

CONTROLLING FACTORS DETERMINING ADDITION AND REDUCTION PRODUCTS IN THE GRIGNARD REACTION OF SUBSTITUTED BENZOPHENONES, ACETOPHENONE AND FLUORENONE WITH 'EtMgBr'

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Addition (Add.) vs reduction (Red.) products in the reactions of substituted benzophenones, acetophenone and fluorenone with 'EtMgBr' were compared in diethyl ether, 1,2-dimethoxyethane and tetrahydrofuran. Plots of log (Add./Red.) vs σ -values or the oxidation potentials of ketones showed characteristic upward curves depending on the polarity of the solvents. The results are discussed on the basis of both the combined effects of the stability of the monomeric radical ion pair and the dimeric radical ion pair derived from ketone and 'EtMgBr', and the well known Schlenk equilibrium of 'EtMgBr' in solutions.

INTRODUCTION

Detailed studies of the controlling factors determining addition vs reduction products in the Grignard reaction have been undertaken in the past.¹ However, a general mechanism that satisfies all of the individual experimental results is still lacking. We previously reported the reaction mechanism of benzil with Grignard reagents.² In this reaction, the intermediacy of two kinds of radical ion pairs, monomer and dimer, was confirmed. Subsequently, conversion of the monomeric radical ion pair to the dimeric radical ion pair during the Grignard reaction of benzophenone with 'PhMgBr' was confirmed spectroscopically.³ Based on these findings, we have reinvestigated the traditional but unsolved problem of addition vs reduction in the Grignard reaction.

The product distribution is controlled mainly by (a) the polarity of solvents, (b) the reduction potential of carbonyl compounds and (c) the steric environment of the reaction centre. The presence of a minute amount of heavy metals drastically affects the product distributions, but this is not discussed in this paper. In addition, the structure of Grignard reagents certainly has a large effect on the product distribution, and this will be discussed in a forthcoming paper.

RESULTS AND DISCUSSION

In the reaction with 'EtMgBr,' substituted benzo-

phenones, acetophenone and fluorenone were selected as the substrates. 'EtMgBr' in a desired solvent was prepared from magnesium metal (99.9999 pure) and EtBr in the usual manner. Grignard reactions were effected in a sealed vessel under strictly dry and deaerated conditions. After standing for 3 days at room temperature, the reaction solution was quenched with saturated ammonium chloride solution in a glove-box under argon. Work-up as usual gave a mixture of products. Because of the simple structure of the products the amount of each component was determined by ¹H NMR spectroscopy, but was separated by column chromatography if necessary. Ethylene as a gaseous product was identified by gas chromatography, but was not measured quantitatively.

Plots of log(Add./Red.) vs σ in the Grignard reaction of benzophenone derivatives are shown in Figure 1 and plots of log(Add./Red.) vs the reduction potentials of ketones in the Grignard reaction with other ketones in Figure 2.

Polarity of solvents and reduction potential of ketones

Figure 1 shows that the log(Add./Red.) values change with the σ values in a systematic manner that varies considerably with the nature of the solvents. In diethyl ether (DEE), for example, the addition products predominated over the reduction products for all combinations of the reactants, but in tetrahydrofuran (THF)

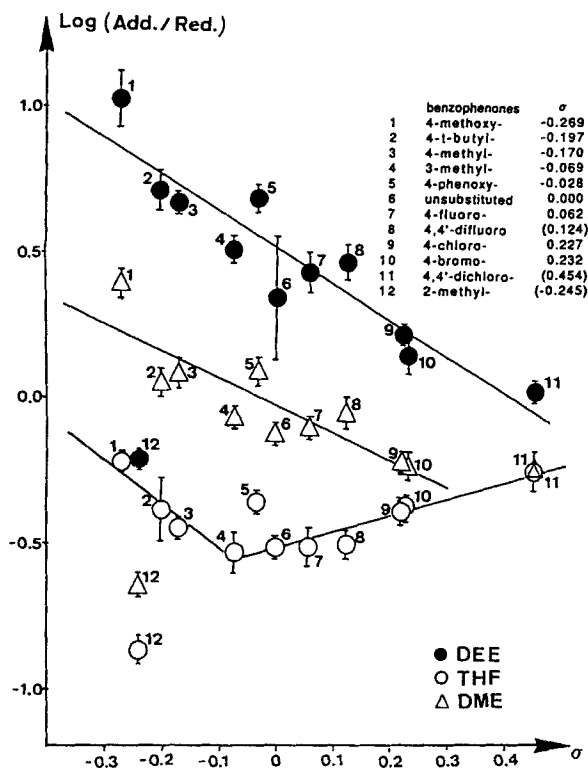


Figure 1. $\log(\text{Add./Red.})$ vs Hammett's σ -values. $[\text{EtMgBr}]_0 = 0.23 \text{ M}$; $[\text{benzophenones}]_0 = 0.046 \text{ M}$; room temperature

