Mechanism of the Grignard Addition Reaction

VII. Correlation of the Rate of Reaction and the Coordination Equilibrium for Grignard Reagents with Various Substrates

TORKIL HOLM

Department of Organic Chemistry, The Technical University, DK-2800 Lyngby, Denmark

The correlation which may be obtained between the rate of reaction and the coordination equilibrium of certain substrates with Grignard reagents in ether solution allows the possibility of reaction occurring within the complex (rearrangement) or outside the complex (collision). With the possible exception of aromatic Grignard reagents, only the latter mechanism seems to be of importance.

The kinetics of the Grignard addition to acetone and to benzophenone is discussed. The apparent reversal of the order of reactivity of Grignard reagents with various alkyls, which is observed by interchanging these substrates may result from the operation of alternative mechanisms and extreme difference in the steric requirements of the respective transition states.

An approximate determination of the position of the Schlenk equilibrium for methylmagnesium bromide in diethyl ether is possible from kinetic results with benzophenone and is in accordance with the value obtained by thermometric titration.

A lthough much progress has been made in recent years in the elucidation of the nature of the Grignard reagent and the mechanism of its reactions many important questions remain unanswered.

It most theories concerning the mechanism of the Grignard addition reaction a common feature has been [1] that the initial step of the reaction must be the formation of a complex by coordination between the Grignard reagent and the substrate. Actually the existence of a coordination equilibrium has been adequately demonstrated and equilibrium constants determined by spectroscopical means for various substrates, and in a few cases (acetone,[2,3] methyl acetate,[4] 4-methylthioacetophenone [5a]) a correlation has been possible between the rate of the reaction and the position of the coordination equilibrium.

Such attempted correlation has, however, more or less failed in the case of the carefully investigated substrate 2,4-dimethyl-4'-methylthiobenzo-

phenone.[5b] Kinetic data obtained in the present investigation (Figs. 1. and 2) with unsubstituted benzophenone are likewise not directly correlative with a coordination equilibrium.

In the present work the kinetics of the Grignard addition to acetone and benzophenone has been compared in an attempt to obtain information about the mechanism.

The kinetics observed with Grignard reagents and acetone in diethyl ether [2,3,6] show, that in the coordinated state the ketone is no longer a substrate for the Grignard reagent, or at least its reactivity is lowered to an insignificant value. This conclusion may be drawn from the fact that for low ketone concentrations the reaction is close to zero order with respect to Grignard reagent when the concentration of this reagent exceeds 0.3 M. Infrared spectroscopy shows [2] that the major fraction of the substrate is complexed at this concentration, but the question raised is whether the complex is an actual intermediate or whether it is merely a passive side equilibrium competing with the formation of product.

Since according to the mass equation for the coordination equilibrium the rate expressions for either a mechanism based on rearrangement of the complex or a mechanism based on collision of free ketone with Grignard reagent would both contain the product of the concentrations of the Grignard reagent and the free ketone, the differentiation between the two possibilities by kinetic means might seem impossible.

The use of low concentrations of butylmagnesium bromide and increasing excess of acetone, however, leads to extremely high and ever increasing rates,[6] which shows that complex formation with the substrate does not reduce the reactivity of the Grignard reagent and that the fraction of uncoordinated substrate may possibly in this case account for all reaction at any ratio of substrate:Grignard reagent.

In the case of reaction occurring exclusively outside the complex the rate expression should then contain the product of the concentration of free, uncoordinated substrate and the total concentration of Grignard reagent with inclusion of the fraction which is coordinated to the substrate.

It may be useful at this point to consider the results obtained by Smith and Su [5] using as substrate a substituted benzophenone. In this case the rate of the reaction continued to increase with the Grignard reagent concentration even when the substrate was fully coordinated. By observing the curve which shows the relation between pseudo first order rate constants for the substrate and concentration of the Grignard reagent it seems possible, however, to differentiate between an initial steep and non-linear part, and a linear, less sloping part valid for Grignard concentrations above ca. 0.3 M.

