

Mechanism of the Grignard Addition Reaction

IV. Reaction of Butylmagnesium Compounds with Methyl Acetate in Diethyl Ether and in Tetrahydrofuran

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The kinetics of the reaction of methyl acetate with ethereal butylmagnesium compounds may be explained by the fast, reversible formation of an ester-Grignard reagent complex which is relatively stable and insensitive to any excess of Grignard reagent. The equilibrium may be determined by infrared spectroscopy, by thermometric titration, or by kinetic measurements. At ester concentrations above *ca.* 0.1 M abnormal high rates are observed, possibly as a result of a shift of the Schlenk equilibrium. The "complex type" kinetics is seen with "basic" substrates like acetone and methyl acetate by reaction in ether but not by reaction in tetrahydrofuran, in which solvent no complex formation takes place. There is no kinetic, calorimetric, or IR indication of complex formation by the reaction of the "acidic" substrate methyl trifluoroacetate with ethereal Grignard reagents.

The reaction of Grignard reagents with esters may lead to a variety of products depending on the choice of reactants and reaction conditions. Addition to or enolization of the ester may take place,¹ and the primary reaction may be followed by further addition, reduction, or condensation reactions. The typical reaction, however, is the formation of tertiary alcohol, and side reactions play a role only as the result of steric hindrance caused by bulky groups in either the alcohol or the acid part of the ester or in the Grignard reagent. Since the purpose of the present investigation was to study the Grignard addition to esters, the non-hindered reagents methyl acetate and *n*-butyl Grignard reagents were selected.

The reaction of methyl acetate to form an alcoholate of a tertiary alcohol is formally a two step process, of which the first step leads to a ketone derivative. The first step must be rate limiting since it was observed that only trace amounts of ketone (or none at all) are obtained when the reaction is stopped halfway. This extreme speed of the second step actually requires that the possibility of simultaneous (concerted) addition of the two butyl groups should be considered.

The kinetic study of the ester-Grignard addition was restricted to initial rates only, since studies of Grignard addition reactions^{2,3} have shown that the reaction products may react with unused Grignard reagent and cause an unpredictable change of rate.

Useful methods for determining initial rates would include infrared analysis and gaschromatography, but the method preferred in this study was the "thermographic" method which in earlier studies,^{4,5} had proved to be especially useful for Grignard reactions.

The results obtained are shown in Figs. 1, 2, 3, and 4 and in Tables 1, 2, 3, and 4. Rates are given in °C/min, but since the total rise in temperature by reaction of 0.1 M methyl acetate with an excess of any butylmagnesium compound is approximately 25° the rates may be converted into moles l⁻¹ sec⁻¹. The results should be regarded as only semiquantitative for the reasons given in Ref. 4. Also limiting the precision of the results is the fact that the time-temperature plots obtained show an initial "jump" indicating a transient phase of very fast reaction occurring during the time of mixing. The fast reaction phase is terminated a fraction of a second after the mixing has been completed, and the term "initial rate" in this work is concerned only with the "regular" reaction phase. See also EXPERIMENTAL.

Although butyl Grignard reagents in ethyl ether react about 100 times more slowly with methyl acetate than with acetone,^{3,4} the kinetics of the two reactions are similar in many respects. The following three features may be mentioned specifically: 1) The halogen of the Grignard reagent is modifying the rate according to the same pattern for both reactions as illustrated by Table 1. 2) It is characteristic for both reactions that for low concentrations of substrate the reaction order with respect to Grignard reagent is decreasing toward zero with increasing excess of Grignard reagent (Fig. 1, lower curve, and Fig. 2). 3) Both reactions are first order with respect to substrate for low concentrations of substrate and large excess of Grignard reagent (Fig. 3), whereas the reaction order for increasing substrate concentrations may assume values above 2.

These three kinetic features are characteristic for the Grignard addition in ether solution but not in tetrahydrofuran solution. Since it has been shown³ that complex formation between substrate and Grignard reagent takes place

Table 1. Initial reaction rates at 20° in °C/sec for 0.1 M substrate in the presence of 0.5 M butylmagnesium reagent in ether and in tetrahydrofuran.