the reduction products predominated in all of the reactions. When the steric environment around the carbonyl group is similar or less hindered, in DEE the $\log(\text{Add./Red.})$ values (black circles) vs σ lie close to one line, except for black circle 12, but in THF (white circles) they align on two lines (or an upward curve with a minimum) except for white circle 12. In the reactions in 1,2-dimethoxyethane (DME) the $\log(\text{Add./Red.})$ values (white triangles) lie between the above two extremes, and in the most of the reactions the amounts of the addition and the reduction products remain generally comparable. However, they appear to lie on a gentle curve with a minimum except for the white triangle 12.

In Figure 2, $\log(\text{Add./Red.})$ values are plotted against the oxidation potentials of ketones. Here there are three curves each with a minimum in the reactions in DEE, DME and THF. All of the reactions done in DEE (black circles) always gave greater amounts of addition products, i.e. $\log(\text{Add./Red.}) > 0$, but in THF the only two, i.e. acetophenone and fluorenone, of the six examined gave greater amounts of addition products. In contrast, in DME only two of the six gave greater amounts of reduction products. Hence the

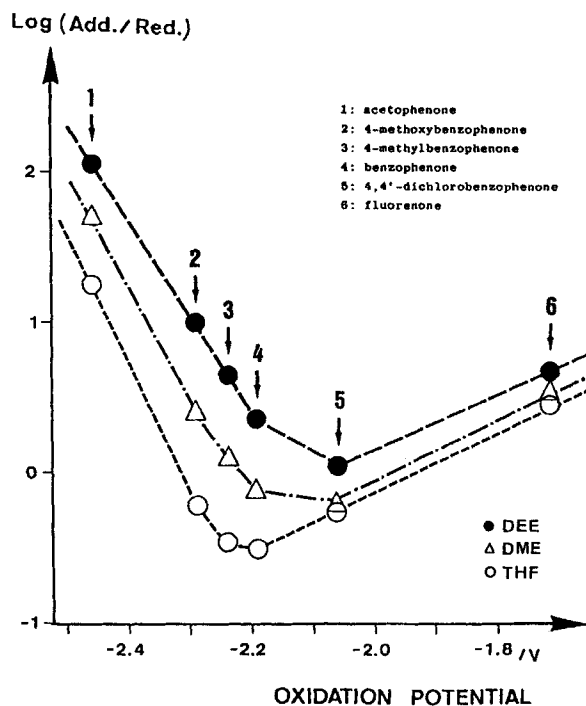
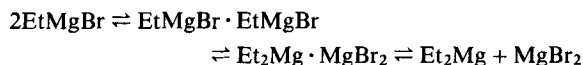


Figure 2. $\log(\text{Add./Red.})$ vs oxidation potentials of ketones. $[\text{EtMgBr}]_0 = 0.23 \text{ M}$; $[\text{ketone}]_0 = 0.046 \text{ M}$; room temperature

polarity of the solvent has a large effect on the product distributions. The polarities of the solvents decrease in the order $\text{THF} > \text{DME} > \text{DEE}$. Hence the smaller the polarity of the solvent the greater were the relative amounts of addition products obtained. Undoubtedly this must be correlated with the composition of Grignard reagents in solvents. It is well known that the Grignard reagent is in a (Schlenk) equilibrium:



We decided to reconfirm the equilibrium in the solvents used. The results are given in Table 1. 'EtMgBr' is mostly monomeric in THF but a few percent of dimeric components are still present. However, in DEE the reagent is mostly dimeric. These differences in solution must be responsible for the product distributions.

On the other hand, from Figures 1 and 2 it is obvious that the reduction potential of ketones has a distinct relationship with the product distributions.

