Solvent Effects in the Grignard Reaction. Ethylmagnesium Bromide with Benzonitrile

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Kinetic data have been obtained for the reaction of ethylmagnesium bromide with benzonitrile in tetrahydrothiophene, ethyl ether, 4-methyl-1,3-dioxane, methylal, tetrahydrofuran, and diglyme. The initial phase of the reaction was found to follow second-order kinetics. A comparison of the rate constants observed in these solvents indicates that the reaction is slower in more basic solvents. The variation of the rate constants with temperature and kinetic data in mixed solvent systems, as well as the infrared spectra of these solutions, indicate that a specific complex is formed between the solvent and the Grignard reagent. The mechanistic implications of these findings are discussed. The n.m.r. spectra of these solutions have also been determined.

For many years the RMgX structure was sufficient to describe not only the structure of Grignard reagents but also reasonable mechanisms by which they were thought to react. In 1957 Dessy and co-workers[3,4] reported exchange experiments which seemed to be conclusive evidence that the RMgX structure could not exist, at least in the case of ethylmagnesium bromide. Consequently much of the data obtained since that time have been interpreted in terms of a dimeric structure $R_2Mg{:}MgX_2$ for the Grignard reagent.[5-12] Recently some doubt has arisen concerning the validity of the exchange experiments.[13] Molecular weight[14-16] and crystallographic[17] studies have indicated that Grignard reagents may actually exist as monomers, at least at low concentrations.

Part of the dichotomy concerning the nature of Grignard reagents and the mechanisms by which they react is certainly in part due to the fact that investigators have sought, justifiably, to extend the results obtained with a particular Grignard reagent, in a particular solvent, at a particular concentration, to other Grignard reagents. This cannot always be done and has led to some of the confusion which exists today. This fact has begun to be recognized.[18]

The purpose of this investigation was to study certain physical–chemical aspects of ethylmagnesium bromide solutions in different solvents. It was anticipated that, by studying the effect of different solvents upon the rate of reaction of ethylmagnesium bromide with benzonitrile, knowledge could be gained not only concerning the role of the solvent in this reaction but also about the constitution of Grignard reagents.

Experimental Section

Syntheses, Sources, and Purification of Reagents. Magnesium.—Sublimed magnesium was obtained from the Dow Chemical Co. and was reported to contain the following impurities: Al, 3 p.p.m.; Cu, 1 p.p.m.; Fe, 100 p.p.m.; Si, 100 p.p.m.; Ag, 3 p.p.m.; Sn, 10 p.p.m.; and Ti, 0.03 p.p.m. Ingots were milled into turnings using a Carballoy cutting tool with special care being taken to prevent contamination by other metals.

Ethyl Bromide.—Ethyl bromide (Matheson, reagent) was purified by washing with cold concentrated sulfuric acid until the acid no longer became colored and then with water. After drying over calcium chloride it was distilled at atmospheric pressure. The fraction boiling at 38.9–39.0° was collected for use.

Benzonitrile.—Benzonitrile (Matheson, b.p. 188–190°) was dried over calcium chloride and distilled at atmospheric pressure. The fraction boiling at 189.8–190.0° was collected for use.

Tetrahydrothiophene.—Tetrahydrothiophene (Matheson, practical) was distilled at atmospheric pressure. The fraction distilling at 120.2–120.9° was collected for use.

Diethyl Ether.—Only freshly opened cans of Mallinckrodt anhydrous ether were used.

4-Methyl-1,3-dioxane.—4-Methyl-1,3-dioxane was prepared by the method of Carlin and Smith[19] from paraformaldehyde (Matheson, 95%) and 1,3-butanediol (Matheson). After distillation at atmospheric pressure, it was redistilled over lithium aluminum hydride. The fraction boiling at 113.4–113.7° was collected for use.

Methylal.—Methylal (Matheson) was dried over anhydrous sodium sulfate and distilled from lithium aluminum hydride in an atmosphere of dry nitrogen. The fraction boiling at 42.8° was collected for use.

Tetrahydrofuran.—Tetrahydrofuran (Matheson) was distilled over lithium aluminum hydride prior to use.

Diglyme.—Diglyme (Matheson) was stored over sodium wire for 2 weeks and then distilled from fresh sodium wire. The fraction distilling at 162.0–162.3° was collected for use.

4-Methylmorpholine.—4-Methylmorpholine (Matheson, practical) was distilled at atmospheric pressure. The fraction distilling at 114.2–115.0° was collected and redistilled over lithium aluminum hydride. The fraction distilling at 114.5–115.0° was collected for use.

1-Methylpiperidine.—1-Methylpiperidine (Aldrich) was distilled at atmospheric pressure. The fraction distilling at 103.7–105.0° was collected and redistilled over lithium aluminum hydride. The fraction distilling at 104.0–105.0° was collected for use.

1-Methylpyrrolidine.—1-Methylpyrrolidine (Matheson) was distilled at atmospheric pressure. The fraction distilling at 79.0–79.3° was collected and redistilled over lithium aluminum hydride. The fraction distilling at 79.1–79.3° was collected for use.

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[1] Taken from the dissertation submitted to the faculty of the Polytechnic Institute of Brooklyn in partial fulfillment of the requirements for the degree of Doctor of Philosophy, 1965.

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[3] R. E. Dessy, G. S. Handler, J. H. Wotiz, and C. A. Hollingsworth, *J. Am. Chem. Soc.*, **79**, 3476 (1957).

[4] R. E. Dessy and G. S. Handler, *ibid.*, **80**, 5824 (1958).

[5] (a) S. J. Storfer, Doctoral Dissertation, Polytechnic Institute of Brooklyn, June 1960; (b) S. J. Storfer and E. I. Becker, *J. Org. Chem.*, **27**, 1868 (1962).

[6] N. M. Bikales and E. I. Becker, *Can. J. Chem.*, **41**, 1329 (1962).

[7] D. O. Cowan and H. S. Mosher, *J. Org. Chem.*, **27**, 1 (1962).

[8] J. Miller, G. Gregoriou, and H. S. Mosher, *J. Am. Chem. Soc.*, **83**, 3966 (1961).

[9] E. W. Smalley and C. A. Hollingsworth, *J. Org. Chem.*, **27**, 760 (1962).

[10] H. O. House, D. D. Traficante, and R. A. Evans, *ibid.*, **28**, 348 (1963).

[11] H. O. House and D. D. Traficante, *ibid.*, **28**, 355 (1963).

[12] M. Anteunis, *ibid.*, **26**, 4214 (1961).

[13] R. E. Dessy, S. E. I. Green, and R. M. Salinger, *Tetrahedron Letters*, 1369 (1964).

