

The Mechanisms of Grignard Reagent Addition to Ketones

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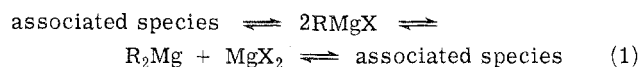
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Grignard reagents represent possibly the most powerful and versatile tool in all of synthetic organic chemistry. Although these reagents have been so important for a long time, a good understanding of the nature of these reagents in solution and the mechanisms whereby they react has been slow to develop. The reasons for this delay are not due to a lack of interest or effort in the past but rather to the complexity of working with systems that are extremely air sensitive and that contain a variety of reactive organometallic and inorganic species in solution. Much of the work involving Grignard reagent composition and reaction mechanisms carried out prior to 1960 has turned out to be either invalid or misleading. More recently, important studies have been made in the area of Grignard reagent solid-state structure and solution composition by Stucky and M. B. Smith and W. Becker in this country, by the French team of Fauvarque, Ducom, and Valino, and the Dutch group of Blomberg and Bickelhaupt. Also since 1960 important contributions have been made in the area of mechanisms of Grignard reagent addition to ketones by S. G. Smith, E. I. Becker, Mosher, and House in this country, by Holm in Denmark, Anteunis and Bruylants in Belgium, and Tuulmets in Estonia. The following Account is our attempt to discuss in summary fashion the mechanisms of Grignard reagent addition to ketones presenting the results of some workers in this area, but focusing mainly on our own contributions.

Although there has been speculation about the mechanism of Grignard reagent addition to ketones since the discovery of the reaction, the use of kinetic studies did not become important until the early 1960's. The first attempts¹⁻³ at quantitative studies of the kinetics of the reaction (determination of the order of the reaction in each reactant, and evalua-

tion of the rate constant) were made with the two reactants in comparable concentrations. Not only was the interpretation of the data hampered by the misunderstanding which existed at that time concerning the composition of Grignard reagents in ether solution, but it was also hampered by the complexity of the later stages of the reaction, a factor unknown at the time. The results of Bikales and Becker^{2,3} provide one of the first clues that the complexity of the reaction in the latter stages was indeed a problem. With the advantage of hindsight it is now quite apparent why experiments of this type, *i.e.*, ones in which the concentrations of the two reactants are comparable, are extremely difficult to interpret.

By 1965 it was apparent that it would be necessary to understand two separate complexities of the reaction of Grignard reagents with ketones: first, the complications at the beginning of the reaction associated with the composition of the Grignard reagent in solution, *i.e.*, the nature of the so-called Schlenk equilibrium and any equilibria involving association



among the various species in solution; second, the structure of and equilibria involving intermediate alkoxide species formed in the later stages of the reaction and the effect of these intermediates on the course of the reaction.

Composition of Grignard Reagents in Ether Solvents. The reactions under discussion take place in solution; thus of first importance is the nature of individual species as well as the equilibria relating these species in the polar solvents used. To clearly identify the major carbon-magnesium species in ether and tetrahydrofuran solutions of Grignard compounds, studies were carried out involving variable-temperature proton nmr. Exchange rates are rapid in diethyl ether and low temperature (-100°) is required before both the CH_3MgBr and $(\text{CH}_3)_2\text{Mg}$ species can be observed in an ether solution of methylmagnesium bromide (Figure 1).⁴ On standing at -105° MgBr_2 precipitates, and the ratio of CH_3MgBr to $(\text{CH}_3)_2\text{Mg}$ decreases. Similar studies with *tert*-butylmagnesium chloride in diethyl ether and tetrahydrofuran show that *tert*-butyl group exchange rates are slower than for the methyl group. Consequently both the $t\text{-C}_4\text{H}_9\text{MgCl}$ and $(t\text{-C}_4\text{H}_9)_2\text{Mg}$ species in diethyl ether are observed at higher temperature (-7°). Exchange rates are even slower in tetrahydrofuran such that the $t\text{-C}_4\text{H}_9\text{MgCl}$

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Dr. Joseph Laemmle was born in Louisville, Ky., and received his B.S. degree from Bellarmine College in Louisville and his M.S. and Ph.D. degrees from Georgia Tech. He is presently Assistant Professor of Chemistry at Kennesaw Junior College. His main area of interest has been kinetics of Grignard reactions.

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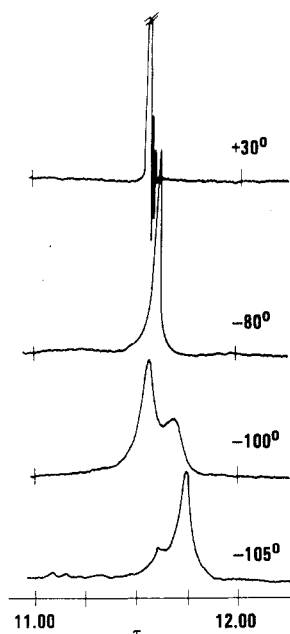
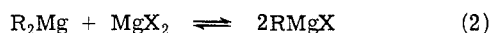


Figure 1. Nmr spectra (100 MHz) of methylmagnesium bromide in diethyl ether.

and $(t\text{-C}_4\text{H}_9)_2\text{Mg}$ species are observed at room temperature.

The presence of associated species is another important aspect of solution composition. Figure 2 shows that typical Grignard reagents and their corresponding R_2Mg counterparts are monomeric in tetrahydrofuran.⁵ Only the more recently reported alkylmagnesium fluorides are dimeric in tetrahydrofuran. On the other hand, it is clear from Figure 3 that Grignard reagents and their R_2Mg and MgX_2 counterparts are associated in ethyl ether.⁵ Alkyl- and arylmagnesium bromides and iodides are apparently associated in a linear polymeric fashion, and a comparison of the association of R_2Mg and MgX_2 compounds indicates that association takes place predominantly through halogen bridge bonds. On the other hand, alkylmagnesium fluorides and chlorides appear to be dimeric over a wide concentration range. The association of Grignard compounds in diethyl ether solvent is an important consideration in obtaining kinetic data on the reaction of Grignard reagents with ketones. Since Figure 3 shows that Grignard reagents are associated at concentrations greater than 0.1 M, it is necessary in kinetic studies to employ Grignard reagents at concentrations below 0.1 M in order to avoid serious complications in the interpretation of kinetic data. Unfortunately, most kinetic studies carried out in the past have employed Grignard reagents at concentrations such that the organomagnesium species were associated.