	Acetone		Methyl acetate		Methyl trifluoroacetate	
	Ether	THF	Ether	THF	Ether	THF
(C ₄ H ₉) ₂ Mg	2000	25	23	0.30	3000	15
C ₄ H ₉ MgCl	390	19	6.5	0.28	600	
C ₄ H ₉ MgBr	22	18	0.23	0.23	30	11
C ₄ H ₉ MgI	6		0.05		7.2	
$\Delta T/1$ molar	150°		250°		120°	

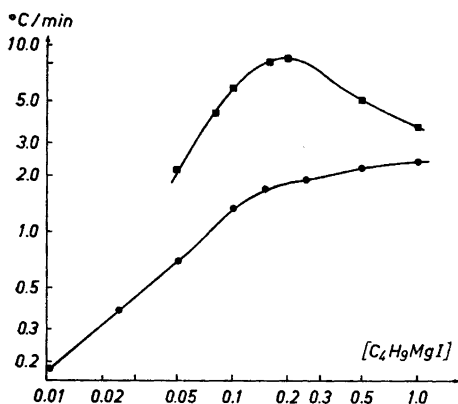


Fig. 1. Upper curve (squares): log rate versus log $[C_4H_9MgI]$ for the reaction in diethyl ether at 4° (initially) of 0.3 M methyl acetate in the presence of various concentrations of butylmagnesium iodide. Lower curve (circles): log rate versus log $[C_4H_9MgI]$ for the reaction in diethyl ether at 25° (initially) of 0.05 M methyl acetate with various concentrations of butylmagnesium iodide.

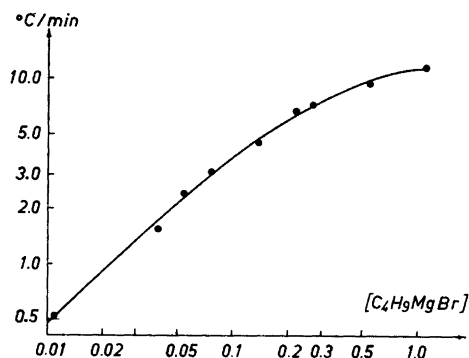


Fig. 2. log rate versus log $[C_4H_9MgBr]$ for the reaction in diethyl ether at 25° (initially) of 0.05 M methyl acetate in the presence of various concentrations of butylmagnesium bromide.

in ether and not in THF it seems reasonable to assume, that the characteristics are caused by the complex formation.

Information about the complex formation is obtainable from the study of infrared spectra of Grignard-substrate mixtures immediately after mixing as described for acetone.⁴ The shift of frequency for the carbonyl absorption by coordination of acetone with Grignard reagents is about 25 cm^{-1} whereas the corresponding shift for methyl acetate varies from $48.6\text{--}61.0\text{ cm}^{-1}$ depend-

Table 2. Fraction of uncoordinated methyl acetate in 0.1 M ethereal solution in the presence of butylmagnesium compounds. Determined by comparison of the carbonyl absorptions 0.1 sec after mixing. Δf = shift of carbonyl absorption by coordination.

Butylmagnesium compound	% free ester	K_{Eq}	Δf (cm^{-1})
1.16 M C_4H_9MgI	10	8.5	61.0
0.58 M »	20	8.0	
0.29 M »	32	8.2	
0.95 M C_4H_9MgBr	20	4.6	57.3
0.47 M »	33	4.9	
0.23 M »	50	5.5	
0.80 M C_4H_9MgCl	21	5.2	48.6
1.80 M $(C_4H_9)_2Mg$	27	1.6	49.3
0.90 M »	35	2.2	

ing on the Grignard-halogen (see Table 2). With methyl acetate the two peaks are thus separated completely and may be measured individually. Since methyl acetate reacts approximately 100 times more slowly than acetone, spectra of the initial Grignard-substrate mixtures are also more easy to obtain.

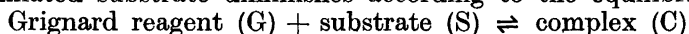
Spectra taken 0.1 sec after mixing Grignard reagent and substrate using 0.1 M methyl acetate and various concentrations of butylmagnesium compounds indicated the equilibrium constants for the complex formation shown in Table 2.

The low kinetic effect of increasing excess of Grignard reagent indicates that complex formation is in a way inhibiting the reaction. Two interpretations may be given. 1) One may assume that a 1:1 complex is formed which rearranges at a characteristic rate, and which is insensitive to attack by the excess Grignard reagent. The maximum rate then corresponds to 100 % coordination. 2) One may alternatively assume that reaction occurs by colli-

Table 3. Initial reaction rates and second order rate constants for the reaction of butylmagnesium chloride (G) and methyl acetate (S) in tetrahydrofuran at 20°.