[14] (a) E. C. Ashby and W. E. Becker, *J. Am. Chem. Soc.*, **85**, 118 (1963); (b) E. C. Ashby and M. B. Smith, *ibid.*, **86**, 4363 (1964).

[15] A. D. Vreugdenhil and C. Blomberg, *Rec. trav. chim.*, **82**, 453 (1963).

[16] A. D. Vreugdenhil and C. Blomberg, *ibid.*, **82**, 461 (1963).

[17] G. D. Stucky and R. E. Rundle, *J. Am. Chem. Soc.*, **85**, 1002 (1963).

[18] R. M. Salinger and H. S. Mosher, *ibid.*, **86**, 1782 (1964).

[19] R. B. Carlin and L. O. Smith, Jr., *ibid.*, **69**, 2007 (1947).

TABLE I

THE ISOLATION OF CRYSTALS FROM SOLUTIONS OF ETHYLMAGNESIUM BROMIDE

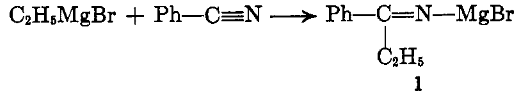
	Original solution			Cold supernatant			Solution of solid			Solid	
Solvent	Concn.[a]	Br/Et[b]	Vol., ml.	Bromide[a]	Base[a]	Br/Et[b]	Vol., ml.	Bromide[a]	Base[a]	Wt., g.	% of total $MgBr_2$ recovered
Methylal	0.624	0.98	60.0	0.310	0.631	0.491	25.0	0.137	0.004	0.315	9.3
4-Methyl-1,3-dioxane	0.801	1.00	50.0	0.527	0.821	0.643	10.0	0.294	0.000	0.271	7.4
Tetrahydrothiophene	0.258	0.94	178	. . .	. . .	. . .	10.0	1.220	0.002	1.13	28.0
Tetrahydrofuran	1.370	1.02	80.0	0.976	1.508	0.650	22.4	0.635	0.001	1.34	13.0

[a] Moles per liter. [b] Ratio of bromide ion to ethyl groups.

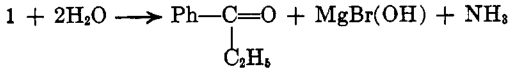
Ethylmagnesium Bromide.—Ethylmagnesium bromide was prepared in the usual manner except that the solvent was distilled into the reaction vessel, in an argon atmosphere, from a solution of ethylmagnesium bromide. This procedure was used in every case except when the solvent was diglyme. When diglyme was the solvent it was distilled into the reaction vessel from lithium aluminum hydride. During the formation of the Grignard reagent the temperature was maintained below 60° in every case. After the reaction was complete, the solution was filtered through a fine-porosity fritted-glass funnel into a 500-ml. reagent bottle which was stoppered with a stopcock. Every solution which was used for kinetics was absolutely clear and colorless.

Tests for cleavage of the solvent were made by carefully decomposing a sample of Grignard reagent in dilute sulfuric acid. The acid solution was then extracted with ethyl ether and the ether solution was analyzed by vapor phase chromatography. The only peaks observed were those for ethyl ether and the solvent.

Methods of Analysis. A. Kinetics.—The reaction rates were followed by the technique developed by Storfer[5] in this laboratory. The stoichiometry of the reaction (1) in such that after hydrolysis (2) of the reaction mixture, an extra mole of



$$C_2H_5MgBr + Ph{-}C{\equiv}N \longrightarrow \underset{\underset{\displaystyle 1}{C_2H_5}}{Ph{-}C}{=}N{-}MgBr \qquad (1)$$



$$1 + 2H_2O \longrightarrow \underset{C_2H_5}{Ph{-}C}{=}O + MgBr(OH) + NH_3 \qquad (2)$$

base is formed for each mole of reaction which has occurred. Consequently, by withdrawing aliquots at different times, determining their base concentration and subtracting the base concentration at $t = 0$, we have a direct measure of the number of moles of reaction which have occurred. Storfer has shown this method of analysis to be accurate by comparing it with another method of analysis which involves the formation and gravimetric determination of the dinitrophenylhydrazone of propiophenone. The two methods gave identical results.

B. Bromide.—Bromide was determined by the Volhard method.[20] The precipitated silver bromide was removed by filtration prior to titration of the excess silver ion with thiocyanate to sharpen the end point.

Kinetics.[21] **A. Apparatus.**—The reaction vessels were cylindrical and had a capacity of *ca.* 30 ml. Reagents were introduced and aliquots were withdrawn through a 2-mm. Teflon stopcock which was attached to the top of the reaction vessel. Becton-Dickinson 1-ml. tuberculin syringes, which were calibrated by titrating the volume of standard acid which they delivered, were used to withdraw aliquots. Hypodermic needles were 6-in., No. 22 gauge stainless steel. All equipment was dried at 150° for at least 2 hr. before use and was allowed to cool in an atmosphere of argon. After the introduction of the ethylmagnesium bromide solution into the reaction vessel with a hypodermic syringe, the reaction vessel was allowed to come to thermal equilibrium with the constant-temperature bath by means of a wrist-action shaker. The only time the reaction vessel was opened was when the benzonitrile was added and when aliquots were removed.

B. Reaction Conditions.—The temperatures of the reactions were controlled to ±0.02° in all cases except those reactions which were run below 0°. In these cases slow heat transfer between the bath and the cooling coil caused variations of ±0.10°. When the temperature of the reaction was more than 10° from room temperature the syringes were thermostatted in the constant-temperature bath. The time of the aliquots was accurate to ±0.03 min. The time necessary to remove an aliquot from the reaction vessel was 0.35 min. The time of an aliquot was the time when half of the aliquot was hydrolyzed. The time necessary to empty a syringe was 0.02 min.

C. Procedure for Following the Reaction.—A measured volume of benzonitrile was added to the thermostatted Grignard reagent at $t = 0$. Aliquots were then withdrawn at various times, decomposed in excess standard sulfuric acid, and digested on a hot plate in order to dissolve the magnesium salts and expel the solvent. Their base concentration was then determined by back titration with standard sodium hydroxide.

D. Extent of Reaction.—In all cases except two the reaction was found to be 85+% complete by titration. When the solvent was either ether or diglyme, the extent of reaction could not be determined by titration since precipitates formed after the initial phase of the reaction. (No kinetic data were obtained after precipitation.) In these cases analysis for the extent of reaction was performed by gravimetric determination of the dinitrophenylhydrazone of propiophenone. These reactions were also found to proceed to 85+% completion.

