Mechanism of the Grignard Addition Reaction

V. The Schlenk Equilibrium and the Reactivity of Butylmagnesium Bromide toward Acetone and Methyl Trifluoroacetate in Diethyl Ether

TORKIL HOLM

Department of Organic Chemistry, The Technical University, Lyngby, Denmark

The change of reactivity of butylmagnesium bromide caused by the addition of magnesium bromide or dibutylmagnesium was studied by the use of two substrates of which methyl trifluoroacetate has no complex forming ability toward electrophilic magnesium compounds, while acetone has an extreme basicity in this sense. The position of the Schlenk equilibrium may be determined on the basis of kinetic results for the reaction of methyl trifluoroacetate and butylmagnesium reagents since collision between ester molecules and dibutylmagnesium molecules seems to be the main mechanism. The reaction between acetone and dialkylmagnesium in ether is inhibited by the presence of alkylmagnesium bromide which competes with dialkylmagnesium in the initial complex formation. The reaction mechanism involves rearrangement of the initial complex between the ketone and dialkyl-magnesium. Rearrangement of a ketone-RMgBr complex may account for a part of the reaction.

In recent years the Schlenk equilibrium in the form

$$R_2Mg + MgX_2 \rightleftharpoons 2\ RMgX \tag{I}$$

seems to be reestablished as the fundamental description of the Grignard reagent in ether solution.

Smith and Becker [1] determined the position of the equilibrium by means of thermometric titration for dilute solutions, but for concentrations above 0.1 M the results were difficult to interpret because of the formation of dimers or trimers of the magnesium compounds as evidenced by ebullioscopic measurements.[2] The use of flowing stream technique reveals that the equilibrium between dibutylmagnesium and magnesium bromide is obtained in less than 1 msec.

Since the reactivity of dialkylmagnesium toward most substrates is very much greater than that of the Grignard reagent, the possibility of evaluating the position of the Schlenk equilibrium by kinetic means seems obvious, and

preliminary semiquantitative rate measurements of the reactivity of butyl-magnesium compounds toward various substrates were interpreted from this point of view.[3]

In the present work an investigation has been undertaken of the change in reactivity of the Grignard reagent caused by changing the equilibrium system-atically by addition of extra magnesium bromide or extra dialkylmagnesium.

The substrates used were acetone and methyl trifluoroacetate. The fluoro-ester reacts with butylmagnesium bromide by adding one butyl group in a very fast reaction. The ketone formed may be obtained in high yield if the reaction is interrupted, but secondary and tertiary alcohols are slowly formed if the reaction is allowed to continue. Only the kinetics of the fast addition reaction was studied.

The thermographic method [5] was used for the kinetic measurements and several improvements in the technique allowed reproducible rate measurements by the use of a substrate concentration of 0.01 M.

Fig. 1 shows the pseudo 1st. order rate constants for the reaction of the two substrates with 0.50 M butylmagnesium bromide in ether to which extra amounts of either magnesium bromide or dibutylmagnesium are added. The reagents were prepared from a stock solution of Grignard reagent which had identical titers by base and bromine titrations. This "balanced" composition is given as 0 %. To the right is shown solutions which have a bromine titer of 0.500 N but which by addition of dibutylmagnesium have obtained basic titers which exceed 0.500 N by the percentage given on the abscissa, 100 % corresponding to an extra addition of dibutylmagnesium of 0.25 M. Likewise
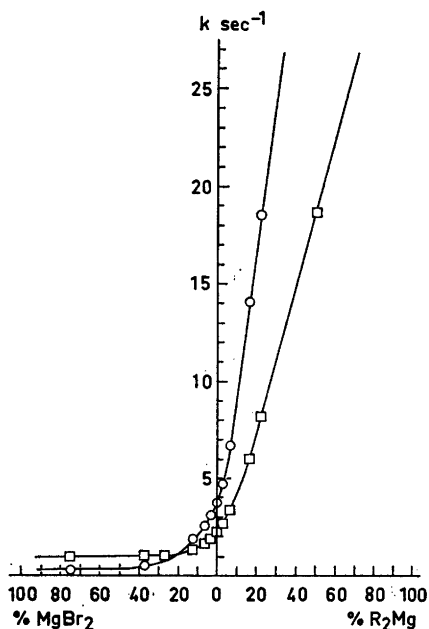

Fig. 1. Pseudo 1st. order reaction constants for methyl trifluoroacetate (circles) and acetone (squares) reacting at 20° with 0.500 M ethereal butylmagnesium bromide containing an excess of magnesium bromide (left) or dibutylmagnesium (right) given as % of 0.25 M.

a reagent given in the left side of the figure has a basic titer of 0.500 N and a bromine titer exceeding 0.500 N by the percentage given as the abscissa.

