

Infrared Observations on the Structure and Reactions of Grignard Reagents

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The infra-red spectrum of dimethylmagnesium has characteristic features common with spectra of methylmagnesium halide/diethyl ether preparations. Complex formation between ethers, esters, and ketones and magnesium halides or Grignard reagents is causing a decrease in frequency of characteristic absorption bands. By means of flow reactor technique it is shown that the complex is formed within 5 msec after mixing of butylmagnesium bromide with either acetone, benzalpinacolone or *sec.* butyl crotonate in diethyl ether solution. The complex formation is thus a fast reaction but from observation of the spectra it may be inferred that the reaction is not complete and that an equilibrium is reached. Disappearance of the initial complex was followed by spectroscopy or by calorimetry and the results indicate a 1. order scheme for the rearrangement of the ketone/Grignard reagent complex. This simple rate law is not followed by the reaction of the crotonic ester/Grignard reagent complex.

In spite of the vast amount of work which has been dedicated to the problems of the constitution of the Grignard reagents as well as to the mechanisms of their reactions, only a few of the basic viewpoints from numerous theories can be said to have developed into established facts.

The theory of an initial complex formation between the Grignard reagent and the substrate seems to be widely accepted, although precise knowledge of details of the problem are missing. According to the theory, as it was formulated by Meisenheimer,¹ the magnesium forms coordination bonds to the oxygen atoms of two solvent molecules (*e.g.* diethyl ether) and in the course of the reaction, ether oxygen is supposed to be exchanged with carbonyl oxygen with the formation of a more or less stable complex. The complex may be capable of unimolecular rearrangement to product (alcoholate, enolate etc.) but most workers seem to accept the theory first presented by Pfeiffer and Blank² and later stressed by Swain,³ that the complex may react by 1,2-addition only with the assistance of a second molecule of Grignard reagent, which may or may not be regenerated during the reaction.

Among the unsettled questions in the theory is that of the relative reaction rates of complex formation and rearrangement or reaction; and the exact composition of the complex is unknown, since several potential attacking

species (RMgX , $\text{MgX}_2\text{R}_2\text{Mg}$, $(\text{RMgX})_2$, RMg^+ etc.) seem to exist in ether solutions.⁴

In the present investigation some of these problems have been tackled by the study of infra-red spectra of Grignard reagents before, during, and after reaction.

As shown by Hamelin and Hayes⁵ the ether molecules which are coordinated to magnesium (RMgX , MgX_2 , R_2Mg) give rise to infra-red absorption peaks at 780, 834, 999, and 1035 cm^{-1} . These bands seem to originate from and replace the peaks at 793, 845, 916, 934, and 1120 cm^{-1} in the undisturbed ether spectrum, and the possibility seems to exist to evaluate the relative amounts of "free" and "bound" ether in a solution of electrophilic magnesium. In contrast to the electrophilic magnesium compounds a solution of magnesium alcoholate (heptanol) showed no absorption corresponding to "bound" ether.

Spectra of solid CH_3MgCl (Fig. 1) and CH_3MgBr prepared as etherates by evaporation of solvent or by precipitation with petroleum ether, and the spectrum of solid MgBr_2 -etherate all showed the ether spectrum in its "disturbed" form without the presence of any absorption corresponding to unbound ether. The three spectra were almost identical, but in the case of CH_3MgCl -etherate and CH_3MgBr -etherate, the spectra showed two narrow and intense bands at 1190 cm^{-1} and 1206 cm^{-1} which were present also in the spectrum of ether-free $(\text{CH}_3)_2\text{Mg}$ (Fig. 1). The bands also became visible in a film of CH_3MgI after removal of some of the bound ether at 80° and 1 mm Hg.