E. Slopes.—The slopes of all graphical plots were determined by the method of least squares.

Degree of Association of Ethylmagnesium Bromide. A.—When solutions of ethylmagnesium bromide, 0.682 *M* in 4-methyl-1,3-dioxane, 0.672 *M* in diglyme, and 0.576 *M* in tetrahydrofuran, were allowed to come to equilibrium, under isopiestic conditions, in a Signer molecular weight apparatus with 0.500 *M* solutions of 9-fluorenone in their respective solvents, it was found that all of the solvent distilled from the Grignard solutions and crystals remained. The solvents were then distilled back to the Grignard side of the apparatus using liquid nitrogen. The crystals dissolved and formed clear colorless solutions. When these solutions were again allowed to come to equilibrium, all of the solvent distilled from the Grignard solution and crystals remained. The crystals were dissolved in their respective solvents and after opening the apparatus all three solutions gave a positive Michler ketone test. Each of the above experiments was performed in duplicate.

B.—When 0.990 ml. of 0.574 *M* solution of ethylmagnesium bromide in tetrahydrofuran was allowed to come to equilibrium under isopiestic conditions with 1.875 ml. of 0.100 *M* 9-fluoronone in tetrahydrofuran, equilibrium was attained when the volumes of the Grignard and 9-fluorenone solutions were 1.884 and 0.978 ml., respectively. The final concentrations of these solutions were 0.301 and 0.192 *M*, respectively.

Isolation of Solids from Ethylmagnesium Bromide Solutions.—Concentrated, *ca.* 1.0 *M*, solutions of ethylmagnesium bromide in tetrahydrothiophene, 4-methyl-1,3-dioxane, methylal, and tetrahydrofuran were allowed to stand at *ca.* 5° for 1 week. Precipitates formed. The supernatants were removed and their bromide and base concentrations were determined. The solids were washed at least three times with 10-ml. portions of their respective solvents. The precipitates were then dissolved in tetrahydrofuran and diluted to a known volume. The bromide and base concentrations of the resulting solutions were then determined. The data are given in Table I.

When solutions of ethylmagnesium bromide, 1.0 *M* in ethyl ether and 1.0 *M* in diglyme, were cooled in a Dry Ice–acetone bath, no precipitates formed.

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[20] I. M. Kolthoff and E. B. Sandell, "Textbook of Quantitative Inorganic Analysis," Rev. Ed., The Macmillan Co., New York, N. Y., 1947, pp. 475–478, 573–574.

[21] The data for all kinetic runs are presented in the dissertation of A. A. Scala, copies of which are available from University Microfilms, Inc., Ann Arbor, Mich.

Instrumentation.—A Perkin-Elmer Model 521 spectrophotometer was used for determining infrared spectra. Barnes Engineering Co. fixed-thickness potassium bromide cells were used with Teflon spacers and plugs. The instrument was calibrated using the method of Blaine, *et al.*[22] The instrument was found to record frequencies, in the region of 500 cm.$^{-1}$, 4 cm.$^{-1}$ higher than their actual value. The frequencies reported here have been corrected to take this into account. N.m.r. spectra were taken on a Varian HR-60 spectrometer using tetramethylsilane as an internal standard.

Results

Six solvents have been found suitable for a kinetic study of the initial stage of the reaction between ethylmagnesium bromide and benzonitrile. This reaction was found to be at least 85% complete in all of the solvents employed. In no case was any condensation product, similar to those reported[23] to form in the reaction between diethylmagnesium and benzonitrile, observed. No cleavage of the solvent was observed.

The reactions of Grignard reagents with nitriles have been reported to be second order by Swain,[24] Vekemans,[25] Bruylants,[26] and Storfer.[5] Our data do not fit rate equations for either zero-, first-, second-, or third-order reactions, for the entire reaction. We have found, however, that a second-order plot of the data gives a good straight line for the first part of the reaction (Figures 1 and 2). This was true in all solvents except tetrahydrothiophene in which the deviation from linearity was considerable (Figure 3). The rate for the latter part of the reaction was considerably slower than that for the initial phase of the reaction. We have not studied the latter part of the reaction but have confined our investigation to the initial phase. Some representative plots of the data are presented in Figures 1–3.

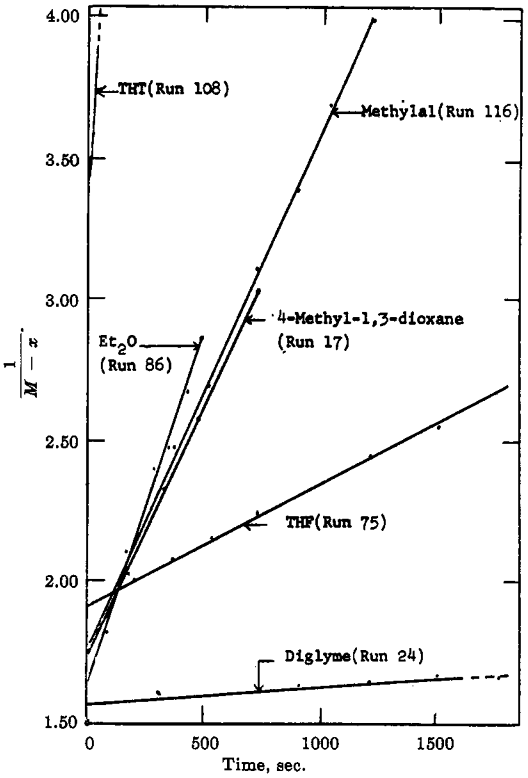

Figure 1.—Second-order plot for the initial phase of the reaction between ethylmagnesium bromide and benzonitrile. $M - x$ = moles of each reactant remaining at time t.

The results of studying the effect of temperature upon the rates in the different solvents employed are presented in Tables II–VII.

Table II

Reaction Rates in Diglyme

Run	Temp., °C.	M^a	Br/Et^b	%^{c}	$k_2 \times 10^4$, l. mole^{-1} sec.$^{-1}$
70	60.00	0.629	0.97	13.7	5.61
71	60.00	0.629	0.97	15.4	5.55
82	60.00	0.618	1.01	13.9	5.12
83	60.00	0.618	1.01	14.5	5.34
				Av.	5.41 ± 0.18
65	50.00	0.629	0.97	13.5	2.76
66	50.00	0.629	0.97	12.7	2.81
81	50.00	0.618	1.01	12.6	2.58
				Av.	2.72 ± 0.09
60	40.00	0.629	0.97	10.5	1.42
62	40.00	0.629	0.97	12.3	1.63
63	40.00	0.629	0.97	12.3	1.44
				Av.	1.50 ± 0.09
23	30.00	0.626	0.97	12.0	0.503
24	30.00	0.628	0.97	13.2	0.445
25	30.00	0.628	0.97	6.8	0.488
27	30.00	0.628	0.97	9.0	0.503
				Av.	0.485 ± 0.079

[a] The molar concentration of ethyl groups = total base and benzonitrile at $t = 0$. [b] The ratio of bromide ion to ethyl groups at $t = 0$. [c] The extent to which the reaction was followed.