Since 2—8 % excess magnesium bromide is present in the natural butyl-magnesium bromide (due to Wurtz-type reaction during the formation), the balanced Grignard reagent corresponding to zero on the abscissa was obtained by "neutralization" of the natural butylmagnesium bromide with sufficient dibutylmagnesium.

In several experiments natural butylmagnesium bromide and "synthetic" reagent made to the same base and bromine titers by mixing appropiate amounts of dibutylmagnesium and magnesium bromide etherate, were found to have identical reactivity toward both substrates used.

The results presented in Fig. 1 for methyl trifluoroacetate are consistent with the assumption that reaction with this substrate occurs with R_2Mg only and that RMgBr is practically inactive.* There is a 10 fold increase in reactivity by the addition of 50 % R_2Mg and a 10 fold decrease in reactivity by the addition of 50 % magnesium bromide indicating a 5 % content of dibutyl-magnesium and magnesium bromide in a 0.50 M butylmagnesium bromide solution in ether at 20°. K_{Eq} for equilibrium I would correspondingly be 400.

The reactivity measurements published earlier [3] indicated 100 times greater reactivity of dibutylmagnesium than of butylmagnesium bromide toward methyl trifluoroacetate. The discrepancy is caused by the neglectance of the Wurtz magnesium bromide in the earlier work and a systematic error in the measurements of the extreme rates which are obtained, when a substrate concentration as high as 0.1 M is used.
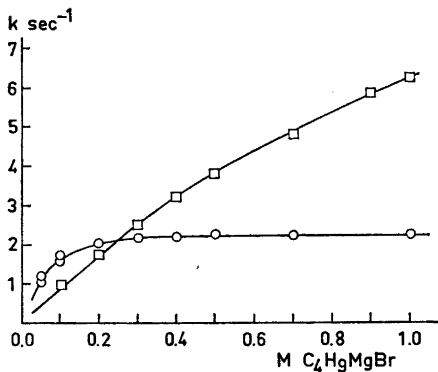

Fig. 2. Pseudo 1st. order reaction constants for the reaction at 20° of methyl trifluoro-acetate (squares) and acetone (circles) with balanced (see text) butylmagnesium bromide at various concentrations.
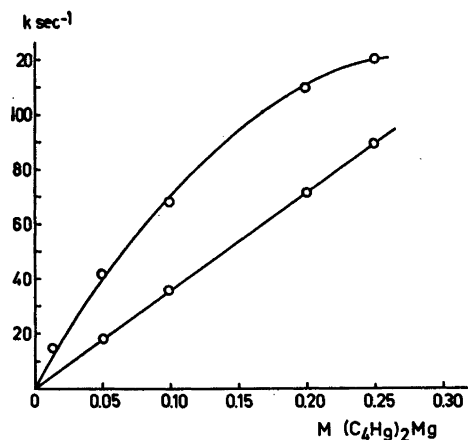
Fig. 3. Pseudo 1st. order reaction constants for the reaction at 20° of methyl trifluoro-acetate (lower curve) and acetone (upper curve) with dibutylmagnesium at various concentrations.

* Here and in the following R stands for butyl.

The results with acetone shown in Fig. 1 are different only in the respect that a niveau for the value of k is reached after addition of 30 % extra magnesium bromide. Further addition has only a small effect on the rate. A simple explanation of this phenomenon might be that RMgBr has a small but definite reactivity toward acetone. The reaction of acetone with balanced butylmagnesium bromide would then be the sum of ca. 60 % reacting with dibutylmagnesium and 40 % reacting with RMgBr. Another possibility is the operation of a reaction mechanism which depends on the presence of magnesium bromide.
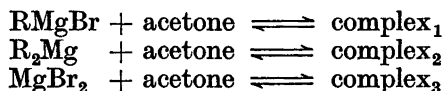
Figs. 2 and 3 show the pseudo 1. order rate constants for acetone and methyl trifluoroacetate reacting with balanced butylmagnesium bromide, respectively dibutylmagnesium, at various concentrations. The striking difference in the shape of the curves may be explained as a result of the difference in basicity of the two substrates.

While the basic acetone very eagerly forms complexes with the electrophilic magnesium compounds (MgX_2, RMgX, and R_2Mg) the non basic methyl trifluoroacetate does not form any complex at all.[4-7] The acetone reaction is then a 1st. order complex rearrangement while the methyl trifluoroacetate reaction depends on collision between R_2Mg molecules and ester molecules without initial complex formation. It is seen from Fig. 1 that starting from 10—15 % added dibutylmagnesium there is an approximate 1st. order dependence of rate on the concentration of added dibutylmagnesium for both substrates, when 0.500 M butylmagnesium bromide is the "solvent". This agrees with the collision theory for methyl trifluoroacetate but may be tentatively explained in case of the complex forming substrate acetone as follows.