[G]	[S]	$\frac{dT}{dt}$ (initial)	$\frac{d[S]}{dt}$ $\frac{(\text{moles})}{1 \cdot \text{sec}}$	k ($\frac{1}{\text{mole} \cdot \text{sec}}$)
0.50 M	0.1 M	17°/min	0.068	1.4
0.50 M	0.2 M	38°/min	0.15	1.5
0.25 M	0.1 M	9°/min	0.036	1.5
0.25 M	0.4 M	41°/min	0.16	1.6

sion between Grignard reagent and free, uncoordinated substrate. This collision, while normally leading to coordination, might in favorable cases lead to reaction. With increasing Grignard excess, the concentration of uncoordinated substrate diminishes according to the equilibrium:



$$\frac{[C]}{[G] \cdot [S]} = K_{\text{Eq}} \quad (1)$$

When the complex formation is nearly complete, the product $[G] \cdot [S]$ is constant and at maximum.

The theory seems to be supported by the rate measurements obtained with a low concentration (0.05 M) of methyl acetate reacting with various concentrations of butylmagnesium bromide and butylmagnesium iodide. Table 4 shows reaction rates as compared with the fractions of complexed ester in the equilibrium calculated from eqn. 1 on the basis of the values of K_{Eq} found by infrared analysis (Table 2). The reaction rate corresponding to 100 % coordination was calculated for each experiment and is shown in the last column.

The reaction of 2,4-dimethyl-4'-methylmercaptobenzophenone with methylmagnesium bromide in diethyl ether has been shown to occur according to a similar pattern.⁸

Table 4. Initial reaction rates of 0.05 M methyl acetate at 25° C in the presence of butylmagnesium compounds compared with the fraction of coordinated ester (E_{complex}) calculated on the basis of an equilibrium constant $K_{\text{Eq}} = 8.2$ for butylmagnesium iodide and $K_{\text{Eq}} = 5.0$ for butylmagnesium bromide. Last column shows the theoretical maximum rate at 100 % coordination calculated from the individual rate measurements. Solvent diethyl ether.

$[C_4H_9MgI]$ (moles/l)	$\frac{dT}{dt}$ (°C/min)	$[E_{\text{complex}}]$ (% of total)	$\frac{dT}{dt}^{\text{max}}$ (°C/min)
0.010	0.18	5.4	3.3
0.025	0.39	13	3.0
0.050	0.70	24	2.9
0.100	1.30	40	3.3
0.150	1.70	51	3.3
0.250	1.90	64	3.0
0.500	2.20	80	2.8
1.000	2.40	89	2.7
$[C_4H_9MgBr]$			
0.011	0.53	4.0	13
0.040	1.55	13.4	12
0.055	2.40	18	13
0.077	3.15	23	14
0.11	4.00	31	13
0.22	6.7	48	14
0.27	7.2	54	13
0.55	9.5	70	14
1.11	11.5	84	14

As explained above no answer to the question of whether the complex formation should be regarded as inhibiting or facilitating the reaction may be given on the basis of rate measurements. Various facts, however, seem to suggest the inhibition-theory. 1) The strongly complex forming butylmagnesium iodide reacts much more slowly than the weakly complex forming bromide or chloride. 2) Methyl trifluoroacetate which does not form complexes with Grignard reagents in ether (see later) reacts exceedingly fast. 3) Methyl acetate reacts at a reasonable rate with butylmagnesium bromide in tetrahydrofuran without complex formation.

It has been shown that there is a constant relative reactivity of the various butylmagnesium compounds toward widely different substrates including acetone, methyl acetate, and methyl trifluoroacetate, and the theory has been proposed^{5,6} that the small amount of dibutylmagnesium which is present in Grignard reagents in accordance with the Schlenk equilibrium is the only active species in the Grignard reagent in ether solution. According to this theory the coordination equilibrium is extremely fast and does not limit the rate of reaction. If the theory is accepted one may wonder how the same relative reactivity of Grignard reagents may be found toward the complex forming methyl acetate and the non complex forming methyl trifluoroacetate, since the theory would predict more pronounced difference of reactivity toward the complex forming substrates. One explanation could be that with these

substrates the Schlenk equilibrium is disturbed to an extent that compensates for the first mentioned effect.