Table III

Reaction Rates in Tetrahydrofuran

Run	Temp., °C.	M^a	Br/Et^b	%^{c}	$k_2 \times 10^4$, l. mole^{-1} sec.$^{-1}$
68	50.00	0.512	1.00	24.8	11.2
69	50.00	0.512	1.00	25.4	12.1
117	50.00	0.480	1.01	38.7	11.7
				Av.	11.7 ± 0.3
51	40.00	0.512	1.00	29.2	7.17
52	40.00	0.512	1.00	26.6	7.04
54	40.00	0.512	1.00	23.5	7.38
				Av.	7.20 ± 0.12
30	30.00	0.512	1.00	27.6	3.57
31	30.00	0.512	1.00	25.0	3.66
32	30.00	0.512	1.00	26.0	3.71
74	30.00	0.520	1.02	25.8	3.68
75	30.00	0.520	1.02	26.7	3.98
76	30.00	0.520	1.02	27.3	4.00
				Av.	3.77 ± 0.15
78	20.00	0.520	1.02	21.0	2.12
79	20.00	0.520	1.02	24.6	2.32
80	20.00	0.520	1.02	24.2	2.15
				Av.	2.20 ± 0.08

[a] The molar concentration of ethyl groups = total base and benzonitrile at $t = 0$. [b] The ratio of bromide ion to ethyl groups at $t = 0$. [c] The extent to which the reaction was followed.

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[22] L. R. Blaine, E. K. Plyler, and W. S. Benedict, *J. Res. Natl. Bur. Std.*, **A66**, 223 (1962).

[23] A. A. Scala, N. M. Bilakes, and E. I. Becker, *J. Org. Chem.*, **30**, 303 (1965).

[24] C. G. Swain, *J. Am. Chem. Soc.*, **69**, 2306 (1947).

[25] J. Vekemans, dissertation for the degree of Docteur en Sciences, Universite Catholique de Louvain, Louvain, Belgium, Jan. 1958.

[26] J. Moris and A. Bruylants, *Bull. soc. chim. Belges*, **65**, 1002 (1956).

TABLE IV

REACTION RATES IN METHYLAL

Run	Temp., °C.	M^a	Br/Et^b	%^{c}	$k_2 \times 10^4$, l. mole^{-1} sec.$^{-1}$
19	30.00	0.627	1.02	53.2	18.9
20	30.00	0.627	1.02	58.2	18.8
109	30.00	0.565	0.96	44.6	17.4
116	30.00	0.565	0.96	57.1	17.6
				Av.	18.2 ± 0.7
96	20.00	0.565	0.96	33.5	8.65
97	20.00	0.565	0.96	33.3	8.73
111	20.00	0.565	0.96	33.5	9.37
				Av.	8.92 ± 0.30
98	10.00	0.565	0.96	31.0	6.14
99	10.00	0.565	0.96	31.2	5.89
				Av.	6.02 ± 0.13
100	0.00	0.565	0.96	23.5	2.84
101	0.00	0.565	0.96	23.7	2.75
112	0.00	0.565	0.96	24.0	3.02
				Av.	2.87 ± 0.12

[a] The molar concentration of ethyl groups = total base and benzonitrile at $t = 0$. [b] The ratio of bromide ion to ethyl groups at $t = 0$. [c] The extent to which the reaction was followed.

TABLE V

REACTION RATES IN 4-METHYL-1,3-DIOXANE

Run	Temp., °C.	M^a	Br/Et^b	%^{c}	$k_2 \times 10^4$, l. mole^{-1} sec.$^{-1}$
57	40.00	0.638	1.01	53.0	38.4
58	40.00	0.638	1.01	53.0	36.8
				Av.	37.6 ± 0.8
17	30.00	0.638	1.01	54.8	19.3
18	30.00	0.638	1.01	53.9	20.8
22	30.00	0.638	1.01	51.7	19.4
140	30.00	0.643	0.96	50.7	21.8
				Av.	20.3 ± 0.1
134	20.00	0.643	0.96	38.2	11.3
135	20.00	0.643	0.96	39.1	12.3
136	20.00	0.643	0.96	40.3	11.9
				Av.	11.8 ± 0.4
137	10.00	0.643	0.96	30.2	5.46
138	10.00	0.643	0.96	33.0	5.30
139	10.00	0.643	0.96	30.2	5.56
				Av.	5.44 ± 0.09

[a] The molar concentration of ethyl groups = total base and benzonitrile at $t = 0$. [b] The ratio of bromide ion to ethyl groups $t = 0$. [c] The extent to which the reaction was followed.

TABLE VI

REACTION RATES IN DIETHYL ETHER

Run	Temp., °C.	M^a	Br/Et^b	%^{c}	$k_2 \times 10^4$, l. mole^{-1} sec.$^{-1}$
86	30.00	0.605	1.05	42.0	22.6
87	30.00	0.605	1.05	37.9	23.7
113	30.00	0.621	1.01	44.0	21.5
114	30.00	0.621	1.01	44.4	22.5
				Av.	22.6 ± 0.6
88	20.00	0.605	1.05	32.0	12.4
89	20.00	0.605	1.05	32.8	12.5
115	20.00	0.621	1.01	31.7	11.5
				Av.	12.1 ± 0.4
92	15.00	0.605	1.05	23.1	8.03
93	15.00	0.605	1.05	27.0	8.22
				Av.	8.13 ± 0.10
90	10.00	0.605	1.05	22.5	6.40
91	10.00	0.605	1.05	22.0	6.19
94	10.00	0.605	1.05	22.0	6.14
				Av.	6.24 ± 0.10

[a] The molar concentration of ethyl groups = total base and benzonitrile at $t = 0$. [b] The ratio of bromide ion to ethyl groups at $t = 0$. [c] The extent to which the reaction was followed.

TABLE VII

REACTION RATES IN TETRAHYDROTHIOPHENE

Run	Temp., °C.	M^a	Br/Et^b	%^{c}	$k_2 \times 10^4$, l. mole^{-1} sec.$^{-1}$
107	0.00	0.291	0.85	50.2	52.2
108	0.00	0.291	0.85	48.1	48.9
110	0.00	0.291	0.85	48.5	49.3
				Av.	50.1 ± 1.4
119	−11.3	0.236	0.85	36.0	25.1
120	−11.3	0.236	0.85	35.6	25.8
121	−11.3	0.236	0.85	36.0	23.9
				Av.	24.9 ± 0.7
122	−19.1	0.241	0.94	26.6	10.4
123	−19.1	0.241	0.94	24.5	11.6
124	−19.1	0.241	0.94	25.7	11.5
				Av.	11.2 ± 0.5
125	−28.2	0.241	0.94	20.0	5.95
126	−28.2	0.241	0.94	17.4	5.92
127	−28.2	0.241	0.94	21.5	6.34
				Av.	6.07 ± 0.19

[a] The molar concentration of ethyl groups = total base and benzonitrile at $t = 0$. [b] The ratio of bromide ion to ethyl groups at $t = 0$. [c] The extent to which the reaction was followed.

