Magnesium bromide in Grignard reagent formation

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Abstract

The progress of the reaction of magnesium with bromocyclopropane in diethyl ether at reflux varies with time in a sigmoid fashion, reflecting an initial induction period during which autocatalysis is evident. The initial addition of $MgBr_2$ to the medium greatly reduces or eliminates the autocatalytic induction period, suggesting that the autocatalysis in the initial absence of $MgBr_2$ is due to its formation. Magnesium does not react with either 1-bromo-2,2,3,3-tetramethylcyclopropane or bromopentamethylbenzene in pure diethyl ether. It reacts smoothly with either in 2.6 M magnesium bromide in diethyl ether, giving the corresponding Grignard reagents (2,2,3,3-tetramethylcyclopropylmagnesium bromide, 28%; pentamethylphenylmagnesium bromide, 49–80%). In the case of 1-bromo-2,2,3,3-tetramethylcyclopropane, by-products representing >44% solvent attack are formed. Magnesium bromide also has more subtle effects. In reactions of magnesium with bromocyclopropane in diethyl ether, the product distribution varies significantly with the initial concentration of the substrate. Initially-added $MgBr_2$ emulates the effect of higher initial concentrations of the substrate, suggesting that the substrate concentration effects are responses to the buildup of polar solutes ($MgBr_2$, RMgBr) as the reaction proceeds. The bromocyclopropane reaction contrasts with that of 5-hexenyl bromide, for which the extent of cyclization is not very sensitive to added magnesium bromide. The early turbidity that usually forms in reactions of magnesium with organic halides in pure diethyl ether is absent for reactions in 2.6 M $MgBr_2$. Turbidity not due to a precipitate (MgX_2, RMgX, or other) may be due to a separation of dilute and concentrated liquid phases of $MgBr_2$ solutions. There are many parallels between Grignard reagent formation and metallic corrosion in contact with aqueous solutions, suggesting that Grignard reagent formation, like aqueous corrosion, involves local galvanic cells.

Key words: Grignard reagent; Magnesium compounds; Bromide compounds

Introduction

Magnesium halides, MgX_2, are by-products of Grignard reagent formation and components of Schlenk equilibria [1, 2]. There is a long and complex history of their effects on Grignard reagent formation [1]. To this we add some observations and interpretations

$$RX \xrightarrow[SH]{Mg} RMgX + RR + MgX_2 + \text{other by-products}$$

$$2RMgX \rightleftharpoons MgX_2 + R_2Mg$$

involving $MgBr_2$ in diethyl ether, focusing on catalysis, entrainment and corrosion theory.

When the solvent is pure ether, the reaction of magnesium with an organic halide typically proceeds in two stages. An induction period, during which little appears to happen, is followed by a period of rapid reaction [1]. The mixture becomes turbid near the end of the induction period. As the reaction proceeds, the solution becomes clear again.

Certain halides are unreactive – the induction period lasts as long as the patience of the experimenter. Other halides are unproductive – they react but give mostly (or entirely) by-products instead of Grignard reagent [3].

Unreactive and unproductive halides have been approached empirically in many ways [1]. The use of finely divided magnesium prepared by special methods has met with considerable success [4], as has mechanical activation of the magnesium [5]. In the case of haloadamantanes, not stirring the reaction mixture increases the yields of Grignard reagents from zero (with stirring) to ~60% [3].

Reactivity problems are often overcome by methods involving magnesium halides (MgX_2) or reactions that

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form them. Thus, iodine is frequently used as an activator, either in a pretreatment of the magnesium or as an additive to the reaction mixture. Bromine has activating effects similar to iodine, and so do reactive

$$I_2 \text{ or } Br_2 \xrightarrow{Mg} MgI_2 \text{ or } MgBr_2$$

alkyl bromides (e.g. ethyl bromide or 1,2-dibromoethane), preformed Grignard reagents (e.g. ethylmagnesium bromide), hydrogen halides and various metal halides [1].

Historically, there are several related threads of ideas concerning the induction period, activation, magnesium halides and entrainment.

Catalysis: MgX_2 promotes reaction

Magnesious halide: $^{\cdot}MgX$ initiates, or otherwise participates in, Grignard reagent formation

Entrainment: simultaneous reactions of an unreactive halide (usually an aryl halide, ArX) and a reactive one (alkyl) lead to both Grignard reagents

Active sites: etching by reaction generates active sites on the magnesium surface

Surface cleaning: etching by reaction cleans the magnesium surface.

Contradicting early speculations that iodine and other agents activate magnesium by etching, cleaning the surface and generating active sites [1], Gomberg and Bachmann found that "a small amount of magnesium iodide activates the metal just as well as does free iodine, so the doctrine of 'etching' is untenable. In this manner, we found it possible to bring about activation in some of the most resistant cases, such as *p*-bromobiphenyl, and apparently even with *p*-iododimethylaniline..." [6]. They proposed that activation is due to magnesious iodide. They also adopted Grignard's explanation of the induction period, that the initial reaction is a Wurtz reaction that forms magnesium halides that catalyze the formation of the Grignard reagent [1, 7]. According to Gomberg and Bachmann, MgX_2 promotes the reaction by reacting with Mg to form $^{\cdot}MgX$, which initiates Grignard reagent formation. However, there is still no substantial evidence sup-

$$2RX + Mg \longrightarrow RR + MgX_2$$

$$MgX_2 + Mg \rightleftharpoons 2^{\cdot}MgX$$

$$RX + {}^{\cdot}MgX \longrightarrow R^{\cdot} + MgX_2$$

$$R^{\cdot} + {}^{\cdot}MgX \longrightarrow RMgX$$

porting this hypothesis or suggesting that magnesious halides play any role at all in Grignard reagent formation. Indeed, the available evidence militates against the last step above [8c]. It is plausible that MgX_2 itself is the active catalyst instead of $^{\cdot}MgX$.

Gilman and Vanderwal found that magnesium bromide etherate, as the solvent, shortens the induction period for the reaction of magnesium with n-butyl bromide from 7.25 min (in pure diethyl ether) to 4.3 min [9]. They also report that the turbidity that usually marks the end of the induction period and the beginning of the reaction does not develop in this medium.