Steric effects around the reaction centre

In all of the reactions in the three different solvents, 2-methylbenzophenone, which has severe steric hindrance

Table 1. Degree of association in DEE and THF (25 °C)

Reagent	Solvent	Degree of association				
		0.2 M	0.4 M	0.6 M	0.8 M	1.0 M
MeMgBr	DEE	1.23	1.54	1.77	1.97	2.19
	THF	0.98	1.03	1.03	0.97	0.93
EtMgBr	DEE	1.08	1.49	1.73	1.90	2.28
	THF	0.95	1.01	1.01	0.98	0.94
<i>n</i> -PrMgBr	DEE	0.93	1.29	1.43	1.56	1.62
	THF	1.10	1.15	1.02	0.88	—
<i>n</i> -BuMgBr	DEE	1.00	1.08	1.31	1.34	1.32
	THF	1.02	1.05	0.99	0.99	0.96
<i>t</i> -BuMgBr	DEE	1.01	1.41	1.69	1.94	2.30
	THF	0.99	1.02	1.01	0.98	0.94
PhMgBr	DEE	1.18	1.57	1.94	1.99	1.96
	THF	0.88	0.94	0.86	0.96	0.93

around the reaction centre, behaved differently, i.e. the reduction product greatly predominated over the addition product. This result is a clear indication of the steric effects on the product distributions in the Grignard reaction, that is, in the R[•] transfer stage in the sphere of the radical ion pair, steric bulkiness of the substituents around the carbonyl carbon atom significantly affects the product distributions, as described below.

DISCUSSION

As in the previous work,² the ketones examined here generate two kinds of ion pair, monomeric and dimeric radical ion-pairs, consisting of the radical anion of the ketone and the radical cation of 'EtMgBr.' When the monomeric radical ion pair (MIP) is stable enough in solution it dimerizes to form the more stable dimeric radical ion pair (DIP).² Structures for MIP and DIP have been proposed (Scheme 1).^{2,3} 'MeMgBr' and 'ArylMgBr,' which have a strong C—Mg bond and no

β -hydrogen atom, belong to this class. Let us classify this type of Grignard reagent as S-class, having a high C—Mg bond energy > 250 kcal mol⁻¹.⁴ Therefore, there is no possibility of obtaining the reduction product of the ketones.

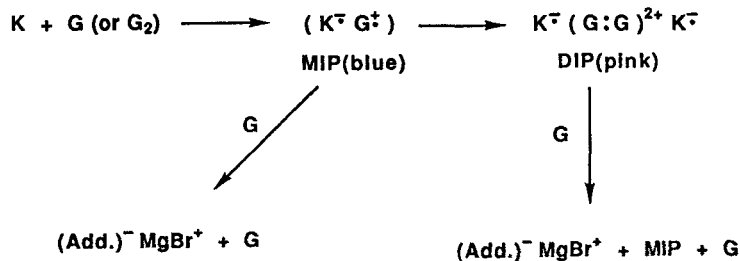
In contrast, when the C—Mg bond is not stable enough to give the DIP, MIP decomposes as soon as it is formed to give solvent-separated 'free R[•]' and MgBr⁺ or H[•] + olefin + MgBr⁺. '*t*-BuMgBr' belongs to this class. Let us classify this type of Grignard reagent as W-class, that is having a low C—Mg bond energy < 200 kcal mol⁻¹.⁴

'EtMgBr,' 'PrMgBr,' 'BuMgBr,' '*i*-PrMgBr' and '*s*-BuMgBr' are intermediate between the S- and W-classes, i.e. their C—Mg bond energy is between 200 and 250 kcal mol⁻¹. Let us classify this type of the Grignard reagent as M-class, i.e. with medium bond strength.

Following the above classifications the Grignard reactions can be differentiated as shown in Scheme 2.

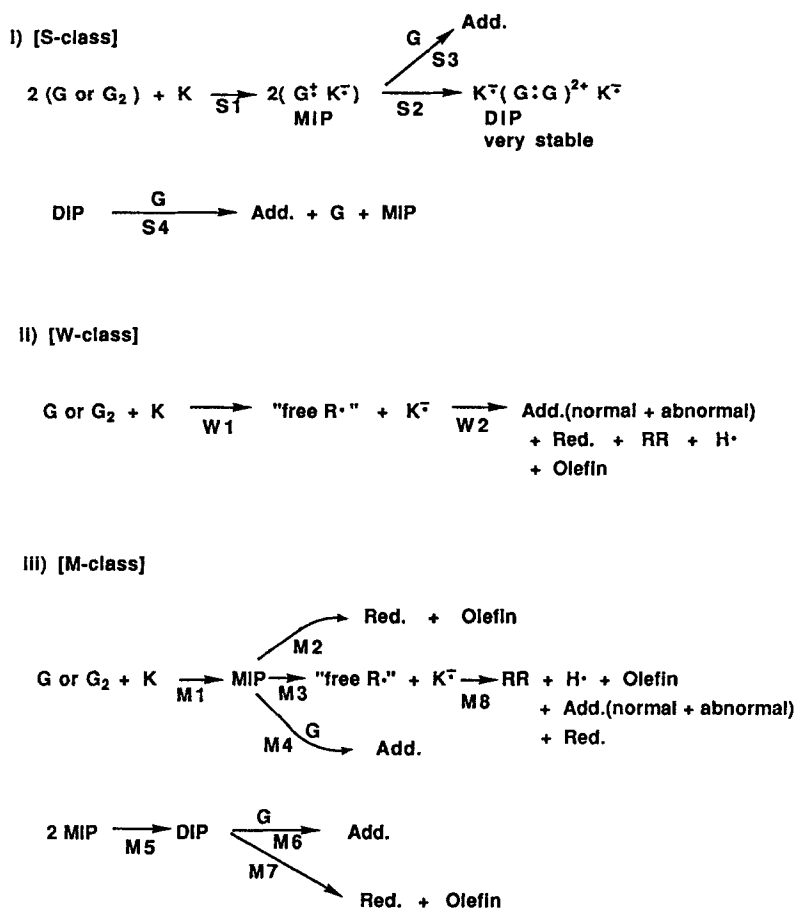
The Grignard reactions of the S-class reagents are simple and give solely addition products, but those of the W-class reagents are more complex, giving a mixture of products. In general, the products consist of a mixture of normal addition product, abnormal addition product, radical coupling product, RR, and reduction product. The Grignard reactions of the M-class reagents are the most complex, and the complexity may depend on the structures of both the Grignard reagent and ketone and also on the polarity of the solvents. Based on the above considerations, we have discussed the Grignard reaction of benzil in previous papers.^{2,5}

