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by

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The Kinetics and Mechanism of Grignard Reactions With Active Hydrogen Compounds *

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The kinetics of Zerewitinoff reaction between ethyl magnesium bromide and amines, alcohols and 1– alkynes, which are very weak Bronsted acids, was investigated in detail by gas evolution method in diethyl ether at 25°C. The reaction was found tobe second order overall and first order with respect to each reactant. S_Ei mechanism (intramolecular electrophilic substitution), which the transition state was believed to involve both electrophilic attack by active hydrogen at the α carbon of ethyl magnesium bromide and nucleophilic attack by the conjugate base of very weak acid at the magnesium atom, was proposed.

INTRODUCTION

The present work was undertaken in order to investigate the kinetics and mechanism of Grignard reactions with active hydrogen compounds, namely Zerewitinoff reaction.

Reaction of Grignard reagents (alkyl and aryl magnesium halides, RMgX) with active hydrogen compounds (AH), giving a halomagnesium salt and a hydrocarbon via the formula

$$RMgX + AH \longrightarrow AMgX + RH$$

is known as Zerewitinoff reaction. The active hydrogen compounds are water, inorganic acids, carboxylic acids, alcohols, phenols, mercaptans, amides, sulfonamids, ammania, primary and secondary amines, aliphatic nitro compounds and 1– alkynes.

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Zerewitinoff reaction, being a quantitative interaction between Grignard reagent and active hydrogen compounds, the number of active hydrogen atoms in an unknown substance, can be found by measaring of gaseous hydrocarbon evolved. This process is known as Tschugaeff-Zerewitinoff active hydrogen determination method.

Although the application of Zerewitinoff reaction is general and wide and the stoichiometry and products of reaction are known; experimental difficulties –like handling the Grignard reagents and the high speed of the reaction– and vexing interpretive problems are the reasons why kinetic methods couldn't be used widely to reveal its mechanism.First, Dessy and coworkers made a series of studies on the reaction of Grignard reagents with 1– alkynes (1951–1965). Then, Assarsson investigated the isotope effect of hydrogen in the reactions of Grignard reagents with hydroxy compounds (1962) and Hashimoto and coworkers investigated solvent effects on the reaction of Grignard reagents with 1– alkynes (1965), being the last study on Zerewitinoff reaction up to our work.

In this work, kinetic investigations were performed at 25 °C, Grignard reagent was ethyl magnesium bromide in diethyl ether and active hydrogen compounds were primary and secondary amines, alcohols and 1– alkynes which the proton is bonded to nitrogen, oxygen and carbon atoms, respectively. These substrates are very soluble in diethyl ether, and they react with Grignard reagent via Zerewitinoff reaction only.

In the following paper, linear free energy relationships (Bronsted equations) between reaction rate constants and relative pK values in McEwen's scale of these very weak acids will be given in order to correlate their thermodynamic and kinetic acidity and a new method for estimating very weak acidity depending upon the results found in this work, will be proposed.

The products of Zerewitinoff reaction of ethyl magnesium bromide with secondary and primary amines, alcohols and 1–alkynes are halomagnesium salts of these active hydrogen compounds and ethane gas:

$$C_2H_5MgBr + AH \longrightarrow AMgBr + C_2H_6$$

where AH is R_2NH, RNH_2, ROH and $R—C \equiv C—H$. (Although the Grignard reagent has considerable complex structure, it can be formulated as C_2H_5MgBr for this reaction.) Grignard reactions have great value in synthetic organic chemistry. Zerewitinoff reaction and its applications, are discussed in detail in organometallic chemistry reference books, especially in "Grignard Reactions of Nonmetallic Substances" by Kharasch and Reinmuth [1] and "Methods of Elemento-Organic Chemistry" by Ioffe and Nesmeyanov [2].

The early investigations about Zerewitinoff reaction have been conducted by Ivonoff and coworkers, to determine the relative strength of R-Mg bond and as a measure of strength of this bond, the evolution rate of hydrocarbon gas in the reaction of alkyl Grignard reagents with inden [3] and chloromagnesium phenylacetate [4], was taken.

Among the others Kleinfeller and Lohman [5] were the first who investigated Zerewitinoff reaction kinetically and they found that the reaction between ethyl magnesium bromide and acetylene in diethyl ether was first order in Grignard reagent.

In the long series of studies on the reactions of Grignard reagents with 1– alkynes, Dessy and coworkers [6–16] measured relative rates of ethyl magnesium bromide with some 1– alkynes [6] and some substituted terminal acetylenes [8], found that diethyl magnesium reacted with 1– hexyne three times as fast as ethyl magnesium bromide [9] and tested the formulation of a Grignard reagent by the Schlenk equilibrium [10]. They proposed a mechanism for the Grignard reaction with 1– alkynes, consistent with deuterium isotope effect, the observed rate laws and previously reported data [11]. Dessy and coworkers also investigated the rate of the reaction of ethyl magnesium bromide with 1– hexyne in the presence of tertiary aliphatic amines [13], in tetrahydrofuran [15] and in various ether solutions [16].

Dessy and coworkers measured the reaction rates of substituted phenyl magnesium bromides with 1– hexyne [17] and found that the reaction was second order, having a negative Hammett reaction constant.

Hamelin [18] proposed mechanisms for hydrolysis of Grignard reagents using excess of water and also controlled hydrolysis by nonkinetic methods.

Assarsson [19] measured the kinetic isotope effect of hydrogen in the solvolysis of Grignard reagents with alcohols and proposed a mechanism in which the rate determining step of the overall reaction was the substitution of the coordination ether by the solvolyzing agent. In these reactions, methyl, n-butyl and phenyl magnesium halides were prepared in anisol, pyridine and tetrahydrofuran.

Solvent effects in the reaction between ethyl magnesium bromide and 1– hexyne and 1,7– octadyne were investigated by Hashimoto and coworkers [20] and the reaction was found to be second order in diethyl ether and di n-butyl ether, of order 2,5 in diethylene glycol dietyl ether and third order in tetrahydrofuran.

EXPERIMENTAL SECTION

A. *Purification and Preparation of Reagents.*

1. *Grignard Reagent.*

In this work, Grignard reagent was ethyl magnesium bromide in diethyl ether which was prepared according to the general method, from ethyl bromide and magnesium turnings in diethyl ether under nitrogen atmosphere and in the concentration range $5.10^{-3} - 700.10^{-3}$ M (M = mole / lt) [21, 22].

A two-necked reaction flask equipped with a nitrogen gas inlet tube and a two way adaptor, carrying an efficient spiral condenser and a dropping funnel, was used. The condenser was prevented from atmospheric moisture by calcium chloride and soda-lime drying tubes. The flask was stirred magnetically and heated on an oil bath.

The pure and dry nitrogen was obtained by passing tank nitrogen succesively through Fieser's solution [23], conc. sulphuric acid and solid potassium hydroxide.

The magnesium turnings were Fisher's Grignard quality. Ethyl bromide was purified by distilling and drying on Drierite and redistilled with a small amount of previously prepared ethylmagnesium bromide in diethyl ether solution. The solvent, absolute grade diethyl ether was dried on sodium wire and redistilled just before the reaction.

The Grignard solutions were kept and filtered through glass wool to remove the remaining solid materials, under nitrogen atmosphere.

