THE SIGNIFICANCE OF HALIDE IN GRIGNARD REAGENTS

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Received May 27, 1964

ABSTRACT

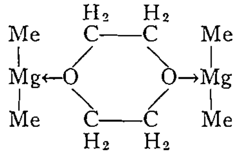
The optical activity of 1-phenylethanol from benzaldehyde and methyl chloride Grignard reagent coordinated with (+)2,3-dimethoxybutane is about one fourth of that found for the same product when bis-methylmagnesium is the reagent. The difference has been attributed to the relative coordinating power of magnesium chloride versus the optically active ether.

Grignard reagents usually contain bound halogen because they are commonly prepared by corrosion of magnesium by means of an organic halide. Indeed, this process historically defines the reagent. However, these reagents may be rendered halogen free by the dioxane precipitation technique of the Schlenks (1) and the resultant solution of bis-organomagnesium also has been considered to be a Grignard reagent. We adhere to this extended definition largely because the amount of magnesium halide in a Grignard reagent is dependent on the type of halide and upon the method of reagent preparation. Thus a reagent series may exist with bis-organomagnesium at one extreme and Grignard reagent saturated with magnesium halide at the other. Such a series would be important only if there is a difference in reactivity in time or type between the extremes. Interest in these differences has increased during recent years (2, 3, 4). In this report the difference in coordination of the organometallic compound with an ether has been investigated.

The method we used is the induction of optical activity in a product of Grignard reagent addition (5, 6, 7) by use of (+)2,3-dimethoxybutane to effect an asymmetric synthesis. We synthesized 1-phenylethanol from methyl Grignard reagent and benzaldehyde and compared yields and optical rotation when either bis-methylmagnesium or methyl chloride Grignard reagent is used.

For the comparison to be meaningful it is important that the first of these reagents be quite free from halide. Mosher (4) found it difficult to attain this condition. By contrast, our precipitate initially contains not only the halide *in toto* but also some of the halogen-free complex. To obtain a reasonable yield of bis-methylmagnesium we must wash the precipitate thoroughly. Subsequently a small amount of white precipitate tends to appear in the solution, presumably because of temperature variations. However, both the solution and the slight precipitate are halogen free by silver halide test. The difference between our results and those of Mosher may be due to our specific reagent or else to the dioxane–Grignard ratio or to our use of heat during the precipitation.

The halide-free solution contains bis-methylmagnesium dioxanate or dioxanate–etherate, so these ethers must be removed to ensure that the optically active ether will be fully effective. Most of the diethyl ether is removed easily at 50 °C under 1 atm of nitrogen, leaving a solid residue. Comparison of the weight of this residue with the basic magnesium equivalence, according to titration (8), indicates a composition of one-half dioxane per mole of bis-methylmagnesium.



The removal of dioxane occurs under a pressure of 0.001 mm of mercury, slowly at 25 °C as is shown by the upper curve of Fig. 1 and more rapidly at 50 °C (lower curves). The weight loss does not reach the level of bis-methylmagnesium even when the final temperature is raised to 140°. This apparent retention of some dioxane even after 4 h is probably an analytical error caused by the necessity of releasing the systems to atmospheric pressure by means of nitrogen to make the intermediate weighings. An alternative possibility, splitting of the ether at elevated temperature, is unlikely because in preparative experiments involving only an initial and final weight (3), the loss conformed with complete removal of ether. Moreover, the amount of dioxane condensed in a dry ice trap during the experiments shown in Fig. 1 is exactly 0.5 mole.

