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SYNTHESIS AND REACTION MECHANISMS IN ORGANOALUMINUM  
AND ORGANOMAGNESIUM CHEMISTRY

A THESIS

Presented to

The Faculty of the Graduate Division

by

Simon H<sup>20-160</sup> Yu

In Partial Fulfillment  
of the Requirements for the Degree  
Doctor of Philosophy in the  
School of Chemistry


Georgia Institute of Technology

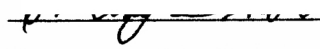
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SYNTHESIS AND REACTION MECHANISMS IN ORGANOALUMINUM  
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## SUMMARY

PART I. THE MECHANISM OF KETONE REDUCTION BY  
ALUMINUM ALKYL

A product analysis, kinetic study, and Hammett study of the reaction of triisobutylaluminum with benzophenone has been carried out in diethyl ether solvent. The reaction is found to produce on hydrolysis the reduction product benzhydrol in quantitative yield. The kinetic data shows a well-behaved second-order reaction, first order in aluminum alkyl and first order in ketone. The formation of a complex between the ketone and aluminum alkyl is observed spectroscopically. Accumulation of kinetic data at several temperatures provides a linear Arrhenius plot, which allows for calculation of activation parameters ( $\Delta S^* = -10.1$  eu and  $\Delta H^* = 15.8$  kcal/mole). A  $\rho$  value of +0.362 is determined from a Hammett study, which indicates that the rate-determining step involves nucleophilic attack of the carbonyl group by the aluminum alkyl. All of the accumulated data is consistent with a two-step mechanism in which the first step involves a fast equilibrium to form a complex. The second step is rate-determining and is consistent with a cyclic intramolecular  $\beta$ -hydrogen attack at the carbonyl carbon.

PART II. PREPARATION AND PROPERTIES OF  
ALKYLMAGNESIUM FLUORIDES

n-Hexyl-, ethyl- and methylmagnesium fluorides have been prepared in high yield by the reaction of alkyl fluorides with magnesium in ether solvents in the presence of specific catalysts. The reaction rate was found to depend significantly on the solvent, reaction temperature and catalyst. Under the most favorable conditions fluorobenzene and benzyl fluoride failed to react with magnesium.

Although alkylmagnesium chlorides, bromides and iodides are monomeric in tetrahydrofuran over a wide concentration range, ebullioscopic studies reported herein show that alkylmagnesium fluorides are dimeric in diethyl ether and tetrahydrofuran over the same concentration range. Low temperature nmr, ir, fractional crystallization and dioxane precipitation studies indicate that the Schlenk equilibrium used to describe the chloro-, bromo- and iodo Grignard systems is not operable in the case of alkylmagnesium fluorides. The unique physical properties of alkylmagnesium fluorides are rationalized on the basis of strong Mg-F-Mg bridge bonds. Alkylmagnesium fluorides react with  $H_2O$ ,  $O_2$ ,  $CO_2$ , PhCN and  $Ph_2CO$  in a manner similar to the corresponding bromo Grignard compound.

PART III. THE STEREOSELECTIVITY OF ORGANOMAGNESIUM  
AND ORGANOALUMINUM ALKYLATION REACTIONS

The stereochemistry of addition of methylmagnesium and methylaluminum compounds to 4-t-butylcyclohexanone in several solvents has been studied. Specifically methylmagnesium fluoride, chloride, and bromide, dimethylmagnesium and trimethylaluminum were allowed to react with 4-t-butylcyclohexanone in hexane, benzene, diethyl ether, tetrahydrofuran, diphenyl ether and triethylamine. Reactions involving organomagnesium compounds and trimethylaluminum in diethyl ether and tetrahydrofuran result in the predominant formation of the cis-alcohol (~73%) regardless of the halide and the mode of addition. In reactions involving trimethylaluminum in hydrocarbon solvent where the  $(\text{CH}_3)_3\text{Al}:\text{ketone}$  ratio is 1:1 or less similar results are observed. However when the ratio is 2:1 or greater a drastic reversal of the stereochemistry is observed resulting in the predominant formation of the trans alcohol (~90%). These results show that in addition to steric effects and torsional strain considerations a most important consideration is the steric requirement and flexibility of the transition state. Thus entirely different stereochemical results are observed in similar reactions depending on the exact nature of the transition state (mechanism).

PART I

THE MECHANISM OF KETONE REDUCTION BY  
ALUMINUM ALKYL

## CHAPTER I

## INTRODUCTION

Organoaluminum compounds react with carbonyl compounds in a similar way to Grignard reagents to give products of either addition, reduction, or enolization reactions or any combination of these reactions. Although the reaction of triethylaluminum with carbonyl compounds produces a mixture of addition and reduction products,<sup>1,2,3,4</sup> the primary reaction of organoaluminum compounds with branched alkyls is reduction.<sup>5,6</sup> For example, the reaction of triisobutylaluminum with carbonyl compounds is very characteristic in that no addition product is formed with most carbonyl compounds.<sup>2,3,7,8,9</sup>

Recent successes in kinetic studies on the addition reaction of trimethylaluminum with benzophenone in benzene<sup>10</sup> and diethyl ether<sup>11</sup> and the reduction reaction of t-butylmagnesium compounds with di-t-butyl ketone in tetrahydrofuran<sup>12</sup> have encouraged the study of the mechanism of the reduction reaction of trialkylaluminum compounds with carbonyl compounds by kinetic methods. An ideal system for this study involves the reaction of triisobutylaluminum with benzophenone, since only the formation of reduction product in high yield has been reported.<sup>2,3</sup> Since this reaction was reported to be too fast to follow kinetically in benzene,<sup>3</sup> kinetic studies on this reaction were carried out in diethyl ether, a solvent which provided a convenient reaction rate for kinetic measurements. Furthermore, since triisobutylaluminum is monomeric in diethyl ether<sup>13</sup> and the reaction of the first alkyl group is much more rapid than

that of the second alkyl group, this particular aluminum alkyl should provide the least complicated kinetic data.



## CHAPTER II

## EXPERIMENTAL

Instrumentation and Apparatus

A Kewaunee inert atmosphere box equipped with a recirculating system to remove moisture and oxygen<sup>14</sup> was used during the manipulation of air-sensitive reagents.

Product analyses were accomplished by an F & M Model 720 gas chromatograph. Chromosorb W supported 6-ft, 10% and 2% Carbowax 20 M matched columns were used.

A Zeiss PMQ II single-beam spectrophotometer was used to follow the disappearance of ketones in the kinetic experiments and to determine extinction coefficients of all the ketones studied. A Cary Model 14 recording spectrophotometer was employed for kinetic determinations in which the reaction was followed directly in the ultraviolet cell. Matched quartz cells (Beckman, 10.0 mm and Zeiss, 1.00 mm) were used for all ultraviolet measurements.

A Sargent constant temperature water bath was used for controlling the temperature of the kinetic solutions; temperatures were monitored with a calibrated thermometer reading to 0.1°C with estimation to 0.02°C possible.

Reactions were timed with a Precision Scientific electric stopwatch reading to 0.1 second.

The kinetic flasks were fabricated by sealing a three-way Teflon stopcock to the top of a 120-ml heavy-walled glass bulb.

Calibrated syringes equipped with stainless steel needles were used for transfer of reagents.

#### Chemicals

Triisobutylaluminum was obtained from Texas Alkyls, Inc. This material was further purified by distillation in the dry box through a 1-ft packed column under vacuum (0.2 mm), taking the center cut for kinetic studies. The pot temperature was kept at 60-70°C in order to minimize olefin elimination.<sup>15</sup> The infrared spectrum of triisobutylaluminum after distillation showed no absorption in the range of 1700-1800 cm<sup>-1</sup> characteristic of the aluminum-hydrogen bond in diisobutylaluminum hydride.<sup>16</sup>

Eastman reagent grade benzophenone was recrystallized from 95% ethanol twice and distilled under vacuum at 88°C (0.05 mm). Glpc analysis indicated a purity of at least 99.95%.

Eastman reagent grade benzhydrol, biphenyl, and the 4-substituted benzophenones (bromo, chloro, fluoro, methyl, and methoxy) were purified by recrystallation. Glpc analysis of these compounds indicated a minimum purity of 99%. 4-Methylmercaptobenzophenone was prepared by Friedel-Crafts acylation of thioanisole with benzoyl chloride in carbon disulfide using aluminum chloride as catalyst. The product was further purified by recrystallation until glpc analysis showed no detectable impurity.

Baker reagent grade anhydrous diethyl ether was distilled under nitrogen from lithium aluminum hydride prior to use.

#### Product Analysis

Glpc analysis of a solution containing benzophenone (0.6 M) and biphenyl (internal standard) showed an area ratio of benzophenone to

biphenyl of 5.41. When 1 ml of this solution was allowed to react with 3 ml of triisobutylaluminum solution (0.452 M, 1.35 mmole) in a bottle fitted with a rubber septum cap for 60 hours, glpc analysis showed an area ratio of benzhydrol to biphenyl of 5.25 without any other detectable peak. This result indicated 97.3% conversion of benzophenone into benzhydrol.

The reaction of triisobutylaluminum with benzophenone was studied at three different ratios (3:1, 2:1, and 1:2) in kinetic flasks. Two milliliters of the reaction solution were withdrawn under nitrogen at appropriate time intervals and quenched in 3 ml of 10% hydrochloric acid. Glpc analyses showed that the 3:1 and 2:1 ratio experiments produced only benzhydrol after 145 minutes. In the 1:2 ratio experiment benzhydrol was produced in 55.7% yield after 100 minutes, 66.2% after 13 hours, and 66.6% after 34.3 hours.

Duplicate samples of triisobutylaluminum (0.904 mmole) and excess benzophenone (1.80 mmole) in diethyl ether (5 ml) were allowed to react for 60 hours. Glpc analysis showed that 62.7% and 62.5% of the benzophenone had reacted.

Triisobutylaluminum ( $4.408 \times 10^{-3}$  M) was allowed to react with excess benzophenone ( $9.453 \times 10^{-3}$  M) in a kinetic flask for 397 hours. Ultraviolet spectral analysis indicated 66.2% reduction.

#### Ultraviolet Spectra of Ketones and Complex

For examining the complex of triisobutylaluminum and benzophenone in diethyl ether, 35  $\mu$ l of a standardized benzophenone solution was introduced into a rubber-capped 10-mm quartz ultraviolet cell containing 3 ml of  $33.590 \times 10^{-3}$  M triisobutylaluminum solution at room temperature (22°C). The mixture was rotated in order to ensure proper mixing of the

reactants and the absorption of the mixture was recorded immediately at appropriate time intervals from 380 to 260 m $\mu$ . A standard triisobutylaluminum spectrum was obtained before addition of benzophenone. A standard benzophenone spectrum was obtained by using 3 ml of pure diethyl ether in the cell in place of the triisobutylaluminum solution for comparison purpose.

The ultraviolet absorption maxima and extinction coefficients of 4-substituted benzophenones in diethyl ether are recorded in Table 1. For each ketone, two standard solutions were prepared and for each standard solution at least three absorbances were determined at different concentrations.

#### Kinetic Studies

The kinetics of the reaction of triisobutylaluminum with benzophenone in diethyl ether were determined by following the disappearance of the benzophenone band at 344.5 m $\mu$ .

All equipment was heated over a burner flame and placed hot in the entry port of a dry box which was subsequently evacuated and refilled with nitrogen twice. All transfer of solutions were performed under a flow of prepurified nitrogen through a three-way Teflon stopcock using syringes; 100 ml of distilled diethyl ether was first added to the reaction flask followed by addition of an aliquot of triisobutylaluminum standard solution. The flask was weighed and the total volume of the solution was obtained from the density of diethyl ether at the kinetic temperature. Then the flask was wrapped with aluminum foil and placed in a constant-temperature bath ( $25 \pm 0.05^\circ\text{C}$ ). The flask and its contents were allowed to reach temperature equilibrium before a nitrogen line was attached to

Table 1. Ultraviolet Spectral Data for 4-Substituted Benzophenones

Substituent	$\lambda_{\text{max}}, \text{m}\mu$	$\epsilon$
H	344.5	119*
Br	346	$166 \pm 1$
Cl	345	$150 \pm 2$
F	343	$130 \pm 1$
Me	344	$151 \pm 2$
MeO	330	$281 \pm 1$
MeS	308	$2120 \pm 30$

\*from ref. 5.

one side opening of the three-way stopcock. The stopcock was then turned to accept a syringe needle from the top with the nitrogen flow from the side, and the desired amount of benzophenone standard solution (0.25-0.65 ml) was added. A 6-ml sample was withdrawn immediately and quenched in a test tube with ground glass stopper containing 5 ml of ether-saturated 10% hydrochloric acid. The timer was read when half the sample was injected into the test tube. Other samples were quenched in the same manner at appropriate intervals. Quenched samples were allowed to stand for one hour before the ether layer was transferred into a quartz cell. The amount of unreacted ketone was then determined at 344.5  $\mu$  against a water-saturated ether sample from the same batch of the distillation.

The syringes (10 ml) used to withdraw the samples were flamed and purged with nitrogen by drawing gas into the barrel through the needle several times. The purging step was repeated after the syringes had cooled, after which approximately 5 ml of nitrogen was retained in the barrel of the syringe. This treatment was found to be necessary in order to avoid contamination of the reaction mixture during sample withdrawal. The procedure of withdrawing samples was shown not to affect the concentration of the reaction mixture. The concentration of a solution of benzophenone in diethyl ether after 14 withdrawals agree within 0.15% of the initial concentration. The method of quenching also proved to be valid since the absorbance of quenched solutions of benzophenone matched exactly the absorbance of the unquenched standard sample.

Triisobutylaluminum concentrations in diethyl ether were determined by decomposing aliquot samples with 10% hydrochloric acid, adding an excess of standard EDTA, and back titrating with standard zinc acetate



solution using dithizone as an indicator. The initial concentration of the triisobutylaluminum in the reaction flask was calculated from dilution. The reliability of the dilution at the kinetic concentration range was checked by diluting an aliquot of standard triisobutylaluminum solution with diethyl ether in a 200-ml volumetric flask. Some of this solution was used for kinetic runs and the remainder was weighed in order to calculate the volume from the density of diethyl ether. The solution was then hydrolyzed, decomposed, and analyzed. The analyzed concentration agree within 0.2% of the concentration calculated by the dilution factor at the lowest concentration of triisobutylaluminum. The initial concentration of benzophenone was obtained from the extrapolation of its absorbance at 344.5 mμ vs. time.

Rate constants were calculated from the second-order equation.

$$k = \frac{1}{t([A]_0 - [B]_0)} \ln \frac{[B]_0 [A]}{[A]_0 [B]}$$

Where  $[A]_0$  and  $[B]_0$  are the initial concentrations of triisobutylaluminum and benzophenone and  $[A]$  and  $[B]$  represent the concentrations at time  $t$ . The average rate constant for each run was calculated from eight to twelve sets of benzophenone concentration-time values.

## CHAPTER III

## RESULTS

The reaction of triisobutylaluminum and benzophenone in diethyl ether was found to produce on hydrolysis the reduction product benzhydrol in essentially quantitative yield without the side reactions of enolization or addition. In product-analysis studies, when triisobutylaluminum and benzophenone were allowed to react in the stoichiometric ratio of 1:2, the reaction proceeded to give benzhydrol in 66.6% yield after 34 hours. Previous workers have pointed out that only one of the isobutyl groups in triisobutylaluminum is available for reduction of benzophenone.<sup>2,3</sup> Because of the importance of this point to the evaluation of kinetic data, the reaction of triisobutylaluminum and benzophenone in 1:2 ratio was repeated in duplicate. After 60 hours, the final product after hydrolysis contained 62.7% and 62.5% benzhydrol with unreacted ketone. The reaction at a ratio of 0.466:1 was further studied by following the disappearance of ketone absorbance. It showed 42% of the second alkyl group was involved in the reaction after 397 hours (Table 2).

The absorption spectrum of  $33.59 \times 10^{-3}$  M triisobutylaluminum in a mixture with  $5.19 \times 10^{-3}$  M benzophenone in diethyl ether was recorded at appropriate intervals of time and is illustrated in Figure 1. In diethyl ether, the ultraviolet spectrum of benzophenone has maximum absorption at 344.5  $m\mu$  ( $\epsilon$  119) and 251  $m\mu$  ( $\epsilon$   $1.8 \times 10^4$ ) with a trough at 305  $m\mu$ .<sup>11</sup> Triisobutylaluminum-diethyl ether solution does not show any appreciable absorbance at wavelengths longer than 270  $m\mu$  in the



Table 2. The Reaction of Triisobutylaluminum and Benzophenone  
in the Stoichiometric Ratio of 0.466:1 at 25°C

Time, hr	Absorbance at 344.5 mμ	% reaction of benzophenone
0	1.125	0
0.36	0.779	30.7%
0.97	0.618	45.1%
1.92	0.538	52.2%
2.94	0.495	56.0%
5.86	0.465	58.7%
14.0	0.448	60.2%
27.5	0.423	62.4%
51.2	0.410	63.6%
102.0	0.396	64.8%
397	0.380	66.2%

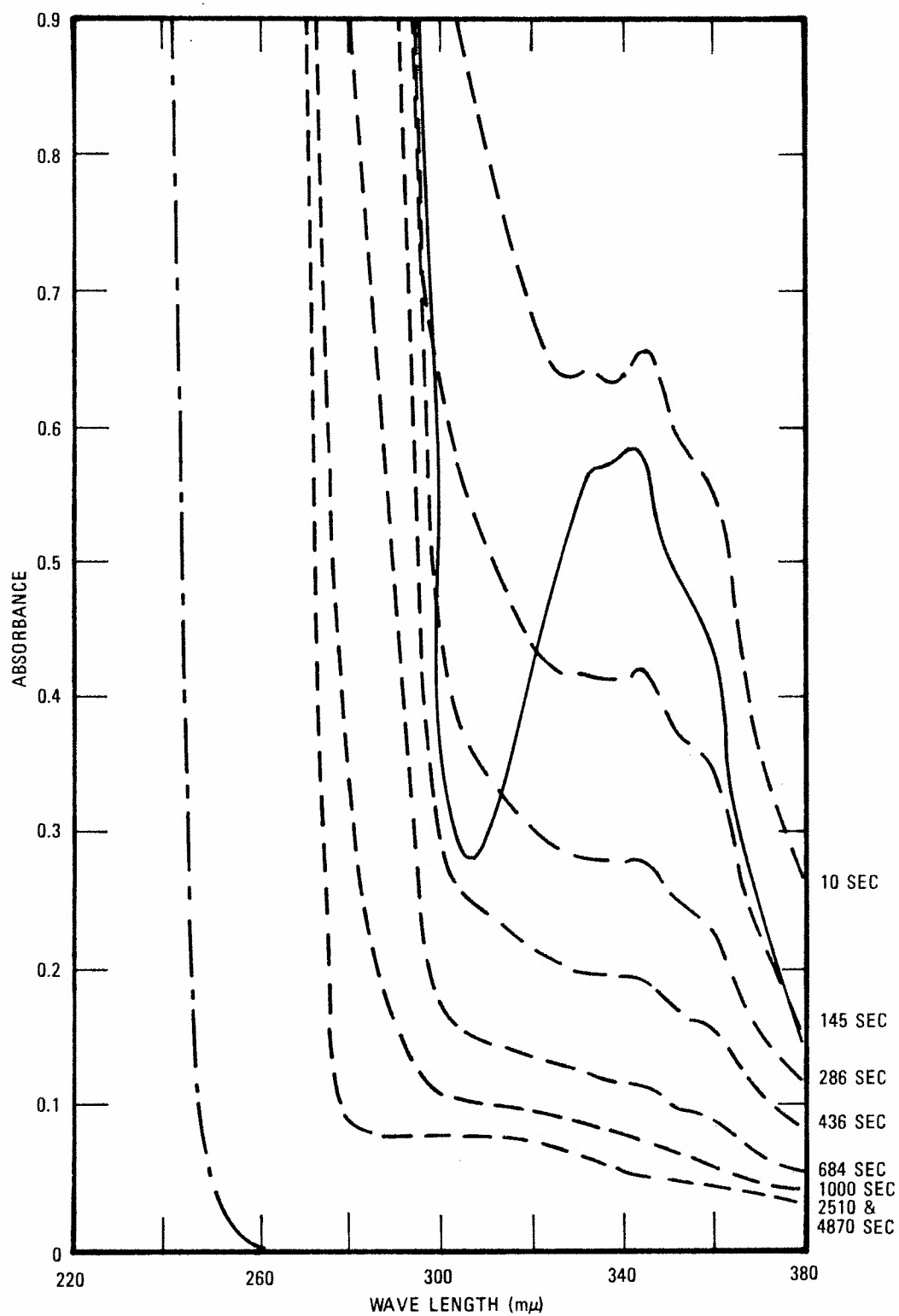


Figure 1. Absorption Spectra of a Diethyl Ether Solution of Triisobutylaluminum and Benzophenone.

concentration range studied. The spectrum of the reaction mixture indicates that the absorbance is greater for the reaction mixture than for the pure ketone at the same ketone concentration and that the absorption gradually decreases as the reaction proceeds. Neither benzophenone nor triisobutylaluminum absorbs at 400  $m\mu$ . The facts, that the mixtures show some absorbance at 400  $m\mu$ , the ketone trough at 305  $m\mu$  disappears completely, and stronger absorbance at 344.5  $m\mu$  is observed, indicate that complexation between triisobutylaluminum and benzophenone occurs, although only to a small extent.

The rate of disappearance of benzophenone was followed by quenching aliquot samples of the reaction mixture at appropriate intervals with 10% hydrochloric acid and determining the absorbance of unreacted benzophenone at 344.5  $m\mu$ . The reaction between triisobutylaluminum and benzophenone in diethyl ether was found to be first order in each reactant and second order overall. The average rate constant is  $0.0994 \pm 0.0039$  l. mole<sup>-1</sup> sec<sup>-1</sup> at 25°C. The second-order behavior was observed between 5% and 95% reaction. The rate constant was found to be independent of the reactant ratio (0.5:1 to 22:1) as well as the initial concentrations of either reactant (initial benzophenone concentrations of  $5.52-9.20 \times 10^{-3}$  M and initial triisobutylaluminum concentrations of  $4.408-160.6 \times 10^{-3}$  M).