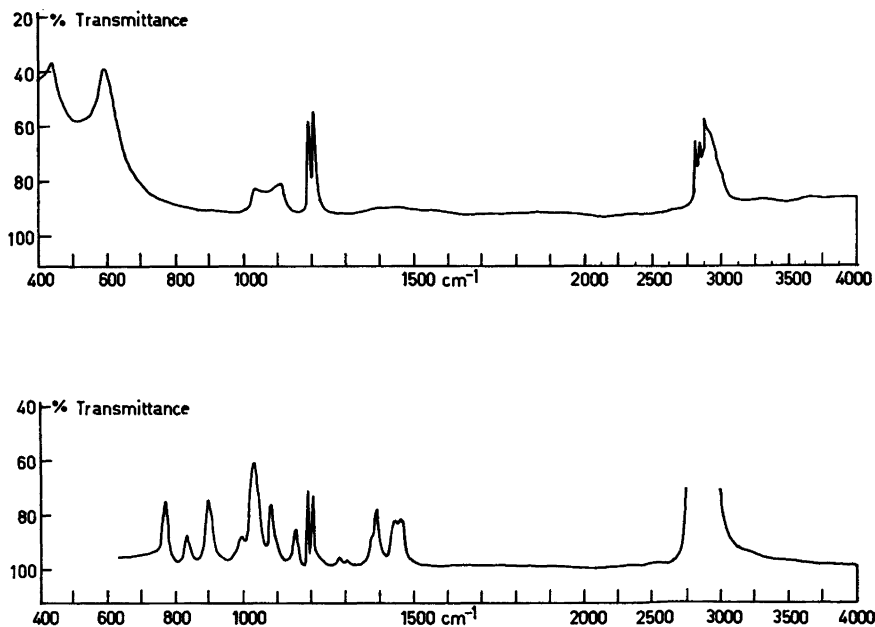


Fig. 1. Infrared spectra of dimethylmagnesium (above) and methylmagnesium chloride etherate. Taken in KBr-discs. Ca. 1–2 mg material/300 mg KBr.

It is believed that the solids obtained from CH_3MgCl and CH_3MgBr represented Grignard reagent and were not mixtures of $(\text{CH}_3)_2\text{Mg}$ and MgX_2 , since the solids retained the bound ether when subjected to 2 mm Hg pressure at 20° which was not the case with the etherates of either $(\text{CH}_3)_2\text{Mg}$ or MgCl_2 . The bands at 1190 cm^{-1} and 1206 cm^{-1} were absent when the methylmagnesium compounds were fully coordinated as in solution and visible only when coordinated solvent was removed totally or in part.

Salinger and Mosher⁶ recently reported a characteristic absorption for the carbon-magnesium bond at *ca.* 520 cm^{-1} . This frequency is not reached by the instrument used, but the dimethylmagnesium spectrum was taken on a Perkin Elmer 125 and showed bands at 440, 590, 1025, 1108, 1190, 1206, 2785, 2825, and 2862 cm^{-1} . The spectra of the methylmagnesium compounds were taken in KBr-discs which were prepared in an atmosphere of dry nitrogen. No weighing of the reactive compounds was possible but the amount of material per 300 mg KBr was adjusted to *ca.* 1–2 mg by “eye-measure”.

It was observed during the investigation that the perturbation of the infra-red spectrum of ether which is exerted by electrophilic magnesium is paralleled by perturbation of the infra-red spectra of other ethers (tetrahydrofuran, dioxan, etc.) and also of carbonyl compounds as, *e. g.*, ketones and esters. The effect could be observed by mixing the carbonyl compound with a Grignard reagent or more conveniently with a magnesium halide solution. The principal effect is a decrease in frequency of the carbonyl absorption amounting to approximately 65 cm^{-1} for an aliphatic ester, *ca.* 50 cm^{-1} for an α,β -unsaturated ester, 27 cm^{-1} for an aliphatic ketone.

This effect is not due to change of solvent since an absorption peak at the original frequency is observable in most cases. The study of α,β -unsaturated esters and ketones showed that the decrease in frequency of the carbonyl absorption was accompanied by a shift in the position of the C,C-double bond absorption.

The development of “disturbed” carbonyl absorption was often equaled by a diminution of the “disturbed” ether spectrum to the point of regeneration of the ordinary ether spectrum. It seems evident that the phenomena observed are spectroscopic evidence of the formation of magnesium/ether and magnesium/ketone complexes as formulated by Meisenheimer.