A shift in the Schlenk equilibrium caused by coordination with substrate may also explain the large kinetic effect of an increase in the substrate concentration (Fig. 3). The magnesium bromide and iodide complexes with excess methyl acetate or acetone are extremely insoluble in ether, while the dibutylmagnesium complexes are soluble. Instantaneous formation of precipitate is characteristic for the reaction of Grignard reagents with excess of these substrates and in this way the very reactive dibutylmagnesium may be formed. The reaction rates obtained with 0.3 M methyl acetate reacting with various concentrations of butylmagnesium iodide (Fig. 1) show that such phenomena may cause an apparent, negative reaction order with respect to Grignard reagent. The results shown in Fig. 1 may be interpreted as indicating a shift in the Schlenk equilibrium even without formation of precipitates at ratios of methyl acetate:Grignard reagent greater than 1:2.

A few kinetic experiments were carried out with methyl trifluoroacetate. The perfluoro ester does not coordinate with magnesium bromide to any measurable degree as observed by infrared spectroscopy and by thermometric titration. The "complex type" kinetics would then not be expected for this ester. The initial rate of reaction at 20° of 0.1 M ethereal methyl trifluoroacetate with various concentrations of butylmagnesium bromide was found to be: 16.7°/sec for 0.25 M, 30°/sec for 0.50 M, and 56°/sec for 1.00 M.

A plot of log rate *versus* $1/T$ for the reaction of 0.1 M methyl acetate with 0.45 M butylmagnesium iodide yields a straight line (Fig. 4), the slope indicating an energy of activation $E_a = 11.5$ kcal/mole.

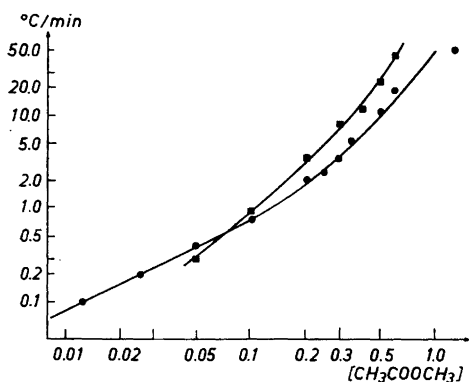


Fig. 3. Upper curve (squares): log rate *versus* log $[\text{CH}_3\text{COOCH}_3]$ for the reaction in diethyl ether at 4° (initially) of 0.16 M butylmagnesium iodide with various concentrations of methyl acetate. Lower curve (circles): log rate *versus* log $[\text{CH}_3\text{COOCH}_3]$ for the reaction in diethyl ether at 4° (initially) of 1.0 M butylmagnesium iodide with various concentrations of methyl acetate.

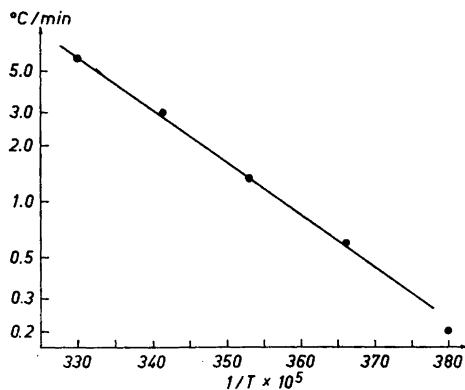
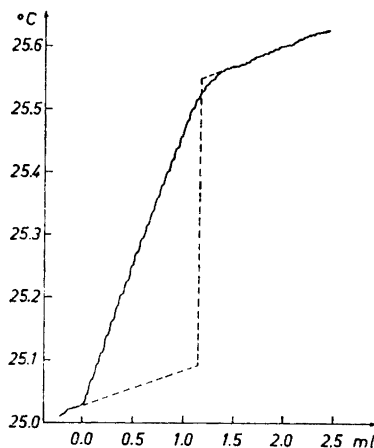


Fig. 4. log rate *versus* $1/T$ for the reaction in diethyl ether of 0.1 M methyl acetate with 0.45 M butylmagnesium iodide at various temperatures.

Fig. 5. Thermometric titration curve for the addition of 0.05 ml/15 sec of an 1.10 M ethereal solution of dibutylmagnesium to 20 ml of an 0.064 M ethereal solution of magnesium bromide. Initial temperature of the solutions 25°.