The method used for the kinetic study proved to be very satisfactory. Reaction mixtures showed no sign of hydrolysis or loss of diethyl ether owing to sample withdrawal over a period of time and the quenching procedure did not affect the actual concentration of benzophenone in solution. Data from a typical kinetic run is graphically illustrated in Figure 2 and the results of all kinetic investigations are

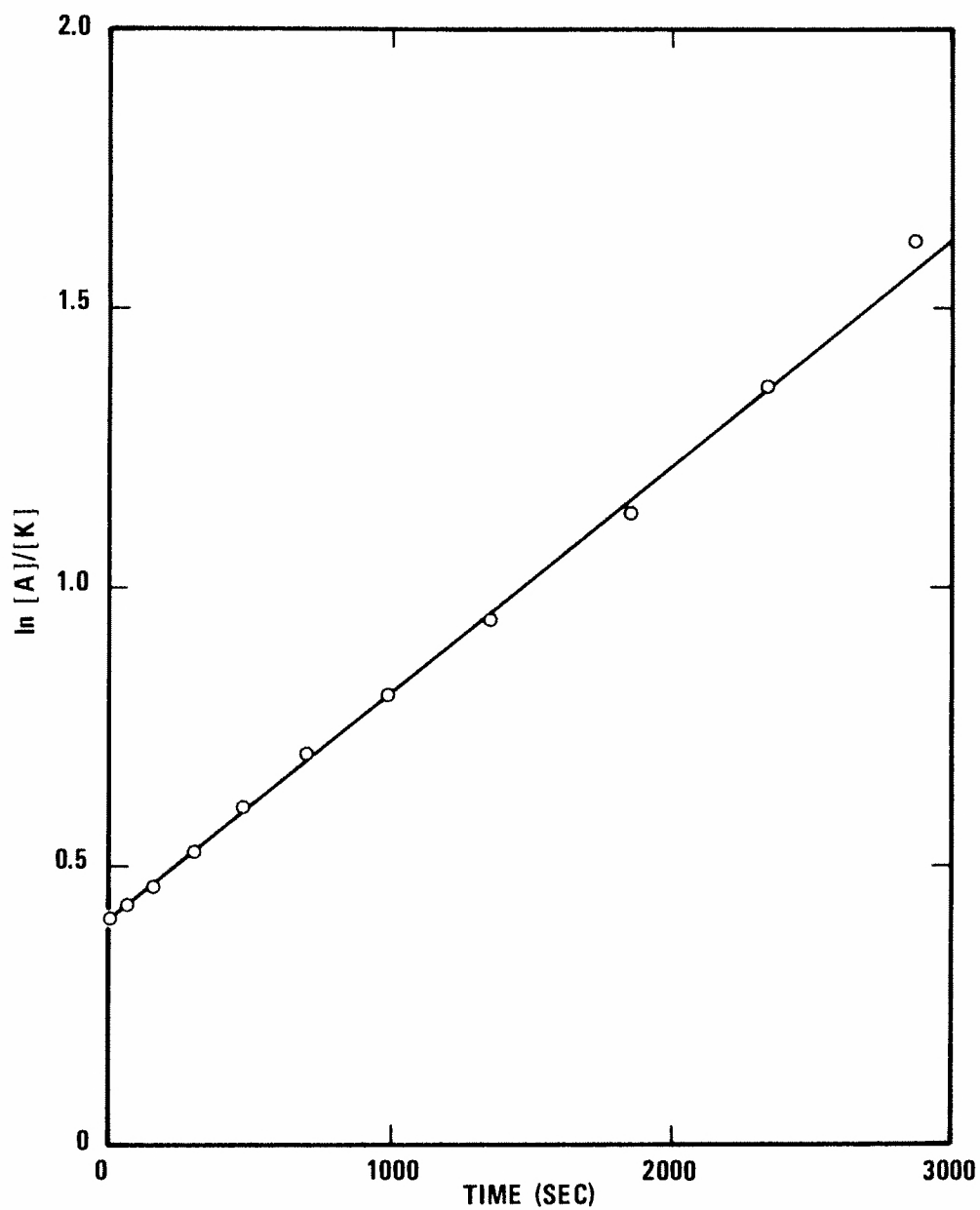


Figure 2. Plot Demonstrating Second-order Behavior of Triisobutylaluminum and Benzophenone in Diethyl Ether at 25°C (Run 6, Table 3).

summarized in Table 3.

Measurement of reaction rates at 11.4°C and 0°C also showed the reaction to be second order. The Arrhenius plot is linear, as shown in Figure 3. The slope of the Arrhenius plot and the standard equations<sup>17</sup> were used to calculate the observed activation parameters listed in Table 4.

The second-order reaction rates of six 4-substituted benzophenones with triisobutylaluminum in diethyl ether at 25°C are listed in Table 5. Variation of the 4-substituents in benzophenone produced a significant but small electronic influence on the rate of reduction. The relative reactivities correlated best with Brown's substituent constant<sup>18</sup>  $\sigma^+$  to give the Hammett equation  $\log k/k_o = (0.362 \pm 0.070) \sigma^+ + 0.00$  ( $r = 0.995$ ) (Figure 4). The 4-thiomethyl substituent resulted in poor correlation and was excluded from the calculation of the reaction constant ( $\rho$ ).

Table 3. Rate Constants for the Reaction of Triisobutylaluminum with Benzophenone in Diethyl Ether

Temp, °C	Run	$\frac{(i-C_4H_9)_3Al}{(C_6H_5)_2CO}$	$(i-C_4H_9)_3Al$ X $10^3$ M	$(C_6H_5)_2CO$ X $10^3$ M	$k_{obsd} \times 10^2$ $1.mole^{-1} sec^{-1}$
25	1	0.50	4.594	9.20	$9.11 \pm 0.42$
	2	0.51	4.594	9.05	$9.75 \pm 0.67$
	3	0.74	4.408	5.92	$10.88 \pm 0.50$
	4	0.85	7.360	8.67	$10.19 \pm 0.26$
	5	0.98	8.260	8.47	$9.35 \pm 0.12$
	6	1.50	8.260	5.52	$9.65 \pm 0.34$
	7	1.50	12.58	8.39	$9.70 \pm 0.22$
	8	2.03	17.75	8.76	$9.80 \pm 0.25$
	9	3.05	22.12	7.25	$10.39 \pm 0.21$
	10	4.02	26.17	6.51	$9.42 \pm 0.19$
	11	5.41	39.23	7.25	$10.27 \pm 0.11$
	12	21.9	160.62	7.33	$10.76 \pm 0.17^*$
11.4	Average				$9.94 \pm 0.39$
	13	2.11	18.17	8.61	$2.68 \pm 0.08$
	14	2.20	18.17	8.24	$2.78 \pm 0.07$
0	Average				$2.73 \pm 0.05$
	15	3.26	27.15	8.32	$0.785 \pm 0.030$
	16	3.14	27.15	8.65	$0.775 \pm 0.028$
	17	3.38	27.15	8.04	$0.791 \pm 0.035$
Average					$0.784 \pm 0.006$

\* Rate constant calculated from the pseudo-first-order equation,

$$k = \frac{1}{[A]_0} \frac{1}{t} \ln \frac{[B]_0}{[B]}$$

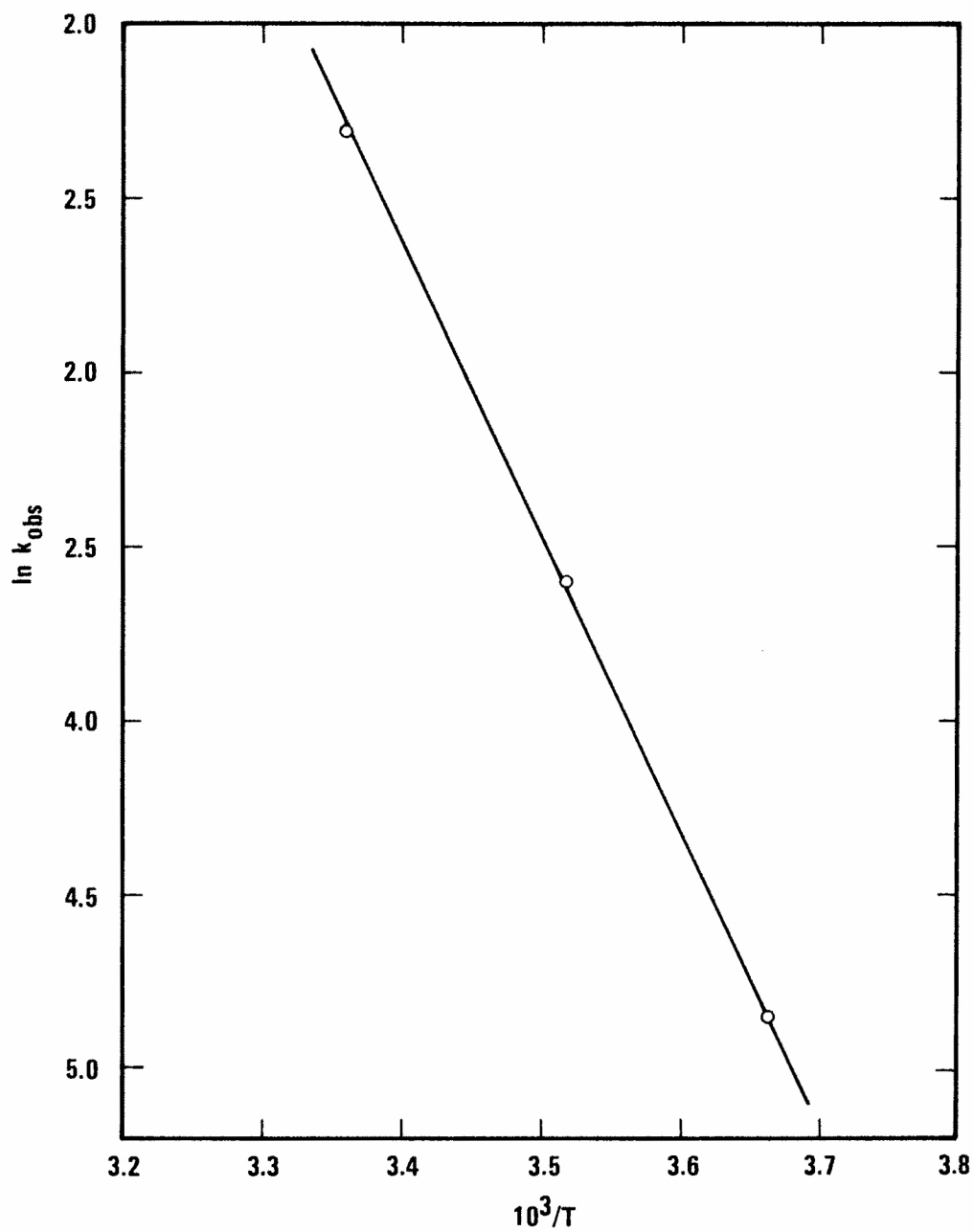


Figure 3. Arrhenius Plot of the Reaction of Triisobutylaluminum with Benzophenone in Diethyl Ether.

Table 4. Activation Parameters for the Reaction of Triisobutylaluminum with Benzophenone in Diethyl Ether at 25°C

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Activation Energy	$E_a = 16.4 \text{ kcal/mole}$
Frequency factor	$A \approx 10^{11} \text{ l.mole}^{-1} \text{ sec}^{-1}$
Free energy of activation	$\Delta G^* = 18.8 \text{ kcal/mole}$
Enthalpy of activation	$\Delta H^* = 15.8 \text{ kcal/mole}$
Entropy of activation	$\Delta S^* = -10.1 \text{ eu}$

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Table 5. Rate Constants for the Reaction of Triisobutylaluminum with 4-Substituted Benzophenones in Diethyl Ether at 25°C

4-Substituents	Run	$(i\text{-C}_4\text{H}_9)_3\text{Al}/(\text{C}_6\text{H}_5)_2\text{CO}$	$(i\text{-C}_4\text{H}_9)_3\text{Al}$ $\times 10^3 \text{ M}$	$(\text{C}_6\text{H}_5)_2\text{CO}$ $\times 10^3 \text{ M}$	$k_{\text{obsd}} \times 10^2$ $\text{l mole}^{-1}\text{sec}^{-1}$
Bromo	18	5.04	19.42	3.85	$11.45 \pm 0.42$
	19	2.52	19.22	7.62	$11.14 \pm 0.23$
				Average	$11.29 \pm 0.15$
Chloro	20	4.23	21.34	5.04	$10.77 \pm 0.12$
	21	3.30	19.20	5.81	$10.78 \pm 0.05$
				Average	$10.78 \pm 0.01$
Fluoro	22	2.30	19.33	8.42	$9.21 \pm 0.22$
	23	2.31	19.33	8.38	$9.10 \pm 0.28$
				Average	$9.16 \pm 0.06$
Methyl	24	9.76	31.73	3.25	$8.11 \pm 0.30$
	25	3.81	31.29	8.27	$8.12 \pm 0.08$
				Average	$8.12 \pm 0.01$
Methoxy	26	6.86	19.48	2.84	$5.07 \pm 0.30$
	27	4.66	19.42	4.18	$5.09 \pm 0.15$
				Average	$5.08 \pm 0.01$
Thiomethyl	28	8.68	4.749	0.547	$8.15 \pm 0.44$
	29	8.41	3.391	0.403	$7.95 \pm 0.20$
				Average	$8.05 \pm 0.10$

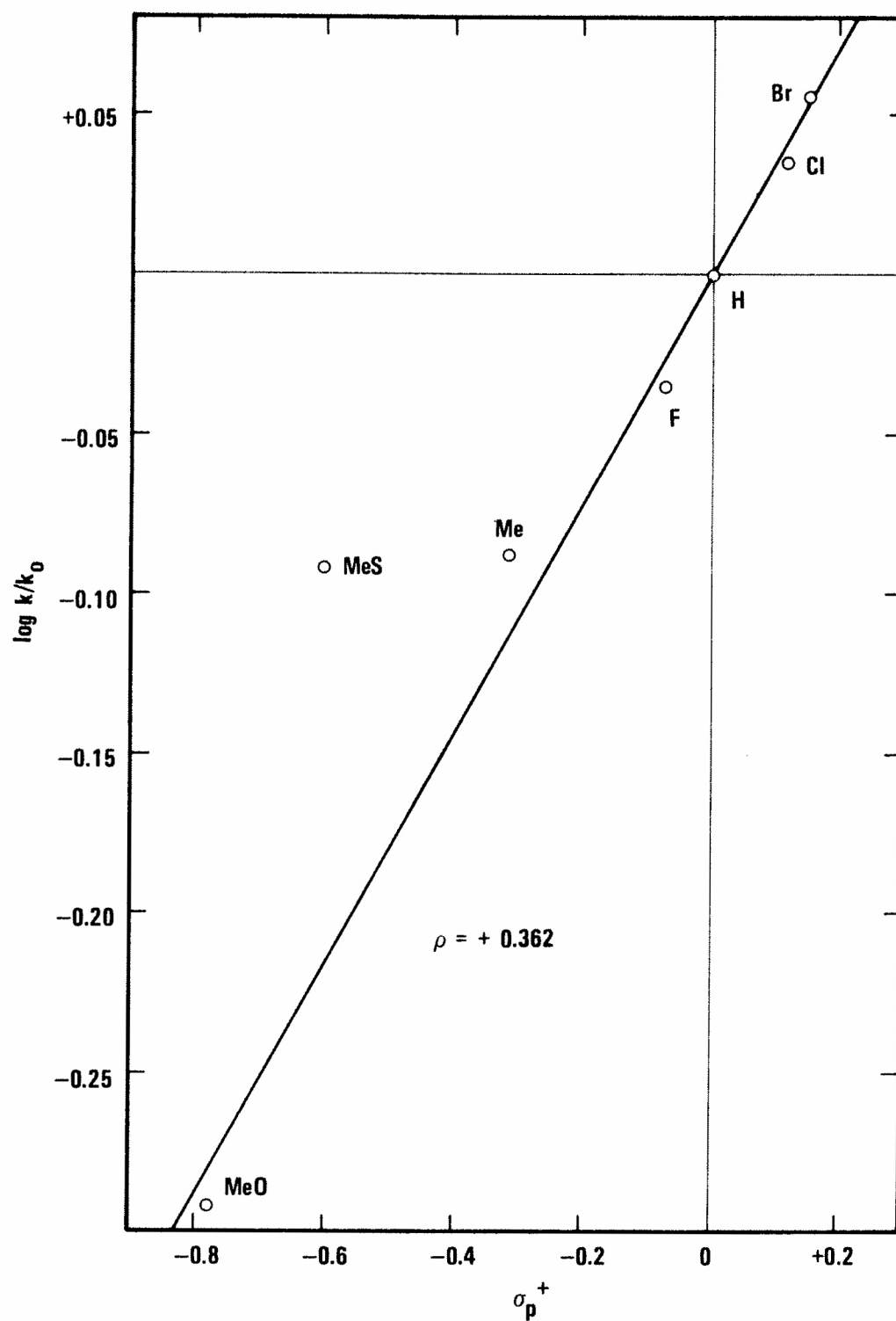


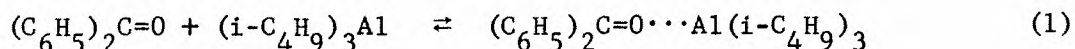
Figure 4. Hammett Plot of the Reaction of Triisobutylaluminum with 4-Substituted Benzophenones in Diethyl Ether at 25°C.

## CHAPTER IV

## DISCUSSION

Previous workers have reported that the reactions of trimethylaluminum<sup>3,10,11</sup> and triphenylaluminum<sup>19,20</sup> with ketones proceed without any occurrence of reduction products. On the other hand, triisobutylaluminum produces entirely reduction product when allowed to react with typical ketones.<sup>2,3,7,8,9</sup> It has been suggested by Wittig that the mechanism of reduction involves the migration of a  $\beta$ -hydrogen from the alkyl group of the aluminum alkyl to the carbonyl carbon. Such a mechanism already has been reasonably well demonstrated for the reduction of ketones by magnesium alkyls (Grignard reagents).<sup>21,22</sup>

Spectroscopic studies indicated complex formation between the reacting species (eq. 1). Similar spectral changes have been attributed



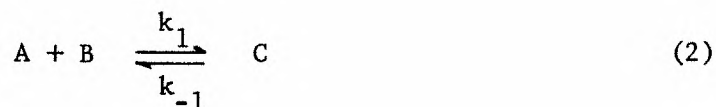
to complex formation in the addition reaction of methylmagnesium bromide<sup>23,24,25,26,27</sup> and trimethylaluminum<sup>10,11</sup> with ketones. Unfortunately, the exact extent of complexation cannot be estimated from the spectral data alone without difficulty. However, the second-order kinetic results indicate that the formation of the complex occurs only to a very small extent. Complexation of benzophenone and trimethylaluminum in diethyl ether was found to be very small,<sup>11</sup> although in benzene it was quantitative.<sup>10</sup> These results are easily explainable on the basis that diethyl

ether will compete with benzophenone as a Lewis base for the Lewis acid, triisobutylaluminum, suggesting that the equilibrium constant (K) for complex formation (eq. 1) is small in diethyl ether. The spectrum of benzophenone and triisobutylaluminum in diethyl ether is similar to that of benzophenone and trimethylaluminum in diethyl ether, and therefore complex formation should be even smaller with the more sterically hindered aluminum alkyl. Since the extent of complexation is relatively small, a steady-state treatment of the kinetic data is in order. In addition, the immediate change of the spectral profile in the complex study (Figure 1) suggests that the complex-formation step is fast on the time scale of conversion of reactants into products.

The second-order kinetic data obtained for the reaction of triisobutylaluminum and benzophenone in diethyl ether are similar to that obtained for the reduction of di-*t*-butyl ketone with di-*t*-butylmagnesium in tetrahydrofuran,<sup>12</sup> except that the second alkyl group reacts at a competitive rate in the case of magnesium. The kinetic data are also similar to that obtained for the reaction of benzophenone and trimethylaluminum in diethyl ether,<sup>11</sup> where the second alkyl group is not involved at all.

The second-order kinetic data and spectroscopic observation of a complex suggests a multiple-step mechanism involving the complex as an intermediate (eq. 2 and 3). In the equations, A = triisobutylaluminum  $[(i-C_4H_9)_3Al]$ ; B = benzophenone  $[(C_6H_5)_2C=O]$ ; C = complex between reacting species; and P = product, benzhydryloxy-diisobutylaluminum  $[(i-C_4H_9)_2AlOCH(C_6H_5)_2]$ . Equation 4 assumes a steady-state approximation. If complex formation is the rate-determining step, i.e.,  $k_2 \gg k_{-1}$ , the rate expression is given in equation 5, where  $k_{obsd} = k_1$ . Alternatively,

if product formation is the rate-determining step, i.e.,  $k_2 \ll k_{-1}$ , the rate expression reduces to equation 6, where  $k_{\text{obsd}} = k_2 K$ .



$$\frac{d[P]}{dt} = k_2 [C] = \frac{k_2 k_1}{k_{-1} + k_2} [A] [B] \quad (4)$$

$$\text{if } k_2 \gg k_{-1} \quad \frac{d[P]}{dt} = k_1 [A] [B] \quad (5)$$

$$\text{if } k_2 \ll k_{-1} \quad \frac{d[P]}{dt} = k_2 K [A] [B] \quad (6)$$

From the Hammett plot (Figure 4), the rate constants of the reduction reaction of triisobutylaluminum with 4-substituted benzophenones in diethyl ether at 25°C were determined and a  $\rho$  value of +0.362 was calculated. The linear Hammett relationship indicates that the substituents do not shift the rate-determining step of the reaction nor produce a new reaction path to form the product. The reaction step requiring complex formation is favored by electron-releasing groups in the ketone. The transfer of the  $\beta$ -hydrogen of the alkyl group in triisobutylaluminum to the carbonyl carbon in the product formation step is aided by electron-withdrawing groups attached to the ketone. Since the overall rate of the reduction depends on both the equilibrium constant  $K$  for the complex formation (eq.2) and the rate constant  $k_2$  for transfer of the  $\beta$ -hydrogen

atom (eq. 3), the two substituent effects nearly cancel each other and thus the observed rates displayed very little variation with changing substituents. A small  $\rho$  value is also consistent with a concerted or nearly concerted process, since substituent effects would tend to be nullified and little charge separation would be expected.