The quantitative determination of Grignard reagent, i.e. the determination of ethyl magnesium bromide content in diethyl ether solutions, were made by gas evolution method in the apparatus used for the reaction rate measurements which will be described later. This method consists of hydrollyzing aliquots by distilled water and measuring the volume of evolved ethane gas.

2 . *Substrates.*

In this work, substrates were some secondary and primary amines, alcohols and 1– alkynes, to react with the Grignard reagent giving Zerewitinoff reaction. These active hydrogen compounds should be very pure and extremely dry because of the sensitivity of reaction to impurities and water.

Liquid aliphatic amines were dried on potassium hydroxide and distilled over calcium oxide. B. p.: (at 760 mm Hg) Diethyl amine; 55.5 °C, Benzylamine: 184.5 °C, n-Butyl amine: 77.8 °C, iso-Propyl amine: 50.0 °C. Aniline (B .p.: 184.4 °C) and N-ethyl aniline (B.p.: 205.5 °C) were treated first with stannous chloride (to reduce the tendency of aromatic amines to become coloured), then dried and redistilled [24]. Diphenyl amine was recrystallized from alcohol (M.p: 52.9 °C).

Methyl and ethyl alcohols (B.p: 64,7 and 78.4 °C) were made absolute by magnesium activated with iodine (Lund-Bjerrum method) [25].

Benzyl and ter-butyl alcohols (B.p: 205.4 °C and 82.6 °C) were made anyhdrous by Lund-Bjerrum method by using barium oxide instead of magnesium [26, 27].

1– alkynes were redistilled, B.p.: 1– octyne: 131 °C and 1– heptyne: 99 °C.

After purification, substrates were kept under nitrogen atmosphere.

B. *Kinetic Procedure.*

1. *The Method.*

The methods used in the kinetic investigation of Grignard reactions depends upon measuring the concentration of Grignard reagent directly or indirectly. The direct methods, are gas analysis and acid-base titration methods. Gas analysis method has been used in the apparatus for active hydrogen determination [28–35] and in the studies concerning the reaction between Grignard reagents and 1– alkynes by Dessy et al. [6–16] and Hashimoto, et al. [20], in the investigation of kinetic isotope effect of hydrogen in the reaction of Grignard reagents with alcohols by Assarsson [19], for determining the strength of C-Mg band by Ivanoff et al. [3, 4] and in the investigation of the reaction between Grignard reagent and nitriles by Swain [36]. Acid-base titration method has many disadvantages [37]; it has been used less frequently than gas-analysis method [38].

The indirect methods which have been used in the kinetic investigation of Grignard reagents up to now, are spectrophotometry [39, 41], vapor-phase chromatography [15], gas-liquid chromatography [42], measurement of dielectric constant [17, 43] and calorimetry [44].

Although one or more of these methods have been applied in the kinetic investigation of Grignard reactions, it was necessary to use particularly gas analysis method in this work. First, the indirect methods have been applied in some special cases and the direct method, acid-base titration would have no value in the high speed of the reaction which is the case in this work. Secondly, the gas analysis is accepted as a standard method for quantitative determination of Grignard reagents.

Consequently, in this work, Zerewitinoff reaction between ethyl magnesium bromide and amines, alcohols and 1– alkynes was investigated kinetically by gas evolution method. The measurement of gas volumes were recorded at constant pressure and at constant time intervals and then the concentration of Grignard reagent was calculated.

The kinetics was conducted at 25,0 ± 0,1 °C. The constant temperature water was circulated throughout the jacketed reaction vessel.

For measuring time, an electric clock which signals at one minute intervals, was used.

For calculating the changing concentration of the Grignard reagent at a time t, in terms of observed gas volume V(ml), at T_g °K, at constant pressure P(mm Hg) (atmospheric pressure) and in the volume of reacting mixture V_l (ml), the following equation can be used [45]

$$A = A_0 - \varkappa = A_0 - 0{,}016 \frac{P.\ V}{T_g.\ V_l} \text{ mole/lt} \qquad (1)$$

where A is the concentration of Grignard reagent at a time t, A_0 the initial concentration and $\varkappa$ the decrease in the concentration of reagent during the reaction.

In order to reduce the gas volumes to the standard conditions, the following equation was used instead of equation (1)

$$A = A_0 - x = A_0 - \frac{V.\ f_r}{22{,}4.\ V_l} \text{ mole/lt} \qquad (2)$$

where f_r is the reducing factor [46].

The initial concentration of Grignard reagent, A_0, was found from the formula

$$A_0 = \frac{(V_f - V_i)\ f_r}{22{,}4\ V_l} \text{ mole/lt} \qquad (3)$$

where V_f is the final volume of gas, after hydrolyzing of the reagent solution by means of 1ml of water; V_i, the initial volume (the blank) and V_l, the volume of reagent plus substrate solution, which was introduced with a syringe usually smaller than 2 ml.

The initial concentration of substrate was found by the formula

$$B_0 = \frac{1000.g_s}{V_1.\,M_s} \tag{4}$$

where g_s is the weight of substrate in syringe solution and M_s, the molecular weight of substrate. Then B, the concentration of substrate at a time t would be:

$$B = B_0 - \varkappa \tag{5}$$

2. *The Apparatus.*

The apparatus used in our work consisted of a 60 ml, three necked, flat bottomed and jacketed reaction flask (A), which was stirred magnetically, a condenser (B_1 or B_2), a connecting tube (C) and a gas burette (D) having a leveling bulb. The flask was equipped with the condenser and a device (E) for introducing the Grignard reagent. The third neck of the flask was stoppered with a rubber serum cap for introducing the substrate solution by means of a syringe (Figure 1).

One of the condensers used had a special design for placing dry-ice cooling mixtures in it; it had two walls and the inside surface of outer wall was silvered and sealed under diminished pressure in order to minimize the heat conduction (B_1). Another one was an efficient double surface condenser (B_2). There was a two way stopcock on the top of the condenser, one way to air and other way to the gas burette.

The gas burette (D) had 100 ml. capacity (graduated in 0.1 ml) and was in a room temperature water jacket and had a two way stopcock on the top. The fluid in the burette was a light oil.

The device for introducing the Grignard reagent solution (E) consisted of a 30 ml cylindir graduated in 0.1 ml, with a stopcock and on the top of this cylindir, a filtering system (F), equipped with a stopcook (G) opening to a nitrogen gas inlet tube (H) was filled with glass wool. The latter was then connected by a curved tube (K) to the reaction flask (L) in which the