The Schlenk Equilibrium. Since both R_2Mg and RMgX can react with ketones, knowledge of the Schlenk equilibrium (eq 2) is vital in understanding



the initial stage of the reaction. Table I provides equilibrium constant values for a number of Grignard reagents in both diethyl ether and tetrahydrofuran solvent. The numerical values, determined by

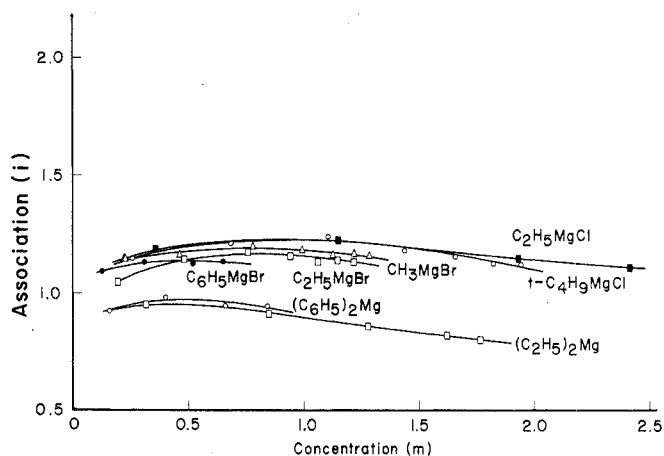


Figure 2. Association of Grignard compounds in tetrahydrofuran.

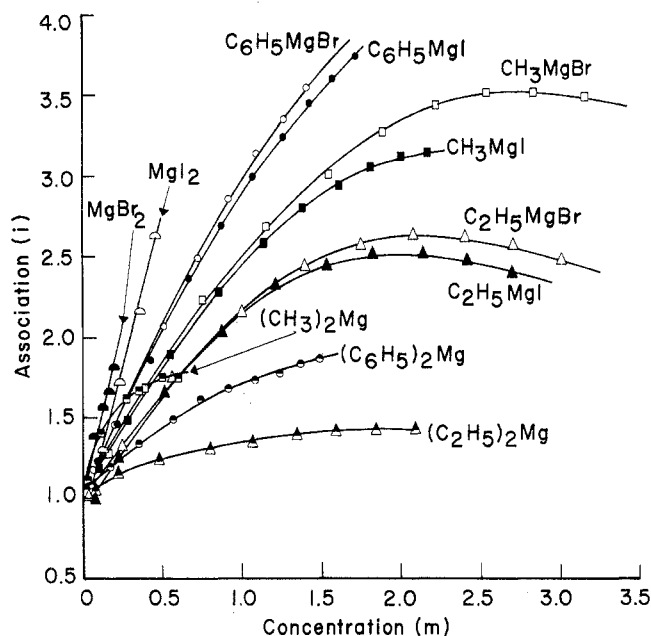


Figure 3. Association of typical Grignard compounds and their R_2Mg and MgX_2 counterparts in diethyl ether.

calorimetric, kinetic, and spectroscopic methods, are of varying degrees of accuracy. In some cases the solutions used were of such concentrations that associated species were undoubtedly present. Even with this limitation, the table displays some rather clear trends. In Et_2O , values of magnitude 10^2 – 10^3 are obtained; in THF, values of 1–10 are most common. Another important feature is the value of ΔH . In diethyl ether the values are negative; in THF the values are positive.

The most accurate values listed for K and the most extensive thermochemical measurements are those of Smith and Becker.⁶ They also measured the enthalpy change on going from the Et_2O solvates to the THF solvates of the species Et_2Mg , EtMgBr , and MgBr_2 , finding values of -4.6 , -7.0 , and -19.1 kcal/mol, respectively. From entropy considerations, they suggested that a larger number of solvent molecules are bound to magnesium when the ether is THF than when it is Et_2O . This conclusion is consistent with other evidence. With MgBr_2 the

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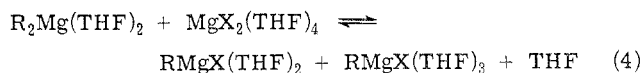
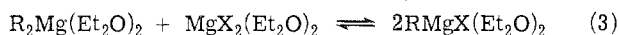
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Table I
Values for Schlenk Equilibrium

Grignard	Solvent	K	Method	ΔH	Reference
CH ₃ MgBr	Et ₂ O	~320	Cal.		21g
		~455	Kin.		15
C ₂ H ₅ MgBr	Et ₂ O	480-484	Cal.	-3.74	6b
C ₄ H ₉ MgBr	Et ₂ O	~10 ³	Cal.	-3.2	21d
		~400	Kin.		21e
C ₆ H ₅ MgBr	Et ₂ O	55-62	Cal.	-2.02	6b
C ₂ H ₅ MgI	Et ₂ O	≥630	Cal.	-4.94	6b
C ₆ H ₅ MgI	Et ₂ O	≥15	Cal.	-2.99	6b
CH ₃ MgCl	THF	4.5	Ir		9
		~1	Nmr		4
C ₂ H ₅ MgCl	THF	5.52	Cal.	3.80	6c
<i>t</i> -C ₄ H ₉ MgCl	THF	1.12	Nmr	9.0	4
C ₆ H ₅ MgCl	THF	1.66	Cal.	2.72	6c
CH ₃ MgBr	THF	3.5	Ir		9
		~4	Nmr		4
C ₂ H ₅ MgBr	THF	5.09	Cal.	6.10	6c
C ₄ H ₉ MgBr	THF	~9	Cal.	3.4	21d
C ₆ H ₅ MgBr	THF	3.77	Cal.	2.82	6c
		4.0	Nmr	3.2	10

etherates MgBr₂·*n*Et₂O (where *n* = 1-3) and MgBr₂·4THF are known.⁷ The same solvation trend is displayed in the solids⁸ MeMgBr·3THF, EtMgBr·2Et₂O and C₆H₅MgBr·2Et₂O.