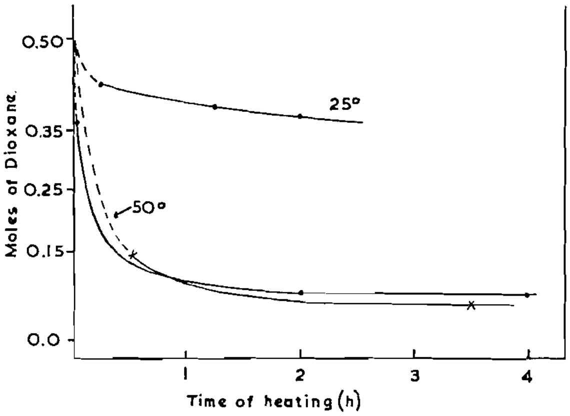
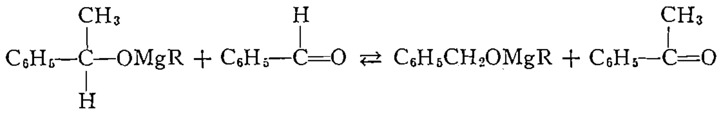


FIG. 1. Removal of ether from MeMg at < 0.001 mm pressure.

Ether-free bis-methylmagnesium is insoluble in benzene but the addition of a molar equivalent of (+)2,3-dimethoxybenzene to the benzene suspension causes immediate solution with heat evolution that is large in consideration of the ease with which dioxane removal is effected. Doubtless the strong coordinating power of the optically active ether is responsible for the ease with which methyl chloride reacts smoothly with magnesium in a solution of 1 molar equivalent of this ether in an equal volume of benzene to give the halide-containing Grignard reagent for our comparative reactions.

There are certain disadvantages in the reaction that we have chosen for demonstration. The chief disadvantage is a concomitant oxidation–reduction of the Meerwein type (9), because the benzyl alcohol so produced is difficult to separate from 1-phenylethanol by distillation or absorption chromatography on alumina. Moreover the by-product formation



$$C_6H_5\text{—}\overset{\displaystyle CH_3}{\underset{\displaystyle H}{C}}\text{—}OMgR + C_6H_5\text{—}\overset{\displaystyle H}{C}{=}O \rightleftarrows C_6H_5CH_2OMgR + C_6H_5\text{—}\overset{\displaystyle CH_3}{C}{=}O$$

is greater in the system containing bis-methylmagnesium than in the halide-containing reagent, so the optical purity may appear to be lower than is warranted by its actual enantiomer content. Nor can it be purified by crystallization for closer evaluation because the racemic compound separates preferentially upon cooling. Against these disadvantages is the reliable knowledge of the specific rotation, +13.02°, of optically pure 1-phenylethanol (10, 11).

The two reactions were carried out with the same ratio of magnesium to carbonyl in order that only one C—Mg linkage would be involved in the comparative reactions. The results are shown in Table I where the halide-containing reagent is nominally described as "MeMgCl".

TABLE I

Asymmetric synthesis of 1-phenylethanol

Expt. No.	Grignard reagent	Yield of product (%)	n_D^{20}	$[\alpha]_D^{25}$ (neat)	Optical purity (%)
1	MeMgCl	74	1.5256	-0.72 ± 0.02	5.5
2	MeMgCl	82	1.5251	-0.59 ± 0.01	4.5
3	Me_2Mg	61	1.5283	-2.40 ± 0.01	18.5+
4	Me_2Mg	67	1.5256	-2.61 ± 0.01	20.0+

It may be seen from these experimental values that the extent of asymmetric synthesis is almost four times higher in absence of halide than in its presence. Actually the difference must be greater, because the product of expt. 3 when it was analyzed by gas–liquid chromatography was found to contain 10–15% of benzyl alcohol and acetophenone and therefore only 85% of the active alcohol, whereas the active alcohol of expt. 1 was essentially pure. Only traces of acetophenone and benzyl alcohol were found in the latter sample.

Thus it is the experimental fact that asymmetry is induced by an optically active ether much more when magnesium halide is absent than when it is present in the reaction between methyl Grignard reagent and benzaldehyde. Unfortunately, interpretation of this phenomenon depends upon a knowledge of the manner in which magnesium halide participates in Grignard system and this knowledge is largely lacking. For example there is still much controversy (ref. 2, p. 99), after 60 years, about the relative importance of the several constituent forms in the so-called Schlenk equilibrium.

$$2RMgX \rightleftarrows R_2Mg + MgX_2 \rightleftarrows R_2Mg\cdot MgX_2$$

However, none of the conclusions is entirely definitive. The demonstration by X-ray diffraction (12) that bromobenzene Grignard reagent yields crystals of structure $RMgX\cdot 2ET_2O$ tells nothing about the composition in solution, as is evident in the fact that diphenylmagnesium may be isolated in good yield from such a solution after the halide in the system is precipitated by dioxane. Actually these observations lead only to the conclusion that Grignard reagent systems are labile.