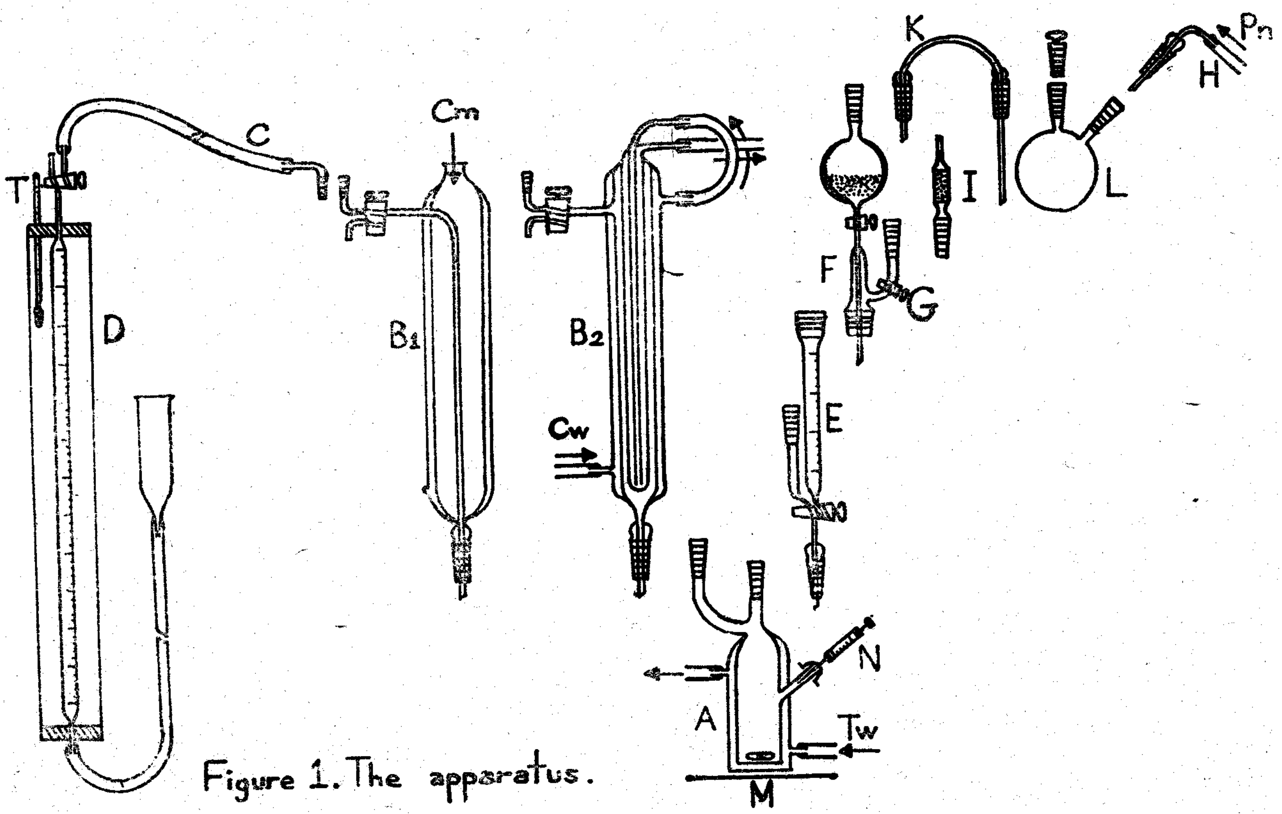


Figure 1. The apparatus.

Grignard reagent has already been prepared. Each part of the system were connected together with standard ground glass joints.

Kinetic procedure:

After the apparatus was set up, the reaction flask was thermostated (Tw). The condenser (B_1) was filled with dry ice-aceton mixture (Cm) (in the case of B_2, thermostated cool water (Cw) was circulated through the condenser). Atmospheric pressure and the temperature of the water jacket of the burette (T) were recorded. The apparatus was flushed out with dry nitrogen (Pn) by opening the stopcocks on the filtering system (G) and turning the stopcock on the condenser to air; after flushing out of the apparatus, the sopcocks were closed and a drying tube (I) was inserted in place of the nitrogen gas inlet tube (H).

The flask in which the Grignard reagent has been prepared (L) was connected to the filtering system (F) by the curved tube (K) on the one neck and the other was fitted to the nitrogen gas inlet tube (H). The filtering system also was flushed out with nitrogen before filtering; under nitrogen pressure, a known volume of reagent was introduced into the reaction vessel by filtering, while the stopcock (G) was opened to air. The magnetic stirrer (M) was started.

The stopcock on the condenser was opened to the gas burette and with the aid of of the stopcock on the top of the burette, the level of the liquid in the burette was adjusted to zero (or the initial volume, V_i was recorded). The electric clock was started. The required amount of substrate solution was introduced into the flask through the serum cap with a tuberculin syringe (N) in 2 seconds.

The gas volume in the burette was measured by means of the bulb in regular intervals, i.e. 5 seconds to 2 minutes according to the speed of the reaction.

At the end of the kinetic measurements, 1ml of water was introduced into the reaction flask and the final volume, V_f, was recorded.

The reactions were followed up to 60–70 % conversion and the measurements were taken by varying the initial concentrations of the reagents.

3. *Evaluation of Rate Data.*

Integrated rate equations and graphic methods were applied in order to find the reaction order. For calculating the rate constants, the long interval method [47] was used. The reaction rate constant of a known substrate was then found by averaging the rate constants of 8–10 kinetic studies.

For accuracy of the values of the rate constants, the pseudo-first order procedure was also applied [48].

The uncertainty of the rate constants was calculated from the standard deviation of directly measured quantities, i.e. concentration and time [49] and the relative error of the rate constants, $\sigma k / k$ was found being no higher than 2 %.

4. *Analysis of Reaction Products.*

The reaction products precipitated while the reaction proceeded. These were filtered under nitrogen atmosphere, washed with the solvent and vacuum dried on silicagel, then were analyzed for basic Mg by acid titration method, the total Mg by gravimetric method using oxine and titration with EDTA and total Br by Volhard method.

Although there are many papers including the nature of the products of Zerewitinoff reaction, the isolation and identification of the reaction products were conducted because of its necessity in all kinetic investigations.

RESULTS AND DISCUSSION

A. *Kinetics of The Reaction Between Ethyl Magnesium Bromide and Amines, Alcohols and 1- Alkynes.*

1.a. *Kinetics of The Reaction Between Ethyl Magnesium Bromide and Secondary Amines.*

Zerewitinoff reactions between ethyl magnesium bromide and diethyl amine, $(C_2H_5)_2NH$; N–ethyl aniline, $C_6H_5NHC_2H_5$ and diphenyl amine, $(C_6H_5)_2NH$ were investigated. The reaction can be formulated as follow:

$$C_2H_5MgBr + R_2NH \longrightarrow R_2NMgBr + C_2H_6$$

The reaction products are bromomagnesyl derivatives of secondary amines (white amorphous solids soluble in water) and ethane gas. Diphenyl amine like pyrrole [50] did not give a solid product but could be precipitated from ether with pyridine as a dipyridine complex, $(C_6H_5)_2NMgBr.(C_5H_5N)_2$, a dark green solid.

It has been found that Zerewitinoff reaction between ethyl magnesium bromide and secondary amines was second order overall and first order in G. R. (Grignard reagent, denoting ethyl magnesium bromide in this paper) and in secondary amine. The differential rate equation for this reaction is

$$\frac{d\varkappa}{dt} = k\,(A_0 - \varkappa)\,(B_0 - \varkappa) \qquad (6)$$

where k is second order rate constant in M^{-1} sec^{-1} (M = mole/lt and mM = milimole/lt) and A_0 and B_0, the initial concentrations of G. R. and amine in M, respectively. The second order rate constants were calculated using the integrated rate equation:

$$k = \frac{1}{t\,(B_0 - A_0)} \ln \frac{A_0}{B_0}\,\frac{B_0 - \varkappa}{A_0 - \varkappa} \qquad (7)$$

The second order rate constants were found from both second order technique and pseudo-first order procedure. For example, in a pseudo-first order reaction with respect to G. R., the differential and integrated rate equations are written as follow:

$$\frac{d\varkappa}{dt} = k'_G\,(A_0 - \varkappa) \qquad (8)$$

$$k'_G = \frac{1}{t} \ln \frac{A_0}{A_0 - \varkappa} \qquad (9)$$

The data and calculated second order rate constants for the reaction between G. R. and diethylamine are given in Table 1A and the pseudo-first rate constants with respect to G. R. for the reaction between G. R. and N-ethyl aniline are given in Table 1 B.