A reinterpretation of the results of Smith and Su seems to require that the substituted benzophenone in the coordinated state has some of its reactivity retained as a substrate for Grignard reagents. Reaction then very probably takes place by collision of the two species without preceding coordination, since two magnesium atoms will not be expected to coordinate to the same carbonyl oxygen.
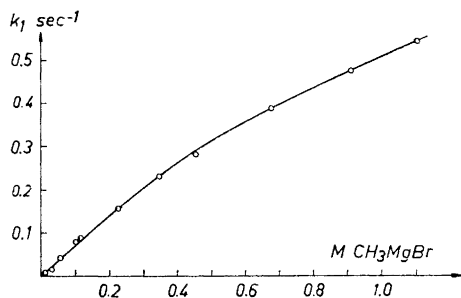
Fig. 1. Pseudo first order rate constants for 0.0010 M benzophenone reacting with methylmagnesium bromide at 20° in diethyl ether.
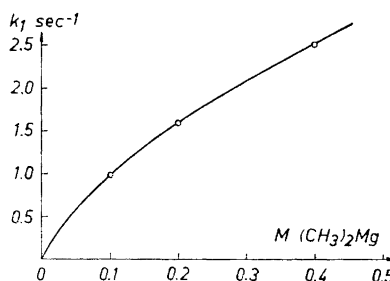
Fig. 2. Pseudo first order rate constants for 0.050 M benzophenone reacting with dimethylmagnesium at 20° in diethyl ether.

In the case of the substituted benzophenone used by Smith and Su there seems to be a considerable difference between the reactivity of the free and the coordinated substrate. The results obtained with unsubstituted benzophenone and methylmagnesium bromide indicate much less difference in reactivity of this ketone in the free and in the coordinated state since the curve (Fig. 1) is much more straight. Actually rate measurements of reaction of dilute methylmagnesium bromide with a large excess of benzophenone indicated a reactivity of free benzophenone of twize the value obtained under conditions when the coordination was supposed to be nearly complete.

There is reason to believe that the difference in the kinetics of the two benzophenones is due to the steric effect of the o-methyl substituent. While coordination with methylmagnesium bromide alone has little effect on the reactivity of unsubstituted benzophenone the combined effect of substitution and coordination causes a relatively low reactivity of the complex formed from methylmagnesium bromide and 2,4-dimethyl-4'-methylthiobenzophenone.

A further illustration of the effect of coordination is obtained when the kinetics of the reaction between benzophenone and tert-butylmagnesium bromide is observed. In this case the reaction rate does not vary significantly when the Grignard concentration is changed from 0.73 M to 0.36 M or 0.18 M (Fig. 3). Furthermore the rate of reaction of a low concentration of Grignard reagent with a large excess of ketone is extremely high. While the half life of 0.05 M benzophenone in 0.50 M tert-butylmagnesium bromide is 10 to 15 msec the reaction of 0.05 M tert-butylmagnesium bromide with 0.50 M benzophenone occurs with a half life less than 1 msec.

This type of kinetics is in many respects similar to the kinetics observed by addition of butylmagnesium bromide to acetone in diethyl ether. The difference is that coordination with any type of Grignard reagent (or magnesium halide) completely destroys the reactivity of acetone, while only very bulky reagents have this effect toward benzophenone.

The conclusion of the kinetics observed with both acetone and benzophenone seems to be that with methyl-, butyl-, or tert-butylmagnesium
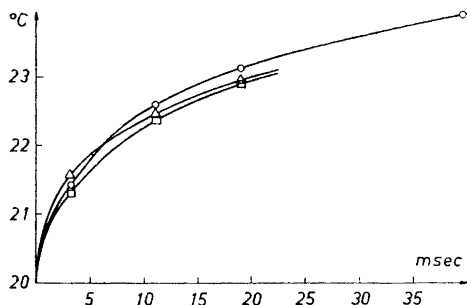
Fig. 3. Time-temperature plots for reaction in diethyl ether at 20° of 0.050 M benzophenone with *tert*-butylmagnesium bromide 0.73 M (triangles), 0.36 M (circles), or 0.18 M (squares).
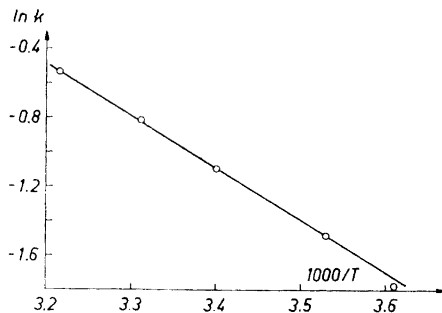
Fig. 4. Plot of $1/T$ *versus* ln k_1 for the reaction of 0.0010 M benzophenone with 0.10 M methylmagnesium bromide in diethyl ether, determined from absorbance measurements at 300 mμ.

bromide there is no significant rearrangement of the complex, and that coordination of the substrate has the effect to reduce or completely cancel the reactivity toward Grignard reagents, while the reactivity of the Grignard reagent is relatively unchanged after coordination.