The entrainment method was introduced by Grignard and applied, usually, to unreactive aryl halides [1, 10]. The method was later modified by Pearson *et al.* [11]. In 'Grignard entrainment', a reactive auxiliary halide (usually ethyl bromide) is introduced along with the aryl halide. In 'Pearson entrainment', the auxiliary

$$ArX + EtBr \xrightarrow[SH]{Mg} ArMgX + EtMgBr$$

(Grignard entrainment)

halide is 1,2-dibromoethane, which forms ethylene and $MgBr_2$ instead of a Grignard reagent, so the only Grignard reagent formed is that from the unreactive

$$RX + BrCH_2CH_2Br \xrightarrow[SH]{Mg} RMgX + CH_2{=}CH_2 + MgBr_2$$

(Pearson entrainment)

halide. In practice, Grignard entrainment appears to have been supplanted by Pearson entrainment.

According to Pearson *et al.*, 1,2-dibromoethane "acts in the main part as a cleanser and activator of the magnesium surface", though the $MgBr_2$ formed from 1,2-dibromoethane may also facilitate the reaction by forming a complex with the Grignard reagent [11]. In terms of the present understanding of the mechanism of Grignard reagent formation [8, 12–16], which involves radical intermediates, it is not clear how such complex

$$RX \xrightarrow[SH]{Mg} R^{\cdot} \xrightarrow[SH]{Mg} RMgX \text{ (radical pathway)}$$

formation could facilitate reaction, unless it be by promoting the dissolution of the Grignard reagent and thereby cleaning, or clearing, the magnesium surface. The results of Gomberg and Bachmann cited above suggest that Pearson entrainment could be due to catalysis by $MgBr_2$ instead of etching [6].

Indeed, both Grignard and Pearson entrainment could be due to the formation of the catalyst $MgBr_2$. In some cases a direct pathway to Grignard reagent (a pathway along which $R^{\cdot}$ is not an intermediate) may compete with the radical pathway [14]. Catalysis by $MgBr_2$ could affect either pathway or both. In addition, Grignard (but not Pearson) entrainment could involve the enhancement of productivity by an exchange reaction between $Ar^{\cdot}$ and RMgX [8f].

$$Ar^{\cdot} + RMgX \longrightarrow ArMgX + R^{\cdot}$$

There is considerable evidence that reactions of typical alkyl halides occur largely, or exclusively, through a radical pathway [8, 16]. Partial retention of config-

uration in reactions of optically active substituted cyclopropyl and vinyl halides suggests that a direct pathway competes with the radical pathway in these cases [14],

$$RX \xrightarrow[SH]{Mg} RMgX \text{ (direct pathway)}$$

or

$$RX \xrightarrow[SH]{Mg} [\text{intermediate(s) other than } R^{\bullet}] \xrightarrow[SH]{Mg} RMgX$$

(direct pathway)

and preliminary results from our laboratory suggest that a direct pathway may compete with the radical pathway in reactions of aryl halides as well [8h].

Here we describe some results that are related to the issues outlined above: (i) kinetic evidence of $MgBr_2$ autocatalysis in the reaction of magnesium with bromocyclopropane in diethyl ether, (ii) $MgBr_2$ catalysis of Grignard reagent formation from 1-bromo-2,2,3,3-tetramethylcyclopropane in diethyl ether, (iii) $MgBr_2$ catalysis of Grignard reagent formation from bromopentamethylbenzene in diethyl ether, (iv) effects of the initial concentration of bromocyclopropane and the initial presence of $MgBr_2$ on the product distribution from the reaction of magnesium with bromocyclopropane in diethyl ether, (v) product distributions in Grignard reagent formation from 5-hexenyl bromide in pure diethyl ether and in a solution of $MgBr_2$. We discuss theories of these reactions and suggest that classical aqueous corrosion may provide a model for Grignard reagent formation.

Experimental

General

Reactions and associated manipulations were carried out under an atmosphere of nitrogen (99.98%, dried by passing through 25 cm Drierite and P_4O_{10} columns) or cyclopropane (J.T. Baker) with oven-dried glassware (assembled hot with silicone grease), using Schlenk techniques [17]. Liquids were transferred using nitrogen-purged stainless-steel cannulas or Hamilton gas-tight syringes. Reactions were carried out in jacketed vessels in which water at 37 °C circulated. Yields in reactions of magnesium with organic bromides are based on the amount of bromide consumed.

Materials

Anhydrous diethyl ether (Baker) was freshly distilled from sodium benzophenone ketyl. Concentrated (2.6 M) solutions of $MgBr_2$ in diethyl ether were prepared periodically, manipulated under dry nitrogen, and subsequently stored under nitrogen, or they were prepared *in situ* in the reaction vessel. Cyclopropane, pentamethylbenzene, 1-hexene, methylcyclopentane and 6-bromo-1-hexene were obtained commercially. Commercial bromocyclopropane (Aldrich, 99%) was distilled under nitrogen. 1-Cyclopropyl-1-ethoxyethane [8d], 2,3-diethoxybutane [18], 1-bromo-2,2,3,3-tetramethylcyclopropane [19], 1,1,2,2-tetramethylcyclopropane [19], and bromopentamethylbenzene [20c] were prepared as described in the literature. Magnesium turnings (Strem, 99.8%, or Alfa, 99.99%) were used without preparation. No difference in results was detected between the two kinds of magnesium.

Gas chromatography

Analyses were performed using a Hewlett-Packard HP 5890 instrument with a 30 m, 0.32 mm i.d., SPB-1 fused-silica capillary column, helium carrier gas, flame-ionization detector, and splitless injection. GC peaks were assigned by co-injection with authentic samples and by GC-MS [8d]. For bicyclopropyl (from cyclopropylmagnesium bromide and $CuCl_2$) [21], 1-(2,2,3,3-tetramethylcyclopropyl)-1-ethoxyethane (from 2,2,3,3-tetramethylcyclopropylmagnesium bromide and 1-chloro-1-ethoxyethane) and 1-(2,2,3,3-tetramethylcyclopropyl)-2,2,3,3-tetramethylcyclopropane (from 2,2,3,3-tetramethylcyclopropylmagnesium bromide and $CuCl_2$) [21], crude product mixtures from syntheses were used in co-injections. GC peak assignments were verified by GC-MS (Finnegan 4000 or 4500 quadrupole instrument). Quantitative analyses were based on measured response factors, relative to octane or benzene internal standards, obtained with model mixtures. Mass-based sensitivity factors of 1.0, relative to octane, were assumed for hydrocarbons not available for model mixtures.