Morever there is evidence that any one system may be altered by the environment and perhaps by the temperature. Ashby and Becker (13) have shown that the state of complexity is dependent on the ether that is involved with the reagent. In tetrahydrofuran their ebullioscopic studies are interpreted to show that ethyl chloride and ethyl bromide Grignard reagents actually exist as RMgX, whereas the boiling point elevation in other ether media (14, 15) have indicated that RMgX is not predominant.

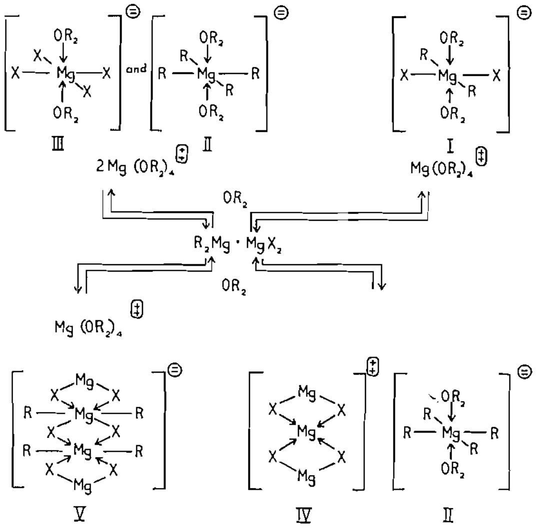
Actually even greater complexity is possible. After Jolibois (ref. 2, p. 109) showed that

Grignard reagents are electrically conducting it was found by electrolytic transport studies (16–19) that they show ionic properties where magnesium is both in the cation and the anion. In this circumstance ebullioscopic evidence for the monomeric form, RMgX, may also be interpreted in terms of an ionized dimer.

$$2\mathrm{RMgX} \rightleftarrows \mathrm{R_2Mg_2X_2} \rightleftarrows \mathrm{Mg^{++}}\text{ and }(\mathrm{MgR_2X_2^{--}})$$

At the present time one cannot say whether monomer, dimer, ion pair, or ions predominate. Probably the predominance depends upon the specific reagent as well as the reaction medium. Each will serve for description, but the ionic formulation seems to be convenient to illustrate the effect of magnesium halide on our asymmetric synthesis.

An explanation is needed for the fact that although halogen-free Grignard reagents ordinarily are less reactive than those in which halide is present (20, 21) the presence of magnesium halide in the present reaction tends to reduce the extent of asymmetric induction due to an optically active solvent. The anomaly is resolved if magnesium halide is considered to be alternative to the ether as a coordinating agent. To the extent that it displaces (+)2,3-dimethoxybutane the tendency for enantiomeric preference cannot occur.



The deleterious effect of magnesium halide is not apparent in the ion pair I nor in ion pairs II and III because III would not enter into product formation with adducts like benzaldehyde. Likewise the asymmetry-inducing ether in the ion pair IV–II ought to be free to exert its influence on the entering adduct because the magnesium halide (even in excess over the composition $\mathrm{R_2Mg \cdot MgX_2}$) is relegated to the cation. However, in the ion pair V the ether would be ineffective because it has been excluded from coordination by magnesium halide which occupies its place in the anion. Although the ether might (or might not) solvate the cation its effectiveness at this distance ought to be minimal, especially if the pair is dissociating in the medium. The existence of a complex species like V in significant amount cannot be excluded. Indeed it may be noted that its composition is such that it could be the source of the $\mathrm{Et_2Mg}$ plus $\mathrm{EtMg_2Cl_3 \cdot THF}$ which was separated from solution by Ashby and Becker if, as seems likely, their $\mathrm{R_2Mg}$ was solvated.