While the complexes of esters or ketones with magnesium halides were stable and could be studied by standard technique, the study of the complexes between ketones and Grignard reagents presented a problem because these complexes are sometimes very shortlived. A technique was developed which allowed the observation of mixtures of reagent and substrate at any moment later than a few milliseconds after mixing.

A modification of the technique allowed the measurement of the amount of heat evolved at any stage of a Grignard reaction starting 1–2 milliseconds after mixing of reagent and substrate. This determination depended of course on the change in temperature during the reaction and required an adiabatic system. Although the temperature control for this reason was limited to a range of, *e. g.*, 5 centigrades, the results obtained nevertheless seem to permit some kinetic and mechanistic conclusions.

It was found that the change in the spectra of ethers, ketones, esters, and α,β -unsaturated esters and ketones characteristic of the formation of Meisenheimer complexes as described above was faster than could be followed by the technique applied, which means that it was complete within 5 milliseconds. A single experiment was carried out at -50° and seemed to show a delay of the reaction at this temperature. Though the reaction was fast it was not complete but reached an equilibrium which depended on the relative basicity of the individual oxygen compound. An exact calculation was not attempted. Qualitatively it was observed that ketones were more basic than esters which again were more basic than diethyl ether. Tetrahydrofuran was seen to be able to displace both esters and ketones as well as diethyl ether from magnesium. This observation is in accordance with the very strong evolution of heat which is observed by mixing Grignard reagents or ether solutions of magnesium bromide with tetrahydrofuran. Little heat is evolved when magnesium bromide-etherate is mixed with a ketone or an ester.

By means of the described infra-red technique and the supplementary calorimetric method a comparison was made between the rates of addition of butylmagnesium bromide to three types of substrate: acetone, benzalpinacolone, and *sec.* butyl crotonate.

Since diethyl ether was used as solvent the runs with acetone were restricted to ratios of Grignard reagent/ketone > 2.5 . When less excess was used precipitates were formed. It seems evident that complex formation takes place

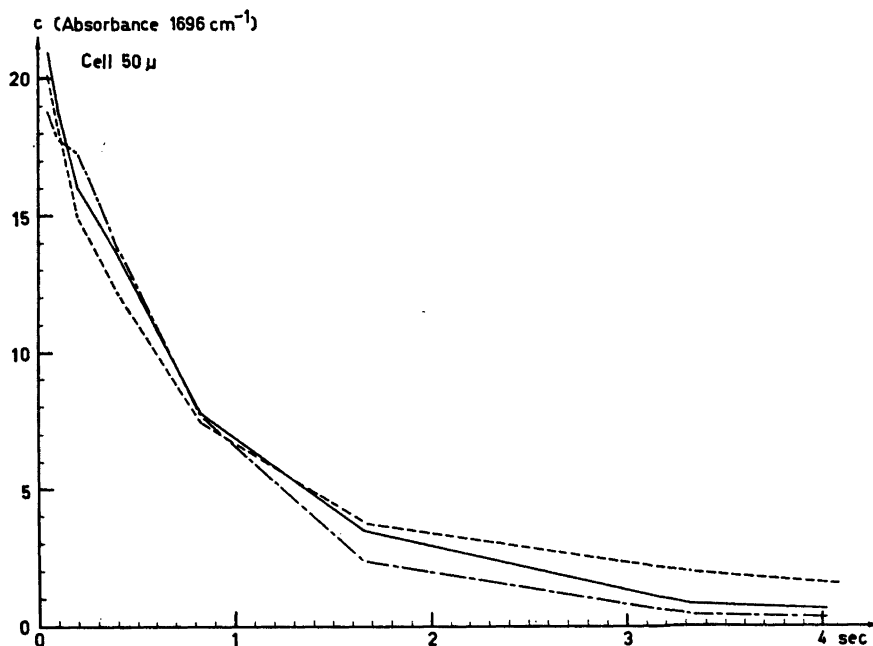


Fig. 2. Time-concentration plots for 0.1 M acetone solution in diethylether in the presence of 1.06 M C_4H_9MgBr ----, 0.53 M C_4H_9MgBr —, and 0.26 M C_4H_9MgBr -.-.

between the reaction product (alcoholate) and unused Grignard reagent, precipitation of the reaction product thereby being prevented. This complex formation may represent a removal of active Grignard reagent and may interfere with reaction rate.