TABLE I

$$C_2H_5MgBr + R_2NH \xrightarrow[25\,°C]{k} R_2NMgBr + C_2H_6$$

The rate constants of typical reactions between G. R. and diethyl amine, second order (A) and with N-ethyl aniline, pseudo-first order in G. R. (B).

A			B		
A_0= 107 mM,	B_0= 167 mM		A_0= 35 mM,	B_0= 303 mM	
t sec	$\varkappa$ mM	10^3. k $M^{-1}sec^{-1}$	t sec	$\varkappa$ mM	10^3. k'_G sec^{-1}
150	22	10.2	30	6	6.3
180	27	10.6	45	8	5.8
210	32	11.3	60	12	7.0
240	35	11.2	75	14	6.8
270	40	11.9	90	15	6.2
300	43	12.0	105	18	6.9
330	46	12.1	120	19	6.5
360	48	11.8	135	21	6.8
390	50	11.7	150	22	6.6
420	52	11.6	165	23	6.5
450	54	11.5			
480	57	11.9			Av: 6.6
540	61	12.0			
		Av: 11.3			

Variation were found in the kinetic investigation of the reaction between G. R. and diphenyl amine: (1) The rate constants decrease while the reaction proceeds, but remain constant in the reactions conducting at low initial concentrations. (See Table 2, No. 6°). (2) The lower the initial concentrations, the higher the rate constants (See Table 2, No: 1°, 2° and 4°). (3) If pseudo-first order procedure is used and the concentration of diphenyl amine is held excess over G. R., it would be possible to get constant pseudo-first order rate constants. So far this method [48] was applied to find the second order rate constant in the reaction of G. R. with diphenyl amine. Similar results were observed in the reaction between G. R. and alcohols and they will be explained later.

TABLE 2

$$C_2H_5MgBr+(C_6H_5)_2NH \xrightarrow[25\,°C]{k} (C_6H_5)_2NMgBr+C_2H_6$$

The second order rate constants in a series of reactions between G. R. and diphenyl amine.

No.	A_0 mM	B_0 mM	k range ($10^3 M^{-1}$ sec^{-1})	Median value of k range
1°	252	260	100.0 — 55.6	70.4
2°	136	136	111.0 — 61.6	78.4
3°	139	100	121.9 — 66.8	79.4
4°	92	96	105.4 — 80.0	92.4
6°	97	85	104.2 — 75.4	92.7
6°	19.6	39.8	117.9	—

Pseudo-first order procedure was applied in a manner that the concentration of G. R. (A_0) was held constant and the concentration of substrate (B_0) was taken great excess over G. R. and was gradually changed in a series of reactions. The second order rate constant (k) was found from the slope of the line by plotting the pseudo-first order rate constants (k'_G) versus the concentration of substrate (B_0). This method gives more accurate results than a single experiment in which the second order rate constant (k) will be calculated by dividing k'_G by B_0. The data is given in Table 3 and the plot of k'_G versus B_0 in applying pseudo-first prodedure in the reaction between G. R. and diphenyl amine is shown in Figure 2.

TABLE 3

The pseudo-first order rate constants in the reaction between G. R. and diphenyl amine in excess concentration over G. R.. A_0= 17.1 mM.

No	1°	2°	3°	4°	5°
B_0 mM	57.2	75.2	82.7	97.6	117.0
$k'_G \cdot 10^3$ sec^{-1}	2.4	2.8	3.0	4.2	4.9

1. *b. Kinetics of The Reaction Between Ethyl Magnesium Bromide and Primary Amines.*

Zerewitinoff reactions between ethyl magnesium bromide and aniline, $C_6H_5NH_2$; benzyl amine, $C_6H_5CH_2NH_2$; n-butyl amine, n–$C_4H_9NH_2$ and iso-propyl amine, iso–$C_3H_7NH_2$ were investigated. The reaction can be formulated as follow:

$$C_2H_5MgBr + RNH_2 \longrightarrow RNHMgBr + C_2H_6 \qquad (1a)$$

The reaction products are monobromomagnesyl derivatives of primary amines (white amorphous solids soluble in water) and ethane gas. The dibromomagnesyl derivatives can be precipitated by reaction of G. R. with primary amine in 2: 1 molar ratio at a higher temperature and in a longer time.

$$C_2H_5MgBr + RNHMgBr \longrightarrow RN(MgBr)_2 + C_2H_6 \qquad (1b)$$

The overall reaetion is:

$$2\ C_2H_5MgBr + RNH_2 \longrightarrow RN(MgBr)_2 + 2\ C_2H_6 \qquad (2)$$

As a rule, primary amines yield only one equivalent of active hydrogen at room temperature like secondary amines, however upon heating, second hydrogen is displaced by MgBr.

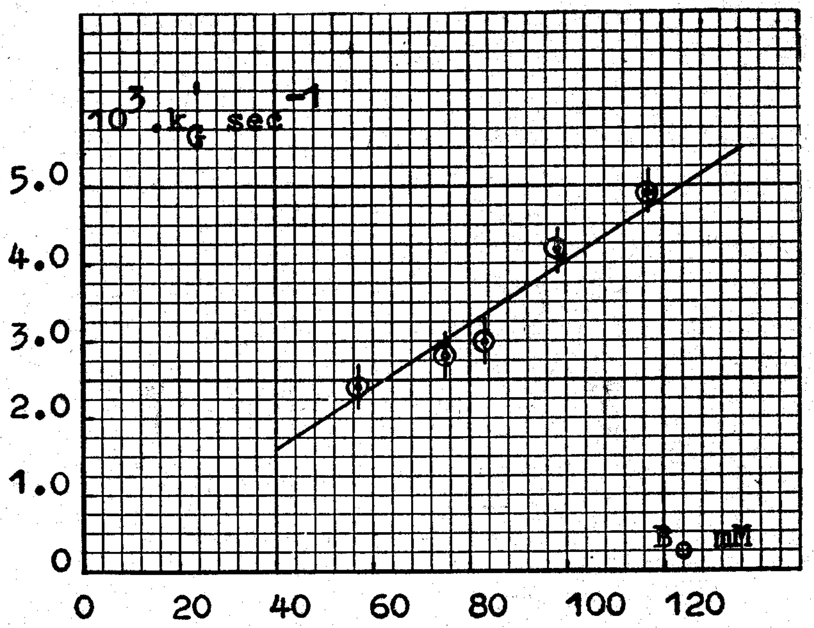


Figure 2. The plot of k'_G, pseudo-first order rate constants of G. R. versus B_0, the concentration of diphenyl amine in Zerewitinoff reaction. The slope of the line is second order rate constant (k).

It was experimentally found that G. R. reacts with primary amines, at 25 °C, giving only monobromomagnesyl derivatives according to the reaction (1a). As a matter of fact, the time-concentration data, did not verify the integrated rate equation of the reaction (2):

$$k = \frac{1}{t\ (2B_0-A_0)} \ln \frac{A_0}{B_0} \ \frac{B_0-\varkappa}{A_0-2\varkappa} \qquad (10)$$

Therefore, the simple second order reaction mechanism could not be proposed, besides of these facts, the stoichiometry of the reaction gave a two-step mechanism.

