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On the Mechanism of the Grignard Addition Reaction in Diethyl Ether and in Tetrahydrofuran Solution

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Time-temperature plots for mixtures of butyl Grignard solutions with acetone are obtained by means of a flow reactor technique. They allow semiquantitative evaluations of initial reaction rates, and striking differences are observed between the Grignard addition to acetone in ether solution and in tetrahydrofuran solution. The halide of the Grignard reagent has a profound influence on the reaction rate in ether solution but has little effect in THF. The presence of excess Grignard reagent accelerates the reaction in THF but exerts less influence in ether. In both solvents the reaction is accelerated by increasing excess of acetone. A mechanistic interpretation is offered. A calorimetric determination of the molar ratio of tetrahydrofuran to magnesium in the Grignard complexes present in THF solution is attempted.

Advancement in the study of the mechanism of the Grignard addition reaction seems to require an increase in the knowledge of the kinetics of the reaction. Among the reasons for the prevailing scarcity of kinetic work in this field may be named difficulties in handling of the sensitive reagents, extreme speed of the reaction, and interference of competing reactions such as enolization and reduction. This means that *lege artis* kinetic investigations are very difficult to conduct and therefore it seems justified to resort to more simple kinetic methods even if the results obtained must be regarded as only semi-quantitative.

Recently, kinetic results concerning the reaction of butylmagnesium bromide with acetone in ether solution were published [1] showing that the reaction rate was independent of the concentration of the Grignard reagent when the latter was present in excess. The rate determinations were made by infrared spectroscopy combined with a flowing stream reactor. This method put several restrictions on the choice of concentrations and reaction times. In the present work a supplementary method was used which is based on measurements of the rate of heat evolution after mixing Grignard reagent and substrate in the flowing stream reactor. This method is fast and the results are reasonably reproducible. Some caution is required for the interpretation

of such results, but the possibility exists for obtaining approximate values of the initial reaction rate by analysis of the time-temperature plots obtained. A similar method was used by Aston and Bernhard,[2] although the results of the present work are in contradiction to theirs. House and Traficante [3] used the flow reactor with quenching of the reaction mixture and gas-chromatographic analysis of the products. They suggest a second order reaction scheme for the reaction of Grignard reagent with 3-pentanone in ether.

A comparison has been made between the initial rates of the reactions of acetone with butylmagnesium chloride, butylmagnesium bromide, butylmagnesium iodide, and dibutylmagnesium both in diethyl ether and in tetrahydrofuran (THF). For several reasons, the results should be considered as only semiquantitative. For example: there has been made no corrections for the effect of the increase in temperature during the reaction resulting from the adiabatic nature of the method. Also, time and temperature readings of smaller values may be inaccurate within $\pm$ 10 % and no correction is made for heat exchange with the surroundings through the wall of the reaction tube. Heat evolution is ascribed to Grignard addition only and side reactions like enolization and reduction which may be assumed to occur to a limited extent [3] are not considered. Only initial rates are compared because of the possibility of interaction between reaction product and unused Grignard reagent.

Reproducible values for the total rise in temperature in reaction mixtures with an initial concentration of 0.1 M acetone and 1.0 M of butyl Grignard reagent were obtained by calorimeter experiments and were 16.9° for butylmagnesium chloride, 15.6° for butylmagnesium bromide, 14.6° for butylmagnesium iodide, and 17.3° for dibutylmagnesium. Considering the difference

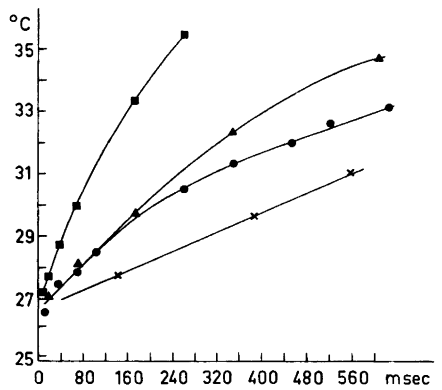

Fig. 1. Time-temperature plots of solutions in tetrahydrofuran of acetone (A) and butylmagnesium bromide (G). Initial concentrations: 0.2 M of A and 0.5 M of G (squares), 0.1 M of A and 0.5 M of G (triangles), 0.2 M of A and 0.25 M G (circles), 0.1 M of A and 0.25 M of G (crosses). Mixing temperature 25°. Initial slopes: 41°/sec, 18°/sec, 18°/sec, and 7.5°/sec.