The reaction of acetone with butylmagnesium bromide in ether solution was found by Edgar *et al.*⁷ to yield 92 % of the tertiary alcohol.

Kinetic runs carried out in the infra-red cell with 0.1 M acetone and with 1.5, 4, and 10 times excess of butylmagnesium bromide at a temperature of $6^\circ \pm 3^\circ$ resulted in very similar time/concentration plots (Fig. 2). The absorption at 1696 cm^{-1} , which corresponds to acetone complexed with magnesium is at maximum before the earliest observation (0.05 sec) and disappears according to a 1. order scheme. This rate law is followed until 90 % reaction with 10 times excess Grignard reagent and until 65 %–50 % when less excess is used. The half-life of the complex is ≈ 0.6 sec at 6° .

The shape of the 1696 cm^{-1} absorption band shows that none or very little free acetone, which absorbs at 1723 cm^{-1} , is present when large excess Grignard reagent is used. When only 150 % excess (0.1 M acetone + 0.26 M $\text{C}_4\text{H}_9\text{MgBr}$) is used, however, a significant amount, probably more than 10 % is present, producing a shoulder or a small peak at 1723 cm^{-1} . This may be an indication of a bimolecular structure of the attacking Grignard reagent or at least of the participation of 2 magnesium atoms in the reactive complex, since the excess Grignard reagent in this way will be only 25 %, which may mean that the equilibrium between complexed and uncomplexed acetone may be displaced somewhat in favor of the free species.

Observation of the "disturbed" ether band at 896 cm^{-1} showed that in this case there is no immediate change in the amount of complexed ether when the acetone-Grignard complex is formed, whereas the amount is reduced as the rearrangement proceeds.

When considering the results obtained it seems reasonable to describe the addition of Grignard reagent to acetone in diethyl ether as a very fast complex formation followed by a rather slow intramolecular rearrangement to alcoholate.

The conjugate addition of ethylmagnesium bromide to benzalpinacolone has been investigated by Kohler,⁸ who obtained quantitative yields. A similar result was obtainable using butylmagnesium bromide; see Experimental. The reaction was too fast to be followed quantitatively by infra-red technique. The enolate obtained (Fig. 4 A) absorbs at 1644 cm^{-1} . Benzalpinacolone has a carbonyl absorption at 1690 cm^{-1} , which is shifted to 1670 cm^{-1} when the ketone is complexed with magnesium bromide. The observation of the spectrum of 0.1 M benzalpinacolone in ether 2–5 milliseconds after mixing with a 150 % excess of butylmagnesium bromide at *ca.* 11° showed a considerable amount of enolate and also absorption at 1666 cm^{-1} corresponding to a complex between the ketone and the Grignard reagent. When the same experiment was carried out at 35° only enolate absorption was registered.

The reaction could be followed by calorimetry. When 0.1 M benzalpinacolone was mixed with 1.5, 4.0 or 9 times excess of butylmagnesium bromide there was a rise in temperature of *ca.* 12° in the first 10 to 20 msec, but the time/temperature plots showed that close to 2/3 of the total heat of reaction