These reactions were found to be competitive consecutive second order reactions mechanism:

$$A + B \xrightarrow{k_1} C + E$$

$$A + C \xrightarrow{k_2} D + E$$

For the reaction investigated, A, B, C, D and E are C_2H_5MgBr, RNH_2, $RNHMgBr$, $RN(MgBr)_2$ and C_2H_6 respectively. The rate constants k_1 and k_2 of these reactions may be found by solving the chemical equations of the system [51–53] or graphical methods [54, 55].

For Frost-Sohwemer method [53], which was used in our investigation, the initial condition was imposed as $A_0 = 2B_0$. In Zerewitinoff reaction at 25 °C, $k_1 = k$ and $k_2 = 0$, so Frost-Schwemer method will be equivalent to the simple second order rate equation

$$k = k_1 = \frac{1}{t\ (B_0-A_0)} \ln \frac{B_0}{A_0} \ \frac{A_0-\varkappa}{B_0-\varkappa} \qquad (11)$$

at the initial condition $A_0 = 2B_0$.

The second order rate constants for the reaction between G. R. and primary amines, were also found by pseudo-first order procedure. Because $k(= k_1)$ can be measured by working up at high B_0 concentration whence a pseudo-first order reaction is observed in competitive consecutive second order reactions [56].

In order to compare the rate constants of primary amines with the rate constants of secondary amines in Zerewitinoff reaction, it must be born in mind that there are two active hydrogens, i.e. primary amines have more reactive sites than secondary amines; therefore, the rate constants must be corrected in statistically [57, 58].

In Zerewitinoff reaction of G. R. with primary amines, the statistical factor,p was found to be 8 and the second order rate constants were divided with this factor. In general, if there are two reagents with p_1 and p_2 equivalent reactive sites, respectively, in a rate process, the rate constant must be divided by a statistical factor of $p_1 \cdot p_2$ [57]. In Zerewitinoff reaction $p_1 = 2$ and $p_2 = 2$ were found; because C_2H_5 group in G. R. has possibility of reacting each of H in primary amine, this results $p_1 = 2$ and MgBr group in G. R., has possibility of reacting with each of –NRH groups, remaining after the removal of H in primary amine, this also results $p_2 = 2$, therefore $p_1 \cdot p_2 = 4$ (For detail, see B. The Proposed Mechanism). However, as the rate constants were found at the initial condition, $A_0 = 2B_0$, the statistical factor which was equal to 4 for the reaction of one equivalent of G. R., became 8 for the two equivalents of G. R..

The rate constants for Zerewitinoff reaction between G. R. and amines in diethyl ether at 25 °C are given in. Table 4. The rate constants of primary amines in Table 4 were found by dividing the calculated rate constants by the statistical factor, $p = 8$.

TABLE 4

$$C_2H_5MgBr + \text{Amine} \xrightarrow[25\,°C]{k} \text{Bromomagnesyl derivative of amine} + C_2H_6$$

Amine	$10^3 . k \ M^{-1}sec^{-1}$
Diethyl amine	11.2
N-ethyl aniline	20.0
Diphenyl amine	45.0
Aniline	24.6
Benzyl amine	15.1
n-Butyl amine	16.4
iso-Propyl amine	11.8

2. *The Kinetics of The Reaction Between Ethyl Magnesium Bromide and Alcohols.*

Zerewitinoff reactions between ethyl magnesium bromide and methyl alcohol, CH_3OH; benzyl alcohol, $C_6H_5CH_2OH$; ethyl alcohol C_2H_5OH and ter-butyl alcohol, ter-C_4H_9OH were investigated. The reaction can be formulated as follow:

$$C_2H_5MgBr + ROH \longrightarrow ROMgBr + C_2H_6$$

The reaction products are bromomagnesium alkoxides and ethane gas. These alkoxides are monoetherates and can be crystallized under some conditions unlike the other bromomagnesyl derivatives.

The results obtained in the kinetic investigation of the reaction between G. R. and alcohols were found different from those of amines but similar to diphenyl amine : (1) The rate constants decrease steadily while the reaction proceeds. (2) The decreasing range (the difference between k_0, the initial rate constant and k, the rate constant at a known percent progress of reaction) is the same in the reactions with the same initial conditions, i.e. the reactions are reproducible (See Table 5, No: 1°–2° and 3°–4°). (3) The lower the initial concentrations, the higher the rate constants (See Table 5, No: 1° and 3°).

TABLE 5

$$C_2H_5MgBr + CH_3OH \xrightarrow[25°C]{k} CH_3OMgBr + C_2H_6$$

The second order rate constants in a series of reactions between G. R. and methyl alcohol.

No	A_0 mM	B_0 mM	k range (10^3 M^{-1} sec^{-1})
1°	18.4	25.7	403 - 255
2°	21.6	23.6	387 - 227
3°	36.3	31.8	238— 95
4°	34.0	28.1	234 - 94

These results and those of diphenyl amine were explained by the effect of ionic strength on reaction rate. Since at the lower initial concentrations, higher and more steady (even constant as with diphenyl amine, See Table 2, No: 6°) rate constants were found, the decrease of the second order rate constants were attributed to the nonideality of the reaction medium [59]. Otherwise, the second order rate constants would become much smaller and decrease at lower concentrations [60].

Primary salt effects: The effect of ionic strength in Zerewitinoff reaction between G. R. and alcohols could be explained according to Bronsted-Bjerrum equation which involves the activity coefficients [61, 62]. The expression for the rate constant for a reaction between A and B proceeding through the activated complex $AB^{\ddagger}$ is given by the transition state theory as

$$A + B \overset{k^{\ddagger}}{\rightleftarrows} AB^{\ddagger} \xrightarrow{k_r} \text{Products}$$

$$k_r = \frac{kT}{h} \, \frac{(AB^{\ddagger})}{(A)\,(B)} = \frac{kT}{h} \, K^{\ddagger} \, \frac{\gamma_A \gamma_B}{\gamma_{AB^{\ddagger}}} \qquad (12)$$

where k_r is rate constant; k, Boltzmann's constant; T, absolute temperature; h, Planck's constant, $K^{\ddagger}$, equilibrium constant and γ's activity coefficients. Since activity coefficients vary with the ionic strength, the rate constant for a reaction should depend upon ionic strength also. The effect of variations in ionic strength may be predicted by the simple Debye-Huckel theory:

$$\log \gamma_A = - A z_A^2 \sqrt{\mu} \qquad (13)$$

where z_A is the charge of the ion; μ, the ionic strength and A, a constant. Substituting such an expression for each of the activity coefficients in the logarithmic form of the equation (12), we obtain

$$\log k_r = \log k_r^{\circ} + 2 A z_A z_A \sqrt{\mu} \qquad (14)$$

where k_r°; rate constant for the reaction in infinitely diluted solution equal to $\frac{kT\,K^{\ddagger}}{h}$. Thus a reaction between a positive and a negative ion will be slowed down by increase in ionic strength. This is the case in our kinetic investigation of Zerewitinoff reaction between G. R. and alcohols and also diphenylamine and we have found that the higher the ionic strength (μ), i.e. the higher the initial concentrations, the lower the rate constants (See Table 2, No: 1°, 2° and 4°; Table 5, No: 1° and 3°). Although the equation (14) is applied quantitatively only to the dilute solutions in which the added salts are fully dissociated and it is necessary to use a more complex expression in a solvent of low dielectric constant, like diethyl ether; the equation (14) still determines the direction of ionic strength on reaction rate.