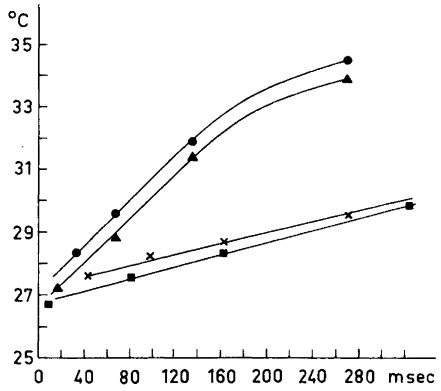

Fig. 2. Time-temperature plots of solutions of 0.1 M of acetone in ether in the presence of 1.0 M butylmagnesium bromide (triangles), 0.5 M butylmagnesium bromide (circles), 1.0 M butylmagnesium iodide (squares), and 0.5 M butylmagnesium iodide (crosses). Mixing temperature 25°. Initial slopes: 35°/sec, 36°/sec, 9.7°/sec, and 8.8°/sec.

in heat capacity of the reaction mixtures, it may be concluded that the heat of reaction for the Grignard addition to acetone in ether varies little for the four different reagents, the magnitude being approximately 60 kcal/mole.

The mixing of Grignard reagent and substrate at a given temperature always led to an almost instantaneous rise in temperature of *ca.* 2° for 0.1 M solutions. This may well represent the heat of coordination and dilution since the coordination of Grignard reagent and substrate has been shown to be extremely fast.[1] The slope of the time-temperature plot after 5 msec is used as an indication of the initial rate of the reaction.

From the results obtained it seems reasonable to conclude that the Grignard addition occurs by different mechanisms depending on which solvent is used.

In tetrahydrofuran the reaction rate shows an approximate 1. order dependence on the concentration of both reactants (Fig. 1), whereas in ethyl ether the rate tends to be dependent only on the concentration of acetone and independent of the excess Grignard reagent (Fig. 2). The latter result confirms the results obtained by means of IR.[1]

Fig. 3. shows the time-temperature plots obtained with mixtures of acetone and ethereal butyl Grignard solutions. If the initial slope of the curve is taken as a relative measure of reaction rate, it is seen that butylmagnesium chloride (650°/sec) reacts 18 times faster than butylmagnesium bromide (36°/sec) which again reacts 3.6 times faster than butylmagnesium iodide (10°/sec). Qualitatively, it was observed that dibutylmagnesium reacts somewhat faster than butylmagnesium chloride.

The reaction in tetrahydrofuran of butyl Grignard reagents yielded the time-temperature plots shown in Fig. 4. Considering the results obtained

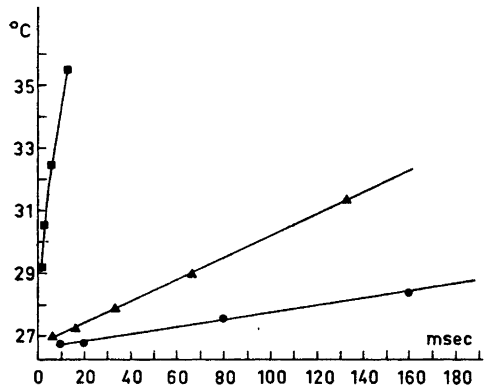

Fig. 3. Time-temperature plots of solutions of 0.1 M of acetone in ether in the presence of 0.75 M butylmagnesium chloride (squares), 1.0 M butylmagnesium bromide (triangles), and 1.0 M butylmagnesium iodide (circles). Mixing temperature 25°. Initial slopes: 650°/sec, 36°/sec, 10°/sec.

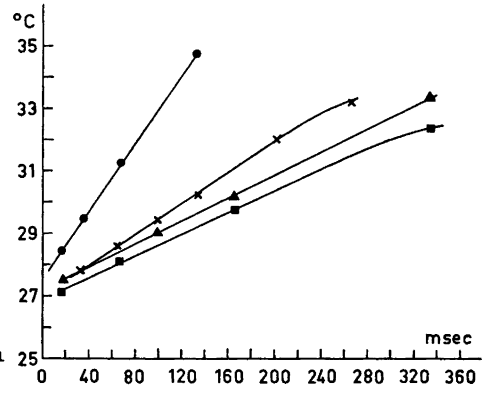

Fig. 4. Time-temperature plots of solutions of 0.1 M of acetone in tetrahydrofuran in the presence of 0.50 M dibutylmagnesium (circles), 0.25 M dibutylmagnesium (crosses), 0.50 M butylmagnesium chloride (triangles), and 0.50 M butylmagnesium bromide (squares). Mixing temperature 25°. Initial slopes: 53°/sec, 25°/sec, 19°/sec, and 18°/sec.