For some multiple-step mechanisms, the sign of the overall reaction constant ( $\rho$ ) is not always consistent with that of the rate-determining step.<sup>28</sup> However, the positive  $\rho$  value, as well as spectroscopic observation of immediate complex formation, indicates that the electrophilic complex formation step is not the rate-determining step of the reaction. Therefore, the nucleophilic product formation step is considered to be the rate-determining step. The considerable negative entropy of activation ( $\Delta S^* = -10.1$  eu) indicates that the transition state of the rate-determining step is cyclic.

A further consequence of the small  $\rho$  value is that the complex is not formed by the attack of a hydride ion at the carbonyl carbon, as postulated in the reaction of sodium borohydride with ketone.<sup>29</sup> This mechanism is analogous to that for ester hydrolysis,<sup>30</sup> both reactions of which possess considerably large  $\rho$  values (+2.61-3.06).<sup>31,32,33,34</sup>

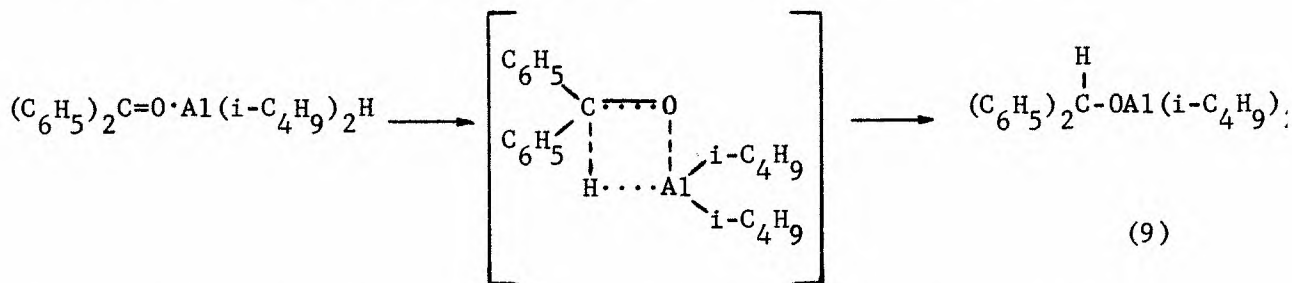
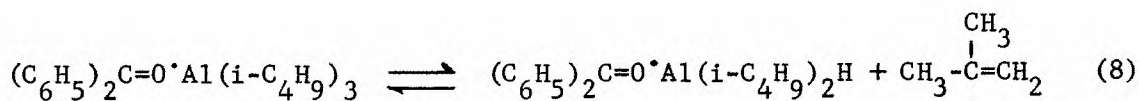
It might be suggested that, since direct spectroscopic evidence has been obtained for the occurrence of complex between the reacting species, a concerted one-step mechanism does not appear as likely. However, the question is raised whether the complex is actually an intermediate in product formation or whether it is merely involved in a nonproduct-forming equilibrium (eq. 7).<sup>24,35</sup> This alternative mechanism is consistent with all observations. If the complex is not involved in





product formation (eq. 7), then the product must be formed by a concerted attack on the carbonyl group (aluminum on oxygen and  $\beta$ -hydrogen on carbon). However, the drastic decrease in the reaction rate from benzene to ether solvent for both the addition and reduction reactions of aluminum alkyls is best explained by the fact that the concentration of complex is much greater in benzene than in ether. Therefore, it is more reasonable to believe that the product is formed via complex formation with the attack of  $\beta$ -hydrogen on the carbonyl carbon via a six-center transition state.

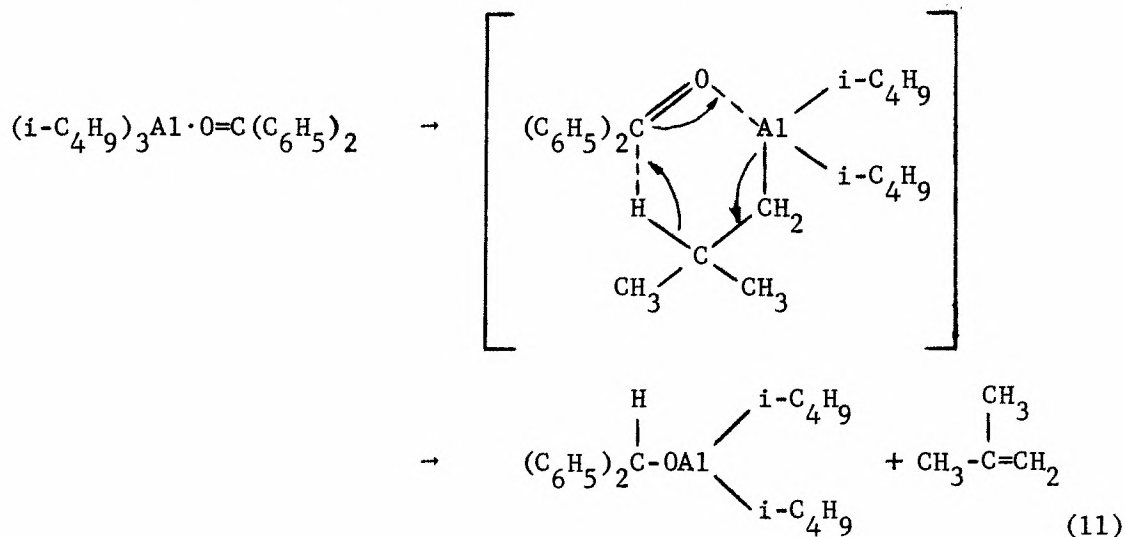
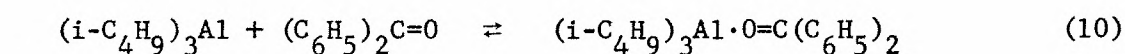
An alternative transfer of the  $\beta$ -hydrogen of triisobutylaluminum to the carbonyl carbon, also proposed as a possibility in the Grignard reduction reaction,<sup>36</sup> can be explained by olefin elimination as a consequence of ketone attack, followed by reduction of the ketone by diisobutylaluminum hydride (eqs 8 and 9). Since diethyl ether has already been shown



to be a stronger base toward aluminum alkyls than benzophenone, if the above mechanism is correct, isobutylene should be displaced from triisobutylaluminum in diethyl ether solvent. However, it is known that triisobutylaluminum etherate can be distilled at 80-90°C without olefin

displacement. Therefore, the above mechanism does not seem probable. This alternative path could be easily tested by asymmetric reduction studies, as was carried out in Grignard reduction studies.<sup>37</sup>

Consistent with all observations, the detailed reduction mechanism proposed for the reaction of triisobutylaluminum with benzophenone in diethyl ether is given in equations 10 and 11. In equation 10, a rapid



equilibrium step, benzophenone forms a complex with triisobutylaluminum in small concentration. In equation 11, an intramolecular rearrangement of the complex occurs in a rate-determining step to form the product via a cyclic six-center transition state as proposed in the Grignard reduction reaction.<sup>22</sup>



## CHAPTER V

## CONCLUSION

A product analysis, kinetic study, and Hammett study of the reaction of triisobutylaluminum with benzophenone has been carried out in diethyl ether solvent. The reaction is found to produce on hydrolysis the reduction product benzhydrol in quantitative yield. The participation of the second alkyl group of triisobutylaluminum in the reaction is indicated by product analysis. However, the reactivity of the second alkyl group turns out to be kinetically unimportant. The kinetic data shows a well-behaved second-order reaction, first order in aluminum alkyl and first order in ketone. The formation of a complex between the ketone and aluminum alkyl is observed spectroscopically. Accumulation of kinetic data at several temperatures provides a linear Arrhenius plot, which allows for calculation of activation parameters ( $\Delta S^* = -10.1$  eu and  $\Delta H^* = 15.8$  kcal/mole). A  $\rho$  value of +0.362 is determined from a Hammett study, which indicates that the rate-determining step involves nucleophilic attack of the carbonyl group by the aluminum alkyl. All of the accumulated data is consistent with a two-step mechanism in which the first step involves a fast equilibrium to form a complex (eq. 10). The second step is rate-determining and is consistent with a cyclic intramolecular  $\beta$ -hydrogen attack at the carbonyl carbon (eq. 11).

## APPENDIX

Table 6. Reaction of Triisobutylaluminum with  
Benzophenone at 25°C (Run 4)

Time Seconds	Absorbance	$k_{\text{obsd}} \times 10^2$ 1. mole <sup>-1</sup> sec <sup>-1</sup>
0	1.032	
58	0.986	10.89
143	0.920	11.60
309	0.840	10.24
490	0.765	9.98
812	0.658	10.00
1219	0.562	10.09
1692	0.488	9.98
2266	0.414	10.48
3003	0.368	9.84
Ave. 10.19 ± 0.26		

Initial Concentrations

Benzophenone	.....	$8.67 \times 10^{-3}$ M
Triisobutylaluminum	.....	$7.360 \times 10^{-3}$ M

Table 7. Reaction of Triisobutylaluminum with  
Benzophenone at 25°C (Run 7)

Time Seconds	Absorbance	$k_{\text{obsd}} \times 10^2$ l. mole <sup>-1</sup> sec <sup>-1</sup>
0	0.998	
58	0.938	9.66
154	0.846	9.41
302	0.722	9.38
468	0.608	10.07
701	0.498	9.94
992	0.403	9.71
1354	0.321	9.45
1852	0.238	9.39
2342	0.178	9.79
2862	0.124	10.07
3804	0.018	9.80
Ave. $9.70 \pm 0.22$		

Initial Concentrations

Benzophenone	.....	$8.39 \times 10^{-3}$ M
Triisobutylaluminum	.....	$12.58 \times 10^{-3}$ M

Table 8. Reaction of Triisobutylaluminum with  
Benzophenone at 25°C (Run 10)

Time Seconds	Absorbance	$k_{\text{obsd}} \times 10^2$ 1. mole <sup>-1</sup> sec <sup>-1</sup>
0	0.775	
66	0.662	9.30
157	0.544	8.98
218	0.462	9.60
328	0.356	9.83
463	0.270	9.64
623	0.202	9.32
804	0.138	9.47
1044	0.091	9.23
1427	0.042	9.43

Ave.  $9.42 \pm 0.19$

Initial Concentrations

Benzophenone	.....	$6.51 \times 10^{-3}$ M
Triisobutylaluminum	.....	$26.17 \times 10^{-3}$ M

Table 9. Reaction of Triisobutylaluminum with  
Benzophenone at 11.4°C (Run 14)

Time Seconds	Absorbance	$k_{\text{obsd}} \times 10^2$ l. mole <sup>-1</sup> sec <sup>-1</sup>
0	0.980	
65	0.950	2.65
165	0.905	2.70
318	0.837	2.83
608	0.730	2.84
1178	0.578	2.76
2135	0.391	2.83
3205	0.280	2.71
5062	0.138	2.92

Ave.  $2.78 \pm 0.07$

Initial Concentrations

Benzophenone	.....	$8.24 \times 10^{-3}$ M
Triisobutylaluminum	.....	$18.17 \times 10^{-3}$ M

Table 10. Reaction of Triisobutylaluminum with  
Benzophenone at 0°C (Run 17)

Time Seconds	Absorbance	$k_{\text{obsd}} \times 10^2$ l. mole <sup>-1</sup> sec <sup>-1</sup>
0	0.957	
56	0.940	
157	0.925	0.800
364	0.880	0.848
612	0.845	0.761
1111	0.761	0.777
1988	0.655	0.737
2931	0.528	0.807
4130	0.425	0.799
5769	0.316	0.805
7840	0.257	0.714
10447	0.128	0.859

Ave.  $0.791 \pm 0.035$

Initial Concentrations

Benzophenone	.....	$8.04 \times 10^{-3}$ M
Triisobutylaluminum	.....	$27.15 \times 10^{-3}$ M

Table 11. Reaction of Triisobutylaluminum with  
4-Bromobenzophenone at 25°C (Run 19)

Time Seconds	Absorbance	$k_{\text{obsd}} \times 10^2$ l. mole <sup>-1</sup> sec <sup>-1</sup>
0	1.265	
39	1.168	10.83
91	1.053	10.54
171	0.895	11.21
248	0.779	11.09
349	0.640	11.43
498	0.500	11.33
698	0.364	11.28
906	0.265	11.29
1100	0.199	11.31
		Ave. 11.14 $\pm$ 0.23

Initial Concentrations

4-Bromobenzophenone	.....	$7.62 \times 10^{-3}$ M
Triisobutylaluminum	.....	$19.22 \times 10^{-3}$ M



Table 12. Reaction of Triisobutylaluminum with  
4-Chlorobenzophenone at 25°C (Run 21)

Time Seconds	Absorbance	$k_{\text{obsd}} \times 10^2$ l. mole <sup>-1</sup> sec <sup>-1</sup>
0	0.872	
46	0.793	10.89
124	0.618	10.75
199	0.590	10.79
280	0.510	10.72
374	0.430	10.78
484	0.357	10.74
677	0.260	10.72
909	0.177	10.83

Ave. 10.78  $\pm$  0.05

Initial Concentrations

4-Chlorobenzophenone	.....	$5.81 \times 10^{-3}$ M
Triisobutylaluminum	.....	$19.20 \times 10^{-3}$ M

Table 13. Reaction of Triisobutylaluminum with  
4-Fluorobenzophenone at 25°C (Run 22)

Time Seconds	Absorbance	$k_{\text{obsd}} \times 10^2$ 1. mole <sup>-1</sup> sec <sup>-1</sup>
0	1.095	
34	1.030	9.44
113	0.897	9.52
205	0.769	9.59
359	0.628	9.03
553	0.487	8.84
810	0.352	8.85
1049	0.246	9.24
1672	0.125	9.22
2155	0.076	9.13
Ave. 9.21 ± 0.22		

Initial Concentrations

4-Fluorobenzophenone	.....	$8.42 \times 10^{-3}$ M
Triisobutylaluminum	.....	$19.33 \times 10^{-3}$ M

Table 14. Reaction of Triisobutylaluminum with  
4-Methylbenzophenone at 25°C (Run 25)

Time Seconds	Absorbance	$k_{\text{obsd}} \times 10^2$ l. mole <sup>-1</sup> sec <sup>-1</sup>
0	1.275	
56	1.115	7.82
123	0.945	8.09
223	0.750	8.11
310	0.615	8.17
474	0.435	8.12
611	0.327	8.14
801	0.222	8.17
1018	0.140	8.31
Ave. 8.12 $\pm$ 0.08		

Initial Concentrations

4-Methylbenzophenone	.....	$8.27 \times 10^{-3}$ M
Triisobutylaluminum	.....	$31.29 \times 10^{-3}$ M

Table 15. Reaction of Triisobutylaluminum with  
4-Methoxybenzophenone at 25°C (Run 27)

Time Seconds	Absorbance	$k_{\text{obsd}} \times 10^2$ l. mole <sup>-1</sup> sec <sup>-1</sup>
0	1.174	
62	1.101	5.39
111	1.048	5.34
190	0.978	5.04
294	0.882	5.15
455	0.762	5.10
681	0.638	4.88
956	0.502	4.93
1294	0.384	4.87

Ave.  $5.09 \pm 0.15$

Initial Concentrations

4-Methoxybenzophenone	.....	$4.18 \times 10^{-3}$ M
Triisobutylaluminum	.....	$19.42 \times 10^{-3}$ M

Table 16. Reaction of Triisobutylaluminum with  
4-Thiomethylbenzophenone at 25°C (Run 29)

Time Seconds	Absorbance	$k_{\text{obsd}} \times 10^2$ l. mole <sup>-1</sup> sec <sup>-1</sup>
0	0.855	
56	0.843	8.23
148	0.822	7.93
307	0.785	8.26
609	0.711	7.97
1203	0.624	7.86
2485	0.442	8.09
4750	0.248	8.09
8141	0.122	7.56
11702	0.054	7.56
Ave. 7.95 ± 0.20		

Initial Concentrations

4-Thiomethylbenzophenone	.....	$0.403 \times 10^{-3}$ M
Triisobutylaluminum	.....	$3.391 \times 10^{-3}$ M

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PART II

PREPARATION AND PROPERTIES OF

ALKYLMAGNESIUM FLUORIDES



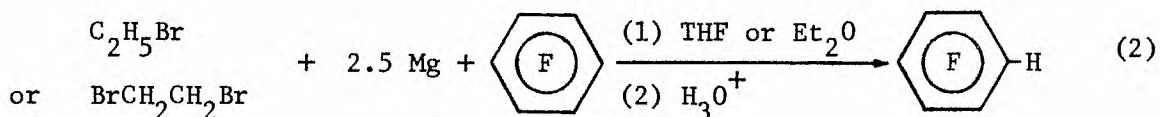
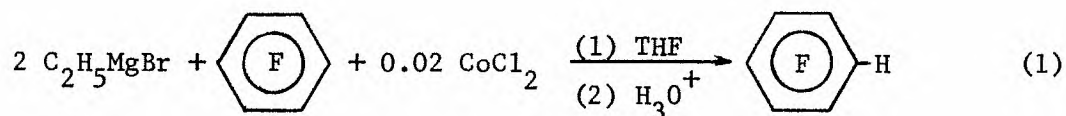
## CHAPTER I

## INTRODUCTION

For over half a century organic chemists have been interested in the preparation of organomagnesium fluorides; however, all attempts to prepare and isolate this class of compounds have been uniformly unsuccessful. The first attempt to prepare an organomagnesium fluoride was reported in 1921 by Swarts.<sup>1</sup> He found that the reaction of amyl fluoride with iodine-activated magnesium in diethyl ether after one hundred hours reflux produced decane and magnesium fluoride. In 1931 Schiemann and Pillarsky<sup>2</sup> reported that neither fluorobenzene nor its o-methyl or p-nitro derivatives reacted with magnesium to form the corresponding Grignard reagent. The same year Gilman and Heck<sup>3</sup> reported that a small quantity of biphenyl was formed when fluorobenzene was heated with magnesium at 300°C for 200 hours in a sealed tube without solvent. When fluorobenzene was sealed in a tube with activated magnesium-copper alloy<sup>4</sup> in diethyl ether at room temperature for six months, the reaction mixture gave a negative color test for the presence of an active organometallic compound; however, at the end of 18 months the color test was positive. Several attempts were made by Bernstein and coworkers<sup>5</sup> to prepare a Grignard reagent from benzyl fluoride. At reflux temperature in diethyl ether, no reaction took place. Addition of an iodine crystal or of phenylmagnesium bromide failed to initiate reaction. Under more vigorous conditions in di-n-butyl ether, polymerization of the benzyl fluoride occurred. While ordinary magnesium gave no reaction, bibenzyl was obtained from

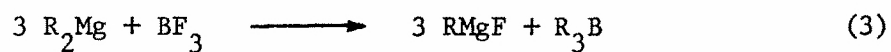
the reaction of benzyl fluoride with activated magnesium in diethyl ether at 100°C for ten days in an autoclave. Thus all attempts to prepare fluoro Grignard reagents were frustrated either by a lack of reaction between the organofluorides and magnesium or the formation of coupling product.

During our study the possible intermediacy of perfluoroaryl-magnesium fluorides was indicated by the reaction of perfluoroaryl compounds with two molar equivalents of ethylmagnesium bromide and a catalytic amount of certain transition metal halides in tetrahydrofuran<sup>6</sup> (eq. 1) and from the reaction of hexafluorobenzene with magnesium and an equal molar amount of an entrainer such as ethyl- or ethylene bromide in tetrahydrofuran or diethyl ether (eq. 2). The intermediacy of a fluoro



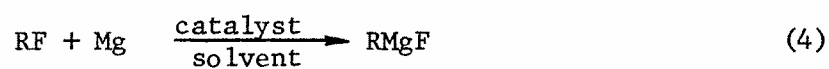
Grignard compound was indicated by hydrolysis of the reaction product to produce pentafluorobenzene and by the reaction of the product with an organochlorosilane; however, no attempt was made to identify or isolate the possible intermediate fluoro Grignard compound.

In a recent communication, Ashby and Nackashi<sup>8</sup> have reported the preparation of both aliphatic and aromatic fluoro Grignard reagents by the reaction of dialkyl- and diarylmagnesium compounds with metal or metalloidal fluoride such as  $\text{BF}_3$ ,  $\text{R}_2\text{AlF}$ , etc.



### Purpose

This study describes an investigation of the scope of the direct synthesis of fluoro Grignard reagents represented by equation 4 with respect to the nature of the alkyl group, the solvent and the catalyst in an attempt to arrive at the optimum conditions. Physical and chemical properties of several fluoro Grignard compounds are also discussed.



## CHAPTER II

### EXPERIMENTAL

All operations were carried out either in a Kewaunee nitrogen filled glove box equipped with a recirculating system to remove oxygen and moisture or on the bench using typical Schlenk tube and syringe techniques.<sup>9</sup> All glassware was flash flamed and flushed with nitrogen prior to use. Triply sublimed magnesium turnings and reflux conditions were employed in all syntheses except when stated otherwise.

#### Instrumentation

All infrared spectra were obtained using a Perkin Elmer 621 high resolution grating spectrophotometer and cesium or potassium iodide absorption cells.

Proton magnetic resonance spectra were obtained using a Varian A-60 magnetic resonance spectrometer (TMS standard). The low temperature profile of methylmagnesium fluoride was obtained on a Jeolco 100 MHz magnetic resonance spectrometer using the standard variable temperature unit.

Glpac analyses were carried out using an F & M Model 720 gas chromatograph with 3-ft Polypak 2 or 6-ft, 10% Carbowax 20 M columns.

#### Chemicals

n-Hexyl fluoride was obtained from Columbia Organics. Its purity was checked by glpc analysis and found to be at least 99% pure. Fluorobenzene was obtained from Eastman Organics, benzyl fluoride from Pierce

Chemical Co., ethyl bromide and ethylene bromide (analytical grade) from Baker Chemicals. Gaseous methyl and ethyl fluorides were obtained from Pierce Chemical Co. All of the above were dried using Molecular Sieve 4-A and employed without further purification.

Analytical grade iodine and bromine were obtained from Baker Chemicals. Cobalt chloride and sodium iodide (Baker analyzed) were made anhydrous by heating under vacuum. Triply sublimed magnesium (Dow Chemicals) and magnesium powder (Fisher Scientific Co.) were dried under vacuum prior to use.