While rearrangement seems unimportant in the reaction of acetone with aliphatic Grignard reagents, it may be of importance in the reaction of the aromatic Grignard reagents. This is indicated by the unexpectedly fast reaction rates observed (Table 1). Furthermore the half life of 0.02 M p-chlorophenyl-magnesium bromide reacting with 0.50 M acetone in ether was found to be

Table 1. Pseudo first order rate constants for the reaction of 0.050 M acetone or 0.050 M benzophenone with various Grignard reagents in diethyl ether at 20°, determined by the thermographic method.

		k_{I} (Acetone) sec^{-1}	k_1 (Benzophenone) sec^{-1}
0.5 M	p-Tolylmagnesium bromide	69	1.0
0.5 M	Phenylmagnesium bromide	42	0.30
0.5 M	p-Chlorophenylmagnesium bromide	14	0.17
0.5 M	Ethylmagnesium bromide	7.5	7.2
0.5 M	Methylmagnesium bromide	3.8	0.30
0.5 M	Butylmagnesium bromide	2.2	
0.5 M	Isopropylmagnesium bromide	1.6	21
0.5 M	*tert*-Butylmagnesium bromide		27
0.5 M	*tert*-Butylmagnesium chloride	0.15	100
0.568 M	Methylmagnesium bromide		0.32
0.568 M	» +0.60 M MgBr$_2$		0.16
0.568 M	» +0.198 M (CH$_3$)$_2$Mg		1.40
0.198 M	Dimethylmagnesium		1.60
0.396 M	»		2.50
0.099 M	»		1.00

0.015 sec as compared with a half life of 0.02 M acetone in 0.50 M p-chloro-phenylmagnesium bromide of 0.050 sec. Since more than 90 % of the acetone is assumed to be complexed in 0.50 M Grignard reagent, reaction of the 10 % free, uncoordinated ketone can not account for the observed rate. A considerable part of the total reaction is then likely to occur by rearrangement of the complex or less likely by reaction between complex and an extra molecule of Grignard reagent.

Kinetic experiments with Grignard reagents using large excess of substrate are difficult to perform, but at present seem the most reliable means to make a distinction between the rearrangement and the collision mechanisms. Related evidence against a rearrangement mechanism for the reaction of benzophenone with dimethylmagnesium in ether has been furnished by House and Oliver [7] who showed that the addition of small amounts of exceedingly effective coordination partners may accelerate the reaction even though the coordination between the dimethylmagnesium and the substrate must be reduced very substantially.

The general inhibitive effect on the reactivity of the substrate by coordination must be caused by a steric shielding of the carbonyl group by the coordinated magnesium reagent. The effect is very pronounced with acetone and relatively weak with benzophenone, indicating that the aromatic, resonance stabilized ketone is less susceptible to steric hindrance.

Rate measurements for the addition of various RMgBr reagents to acetone has been carried out and showed (Table 1) decreasing reactivities in the order: allyl$>p$-tolyl$>$phenyl$>p$-chlorophenyl$>$ethyl$>$methyl$>$butyl$>$isopropyl$>$ $tert$-butyl. This same order of reactivity has been observed also for benzo-nitrile [8] and it seems to be correlated to some extent to the order of increasing bulk of R.

Using benzophenone as the substrate for RMgBr the order of reactivity was: $tert$-butyl$>$isopropyl$>$ethyl$>p$-tolyl$>$phenyl$>$methyl$>p$-chlorophenyl (confirming the experiments of Kharash [10]) which is more or less a reversal of the order observed with acetone and benzonitrile, while it bears resemblance to the order of reactivity of Grignard reagents in the reaction with 1-hexyne,[11] indene,[12] or chloromagnesiumphenyl acetate.[13]

The apparent reversal of the order of reactivity of Grignard reagents by changing the substrate from acetone or benzonitrile to benzophenone or 1-hexyne is very likely for a large part depending on the difference in steric requirements of the various transition states. The high reactivities of the aromatic reagents toward acetone and benzonitrile may as mentioned above result from the simultaneous operation of both the collision and the rearrangement mechanism.