For more than 15 % added dibutylmagnesium an eventual contribution to rate from rearrangement of an acetone-RMgBr complex would be insignificant. The rate may be assumed to vary in proportion to the concentration of the R_2Mg-acetone complex. For reasons mentioned below the acetone may be assumed to be fully complexed at this concentration of the reagent, but a competition exists between the magnesium compounds of the Schlenk equilibrium in the coordination with the acetone. While the concentration of RMgBr is kept constant, the fraction of the substrate which is captured by R_2Mg will vary in proportion with the ratio between the concentrations of R_2Mg and RMgBr in the solution.

That the magnesium compounds are competing for forming complex with acetone may be concluded from the observation that the rate constant for the reaction of 0.01 M acetone with 0.25 M dibutylmagnesium is reduced from 120 sec^{-1} to 55 sec^{-1} and 36 sec^{-1}, when respectively 0.25 M or 0.50 M butylmagnesium bromide is added. Contrary to this, the rate of reaction of methyl trifluoroacetate with 0.10 M dibutylmagnesium is almost unchanged by addition of 0.10—0.40 M butylmagnesium bromide.

Since the reactivity of butylmagnesium bromide toward acetone is nearly constant in the concentration range 0.2—1.0 M as seen in Fig. 2, it may be assumed that acetone is close to 100 % coordinated under these conditions according to the equilibria:

$$RMgBr + acetone \rightleftharpoons complex_1$$
$$R_2Mg + acetone \rightleftharpoons complex_2$$
$$MgBr_2 + acetone \rightleftharpoons complex_3$$

An estimate of the equilibrium constant for the RMgBr equilibrium which probably accounts for 90 % of the acetone may be obtained by noting, that the reaction rate is reduced to 50 % at a concentration of butylmagnesium bromide of approximately 0.05 M. At infinite substrate dilution this would indicate $K_{Eq} = 20$.

It is seen from Fig. 2 that the reactivity of butylmagnesium bromide toward methyl trifluoroacetate is deviating from the straight line which would indicate independence of dilution of the position of the Schlenk equilibrium as required by eqn. (I). Since the reaction of this substrate with dibutylmagnesium is 1st. order with respect to either reactant, the rate measurements should indicate the concentration of free R_2Mg in the Grignard reagent. The reason for the relatively lower R_2Mg content at higher concentrations might possibly be the different tendencies to polymerization shown by the components of equilibrium (I).[2] On the other hand the results obtained with acetone show that an eventual lower percentage of R_2Mg at high concentrations of the Grignard reagent must be compensated by a relatively lower competition of RMgBr in the coordination equilibrium, the rate being unchanged.

From the present work it seems possible to conclude, that dibutylmagnesium is the reactive species in butylmagnesium bromide in the reaction with methyl trifluoroacetate. In the reaction with acetone more than one mechanism seem to be operating, but further work is needed in order to clarify the problem.

EXPERIMENTAL

The flowing stream reactor described in Ref. 5 was used with some modifications.

The constant speed burettes were driven by a 60 RPM synchronous motor and delivered each 0.345 ml/sec corresponding to a liquid speed in the polyethylene reaction tube of 1260 mm/sec. Parallel connected reference junctions of the thermocouple were placed in each delivery tube 10 mm ahead of the mixing point, and the position of the measuring junction was adjustable between 2 and 300 mm after the mixing point.

The EMF was registered to within ± 1 μV by means of a DC microvoltmeter (Phillips PM 2440) combined with a Servogor recorder. An equilibration period of 40 sec preceded every reading.

The diethyl ether was dried with lithium aluminum hydride and kept under positive argon pressure (argon dried with P_2O_5). Dilutions of reagents were performed in measuring flasks under argon cover by the use of Metrohm piston burettes, and solutions were transferred by siphoning under argon pressure or by means of syringes with perforation of the rubber stoppers of the measuring flasks.

The composition of reagents was controlled by titration of a 2 ml sample with 0.1 M nitric acid and of the same sample with 0.1 M silver nitrate using a potassium sulphate reference electrode for the electrometric registration in both titrations.

All measurements were carried out in a thermostated room at 20°C. Calculation of 1. order rate constants were based on measurements of the temperature T_1 immediately after the mixing and T_2 after the reaction of 30−70 % of the substrate. k_1 was calculated from the equation

$$k_1 = \frac{1}{t} \ln \frac{a}{a-x} = \frac{1}{t} \ln \frac{T_\infty - T_1}{T_\infty - T_2}$$

where a is the concentration of unreacted substrate at the first measurement, and x is the fraction which has reacted at the second measurement. t is the reaction time. $T_\infty - T_1$ could be measured directly with more reactive reagents, and with less reactive reagents it was calculated by assuming that no reaction had occurred at the first temperature reading. t was measured as the distance between the position of the reference junction of the thermocouple at the first and the second reading, 1 mm corresponding to 0.793 msec.

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