In this work we studied the Grignard reaction with 'EtMgBr,' of M-class, and we can rationalize the experimental results along the lines discussed above. In the reactions with substituted benzophenones in DEE the log(Add./Red.) values decrease monotonically with increase in σ -values, but nevertheless the amount of Add. is always greater than that of Red. As shown in



K: ketone, G: Grignard reagent

Scheme 1



Scheme 2

Table 1, 'EtMgBr' is mostly dimeric in DEE. Therefore, the M1 → M4 and M1 → M2 processes could contribute substantially to the overall reaction. In the reaction of benzophenones with a negative σ , the M1 process is slow, but the M4 process is still fast, giving a larger amount of Add. In contrast, in the reaction of benzophenones with positive σ , the M1 process is fast and the concentration of the MIP transiently becomes greater in the reaction solution, giving the M2 process a greater chance of participating because of the higher ionic strength of the reaction solution. Accordingly, participation of the M3 process could be suppressed.

In contrast to the reactions in DEE, in THF 'EtMgBr' is almost monomeric, but a few percent of it still remains dimeric (see Table 1). The reactions in THF are very different from those in DEE. All reactions carried out in THF gave, in general, a greater amount of Red. than Add. and plots of $\log(\text{Add.}/\text{Red.})$ vs σ showed an upward curve having a minimum

near $\sigma = 0$, except for 2-methylbenzophenone. In these reactions, M1 → M2, M1 → M5 → M6 and M1 → M5 → M7 processes could participate substantially, while the contribution of the M1 → M3 process would be negligibly small, since no butane was found in the products.

Although the proportion of the M4 process relative to the M5 process is difficult to predict in a straightforward manner, it certainly depends on the relative concentration of the Grignard reagent. The M4 process would become important in reactions at higher Grignard reagent concentrations, especially in reactions with benzophenones bearing electron-donating substituents. Since in all the reactions in THF we observed the presence of DIP from the characteristic coloration and ESR spectra, the contributions of M5 → M6 and M5 → M7 processes could not be excluded. For $\sigma < 0$, the $\log(\text{Add.}/\text{Red.})$ values decrease with the increase in σ , but for $\sigma > 0$ the values increase with increase in σ .

Comparing the electron-donating abilities of G and G₂, one can safely conclude that that of the latter is larger. Therefore, in the reactions of benzophenones with highly electron-donating substituents such as 4-phenoxy- or 4-methoxybenzophenone, electron transfer from G₂ rather than G will be favoured, and so M4 process giving Add. become relatively more important because another molecule of the Grignard reagent is present near the MIP. With decreasing reduction potential of substituted benzophenones, however, the concentration of MIP in the reaction media increases. Therefore, the M5 → M6 processes via DIP will increase to give again relatively larger amounts of Add. Because of the high stability of DIP, the contribution of the M7 process could be relatively small.