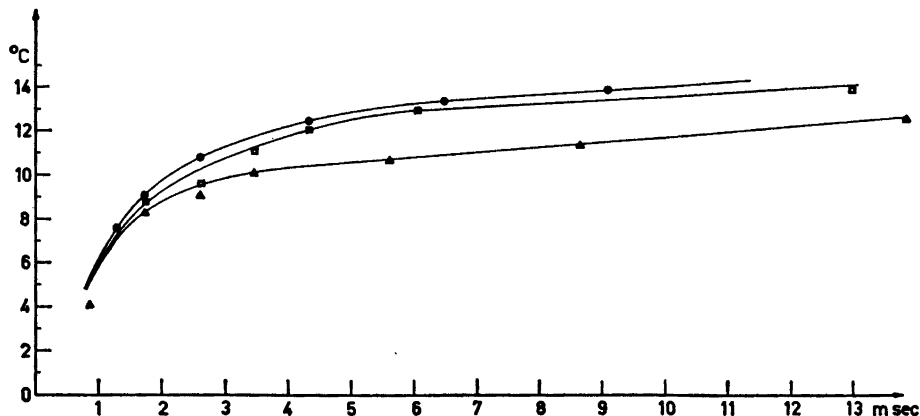


Fig. 3. Time-temperature plots for mixtures of 0.1 M benzalpinacolone in diethyl ether in the presence of 0.50 M C_4H_9MgBr , circles, 0.25 M C_4H_9MgBr , squares, and 0.125 M C_4H_9MgBr , triangles.

was produced 2 msec after mixing with any of the three different Grignard concentrations (Fig. 3). The coordination reaction between 0.1 m benzalpinacolone and an excess magnesium bromide etherate leads to a rise in temperature of less than 2° . If the coordination of the ketone with Grignard reagent and with $MgBr_2$ is assumed to have the same ΔH , the half life of the Grignard-complex is ≈ 1.5 msec.

In this reaction one is again led to assume a mechanism with an extremely fast complex formation followed by a fast rearrangement to enolate. Since the reaction proceeds smoothly and quantitatively even with an excess of ketone the generally accepted cyclic mechanism (Fig. 4 A) proposed by Lutz and Reveley,⁹ which involves 1 mole of monomeric $RMgX$ may be operating, and this steric favoured reaction path might explain in part the extreme speed of the reaction.

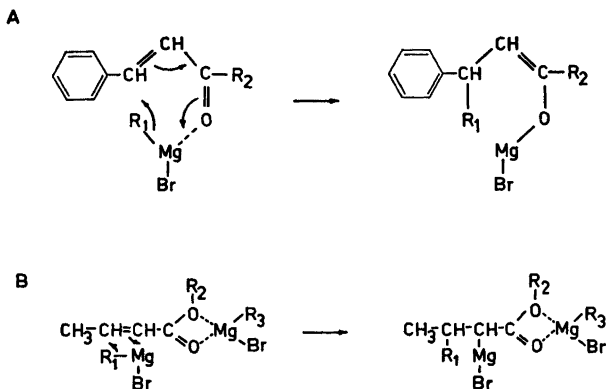


Fig. 4.

Through the transparent polyethylene tube it was possible to observe a red color for *ca.* 2–6 mm after the mixing point. This is the period in which the complex exists. The complex of MgBr_2 and ketone was not colored.

The reaction of butylmagnesium bromide and *sec.* butylcrotonate has been studied by Munch-Petersen.¹⁰ The close analogy of the unsaturated ester to the unsaturated ketone would lead one to assume a fast reaction also in this case. Actually the rate of disappearance of the displaced C,C-double bond absorption at 1642 cm^{-1} corresponded to *ca.* 11 % reaction after 30 sec at 0°C using 0.33 M crotonic ester and 100 % excess butylmagnesium bromide. Larger excess of Grignard reagent increased the rate, and it is concluded that the mechanism for this reaction is different from the mechanism of the benzalpinacolone/Grignard reaction. The product obtained by the reaction showed one single intense absorption at 1680 cm^{-1} , which is close to the band (1667 cm^{-1}) obtained with an ester (*e.g.* *sec.* butyl-3-methylheptanoate), which is complexed with either magnesium bromide or butylmagnesium bromide. An ester structure (Fig. 4 B) is therefore assumed for the reaction product. The addition of carbon dioxide to the reaction product resulted in a high yield of the malonic ester. This result is in good keeping with structure suggested in Fig. 4 B.

The failure of the crotonic ester in forming an enolate may be part of the explanation of the extreme difference in rate ($> 10^5:1$) for the two conjugate Grignard addition reactions.