TABLE VIII

EFFECT OF SOLVENT ON ACTIVATION PARAMETERS

Solvent	E_a,^{a} kcal./mole	ΔH^*, kcal./mole^a	ΔF^*, kcal./mole	ΔS^*, e.u.^{b}
Tetrahydrothiophene	10.1^c	. . .	. . .	. . .
Diethyl ether	10.8	10.8	21.3	−35
4-Methyl-1,3-dioxane	11.1	11.1	21.4	−34
Methylal	9.7	9.7	21.4	−39
Tetrahydrofuran	10.6	10.6	22.4	−39
Diglyme	15.6	15.7	23.6	−26

[a] ±1 kcal./mole. [b] ±3 e.u. [c] This value is imprecise because of the deviation from linearity in this solvent and because of the limited accessibility to the early stages of the reaction due to the rapid rate of reaction in this solvent.

A plot of the logarithms of the rate constants at various temperatures as a function of the reciprocal of the absolute temperature is given in Figure 4.

The Arrhenius energy of activation (E_a) for the reaction in each of the solvents employed is given in Table VIII along with the corresponding enthalpy of activation (ΔH^*), free energy of activation (ΔF^*), and entropy of activation (ΔS^*). The value of ΔH^* was taken to be the same as E_a since the error in E_a is greater than the correction ($-RT \cong 0.6$ kcal./mole) for the conversion.

Table IX presents the rate constants at 30° for each of the solvents studied along with the relative basicity of the solvents, where these data are available.

Based on the data in Table IX, we have examined the possibility of reducing the reactivity of the Grignard reagent by the addition of a second more basic cosolvent, which, because of its greater basicity, might be expected to coordinate selectively to the reagent. The data for these mixed solvent systems are presented in Table X. A comparison of respective rate constants for these mixed solvent systems is presented in Table XI, along with the pK_a of the conjugate acid of the amine. See Table XII for kinetic data.

Table IX

Dependence of Rate Constant upon Basicity of Solvent

Solvent	$k_2 \times 10^4$, l./mole sec.	Relative basicity
Tetrahydrothiophene (THT)	300[a]	0.16[b]
Diethyl ether	22.6	0.24[b]
4-Methyl-1,3-dioxane	19.8	
Methylal	18.2	
Tetrahydrofuran (THF)	3.77	500[b]
Diglyme	0.485	0.24[c]

[a] This value was obtained by extrapolation from the rate constant at 0 to 30° using the value of $E_a \cong 10$ kcal./mole which was determined. [b] H. E. Wirth and P. I. Slick, *J. Phys. Chem.*, 66, 2277 (1962). [c] J. L. Down, L. Lewis, B. Moore, and G. Wilkinson, *J. Chem. Soc.*, 6767 (1959).

Table X

Reaction Rates in Mixed Solvents at 30°

Solvent	Run	M[a]	Br/Et[b]	%[c]	$k_2 \times 10^4$, l. mole^{-1} sec.$^{-1}$
THF[d]	34	0.424	1.00	23.6	3.45
THF[d]	41	0.424	1.00	26.7	3.47
				Av.	3.46 ± 0.01
THF[e]	45	0.454	1.00	24.1	3.12
THF[e]	46	0.454	1.00	25.4	3.25
THF[e]	47	0.454	1.00	24.5	3.39
				Av.	3.25 ± 0.09
THF[f]	35	0.436	1.00	24.5	2.09
THF[f]	38	0.436	1.00	25.0	2.06
THF[f]	42	0.436	1.00	24.5	2.05
				Av.	2.07 ± 0.02
THT[g]	129	0.245	0.94	34.7	2.41
THT[g]	130	0.245	0.94	31.9	2.43
				Av.	2.42 ± 0.01

[a] The molar concentration of ethyl groups = total base and benzonitrile at $t = 0$. [b] The ratio of bromide ion to ethyl groups at $t = 0$. [c] The extent to which the reaction was followed. [d] Two moles of N-methylmorpholine/mole of magnesium. [e] Two moles of N-methylpiperidine/mole of magnesium. [f] Two moles of N-methylpyrrolidine/mole of magnesium. [g] One mole of N-methylpyrrolidine/mole of magnesium. The temperature here is 0.00°.

Table XI

Comparison of Rates in Mixed Solvents

Solvent	Cosolvent	$k \times 10^4$ (30°)	pK_a[a]
THF	...	3.77	
THF	N-Methylmorpholine[b]	3.46	7.41
THF	N-Methylpiperidine[b]	3.25	10.08
THF	N-Methylpyrrolidine[b]	2.07	10.46
THT	...	50.1[c]	
THT	N-Methylpyrrolidine[d]	2.42[c]	10.46

[a] H. K. Hall, *J. Am. Chem. Soc.*, 79, 5441 (1957). [b] Two moles of cosolvent/mole of ethylmagnesium bromide. [c] The temperature is 0.00°. [d] One mole of cosolvent/mole of ethylmagnesium bromide.

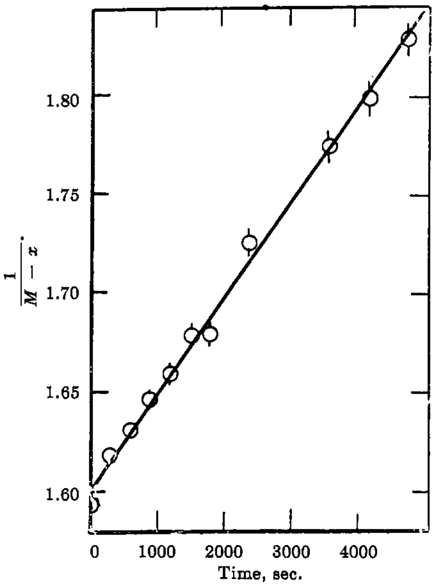


Figure 2.—Second-order plot for the initial phase of the reaction between ethylmagnesium bromide and benzonitrile in diglyme (run 24). $M - x$ = moles of each reactant remaining at time t.