Reaction rates for the reaction of butylmagnesium chloride with methyl acetate in tetrahydrofuran are shown in Table 3 and indicate a second order scheme for the reaction in this solvent. This result is understandable on the basis that according to infrared analysis there is no coordination between Grignard reagents and methyl acetate in THF.

Thermometric titrations are useful for the determination of Grignard reagent coordination equilibria including the Schlenk equilibrium as shown by Smith and Becker.⁷ A titration curve (Fig. 5) for magnesium bromide and dibutylmagnesium in ether indicates 94 % conversion to butylmagnesium bromide at equilibrium $K_{Eq} \cong 10^3$.

The titration of dibutylmagnesium with magnesium bromide in THF yielded the curve shown in Fig. 6. A negative heat of reaction corresponding to ca. 3.4 kcal/mole was observed and an estimation of the Schlenk equilibrium indicated a 60 % content of butylmagnesium bromide at 1:1 concentrations, $K_{Eq} = 9$.

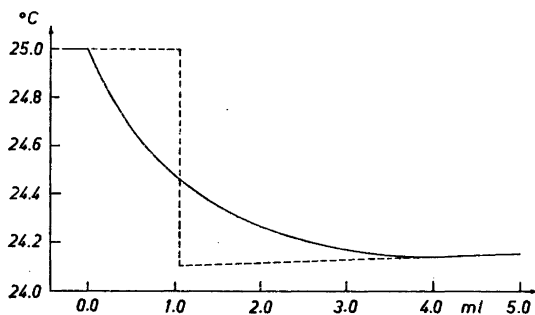


Fig. 6. Thermometric titration curve for the addition of 0.025 ml/10 sec of a 1.90 M solution of dibutylmagnesium in tetrahydrofuran to 20 ml of a 0.1 M solution of magnesium bromide in THF. Initial temperature of the solutions 25°.

EXPERIMENTAL

Materials. Concerning the raw materials and the preparation of Grignard reagents see Refs. 3 and 4.

Apparatus. Reactions faster than 30°/min (initially) were measured in a flowing stream reactor as described.¹ For slow reactions time-temperature plots were obtained by fast (< 5 sec) mixing of 20 ml of each of the reactants in a nitrogen atmosphere using a light weight (inner bulb 2–3 g) Dewar flask with an inlet tube of 8 mm. The temperature was recorded continuously while shaking by means of a 0.1 mm copper-constantan thermocouple and a Phillips microvoltmeter Type 2440 combined with a Honeywell recorder. Initial rates were obtained from the slope of the time-temperature curve after the reaction of approximately 5 % of the reactant which was added in the stoichiometrically lowest concentration.

Thermometric titrations. 20 ml of 0.072 M magnesium bromide in ether was placed in the 50 ml Dewar flask in a nitrogen atmosphere at 25° and the temperature was recorded continuously while 0.05 ml of 1.1 M dibutylmagnesium in ether adjusted to 25° was added every 15 sec from a 10 ml Metrohm piston burette. A small amount (10 %) of the dibutylmagnesium was added before the titration was started to ensure dryness. ΔH for the reaction was calculated from the slope of the straight line obtained initially, while an estimate of the fraction of unreacted dibutylmagnesium was obtained by finding the point of intersection of the prolonged initial and final part of the titration curve. The estimated equilibrium concentration of dibutylmagnesium was approximately 6 % $K_{Eq} \cong 10^8$. Values for ΔH of 3.0 and 3.4 kcal/mole dibutylmagnesium reacted were obtained in two experiments.

In a similar way 20 ml of 0.1 M magnesium bromide in tetrahydrofuran at 25° were titrated by the addition of 0.025 ml/10 sec of a 1.90 M solution of dibutylmagnesium in tetrahydrofuran adjusted to 25°. Because of the long duration of the experiment the results should not be considered very accurate. ΔH may be estimated to be –3.4 kcal/mole dibutylmagnesium reacted and the fraction of butylmagnesium bromide in the equilibrium resulting from initial concentrations of 0.095 M of each of the reactants may be estimated to be 60 %, $K_{Eq} = 9$.

The temperature change by the addition of 2 M methyl trifluoroacetate to 0.1 M ethereal magnesium bromide at 25° was negligible.

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