2.6 M $MgBr_2$ in diethyl ether

These solutions were prepared in reactions of magnesium with 1,2-dibromoethane in the appropriate amount of diethyl ether, under nitrogen. Since the reaction can be violent, care must be taken to provide adequate venting to release the pressure of the ethylene formed. If the product solution was not used *in situ*, it was filtered (under nitrogen) through a P4 fritted glass filter and stored under nitrogen in a vessel wrapped in foil. Solutions were clear and colorless initially, but after a day they would often discolor (faint yellow).

Reaction of magnesium with bromocyclopropane, 1-bromo-2,2,3,3-tetramethylcyclopropane or 6-bromo-1-hexene in diethyl ether or a solution of $MgBr_2$

The experiment is described in detail for bromocyclopropane. The procedure is similar for the other substrates.

A dry Teflon-coated magnetic stirring bar and magnesium turnings (0.6 or 0.2 g) were placed in a three-necked, water-jacketed (37 °C) reaction vessel fitted

with a reflux condenser (ice water) connected to a thermostatted gas burette and a U-shaped manometer filled with undecane, a silicone-disk-capped stopcock, and a stopper (when reaction mixture was to be quenched on workup) or adapter (when the volatile components were to be distilled from the unquenched reaction mixture). The adapter connected the reaction vessel through a closed stopcock (3 mm bore) to an evacuated, cold (−79 °C) Schlenk tube. Diethyl ether (6.0 or 2.5 ml) was added, stirring begun, and bromocyclopropane (200 or 80 μl) was injected (all at once) into the refluxing solvent. Within 5 min, turbidity, a faint yellow color, and gas evolution (Fig. 1) indicated the beginning of the reaction. The reaction was complete in about 15 min. After 30 or 60 min, the reaction mixture was cooled to room temperature for workup.

When the medium contained $MgBr_2$ initially, the appropriate solution was used in place of pure diethyl ether. When 2.6 M $MgBr_2$ was prepared *in situ*, an appropriate excess of magnesium was placed in the reaction vessel and diethyl ether was added, followed by the required amount of 1,2-dibromoethane, which was allowed to react to completion before bromocyclopropane was added.

Workup A. The volatile components were distilled into the cold (−79 °C) Schlenk tube by slowly opening the stopcok on the adapter (room temperature) and gradually raising the temperature to 37 °C. After the addition of octane (50 μl, Aldrich, 99+%, internal standard for GC), the distillate was analyzed by GC. To the residue in the reaction vessel, diethyl ether (6 ml) and 2,2′-biquinoline (0.5 mg in 100 μl diethyl ether) were added. The purple solution was titrated to the sharp end point (colorless) with anhydrous (±)-2-butanol (Aldrich, 99%) from a microburette [22], from which the 2-butanol was delivered through Teflon spaghetti tubing and a needle through the silicone-capped stopcock on the reaction vessel. Octane (50 μl) was added and a sample of the mixture (2 ml) was taken. The latter was shaken with cold brine (0 °C, 0.5 ml) and the non-aqueous layer was analyzed by GC.

Workup B. Benzene (5 μl, Baker) internal standard for GC and NMR was added and the reaction mixture was cooled to 0 °C. For NMR experiments and for quenching with brine, samples of the solution were withdrawn using a cold (0 °C), gas-tight Hamilton syringe. The non-aqueous layers of quenched samples were analyzed by GC, GC-MS and NMR spectroscopy.

Measurement of change in gas volume. The reaction vessel was purged and filled with cyclopropane from a cylinder. Magnesium and diethyl ether were introduced into the apparatus, stirred, and brought to reflux in a thermostatted bath (37 °C). Additional cyclopropane was admitted until the gas burette indicated that the solution was saturated in cyclopropane. The system was closed and bromocyclopropane was injected, using a syringe, through a septum. Gas volume changes were measured with a thermostatted gas burette.

Correction for extraction of 2,3-diethoxybutane (SS). With either workup, part of the SS formed is extracted into the brine and lost. A series of control experiments shows that the loss is constant, for a variety of conditions and concentrations, such that the actual yield is 1.2×(yield determined by GC on non-aqueous phase after treatment with brine). The yields of SS reported here are computed in this way. Also, the yields of SS reported by Garst *et al.* should be multiplied by 1.2 [8d].

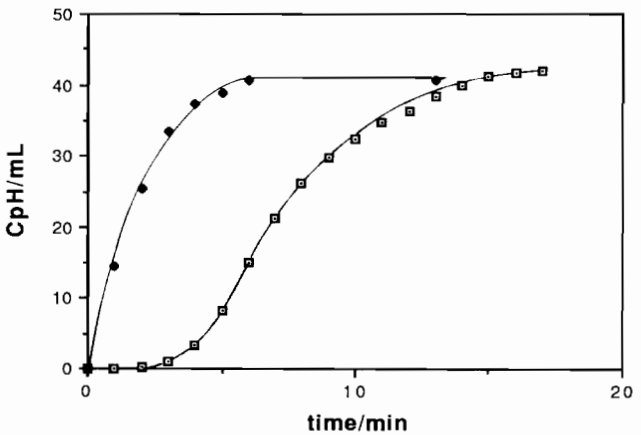


Fig. 1. Evolution of cyclopropane in reactions of magnesium with bromocyclopropane in diethyl ether. □: $[MgBr_2]_0 = 0$. ◆: $[MgBr_2]_0 = 0.18$ M. In each experiment, $[CpBr]_0 = 0.18$ M in diethyl ether under an atmosphere of cyclopropane with Mg turnings in excess by 23–26 fold.