In analogy with benzalpinacolone crotonic ester becomes colored (yellow) when complexed with butylmagnesium bromide. The color disappears slowly as the reaction proceeds. The magnesium bromide complex is also in this case colorless.

EXPERIMENTAL

Materials. The purity of volatile raw materials was checked by gas chromatography. Triply sublimed magnesium was used (courtesy Dow Chemical Corp.). Grignard reagent was prepared while observing the usual precautions against oxygen and moisture. The solutions were titrated with standard acid and the halogen content was determined and found to be within 105 and 108 % of theory. The solutions were kept in all filled and well stoppered bottles until use. The different concentrations were obtained by dilution of a *ca.* 2 M standard solution.

Apparatus. Infrared spectra were taken in a Perkin Elmer Model 421 recording spectrophotometer. $15\ \mu$ and $50\ \mu$ infrared cells were made from pressed KBr discs 0.8 mm thick 13 mm in diameter, which were cemented with "Araldit" using an aluminum foil spacer. The cells were fitted with an inlet and an outlet of polyethylene tubing of 0.8 mm internal diameter. When observing fast reactions the cells were filled from two 20 ml standard glass syringes with Teflon-tipped plungers which could be emptied at exactly the same speed by means of an electric motor with adjustable speed. The mixing occurred in a T made from 0.6 mm internal diameter stainless steel tubing and the liquids were precooled in icewater through 95 cm coils of the same material. The temperature at the cell exit was observed by means of a 0.1 mm copper constantan thermoelement using a vacuum tube direct current microvoltmeter (1 M Ω internal resistance). The connection between the T and the cell was made from polyethylene tubing (0.8 mm internal diameter). With a total displacement from the syringes of 0.615 ml/sec the liquid speed in the tube was found to be *ca.* 115 cm/sec. By using the appropriate length of connecting tube any time of reaction down to *ca.* 2 msec was obtainable. A period of 45 sec of equilibration of the system preceded the recordings.

The apparatus was also used for the calorimetric measurements, in which case the cell was omitted and the thermocouple was placed in the transparent reaction tube. The temperature of the reaction mixture could be observed at any distance from the mixing point starting at 1.5 mm.

β -Phenylhexyl-tert.butyl-ketone. A solution of 9.4 g (0.05 mole) benzalpinacolone in 50 ml ether is added with stirring and cooling to 100 ml 1 M butylmagnesium bromide in ether. The mixture is poured onto ice and HCl. The ether layer is washed, dried and distilled. Yield 11.8 g, 96 %. The oil is crystallized from petroleum ether, m.p. 30.5°–31.5°. (Found: C 82.55; H 10.4. Calc. for $C_{17}H_{26}O$: C 82.87; H 10.6).

2-Hexylmalonic acid. A solution of 14.2 g (0.1 mole) *sec.* butyl crotonate in 100 ml ether is added slowly with stirring and cooling in icewater to 250 ml 1 M butylmagnesium bromide in ether. Stirring is continued 30 min at 0° and 30 min at 20° and the mixture is poured onto a mixture of dry ice and ether. When the reaction has subsided (1 h) water and excess HCl is added. The ester layer is distilled and the fraction boiling > 100° at 11 mm Hg is collected. 20 g, 82 %. The half ester is saponified by boiling for 2 h with 100 ml 4 N sodium hydroxide. The mixture is acidified and extracted with ether which is separated, dried, and evaporated to leave an oil, which crystallizes on standing. Yield 13.1 g, 70 % from crotonic ester. M.p. 80°–88°. (Found: C 57.85; H 8.88. Calc. for $C_9H_{16}O_4$: C 57.43; H 8.57).

Dimethylmagnesium was prepared from an ether solution of methylmagnesium chloride by precipitation of the magnesium chloride with dioxane and removal of solvent by heating to 200° at 1 mm Hg. Methylmagnesium chloride was prepared as the etherate by evaporation of ether from the solution at 20 mm Hg. Methylmagnesium bromide was prepared as the etherate by adding 5 volumes of petroleum ether to an ether solution and separating the solid by centrifugation. The magnesium compounds were handled under dry nitrogen. They were not analysed.

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