Table XII

Data for Kinetic Runs

Run no. 17		Run no. 24		Run no. 75	
M = 0.638		M = 0.628		M = 0.520	
Br/Et = 1.01		Br/Et = 0.97		Br/Et = 1.02	
Temp. = 30.00°		Temp. = 30.00°		Temp. = 30.00°	
Dioxane		Diglyme		THF	
t[a]	N[b]	t[a]	N[b]	t[a]	N[b]
1.50	0.733	5.00	0.638	3.00	0.536
3.00	0.788	10.00	0.642	6.00	0.559
5.00	0.847	15.00	0.648	9.00	0.578
8.00	0.892	20.00	0.653	12.00	0.590
12.00	0.951	26.00	0.660	15.00	0.608
17.00	0.987	30.00	0.660	20.00	0.633
250.00	1.197	40.00	0.676	25.00	0.645
		60.00	0.693	30.00	0.659
		70.00	0.700		
		80.00	0.709		
		Crystallization			

Run no. 86		Run no. 108		Run no. 116	
M = 0.605		M = 0.291		M = 0.565	
Br/Et = 1.05		Br/Et = 0.85		Br/Et = 0.96	
Temp. = 30.00°		Temp. = 0.00°		Temp. = 50.00°	
Et_2O		THT		THF	
t[a]	N[b]	t[a]	N[b]	t[a]	N[b]
1.25	0.669	1.30	0.349	2.00	0.660
2.00	0.698	2.30	0.371	4.00	0.693
2.75	0.726	3.40	0.392	6.00	0.726
3.50	0.741	4.20	0.397	8.00	0.760
4.30	0.771	5.20	0.409	10.00	0.780
5.20	0.784	6.20	0.416	12.00	0.810
6.15	0.811	7.10	0.419	14.00	0.821
7.25	0.833	8.10	0.428	17.00	0.860
8.50	0.859	9.05	0.431	20.10	0.880
Crystallization					

[a] Minutes. [b] N = normality of solution.

Salinger and Mosher[18] have reported the infrared spectra of diethylmagnesium and ethylmagnesium bromide in ethyl ether and tetrahydrofuran. These investigators reported a band at 500 cm.$^{-1}$ for the C–Mg bond of ethylmagnesium bromide in tetrahydrofuran and bands at 512 and 508 cm.$^{-1}$ for the C–Mg bond of diethylmagnesium and ethylmagnesium bromide, respectively, in ethyl ether. We have observed the same uncorrected frequencies for ethylmagnesium bromide in these two solvents. The corrected frequencies for the above absorption bands are, therefore, ethylmagnesium bromide (THF), 496 cm.$^{-1}$; diethylmagnesium (Et_2O), 508 cm.$^{-1}$; and ethylmagnesium bromide (Et_2O), 504 cm.$^{-1}$. Solvent compensation is necessary when the solvent is ethyl ether.

Upon the addition of 2 moles of N-methylpyrrolidine/mole of magnesium to a solution of ethylmagnesium bromide in tetrahydrofuran, no change in the position of the absorption occurred. However, upon the addition of 2 moles of this amine to a solution of ethylmagnesium bromide in ethyl ether the absorption band

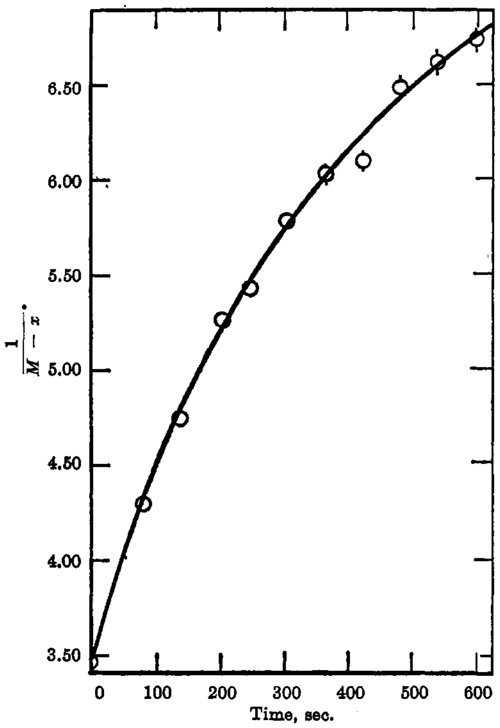


Figure 3.—Second-order plot for the initial phase of the reaction between ethylmagnesium bromide and benzonitrile in tetrahydrothiophene (run 108). $M - x$ = moles of each reactant remaining at time t.

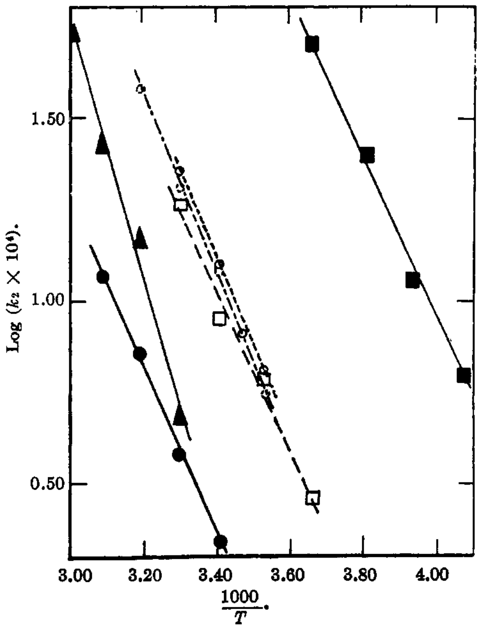


Figure 4.—Effect of temperature on rates: —■—■—, THT; - -○- -○- -, Et₂O; -○- — -○-, methylal; -□- - -□-, 4-methyl-1,3-dioxane; —●—●—, THF; and —▲—▲—, diglyme.

at 504 cm.$^{-1}$ was displaced to 496 cm.$^{-1}$. Spectra were taken *ca.* 10 min. after the addition of the amine and before any precipitate had formed. When the solvent was ether, a precipitate formed after 30 min. Analysis of the supernatant for bromide and nonvolatile base indicated that the precipitate was magnesium bromide, probably complexed with the amine, and contained 7% of the total bromide present. Further investigation of the infrared spectra in the other solvents was impossible since they all absorbed strongly in the 500-cm.$^{-1}$ region of the spectrum.

The n.m.r. spectra of these solutions are given in Table XIII. The α- and β-hydrogen atoms of ethylmagnesium bromide appear as a quartet and a triplet, as expected.

TABLE XIII
THE N.M.R. SPECTRA OF ETHYLMAGNESIUM BROMIDE SOLUTIONS

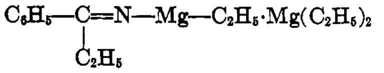
Solvent	α-CH_2 (τ)	β-CH_3 (τ)
THT	10.44	...
THT + 2 equiv. of N-methylpyrrolidine	10.44	...
THT + N-methylpyrrolidine, 1:1	10.67	...
Diethyl ether	10.65	8.80
4-Methyl-1,3-dioxane	10.73	..
Methylal	10.59	...
THF	10.76	8.83
Diglyme	10.81	8.84

Discussion

We have succeeded in obtaining precise kinetic data for the reaction of ethylmagnesium bromide with benzonitrile. To our knowledge there have been no kinetic data reported for the homogeneous reaction of any Grignard reagent with any substrate which fit a particular rate equation throughout the entire reaction and in which the rate constant has not been a function of the concentration or the ratio of reactants. Storfer and Becker[5] have studied the reaction of diethylmagnesium with benzonitrile and found that only half of the ethyl groups react. They also found that although the initial stage of the reaction appeared to be second order, the reaction did not follow good second-order kinetics throughout. They interpreted these observations as being the result of a competitive, consecutive second-order reaction which arises because the diethylmagnesium exists as a dimer (2) and the reactivity of 2 is much greater than the reactivity of the second ethyl group which is present in the ketiminate 3.