That electronic factors have a parallel effect in the reactions of Grignard reagents is indicated by the observation of negative values of ϱ in the Hammett relations for the reaction of p-substituted phenylmagnesium bromide with either benzophenone, acetone, 1-hexyne,[14] or benzonitrile.[15] Likewise a positive value for ϱ has been observed for the reaction of methylmagnesium iodide with p-substituted benzophenones [16] or for reaction of diethylmagnesium with p-substituted benzonitriles.[17]

Experimental values for the activation energy and the entropy of activation were found for the reaction of methylmagnesium bromide with benzophenone in diethyl ether from rate measurements at temperatures between 0° and 40° by means of the Arrhenius plot (Fig. 4). A value of 13.9 kcal/mole was found for the activation energy, and the entropy of activation at 20° was found to be 14.3 e.u.

In the reactions of "Grignard reagents" of cause at least two reactive species are involved, in accordance with the Schlenk equilibrium. While the position of this equilibrium is independent of the concentration up to 0.1—0.2 M a shift toward alkylmagnesium halide is likely at higher concentrations.[18]

Within the limits set by the uncertainty concerning the exact nature of the Grignard reagent at concentrations above 0.2 M, one may study the role of complex formation in the Grignard addition reaction also by means of competition experiments, in which the reactivity of the components of the Schlenk equilibrium are compared.

Certain acidic substrates like methyl trifluoroacetate react with Grignard reagents in ether without any observable complex formation.[4] Reaction of this substrate with a wide range of mixtures of dibutylmagnesium and magnesium bromide showed a fair correlation between the reactivity of the "Grignard reagent" and the calculated value for the concentration of free dibutylmagnesium as obtained from the mass equation for the Schlenk equilibrium. As a typical observation it may be mentioned that the addition to a solution of 0.1 M dibutylmagnesium in diethyl ether of 0.3 M butylmagnesium bromide led to very little change in reactivity toward methyl trifluoroacetate. According to the Schlenk equilibrium the addition should cause very little change in the concentration of dibutylmagnesium and the result therefore indicates both relative inertness of butylmagnesium bromide toward this substrate and absence of complex formation.

When acetone was used as the substrate the reactivity of dibutylmagnesium was strongly inhibited by the addition of butylmagnesium bromide. This phenomenon has been explained on the basis of the complex-rearrangement theory [3] but is understandable also in case of reaction outside the complex, since the amount of reactive, uncoordinated acetone is roughly inversely proportional to the sum of the concentrations of dibutylmagnesium, butylmagnesium bromide, and magnesium bromide.

Competition experiments as described have now been performed using benzophenone as the substrate. The results (Table 1) showed a slight (12 %) reduction in the reactivity of a 0.198 M solution of dimethylmagnesium by the presence of 0.568 M methylmagnesium bromide. In accordance with theory this may be explained by a change in the coordination equilibrium toward more substrate in the coordinated and less reactive state.

From the results of the competition experiments shown in Table 2 an approximate calculation of the position of the Schlenk equilibrium for methylmagnesium bromide is possible.

The pseudo first order rate constant for benzophenone-Grignard complex reacting with 0.568 M methylmagnesium bromide was found to be 0.32 sec^{-1}. It is assumed that the coordination was nearly complete. In the presence of a large excess of magnesium bromide (0.60 M) this value was reduced to 0.16

sec^{-1}. Since according to the Schlenk equilibrium practically no dimethyl-magnesium could be left in the solution, this result indicates that the reactivity of methylmagnesium bromide toward this substrate is the sum of two almost equal contributions from the CH_3MgBr and the dimethylmagnesium present.

When 0.198 M dimethylmagnesium was added to 0.568 M methylmagnesium bromide the rate constant was found to be 1.40 sec^{-1}. In this experiment the concentration of free dimethylmagnesium may be assumed to deviate very little from 0.198 M and the contribution on the rate constant from this concentration of dimethylmagnesium is then found by substraction of the CH_3MgBr contribution 0.16 sec^{-1}. The result is 1.24 sec^{-1} and the concentration of free dimethylmagnesium is then: $0.16 \times 0.198/1.24 = 0.0255$ M corresponding to 9.0 %.