Anhydrous diethyl ether, tetrahydrofuran (THF), 1,2-dimethoxyethane (DME), N,N,N',N'-tetramethylethylene diamine (TMED) and 1,4-dioxane were distilled from lithium or sodium aluminum hydride and triethylamine (TEA) from calcium hydride prior to use.

#### Elemental Analyses

Elemental analyses were carried out on hydrolyzed samples of the organometallic supernatant solution. Total alkalinity analysis, which gave the concentration of basic-magnesium ( $Mg_B$ ) bonded to carbon, was determined by adding a known amount of acid and back-titrating with standard base using methyl red as an indicator.<sup>10</sup> The same sample was then analyzed for total-magnesium ( $Mg_T$ ) by conventional EDTA complexometric titration at pH 10 using Eriochrome Black T as an indicator; occasionally back-titration with zinc acetate was applied for sharper end point. Chloride, bromide and iodide were determined by potentiometric titration. The same sample was then analyzed for fluoride by the method described by Hogen and Tortoric.<sup>11</sup>

Preparation of Hexylmagnesium Fluoride from Hexyl  
Fluoride and Magnesium in Tetrahydrofuran

The standard procedure used for the preparation of hexylmagnesium fluoride is as follows. A weight of 2.5-5.0 g of magnesium and a certain amount of solid activator (e.g.,  $\text{CoCl}_2 \cdot \text{I}_2$ ) were placed in a 100-ml, one-neck flask, with a side arm equipped with a Teflon stopcock. To the neck was attached a water condenser and to the flask was added a magnetic stirring bar. Then 50-70 ml of freshly distilled THF, 2-3 ml of hexyl fluoride and 2-3 ml of internal standard (toluene or octane) were added via syringe through the side-arm stopcock under strong nitrogen flow. The mixture was allowed to react at reflux temperature for a specified period of time. Liquid entrainers ( $\text{C}_2\text{H}_5\text{Br}$ ,  $\text{BrCH}_2\text{CH}_2\text{Br}$  or  $\text{Br}_2$ ), were first dissolved in THF and added dropwise to the reaction mixture at reflux temperature. In some cases the magnesium was first activated by reaction with butyllithium or ethyl bromide in an appropriate solvent. The solution was then decanted prior to reaction.

Without Activator (Reaction 1)

Hexyl fluoride (3 ml, 23 mmole) was allowed to react with magnesium (3 g, 123 mmole) in 60 ml of THF for 13 days. After standing, analysis of the clear supernatant solution showed no soluble magnesium and the ratio of hexyl fluoride and octane was constant during the reaction.

Butyllithium as Activator (Reaction 2)

Magnesium (5 g, 206 mmole) was activated by stirring with 15 ml of butyllithium hexane solution (1.6 N) in 250 ml of distilled hexane for one day. Then the solution was decanted and hexyl fluoride (3 ml,



23 mmole) and 60 ml of THF added. Analysis indicated the solution contained no magnesium after nine days stirring at room temperature or after three days additional reflux.

Bromine as Activator (Reaction 5)

Hexyl fluoride (3 ml, 23 mmole) was allowed to react with magnesium (3 g, 123 mmole) in 50 ml of THF using bromine (0.1 ml) as an activator. A light brown solution was formed after five days. Anal:  $Mg_T$ , 0.529 N; F, 0.418 N; Br, 0.073; reaction = 97%, yield = 72%.

Ethylene Bromide as Activator (Reaction 6)

Hexyl fluoride (5 ml, 38 mmole) was allowed to react with magnesium powder (3 g, 123 mmole) in 75 ml of THF with ethylene bromide (0.1 ml) as an activator for 22 days. Anal:  $Mg_B$ , 0.879 N;  $Mg_T$ , 0.699 N; F, 0.578 N; Br, 0.011 N; reaction = 100%, yield = 42%.

Ethyl Bromide as Activator (Reaction 7)

Hexyl fluoride (3 ml, 23 mmole) was allowed to react with magnesium (3 g, 123 mmole) in 50 ml of THF using ethyl bromide as an activator.

One drop of ethyl bromide used (Reaction 7a): Anal. after 22 days:  $Mg_B$ , 0.458 N;  $Mg_T$ , 0.288 N; F, 0.199 N; Br, 0.02 N; reaction = 100%, yield = 94%.

One Milliliter (13 mmole) ethyl bromide used (Reaction 7b): Anal. after eight days:  $Mg_B$ , 0.633 N;  $Mg_T$ , 0.550 N; F, 0.266 N; Br, 0.201 N; reaction = 95%, yield = 92%.

Two milliliters (26 mmole) ethyl bromide used (Reaction 7c): Anal. after eight days:  $Mg_B$ , 0.936 N;  $Mg_T$ , 0.850 N; F, 0.257 N; Br, 0.567 N; reaction = 99%, yield = 97%.

Magnesium powder (4 g, 165 mmole) activated by ethyl bromide

(4 ml, 53 mmole) followed by decantation of ethylmagnesium bromide solution (Reaction 7d): Anal. after 8.5 days: reaction = 63%, yield = 51%. After 20 days:  $Mg_B$ , 0.574 N;  $Mg_T$ , 0.409 N; F, 0.288 N; Br, 0.012 N; reaction = 96%, yield = 63%.

#### Anhydrous Sodium Iodide as Activator (Reaction 3)

Hexyl fluoride (3 ml, 23 mmole) was allowed to react with magnesium (3 g, 123 mmole) in 60 ml of THF using sodium iodide (0.17 g, 1.1 mmole) as an activator. No reaction took place after 11 days.

#### Anhydrous Cobalt Chloride as Activator (Reaction 4)

Hexyl fluoride (3 ml, 23 mmole) was allowed to react with magnesium (3 g, 123 mmole) in 50 ml of THF using cobalt chloride (0.06 g, 0.5 mmole) as an activator for 21 days. Anal:  $Mg_B$ , 0.504 N;  $Mg_T$ , 0.389 N; F, 0.313 N; Cl, 0.011 N; reaction = 98%, yield = 95%.

#### Iodine as Activator (Reaction 8)

Hexyl fluoride (3 ml, 23 mmole) was allowed to react with magnesium (3 g, 123 mmole) in 70 ml of THF using iodine as an activator.

When 0.025 g (0.1 mmole) of iodine was used (Reaction 8a), no reaction took place even after 24 days.

0.068 g (0.3 mmole) iodine used (Reaction 8b): Anal. after five days:  $Mg_B$ , 0.338 N;  $Mg_T$ , 0.285 N; F, 0.232 N; I, 0.004 N; reaction = 97%, yield = 95%.

0.26 g (1.0 mmole) iodine used (Reaction 8c): Anal. after five days:  $Mg_B$ , 0.380 N;  $Mg_T$ , 0.340 N; F, 0.306 N; I, 0.01 N.

When reaction 8c using 0.26 g of iodine was repeated in 40 ml of THF for a longer period of time (Reaction 8d), the yield did not decrease over a six to 14 day reflux period. Anal:  $Mg_B$ , 0.511 N;  $Mg_T$ , 0.473 N;



F, 0.489 N; I, 0.014; reaction = 100%, yield = 94%.

0.33 g (1.3 mmole) iodine used and the reaction was carried out in 60 ml of THF at 24°C (Reaction 8e): Anal. after 36 days:  $Mg_B$ , 0.306 N;  $Mg_T$ , 0.285 N; F, 0.256 N; I, 0.008 N; reaction = 95%, yield = 93%.

#### Hexylmagnesium Fluoride Solution as Activator (Reaction 9)

Hexyl fluoride (3 ml, 23 mmole) was allowed to react with magnesium (3 g, 123 mmole) in 60 ml of THF using 10 ml of 0.285 N hexylmagnesium fluoride solution from Reaction 8b as an activator. Anal. after 12 days:  $Mg_B$ , 0.390 N;  $Mg_T$ , 0.264 N; F, 0.181 N; I, 0.002 N; reaction = 97%, yield = 95%.

#### Preparation of Hexylmagnesium Fluoride in Other Solvents

The method used for the preparation of hexylmagnesium fluoride in other solvents is similar to that used for the preparation in THF.

#### Diethyl Ether (Reaction 10)

Hexyl fluoride (3 ml, 23 mmole) was allowed to react with magnesium (3 g, 123 mmole) in 70 ml of diethyl ether using iodine (0.251 g, 0.99 mmole) as an activator. Anal. after 13 days:  $Mg_B$ , 0.346 N;  $Mg_T$ , 0.274 N; F, 0.195 N; I, 0.03 N; reaction = 88%, yield = 83%.

#### 1,2-Dimethoxyethane (Reaction 11)

Hexyl fluoride (3 ml, 23 mmole) was allowed to react with magnesium (3 g, 123 mmole) in 55 ml of DME using iodine (0.186 g, 0.73 mmole) as an activator. Anal. after seven hours:  $Mg_B$ , 0.327 N;  $Mg_T$ , 0.334 N; F, 0.295 N; I, 0.019 N; reaction = 99%, yield = 95%.

N,N,N',N' -tetramethylethylene Diamine (Reaction 12) and Triethylamine (Reaction 13)

Hexyl fluoride (3 ml, 23 mmole) was allowed to react with magnesium (3 g, 123 mmole) in 50 ml of TMED with iodine (0.20 g, 0.7 mmole) and in a separate experiment using 60 ml of TEA with iodine (0.30 g, 1.2 mmole) for seven hours. Analyses showed in each case a negligible amount of magnesium in solution, and the formation of hexene.

Attempted Preparation of Phenylmagnesium Fluoride

Fluorobenzene (3 ml, 32 mmole) was allowed to react with magnesium (3 g, 123 mmole) in 75 ml of THF using iodine (0.36 g, 1.4 mmole) as an activator. After 14 days, analysis showed negligible reaction. The reaction also did not take place in 60 ml of DME using iodine (0.34 g, 1.3 mmole) as an activator after eight days.

Attempted Preparation of Benzylmagnesium Fluoride

Benzyl fluoride (3 ml, 20.8 mmole) was allowed to react with magnesium (3 g, 123 mmole) in 75 ml of THF using iodine as an activator. After 13 days, analysis showed negligible reaction.

Preparation of Ethylmagnesium Fluoride

Ethyl fluoride (4.9 g, 102 mmole) was passed through a tube of Molecular Sieve (4A) and then introduced through a side arm at the bottom of a Dry Ice condenser into the reaction flask containing magnesium (3 g, 123 mmole), iodine (0.23 g, 0.9 mmole) and 75 ml of THF. Anal. after 2.5 days:  $Mg_B$ , 0.339 N;  $Mg_T$ , 0.300; F, 0.278 N; I, 0.014 N; yield = 36%.

Preparation of Methylmagnesium Fluoride and Other  
Alkylmagnesium Fluorides by Autoclave Techniques

The preparation of methylmagnesium fluoride will illustrate the method employed. A weighed amount of magnesium was placed in the autoclave. The autoclave was sealed, flash flamed under nitrogen and kept under vacuum for three hours. Then the apparatus was cooled with Dry Ice-acetone and the desired solvent containing a certain amount of iodine was introduced under a nitrogen flow. After the solvent was cooled, methyl fluoride was passed through a tube of molecular seive and introduced into the autoclave. The autoclave was then sealed and the reaction carried out at the desired temperature with stirring.

Methylmagnesium Fluoride

The reaction was carried out with excess methyl fluoride (32.4 g, 953 mmole), magnesium (5 g, 205 mmole) and iodine (0.57 g, 2.2 mmole) in 100 ml of THF at 70°C for five days. Analysis showed negligible magnesium in solution and glpc analysis of the solution indicated more than 25 peaks.

The reaction was then carried out with methyl fluoride (8 g, 235 mmole), magnesium (5 g, 205 mmole) and iodine (0.38 g, 1.5 mmole) in 100 ml of THF at 60°C for three days. Analyses showed the solution to be 0.0295 N in  $Mg_B$  and 0.0175 N in  $Mg_T$ . Glpc analysis of the solution showed 10 peaks.

A similar reaction was carried out in 60 ml of DME with methyl fluoride (10 g, 290 mmole), magnesium (10 g, 410 mmole), and iodine (0.47 g, 1.9 mmole) at 60°C for four hours. Anal:  $Mg_B$ , 0.910 N;  $Mg_T$ , 0.519 N; F, 0.070 N; I, 0.039 N.

The reaction was then carried out under milder condition with methyl fluoride (6.8 g, 200 mmole), magnesium (10 g, 410 mmole) and iodine (0.54 g, 2.1 mmole) in 75 ml of THF at room temperature for 1.5 days. Anal:  $Mg_B$ , 2.21 N;  $Mg_T$ , 2.23 N; F, 2.24 N; I, 0.03 N.

The reaction was also carried out in 70 ml of diethyl ether with methyl fluoride (6.7 g, 197 mmole), magnesium (10 g, 410 mmole) and iodine (0.50 g, 1.8 mmole) at room temperature for three days. Analyses showed it to be 0.36 N in  $Me_2Mg$  and to have a negligible F concentration.

#### Ethylmagnesium Fluoride

An attempt was also made to prepare ethylmagnesium fluoride at room temperature in an autoclave by reaction of ethyl fluoride (7.48 g, 154 mmole), magnesium (10 g, 410 mmole), and iodine (0.62 g, 2.4 mmole) in 75 ml of diethyl ether for two days. Anal:  $Mg_B$ , 0.270 N;  $Mg_T$ , 0.173 N; F, 0.0 N; I, 0.03 N.

#### Hexylmagnesium Fluoride

An attempt was made to prepare hexylmagnesium fluoride in diethyl ether at 90°C in an autoclave by reaction of hexyl fluoride (2 ml, 15 mmole), magnesium (4 g, 164 mmole), and iodine (0.21 g, 0.82 mmole) for 24 hours. Anal:  $Mg_B$ , 0.122 N;  $Mg_T$ , 0.0726 N; F, 0.0165 N; I, 0.009 N; reaction = 98%.

### Ebullioscopic Determination of Molecular Association

A complete description of the apparatus and its operation has been presented elsewhere.<sup>12,13</sup> The association studies were carried out in diethyl ether and tetrahydrofuran at a pressure of 740.0 mm. The results are calculated in terms of solute association expressed as an i

value. The relationship employed is shown by equation 5.  $\Delta T_B$ , observed

$$i = \frac{W_2 M_1}{W_1 M_2} \left[ \frac{1}{e^{-\Delta T_B M_1 / 1000 K_B} - 1} \right] \quad (5)$$

boiling point elevation;  $K_B$ , boiling point elevation constant (2.01 for  $(C_2H_5)_2O$  and 2.20 for THF at 740 mm);  $W_1$ , grams of solvent;  $W_2$ , grams of solute;  $M_1$ , molecular weight of solvent and  $M_2$ , the calculated formula weight of solute. Since analytical results indicate that the R:Mg:F ratio is not exactly 1:1:1 in the solutions used (a typical ratio is 1.1:1.0:0.9, although some compounds exhibited a slightly better or worse ratio), the formula weight of solute was calculated according to the analyses in terms of a mixture of  $R_2Mg$  and  $MgF_2$ .<sup>\*</sup> For reason given before,<sup>13</sup> the monosolvated formula weight of the solute was chosen for the computation of  $i$  values.

### Stability of Alkylmagnesium Fluorides

#### Ethylmagnesium Fluoride

A THF solution of freshly prepared ethylmagnesium fluoride (Reaction 16a) gave the following analysis: 0.339 N in  $Mg_B$ , 0.300 N in  $Mg_T$  and 1.12 in  $Mg_B/Mg_T$ . After standing for four months, the analysis was: 0.325 N in  $Mg_B$ , 0.298 N in  $Mg_T$  and 1.09 in  $Mg_B/Mg_T$ .

#### Hexylmagnesium Fluoride

A THF solution of hexylmagnesium fluoride was 1.086 N in  $Mg_B$ , 0.998 N in  $Mg_T$  and 1.09 in  $Mg_B/Mg_T$ . After standing for four months at

<sup>\*</sup>For example  $C_6H_{13}MgF$  in  $Et_2O$  was calculated according to  $M_2 = 54.3\% R_2Mg + 45.7\% MgF_2 + Et_2O$ .

room temperature the solution analyzed 1.051 N in  $Mg_B$ , 1.044 N in  $Mg_T$  and 1.01 in  $Mg_B/Mg_T$ .

A diethyl ether solution of freshly prepared hexylmagnesium fluoride gave the following analysis: 1.290 N in  $Mg_B$ , 1.188 N in  $Mg_T$  and 1.08 in  $Mg_B/Mg_T$ . When 15-ml of the solution was heated at 85°C for 15 days in a sealed tube, the following analysis was obtained: 1.514 N in  $Mg_B$ , 1.316 N in  $Mg_T$  and 1.15 in  $Mg_B/Mg_T$ .\*

#### Fractional Crystallization and Dioxane Precipitation Studies

A diethyl ether solution of hexylmagnesium fluoride (Anal:  $Mg_B$ , 1.514N;  $Mg_T$ , 1.316 N;  $Mg_B/Mg_T$ , 1.15) was cooled slowly in a Dry Ice-acetone bath by the periodic addition of Dry Ice. An appreciable amount of needle-like crystals were formed. Anal. of the supernatant solution:  $Mg_B$ , 1.644 N;  $Mg_T$ , 1.502 N;  $Mg_B/Mg_T$ , 1.09.

A THF solution of hexylmagnesium fluoride (Anal:  $Mg_B$ , 1.051 N;  $Mg_T$ , 1.044 N;  $Mg_B/Mg_T$ , 1.01) did not form crystals when cooled to -78°C. Unfortunately, no appreciable amount of crystal formation took place before the freezing of solvent when the solution was cooled in liquid nitrogen. The frozen solution was partially melted at -78°C, and the supernatant analyzed. Anal:  $Mg_B$ , 1.077 N;  $Mg_T$ , 1.04 N;  $Mg_B/Mg_T$ , 1.04.

When 2 ml of dioxane (23.2 mmole) was mixed with 2 ml of hexylmagnesium fluoride THF solution (2.1 mmole), a fine white precipitate was formed slowly. Anal. of the supernatant after standing overnight:  $Mg_B$ ,

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\*The differences in concentration observed is probably due to evaporation of ether solvent during the handling of these highly volatile solutions under conditions of rapid nitrogen purge.



0.4579 N;  $Mg_T$ , 0.4532 N;  $Mg_B/Mg_T$ , 1.01. When 0.5 ml of dioxane (5.8 mmole) was mixed with 4 ml of hexylmagnesium fluoride THF solution (4.2 mmole), only a very small amount of precipitate was formed. Anal:  $Mg_B$ , 0.9781 N;  $Mg_T$ , 0.9600 N;  $Mg_B/Mg_T$ , 1.02.

#### Preparation of Magnesium Fluoride

Anhydrous hydrogen fluoride was allowed to bubble through a polyethylene bottle employing magnetic stirring and containing 2 g of magnesium in 250 ml of THF. Even after the addition of 0.5 ml of water, analysis of the solution showed a negligible concentration of magnesium. Then anhydrous hydrogen fluoride was allowed to bubble through 66 ml of THF solution of dimethylmagnesium (9.6 mmole) for 15 minutes. Anal:  $Mg_B$ , 0.296 N;  $Mg_T$ , 0.148 N;  $Mg_B/Mg_T$ , 1.99.

Another attempt to prepare anhydrous magnesium fluoride was made by reacting mercury fluoride (4.1 g, 17 mmole) (Alfa Inorganics) with magnesium (2.5 g, 102 mmole) in 60 ml of THF under reflux condition. After four days, analysis showed negligible reaction. The same reaction also did not occur in 50 ml of DME during a three-day reflux period.

Distilled boron trifluoride etherate (4.4 ml, 33 mmole) (Eastman Purified) was first dissolved in 20 ml of  $(C_2H_5)_2O$  and added dropwise into a reaction flask containing 100 ml of 0.5 M (50 mmole) dimethylmagnesium in diethyl ether solution. A white solid precipitate was observed after the addition of a few drops of the  $BF_3 \cdot O(C_2H_5)_2$  solution and the reaction was exothermic. The addition was completed in three minutes and the reaction was stirred overnight. Analysis of the solution showed negligible amount of magnesium and boron and the solid after

filtration and washing with diethyl ether showed a  $F/Mg_T$  ratio of 2.11.

Redistribution of Dialkylmagnesium Compounds  
with Magnesium Fluoride

A solution of diethylmagnesium (1.15 M, 19.5 mmole) in diethyl ether was allowed to redistribute with commercially available magnesium fluoride (3.4 g, 55 mmole) (Alfa Inorganics) in 60 ml of THF. After three-day reflux, analysis showed no increase in  $Mg_T$  in solution and the ratio of  $Mg_B$  to  $Mg_T$  corresponded to unreacted dialkylmagnesium.

Magnesium fluoride (2.4 g, 38 mmole) prepared from boron trifluoride and dimethylmagnesium in diethyl ether (above) was allowed to react with dimethylmagnesium (30 mmole) in 50 ml of equal volume mixture of  $(C_2H_5)_2O$  and THF. After two-day stirring, analysis of the solution showed the ratio of  $Mg_B$  to  $Mg_T$  to be 1.99.

Chemical Reactions of Hexyl- and  
Ethylmagnesium Fluorides

Standard solutions of hexyl- and ethylmagnesium fluorides (0.33 M and 0.37 M) and bromides (0.49 M and 0.78 M) in THF were prepared. All reactions were carried out in 15-ml bottles fitted with a rubber septum cap at 25°C. A 2-ml sample of 0.78 M benzonitrile (1.56 mmole) and 0.74 M benzophenone (1.48 mmole) solutions were allowed to react with 5 ml of each of the above Grignard reagents for 5 days and 13 hours, respectively. Glpc analyses showed that the fluoro and bromo Grignard reagents gave the same products.

Oxygen and carbon dioxide were injected via a 50-ml syringe into separate bottles each containing 5 ml of hexylmagnesium fluoride solution. The reactions were exothermic and were stopped when gas absorption ceased.



GlpC analyses showed the reaction of oxygen gave hexanol quantitatively and carbon dioxide gave 19% heptanoic acid.