$[(C_2H_5)_2Mg]_2$

2



$C_6H_5—\underset{C_2H_5}{\underset{|}{C}}=N—Mg—C_2H_5\cdot Mg(C_2H_5)_2$

3

Because our data did not fit any rate equation throughout the entire reaction and because this reaction proceeded beyond 50% utilization of ethyl groups, we have confined this investigation to the initial phase of the reaction and have treated the reaction as being second order, first order in ethylmagnesium bromide monomer and first order in benzonitrile. We have also confined the ratio of reactants to 1.

Aside from the work of Lewis and Wright,[27] who studied the effect of solvent upon the products of the reaction between alkyl Grignard reagents and benzophenone, this is the only systematic study of the role of solvent in any Grignard reaction.[28] These workers found that strongly basic solvents such as pyridine retard the reaction, while weakly basic solvents, such as anisole, permit a rapid reaction. Solvents of intermediate basicity such as tetrahydrofuran were found

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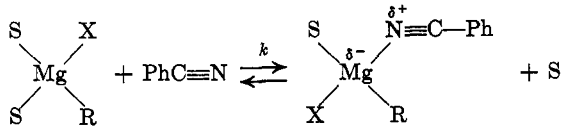
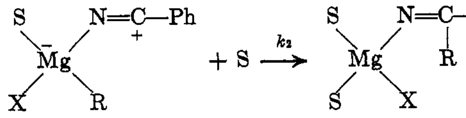
[27] R. N. Lewis and J. R. Wright, *J. Am. Chem. Soc.*, **74**, 1253 (1952).

[28] Since the completion of this work, two papers have appeared concerning the effect of solvent upon the reaction of ethylmagnesium bromide with 1-hexyne: (a) H. Hashimoto, T. Nakano, and H. Okada, *J. Org. Chem.*, **30**, 1234 (1965); (b) J. H. Wotiz and G. L. Proffitt, *ibid.*, **30**, 1240 (1965).

to give abnormal products. Our findings that the reaction studied is fastest in the least basic solvents are similar to those of Lewis and Wright and are consistent with the usually accepted mechanism for the reaction of Grignard reagents with nitriles. This mechanism, originally proposed by Swain,[24] involves complex formation in a fast equilibrium (3), followed by the nucleophilic attack of a carbanion on the nitrile carbon atom (4).



(3)



(4)

The more basic solvents would make complex formation less favorable; *i.e.*, K would be smaller and the rate would be reduced.[29]

That eq. 4 is the rate-determining process is unquestionable especially in view of the work of Citron and Becker[30] who have found a value of +1.57 for the value of ρ from a Hammett plot of the data from the reaction of diethylmagnesium with substituted benzonitriles.

For addition to ketones, a rate-determining step involving complex formation between the ketone and disolvated alkylmagnesium bromide has been postulated.[14b] For nitriles, the rate-determining step has been presented as involving transfer of R in the complex to the nitrile group. A positive ρ of 1.57 for the nitrile reaction[30] and a smaller, but positive, value of 0.362 for ketones observed by Lewis and Wright[31] support a slow transfer of R to the nitrile or ketone, and render less acceptable the solvent displacement as the slow step. This is not to say that the data would be the same for a system in which solvent, solvate, and substrate would be present in approximately equal concentrations. Such studies have not yet been reported.

If the interpretation of the n.m.r. spectra of Grignard reagents put forth by Frankel, *et al.*,[32] is correct, then it follows that the solutions in which the highest τ values are observed for the α-hydrogen atoms should have the greatest carbanion character. If this reaction occurred without complex formation (eq. 3), then we would expect these solutions to give the fastest rates. Exactly the reverse is observed. This constitutes direct evidence that complex formation is the first step in this reaction.

This interpretation would also imply that Grignard reagents are most stable in more basic solvents. Normant[33] has suggested that the success in preparing alkenyl Grignard reagents in tetrahydrofuran is due to the greater stability of these reagents in this more basic solvent. Sachs and Sachs[34] have observed that phenylmagnesium bromide in quinoline does not react with Michler's ketone and have attributed this fact to the extreme stability of the Grignard–quinoline complex.

That the basicity of the solvent is a factor which influences the rates and that a specific complex is formed between the solvent and the Grignard reagent can be seen from the results presented in Table XI for the mixed solvent systems. Not only have the rates been slowed down by the addition of stoichiometric amounts of more basic cosolvents, but the extent of this effect is a function of the basic strength of the amine.

These observations appear to be contrary to the results reported by Wotiz, *et al.*,[35] who found that the reaction between methyl- and ethylmagnesium halides and 1-hexyne was faster when a tertiary amine was added to the solution. This effect was shown not to be due to any increased lability of the hydrogen atom since no increase in the rate was observed when diethylmagnesium replaced the Grignard reagent. However, if this reaction proceeds without prior coordination of the magnesium to the alkyne, as is likely, then we would expect this effect, and no inconsistency exists. The somewhat anomalous behavior of diglyme may be due to the formation of a chelate-type coordination between one molecule of the reagent and two oxygen atoms in the same molecule of diglyme. This type of coordination would lead to the formation of a cyclic complex which normally results in the formation of a relatively stable reagent. The effect of diglyme upon the rate of oxidation of mercaptans by oxygen has been attributed to this type of cyclic coordination complex.[36] Further evidence for the existence of a specific complex between the Grignard reagent and the solvent and also for chelate-type coordination can be found in the work of Allentoff and Wright,[37] who have found that asymmetric induction of optical activity, in the reaction of an unsymmetrical ketone with a Grignard reagent, was possible only when the optically active solvent was a diether. When an optically active monoether was used as the solvent, no optical activity was observed in the product. Cohen and Wright[38] have also found that the same degree of optical purity in the product could be obtained when stoichiometric amounts of diether in benzene were used as the solvent as when the solvent was the pure diether.