The evidence available then suggests that the difference in the Schlenk equilibrium in THF and Et₂O is associated with the increased coordination number of the magnesium species in THF, with the dominant effect being associated with the solvation of MgBr₂. The Schlenk equilibrium in the two solvents might then better be represented by eq 3 and 4. The



positive value of ΔH that results in THF leads to smaller values of *K*. In THF all three of the species R₂Mg, RMgX, and MgX₂ are present in appreciable concentration, and quantitative measurements of the equilibrium constant can be made by ir⁹ and nmr.^{4,10}

Mechanisms of Grignard Reagent Addition to Ketones

Complexation of Grignard Reagent with Ketones. The importance of complexation between the ketone and the Grignard reagent has been recognized since speculation about the mechanism of the reaction began. Evidence, some direct and some indirect, for complexation comes from a variety of experiments. The most direct evidence comes from ultraviolet and infrared spectroscopy. Smith¹¹ first reported the appearance of two bands in the ultraviolet spectrum when (CH₃)₂Mg, the methyl bromide Grignard

reagent, or MgBr₂ are added to certain aryl ketones in ethyl ether. The shorter wavelength band is due to the carbonyl group of the uncomplexed ketone, while the longer wavelength band is attributed to the carbonyl group in the complex. Holm¹² has observed that the frequency of the carbonyl band in the ir is sufficiently shifted (25-70 cm⁻¹) so that the complexed carbonyl can be distinguished from the free carbonyl.

Determination of the value of the equilibrium constant for complexation ($K = [\text{complex}]/[\text{ketone}] \cdot [\text{magnesium species}]$) can be accomplished by measurements of the ultraviolet spectra of solutions containing the ketone and the magnesium species. More commonly constants have been determined indirectly from kinetic data, assuming complexation as part of the mechanism, or from a combination of the two methods when the kinetic data have been obtained by spectroscopic means. Table II contains equilibrium constant values that have been obtained by Smith,^{11,13} Tuulmets,¹⁴ and ourselves.¹⁵

Holm¹² has observed that little heat is evolved when magnesium bromide in diethyl ether is mixed with a ketone or an ester. This observation is consistent with the general conclusion¹⁶ that the enthalpies for binding ethers and ketones to a given Lewis acid are generally the same within 10%, assuming the displacement of one molecule of ether by the ketone.

Complexation between Grignard reagent species and ketones is quite unfavorable in THF.^{2,3} Although this is undoubtedly due, in part, to the fact that THF is a stronger base than diethyl ether or ketones, the higher coordination number of magnesium with attached THF molecules may play a part. In many cases the formation of the Grignard-ketone complex in THF may require the displacement of two THF molecules.

The Later Stages of the Reaction. In addition to the complexities associated with the Schlenk equilibrium in terms of several species in equilibrium capable of reaction, it has been appreciated for some time that there are complexities in the reaction course that increase as the reaction proceeds. A large body of evidence suggests that the complexities are due to the presence of the product alkoxide formed throughout the course of the reaction.¹⁷

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Table II
Equilibrium Constants for Complexation with Ketones

Magnesium compound	Ketone	K	Solvent	Reference
MgBr ₂	2,4,6-[(CH ₃) ₂ CH] ₂ C ₆ H ₃ COC ₆ H ₄ OCH ₃ -4	6.5	Et ₂ O	11
CH ₃ MgBr	2,4,6-[(CH ₃) ₂ CH] ₂ C ₆ H ₃ COC ₆ H ₄ OCH ₃ -4	3.7	Et ₂ O	11
(CH ₃) ₂ Mg	2,4,6-[(CH ₃) ₂ CH] ₂ C ₆ H ₃ COC ₆ H ₄ OCH ₃ -4	1.3	Et ₂ O	11
CH ₃ MgBr	2,4-(CH ₃) ₂ C ₆ H ₃ COC ₆ H ₄ SCH ₃ -4	8.4	Et ₂ O	13b
CH ₃ MgBr	4-H ₃ CSC ₆ H ₄ COCH ₃	15.1	Et ₂ O	13d
(CH ₃) ₂ Mg	4-H ₃ CSC ₆ H ₄ COCH ₃	6.2	Et ₂ O	13c
CH ₃ MgCl	4-H ₃ CSC ₆ H ₄ COCH ₃	~20	Et ₂ O	13e
MgBr ₂	2-CH ₃ C ₆ H ₄ COC ₆ H ₅	4	Et ₂ O	15b
CH ₃ MgBr	2-CH ₃ C ₆ H ₄ COC ₆ H ₅	1.35	Et ₂ O	15b
(CH ₃) ₂ Mg	2-CH ₃ C ₆ H ₄ COC ₆ H ₅	<0.7	Et ₂	15c
sec-BuMgCl	CH ₃ COC(CH ₃) ₃	4.1	Et ₂ O	14a
Ph(CH ₂) ₂ MgBr	CH ₃ COC(CH ₃) ₃	5.8	Et ₂ O	14a
n-C ₃ H ₇ MgBr	CH ₃ COC(CH ₃) ₃	5.8	Et ₂ O	14b
n-C ₃ H ₇ MgBr	CH ₃ COC(CH ₃) ₃	31	(i-Pr) ₂ O	14b
n-C ₃ H ₇ MgBr	CH ₃ COC(CH ₃) ₃	48	Bu ₂ O	14b
n-C ₃ H ₇ MgCl	CH ₃ COC(CH ₃) ₃	1.9	Et ₂ O	14b

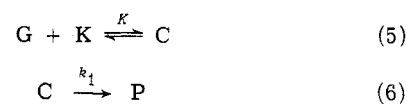
Kinetic Studies. The earliest kinetic studies¹⁻³ concerning the reaction of Grignard reagents with ketones were performed with the reactants at comparable concentrations and the data were analyzed by attempting to describe the reaction in terms of either simple second- or third-order behavior. It is now recognized that the complications that arise from the later stages of the reaction make this an impossible task.