## CHAPTER III

## RESULTS AND DISCUSSION

For the direct synthesis of difficulty formed Grignard reagents three modification of the usual procedure for reacting an organic halide with magnesium have been employed: (1) use of a stronger coordinating solvent, (2) application of higher reaction temperatures and (3) activation of the magnesium metal.<sup>14</sup> The third method consists of activation of the magnesium by reduction of the size of the metal particles or by chemical reaction. The Gilman catalyst (a combination of magnesium and iodine) is a well known example of chemical activation. Ethyl bromide or ethylene bromide is also used in catalytic amount to activate the magnesium surface and in molar quantities as an entrainer. Using a combination of all three methods (solvent, temperature and catalyst), we have been able to prepare for the first time alkylmagnesium fluorides conveniently and in high yields (eq.4). The following facts are most certain evidences for the formation of the alkylmagnesium fluorides. First, elemental analyses show that the solutions produced on reaction of alkyl fluorides and magnesium contains C-Mg, Mg and F in the ratio of approximately 1:1:1. Second, the formation of the C-Mg bond is indicated by both ir and nmr spectral analysis and by the alkylating properties of the solutions. And third, molecular association studies show a behavior different from that of organomagnesium chlorides, bromides and iodides.

## Preparation of Organomagnesium Fluorides

### Hexylmagnesium Fluoride

In order to investigate the effect of solvent, catalyst, temperature, reaction time, etc. on the formation of fluoro Grignard reagents from organo fluorides and magnesium, hexyl fluoride was allowed to react with magnesium under a variety of experimental conditions. Hexyl fluoride was chosen for this study since it is a liquid at room temperature and is readily available. During the reactions to be studied, samples were withdrawn periodically. The yield was calculated from the amount of hexane formed after hydrolysis as determined by glpc analysis. At the end of the reaction, the solution was subjected to elemental analyses (total alkalinity, EDTA, fluoride and other halides) and in addition, in some cases, ir and nmr spectra were obtained. The results are summarized in Table 1.

Without a catalyst, no reaction was observed when hexyl fluoride was allowed to react with magnesium in tetrahydrofuran for 13 days (Reaction 1). No reaction occurred even when attempts were made to activate the magnesium by stirring with n-butyllithium in hexane overnight before attempting to initiate the reaction (Reaction 2). Addition of sodium iodide (Reaction 3) or cobalt chloride (Reaction 4) had no effect except after an induction period of seven days when cobalt chloride was used as a catalyst. Although the reaction is slow, the fluoro Grignard compound was produced in 95% yield after 21 days. Addition of a catalytic amount of bromine (Reaction 5), ethylene bromide (Reaction 6) ethyl bromide (Reaction 7) and iodine (Reaction 8) also catalyzed the formation of the fluoro Grignard. In an attempt to decrease the contamination of

Table 1. Preparation of Hexylmagnesium Fluoride<sup>a,b,c</sup>

Reaction no.	Solvent	Catalyst	Mole % of catalyst <sup>d</sup>	Reaction time, day	% yield <sup>e</sup>	Mg <sub>B</sub> :Mg <sub>T</sub> :F <sup>f</sup>
1	THF	none	0	13	0	
2	THF	n-BuLi <sup>g</sup>	...	9	0	
3	THF	NaI	4.8	11	0	
4	THF	CoCl <sub>2</sub>	2.1	7	0	
				21	95	1.29:1:0.80
5	THF	Br <sub>2</sub>	8	5	72	...:1:0.92
6	THF	BrCH <sub>2</sub> CH <sub>2</sub> Br	1.1	7.5	88	
				22.5	42	1.26:1:0.84
7a	THF	C <sub>2</sub> H <sub>5</sub> Br	2.2	5	0	
				14	87	
				22	94	1.60:1:0.44
7b	THF	C <sub>2</sub> H <sub>5</sub> Br	58	1.5	86	
				2.5	91	
				8.0	92	1.24:1:0.76
7c	THF	C <sub>2</sub> H <sub>5</sub> Br	113	1.5	91	
				8.0	96	
				14.0	97	1.30:1:0.91
7d	THF	C <sub>2</sub> H <sub>5</sub> Br <sup>g</sup>	2.6	8.5	51	
				20	63	1.41:1:0.71
8a	THF	I <sub>2</sub>	0.4	24	0	
8b	THF	I <sub>2</sub>	1.3	1.2	48	1.18:1:0.82

(Continued)

Table 1. Preparation of Hexylmagnesium Fluoride<sup>a,b,c</sup>  
 (Continued)

Reaction no.	Solvent	Catalyst	Mole % of catalyst <sup>d</sup>	Reaction time, day	% yield <sup>e</sup>	Mg <sub>B</sub> :Mg <sub>T</sub> :F <sup>f</sup>
					1.8	71
					3.8	95
					5	97
8c	THF	I <sub>2</sub>	4.3	0.3	41	
				0.8	77	
				1.2	92	
				5	97	1.12:1:0.93
8d	THF	I <sub>2</sub>	4.3	6	95	
				14	94	1.06:1:1.06
8e	THF	I <sub>2</sub>	5.7	3	11	
				13	46	
				20	68	
				28	84	
				36	93	1.07:1:0.92
9	THF	n-C <sub>6</sub> H <sub>3</sub> MgF <sup>h</sup>	12.5	2	26	
				6	73	
10	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> O	I <sub>2</sub>		12	95	1.48:1:0.68
			4.3	3	11	
				7	36	
				10	61	
				13	83	1.27:1:0.72

(Continued)

Table 1. Preparation of Hexylmagnesium Fluoride<sup>a,b,c</sup>  
(Concluded)

Reaction no.	Solvent	Catalyst	Mole % of catalyst <sup>d</sup>	Reaction time, day	% yield <sup>e</sup>	Mg <sub>B</sub> :Mg <sub>T</sub> :F <sup>f</sup>
11	DME	I <sub>2</sub>	3.2	0.2	92	
				0.3	95	1.01:1:0.91
12	TMED <sup>i</sup>	I <sub>2</sub>	3.0	0.3	0	
13	TEA <sup>i</sup>	I <sub>2</sub>	5.2	0.3	0	

<sup>a</sup>All reactions run at reflux temperatures and using magnesium turnings except Reaction 8e at room temperature and Reactions 6 and 7d using magnesium powder. <sup>b</sup>Mg/RF = 5.4 except in Reactions 2 and 6 where Mg/RF = 8.9 and 3.2 respectively. <sup>c</sup>Dots indicated no measurement was made. <sup>d</sup>Based on organofluoride. <sup>e</sup>Based on the formation of hexane by glpc analysis. <sup>f</sup>Impurities introduced by catalysts are excluded. Mg<sub>B</sub> = total alkalinity; Mg<sub>T</sub> = total magnesium; F = fluoride. <sup>g</sup>After magnesium was activated, the solution was withdrawn before adding hexyl fluoride. <sup>h</sup>Hexylmagnesium fluoride (10 ml) from Reaction 8b. <sup>i</sup>Dehydrohalogenation occurred.

the product brought about by the addition of a catalyst, hexylmagnesium fluoride from Reaction 8b was used as an activator (Reaction 9). After 12.5 days, 95% yield of soluble magnesium product was obtained, however the reaction was slow and the reaction product exhibited a low Mg:F ratio of 1.0:0.68.

It is interesting to note that no coupling product, dodecane or octane (when ethylmagnesium bromide used as an entrainer) was observed. On the other hand three unidentified peaks were observed by glpc analysis of a hydrolyzed sample of hexylmagnesium fluoride. Except when magnesium powder was used (Reactions 6 and 7d), less than 5% by-product was observed. The amount of by-product did not vary substantially from experiment to experiment regardless of the nature of the catalyst or reaction time (Reactions 7c and 8d).

The best results in tetrahydrofuran solvent were obtained when iodine (4%) was used as a catalyst. Hexylmagnesium fluoride (Mg:F = 1.0:0.93) was produced in 92% yield in only 1.2 days (Reaction 8c). Iodine is not only the most efficient catalyst studied (Table 2), but also the reaction product is less contaminated due to the unusually low solubility of magnesium iodide in tetrahydrofuran. For this reason iodine was selected as the catalyst to be used in subsequent studies involving solvent and temperature effects in the preparation of hexylmagnesium fluoride.

Reference to Table 3 shows that the solvent and reaction temperature have a dramatic effect on the reaction rate. For the same amount of iodine catalyst used, the time required for 90% reaction at reflux temperature became much less as the solvent was changed from diethyl

Table 2. Effect of Catalyst on the Reaction Rate<sup>\*</sup>

Reaction No.	Catalyst	Catalyst (%)	Time (days)
8b	I <sub>2</sub>	1.3	3
6	BrCH <sub>2</sub> CH <sub>2</sub> Br	1.1	6
7a	C <sub>2</sub> H <sub>5</sub> Br	2.2	13
4	CoCl <sub>2</sub>	2.1	20.5

<sup>\*</sup>For 90% reaction of hexyl fluoride with magnesium in THF.



Table 3. Effects of Solvent and Temperature on Reaction Rate<sup>\*</sup>

Reaction No.	Solvent	Temp.	Time, Days
10	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> O	35°	13.5
8c	THF	66°	1.2
11	DME	90°	< 0.2
8e	THF	25°	24
18	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> O	90° **	< 1

\* For 90% reaction of hexyl fluoride.

\*\* Only 25% of hexylmagnesium compound is fluoride.

ether to tetrahydrofuran to 1,2-dimethoxyethane. When the reaction was carried out in tetrahydrofuran at room temperature ( $24^{\circ}\text{C}$ ), the time required for 90% reaction was longer than that required in diethyl ether at reflux temperature ( $35^{\circ}\text{C}$ ). When the reaction was carried out in diethyl ether at  $90^{\circ}\text{C}$  (Reaction 18), the rate was similar to that achieved in tetrahydrofuran at reflux temperature. These results clearly indicated that the reaction temperature, and to a lesser extent solvent, plays an important role in the rate of reaction. Attempts to prepare hexylmagnesium fluoride in N,N,N',N'-tetramethylethylene diamine and triethylamine failed (Reactions 12 and 13). Dehydrohalogenation of hexyl fluoride by these solvents appeared to be a major reaction at reflux temperature.

The data in Table 4 show that although reaction time can be substantially shortened by addition of a larger amount of catalyst, a low optimum catalyst concentration exists beyond which only a slight increase in reaction rate is observed.

#### Phenyl- And Benzylmagnesium Fluorides

All attempts to prepare phenyl- and benzylmagnesium fluorides failed (Reactions 14 and 15 in Table 5). Even in the presence of iodine as a catalyst, fluorobenzene and benzyl fluoride failed to react with magnesium in tetrahydrofuran during a 13-day reflux period.

#### Ethylmagnesium Fluoride

Ethylmagnesium Fluoride was successfully prepared in tetrahydrofuran using iodine as an activator (Reaction 16a). Because of the low boiling point of ethyl fluoride ( $-37.7^{\circ}\text{C}$ ), the conventional apparatus using a Dry Ice condenser under the conditions of tetrahydrofuran reflux was very inconvenient and only 36% of product was obtained due to the

Table 4. Effect of Catalyst Concentration on Reaction Rate\*

Reaction No.	Catalyst	Catalyst (%)	Time (days)
7a	$\text{C}_2\text{H}_5\text{Br}$	2.2	17.5
7b	$\text{C}_2\text{H}_5\text{Br}$	58	2
7c	$\text{C}_2\text{H}_5\text{Br}$	113	1.4
8a	$\text{I}_2$	0.4	$\infty$
8b	$\text{I}_2$	1.3	3
8c	$\text{I}_2$	4.3	1.2

\* For 90% reaction of hexyl fluoride.

Table 5. Preparation of Organomagnesium Fluorides in Ether Solvents  
Using Iodine as a Catalyst<sup>a</sup>

Reaction no.	Organo-fluoride	Solvent	Reaction temp., °C	Mg/RF	Mol % of catalyst <sup>b</sup>	Reaction time, day	% yield <sup>c</sup>	Mg <sub>B</sub> :Mg <sub>T</sub> :F <sup>d</sup>
14a	PhF	THF	66°	3.8	4.4	14	0	
14b	PhF	DME	90°	3.8	4.1	8	0	
15	PhCH <sub>2</sub> F	THF	66°	6.1	4.2	13	0	
16a	C <sub>2</sub> H <sub>5</sub> F	THF	66°	1.2	0.9	2.5	36	1.13:1:0.96
16b	C <sub>2</sub> H <sub>5</sub> F	THF	25°	2.7	1.5	2	13	1.57:1:0
17a	CH <sub>3</sub> F	THF	70°	0.22	0.2	5	0	
17b	CH <sub>3</sub> F	THF	60°	0.88	0.6	3	1.2	1.68:1:··· <sup>e</sup>
17c	CH <sub>3</sub> F	DME	60°	1.4	0.6	0.2	19	1.82:1:0.15
17d	CH <sub>3</sub> F	THF	25°	2.1	1	1.5	95	0.99:1:1.02
17e	CH <sub>3</sub> F	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> O	25°	2.1	1	3	13	2.12:1:0
18	n-C <sub>6</sub> H <sub>13</sub> F	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> O	90°	11	5.5	1	95	1.77:1:0.25

<sup>a</sup>Reactions were carried out in an autoclave except for Reactions 14, 15, and 16a. <sup>b</sup>Based on organo-fluoride. <sup>c</sup>Yield determined by titration. <sup>d</sup>Impurities introduced by catalysts are excluded. Mg<sub>B</sub> = total alkalinity; Mg<sub>T</sub> = total magnesium; F = fluoride. <sup>e</sup>Dots indicate no measurement was made.

escape of ethyl fluoride during the reaction.

Methylmagnesium Fluoride and Other Alkylmagnesium  
Fluorides by Autoclave Techniques

Because of the unusually low boiling point of methyl fluoride ( $-78^{\circ}\text{C}$ ), the synthesis of methylmagnesium fluoride was carried out in an autoclave. The reaction was carried out using excess methyl fluoride since fluoride could be easily removed from the reaction mixture. A reaction was therefore carried out with excess methyl fluoride ( $\text{MeF/Mg} = 4.6$ ) at  $70^{\circ}\text{C}$  for five days (Reaction 17a). However, analysis showed negligible magnesium in solution and glpc analysis of the solution showed more than 25 different components to be present. The reaction was then carried out using a slight excess of methyl fluoride ( $\text{MeF/Mg} = 1.1$ ) at a lower temperature for three days (Reaction 17b). Although glpc analysis of the solution showed only ten peaks, magnesium analyses ( $\text{Mg}_B$  and  $\text{Mg}_T$ ) showed only a very small amount (1.2% yield) of dimethylmagnesium was formed. The failure of these reactions was probably due to the polymerization of methyl fluoride. The reaction was then carried out in 1,2-dimethoxyethane with excess magnesium at  $60^{\circ}\text{C}$  for four hours (Reaction 17c). Although 19% yield of a  $\text{CH}_3\text{-Mg}$  compound was formed, only 15% of this was  $\text{CH}_3\text{MgF}$ . Finally the reaction was successfully carried out with excess magnesium in tetrahydrofuran at room temperature for 1.5 days (Reaction 17d). Methylmagnesium fluoride was obtained in 95% yield. Attempts to prepare methyl- and ethylmagnesium fluorides in diethyl ether using autoclave techniques failed (Reactions 17e and 16b); the reactions were slow and only dialkylmagnesium compounds were obtained. Since the preparation of hexylmagnesium fluoride in diethyl ether is extremely slow, the reaction was carried out at  $90^{\circ}\text{C}$  in an

autoclave. The reaction was indeed accelerated dramatically at higher temperature and gave 95% yield based on soluble magnesium in 24 hours (Reaction 18). However, analyses indicated that the product contained only 25% of the fluoro Grignard.

### Physical Properties

#### Elemental Analyses

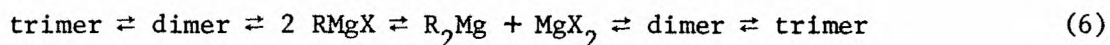
The elemental analyses (Tables 1 and 5) show that the products from the reactions of alkyl fluorides and magnesium contain in most cases a ratio of  $Mg_B:Mg_T > 1$  and a  $Mg:F$  ratio of  $< 1$ . The basic magnesium is obtained by acid-base titration ( $Mg_B$  for  $RMgF = 1$  and  $R_2Mg = 2$ ) and total magnesium is obtained by EDTA analysis ( $Mg_T$  for  $RMgF = 1$  and  $R_2Mg = 1$ ). These results clearly indicate that disproportionation occurs producing a product of low fluoride content and therefore high  $R_2Mg$  content. However, disproportionation was not complete in most cases and usually solutions had a  $Mg_B:Mg_T$  ratio between 1.3 and 1.0. It is presumed that disproportionation took place during the formation step since alkylmagnesium fluorides appear to be very stable in solution once formed. Magnesium analyses showed no change in concentration or  $Mg_B:Mg_T$  ratio for tetrahydrofuran solutions of ethyl- and hexylmagnesium fluoride after four months. Also hexylmagnesium fluoride in diethyl ether showed no change in the  $Mg_B:Mg_T$  ratio after heating at  $85^\circ C$  for 15 days in a sealed tube.

The low  $Mg:F$  ratios are not surprising since disproportionation in Grignard systems is well known. For example, the attempted preparation of organomagnesium iodides in tetrahydrofuran results in the

precipitation of  $\text{MgI}_2 \cdot 6 \text{ THF}$  leaving the dialkylmagnesium compound in solution.<sup>15</sup> The failure of the preparation of methyl- and ethylmagnesium fluoride in diethyl ether is probably due to the complete disproportionation in this solvent resulting in the precipitation of  $\text{MgF}_2$  and solution of the dialkylmagnesium compound which is exactly what was observed. Presumably tetrahydrofuran being a more polar solvent solvates the reaction intermediates better during formation of the Grignard compound and lessens disproportionation. Once the fluoro Grignard compound is formed in either diethyl ether or tetrahydrofuran the compound is stable indefinitely.

#### Ebullioscopic Determination of Molecular Association

The composition of chloro, bromo, and iodo Grignard compounds in solution<sup>16,17</sup> should be considered briefly before discussing the composition of alkylmagnesium fluorides in solution. It is already known that bromo and iodo Grignard compounds exist in diethyl ether as monomeric species at low concentration and that the molecular association increases with concentration (Figure 1). Bromo and iodo Grignard compounds are best represented by an equilibria (eq.6) in diethyl ether in which the association has been shown to exist predominantly through halogen bridge



bonds.<sup>13</sup> On the other hand chloro Grignard compounds are believed to be dimeric over a wide concentration range<sup>13</sup> although some dissociation to monomeric species probably takes place at very low concentration. Whereas chloro, bromo and iodo Grignard compounds are associated in diethyl ether at concentrations  $> 0.1 \text{ m}$ , the same compounds are monomeric in



tetrahydrofuran even at concentrations as high as 2 m (Figure 2).<sup>13</sup>

The radical difference in association in these two solvents presumably results from a stronger coordination of the magnesium atom by tetrahydrofuran as compared to diethyl ether, thus preventing association through halogen bridge bonds. The association of organomagnesium compounds in tetrahydrofuran has been reported recently for alkylmagnesium alkoxides,<sup>18</sup> thio-<sup>19</sup> and aminomagnesium alkyls.<sup>20</sup> The association in tetrahydrofuran is explained on the basis of available electron pairs on oxygen, sulphur and nitrogen interacting with the vacant orbitals of magnesium. Presumably the competition involves stability due to bridge bond formation versus solvate formation. Weak bridge bonds (e.g.  $\text{CH}_3$ , Br) are not formed in tetrahydrofuran due to the greater heat of solvation on reaction of a Grignard species with tetrahydrofuran as compared to the  $\Delta H$  as a result of bridge bonding. However, stronger bridge bonds are apparently formed as the electro-negativity of the bridging atom increases. From this consideration fluorine should be an even stronger bridging atom. Therefore in tetrahydrofuran it is not too surprising that fluoro Grignard compounds associate through stable  $\text{Mg-F-Mg}$  bridge bonds.

Figures 1 and 2 show the association of a number of organomagnesium compounds in diethyl ether and tetrahydrofuran expressed as an  $i$  value (observed molecular weight/calculated molecular weight) plotted against the monoetherate solute concentration (molality). It is very interesting to note that the  $i$  value curves representing hexylmagnesium fluoride in diethyl ether and tetrahydrofuran as well as methyl- and ethylmagnesium fluorides in tetrahydrofuran are clustered around the dimer value ( $i = 2$ ) and display a very small concentration dependent line curvature. On the



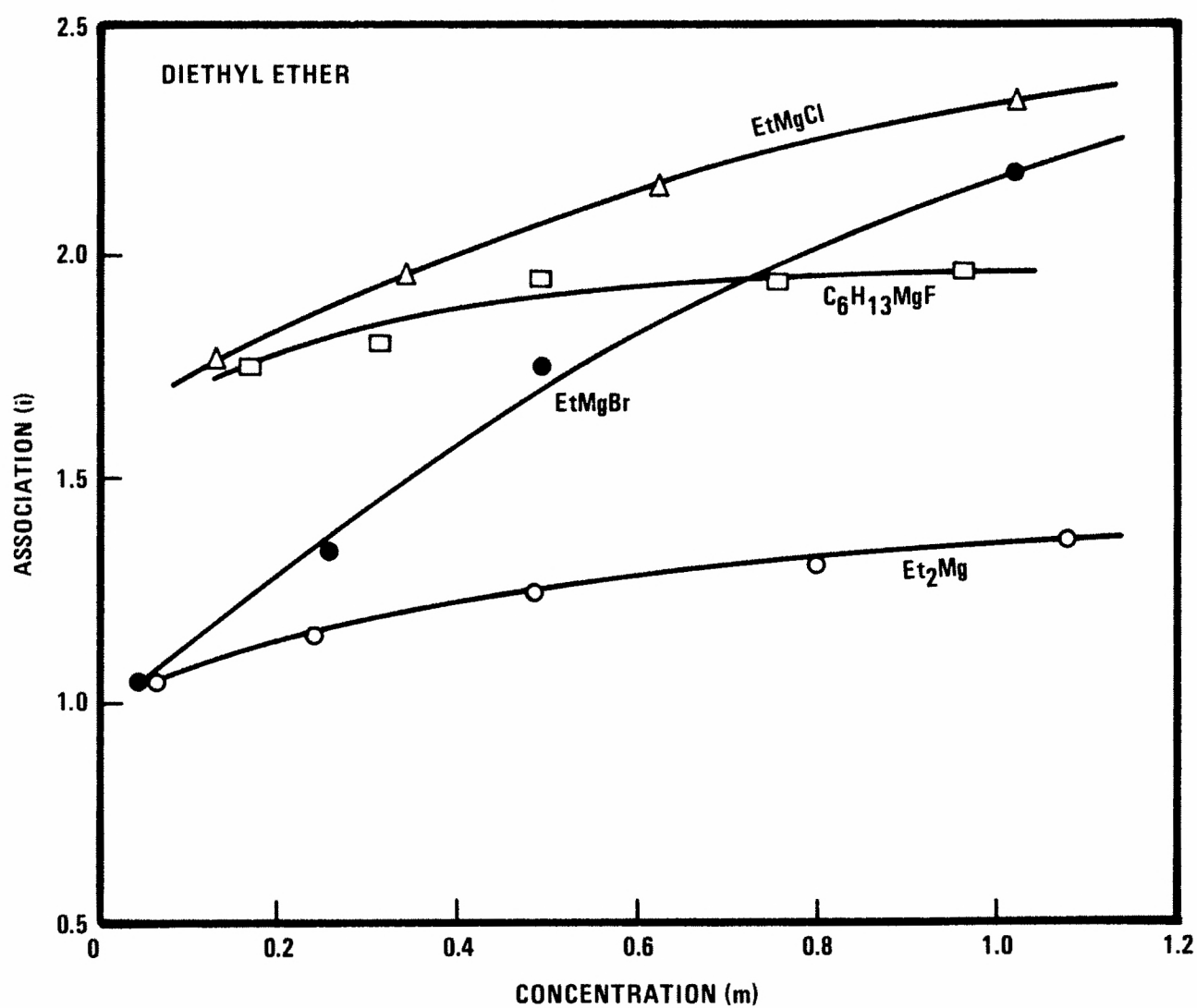


Figure 1. Association of Grignard Compounds in Diethyl Ether.