The result that Zerewitinoff reaction is an interaction between a positive and a negative ion or more exactly a reaction between species bearing partial positive and negative charges ($+\delta$ and $-\delta$) could be explained as follow: Amines, alcohols and 1–alkynes are very weak Bronsted acids but alcohols are the strongest of them [63] and diphenyl amine is the most acidic amine with a pK value close to ter-butyl alcohol's; therefore these substrates are capable to give more ions even in ether, which has low dielectric constant. (Of course, very weak acids exist as ion aggregates, in such a solvent, so that the lone ion concentration, like RO^- and H^+ are very low.)

Consequently, Zerewitinoff reaction of G. R. with alcohols (and more acidic amines like diphenyl amine) could be an ion-ion reaction between $C_2H_5^{-\delta}$ and $H^{+\delta}$ rather than a neutral molecule-ion reaction. However, the C-MgBr bond in G. R. is polar-covalent having 18 % ionic character and it has been found that the reagent consists of highly associated ion poirs R^-: Mg^+Br with the aid of PMR studies [64, 65]. And also, the charged species produced with dissociation of an alcohol can polarize this bond to a higher degree of ionic character.

Decreasing of k_r while the reaction proceeds was also shown as a result of decreasing ionic strength, because a low soluble salt forms and a gas evolves from the ionic reactants. The activated complex in this reaction has a charge at the beginning because of the charged reactive species and being a strong dipole when the charge seperation already takes place. Its activity coefficient, $\gamma_{AB\neq}$ increases while decomposing to the reaction products with a decrease in ionic strength (equation (13); thus k_r decreases while $\gamma_{AB\ddagger}$ increases which appear in the denominator of equation (12). At the low initial concentrations, this dipole is small and the effect of ionic strength on k_r is negligible (See Table 2, No: 5 °).

The slowness of the Zerewitinoff reaction with alcohols at high concentrations and the decrease of rate constants during a reaction are primary salt effects [66–68].

The decrease of rate constants was attributed to the decrease of ionic strength in the reaction, and the constant rate values should be found at the constant ionic strength. In order to provide constant ionic strength, some salts, like sodium alkoxides, RONa; bromomagnesium alkoxides, ROMgBr and magnesium hydroxybromide, HOMgBr, were added to the reaction medium ([69, 70]. Two examples are given in Table 6; ionic strength was kept constant by adding the salt in 10–20 fold excess over the equivalent of the reagents: A is a reaction between G. R. and methyl alcohol and B. between G. R. and diphenylamine.

TABLE 6

The rate constants of reactions between G. R. and methyl alcohol (A) and diphenyl amine (B) at constant ionic strength at 25 °C.

A			B		
$A_0 = 9.9$ mM, $B_0 = 11.2$ mM Salt:* CH_3ONa			$A_0 = 47.0$ mM, $B_0 = 49.4$ mM Salt:* NH_2MgBr. $(C_2H_5)_2O$		
t sec	$\varkappa$ mM	10^3k M^{-1} sec^{-1}	t sec	$\varkappa$ mM	10^3k M^{-1} sec^{-1}
120	4.0	486	60	9.7	93
150	4.5	473	90	13.4	94
180	4.8	445	120	15.9	91
210	5.2	443	150	18.5	92
240	5.5	433	180	20.2	89
270	5.7	417	210	21.0	82
300	6.1	440	270	24.8	88
330	6.3	432	300	25.8	87
360	6.6	448	330	26.9	87
390	7.0	488	360	27.8	86
420	7.2	494	390	28.9	87
			420	30.0	90
		Av: 455	450	30.8	90
			480	31.7	92
					Av: 89

* The concentration of the salt is 10–20 fold excess over the equivalent of reagents.

In this work "swamping" method was used for determining the reaction order in the presence primary salt effects by keeping constant the ionic strength of the solution [60]. This is a suitable method for determining the order of a reaction proceeding with a change in ionic strength. The ionic strength is taken such a large value that small changes in it would not affect on the reaction rate. An example of the results taken by applying this method in our kinetic investigation of Zerewitinoff reaction with alcohols is shown in Table 6A. In general, the solubility of the salts are low in diethyl ether, but the produced ions were found to be able to keep ionic strength constant enough.

Secondary salt effect: It was found that Zerewitinoff raction rate contants increase as the relative acidity of substrates increase, e.g. with amines, the rate and relative acidity increase in the same order, diphenylamine > aniline > diethyl amine (For detail, see B. The Proposed Mechanism and the following paper). If this relative acidity is increased by increasing the ionic strength of the reaction medium, i. e. increasing the concentration of the addet salt, the rate is expected to increase in the reactions of uncharged weak acids [69].

Secondary salt effect was also investigated in the Zerewitinoff reaction with amines and 1-alkynes (not with alcohols, the ionic strength was kept constant by adding the salt in this case) by plotting the rate constant versus the changing concentration of the addet salt, together with the rate constant at zero ionic strength. It was found that secondary salt effect in Zerewitinoff reaction was negligible.

The rate constants of alcohols which were calculated at the 10–20 mM initial concentrations and in the presence of HOMgBr which is great excess over the equivalent of reagents, are given in Table 7. (HOMgBr is the solid product of the reaction between G. R. and water.)

TABLE 7

$$C_2H_5MgBr + ROH \xrightarrow[25\,°C]{k} ROMgBr + C_2H_6$$

($A_0 \approx B_0$ = 10–20 mM and [HOMgBr]: excess over the equivalent of reagents)

Alcohol	10^3 k M^{-1} sec^{-1}
Methyl alcohol	377
Benzyl alcohol	347
Ethyl alcohol	335
Ter-Butyl alcohol	277

3. *The Kinetics of The Reaction Between Ethyl Magnesium Bromide and 1– Alkynes.*

Zerewitinoff reactions between ethyl mangesium bromide and 1– octyne, n– C_6H_{13}—C≡C—H and 1– heptyne, n–C_5H_{11}—C≡C—H were investigated. The rate constants of the reactions between G. R. and 1– hexyne, n–C_4H_9—C≡C—H and 1,7– octadyne, H—C≡C—$(CH_2)_4$—C≡C—H were taken from the results of Hashimoto, et al. [20]. The reaction can be formulated as follow:

$$C_2H_5MgBr + R—C\equiv C—H \longrightarrow R—C\equiv C—MgBr + C_2H_6$$

It has been found that the reaction between G. R. and 1– alkynes was second order overall and first order with respect G. R. and 1– alkyne by applying both second order and pseudo-first order procedures. The rate constants of Zerewitinoff reaction between G. R. and 1– alkynes are given in Table 8.