Reaction of magnesium with bromopentamethylbenzene

The procedure is similar to the general procedure for the reaction of bromocyclopropane with the following variations. A special reaction vessel was used with a horizontal female ground-glass port in the side. A male ground-glass joint fitted with a glass spoon, facing up and containing magnesium, was seated in the port so that the spoon was held in the interior of the vessel above the reaction solution. The solvent and bromopentamethylbenzene (a solid) were added and stirred to effect dissolution. Then the magnesium was dumped into the reaction mixture by rotating the male ground-glass joint so that the spoon turned over.

Isolation of pentamethylbenzenecarboxylic acid

The cooled product solution from the reaction of excess magnesium with 0.46 g (2 mmol) bromopentamethylbenzene in 2.6 M $MgBr_2$ in diethyl ether was carbonated by bubbling in dry CO_2. Workup by acidification, filtration, and washing gave 0.20 g penta-

methylbenzenecarboxylic acid (49%). M.p. 202.5–205.5 °C (lit. 210 °C) [20c]. ^{1}H NMR ($CDCl_3$): δ 2.3 (s, 6H), 2.25 (s, 6H), 2.2 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$): δ 177.2, 136.5, 132.9, 132.0, 128.9, 17.7, 16.8, 16.1 ppm.

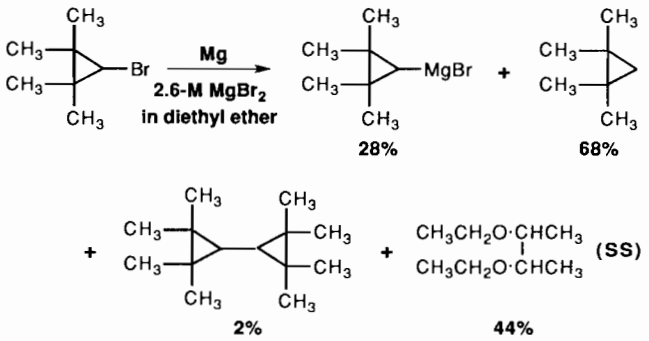
Results and discussion

Reactions of magnesium with bromocyclopropane: catalysis by $MgBr_2$ in diethyl ether

The formation of large amounts of cyclopropane allows reaction progress to be monitored by gas evolution (Fig. 1). In pure ether, reaction progress varies with time in the sigmoid fashion that is characteristic of an autocatalytic reaction. During the induction period (the first three to five minutes), the reaction is imperceptible or slow but accelerating. When the same reaction is carried out in 0.18 M $MgBr_2$ in ether, no induction period is apparent, suggesting that $MgBr_2$ is the autocatalytic product. Alternatively, autocatalysis may be a general polarity effect to which both $MgBr_2$ and RMgBr contribute.

Reactions of magnesium with 1-bromo-2,2,3,3-tetramethylcyclopropane in diethyl ether

In the pure solvent there is no discernible reaction in an hour of stirring. In 2.6 M $MgBr_2$, a smooth reaction begins immediately, with the results shown below. In these experiments, the initial concentration of the substrate was 0.16–0.18 M. The reported yields are representative values from five replications in which there was little variation except for the yield of SS, which spanned the range 27–49% (control experiments show that SS is reactively stable in 2.6 M $MgBr_2$). In this case $MgBr_2$ is a powerful and practically useful catalyst.



Additional experiments cast more light on the question of etching. When magnesium is allowed to react first with 1,2-dibromoethane, the medium replaced by pure diethyl ether, and the substrate added, there is no reaction. When 2.6 M $MgBr_2$ in ether is the medium, the reaction begins immediately, even with untreated magnesium taken directly from the original bottle. Thus, etching is neither necessary nor sufficient, but the presence of $MgBr_2$ appears to be both necessary and sufficient for activation. Surface cleaning could be a factor if the polar medium (2.6 M $MgBr_2$) dissolved surface-bound species (oxides, carbonates, or reaction products) that would otherwise passivate the surface.

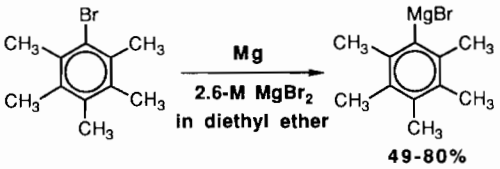
Our original interest in 1-bromo-2,2,3,3-tetramethylcyclopropane was in blocking reactions in which hydrogen atoms are lost from the β-positions, which complicate reactions of bromocyclopropane. The 44% yields of solvent-attack products from the reaction of magnesium with this substrate in 2.6 M $MgBr_2$ represents much more solvent attack than has been reported for reactions of other substituted bromocyclopropanes, such as 1-methyl-2,2-diphenylbromocyclopropane and 1-bromo-1-methylspiro[2.5]octane, in diethyl ether [14]. Some of these reports are based on the yields of RD from reactions in perdeuterated solvents without taking into account kinetic isotope effects on the rate constants for solvent attack. In such cases, the extents of solvent attack in undeuterated solvents are almost certainly underestimated.

If solvent attack occurs when intermediate radicals leave the magnesium surface and go into solution, then a large fraction of the reaction of 1-bromo-2,2,3,3-tetramethylcyclopropane in 2.6 M $MgBr_2$ occurs through radicals that diffuse in solution. This is consistent with our similar previous observations and conclusions about the reaction of dilute (0.18 M) bromocyclopropane in pure ether, where there is evidence of >25% solvent attack [8d] (data for SS corrected as described in 'Experimental'). However, the extent of solvent attack decreases at higher concentrations (see below). For the reaction of 0.18 M bromocyclopropane in 2.6 M $MgBr_2$, the yield of residues from solvent attack is only ~7%.

Reactions of magnesium with bromopentamethylbenzene

Bromopentamethylbenzene is the substrate that was most intensely studied by Grignard and Clément in their classic experiments on entrainment [1, 10, 20]. With ethyl bromide as the auxiliary halide, pentamethylphenylmagnesium bromide is obtained in yields of up to 60% (90% using methyl bromide). In these experiments, bromopentamethylbenzene and the auxiliary halide were allowed to react simultaneously.