using ether as the solvent, it is remarkable that there is very little difference between the slope of the curve for 1.0 M butylmagnesium chloride (19°/sec) and butylmagnesium bromide (18°/sec). A tempting explanation would be that the Grignard reagent dissociates in tetrahydrofuran to a mixture of R_2Mg and MgX_2 according to the Schlenk equilibrium:

$$2\ RMgX \rightleftharpoons R_2Mg + MgX_2$$

If this is the case a solution of pure dibutylmagnesium of half the molar strength of a given butylmagnesium halide solution should react at the same rate. Fig. 4 shows that this is not far from being the case since 0.5 M dibutylmagnesium in THF reacts only 30 % faster than 1.0 M butylmagnesium chloride (25°/sec against 19°/sec). The increase of the concentration of dibutylmagnesium to 1.0 M increased the rate by *ca.* 100 % (53°/sec against 25°/sec).

The reason for the difference between the results using the two solvents may be the much stronger affinity of tetrahydrofuran than of diethyl ether for the Grignard reagent. When tetrahydrofuran is used as solvent, complex formation between the Grignard reagent and the ketone does not take place. Ethyl ether is much less "basic" than THF and complex formation occurs as observable by infrared spectroscopy.[1] The complex, which is formed extremely rapidly,[1] reacts by intramolecular rearrangement at a rate which is not influenced by the presence of excess Grignard reagent.

While the Grignard reagent-ketone complex in ether solution is unreactive toward excess of the organometallic compound, the results shown in Figs. 5, 6, and 7 indicate a reactivity of the complex toward excess acetone. It is seen that increasing the excess of acetone results in enhanced rate of the reaction. An explanation would be that a Grignard reagent molecule may coordinate with more than one molecule of acetone and that a diacetone-Grignard complex is much less stable than the monoacetone-Grignard complex. The initial

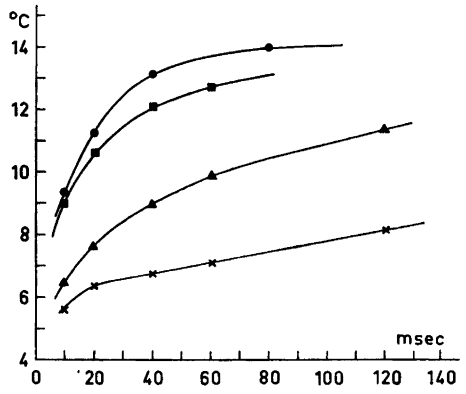

Fig. 5. Time-temperature plots of solutions of 0.1 M butylmagnesium bromide in ether in the presence of 1.0 M of acetone (circles), 0.5 M acetone (squares), 0.25 M acetone (triangles), and 0.1 M acetone (crosses). Mixing temperature 0°.

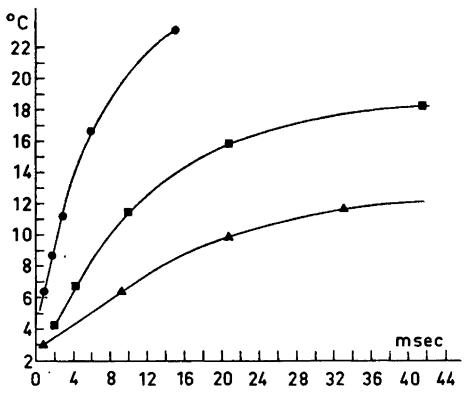

Fig.6 . Time-temperature plots of solutions of 0.1 M dibutylmagnesium in ether in the presence of 0.1 M of acetone (triangles), 0.2 M acetone (squares), and 0.5 M acetone (circles). Mixing temperature 0°. Initial slopes: 400°/sec, 1100°/sec, and 2400°/sec.

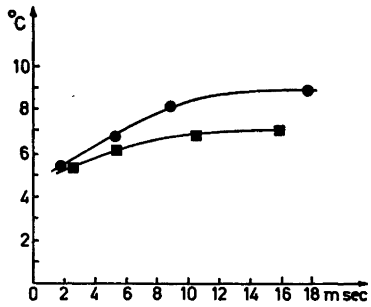

Fig. 7. Time-temperature plots of solutions of 0.1 M of acetone in ether in the presence of 0.05 M butylmagnesium bromide (circles), and 0.1 M butylmagnesium bromide (squares). Mixing temperature 0°. Initial slopes: 44°/sec, 27°/sec.

reaction rate measured after mixing 0.2 M acetone and 0.2 M butylmagnesium bromide in ether is slower than the rate after mixing 0.2 M acetone and 0.1 M butylmagnesium bromide which shows the importance of *excess* acetone (Fig. 7). The reaction of butylmagnesium bromide with excess acetone was complicated by the formation of precipitates, which necessitated cleaning of the system for every reading.