TABLE 8

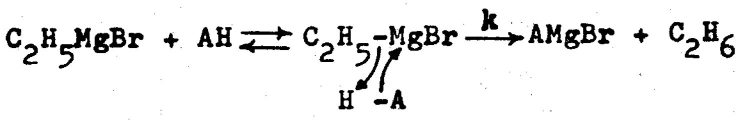
$$C_2H_5MgBr + R—C\equiv C—H \xrightarrow[25\,°C]{k} R—C\equiv C—MgBr + C_2H_6$$

1– alkyne	10^3 k M^{-1} sec^{-1}
1– Hexyne*	0.6
1– Heptyne	1.0
1– Octyne	1.4
1,7– Octadyne*	1.0

* From the results of Hashimoto, et al. [20].

B. *The Proposed Mechanism.*

The S_Ei mechanism (substitution electrophilic intramolecular) with nucleophilic assistance was proposed for Zerewitinoff reaction of ethyl magnesium bromide with amines, alcohols and 1– alkynes in diethyl ether at 25 °C, in this work. The reaction may be shown as:



$$C_2H_5MgBr + AH \rightleftarrows \underset{H\ -A}{C_2H_5\text{-}MgBr} \xrightarrow{k} AMgBr + C_2H_6$$

The C-MgBr bond is a polar-covalent type with 18 % ionic character. It has been found with the aid of N. M. R. that G.R. contains of highly associated ion pairs R^-: Mg^+Br [64,71,72] and it was given an equilibrium between dimer and monomer reagent species (For the nature of G. R., see [73–75]):

$$R_2Mg.\ MgBr_2 \rightleftarrows R^- + RMg^+.\ MgBr_2$$

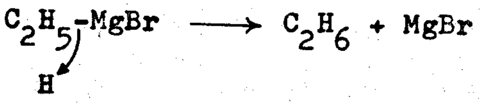
The polarity of the bond is partial $(C^{-\delta} - Mg^{+\delta}Br)$ and the electrons are closer to the carbon atom; transfering an electron from magnesium to the carbon, produces a carbanion, in fact, high degree of carbonion character due to the considerable polarity of the C–MgBr bond, has been shown by means of P. M. R. [65, 76].

The generation and stability of carbanions are discussed by March [77]. A carbanion is a base because of its unshared pair of electrons and it gives conjugate acid by accepting a proton; such as $C_2H_5^-$ gives C_2H_6. The stability of carbanion is directly related to the strength of the conjugate acid. The weaker the acid, the greater the base strength. Since a stronger base has more tendecy to accept a proton than a weaker base, its stability as a carbanion will be lower. In the Zerewitinoff reaction, the conjugate acid of the carbanion is ethane C_2H_6, in this work, which is considered as a very weak acid. Then the stability of $C_2H_5^-$ is very low and easily accepts a proton from an acid: this is the reason of the high speed of Zerewitinoff reaction and the stronger the acid from which this proton comes, the higher the reaction rate. These facts were confirmed in our work: Ethyl magnesium bromide was found to react faster with alcohols than with amines which are weaker acids than alcohols and in a series of amines, for example, it reacted faster with diphenyl amine than with aniline which is a weaker acid than diphenyl amine.

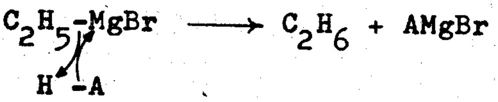
Consequently, Zerewitinoff reaction can be treated as an acid-base reaction (protolysis) and the driving force is the production of a new base (A^-) such as RNH^-, R_2N^-, RO^- and $R-C\equiv C^-$ that is weaker than the alkide ion ($C_2H_5^-$) of the reagent:

$$C_2H_5^- + RNH_2 \longrightarrow C_2H_6 + RNH^-$$

Furthermore, organometallic compounds would undergo electrophilic substitution reactions. In Zerewitinoff reaction, electrophilic substitution follows bimolecular mechanism because it has been found that the reaction of G. R. with amines, alcohols and 1– alkynes is second order, first order with respect to G. R. and substrate. But S_Ei mechanism is more probable than S_E2. The S_Ei mechanism is similar to the S_E2 mechanism, the difference between them is that another part of the attacking entity (in this reaction A of HA) assists in removal of the leaving group (MgBr) forming a bond with it; at the same time the new bond is formed between $C_2H_5^-$ in G. R. and electrophile, H. These mechanisms may be formulated as follow:



S_E2



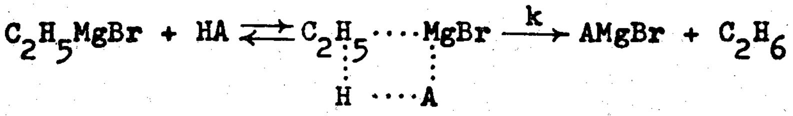
S_Ei

S_Ei is a one step reaction, it has a frontside attack and should also exhibit second order kinetics with retention of configuration. Some authors prefer to name it S_F2 instead of S_Ei [77].

Since S_E2 mechanism exhibit the some characteristics with S_Ei, a way of distinguishing them has been devised [77]. For applying this method to Zerewitinoff reaction, the A group in HA was chosen more attractive toward MgBr. Since this promoted the reaction, the S_Ei mechanism would be evident. Since a bond formation between MgBr and A occurs in one step which is the rate determining step, anything which assists this bond formation should increase the rate of S_Ei reaction, or A should increase the activity of C_2H_5MgBr by coordination with MgBr. This process occur where electron defficiency is present near the attacking side and it is known as "nucleophilic assistance" [78–80]. The criterion of electron defficiency is met admirably by organometallic compounds where the metal is always electron-defficient or capable of expanding its octet.

In the Zerewitinoff reaction between G. R. and alcohols, amines and 1– alkynes, there is nucleophilic assistance of O, N and C atoms, respectively; however O is a more nucleophilic atom than N and C atoms, it can coordinate with MgBr more easily than the others and as a consequence of this, the rate of Zerewitinoff reaction diminishes in the order of alcohols> amines> 1– alkynes in which the active proton is bonded to these nucleophilic atoms. But in the reaction of G. R. with a series of alcohols only, the nucleophilic assistance remain the same and the reaction rate vary with the relative acidity of alcohols. The correlations between reaction rate constants and relative pK values of substrates in Zerewitinoff reaction, which expressed in some linear free energy relationships will be reported in the following paper.

However in the literature, for one-step reactions which electrophile and nucleophile are in the same molecule and esspecially for reactions of organometallic compounds, four-centered mechanism [74, 78–80] has been proposed generally:



$$C_2H_5MgBr + HA \rightleftarrows \begin{array}{ccc} C_2H_5 & \cdots & MgBr \\ \vdots & & \vdots \\ H & \cdots & A \end{array} \xrightarrow{k} AMgBr + C_2H_6$$

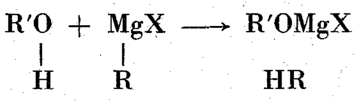
As in this mechanism, all bonds in the reacting and attacking molecule would affect the reaction, S_F2 is a mechanistic possibility as well as S_Ei for Zerewitinoff reaction but multicenter mechanisms are never ionic and no solvent effect has been observed. However, we observed the salt effects in this reaction resulting a high degree of ionic character of G. R., which was also expected from the polarity of the C–Mg bond and Hashimoto, et al. [20] have found solvent effects in the reaction between G.R. and 1– alkynes. Consequently, S_Ei is a more probable mechanism than S_F2 for Zerewitinoff reaction.

The mechanisms proposed for Zerewitinoff reaction of both Grignard reagents and other organometallic compounds of Group II A, by the other investigators are discussed below.