In our hands, magnesium does not react with bromopentamethylbenzene in pure diethyl ether. In 2.6 M $MgBr_2$, however, it reacts smoothly, giving a titrated yield of Grignard reagent of 80%. After carbonation, a 49% yield of pentamethylbenzoic acid was isolated. Gas chromatography indicates that the solvent-derived dimer (SS) is formed in very low yield, <0.05%.



Our results show that simultaneous reaction of the substrate and auxiliary halide is not necessary. It is only necessary that the medium contains a high concentration of $MgBr_2$. This suggests that the effectiveness of both Grignard and Pearson entrainment is due to the formation of $MgBr_2$ (along with RMgBr from the auxiliary halide in the case of Grignard entrainment).

In our initial series of experiments, we prepared a stock solution of 2.6 M $MgBr_2$ in diethyl ether and dispensed it as needed. This gave reproducible experimental results at first. Later, they became erratic. This may have been due to some deterioration of the stock solution, even though it was stored in a vessel that protected it from the atmosphere. Perhaps water or some other deleterious substance is leached from the glass of the vessel on prolonged storage. We now prepare fresh 2.6 M $MgBr_2$ from 1,2-dibromoethane, *in situ*, for each experiment.

Reactions of magnesium with bromocyclopropane (CpBr): effects of initial substrate concentration and added $MgBr_2$

Figure 2 shows how the products of reactions in pure diethyl ether vary with the initial concentration of bromocyclopropane. The titer for RMgBr increases with increasing concentration, as does the yield of CpCp, but the yields of CpH, SS and CpS decrease, indicating relatively less solvent attack during reactions with higher initial concentrations of CpBr.

As reaction occurs, $MgBr_2$ and CpMgBr build up. This suggests that the observed effects could be due to increases in the average concentration of $MgBr_2$ (and perhaps CpMgBr) at higher initial concentrations of CpBr. Indeed, the inclusion of $MgBr_2$ in the medium has effects that are similar to an increased initial concentration of CpBr in pure ether (Fig. 3). The CpBr concentration effects tend to level off above 0.5 M (Fig. 2), but added $MgBr_2$ has additional effects even at high initial concentrations of CpBr (Fig. 3). This suggests that it is $MgBr_2$, and not CpMgBr, that has the major effect and that relatively little additional $MgBr_2$ is formed when a large amount is already present. With $MgBr_2$ present initially, Grignard titers representing yields as high as 72% are obtained.

In the absence of initial $MgBr_2$ and at low initial concentrations of CpBr, the yield of CpMgBr is relatively low and those of the products of solvent attack are relatively high. These conditions maximize the fraction of the reaction that occurs at low concentrations of $MgBr_2$, mimicking the induction period. This suggests

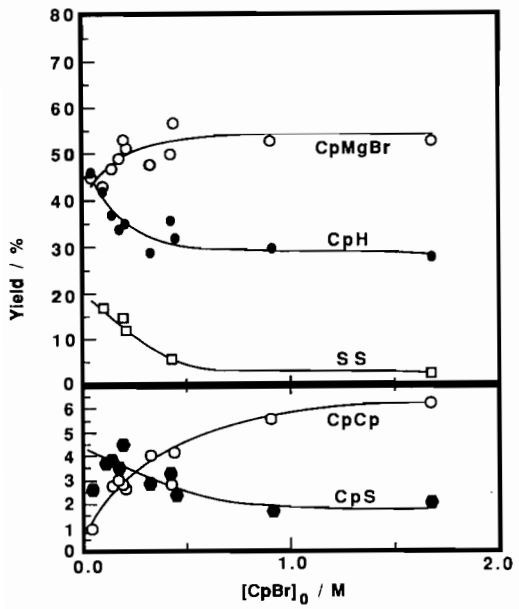


Fig. 2. Yields of products of reactions of magnesium with bromocyclopropane (CpBr) in diethyl ether (SH) as a function of the initial concentration of bromocyclopropane ($[CpBr]_0$).

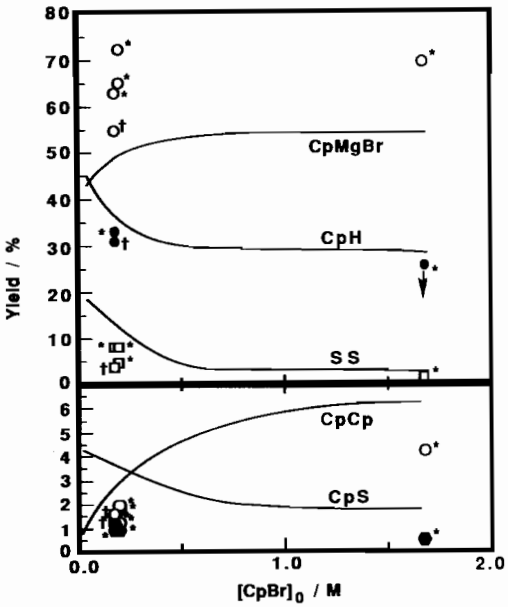


Fig. 3. Yields of products of reactions of magnesium with bromocyclopropane (CpBr) in diethyl ether (SH) as a function of the initial concentrations of magnesium bromide ($[MgBr_2]_0$) and bromocyclopropane ($[CpBr]_0$). The curves represent the yields when $[MgBr_2]_0 = 0$ and are taken from Fig. 2. The points labeled with daggers (†) are for $[MgBr_2]_0 = 0.18$ M and those labeled with stars (★) are for $[MgBr_2]_0 = 2.6$ M. The other symbols are the same as those used in Fig. 2. Since individual experiments are plotted separately, the scatter illustrates experimental variations. The point with a down arrow represents an upper limit; the actual value of the yield was not determined.

that the yield of CpMgBr is relatively low and that of $MgBr_2$ is relatively high during the induction period. The presence of $MgBr_2$, whether generated during the induction period or added initially, promotes the formation of CpMgBr at the expense of solvent attack.