Another procedure for kinetic studies is the use of one of the reactants in large excess. In this way the integral order behavior of the reactant not in excess can be determined unequivocally. The use of excess Grignard reagent has both advantages and disadvantages. One significant advantage is that there is more than enough of the reactive species (R₂Mg and RMgX) present to react with ketone; therefore, the formation of the less reactive alkoxide species (R'OMgBr·RMgX, etc.) is of no consequence, and the later stages of the reaction can be ignored. Pseudo-first-order kinetics in excess Grignard reagent thus determine unambiguously the reaction order in ketone. A further complication is that kinetic experiments should be limited to concentrations at which only monomeric magnesium species are present (<0.1 M), therefore necessitating the concentration of the ketone at ~10⁻⁴ M. A second disadvantage is the occurrence of several unexpected phenomena when the ratio of Grignard reagent to ketone is high. The pseudo-first-order rate constant is not independent of the ketone concentration at a fixed Grignard concentration; on the contrary, its value is dependent on the purity of the magnesium used in preparing the Grignard reagent,¹⁸ on the mode of formation of the reagent,¹⁸ and on whether or not the Grignard reagent has been recrystallized.^{13a} Coincident with these phenomena is the appearance of pinacol (interpreted as resulting from a radical mechanism) as a by-product. These problems will be discussed in more detail later. On the other hand, studying the reaction in excess ketone has the advantage that the complications just described do not occur to any measurable extent. The disadvantage is that the Grignard reagent now associates with products so that initial rates must be employed in inter-

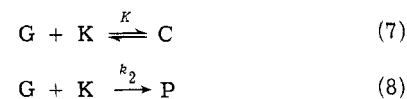
preting the behavior of the initial stage of the reaction. Nevertheless, our most successful results¹⁵ have been obtained in experiments using excess ketone. Such experiments, in contrast to those using excess Grignard reagent, provide information about the later stages of the reaction.

Mechanistic Schemes. In considering the behavior of any organomagnesium species capable of alkylating a ketone, three general mechanistic schemes have received attention. Each scheme assumes the existence of a complex, C, formed between ketone, K, and the organomagnesium compound, G.

Scheme I. In this scheme, first suggested by Meisenheimer and Casper,¹⁹ the alkylation product (P) is formed directly by internal rearrangement of the complex. The rate laws $d[P]/dt = k_1[C]$ and $d[P]/dt = k_1K[G]/[K]$ are equally valid expressions corresponding to this scheme.



Scheme II. In this scheme, complex formation (eq 7) between G and K is a nonproductive equilibrium, and alkylation occurs by a bimolecular reaction (eq 8) between the free organomagnesium reagent and ketone.



The rate laws $d[P]/dt = k_2[G][K]$ and $d[P]/dt = (k_2/K)[C]$ are equally valid expressions corresponding to this scheme.

It is not possible to distinguish between Schemes I and II on the basis of the rate law since both lead to the same phenomenological rate law, $d[P]/dt = k_a[C]$ or $d[P]/dt = k_b[G][K]$ where k_a is a first-order rate constant and k_b is a second-order rate constant. This is to be expected since the transition states are the same in both cases and thus it is not important how the transition state comes about. Distinction between these two possibilities must be made on

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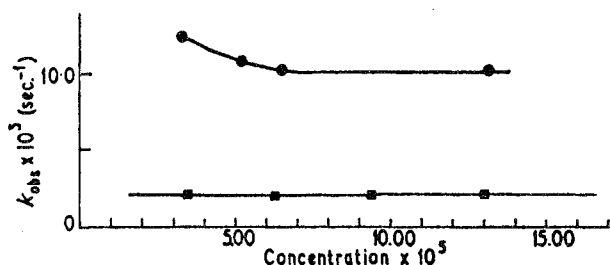
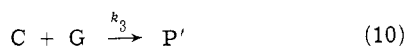


Figure 4. Variation of the pseudo-first-order rate constant (k_{obs} , from extrapolated initial slope in first-order plot) with initial benzophenone concentration at a constant methylmagnesium bromide concentration. (●) Triply sublimed magnesium (methylmagnesium bromide concentration, $[\text{Mg}]_0 = 6.45 \times 10^{-3} \text{ M}$); (■) ultrapure magnesium ($[\text{Mg}]_0 = 2.43 \times 10^{-3} \text{ M}$).

some additional basis. For example, we have attempted to make the distinction on the basis of activation energies in the case of the reaction of trimethylaluminum with benzophenone.¹⁶

Scheme III. In this scheme, first suggested by Swain and Boyles,²⁰ the rate-determining step is a bimolecular reaction of the organomagnesium compound with the complex. Rate laws corresponding to



this scheme would be $d[\text{P}']/dt = k_3[\text{C}][\text{G}]$ or $d[\text{P}']/dt = k_3K[\text{K}][\text{G}]^2$. Since Scheme I and Scheme II cannot be distinguished from each other, but can be distinguished from Scheme III, one of the main purposes of the kinetic studies in the past decade has been to decide between Schemes I and II *vs.* Scheme III as the correct description of the reaction.

Kinetics in Excess Grignard Reagent. The measurements of rates using a large excess of the Grignard reagent have been used extensively by Smith, Tuulmets, and Holm, and to a lesser extent by ourselves. In such studies different workers have chosen to examine certain systems or certain features of the reaction. Smith and coworkers¹³ have carried out kinetic studies of the reaction of methylmagnesium bromide with a small number of select ketones in diethyl ether. On the other hand, Tuulmets has studied the reaction of a variety of Grignard reagents in a variety of solvents, with pinacolone being the ketone most often used. (Unfortunately, his work is written in Russian and has received less attention than it deserves.) Holm²¹ has studied the reaction of a wide variety of Grignard reagents and carbonyl compounds, in both diethyl ether and tetrahydrofuran as solvents. He was the first to attempt a quantitative evaluation of the importance of the R_2Mg species in Grignard reactions.^{21e,g}

The study by Smith and Su^{13b} on the reaction of methylmagnesium bromide with 2,4-dimethyl-4'-methylmercaptobenzophenone was one of the first kinetic studies using excess Grignard reagent. Using spectrophotometric methods these workers estab-

lished that both ketone and complex disappear in a first-order fashion with the same rate constant. On the basis of the variation of the pseudo-first-order rate constant with Grignard concentration they suggested that Scheme I applied, although recognizing that Scheme II was also possible. Unfortunately, experiments utilized methylmagnesium bromide at concentrations in the range 0.04 to 1.5 M, and in order to fit the data over the entire concentration range it was necessary to append additional features to Scheme I such as the influence of salt effects and dimeric Grignard species on the rate of reaction.