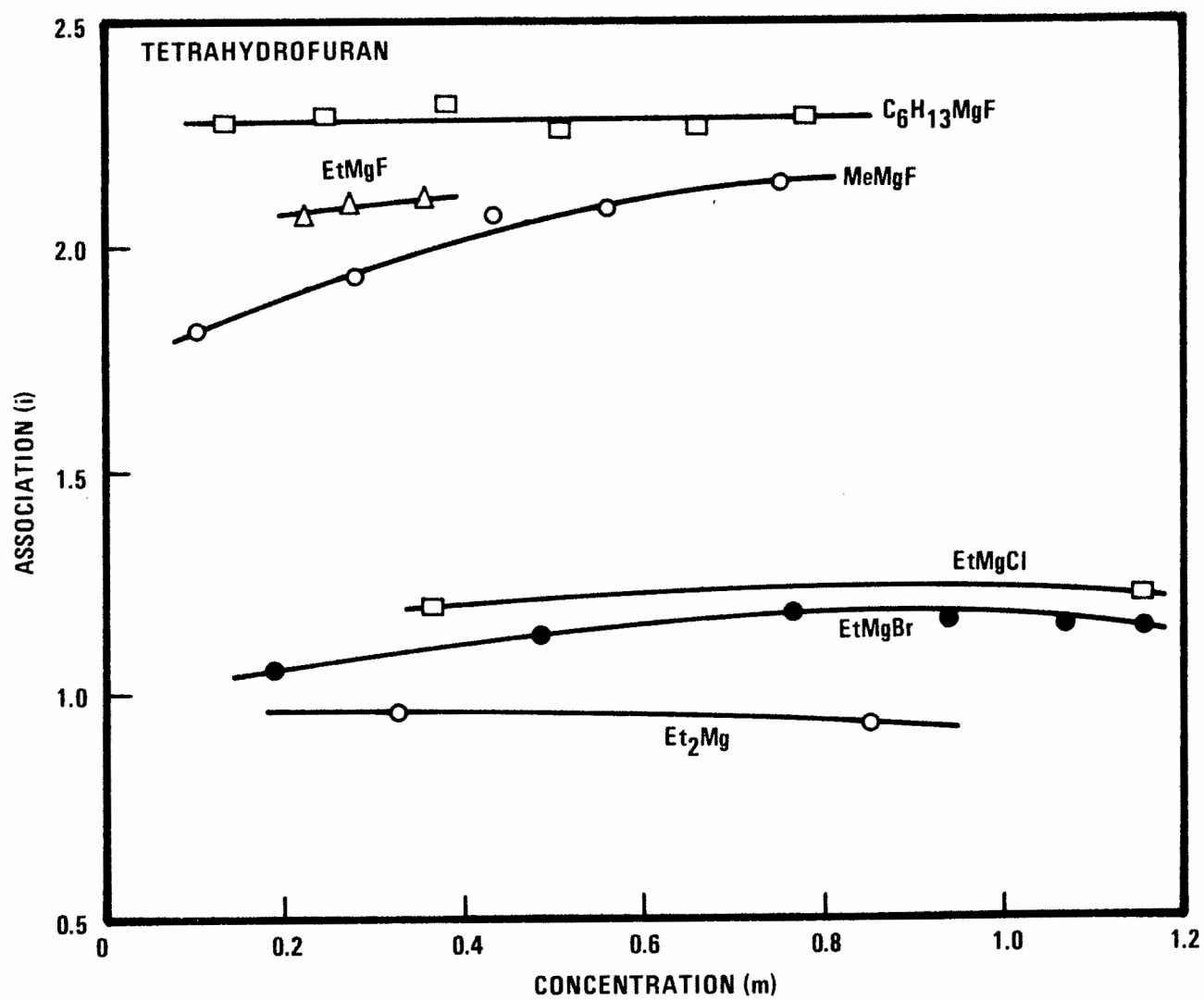


Figure 2. Association of Grignard Compounds in Tetrahydrofuran.

other hand chloro and bromo Grignard compounds in tetrahydrofuran show an  $i = 1$  indicating only monomeric species whereas in diethyl ether association is observed as a function of concentration. The lack of significant curvature in the line plots describing alkylmagnesium fluorides argues against an equilibrium-type association (eq. 6) since the  $i$  values would be expected to increase with an increase in concentration. For this kind of association data, the most obvious interpretation<sup>13</sup> is that alkylmagnesium fluorides are essentially dimeric over a wide concentration range in both diethyl ether and tetrahydrofuran and the slight curvature observed for the  $i$  value curves is due to a deviation of the solutions from ideal behavior, impurities and experimental error. This unusual association data in tetrahydrofuran is the first evidence showing association of organomagnesium halides in this solvent.

#### Infrared Spectra

The infrared spectra of the alkylmagnesium fluorides and related organomagnesium compounds are shown in Table 6. From previous high-resolution infrared studies,<sup>15</sup> the absorption band between 500 and 535  $\text{cm}^{-1}$  has been assigned to the C-Mg stretching frequency for alkylmagnesium compounds in diethyl ether and tetrahydrofuran. The infrared spectrum of dimethylmagnesium in diethyl ether exhibited a shoulder on the high frequency side of the C-Mg stretching band which is ascribed to  $\text{Mg}-\text{CH}_3-\text{Mg}$  bridge bonds. Since Grignard compounds are monomeric in tetrahydrofuran and organomagnesium halides are associated through the halogen in diethyl ether, a shoulder is not observed in these cases. Examination of Table 6 reveals that all alkylmagnesium fluorides exhibit C-Mg stretching at a frequency between 500 and 535  $\text{cm}^{-1}$ . However, the alkylmagnesium

Table 6. Comparison of Infrared Spectra of Alkylmagnesium Fluorides, Chlorides, Bromides and Dialkylmagnesium Compounds\*

Grignard Compound RMgX		Frequency, $\text{cm}^{-1}$	
R	X	$(\text{C}_2\text{H}_5)_2\text{O}$	THF
$\text{CH}_3$	F		535
	Cl		527
	Br	520	513
	$\text{CH}_3$	525 (593)	535
$\text{C}_2\text{H}_5$	F		505 (560)
	Br	508	500
	$\text{C}_2\text{H}_5$	512	512
$n\text{-C}_6\text{H}_{13}$	F	501 (550)	500 (548)
	$n\text{-C}_6\text{H}_{13}$	501 (551)	

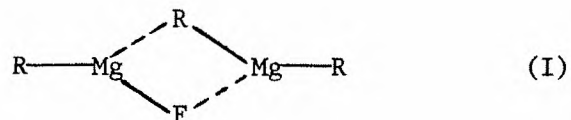
\*

<sup>a</sup> Except for the alkylmagnesium fluorides and dihexylmagnesium, all spectra are from ref. 15.

<sup>b</sup>

Bands as shoulders are given in parentheses.

fluorides, except methylmagnesium fluoride which contained no excess dimethylmagnesium, exhibit a shoulder even in tetrahydrofuran of the type previously observed for dimethyl- and dihexylmagnesium in diethyl ether. Furthermore, the intensity of the shoulder is as function of the  $R_2Mg:RMgF$  ratio. The presence of this shoulder observed in the spectra of ethyl- and hexylmagnesium fluorides is attributed to a mixed alkyl-fluorine bridge species (I). Since the ethyl- and hexylmagnesium fluo-



rides prepared from the corresponding alkyl fluorides and magnesium contains some of the corresponding dialkylmagnesium compound (see preparation), the strong bridging capability of alkylmagnesium fluorides make them capable of associating with one mole of dialkylmagnesium during the preparation even in highly basic tetrahydrofuran.

Unlike the shoulder observed for dimethylmagnesium in diethyl ether, the relative intensity of the shoulder absorption for hexylmagnesium fluoride in tetrahydrofuran is not affected on dilution from 0.4 to 0.08 N. This is additional evidence to argue in favor of a stable dimeric structure I to represent the shoulder band observed in solutions and to argue against an equilibrium-type association (eq.6). Unfortunately, direct observation of the mixed bridge structure I by low temperature nmr using the optimum system,  $(CH_3)_2Mg-CH_3MgF$  was not possible due to the similar proton resonance bands observed for  $(CH_3)_2Mg$  and  $CH_3MgF$  in tetrahydrofuran (Table 8).

### Nuclear Magnetic Resonance Spectra

The nuclear magnetic resonance spectra of alkylmagnesium fluorides are summarized in Table 7. The nmr spectra of all the alkylmagnesium fluorides studied exhibit  $\alpha$ -proton resonance signals upfield from TMS as do all other alkyl Grignard compounds.<sup>21</sup>

Low temperature nmr profiles of several methylmagnesium compounds in tetrahydrofuran are shown in Table 8. The  $\alpha$ -proton resonance signal for dimethylmagnesium shifts from 11.76  $\tau$  at 20°C to 11.83  $\tau$  at -76°C with a small signal at 11.70  $\tau$  attributed to terminal sites in an associated species.<sup>22</sup> The signals of methylmagnesium bromide and chloride are observed at 11.70  $\tau$  and 11.72  $\tau$  respectively at 20°C and approach that of dimethylmagnesium at -100°C due to precipitation of the corresponding magnesium halide at the low temperature. No distinct signals for dimethylmagnesium and methylmagnesium halide are observed in tetrahydrofuran as in diethyl ether.<sup>22</sup> Methylmagnesium fluoride has the same chemical shift as dimethylmagnesium at 20°C. At -100°C only a single signal is observed and at a position similar to that of dimethylmagnesium and the bromo and chloro Grignard compounds. However, unlike the bromo and chloro Grignard compounds, the similarity in chemical shift of methylmagnesium fluoride to that of dimethylmagnesium at low temperature is probably not due to the precipitation of the corresponding magnesium halide. If it were, then the change of the chemical shift for methylmagnesium fluoride should occur at higher temperature for the least soluble magnesium fluoride and magnesium fluoride should remain undissolved on warming since we have shown that magnesium fluoride does not redistribute with dimethylmagnesium to form methylmagnesium fluoride.

Table 7. NMR Spectra of Alkylmagnesium Fluorides\*

RMgF	Solvent	Chemical Shift ( $\tau$ )**
$\text{CH}_3\text{MgF}$	THF	11.76 (0, s)
$\text{C}_2\text{H}_5\text{MgF}$	THF	11.01 (8.2, q)
$\text{C}_6\text{H}_{13}\text{MgF}$	THF	10.55 (7.5, t)
$\text{C}_6\text{H}_{13}\text{MgF}$	$(\text{C}_2\text{H}_5)_2\text{O}$	10.93 (7.4, t)
$\text{C}_6\text{H}_{13}\text{MgF}$	DME	11.03 (7.5, t)

\* For protons on  $\alpha$ -carbon attached to the magnesium atom.

\*\*  
<sup>a</sup> Except methylmagnesium fluoride, all the signals refer to external TMS.

<sup>b</sup> Coupling constants are given in cps and the multiplicities (s = singlet, t = triplet and q = quartet) are given in parentheses.

Table 8. Low Temperature NMR Profile of Methylmagnesium Compounds in Tetrahydrofuran\*

Temp. (°C)	Chemical				Shift (τ)
	(CH <sub>3</sub> ) <sub>2</sub> Mg (0.86 M)	CH <sub>3</sub> MgBr (0.68 M)	CH <sub>3</sub> MgCl (0.49 M)	CH <sub>3</sub> MgF (2.24 M)	
+20	11.76	11.70	11.72	11.76	
-20		11.77		11.76	
-40		11.78	11.77		
-60	11.81	11.80		11.77	
-76	11.70, 11.83				
-100		11.85	11.83	11.82	

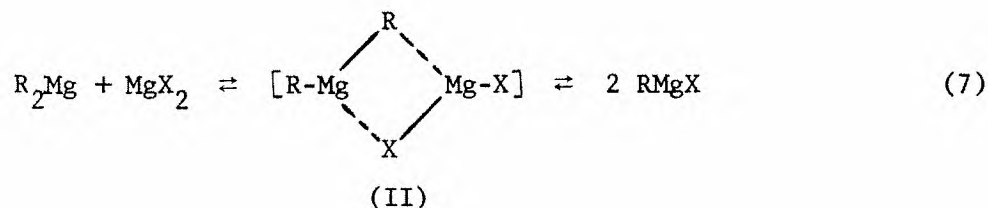
\*<sup>a</sup> Except for methylmagnesium fluoride, all data from ref. 22.

<sup>b</sup> All signals refer to internal TMS.



### Schlenk Equilibrium

The Schlenk equilibrium (eq. 7) is generally accepted as an adequate description of the basic composition of Grignard compounds in diethyl ether and tetrahydrofuran.<sup>13,16,17</sup> The existence of this equi-



librium has been established by association,<sup>13</sup> ir<sup>15</sup> and nmr<sup>22</sup> studies in addition to dioxane precipitation and fractional crystallization studies. The interconversion among the species is suggested to proceed via a mixed alkyl-halogen bridge intermediate II.<sup>23</sup> In triethylamine,<sup>24</sup> redistribution of dialkylmagnesium compounds with magnesium halides takes place; however, fractional crystallization studies have shown that in the case of primary alkylmagnesium chlorides and bromides in triethylamine, RMgX and not MgX<sub>2</sub> species crystallize from solution. Thus it is considered that the Schlenk equilibrium is inhibited simply by changing the nature of the solvent. Since the fluorine atom is a remarkably strong bridging agent in alkylmagnesium fluorides, it would be interesting to know whether or not the Schlenk equilibrium would also be affected by the nature of the bridging agent. Both fractional crystallization and dioxane precipitation studies of hexylmagnesium fluoride demonstrate that precipitation of C<sub>6</sub>H<sub>13</sub>MgF occurs instead of insoluble magnesium fluoride. Because of the insolubility and stronger Lewis acid character of magnesium fluoride, precipitation would be expected either on cooling or on addition

of dioxane if a Schlenk equilibrium exists.

### Chemical Properties

The chemical properties of alkylmagnesium fluorides have also been studied. The fluoro Grignard compounds give the same products as the corresponding bromo Grignard compounds in their reactions with water, oxygen, carbon dioxide, benzonitrile and benzophenone in comparable yields except for the reaction with carbon dioxide. Since it has already been shown that the physical properties of alkylmagnesium fluorides are different from chloro, bromo and iodo Grignard compounds, it was speculated that some differences in the reactions of alkylmagnesium fluorides with organic substrates may be noted.

Examination of Table 9 reveals that the nature of the halogen in the Grignard compound has a strong influence on the course of the reaction with benzophenone. It has been reported that the ratio of addition is proportional to the Grignard reagent:ketone ratio and independent of their concentration.<sup>25</sup> Although the ratio of Grignard reagent to ketone is lower for the fluoro Grignard compound than the bromo Grignard compound, the addition:reduction ratio is greater. The present result is compatible with previous reports that reactions of diisopropyl ketone with n-propylmagnesium halides in diethyl ether<sup>26</sup> and benzaldehyde with ethyl- and sec-butylmagnesium halides in triethylamine<sup>24</sup> give more addition and less reduction as the halide is changed from iodide to bromide to chloride. By comparison of reaction rates for hexylmagnesium compounds, it was found that the fluoro Grignard is more reactive than the bromo Grignard compound. This result is also consistent with the previous report that

Table 9. Reaction of Grignard Compounds with Benzophenone in Tetrahydrofuran

Grignard reagent	RMgX/ketone	Reaction, %	Addn/Reduc
$n\text{-C}_6\text{H}_{13}\text{MgF}$	1.09	67	0.23
$n\text{-C}_6\text{H}_{13}\text{MgBr}$	1.66	61	0.09
$\text{C}_2\text{H}_5\text{MgF}$	1.26	91	0.28
$\text{C}_2\text{H}_5\text{MgBr}$	2.64	96	0.18

the rate of reaction between butylmagnesium compounds and acetone decreases from chloride to bromide to iodide.<sup>26</sup> All results are consistent with the fact that the rate and the ratio of addition to reduction are not only a function of the nature of the halide, but also a function of the positive character of the metal, i.e.,  $\text{Li} > \text{Mg} > \text{Al}$ .

## CHAPTER IV

## CONCLUSIONS

Alkylmagnesium fluorides have been prepared in high yield by the reaction of alkyl fluorides with magnesium in ether solvents in the presence of specific catalysts. The reaction rate was found to depend significantly on the solvent, reaction temperature and catalyst. The best solvents for the reaction were found to be tetrahydrofuran and dimethoxyethane and the best catalyst found was iodine. Under conditions of atmospheric pressure reflux using iodine as a catalyst, hexylmagnesium fluoride was produced in 90% yield in 14 days in diethyl ether, in 92% yield in 1.2 days in tetrahydrofuran and in 95% yield in four hours in dimethoxyethane. Under the most favorable conditions fluorobenzene and benzyl fluoride failed to react with magnesium.

Although alkylmagnesium chlorides, bromides and iodides are monomeric in tetrahydrofuran over a wide concentration range, ebullioscopic studies reported herein show that alkylmagnesium fluorides are dimeric in diethyl ether and tetrahydrofuran over the same concentration range. Low temperature nmr, ir, fractional crystallization and dioxane precipitation studies indicate that the Schlenk equilibrium used to describe the chloro-, bromo- and iodo Grignard systems is not operable in the case of alkylmagnesium fluorides. The unique physical properties of alkylmagnesium fluorides are rationalized on the basis of strong Mg-F-Mg bridge bonds. Alkylmagnesium fluorides react with  $H_2O$ ,  $O_2$ ,  $CO_2$ ,  $PhCN$  and  $Ph_2CO$  in a manner similar to the corresponding bromo Grignard compound.

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## PART III

THE STEREOSELECTIVITY OF ORGANOMAGNESIUM AND  
ORGANOALUMINUM ALKYLATION REACTIONS



## CHAPTER I

## INTRODUCTION

Background

The steric course of alkylation and metal hydride reduction reactions involving cyclic ketones is a very interesting problem for both theoretical and synthetic organic chemists. It was originally proposed by Dauben and co-workers<sup>1</sup> that the course of hydride reduction reactions is determined primarily by the relative stabilities of the two isomeric products in the absence of significant steric influence involving the attacking reagent on the substrate. However, when steric influences are sufficiently large, the reaction path can change from axial attack to equatorial attack producing the less stable isomer. These reaction paths are termed "product development control" and "steric approach control," respectively. As shown in Table 1, for additional reactions involving 4-*t*-butylcyclohexanone, the relative amount of the *cis*-alcohol obtained from equatorial attack increases as the size of the entering groups increases.

An alternate explanation based on pure steric approach has been suggested.<sup>4</sup> For a small entering group which does not interfere with the 3,5 axial substituents, the reaction will be directed exclusively by the 2,6 axial substituents which hinder equatorial attack. However, as the size of the entering group becomes larger, the interactions with 3,5 axial substituents increase and the reaction proceeds in favor of equatorial attack. This proposal was later supported and advanced by

Table 1. Addition Reactions to 4-t-Butylcyclohexanone<sup>a</sup>

Reagent	A <sup>b</sup>	cis-alcohol, %
$\text{LiAlH}_4$	0	8 <sup>c</sup>
$\text{LiAlH}[\text{OC}(\text{CH}_3)_3]_3$	0	10 <sup>d</sup>
$\text{HCN}$	0.17	10 <sup>e</sup>
$\text{HC}\equiv\text{CH}$	0.18	11 <sup>f</sup>
$\text{CH}_2=\text{CHCH}_2\text{MgBr}$		48 <sup>g</sup>
$\text{CH}_3\text{MgBr}$	1.70	65 <sup>h</sup>
$\text{C}_2\text{H}_5\text{MgBr}$	1.75	69 <sup>i</sup>
$n\text{-C}_3\text{H}_7\text{MgBr}$		74 <sup>g</sup>
$(\text{CH}_3)_2\text{MgBr}$	2.15	82 <sup>i</sup>
$(\text{CH}_3)_3\text{CMgBr}$	74.2	100 <sup>i</sup>

<sup>a</sup>In  $(\text{C}_2\text{H}_5)_2\text{O}$  except for  $\text{HCN}$  and  $\text{HC}\equiv\text{CH}$ . <sup>b</sup>See ref. 2. <sup>c</sup>See ref. 3.

<sup>d</sup>See ref. 4. <sup>e</sup>See ref. 5. <sup>f</sup>See ref. 6. <sup>g</sup>See ref. 7. <sup>h</sup>See ref. 13.

<sup>i</sup>See ref. 8.