At low initial concentrations of CpBr, in the absence of added $MgBr_2$, solvent attack by Cp$^\cdot$ dominates over its coupling and disproportionation. This can be understood by considering the rate constants and probable concentrations of Cp$^\cdot$. Near the magnesium surface, the latter are probably no more than $\sim 10^{-4}$ M, the magnitude calculated for 5-hexenyl radicals during reactions of 5-hexenyl bromide [8b]. A typical value of k_C, the rate constant for coupling and disproportionation of reactive radicals, is 3×10^9 M^{-1} s^{-1}, giving an effective pseudo-first-order rate constant for coupling/disproportionation of $\sim 3 \times 10^5$ s^{-1} (less if the concentration of Cp$^\cdot$ is less than 10^{-4} M). The pseudo-first-order rate constant for solvent attack is $> 10^6$ [8d, g, 23]*, so more solvent attack than coupling/disproportionation is expected.

As the yield of CpMgBr increases with increasing $[CpBr]_0$, the yield of CpH decreases, but the decrease is proportionally less than the decrease in SS. This is expected because at higher concentrations the increased disproportionation of Cp$^\cdot$ will replace some of the CpH formed by solvent attack at lower initial concentrations. Even so, it is not evident that disproportionation and solvent attack are the only sources of CpH. The attack of Cp$^\cdot$ on CpBr or CpMgBr has not been ruled out as a possible additional source of CpH.

Radical (D model) and direct pathways

For typical alkyl halides, the available data are consistent with the D model (Fig. 4), a radical pathway in which the intermediate radicals diffuse freely in solution [8, 16]. Data for reactions of bromocyclopropane are also consistent with the D model [8d, g]. For optically active substituted cyclopropyl halides, using rate parameters derived from the product distribution for bromocyclopropane, D-model analyses predict ~1% retention of configuration in the Grignard reagent [8d, g], much less than the 10–20% that is observed [14]. Although all other possibilities have not been ruled out [8g], the most likely explanation may be that 10–20% of the reactions of the substituted cyclopropyl halides are through a direct retention pathway, as proposed by Walborsky and co-workers [14].

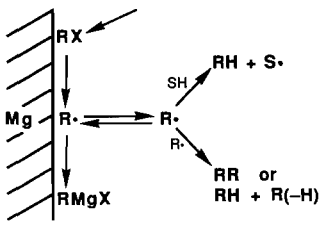


Fig. 4. The D (diffusion) model, in which the intermediate radicals R$^\cdot$ diffuse freely in solution. Reactions of S$^\cdot$ are omitted for clarity. S$^\cdot$ couples and disproportionates with itself and R$^\cdot$. It may also be converted to a Grignard reagent, although we have found no evidence of this when the solvent is diethyl ether and S$^\cdot$ = 1-ethoxyethyl.

*In ref. 23 the authors have determined the pseudo-first-order rate constant for solvent attack by the 2-phenylcyclopropyl radical in diethyl ether as 1.6×10^6 s^{-1}.

The data in Table 1 show that the concentration of $MgBr_2$ does not significantly affect the amount of cyclization that occurs in reactions of magnesium with 5-hexenyl bromide in diethyl ether. Thus, $MgBr_2$ does not increase reactivity in the conversion of intermediate 5-hexenyl radicals to RMgBr. If intermediate cyclopropyl radicals behave similarly, then the increased yields of CpMgBr from CpBr in the presence of $MgBr_2$ are not due to an increased reactivity in the conversion of Cp$^\cdot$ to CpMgBr. As a tentative working hypothesis, we suggest that $MgBr_2$ may enhance the rate of the direct pathway more than that of the radical pathway.

Turbidity

Kharasch and Reinmuth describe (in part) Grignard's method for the preparation of alkylmagnesium halides as follows [1]. "One gram-molecular weight of the desired halide (say methyl iodide) is dissolved in an equal volume of anhydrous ethyl ether, and about 40–50 ml of the solution are added to the magnesium (one gram-atom in a suitably prepared flask). Almost immediately there appears at various points on the surface of the magnesium a brownish (in the case of iodides) or white (in the case of bromides) turbidity, accompanied by a very feeble effervescence. As the reaction accelerates, a white flocculation appears and the ether undergoes lively ebullition. A total of 250–300 g of anhydrous ether is then added in two or three portions, with simultaneous cooling of the flask by means of a stream of cold air. The ebullition moderates, the flocculation (momentarily augmented) disappears almost immediately, the solution regains clarity, and the reaction is resumed with renewed vigor". The initial

TABLE 1. Cyclization in reactions of magnesium with 5-hexenyl bromide in diethyl ether at 37 °C[a]

$[MgBr_2]_0$	RMgBr	QMgBr
0	78	3.8
0.18	73	5.5
2.6	78	4.7

[a]In each experiment the initial concentration of 5-hexenyl bromide was 0.18 M. $[MgBr_2]_0$ = initial concentration of $MgBr_2$ (M). R = 5-hexenyl. Q = cyclopentylmethyl. Values tabulated under 'RMgBr' and 'QMgBr' are the corresponding yields (% based on RBr).

turbidity is absent when the solvent is 'magnesium bromide etherate' or 2.6 M $MgBr_2$ in diethyl ether, according to both our observations and those of Gilman and Vanderwal [9].

The phase diagram for solutions of $MgBr_2$ in diethyl ether suggests an explanation [24]. As $MgBr_2$ dissolves at 37 °C, there is first one clear liquid phase (a dilute solution), then two (dilute and concentrated solutions), then one again (a concentrated solution). In the dilute phase, the concentration of $MgBr_2$ ranges up to about 0.2 M. In the concentrated phase, it is over 2 M.

In reactions promoted by 1,2-dibromoethane (Pearson entrainment), we sometimes find two clear liquid phases at the end of the reaction. The two phases are similar in appearance, and we had visually overlooked their presence, but it was revealed dramatically on one occasion by the doubling of every peak in the ^1H NMR spectrum of the product mixture. One of these phases is probably the dilute $MgBr_2$ phase and the other the concentrated one, both containing dissolved RMgBr and other products of the reaction.