Since very little of the data had been obtained at concentrations at which the Grignard reagent was monomeric, and because Scheme I (or II) by itself could not fit the data, we were not convinced of the assignment of Scheme I to describe this reaction. Thus, we reported²² in a preliminary communication some results with methylmagnesium bromide (at concentrations $\sim 10^{-2}$) and benzophenone (at concentrations $\sim 10^{-3}$) supporting Scheme III. Later Smith and Billet reported on the reaction of $(\text{CH}_3)_2\text{Mg}^{13c}$ and methylmagnesium bromide^{13d} with the ketone 4-methylmercaptoacetophenone. The results with methylmagnesium bromide were similar to those obtained with the first ketone. The results with $(\text{CH}_3)_2\text{Mg}$ could be fitted to the Scheme I-II description; however, the concentration range covered (0.01 to 0.6 M) was well into the range where $(\text{CH}_3)_2\text{Mg}$ is no longer monomeric.

The resulting difference of opinion led to further examination of the reactions, with particular emphasis on the reaction of benzophenone with excess methylmagnesium bromide. Both Billet and Smith^{13d} and this laboratory¹⁸ have shown that the pseudo-first-order rate constants at a constant Grignard concentration are dependent on the initial ketone concentration, certainly a surprising result. In the case of benzophenone, rate constants obtained are much larger at high Grignard to ketone ratios when the concentration of the Grignard reagents is held constant (see Figure 4). The high rate constants are accompanied by significant yields of nonaddition by-products, benzopinacol and benzhydrol. The appearance of benzophenone magnesium ketyl was also reported on the basis of electron spin resonance spectroscopy and visible absorption spectroscopy carried out on reacting samples.^{13d}

These observations suggested to us that the effects described above occur due to a small amount of transition-metal impurities in the magnesium metal used to prepare the Grignard reagent. Studies were carried out relating these effects to magnesium metal purity and the method of preparation of the reagent.²³ Reagents were prepared from several grades of magnesium, employing both an excess of magnesium and an excess of methyl bromide. The two effects (the variation of rate constant with ketone concentration (Figure 4) and the amount of nonaddition product (Table III)) could both be decreased by using magnesium of higher purity and by preparing the Grignard reagent with an excess of alkyl halide

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Table III
Product Analysis and Pseudo-First-Order Constants from the Reaction of Methylmagnesium Bromide with Benzophenone in Diethyl Ether at 25°

Source of magnesium	Grignard prepared with excess	$[G]_0, M$	$10^6 [K]_0$	$[G]_0/[K]_0$	$k_{\text{obsd}}, \text{sec}^{-1}$	$k_{\text{obsd}}/[G]_0$	% addition
Doubly sublimed	Mg	0.00958	2.04	470	0.0218	2.28	72.7
	Mg	0.00958	8.52	112	0.0134	1.40	84.6
	Mg	0.00958	16.7	57	0.0117	1.23	91.9
	CH ₃ Br	0.00995	2.04	487	0.0128	1.29	92.2
	CH ₃ Br	0.00995	8.52	117	0.0106	1.07	96.9
	CH ₃ Br	0.00995	16.7	60	0.00994	1.00	98.1
Single crystal	Mg	0.00953	2.04	467	0.0155	1.63	88.1
	Mg	0.00953	8.52	112	0.0126	1.33	94.6
	Mg	0.00953	16.7	57	0.0119	1.25	96.3
	CH ₃ Br	0.00978	2.04	479	0.0135	1.38	95.0
	CH ₃ Br	0.00978	8.52	115	0.0135	1.23	97.9
	CH ₃ Br	0.00978	16.7	58	0.0114	1.17	98.1

rather than the usual method which uses excess magnesium. When ultrapure magnesium was used, the anomalous effects were essentially eliminated.

The complications discussed above only arise when the kinetic studies are carried out in excess Grignard reagent. When the kinetics were carried out in excess ketone,²³ no by-products were detected, and the rate constants were found to be independent of the magnesium purity and the method of preparation of the reagent.

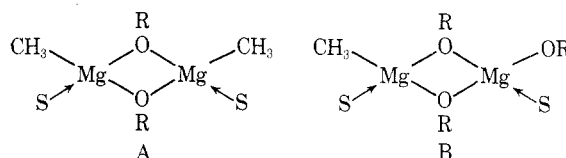
Kinetics of the Reaction of Dimethylmagnesium in Excess Ketone. In an attempt to determine the integral order behavior of the Grignard reagent in its reaction with ketones we chose to study the kinetics of the reaction of methylmagnesium bromide with excess 2-methylbenzophenone in diethyl ether. This ketone was chosen because it gave reaction rates that could conveniently be measured spectrophotometrically. Also this system eliminates the possible formation of by-products observed in other systems that have been studied. The formation of reduction product is eliminated since the Grignard reagent contains no β hydrogen and enolization product is eliminated since the ketone contains no α hydrogen. The use of excess ketone causes one to deal with both the initial and later stages of the reaction, unlike the reaction in excess Grignard reagent where the later stages of the reaction are no problem.

The study^{15c} of the reaction of dimethylmagnesium with 2-methylbenzophenone provided an important preliminary to the study of the Grignard reaction itself. In this case, the initial stage of the reaction would be simple, and would provide a measure of the order of the reaction in R_2Mg and a value of the rate constant. The rate was studied by measuring the change of absorbance at 410 nm. Significant changes in absorbance occur at this wavelength during the course of the reaction; the absorbance is low immediately on mixing the reactants, increases rapidly to a maximum value, and then slowly decreases to a small infinite time value. The absorption is not due to a complex between ketone and $(CH_3)_2Mg$ since such a complex would form immediately, leading to a large initial absorbance. Apparently the absorbance is due to complexes formed between the ketone and intermediate alkoxide species since the absorbance reached a maximum after the initial reaction producing $RMgOR$. Parallel experiments showed that the amount of addition product

formed (measured by glpc) was related to the change in the absorbance at 410 nm.

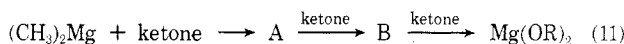
The results for the first stage of the reaction were quite straightforward. In this stage, corresponding to the rapid rise to maximum absorbance, 50% of the alkyl groups of $(CH_3)_2Mg$ had reacted. The reaction was first order in ketone and first order in $(CH_3)_2Mg$.