Assarsson [19] investigated kinetic isotope effect in the solvolysis of Grignard reagents with alcohols and found the k_T / k_H values (the ratio of the rate constant of the reaction with an alcohol labeled with tritium to the rate constant of an unlabeled alcohol) generally lying between 0,6 and 1. According to these results, there is agreement with neither a mechanism consisting chiefly of a neutralization of an R^- with an ionizable hydrogen

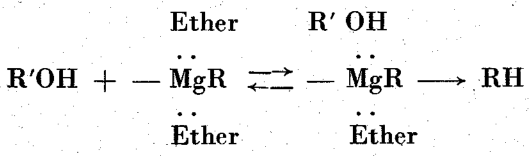
$$R'OH + R^- \longrightarrow RH + R'O^-$$

nor a mechanism which does not include dissociation of the Grignard reagent:



$$\underset{H}{\underset{|}{R'O}} + \underset{R}{\underset{|}{MgX}} \longrightarrow \underset{HR}{R'OMgX}$$

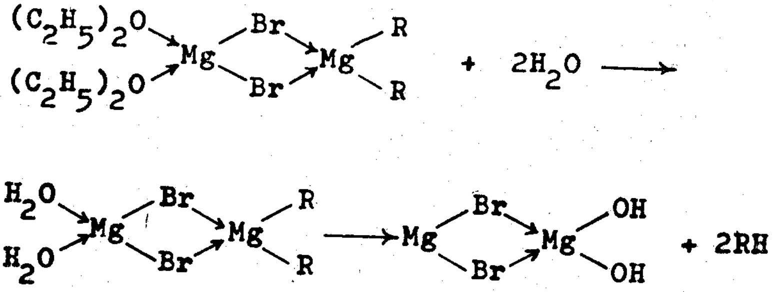
As expected, these two mechanisms could give fairly strong isotope effects, i.e. k_T / k_H ratio of the order of the magnitude of 0 .1–0 .2 at room temperature. According to Assarsson, solvated ether molecules in Grignard reagent may be expected to exchange with R'OH and a rapid proton transfer will take place giving a hydrocarbon:



$$R'OH + \overset{\text{Ether}}{\overset{\cdot\cdot}{\underset{\text{Ether}}{\underset{\cdot\cdot}{-\,MgR}}}} \rightleftarrows \overset{R'\,OH}{\overset{\cdot\cdot}{\underset{\text{Ether}}{\underset{\cdot\cdot}{-\,MgR}}}} \longrightarrow RH$$

Before giving the results taken from the investigation of kinetic isotope effect in the reaction of G. R. with 1– hexyne by Dessy [11], agreeing well with our mechanism, it might be determined that Assarsson investigated the kinetics only in pseudo-first order conditions and the k_T and k_H values were not found by kinetic methods.

Hamelin [8] has also proposed a mechanism consisting of displacement of coordinated ether molecules by water and the intramolecular transfer of G. R. with water,

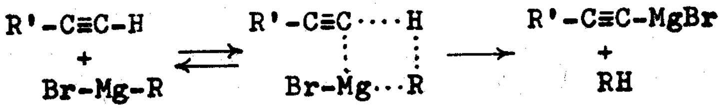


but this mechanism has not been supported by any kinetic data.

In hydrolysis of G. R. ,Roshow, et al. [81] supposed an attraction of H—O dipole to the carbon-metal dipole with the formation of an intermediate which decomposes into a hydrocarbon containing the C—H bond and MOH.

According to Evans and Pearson [82], Grignard reagents in most of their reactions including protolysis, behave an R^- anion and Mg^+X cation.

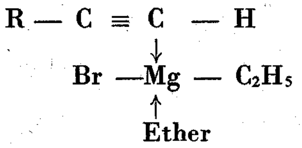
Dessy, et al. [11] has postulated a four centre mechanism for the second order reaction of G. R. with 1– hexyne, consistent with previously reported data and deuterium isotope effect by comparing the rates of reaction of $R - C \equiv C - H$ and $R - C \equiv C - D$:



These authors concluded that the rate determining step involved the cleavage of the $\equiv C—H$ bond. Since the observed and maximum therotical isotope effect are relatively close to each other, the hydrogen must be very weakly bound in the transition state. This could arise only if the $\equiv$C—H bond was almost completely broken in the transition state and the new bond to the alkyl group of the G. R. had just begun to form. This result agrees with $S_E i$ mechanism proposed in our work as well as $S_F 2$ mechanism proposed by Dessy, et al.

Dessy and Salinger [17] found the Hammett reaction constant, ρ being equal to –2,5 in the reaction of substituted phenyl magnesium bromides with 1– hexyne. The negative value of this constant indicates that the reaction goes faster by substitution of electron donating groups on α-carbon; this result is in agreement with the electrophilic attraction on α-carbon.

Hashimoto, et al. [20] postulated the following activated complex



$$\begin{array}{c} R - C \equiv \underset{\displaystyle\downarrow}{C} - H \\ Br - \overset{}{Mg} - C_2H_5 \\ \uparrow \\ \text{Ether} \end{array}$$

in the reaction of G. R. with 1– hexyne and 1,7– octadyne, which is formed by the coordination of the conjugate base of 1– alkyne with Mg. This is the "nucleophilic assistance" explained with the proposed mechanism in our work.

Kleinfeller and Lohman [5] had given the following mechanism in the reaction of G. R. with acetylene:

$$C_2H_5MgBr + H—C\equiv C—H \longrightarrow H—C\equiv C—MgBr + C_2H_6$$

$$2\ H—C\equiv C—MgBr \longrightarrow BrMg—C\equiv C—MgBr + H—C\equiv C—H$$

But the experiments had been conducted only in pseudo-first order conditions. The other mechanism which was thought to be is:

$$2\ C_2H_5MgBr + H—C\equiv C—H \longrightarrow BrMg—C\equiv C—MgBr + 2\ C_2H_6$$

$$BrMg—C\equiv C—MgBr + H—C\equiv C—H \longrightarrow 2\ H—C\equiv C—MgBr$$

The second mechanism is more probable than the previous one. Because its first step is found consistent with the results of Hashimoto, et al. [20] and the second with the works of Iotsich [83].

The proposed reaction mechanism of other organometallic compounds of Group II A with active hydrogen is generally the four centre type mechanism and it has been found that the rate of cleavage of carbon-metal bond is a function of both the acidity of substrate and the ability of the atom to which H is attached, to coordinate with the metal atom i.e. nucleophilic assistance.

Coates and Huck[84] reported the rate of cleavage of $(CH_3)_2Be$ by active hydrogen is in the order $ROH > R_2NH > RSH$.

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ÖZET

Etil mağnezyum bromürle, çok zayıf Bronsted asitleri olan aminler, alkoller ve 1- alkinler arasındaki Zerewitinoff reaksiyonunun kinetiği, dietil eterde, 25 °C de ve gazometrik metodla ayrıntılı olarak incelenmiştir. Reaksiyonun herbir reaktife göre 1. ve toplam 2. mertebeden olduğu bulunmuş ve aktiflenmiş kompleksin, hem aktif hidrojenin, etil mağnezyum bromürdeki α-karbonuna elektrofilik etkisi ve hem de asidin konjüge bazının mağnezyuma nukleofilik etkisi ile oluştuğu, S_Ei (moleküller arası elektrofilik substitüsyon) mekanizması teklif edilmiştir.

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