Obviously there may be many variations of these five typical ions pairs, and it is apparent that complexity and not necessarily charge separation is the significant factor. No matter how the Grignard reagent is described the effect of magnesium halide is best explained as a displacement at the reaction site of the asymmetry-inducing ether. No doubt the explanation is incomplete because the geometry of the complex must also be a factor. But this geometry is an additional attribute which will be discussed in a forthcoming extension of the present work.

EXPERIMENTAL

Methyl Chloride Grignard Reagent

Into a dry, nitrogen-filled flask fitted with a dry ice cold-finger condenser, mercury-sealed stirrer, and gas inlet tube leading near the bottom of the flask were placed 9.7 g (0.40 g-atom) of distilled magnesium and 30 ml of diethyl ether. Approximately 2 g of methyl chloride was introduced, and the mixture stirred until reaction started (ca. 10 min). When the reaction ceased the mixture was diluted with 200 ml of diethyl ether, and the rest of the methyl chloride (initially 15.7 g, 0.31 mole) was introduced during 15 h with occasional cooling of the mixture to control the rate of reaction. The reaction was accompanied by the formation of a thick, gray precipitate. The mixture was stirred 4 h longer at 25°, then poured under nitrogen into a centrifuge bottle. The clear colorless supernatant layer obtained by centrifuging at 1 500 r.p.m. for 20 min was transferred by syringe to a second three-necked flask, and the precipitate washed with four 30 ml portions of ether (Gilman test, negative). Titration of an aliquot of the ether solution indicated 0.272 equivalents (88%) of basic magnesium.

Solvent-Free Dimethylmagnesium

To the rapidly stirred methyl chloride Grignard reagent, described above, was added 27.3 g (0.31 mole) of dioxane during 15 min. The mixture was heated under gentle reflux with stirring for 30 min longer, then was poured under nitrogen into a centrifuge bottle. The supernatant layer formed on centrifugation was found to contain 0.118 equivalents (38%) of magnesium. Six washings of the precipitate with 25 ml portions of ether raised the yield to 0.130 equivalents (42%). A test of an aliquot was made in acidified silver nitrate. The chlorine-free ethereal solution of dimethylmagnesium slowly deposited a white solid on standing.

In order to obtain solvent-free dimethylmagnesium, the ether content of the dimethylmagnesium was determined at various temperatures in the following way.

Into a weighed nitrogen-filled 50 ml distilling flask, connected through an interchangeable joint to a liquid nitrogen trap and thence to a vacuum system, was placed 10 ml of a stock solution of dimethylmagnesium in ether (0.169 mmole/ml by titration, or gravimetrically as the oxinate). The ether was removed by distillation with an external bath at 50° leaving a white solid. The flask was then cooled in dry ice and evacuated to < 0.001 mm pressure. The dry ice was removed and the flask temperature returned to 25° during 20 min. At suitable intervals (ca. 1 h), the flask was filled with nitrogen, removed from the vacuum line, and weighed. The above procedure was repeated at various temperatures so that plots of weight vs. time were obtained. No magnesium was lost from the flask at high temperatures since the magnesium content of the residue was the same after heating as before. The magnesium content was determined by first dissolving the residue in dry ether, hydrolyzing with 15 ml of 0.5 *N* HCl, and precipitating the magnesium as the oxinate (22).

In another experiment, the solvent was removed from an ether solution containing 0.0514 mole (2.79 g) of dimethylmagnesium. Evaporation of the ether with an external bath at 50° left 5.36 g (corresponding to $Me_2Mg \cdot 0.57$ dioxane) of white solid. The flask was cooled in dry ice and evacuated to < 0.001 mm pressure, then warmed to 25° during 20 min. After 10 min at 25° (0.001 mm), the residue weighted 4.79 g (corresponding to $Me_2Mg \cdot 0.44$ dioxane). The cold trap between the sample and the vacuum system was cleaned and the apparatus reassembled. After evacuating the system to < 0.001 mm again, the dimethylmagnesium was heated to 75°. At the end of 4 h, the residue weighed 3.072 g (corresponding to $Me_2Mg \cdot 0.07$ dioxane). This weight is 10% higher than expected from the analysis of the starting solution by titration, but the preceding experiment (Fig. 1) also shows that a 10% weight excess exists even when the ether is removed at a higher temperature. The volatile material collected in the cold trap was distilled *in vacuo* into a weighed tube. The colorless liquid weighed 1.720 g (100%) and melted at 8.5–9.5°. A mixture melting point with dioxane was not lowered.