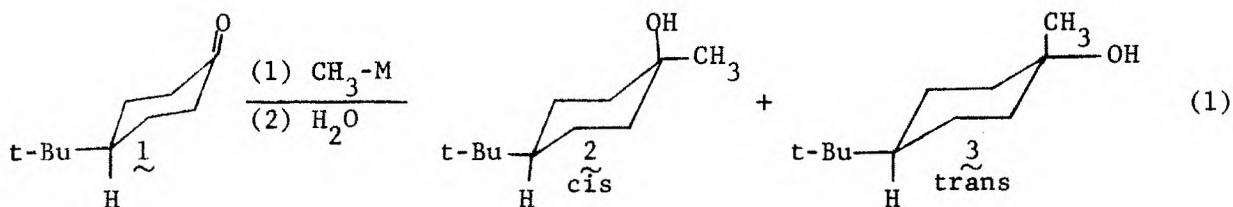
a consideration of the transition state geometry.<sup>9</sup> The relative magnitudes of the interaction of 3,5 and 2,6 axial substituents with the entering group is purely based on the transition state bond lengths, i.e., the extent of axial attack will increase as the bond distance decreases. Therefore, the greater domination by the 3,5 axial substituents in the case of Grignard alkylation reactions can be rationalized on the basis that the transition state for the addition of a Grignard reagent occurs at a greater distance from the carbonyl carbon than the analogous addition of the hydride. More recently, the relative magnitudes of "torsional strain" with respect to equatorial attack and of "steric strain" with 3,5 axial substituents with respect to axial attack in the reaction-like transition state were claimed to be the major factors controlling the stereochemistry of hydride reduction and alkylation reactions.<sup>7</sup> In the reactions between hydrides and unhindered cyclohexanones, the "steric strain" in axial attack is expected to be smaller than the "torsional strain" in equatorial attack, therefore the predominant alcohol is the equatorial one from axial attack. However, as the "effective bulk" of the entering groups or the 3,5 axial substituents become larger, the situation is reversed. It has also been pointed out that the "effective bulk" of the entering reagent depends not only on the "intrinsic bulk" but also on solvation, the bond distance in the transition state and the mechanism of the reaction.

#### Purpose

Although organometallic alkylation reactions have found extensive application in synthesis, this type of reaction has attracted much less attention in comparison with metal hydride reduction reactions with

respect to stereochemical studies. In view of the recent better understanding of both the composition of organometallic compounds in solution and the mechanisms of organometallic alkylation reactions, we feel that a better understanding of the stereochemistry of such reactions is now possible. Hopefully, a better understanding of the stereochemistry of these reactions will bring new and exciting developments to a field which is already considered well "worked over."

An ideal system for investigating the stereochemistry of organometallic alkylation reactions involves the reaction of 4-*t*-butylcyclohexanone (**1**) with trimethylaluminum and methyl Grignard reagents. Studies involving Grignard reagents are desirable because of the side scope and versatility of these reagents and studies involving trimethylaluminum are desirable since this reagent is soluble in both ether and hydrocarbon solvents and thus solvent effects can be evaluated. As shown in equation 1, the reaction gives a mixture of *cis*- and *trans*-methyl-4-*t*-butylcyclohexanol (**2** and **3**), in which the hydroxyl function is either axial or equatorial. Since alkylation reactions involving trimethylaluminum can give no reduction product and involve only one of



the methyl groups,<sup>10,11</sup> results involving this compound should provide the least complicated data. Furthermore, the mechanisms of trimethylaluminum addition to ketones are well understood both in benzene<sup>10</sup> and in diethyl ether.<sup>11</sup> This reaction is known to proceed via two distinct

mechanisms depending on the ratio of  $R_3Al$ :ketone. At 1:1 ratio (or less) the reaction is described by a four-center transition state whereas at 2:1 ratio (or greater) the reaction is described by a six-center transition state. Thus the  $R_3Al$ -ketone system is ideal for comparing and evaluating the resulting stereochemistry of a four-center and a six-center transition state.

In addition numerous stereochemical addition studies<sup>8,12,13,14,15</sup> have already been carried out using ketone 1, which should make the present studies easier to interpret. Although the importance of the solvent involved in these reactions is well recognized, it is surprising that systematic studies of the solvent effect on stereochemical addition are very limited. Therefore, the reaction of trimethylaluminum and ketone 1 in several selected solvents was undertaken. Since methylmagnesium fluoride has recently been prepared in this laboratory in tetrahydrofuran and shows unique properties,<sup>16</sup> it was decided to investigate the behavior of this particular reagent and other Grignard reagents toward 4-t-butylcyclohexanone under the same conditions involving alkylation with trimethylaluminum. Since trimethylaluminum is known to react with ketones by two different mechanistic paths in benzene solvent, the determination and comparison of cis:trans alcohol ratios obtained via each mechanistic path and further comparison with ratios found for Grignard reagent alkylation was considered to be most important.

## CHAPTER II

### EXPERIMENTAL

#### Chemicals

Trimethylaluminum was obtained from Texas Alkyls, Inc. and was purified by distillation under vacuum through a 1-ft packed column, taking the center cut for the present studies. 4-t-Butylcyclohexanone (Frinton Lab.) was distilled under vacuum and its purity was estimated by glpc to be at least 99.9% pure. Tetradecane (99.9% pure, Chemical Samples Co.) was used as an internal standard in the glpc analyses. Methylmagnesium fluoride was prepared as described previously.<sup>16</sup> Clear and colorless solutions of methylmagnesium chloride and bromide were prepared by reaction of methyl halides with magnesium turnings (doubly sublimed, Dow Chemical Co.) in tetrahydrofuran. Dimethylmagnesium was prepared from the corresponding mercury compound by reaction with magnesium metal.<sup>17</sup> Benzene, hexane, diethyl ether, tetrahydrofuran (THF), diphenyl ether and triethylamine were distilled from lithium or sodium aluminum hydride prior to use.

#### Analyses

The concentrations of trimethylaluminum solutions were determined by hydrolysis of an aliquot followed by aluminum analysis. Aluminum analysis was carried out by EDTA-zinc acetate titration at pH 4 using dithizone as an indicator. The concentrations of Grignard reagent solutions were determined by hydrolysis of an aliquot followed by



magnesium analysis. Magnesium analysis was carried out by EDTA titration at pH 10 using Eriochrome Black T as an indicator.

Glpc analyses were performed using 6-ft matched columns of 10% FFAP on 80-100 mesh Diatoport S. The identity of the peaks was determined by comparison of the products formed on reaction of ketone 1 with methyllithium and methylmagnesium bromide.<sup>15</sup> Under the conditions of flow rate, 55 ml/min; injection temperature, 200°C and detector temperature, 310°C; the retention times for tetradecane, cis-alcohol, ketone and trans-alcohol are 12, 28, 31 and 36 min at a column temperature of 80°C. Analyses were carried out on the hydrolyzed samples and no correction was made for mass balance. In no case was the presence of 1-methyl-4-t-butylcyclohexene (from the dehydration of the alcohols) detected.<sup>15</sup> The two alcohols are known to have the same response ratio.<sup>18</sup> The amount of the recovered ketone was calculated from the area ratio of ketone to internal standard before and after the reaction.

### Reactions

All the reactions were carried out under a nitrogen atmosphere and the glassware was flash flamed and flushed with nitrogen prior to use. The standard solutions of trimethylaluminum and 4-t-butylcyclohexanone in benzene and in THF were stored in a heavy-walled glass bulb sealed with a three-way Teflon stopcock. The reactions were carried out in 15-ml bottles fitted with a rubber septum cap.

The following standard procedure will serve to illustrate the reactions in benzene. A 1.6-ml standard benzene solution of trimethylaluminum (0.985 M, 1.58 mmole) was added via a syringe into a bottle containing 3 ml of benzene. The bottle was then placed in a constant

temperature bath at 25°C. A 1-ml standard benzene solution of ketone 1 (0.479 M, 0.479 mmole) with internal standard was introduced at a very slow rate. After the reaction was completed, the solution was cooled in an ice bath and slowly hydrolyzed with 2 ml of saturated ammonium chloride solution. Analysis was carried out by glpc as previously described. When more than two samples were required to examine the reactions, the reactions were carried out in a glass bulb fitted with a three-way Teflon stopcock using a larger amount of the reaction solution and withdrawing samples at appropriate time intervals. Since the reactions were fast in benzene, the inverse addition (addition of trimethylaluminum to ketone) was applied when the reactions were carried out in excess ketone. The reactions in THF were carried out as in benzene. Since the reaction is slow in THF, the order of the addition is not important. The same procedure was followed for solvent studies except that the solvents (THF,  $(C_2H_5)_2O$ ,  $(C_6H_5)_2O$  or  $(C_2H_5)_3N$ ) were introduced into the bottle containing benzene solution of trimethylaluminum at 0°C before addition of the ketone solution at 25°C. The reactions of methylmagnesium compounds were carried out in a similar fashion.



## CHAPTER III

## RESULTS

The results of the reactions of 4-t-butylcyclohexanone with trimethylaluminum and methylmagnesium compounds are summarized in Tables 2 and 3. The following observations can be noted by examination of the tables.

1. The stereochemical results of the reactions of trimethylaluminum in benzene and in diphenyl ether are dependent on the ratio of trimethylaluminum to ketone. The amount of cis-alcohol decreases from 61% to 10% in benzene and from 72% to 15% in diphenyl ether as the  $(\text{CH}_3)_3\text{Al}:\text{ketone}$  ratio increases. On the other hand, the stereochemical results in diethyl ether and tetrahydrofuran are independent of the  $(\text{CH}_3)_3\text{Al}:\text{ketone}$  ratio and give 72-74% yield of cis-alcohol in both solvents. The reactions of  $(\text{CH}_3)_3\text{Al}$  and ketone in triethylamine give no additional product.

2. The presence of a weakly coordinating solvent, such as benzene (Runs 14 and 15), or addition of a free radical promoter,  $\text{CoCl}_2$  (Run 24), in the reactions of  $(\text{CH}_3)_3\text{Al}\cdot\text{THF}$  or  $(\text{CH}_3)_2\text{Mg}\cdot\text{THF}$  with ketone has no effect on the stereochemical results.

3. The stereochemical results of the reactions of methylmagnesium compounds in THF were also independent of the ratio of reactants and the yield of cis-alcohol (71-75%) was essentially independent of the particular methylmagnesium compound used. Reaction of dimethylmagnesium with ketone in triethylamine gave results similar to those

Table 2. Reactions of 4-t-Butylcyclohexanone with Trimethylaluminum

Solvent	Run	$(\text{CH}_3)_3\text{Al}$ ketone	Concn of $(\text{CH}_3)_3\text{Al}$ (M)	Time	Recovery of ketone (%)	Total yield of alcohol products (%)	Yield of cis- alcohol (%) <sup>a</sup>
Benzene	1	6.58	0.506	12 hr	0	89	11
	2	3.29	0.281	12 hr	0	87	10
	3	2.00	0.476	15 min	6		17
				24 hr	7	_b	15
	4	1.50	0.443	15 min	29		40
				24 hr	26	_b	41
	5	1.00	0.388	15 min	50		61
				24 hr	45	_b	61
	6	0.50	0.283	15 min	75		61
				24 hr	56	_b	61
Hexane	7	4.50	0.54	2 hr	0	90	9
$(\text{C}_6\text{H}_5)_2\text{O}^c$	8	3.08	0.329	6 day	0	99	15
	9	1.54	0.269	5 day	3	70	26
	10	1.03	0.228	6 day	23	56	53
	11	0.79	0.176	4 min	49	39	72
				5 day	33	37	72
	12	0.49	0.116	6 day	21	30	72
THF	13	3.02	0.211	3 day	53	12	74
				38 day	20	16	73
	14	2.94	0.308	3 day	55	15	74 <sup>c</sup>
	15	1.03	0.164	3 day	55	10	72 <sup>c</sup>
	16	1.00	0.176	3 day	53	8	73
	17	0.50	0.042	16 day	35	5	73
				38 day	26	7	73

(Continued)

Table 2. Reactions of 4-t-Butylcyclohexanone with Trimethylaluminum  
(Continued)

Solvent	Run	$(\text{CH}_3)_3\text{Al}$ ketone	Concn of $(\text{CH}_3)_3\text{Al}$ (M)	Time	Recovery of ketone (%)	Total yield of alcohol products (%)	Yield of cis- alcohol (%) <sup>a</sup>
$(\text{C}_2\text{H}_5)_2\text{O}^c$	18	3.01	0.329	4 day	38	40	75
	19	0.51	0.141	4 day	20	23	74
$(\text{C}_2\text{H}_5)_3\text{N}^c$	20	3.08	0.329	6 day	31	0	_b
	21	1.03	0.228	6 day	19	0	_b
	22	0.49	0.116	6 day	21	0	_b

<sup>a</sup>Normalized %: % trans + % cis = 100.

<sup>b</sup>No measurement was made.

<sup>c</sup>The reactions were carried out using benzene solutions of  $(\text{CH}_3)_3\text{Al}$  and ketone containing the polar solvent.

Table 3. Reactions of 4-t-Butylchyclohexanone with Methylmagnesium Compounds

Reagent	Run	Solvent	$\frac{\text{CH}_3\text{MgX}}{\text{ketone}}$	Concn of $\text{CH}_3\text{MgX}$ (M)	Time (hr)	Recovery of ketone (%)	Total yield of alcohol products (%)	Yield of cis-alcohol (%) <sup>a</sup>
$(\text{CH}_3)_2\text{Mg}$	23	THF	3.04	0.25	20	2	98	74
	24	THF	3.04	0.25	20	2	85	75 <sup>b</sup>
	25	THF	0.52	0.06	0.2	75	19	74
					20	53	18	74
	26	$(\text{C}_2\text{H}_5)_3\text{N}$	1.49	0.10	8	20	56	76
	27	$(\text{C}_2\text{H}_5)_3\text{N}$	0.55	0.08	1	34	39	76
					8	23	40	77
	28	Benzene <sup>c</sup>	3.50	0.96	0.5	27	52	72
			0.47	0.15	0.5	48	32	68
$\text{CH}_3\text{MgF}$	29	THF	3.2	0.61	20	1	92	73
	30	THF	0.53	0.17	20	55	29	74
$\text{CH}_3\text{MgBr}$	31	THF	2.8	0.37	20	0	97	70
	32	THF	0.47	0.10	20	42	26	72
$\text{CH}_3\text{MgCl}$	33	THF	3.0	0.49	20	1	100	71
	34	THF	0.52	0.23	20	29	37	71

<sup>a</sup>Normalized %: % trans + % cis = 100.<sup>b</sup>With the addition of 5% of  $\text{CoCl}_2$ <sup>c</sup> $(\text{CH}_3)_2\text{Mg}$  as unsolvated solid.

observed in THF.

4. The isomeric ratios in all reactions studied are independent of reaction time. Consequently, isomer equilibration is not a factor under the conditions of these reactions.

5. The reactions with excess methylmetallic compounds yield predominantly the alcohols with little enolization. However, the reactions with excess ketone and of trimethylaluminum in the more basic solvents appear to produce a considerable amount of higher molecular weight products from aldol condensation.<sup>13</sup>

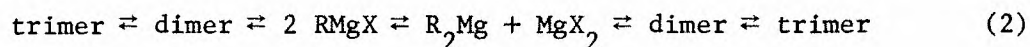
## CHAPTER IV

## DISCUSSION

Composition and Reaction Mechanisms  
of Methylmetallic Compounds

The results of the present and previous studies concerning the stereochemistry of methylmetallic compound addition to 4-t-butylcyclohexanone are summarized in Table 4. If a true understanding of these stereochemical results is to be forthcoming, one should consider in detail the mechanism of the alkylation reactions involved and the nature of the organometallic species present in solution.

The composition of methylmetallic compounds in both hydrocarbon and ether solvents is reasonably well understood at the present time. Methyl lithium is tetrameric in diethyl ether.<sup>19</sup> Methylmagnesium compounds are best represented by an equilibrium-type association (eq. 2)<sup>20,21,22</sup>



in diethyl ether, except methylmagnesium chloride<sup>22</sup> and 3-methylpentyl-3-oxide<sup>23</sup> which are dimeric. All methylmagnesium halides and dimethylmagnesium are monomeric in tetrahydrofuran<sup>22</sup> and triethylamine,<sup>24</sup> except methylmagnesium fluoride which is dimeric in tetrahydrofuran.<sup>16</sup> Trimethylaluminum is dimeric in benzene,<sup>25,26</sup> monomeric in diethyl ether<sup>27</sup> and is expected to be monomeric in tetrahydrofuran and triethylamine and dimeric in diphenyl ether.<sup>28</sup> Dimethylzinc and dimethylcadmium are monomeric in diethyl ether.<sup>29</sup>

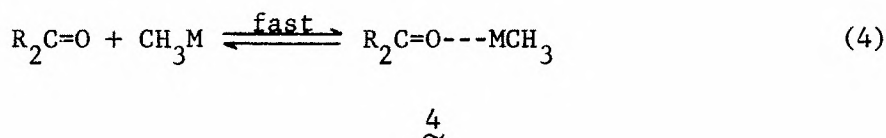
Table 4. Reactions of 4-t-Butylcyclohexanone with Methylmetallic Compounds

Reagent	$(C_2H_5)_2O$		THF	
	Association	Cis-alcohol (%)	Association	Cis-alcohol (%)
$CH_3Li$	4	64 <sup>a</sup>		
$(CH_3)_2Mg$	1-2 <sup>b</sup>	65 <sup>c</sup>	1	74
$CH_3MgF$			2	74
$CH_3MgCl$	2	59 <sup>d</sup>	1	71
$CH_3MgBr$	1-2 <sup>b</sup>	61 <sup>a,c</sup>	1	71
	1 <sup>e</sup>	68 <sup>a</sup>		
$CH_3MgI$	1-2 <sup>b</sup>	54 <sup>a</sup>		
	1 <sup>e</sup>	62 <sup>a</sup>		
$CH_3MgOCCH_3(C_2H_5)_2$	2	74 <sup>c</sup>		
$(CH_3)_3Al$	1	75 <sup>f</sup>	1	73
$(CH_3)_2Zn$	1	38-46 <sup>a</sup>		
$(CH_3)_2Cd$	1	41-54 <sup>a</sup>		

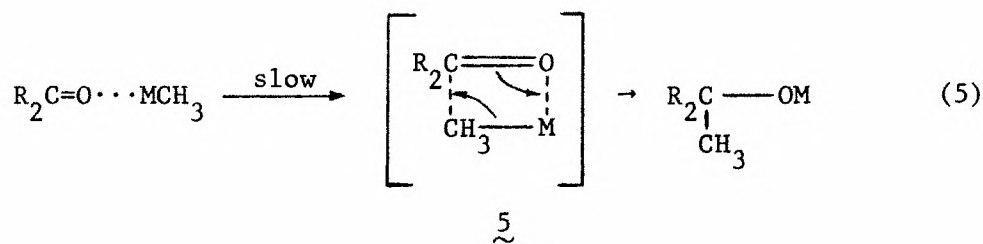
<sup>a</sup>See ref. 15. <sup>b</sup>monomer  $\rightleftharpoons$  dimer equilibrium at the concentrations employed.

<sup>c</sup>See ref. 13. <sup>d</sup>See ref. 12. <sup>e</sup>Monomeric at 0.1 M. <sup>f</sup>Namy et al.<sup>14</sup> reported 75% at 35°C.

Three mechanisms of addition reactions of organometallic compounds with ketones have been proposed from kinetic studies. In spite of the fact that most organometallic compounds are associated in solution, it is believed that it is the monomeric species (in equilibrium (eq. 3) with the associated species) that reacts with the ketone to form a complex 4 in a fast equilibrium step (eq. 4).<sup>10</sup> The product is then formed either by a relatively slow intramolecular rearrangement of the complex presumably via a cyclic four-center transition state 5 (mechanism A) or by a relatively slow attack on the complex by a second molecule of monomeric organometallic species presumably via a cyclic six-center transition state 6 (mechanism B) or by a single electron transfer mechanism involving free radical intermediates (mechanism C).

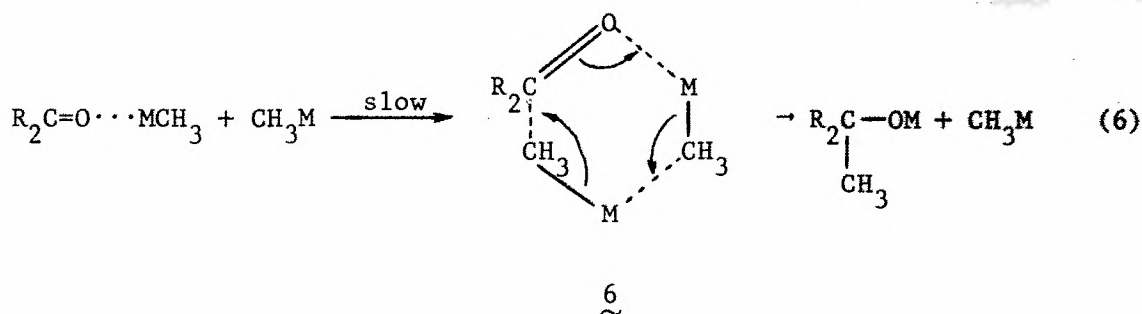


#### Mechanism A

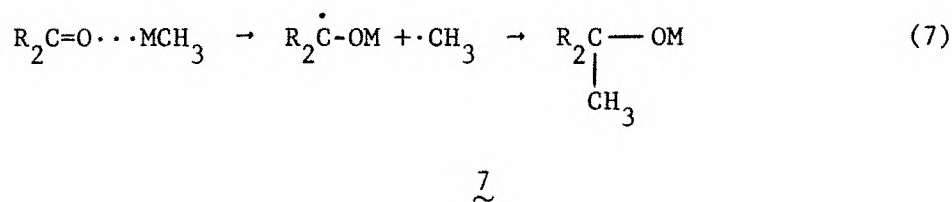




## Mechanism B



## Mechanism C



Compared to most organometallic alkylation reactions the mechanism of aluminum alkyl addition to ketones seems to be well understood. The reaction path in benzene is dependent on the ratio of reactants. The reaction proceeds entirely via mechanism A when the aluminum alkyl:ketone ratio is 1:1 or less and entirely via mechanism B when the aluminum alkyl:ketone ratio is 2:1 or greater.<sup>10</sup> However, the same reaction in diethyl ether proceeds via mechanism A independent of the ratio of reactants.<sup>11</sup> Since the reaction of organomagnesium compounds with ketones has proven to be very complex kinetically for a number of reasons, the mechanism has been the subject of considerable controversy for a number of years. Although the existence of mechanism C as a major pathway has been

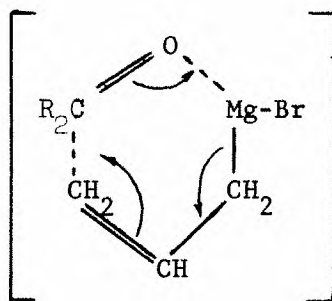
over-ruled at least in the case where ultrapure magnesium metal is used to prepare the organomagnesium reagent,<sup>30</sup> presumably using Grignard grade turnings to prepare the reagent can result in the reaction proceeding via mechanism C to a significant degree. Since mechanism C presumably represents a side reaction and not a major reaction pathway, only mechanisms A<sup>31-36</sup> and B<sup>37,38,39</sup> will be considered further. Since the reactions of organolithium compounds with ketones are extremely fast, there are few reports concerning detailed mechanistic studies of this reaction and thus the mechanism still remains in doubt.