The observations made with respect to the second stage of the reaction were quite interesting and valuable. Two intermediate products, disappearing in a series of pseudo-first-order reactions, were observed. Both of these intermediates were capable of forming complexes with the ketone and of alkylating the ketone. Reasonable structures for these intermediates are



where S represents a solvent molecule and R represents the $C(CH_3)(C_6H_5)(C_7H_7)$ group. Calculated yields of addition product, based on these structures and the rate constants measured spectrophotometrically, gave excellent agreement with the yields measured at various times. The complexes with ketones, which are responsible for the absorbance at 410 nm, result from the replacement of one or both solvent molecules by a ketone molecule.

Each of the three steps observed (eq 11) in the se-

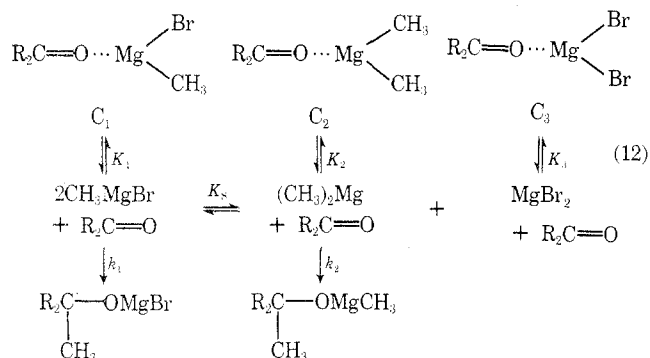


ries of reactions was first order in the organomagnesium species, indicating that Scheme I or II is applicable. The variation of the pseudo-first-order rate constant for each step with ketone concentration was also consistent with Scheme I or II. Because no complex was observed with $(CH_3)_2Mg$, the rate law for it can only be expressed in a second-order form; however, this should not imply that Scheme II is favored over Scheme I. A detailed description of the mechanism proposed for this reaction is given in ref 15c.

Kinetics of the Reaction of Methylmagnesium Bromide in Excess Ketone. The same general approach that had been successful with $(CH_3)_2Mg$ was

used in studying the reaction of methylmagnesium bromide with excess 2-methylbenzophenone in diethyl ether.^{15a,b} The rate measurements were made by following both the disappearance of the complex band (by uv) formed on addition of the Grignard reagent to the ketone and the appearance of the product by glpc analysis. The product was found to appear at essentially the same rate that the complex band disappeared; however, a first-order plot describing the disappearance of the complex band in excess ketone was not linear, indicating a complex disappearance of the Grignard reagent species. Fortunately, treatment of the initial rates indicated that the reaction at this stage was first order in Grignard reagent since the rate constant calculated on this basis was constant over a series of kinetic experiments in which the initial Grignard concentration was varied threefold.

Since neither $(\text{CH}_3)_2\text{Mg}$ nor MgBr_2 produces immediate absorption in the 400–600 nm region when added to 2-methylbenzophenone, the absorption observed in this region when the methyl bromide Grignard is added to this ketone must be due to the complex involving the CH_3MgBr species. Thus, in order to test the proposal that the reaction is first order in CH_3MgBr species (as well as in $(\text{CH}_3)_2\text{Mg}$), kinetic experiments were carried out using methyl bromide Grignard reagent to which had been added an excess of MgBr_2 . Addition of MgBr_2 to the Grignard reagent would be expected to result in a shift of the Schlenk equilibrium in the direction of CH_3MgBr species. When this mixture is allowed to react with the ketone, the rate measured should be that of the CH_3MgBr species alone. Two noteworthy observations were made: first, the reaction was first order in CH_3MgBr species throughout 80% of the reaction (presumably the excess MgBr_2 available to complex with product as $\text{ROMgX}\cdot\text{MgBr}_2$ left the CH_3MgBr species available for reaction only with the ketone); second, the observed rate constant was in excellent agreement with the value of the same rate constant (k_1) calculated from initial rate data on the normal Grignard reagent assuming the reaction scheme of eq 12. The initial rate is dependent on



the six constants and the ketone concentration in a specific way (see ref 15b); thus, we chose to check the consistency of this interpretation by calculating k_1 from the initial rate and the other constants. The work with $(\text{CH}_3)_2\text{Mg}$ had provided a value of k_2 and had shown that K_2 was small enough so that it could be neglected. The value of K_3 was obtained from experiments independent of the kinetics, and values of

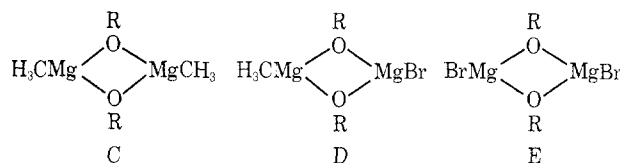
K_S and K_1 came from absorbancy measurements in the kinetic experiments. When K_2 is neglected, the initial rate of change of the complex (C_1) is given by eq 13.

$$\frac{d[\text{C}_1]}{dt} = \frac{(k_2\sqrt{K_S(1+K_3[\text{K}])} + k_1)[\text{K}]}{(1+K_1[\text{K}] + 2\sqrt{K_S(1+K_3[\text{K}])})} [\text{C}_1]_0 \quad (13)$$

The values of k_1 obtained by this procedure at varying ketone concentrations agreed well among themselves and agreed with the values obtained from the experiments containing added MgBr_2 . Not only was the internal consistency excellent, but the values of the equilibrium constants were reasonable in comparison with values obtained for similar systems (see Tables I and II). Because the calculated and observed rate constants agreed within experimental error, confidence in the above scheme was established. The rate constant for reaction of the CH_3MgBr species (k_1) and the $(\text{CH}_3)_2\text{Mg}$ species (k_2 , determined independently) indicates that the R_2Mg species is ~ 10 times more reactive than the RMgX species. On the other hand, the concentration of RMgX species in solution is approximately ten times that of R_2Mg . Thus it appears that the formation of the product is taking place by reaction of both the RMgX and R_2Mg species to about the same extent.