1-Phenylethanol

(a) From Dimethylmagnesium

To solvent-free dimethylmagnesium (0.0514 mole, 2.79 g) was added 50 ml of benzene, then 6.0 g (0.051 mole) of dextro-2,3-dimethoxybutane (5). Although the solid was insoluble in benzene, dissolution was rapid on addition of the ether and the system became very warm. The ether solution was cooled in an ice bath; then a solution of 6.05 g (0.057 mole) of freshly distilled benzaldehyde in 15 ml of benzene was added to it during 20 min. Fifty min after the addition was complete, the pale yellow solution was hydrolyzed with 50 ml of cold 15% aqueous ammonium chloride. The organic layer was separated, washed with water, and dried over anhydrous potassium carbonate. The solvents were removed under reduced pressure and the pale yellow residual oil distilled at 12 mm pressure. The main fraction boiling at 85–86° (12 mm) weighed 4.20 g (67%). The before- and after-fractions, boiling two degrees on either side of this range, amounted to 0.76 g. The oil boiling at 85–86° (12 mm) had a melting range of 5.0–7.5°, $n_D^{20} = 1.5283$, and showed $[\alpha]_D^{25} = -2.43 \pm 0.04°$ in 95% ethanol ($c = 10.03$), $[\alpha]_D^{25} = -3.06 \pm 0.08°$ in chloroform ($c = 5.95$), and $[\alpha]_D^{25} = -2.40 \pm 0.01$ (neat). A portion (1%) of the product was analyzed by gas–liquid chromatography. It contained 15–20% of benzyl alcohol and acetophenone. The rest of the oil was dissolved in 15 ml of petroleum ether and cooled to −12°. The solid which separated was crystallized twice more by the same method to give 0.90 g of material melting at 15–17°. A small amount of material melting at 20.0–20.5° was obtained by further crystallization. The specific rotation of the material melting at 15–17° was −1.0° (neat), $n_D^{20} = 1.5233$. The material in the filtrate from the above purification procedure showed $[\alpha]_D^{25} = -2.75 \pm 0.01°$ (neat).

(b) From Methyl Chloride Grignard Reagent

To 2.43 g (0.10 g-atom) of sublimed magnesium under nitrogen was added 7.0 g (0.06 mole) of dextro-2,3-dimethoxybutane (5) in 25 ml of benzene. Methyl chloride was then slowly added to the stirred mixture through a gas inlet tube leading beneath the surface of the organic liquid (the reaction started within 10 min). The reaction mixture was stirred a further 1.5 h at 25° after the addition of methyl chloride (3.0 g, 0.06 mole) was complete, then was diluted with 25 ml of benzene. Titration of an aliquot of the clear, colorless supernatant layer (unchanged magnesium removed) indicated 0.047 equivalents (78%) of basic magnesium.

The stirred ice-cold Grignard solution was treated with 2.66 g (0.025 mole) of freshly purified and distilled benzaldehyde in 15 ml of benzene over a period of 15 min. A colorless oil separated from the reaction medium during the addition. Stirring was continued 20 min longer, then the mixture was hydrolyzed with 50 ml of cold 15% ammonium chloride solution. The organic layer was separated, washed with water, and dried over anhydrous sodium sulphate. Removal of the organic solvents by distillation left a colorless oil that was distilled under reduced pressure. The main fraction distilled at 79–80° (9 mm), weighed 2.5 g (82%), n_D^{20} 1.5251, and had a specific rotation of $[\alpha]_D^{25} = -0.59 + 0.01°$ (neat).

ACKNOWLEDGMENTS

The authors are grateful for financial support from the National Research Council during this investigation. Technical aid from M. Malaiyandi is acknowledged.

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