Similar considerations could be applied to the reactions with acetophenone, substituted benzophenones and fluorenone (see Figure 2). In the reactions of 'EtMgBr' with acetophenone, all reactions in DEE, DME and THF gave larger amounts of Add. than of Red. Of the six ketones examined, acetophenone (point 1) is the most difficult to reduce, and in the electron transfer from 'EtMgBr' participation of G₂ will be relatively high, giving larger amounts of Add. In DEE, 4,4'-dichlorobenzophenone (point 5) gave the largest amount of Red., but in THF benzophenone (point 4) gave the most Red. Fluorenone (point 6) gave larger amounts of Add. than did 4-methylbenzophenone, benzophenone and 4,4'-dichlorobenzophenone in all solvents, indicating that the M1 → M4 and M1 → M5 → M6 processes are dominant in the reaction. Steric factors around the carbonyl groups and the radical centre of R· also should not be forgotten. In Figure 1, 2-methylbenzophenone (point 12) gave much larger amounts of Red. than those expected from the σ -values in DEE, DME, and THF. Within the S- and M-classes the R· transfer to give Add. and H· transfer to give Red. should proceed in the sphere of the ion-paired MIP and DIP in the solvent cage, but not via the solvent-separated 'free R·' state. The situation is different from that in the reaction of the W-class reagents. In this case, R· and H· transfers proceed in the solvent-separated 'free R·' state, giving complex mixture of products. The products include RR, abnormal Add. and olefins.

In addition, the structure of the Grignard reagent, especially its steric environment around the β -hydrogen, has a significant effect on the product distribution, but this aspect will be considered in a subsequent paper.

EXPERIMENTAL

Materials. Benzophenone, 4-phenoxybenzophenone and 4,4'-dichlorobenzophenone were recrystallized from ethanol. Acetophenone, 4-methylbenzophenone, 4-methoxybenzophenone, 4-*tert*-butylbenzophenone, 4-fluorobenzophenone, and 4-chlorobenzophenone

were prepared by the Friedel-Crafts reaction and recrystallized from ethanol. 2-Methylbenzophenone was prepared by the Friedel-Crafts reaction and distilled twice under reduced pressure before use. A JEOL JNM 100-MHz ¹H NMR and a JEOL JNM-FX 400 MHz Fourier transform NMR spectrometer were used for product analyses.

Oxidation potentials of ketones. Electrochemical measurements were made with a PAR Model 174 polarographic analyser, a standard H-cell, a glassy carbon working electrode and a platinum wire counter electrode. A solution of a ketone (10⁻³ M) in *N,N*-dimethylformamide containing 0.1 M tetrabutylammonium perchlorate was used. Cyclic voltammograms were recorded at 20 °C under single-sweep conditions. Peak potentials were corrected by applying a ferrocene/ferrocenium electrode.

Determination of degree of association in solutions. The concentration of a Grignard reagent was determined according to the Gilman procedure.⁶ The degree of association of Grignard reagents in solutions was determined by the vapour-pressure depression method using the apparatus shown in Figure 3. First, reservoir A containing a pure solvent and reservoir B

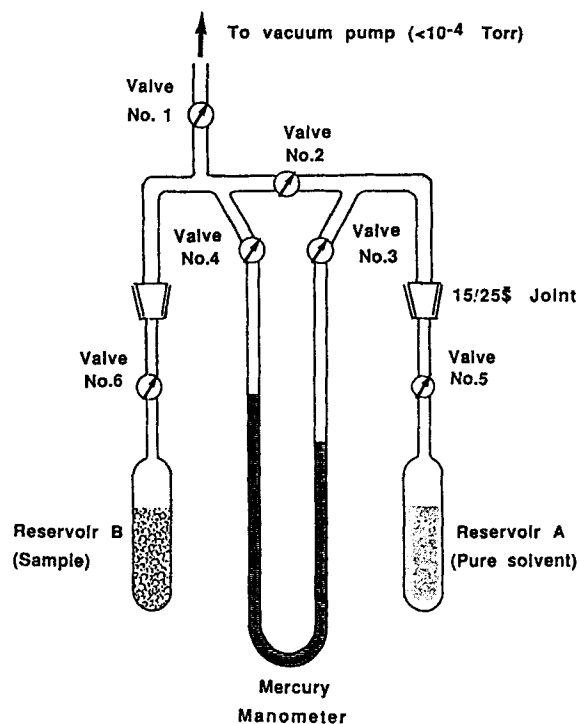


Figure 3. Apparatus for vapour pressure measurement

containing a Grignard reagent in the same solvent were thoroughly deaerated by the freeze-pump-thaw method separately after closing valves 3 and 4. Then valves 5 and 6 were closed, and valves 2, 3 and 4 were opened and the apparatus was deaerated completely. After closing valves 1 and 2, valves 3, 4, 5 and 6 were opened and equilibrated. The vapour-pressure depression was determined from the difference of the two mercury columns.

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