The value for the position of the Schlenk equilibrium for 0.4 M methylmagnesium bromide obtained by thermometric titration was 9.2 %. In spite of the approximative calculations and the uncertainty concerning the variation with concentration in the state of the Grignard reagent, the result seems to be more than mere coincidence.

EXPERIMENTAL

The kinetic data were obtained by the thermographic method [2,3] or by means of ultraviolet spectroscopy. The last method was analogous to the method used by Smith and Su [5] and based on the assumption that the strong absorption ($\lambda_{max} = 300$ mμ) observed by mixing benzophenone and methylmagnesium bromide can be ascribed to a complex. The disappearance of the absorption was recorded and pseudo first order rate constants were derived from the half life obtained as the average or 4 or 5 halvings of the absorbance, using the final reaction mixture as the reference.

A stopped flow arrangement was obtained using a 10 mm quartz microcell with an inlet and outlet of stainless steel tubing combined with the two motorburettes and the mixing arrangement described earlier.[2,3] A Beckmann DU spectrophotometer with 1P28 photomultiplier was used in combination with a Servogor recorder. Thermostated water was pumped through the cell compartment and the cell temperature was controlled by means of an internal thermocouple. The measurements were carried out at a room temperature of $20 \pm 0.5°$.

Materials and reagents were handled as described in Ref. 3.

For spectroscopic determinations a concentration of benzophenone of 0.001 M was used, while concentrations of 0.05 M and 1.0 M were used in the thermographic measurements.

The increase in temperature by 100 % reaction of 0.050 M benzophenone in the presence of 0.57 M methylmagnesium bromide was found to be 5.25°.

Thermometric titration of 20 ml 0.20 M dimethylmagnesium with 2.48 M magnesium bromide in diethyl ether was performed and the resulting curve interpreted by the methods described for dibutylmagnesium in Ref. 4. The results obtained indicated a percentage of dimethylmagnesium of 9.2 % in a methyl magnesium bromide of 0.40 M $\sim K_{Eq} = ca.$ 320.

REFERENCES

1. Kharash, M. S. and Rheinmuth, O. Grignard Reactions of Nonmetallic Substances, Prentice-Hall, New York 1954.
2. Holm, T. Acta Chem. Scand. 19 (1965) 1819.
3. Holm, T. Acta Chem. Scand. 21 (1967) 2753.
4. Holm, T. Acta Chem. Scand. 20 (1966) 2821.

5a. Smith, S. G. and Billet, J. *J. Am. Chem. Soc.* **89** (1967) 6948.
5b. Smith, S. G. and Su, G. *J. Am. Chem. Soc.* **88** (1966) 3995.
6. Holm, T. *Acta Chem. Scand.* **20** (1966) 1139.
7. House, H. O. and Oliver, J. E. *J. Org. Chem.* **33** (1968) 929.
8. Gilman, H., St. John, E. L., St. John, N. B. and Lichtenwalter, M. *Rec. Trav. Chim.* **55** (1936) 577.
9. Vavon, G., Barbier, M. and Thiebant, G. *Bull. Soc. Chim. France* [5] **1** (1934) 806.
10. Kharash, M. S. and Weinhouse, S. *J. Org. Chem.* **1** (1936) 209.
11. Wotiz, J. H., Hollingsworth, C. A. and Dessy, R. E. *J. Am. Chem. Soc.* **77** (1955) 103.
12. Ivanoff, D. and Abduloff, I. *Compt. Rend.* **196** (1938) 491.
13. Ivanoff, D. and Spassoff, A. *Bull. Soc. Chim. France* [4] **51** (1932) 619.
14. Dessy, R. E. and Salinger, R. M. *J. Org. Chem.* **26** (1961) 3519.
15. Swain, C. G. *J. Am. Chem. Soc.* **69** (1947) 2306.
16. Lewis, R. N. and Wright, J. R. *J. Org. Chem.* **17** (1952) 1257.
17. Becker, E. I. and Citron, J. D. *Can. J. Chem.* **41** (1963) 1260.
18. Smith, M. B. and Becker, W. E. *Tetrahedron* **22** (1966) 3027.