During the induction period in pure diethyl ether, $MgBr_2$ is being formed at the magnesium surface. The balance of its rate of formation, at a particular surface site, and its loss into solution by diffusion may allow its concentration near that site to build up to the point that the concentrated $MgBr_2$ phase forms and separates. This would account for any turbidity that is not due to the precipitation of a solid. The clearing as the reaction proceeds is due either to the development of a single phase or, where two liquid phases are present at the end of the reaction, to the consolidation of liquid phases into macroscopic domains. When the medium is 2.6 M $MgBr_2$, there is no separation of liquid phases because the dilute phase is never present.

These considerations suggest that the layer of the medium immediately adjacent to the magnesium surface may be converted to the concentrated $MgBr_2$ phase during the induction period. Then the main part of the reaction would occur with this medium adjacent to the surface.

Corrosion and Grignard reagent formation

The corrosion of metals in contact with aqueous solutions has been studied intensely [25]. These reactions are valuable models for Grignard reagent formation, which is also a metallic corrosion process.

There is a striking contrast between some mechanisms of Grignard reagent formation and the general theories of corrosion. It is often proposed that Grignard reagent formation occurs at a particular site through intermediates R· and ·MgX [1, 3, 14]. However, corrosion is regarded as an electrochemical process involving

$$\underset{/Mg/}{RX} \longrightarrow \underset{/Mg/}{[R^{\bullet\bullet}MgX]} \longrightarrow \underset{/Mg/}{RMgX}$$

local galvanic cells with separate anodic sites (where the metal is oxidized by cationic dissolution) and cathodic sites (where solutes are reduced) [25].

A scheme like that of Fig. 5 results from the application of the local cell hypothesis to Grignard reagent formation. It is assumed here that halide ions are at or near the magnesium surface as MgX_2 (in some state of aggregation). The halide ions facilitate the dissolution of Mg^{2+}, which (if uncompensated) leaves the metal negatively charged. The (possibly incipient) negative charge and MgX_2 in solution promote the reductions of RX and R· and the formation of RMgX.

This scheme is consistent with several recent findings. Bickelhaupt and co-workers have found evidence of a carbanion (or carbanionoid) intermediate $R:^-$ in a reaction of a special halide [13i]. Corrosion theory suggests that this could be the general case.

Hill *et al.* applied metallurgical techniques and optical and electron microscopes to study the corrosion of magnesium by ethereal alkyl halide solutions [16e]. Pits are formed during the initiation phase. The pits enlarge, eventually overlap, chemical polishing ensues, and a major part of the reaction occurs at a smooth, polished magnesium surface (general corrosion). The initial pitting occurs preferentially at surface defects, especially dislocations [16e]. Bowyer and co-workers also report pitting [26].

Pitting is common in aqueous corrosion [25], where it is an intermediate stage between no corrosion and general corrosion. It is autocatalytically promoted by halide ions (most often chloride ions in practice) [27].

Pitting autocatalysis can be explained with reference to Fig. 6, a diagram of a pitted metal in contact with an oxygenated aqueous solution of NaCl. A high local concentration of Cl^- (perhaps a random fluctuation) promotes the dissolution of M^+ at that site, starting the formation of a pit (frequently at a defect). The dissolution of M^+ makes electrons available for reducing

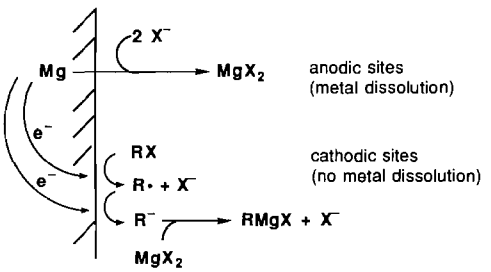


Fig. 5. Local-cell hypothesis applied to Grignard reagent formation. Mg^{2+} goes into solution at anodic sites, RX and R· are reduced at cathodic sites.

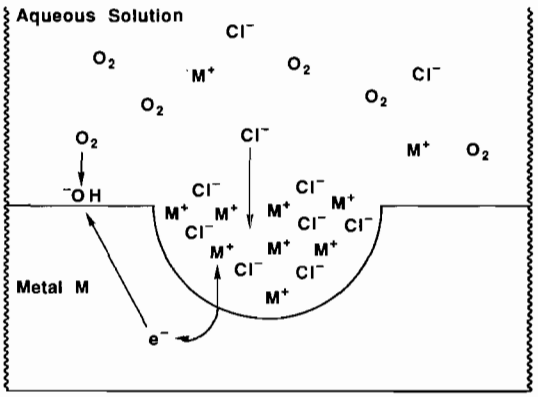


Fig. 6. Pitting corrosion of a metal in contact with an oxygenated aqueous solution of NaCl. (Adapted from ref. 25c, p. 67; Na^+ and H^+ omitted). The solution within the pit (anodic site) becomes very concentrated in MCl as M^+ enters the solution there and attracts charge-balancing ions Cl^-. Oxygen is reduced at points on surfaces adjacent to the pit (cathodic sites). To adapt this to Grignard reagent formation, let M be Mg and replace water with diethyl ether, Cl^- with X^-, O_2 with RX (and intermediate radicals R·), and ^-OH with R^- (RMgX).

O_2, and the loss of electrons allows more M^+ to dissolve. As M^+ dissolves, it attracts Cl^- and the solution that fills the pit becomes more concentrated in MCl, promoting further dissolution of M^+ and concomitant reduction of O_2. The reduction of O_2 occurs mostly on the surfaces adjacent to the pit, partly because O_2 is not very soluble in concentrated electrolyte solutions such as that within the pit [27]. If the metal in Fig. 6 is magnesium, the water is replaced by diethyl ether, the oxygen is replaced by RX (and the intermediate radical R·) and the hydroxide ion by RMgX, and the halide ion is allowed to be bromide or iodide, as well as chloride, then this figure could describe pitting in Grignard reagent formation.