The results obtained with dibutylmagnesium in ether using excess acetone are shown in Fig. 6. The total heat evolved by mixing equal volumes of 0.2 M dibutylmagnesium and 1.0 M of acetone is approximately twice the heat resulting from reaction of 0.2 M of acetone with 1.5 M of dibutylmagnesium (Fig. 8). It is known [3,4] that the initially formed alkoxy Grignard reagent RMg-O-*tert*-R [3] reacts with a ketone preferentially by enolization. The combination of addition and enolization causes the very fast rate of heat evolution (2400°/sec at 4°).

The independence of reaction rate on excess Grignard reagent, which is characteristic for butylmagnesium bromide and iodide reacting with acetone in ether solution, is only partially valid for butylmagnesium chloride and dibutylmagnesium. An increasing excess of the organomagnesium compound in these cases did cause a small increase in reaction rate (Fig. 8). This effect may be due to the operation of a competing mechanism made possible by the "loose"

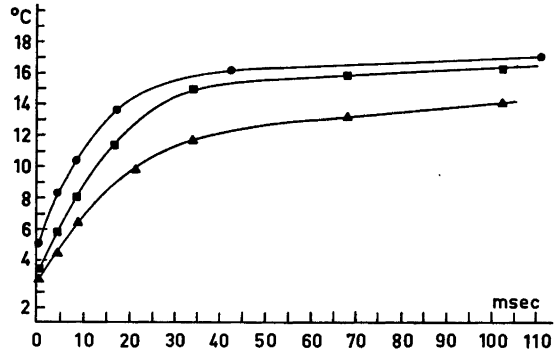

Fig. 8. Time-temperature plots of solutions of 0.1 M of acetone in ether in the presence of 0.1 M dibutylmagnesium (triangles), 0.37 M dibutylmagnesium (squares), and 0.75 M dibutylmagnesium (circles). Mixing temperature 0°. Initial slopes: 410°/sec, 530°/sec, and 720°/sec.

nature of the acetone complexes formed with these reagents. The less effective "protection" of the acetone by complex formation may favour an attack of the Grignard reagent on already formed Grignard-acetone complex so that the reaction no longer takes place only by rearrangement of the complex.

A determination of the molar ratio of tetrahydrofuran to magnesium in the Grignard complex was attempted by means of the calorimetric method. The mixing of 0.5 M ethereal butylmagnesium bromide with 0.2 M ethereal tetrahydrofuran at 25° caused an almost instantaneous rise in temperature of 1.55°. Since the heat of dilution of 0.5 M butylmagnesium bromide with an equal volume of ether caused a ΔT of 0.52° it is assumed that the heat of coordination (by displacement of ether) of 0.1 M THF with magnesium is responsible for 1.03°. The mixing of 0.2 M of etheral butylmagnesium bromide with pure THF caused a ΔT of 2.10°. Since there is almost no change of temperature by mixing ether and THF, this may be interpreted as an indication of the attachment of two molecules of THF to every magnesium atom in Grignard solutions containing an excess of this solvent.

EXPERIMENTAL

Materials. Concerning the raw materials and the preparation of Grignard reagents, *etc.*, see Ref. 1. Tetrahydrofuran was freshly distilled from butylmagnesium bromide prepared using magnesium in excess. Dibutylmagnesium was prepared from butylmagnesium chloride in ether by precipitation of the magnesium chloride with dioxane and removal of solvent by heating to 150° at 1 mm Hg for one hour. The white powder was protected by dry nitrogen and dissolved in THF or ether as required.

Apparatus. The constant speed burettes and flow reactor technique was used as described.[1] The liquid speed in the reaction tube was 290 mm pr. sec. Very fast reactions were measured at 1150 mm/sec. For the measurements of the final temperature of the reaction mixtures, a 50 ml narrow-neck glass calorimeter was used. The calorimeter was saturated with ether vapor and its temperature adjusted to the expected value. It was then isolated with polyurethane foam and two 20 ml syringes filled with Grignard reagent and substrate were cooled to 0° and emptied into the calorimeter. The temperature was read every 30 sec (thermocouple), and the final temperature was obtained by graphic extrapolation.

REFERENCES

1. Holm, T. *Acta Chem. Scand.* **19** (1965) 1819.
2. Aston, J. G. and Bernhard, S. A. *Nature* **165** (1950) 485.
3. House, H. O. and Traficante, D. D. *J. Org. Chem.* **28** (1963) 355.
4. Cowan, D. O. and Mosher, H. S. *J. Org. Chem.* **27** (1962) 1.

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