#### Effect of Transition State on the Stereoselectivity

The results of this investigation are represented by the data in Tables 2 and 3. The reactions of  $(\text{CH}_3)_3\text{Al}$  with ketone 1 in diethyl ether, THF and triethylamine give ~73% of the cis-alcohol (27% axial attack) regardless of the ratio of alkylating agent to ketone. Likewise the reactions of  $(\text{CH}_3)_2\text{Mg}$ ,  $\text{CH}_3\text{MgF}$ ,  $\text{CH}_3\text{MgCl}$  and  $\text{CH}_3\text{MgBr}$  in THF give similar results (~73% cis-alcohol). On the other hand the reaction of  $(\text{CH}_3)_3\text{Al}$  in benzene with ketone 1 gives substantially different results (~10% cis-alcohol or 90% axial attack) when the  $(\text{CH}_3)_3\text{Al}$ :ketone ratio is 2:1 or greater.

The unusual stereochemical results found for the reaction of trimethylaluminum with 4-t-butylcyclohexanone in benzene can be explained on the basis that the reaction has previously been shown to proceed by two distinct paths depending on the  $(\text{CH}_3)_3\text{Al}$ :ketone ratio; via mechanism A under conditions of excess ketone and via mechanism B under conditions of excess aluminum alkyl. Thus, the two different mechanistic paths

produce substantially different stereochemical results, namely 90% axial attack when the  $(\text{CH}_3)_3\text{Al}$ :ketone ratio is 2:1 or greater (mechanism B) and 39% axial attack when the ratio is 1:1 or less than 1:1 (mechanism A). A previous report<sup>7</sup> concerning the stereochemistry of reactions of ketone 1 with similar "intrinsic bulk" reagents, allyl- and n-propylmagnesium bromides, indicated that the "effective bulk" of allylmagnesium bromide was found to be much less by proceeding through a cyclic six-center transition state 7.<sup>40</sup> In this reaction 48% of the cis-alcohol (52% axial attack) is formed whereas 74% (26% axial attack) is formed using n-propylmagnesium bromide (Table 1). The actual reasons for the unusual stereochemical



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results obtained from the reactions via a six-center transition state are subtle. However, one of the possible reasons involves the flexibility of the resulting six-center transition state (6 and 7) resulting in a minimization of steric interactions. Thus axial attack via 6 or 7 should be a lower energy pathway than that experienced via 5, which is presumably the transition state involved in the reactions involving n-propylmagnesium bromide. Clarification of this latter point revolves about the following argument. The results obtained from the reactions of trimethylaluminum

and methylmagnesium compounds in diethyl ether and tetrahydrofuran are independent of the ratio of reactants. Therefore, these reactions presumably proceed via only one mechanism. Furthermore, since the amount of cis-alcohol obtained from these reactions is close to the 75% observed in the reaction of trimethylaluminum in diethyl ether, the present data indicate that the reaction of ketones with Grignard reagents proceeds via mechanism A in spite of the controversial results obtained from previous kinetic studies.<sup>31-39</sup>

The answer to the question as to why the six-center transition produces substantially different stereochemical results than the four-center transition can also be explained by a mechanism involving a transition state in which the cyclohexane ring is in the boat form. In the boat form attack should take place preferentially at the position opposite to the flag pole hydrogen. When the ring flips back to the chair form, the alkyl group is in the axial position and the bulky  $-OAl(CH_3)_2$  group is in the more favorable equatorial position. We have recently determined  $E_a$  for the reaction of  $(CH_3)_3Al$  with benzophenone in benzene in 1:1 ratio to be 19.2 Kcal/mole and in 2:1 ratio to be 10.9 Kcal/mole.<sup>41</sup> Assuming that the boat conformation in a cyclohexanone derivative is of somewhat lower energy (4-5 Kcal/mole) than a cyclohexane derivative (6 Kcal/mole) due to the absence of 1-4 flag pole interactions, the proposal of a boat conformation is well within the existing energy considerations. There seems to be no preference at this time for either the chair or boat mechanisms in the absence of definite information concerning the early or late nature of the transition state. It is believed that similar stereochemical studies using cis-3-methyl-4-*t*-butylcyclohexanone should

definitely resolve this problem. With an axial 3-methyl group in the 4-*t*-butylcyclohexanone system, axial attack would be deterred if the reaction proceeds through the chair conformation and should be relatively undisturbed if the reaction proceeds through the boat conformation.

### The Role of Solvent in Addition Reactions

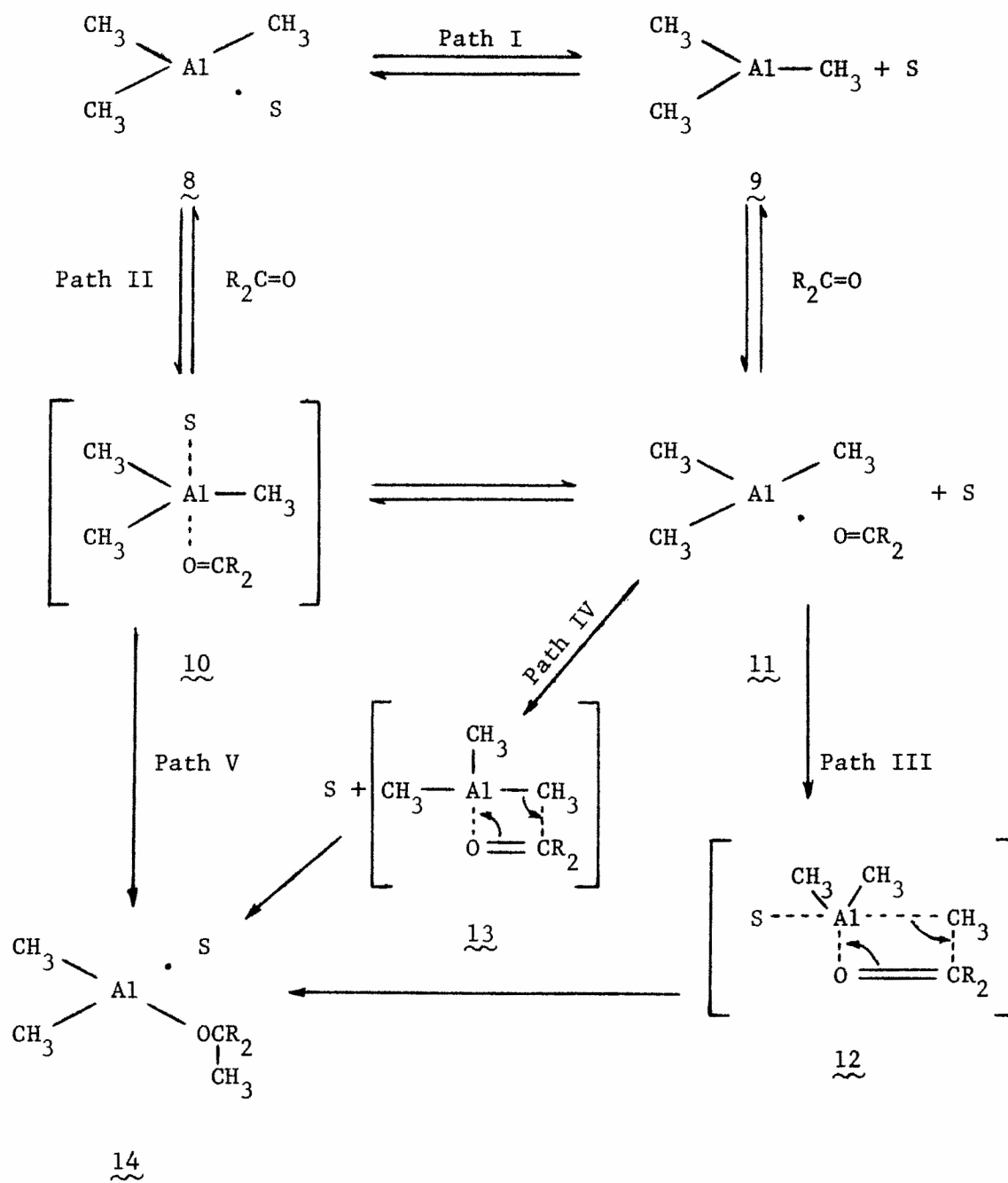
Before discussion of the importance of the solvent in determining the stereochemistry of organometallic alkylation reactions, the number of solvent molecules coordinated to the organometallic compound must be considered. Trialkylaluminum compounds have been investigated by nmr and found to coordinate to only one mole of solvent (THF,  $(C_2H_5)_2O$  and  $(C_2H_5)_3N$ ).<sup>42</sup> A sharp break in the curve produced on plotting chemical shift vs. mole fraction at 1:1 ratio in toluene was observed. Furthermore, the monoetherates of trimethylaluminum and diethyl ether or tetrahydrofuran are distillable under vacuum.<sup>28</sup> Organomagnesium compounds are normally coordinated with two moles of solvent as reported by analysis, molecular weights<sup>43</sup> and nmr<sup>44</sup> studies.

Unfortunately, the role of solvent in the addition reaction is usually neglected in the proposed mechanisms for the sake of simplicity. Recently, however, the importance of solvent in Grignard alkylation reactions has been discussed.<sup>35</sup> Scheme I using trimethylaluminum as the alkylating agent and S as the solvent molecule represents the possible reaction pathways involving alkylation reactions. The solvent ligand can either be dissociated to form the tricoordinated intermediated  $9^*$

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\*The existence of a monosolvated-disolvated equilibrium in dimethylberyllium-dimethylsulfide has been presented through nmr studies.<sup>45</sup> Furthermore, typical organomagnesium compounds are isolated as monoetherates from solution by vacuum drying at room temperature.

Scheme I





(Path I) or be displaced by the ketone via a pentacoordinate transition state 10 (Path II) prior to the formation of the tetracoordinated complex 11. The product 14 can be formed either with or without the presence of solvent on complex 11 by the rearrangement of the methyl group via a four center transition state involving pentacoordinate aluminum 12<sup>\*</sup> (Path III) or tetracoordinate aluminum 13 (Path IV).

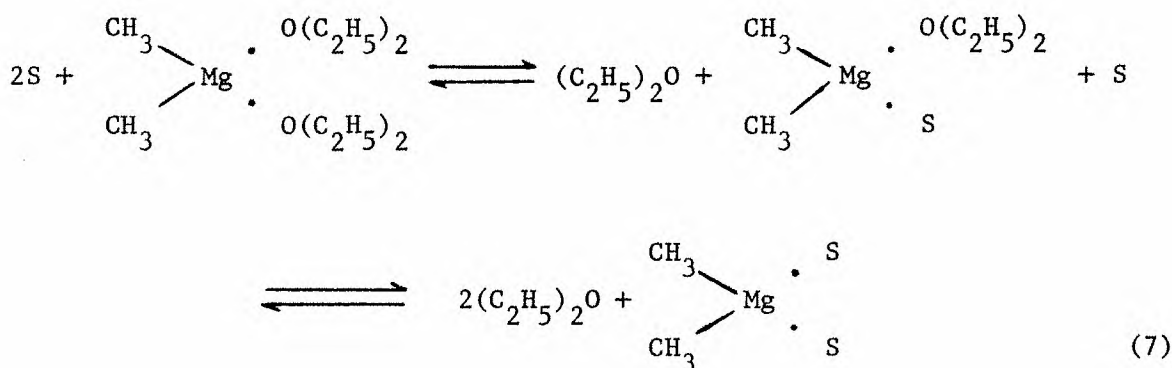
It appears reasonable to expect that the reaction which requires the dissociation or the displacement of the ligand prior to formation of the complex will be retarded by the presence of a good donor solvent. Actually the decrease in reaction rate as the solvent basicity increases has been observed in the addition reactions of Grignard reagents to nitriles<sup>46,47</sup> and aluminum alkyls to ketones,<sup>10,11</sup> and also in the reduction of ketones with Grignard reagents,<sup>48</sup> and abstraction of the acidic hydrogen atom from terminal acetylenes by Grignard reagents.<sup>49</sup>

The effect of solvent on the rate determining product formation step via Path III should be considered in some detail. For example, a strong donor solvent may accelerate the rate of alkyl transfer by assisting the dissociation of the carbon-metal bond in transition state 12. However, in view of the rate retardation observed, if Path III is followed, it is more likely that the nature of the ketone, the metal and the alkyl group have a greater effect on the reaction rate than the solvent. However, the alternative possibility involving formation of a pentacoordinate transition state (10) without dissociation or

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\*Both pentacoordinate transition states 10 and 12 are assumed to be similar to the transition state in a  $S_N2$  reaction, however, the leaving and attacking position of the solvent ligand are different in the two transition states.

displacement of the initial solvating ligand (Path V) has been recently proposed from kinetic studies involving the reaction of benzophenone and dimethylmagnesium.<sup>35</sup> Because the addition of monodentate ligands had little effect on reaction rate except on addition of a large excess of ligand and the addition of the bidentate ligands had a substantial effect either to accelerate or to retard the rate of addition reaction in diethyl ether, it was suggested that only the steric bulk properties of the ligand affects the reaction rate via transition state 10 (Path V). However, the same results can also be rationalized by the mechanisms involving the loss of the initial solvating ligand. Equation 7 shows the exchange of ligands in a diethyl ether solution of dimethylmagnesium.



Since diethyl ether itself is a good donor ligand, the addition of a 1- to 2-fold excess of tetrahydrofuran (a better donor and less bulkier ligand) cannot shift the equilibrium completely to the right. Furthermore, since the equilibrium is expected to be very rapid, the reaction obviously will proceed via the more active diethyl etherate species. Therefore, the significant retardation is only observed with a large excess of tetrahydrofuran. On the contrary, the bidentate ligands form a stable chelated coordination. The addition of a small amount of these



ligands can shift the equilibrium completely to the right and thus show a significant change in the reaction rate. The reasons for the different rates of the reaction with the addition of the bidentate ligands does not seem to be well understood. It is possible that the solvent effect on the product formation step (12) becomes important in the presence of the bidentate ligands. Thus, it appears that the relative magnitude of the solvent effects on the complex and product formation steps determines the acceleration or retardation of the reaction rate.

#### Effect of Solvent on the Stereoselectivity

Although no mechanism has been proposed for the reaction of trimethylaluminum in diphenyl ether, it is obvious from the stereochemical results that the reaction proceeds via two different mechanistic pathways depending on the reactant stoichiometry as was observed in the case of benzene solvent. The weak coordination of trimethylaluminum with diphenyl ether has already been indicated by nmr.<sup>28</sup> Thus it seems that whether or not an alkylation reaction is able to proceed via a six-center transition state 6 depends on the nature of solvent. These results can be rationalized by the necessity of the displacement of a solvent ligand on the second molecule of organometallic compound which attacks complex 4 prior to formation of the product or the greater capability of free ketone to coordinate with the tricoordinate intermediate 9 rather than complex 4 making mechanism B more difficult in the presence of a good donor solvent. Although organo-cadmium and -zinc compounds are unsolvated, the poor capability of association for these types of compounds makes the reactions impossible via six-center transition states.

The amount of cis-alcohol obtained from the reactions of

trimethylaluminum in diethyl ether and tetrahydrofuran is independent of the ratio of reactants (Table 2). Therefore, the reactions in tetrahydrofuran are expected to proceed only via mechanism A as in diethyl ether. It is interesting to note the amount of cis-alcohol obtained from the reaction with excess ketone in diphenyl ether is the same as in diethyl ether and tetrahydrofuran. The fact that the stereochemistry via mechanism A is independent of the nature of the solvent is compatible with the mechanism involving displacement or dissociation of the solvent prior to formation of the product. Without the loss of the solvent (Path V), the amount of cis-alcohol would be expected to increase as a function of the bulk property of the solvent from tetrahydrofuran to diethyl ether to diphenyl ether. The similar stereochemical results obtained from the reaction of  $(\text{CH}_3)_3\text{Al}$  with excess ketone 1 in benzene as compared to the reactions in diethyl ether or THF indicate once again the absence of the solvent ligand in the transition state 13. The stereochemistry of addition in benzene vs. ether solvents (61 vs. 73% axial alcohol) is not indicative of solvent attached to aluminum in the transition state.

The participation of at least one ether ligand in the transition state involving organomagnesium compounds has been indicated by asymmetric induction studies involving the reaction of dimethylmagnesium and benzaldehyde in the presence of an optically active ether.<sup>50</sup> Therefore, after one of the ligands is displaced, the remaining solvating ligand may affect the stereochemistry of addition in the case of organomagnesium compounds. However, the stereochemistry of the addition reactions of 3-t-butylcyclopentanone with methyl-, ethyl- and i-propylmagnesium compound was found to be independent of the solvent (THF,  $(\text{C}_2\text{H}_5)_2\text{O}$  and anisole).<sup>51</sup> In the

present studies only small differences in stereochemistry are observed in the reactions of methylmagnesium compounds in diethyl ether and in tetrahydrofuran and dimethylmagnesium in triethylamine. These results indicate once again that solvent attachment to the metal in the transition state is not important.

Effect of the Identity of the Halide  
and the Metal on the Stereoselectivity

The reaction rate and the product ratio of addition to reduction was found to decrease as the electropositivity of the metal in the organo-metallic compound varies from lithium to magnesium to aluminum and the halide in the Grignard compound varies from chloride to bromide to iodide. It is surprising to find out that the identity of the halide except iodide and the metal except aluminum in diethyl ether has little effect on the stereochemistry of the addition reaction in both tetrahydrofuran and diethyl ether (Table 4). It is most likely that the stereochemistry of alkylation is dependent on pure steric factors and the electronic factor plays only a minor role. Hence, the same stereochemical results do not imply the nature of the actual reacting species involved as suggested in a previous report.<sup>13</sup>

Effect of the Association of Methylmetallic  
Compounds on the Stereoselectivity

Methylmagnesium alkoxide addition to 4-t-butylcyclohexanone has been reported to give a higher cis-alcohol yield than the corresponding methylmagnesium compounds and the reaction was suggested to involve a different reacting species.<sup>13</sup> Indeed, recent kinetic studies from this laboratory concerning the reaction of excess benzophenone with

dimethylmagnesium show that the alkoxide  $[\text{CH}_3\text{MgOC}(\text{CH}_3)(\text{C}_6\text{H}_5)_2]$  is an intermediate reacting species and it reacts as a dimer.<sup>31</sup> This result is compatible with the prediction that the bulkier dimer should give more cis-alcohol.

A recent report suggested that the stereochemistry of addition is a function of the association of the reacting species.<sup>15</sup> Since dimer is bulkier, according to this suggestion the reactions of methylmagnesium bromide and iodide at 0.1M and 0.8M concentration should lead to less cis-alcohol at the lower concentration which is exactly the reverse of the observed results (Table 4). If the dimeric species were to react via a six-center transition state, it would give predominant trans-alcohol. However, in this case the amount of trans-alcohol should be much greater than was observed, since reactions via the six-center transition states 6 and 7 have already been shown to give much more axial attack than reactions via a four-center transition state. Consequently, the difference caused by change in the concentration must be explained with other reasons.

#### Applications of the Present Studies in Organic Synthesis

Concerning the applications of organometallic compounds in the stereoselective alkylation of 4-t-butylcyclohexanone, we have found that in non-coordinating solvents such as benzene axial attack is highly favored (~90%) when the organometallic compound is trimethylaluminum and the ratio of organometallic compound to ketone is 2:1 or greater. On the contrary, in polar solvents a high percentage of equatorial attack is observed. Synthetic applications are not recommended in the

latter case since the reaction is quite slow and the yields of alcohol are low because of enolization and condensation reactions. Thus for the preparation of axial alcohol from equatorial attack, excess methylmagnesium compound in tetrahydrofuran is recommended. These reactions are fast and the yields of alcohol are quantitative. Although reactions of methylmagnesium alkoxides also give satisfactory amounts of axial alcohol, the reactions do not have the first two advantages relating to the reactions of methyl Grignard compound in tetrahydrofuran.

## CHAPTER V

## CONCLUSIONS

The stereochemistry of addition of methylmagnesium and methylaluminum compounds to 4-t-butylcyclohexanone in several solvents has been studied. Specifically methylmagnesium fluoride, chloride, and bromide, dimethylmagnesium and trimethylaluminum were allowed to react with 4-t-butylcyclohexanone in hexane, benzene, diethyl ether, tetrahydrofuran, diphenyl ether and triethylamine. Reactions involving organomagnesium compounds and trimethylaluminum in diethyl ether and tetrahydrofuran result in the predominant formation of the cis-alcohol (~73%) regardless of the halide and the mode of addition. In reactions involving trimethylaluminum in hydrocarbon solvent where the  $(\text{CH}_3)_3\text{Al}:\text{ketone}$  ratio is 1:1 or less similar results are observed. However, when the ratio is 2:1 or greater a drastic reversal of the stereochemistry is observed resulting in the predominant formation of the trans-alcohol (~90%). These results show that in addition to steric effects and torsional strain considerations a most important consideration is the steric requirement and flexibility of the transition state. Thus entirely different stereochemical results are observed in similar reactions depending on the exact nature of the transition state (mechanism).



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He graduated in 1964 from the Department of Chemical Engineering, Tunghai University with a Bachelor of Science degree. After one year's service in the Army ROTC in the Republic of China, he began his graduate work at the Georgia Institute of Technology in 1966. Since that time, he has been conducting research in the field of organometallic chemistry under the direction of Dr. E. C. Ashby.

Mr. Yu was married to Ling Chu in 1967 and they are expecting a baby in the summer of 1971.