Indeed, there are striking correspondences between aqueous pitting corrosion and pitting in Grignard reagent formation [16e, 25–27]. (i) In both cases metal halides catalyze the reaction. (ii) In both cases pits tend to form at defects or other imperfections. (iii) In both cases there is an autocatalytic initial (induction) period (Fig. 1). (iv) In both cases initial pitting is followed eventually by general corrosion.

The local-cell formulation of Grignard reagent formation is further supported by the finding that pitting patterns depend on the nature of the halogen X but not on the nature of the organic group R [16e]. This suggests that X is present in the transition state for the dissolution of magnesium but that R is not. This is expected under the local cell hypothesis, where the dissolution of the metal occurs at an anodic site (promoted by X^-) while no metal dissolution occurs at the sites where RX and R· are reduced (Fig. 5).

After the pits overlap, the reaction of magnesium with an organic halide is interpreted as typical general (uniform-attack) corrosion involving local galvanic cells. This is also well known in aqueous corrosion: "For a smooth, single-component metal surface the anodic and cathodic sites will be separated, at any one instant, by only a few nanometers. The areas will shift with time so that the surface reacts evenly, thus undergoing general corrosion" [28].

The corrosion picture of Grignard reagent formation provides an interesting perspective on the question of the roles, if any, of magnesious halides. As far as reduction is concerned, the metal is an inert electrode; it merely supplies electrons. The uncompensated loss of electrons would leave the metal with a delocalized net positive charge. No $^{\cdot}Mg^+$ would be present as a definite species such as ·MgBr. However, one could salvage the notion that magnesious ions are involved by assigning all of the net positive charge to individual atoms of the metal lattice, one unit per Mg atom, thereby describing the reacting metal as a mixture of $:Mg^0$ and $^{\cdot}Mg^+$.

Even this picture is not justified. The uncompensated loss of Mg^{2+} from the metal would leave it with a delocalized net negative charge. In this case, the charged metal would have to be reviewed as a mixture of $:Mg^0$ and $:Mg^{\cdot-}$ instead of $:Mg^0$ and $^{\cdot}Mg^+$.

We have no definitive information about the charge that develops on the magnesium during Grignard reagent formation. If the loss of electrons precedes that of Mg^{2+}, then it will be positive, but if the loss of Mg^{2+} precedes that of electrons, then it will be negative. Either situation could obtain. However, the fact that reactions of alkyl bromides are (nearly) diffusion-limited [16] suggests that the loss of Mg^{2+} is not rate-determining, that it is (nearly) equilibrated (as it would be in the absence of a concomitant reduction process), that a negative charge develops on the magnesium during the reaction, and that magnesious species are not intermediates in any sense.

The local cell hypothesis and pitting can also provide a framework that may help explain a preference for forming $MgBr_2$ instead of RMgBr during the induction period. Since Mg^{2+} dissolution takes place only in the pits, the active anodic area of the magnesium is relatively small, the anodic current density is relatively high, and concentrated solutions of $MgBr_2$ build up in the pits. If the reduction of RBr to R· takes place mostly at points outside the pits, the active cathodic area may be relatively large, the cathodic current density relatively low, and the concentration buildup of $MgBr_2$ relatively slow. The radicals R· may diffuse considerable distances and may frequently re-encounter the magnesium surface at inactive or not very active spots (insufficient $MgBr_2$ concentration, surface passivated by an oxide or other

coating). This would decrease the probability of RMgBr formation and increase that of solvent attack or coupling/disproportionation, both of which result in $MgBr_2$ formation.

Conclusions

$MgBr_2$ can have dramatic effects on Grignard reagent formation from organic bromides in diethyl ether. It is a catalyst for the reactions of magnesium with organic bromides, and its presence may also be necessary for the conversion of intermediate radicals to Grignard reagent. Its initial absence is responsible for the induction period, during which it is formed autocatalytically. During the induction period, the formation of $MgBr_2$ appears to be favored, relative to Grignard reagent. The induction period and autocatalysis are greatly attenuated or eliminated when the medium contains $MgBr_2$ initially.

Catalysis by $MgBr_2$ can be synthetically useful. The presence of $MgBr_2$ brings about reactions of substrates such as 1-bromo-2,2,3,3-tetramethylcyclopropane and bromopentamethylbenzene, which fail to react in pure diethyl ether. The effectiveness of both Grignard (using ethyl bromide) and Pearson (using 1,2-dibromoethane) entrainment can be ascribed to the formation of $MgBr_2$. In the case of bromopentamethylbenzene, a substrate studied intensely by Grignard, the entrainment procedure (co-reaction of halides) is not necessary if $MgBr_2$ is pre-formed in sufficient concentration.

In reactions of 1-bromo-2,2,3,3-tetramethylcyclopropane in 2.6 M $MgBr_2$, the large amount of solvent attack ($>44\%$) implies that a large fraction of the reaction is through intermediate 2,2,3,3-tetramethylcyclopropyl radicals that diffuse in solution. However, part of the reactions of bromocyclopropanes may be through a direct, rather than a radical, pathway. There is no evidence of a direct pathway in reactions of typical alkyl halides, and there is no significant effect of $MgBr_2$ on the extent of cyclization in reactions of 5-hexenyl bromide, indicating that the presence of added $MgBr_2$ does not affect significantly the rate at which intermediate 5-hexenyl radicals are converted to Grignard reagent, relative to their rate of cyclization. This suggests that the effects of $MgBr_2$ on the reaction of bromocyclopropane might be to enhance the direct pathway, rather than to enhance the rate of conversion of intermediate cyclopropyl radicals to Grignard reagent, relative to the rate of solvent attack.

The turbidity that forms early in reactions in pure diethyl ether is absent in reactions in 2.6 M $MgBr_2$. Where it is not due to a solid precipitate, it may be due to the separation of a liquid phase that is concentrated in $MgBr_2$.

Grignard reagent formation has many features in common with the corrosion of metals in contact with aqueous solutions. A mechanism patterned after the local galvanic cell model for aqueous metallic corrosion provides reasonable hypotheses describing some of the features of Grignard reagent formation that remain to be explored in detail, e.g. the dissolution of magnesium and the conversion of intermediate radicals into Grignard reagents.

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