In considering the mechanisms by which Grignard reagents react, the solvent is usually neglected. That the solvent should not be neglected and that a specific species exists in solution is also indicated by the infrared spectra of these solutions. The observed shift in the frequency of the C–Mg absorption of ethylmagnesium bromide in diethyl ether upon the addition of a tertiary amine can only be due to the presence of a new species in solution. This shift cannot be the result of a displacement of the equilibrium (eq. 5) since no

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(29) We thank the referee for pointing out that, while the data are consistent with the postulation of 3 as an additional slow step, the mechanism involving 3 as an equilibrium is also consistent with the data and makes the postulation of a second slow step unnecessary.

(30) J. D. Citron and E. I. Becker, *Can. J. Chem.*, **41**, 1260 (1962).

(31) R. N. Lewis and J. R. Wright, *J. Am. Chem. Soc.*, **74**, 1257 (1952).

(32) G. Frankel, D. G. Adams, and J. Williams, *Tetrahedron Letters*, 767 (1963).

(33) H. Normant, *Advan. Org. Chem.*, **2**, 6 (1960).

(34) F. Sachs and L. Sachs, *Ber.*, **37**, 3088 (1904).

(35) J. H. Wotiz, C. A. Hollingsworth, R. E. Dessy, and L. C. Liu, *J. Org. Chem.*, **23**, 228 (1958).

(36) T. J. Wallace and A. Schriesheim, *ibid.*, **27**, 1514 (1962).

(37) N. Allentoff and G. F. Wright, *ibid.*, **22**, 1 (1957).

(38) H. L. Cohen and G. F. Wright, *ibid.*, **18**, 432 (1953).

$$\underset{\mathbf{5}}{2\mathrm{RMgX}} \rightleftarrows (\mathrm{C_2H_5})_2\mathrm{Mg} + \mathrm{MgBr_2} \qquad (5)^{39}$$

absorption in the region of the C–Mg absorption of diethylmagnesium in diethyl ether was observed. The expected shift in the n.m.r. spectrum upon the addition of amine to a solution of ethylmagnesium bromide in tetrahydrothiophene was not observed and remains anomalous.

The large negative values observed for the entropy of activation (Table VIII) indicate that there is a considerable degree of order in the transition state. Previous work by Swain,[21] who studied the reaction of *n*-butylmagnesium bromide with benzonitrile in ethyl ether and found a value of −34 e.u., indicates that a high entropy of activation is characteristic of this type of reaction. The only real difference in the values presented in Table VIII is in the case of diglyme. In this solvent there seems to be a considerable degree of solvent participation in the ground state as well as in the transition state, resulting in a less negative value for the energy of activation. No linear relationship exists between the values of ΔH^* and ΔS^*.

It is well known that magnesium halide can be precipitated from solutions of Grignard reagents by the addition of 1,4-dioxane to these solutions. Attempts to measure the position of the equilibrium (5) were futile from the start since the precipitation of magnesium halide would result in displacement of the equilibrium.[40] We have been able to obtain magnesium bromide from solutions of ethylmagnesium bromide without the aid of a precipitant. Hamelin, *et al.*,[41,42] have studied crystallization from solutions of ethylmagnesium bromide in a number of solvents and have found that the bromide content of these solids was high in all cases except when ethyl ether was the solvent. The solvents employed by Hamelin were anisole, isopropyl ether, ethyl ether, *n*-butyl ether, and tetrahydrofuran. These data indicate only that an equilibrium similar to 5 involving magnesium bromide exists in solutions of ethylmagnesium bromide. It seems likely in view of the limited solubility of magnesium bromide in most of these solvents and in view of the infrared spectra of these solutions (at least in diethyl ether and tetrahydrofuran), which show no absorption in the region of absorption of diethylmagnesium solutions, that the equilibrium constant for this reaction is small. Ashby and Becker[14] have reported a compound, $\mathrm{C_2H_5Mg_2Cl_3}$, which they obtained by crystallization of a solution of ethylmagnesium chloride in tetrahydrofuran. We have not observed any material having a similar composition in solutions of ethylmagnesium bromide. The difference between these two solutions may be the result of the effect of the halogen upon the constitution of the reagent.

Since we have shown that the degree of association of ethylmagnesium bromide increases with increasing concentration, the failure to take this phenomenon into account may lie at the origin of much of the seemingly contradictory information reported for the degrees of association of various Grignard reagents in various solvents.

Acknowledgment.—We are glad to acknowledge generous support of parts of this work by the National Science Foundation under its Grant NSF-G-14558 (A. A. S.)

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[39] The nature of **5** is unspecified.

[40] M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, pp. 104–109.

[41] R. Hamelin and S. Goypiron, *Compt. rend.*, **246**, 2382 (1958).

[42] R. Hamelin and S. Hayes, *Bull. soc. chim. France*, 692 (1961).

Relationship between Structure and Solubility of Organic Lithium Compounds

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It has been found that organic lithium compounds with branching along the main chain of the organic moiety have increased solubility in hydrocarbon solvents such as benzene, heptane, and pentane. For example, branched-chain lithium alcoholates such as lithium isobutoxide and *sec*-butoxide have excellent solubility in *n*-heptane (*ca.* 50 wt. %), while the normal isomer is soluble only to the extent of about 5%. Conversely, straight-chain lithium alcoholates such as the *n*-butoxide have excellent solubility in alcohols (*ca.* 50%), while the branched chain isomers have very low solubility (less than 5%). This behavior has also been found to a lesser extent with disubstituted lithium amides. Association of the organic lithium compounds with concomitant micelle formation is offered as one explanation for such behavior.

The effect of molecular oxygen on excess butyllithium is to convert it to lithium *n*-butoxide.[1] Hydrocarbon solutions of *n*-butyllithium which have been oxidized retain this lithium *n*-butoxide in solution as a vanadium pentoxide inactive impurity.[2] This observed solubility of lithium *n*-butoxide in hydrocarbon solutions of *n*-butyllithium led us to an examination of the solubility properties of various lithium alcoholates in hydroxylic as well as aprotic solvents. There are very few references to any actual solubilities of lithium alcoholates in the chemical literature. Dermer,[3] in a review article on the metallic salts of alcohols, indicates that lithium ethoxide is soluble in alcohols, partially soluble in organic solvents, and insoluble in liquid ammonia. Jones and Thomas[4] describe the preparation of lithium ethoxide from lithium chloride and sodium ethoxide in ethanol, taking advantage of an apparent inverse temperature–solubility relationship of lithium

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[1] C. Walling and S. Buckler, *J. Am. Chem. Soc.*, **77**, 6032 (1955).

[2] P. F. Collins, C. W. Kamienski, D. L. Esmay, and R. B. Ellestad, *Anal. Chem.*, **33**, 468 (1961).

[3] O. C. Dermer, *Chem. Rev.*, **14**, 385 (1934).

[4] J. H. Jones and J. S. Thomas, *J. Chem. Soc.*, **123**, 3284 (1923).