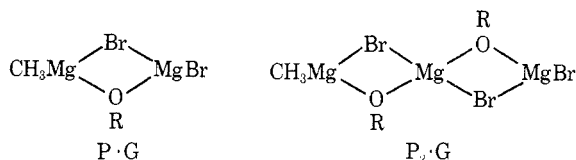
The later stages of the reaction were more difficult to define. Deviations from simple pseudo-first-order behavior occur early in the reaction, but fortunately the absorbancy data parallel the disappearance of active methyl groups, so that the change in absorbancy can be used as a measure of the rate of the addition reaction. All prior evidence suggested that the presence of alkoxide species is the cause of the complications in this stage of the reaction.

The immediate products of the reaction of $(\text{CH}_3)_2\text{Mg}$ and CH_3MgBr species with ketone are ROMgCH_3 and ROMgBr , respectively. Because of the marked tendency for alkoxide species to dimerize, it is possible that any of the dimers C–E (indi-

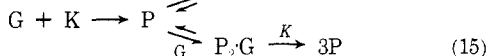
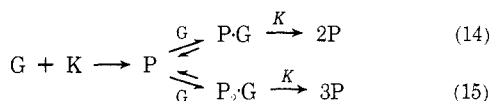


cated without solvent molecules) could be formed early in the reaction. Indeed, we have determined that each species prepared independently is dimeric in solution.²⁴ Either dimer C or D could arise from reactions of $(\text{CH}_3)_2\text{Mg}$ in the first stage; however, these intermediates would be formed in the presence of MgBr_2 which is present in the Schlenk equilibrium. When dimer C was made independently and mixed with a solution of MgBr_2 it immediately underwent redistribution to form CH_3MgBr and BrMgOR . A similar experiment with D gave a similar result. Thus, dimers C and D, if formed at all, have but fleeting existence in the Grignard reaction. Dimer E is incapable of alkylation, but its formation affects the reaction rate.

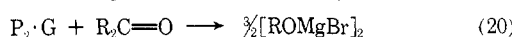
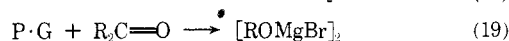
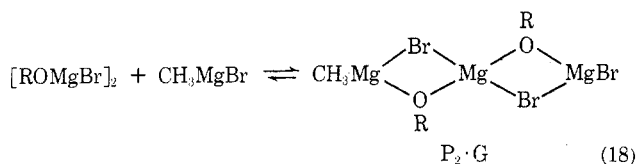
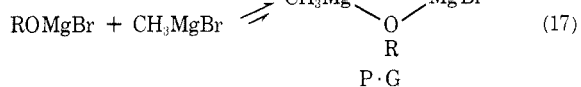
By intentionally adding the final product ROMgBr to the reaction mixture, it was possible to accentuate the features of the later stages of the reaction. The results of these experiments indicated the presence of two intermediate species being formed in the reaction, P·G and P₂·G (where P = ROMgBr and G = RMgX), both capable of acting as alkylating agents, and both reacting in a pseudo-first-order way. In time P·G appears first, followed by P₂·G. The amount of P₂·G increases relative to that of P·G the greater the amount of ROMgBr added to the reaction. The suggested structures of P·G and P₂·G (with solvent molecules omitted) are shown below.



P·G can be formed directly by combination of CH₃MgOR with MgBr₂, or by combination of ROMgBr with CH₃MgBr; P₂·G can be formed from (ROMgBr)₂ and CH₃MgBr. The proposed second species, designated P₂·G, reflects the fact that it appears in greater amount when the alkoxide content of the solution becomes greater. All of the data indicate the overall scheme given in eq 14 and 15.

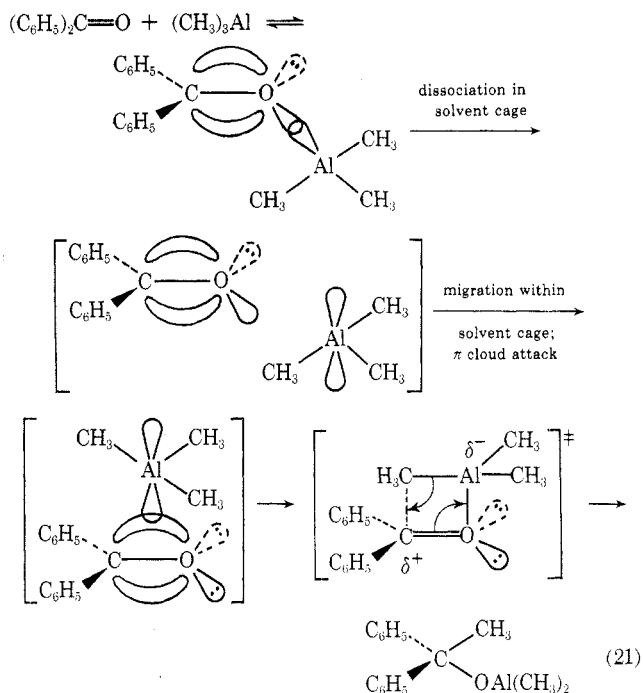


In summary, then, it appears that the R₂Mg species which exists in the Schlenk equilibrium reacts with ketone to produce CH₃MgOR, which then reacts with MgBr₂ to form P·G. The RMgX species present in the Schlenk equilibrium reacts with ketone to form ROMgBr, which also forms P·G by complexing with another RMgX. The complicating feature of the reaction is that P·G and P₂·G then react with ketone at a slower rate than either RMgX or R₂Mg. Furthermore, the Grignard species are disappearing in a complex fashion in that they are reacting not only with the ketone, but also with ROMgBr. The latter stages of the reaction can now be described in detail using eq 16–20.



It has been pointed out that a distinction between the mechanisms called Scheme I and Scheme II cannot be made on the basis of the rate law, but that some other information must be used. Recently¹⁶ we

have attempted to choose between these two possibilities in the reaction of trimethylaluminum with benzophenone, a reaction of some similarity to the Grignard addition, by consideration of the activation enthalpies. The conclusion in this case was that the rate determining step of the reaction involves dissociation of the R₂C=O...AlR'₃ complex in the solvent cage followed by a rapid bimolecular attack of the R'₃Al species on the ketone. The detailed mechanism describing the mode of alkyl transfer is as follows.



The reaction through the complex would require rotation of the C=O bond of the complex so that the methyl group on aluminum would be in the right proximity to attack the π cloud of the carbonyl carbon atom. The energy required to do this far exceeds the activation energy of the reaction. The thermodynamic data suggest that the enthalpy for binding RMgX to ethers is similar to the activation energies (11–14 kcal) observed for RMgX–ketone reactions. Although it is not certain that the rate-determining step of the Grignard–ketone reaction involves dissociation of the complex bond as in the case of the R₃Al reaction, the possibility is certainly a real one.

