the introduction of β -deuterium in isobutylmagnesium bromide. This ratio changes by a factor of 2.4 (Table 2). Competition between equal amounts of deuterio and non deuterio

Table 2. Ratio between the amount of reduction product and addition product in the reaction of isobutylmagnesium bromide with benzophenone at 20° in diethyl ether at various concentrations of the reagents.

	red/add
0.25 M (CH ₃) ₂ CHCH ₂ MgBr + 0.01 M benzophenone	10.8
0.50 M » + 0.05 M »	10.6
1.00 M » + 0.05 M »	10.6
1.50 M » + 0.05 M »	6.1
0.50 M (CH ₃) ₂ CDCH ₂ MgBr + 0.05 M »	4.55
0.02 M » + 0.25 M »	8.40
0.02 M (CH ₃) ₂ CHCH ₂ MgBr + 0.25 M »	21.4
0.02 M » + 1.50 M »	22

isobutylmagnesium bromide for a very small amount of benzophenone was shown by mass spectroscopic analysis to give a ratio of benzhydrol to α -deuteriobenzhydrol of 2.4. The lack of correlation between the values of the deuterium isotope effects found directly by rate measurements or indirectly by product analysis requires in some way a separation of the rate determining step and the product determining step. It is therefore concluded that the reaction occurs partly by a SET mechanism as for example the two step mechanism Fig. 1 (II). It remains undecided whether mechanisms I and II are independent and separate mechanisms or whether a mechanism is possible which is a hybrid between I and II.

As supplementary evidence for a SET mechanism may be taken the occurrence of a magnesium benzophenone ketyl signal in the ESR and correspondingly a transient color in the reaction mixture. On the other hand there have been no reports of CIDNP effects in the reduction and addition reactions of Grignard reagents. Likewise attempts to find benzopinacol either by crystallization or thin layer chromatography were unsuccessful.

The over all rates observed with pseudo first order concentrations of benzophenone at various concentrations of isobutylmagnesium bromide are shown in Fig. 2. Increasing concentrations of Grignard reagent lead to increasing values of k_{obs} , but the slope of the curve is steadily decreasing, and a saturation effect is observed at concentrations above *ca.* 1 M. It seems reasonable to assume that the saturation effect is connected with the formation of complexes between the reagents and substrate.⁹

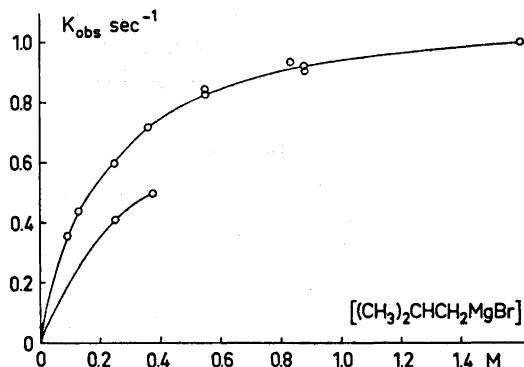
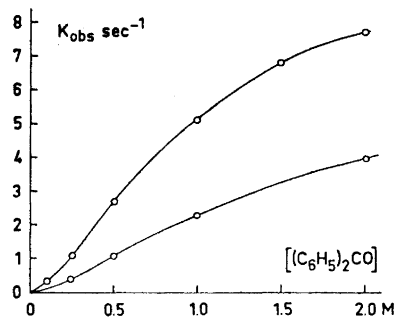


Fig. 2. Upper curve, pseudo first order rate constants k_{obs} for the reaction in diethyl ether at 20° of 0.020 M benzophenone with isobutylmagnesium bromide (9.6 % excess bromide). Lower curve, values of k_{obs} for the reaction in ether at 20° of β -deuterioisobutylmagnesium bromide (7.5 % excess bromide) with 0.02 M benzophenone.

Fig. 3. Upper curve, pseudo first order rate constants k_{obs} for the reaction in diethyl ether at 20° of 0.020 M isobutylmagnesium bromide (9.6 % excess bromide) with benzophenone (see text). Lower curve, values of k_{obs} for the reaction of 0.02 M β -deuterioisobutylmagnesium bromide (7.5 % excess bromide) with benzophenone.



Rates observed with pseudo first order concentrations of Grignard reagent (0.02 M) are shown in Fig. 3. It appears from the curve that the reaction order with respect to benzophenone is above one in the concentration range up to 0.5 M benzophenone and that a saturation effect is beginning at concentrations above 1 M. Since the Grignard reagent under the reaction conditions is likely to change composition during the reaction, it is rather surprising that 40–60 % of the reaction followed the first order rate law. The half life of 0.02 M isobutylmagnesium bromide in 1.5 M benzophenone is *ca.* 8 times lower than the half life of 0.02 benzophenone in 1.5 M isobutylmagnesium bromide. As a tentative explanation one could suggest the formation of a highly reactive complex between one molecule of magnesium compound and two molecules of benzophenone.

The deuterium isotope effect in the case of a large excess of benzophenone was $k_{\text{H}}/k_{\text{D}}=2.5$ and the ratio of addition to reduction was changed by the introduction of deuterium in the β -position by a factor 2.55. The agreement

between the two values in this case indicates a one step mechanism, *e.g.* the cyclic hydride transfer mechanism of Whitmore effective when isobutylmagnesium bromide reacts with excess benzophenone.

EXPERIMENTAL

Isobutyl bromide and β -deuterioisobutyl bromide⁶ were fractionally distilled at 40°, 100 mmHg through a 45 cm glass helices column. The maximum impurity of *tert*-butyl bromide was found by GLC (silicone column) and NMR (Varian A 60) to be 0.4 %, comparing the 9 H singlet of *t*-butyl bromide with one absorption of the observed sextet of the β -H in isobutyl bromide. The bromide was converted to the Grignard reagent immediately after its preparation. Hexadeuterio-*t*-butylmagnesium chloride was prepared as described.¹ Dow sublimed magnesium was used and ether was freshly distilled from lithium aluminium hydride. Product distributions were determined by GLC and NMR. A 1.5 m diethyleneglycol succinate column at 195° separated benzophenone from α -isobutylbenzhydrol and benzhydrol. The areas of the peaks (flame detector) were measured with a planimeter and related to yields and concentrations by means of standard mixtures.

The rate measurements were performed at 20° by means of the thermographic method described earlier.¹ T_0 was recorded 1–2 msec after mixing and the final temperature was T_∞ . The temperatures recorded in between (from 2–10 observations depending on conditions) were fitted to the first order expression

$$\ln \frac{a}{a-x} = \ln \frac{T_\infty - T_0}{T_\infty - T} = kt.$$

The disappearance of 0.02 M benzophenone in excess Grignard reagent was pseudo first order and k_{obs} for the total reaction was obtained from the first order plots. The disappearance of 0.02 M isobutylmagnesium bromide in excess benzophenone was analysed in the same way and first order rate constants were obtained from the linear part of k_{obs} versus time. The plot was linear for the first 40–65 % of the reaction.

Concentrations of isobutylmagnesium bromide above 0.8 M were obtained by mixing in the flowing stream apparatus 20 volumes of reagent with 1 volume of 0.42 M benzophenone solution.

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