Summary and Final Conclusions

The addition of methylmagnesium bromide to 2-methylbenzophenone occurs *via* several alkylating species; each of these reaction paths is first order in ketone and first order in the magnesium species. In the initial stage of the reaction CH₃MgBr and (CH₃)₂Mg are the alkylating species. Formation of a complex between the ketone and the organomagnesium species is followed by a first-order disappearance of the complex. When the reaction is run in large excess of ketone, the reaction rapidly becomes complicated because the reaction product, ROMgX, complexes the Grignard species. However, it was possible to show that in this stage of the reaction the product–Grignard species complex also alkylates the ketone in a series of reactions first order in the com-

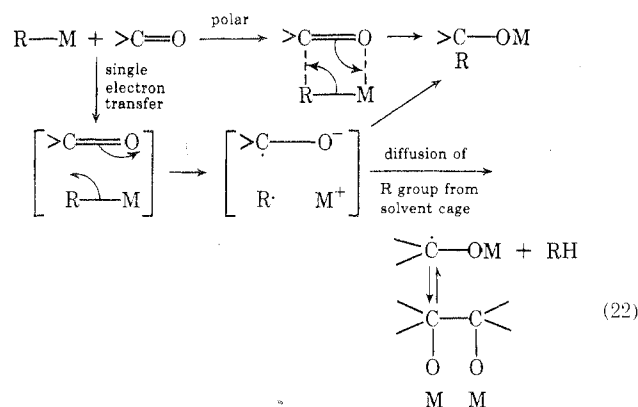
plex. Obviously, when the Grignard reagent is used in large excess, the later stages of the reaction are not observed since ROMgX has plenty of Grignard species to complex without effectively changing the concentration of Grignard species.

Possibly the most complicating feature of these kinetic studies was the observation that, in large excess of Grignard reagent, the pseudo-first-order rate constant was a function of the initial concentration of ketone, although the reaction was first order in ketone. Simultaneously, substantial amounts of by-products are formed. Both problems were essentially eliminated by preparation of the Grignard reagent in excess methyl bromide using single-crystal magnesium. Our feeling is that parts per million of transition-metal impurities in the magnesium catalyzes single electron transfer, producing ketyl in solution which gives rise to an esr signal and also to benzopinacol and benzhydrol by-products. Since the formation of by-product was essentially eliminated by changing the source of magnesium from doubly sublimed to single crystal, our conclusion concerning ketyl intermediates in the systems we have studied is that ketyl formation is an artifact of the purity of the magnesium metal used to prepare the Grignard reagent and not a function of the fundamental course of the reaction.

There is no intention here to propose that the mechanism suggested for methylmagnesium bromide addition to 2-methylbenzophenone also holds true for all reactions of Grignard reagents with ketones. Indeed, a recent report by Fauvarque²⁵ shows that considerable (36%) ketyl is produced in the reaction of dibenzylmagnesium with fluorenone when the reaction is carried out in HMPA, although only a trace of the ketyl is observed in diethyl ether. Also Mosher and Blomberg²⁶ have reported the formation of 20% benzopinacol and 20% neopentane in the reaction of neopentylmagnesium chloride with benzophenone in diethyl ether, indicating that a significant amount of the reaction is proceeding by a single-electron-transfer pathway. Finally, Holm^{21b} has recently reported that the reaction of *tert*-butylmagnesium chloride with substituted benzophenones produces considerable amounts of 1,2-, 1,4-, and 1,6-addition products in addition to benzopinacol, indicating the formation of a ketyl intermediate *via* a single-electron-transfer pathway. We have recently repeated some of Holm's work using Grignard reagents prepared from single-crystal magnesium in excess alkyl halide in order to make sure that his observations were not a result of transition-metal-catalyzed single electron transfer. We found all results reproducible and that *tert*-butylmagnesium chloride does indeed react with benzophenone in diethyl ether by a single-electron-transfer pathway. We also found that, although the reaction of methylmagnesium bromide with benzophenone in diethyl ether shows no evidence whatsoever for reaction *via* single electron transfer, the reaction could be made to pro-

ceed to a significant extent *via* single electron transfer by simply adding parts per million of certain transition-metal halides.

It seems clear at the present time that Grignard reagents react with ketones either by a polar mechanism or by a single-electron-transfer mechanism (or both simultaneously) and that the reaction pathway depends on the nature of the ketone, the solvent, the R group in the Grignard reagent, and the purity of the magnesium metal. The polar mechanism is favored when the oxidation potential of the Grignard reagent and the reduction potential of the ketone are high, when the solvent is not very polar, and when the magnesium metal contains only trace transition-metal impurities. All evidence indicates that the reaction of methylmagnesium bromide (prepared in diethyl ether from single-crystal magnesium in excess methyl bromide) with benzophenone proceeds *via* a polar mechanism. On the other hand, a single-electron-transfer mechanism is favored when the oxidation potential of the Grignard reagent and the reduction potential of the ketone are low, when the solvent is highly polar, or when the magnesium metal used to prepare the Grignard contains substantial amounts of transition metal impurities. The reaction of *tert*-butylmagnesium chloride with benzophenone in diethyl ether does indeed proceed *via* single electron transfer. Apparently reacting benzophenone with *tert*-butylmagnesium chloride instead of methylmagnesium bromide is sufficient for the reaction to change reaction pathways. We have recently found that even the reaction of methylmagnesium bromide with benzophenone can be made to proceed *via* a single-electron-transfer pathway either by changing the solvent from diethyl ether to HMPA or by maintaining the ether solvent and adding 0.05 mol % FeCl_3 to the reaction mixture. Therefore, at this time it appears that one might predict whether a given reaction proceeds *via* a polar mechanism or single electron transfer by simply considering the factors described above. Obviously much work is needed to describe these parameters in as much detail as possible, and we are actively engaged in doing this. The overall reaction scheme indicating the possible reaction pathways is shown in eq 22.



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(26) C. Blomberg and H. S. Mosher, *J. Organometal. Chem.*, 13, 519 (1968).

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