I. THE EFFECT OF N,N,N',N'-TETRAMETHYLETHYLENEDIAMINE ON THE SCHLENK EQUILIBRIUM

II. THE NATURE OF THE DI-GRIGNARD REAGENT

Thesis by

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ABSTRACT

I. THE INFLUENCE OF N,N,N',N'-TETRAMETHYLETHYLENEDIAMINE ON THE SCHLENK EQUILIBRIUM

The equilibrium between ethylmagnesium bromide, diethylmagnesium, and magnesium bromide has been studied by nuclear magnetic resonance spectroscopy. The interconversion of the species is very fast on the nmr time scale, and only an averaged spectrum is observed for the ethyl species. When N,N,N',N'-tetramethylethylenediamine is added to solutions of these reagents in tetrahydrofuran, the rate of interconversion is reduced. At temperatures near -50°, two ethylmagnesium species have been observed. These are attributed to the different ethyl groups in ethylmagnesium bromide and diethylmagnesium, two of the species involved in the Schlenk equilibrium of Grignard reagents.

II. THE NATURE OF DI-GRIGNARD REAGENTS

Di-Grignard reagents have been examined by nuclear magnetic resonance spectroscopy in an attempt to prove that dialkylmagnesium reagents are in equilibrium with alkylmagnesium halides. The di-Grignard reagents of compounds such as 1,4-dibromobutane have been investigated. The dialkylmagnesium form of this di-Grignard reagent can exist as an intramolecular cyclic species, tetramethylenemagnesium. This cyclic form would give an nmr spectrum different from that of the classical alkylmagnesium halide di-Grignard reagent. In dimethyl ether-tetrahydrofuran solutions of di-Grignard reagents containing N,N,N',N'-tetramethylethylenediamine, evidence has been found for the existence of an intramolecular dialkylmagnesium species. This species is rapidly equilibrating with other forms, but at low temperatures, the rates of interconversion are reduced. Two species can be seen in the nmr spectrum at -50°. One is the cyclic species; the other is an open form.

Inversion of the carbon at the carbon-magnesium bond in di-Grignard reagents has also been studied. This process is much faster than in corresponding monofunctional Grignard reagents.

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Introduction

Early studies suggested that an equilibrium might exist in solutions of Grignard reagents between alkylmagnesium halide, dialkylmagnesium, and magnesium halide (1). Later studies have indicated that these species might also exist as association complexes involving one, two, or possibly more of these species. Therefore, the original equilibrium proposed by Schlenk is usually expanded to include associated species:

$$n\ RMgX \rightleftharpoons (RMgX)_n \rightleftharpoons n/2\ R_2Mg + n/2\ MgX_2 \qquad (1)$$

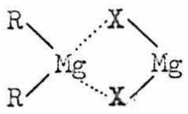
In recent years, chemical and physical methods have been used extensively in attempts to determine the nature of Grignard reagents in solution (2). The voluminous literature on the subject testifies to the complexity of the system, but with the physical methods now available, the general nature of the Grignard reagent is gradually becoming better defined.

Because complex formation in the expanded Schlenk equilibrium would reduce the number of species in solution, monitoring the number of species in solution provides one method for studying the nature of the equilibrium. Many of the early attempts to study association phenomena have been rejected by later workers for various reasons. As shown by Slough and Ubbelohde (3) and later by Vreugdenhil and Blomberg (4), the presence of oxygen can cause a large increase in the apparent association in solutions of Grignard reagents. For this reason, any studies concerned with the nature of the alkylmagnesium halide must be carried out with rigid exclusion of oxygen. Reactions with oxygen are not the only possible sources of experimental difficulty. The preparation of Grignard reagents from alkyl halides and magnesium is usually accompanied by Wurtz coupling. The resulting hydrocarbon and magnesium halide may affect the equilibrium being studied. A third problem which arises in these association studies is possible deviations from ideality by the solution and the subsequent effect on the colligative properties of the solutions. Such effects must occur at the higher concentrations of Grignard reagent. Any definitive study in which vapor pressure or boiling-point measurements are made must include precautions to avoid these three sources of error.

In the most recent studies of Grignard reagents, careful experimental techniques have reduced the above errors, and show that in diethyl ether, association occurs and indicate that it increases with concentration. Ashby and Smith (5) have observed such phenomena with several Grignard reagents including methylmagnesium iodide, ethylmagnesium bromide, and phenylmagnesium bromide. At extremely low concentrations such as 0.01 to 0.001 M (6), association is generally negligible in diethyl ether. In tetrahydrofuran, with the concentrations of Grignard reagent which show association in diethyl ether, almost no association has been detected. In early work by Blomberg (7) and Ashby (8), little if any association of species was detected, although recently published work by

Hashimoto, Nakano, and Okada (9) indicates association in both diethyl ether and tetrahydrofuran which may increase or decrease with increasing concentration. However, Ashby (10) has refuted this work on the basis of nonexclusion of oxygen and the use of concentrations so high that the solutions were no longer ideal.

From the association studies, one can conclude that the Grignard reagents appear to be associated in ethyl ether but not in tetrahydrofuran. In diethyl ether, the Grignard reagent is apparently associated into dimers such as:



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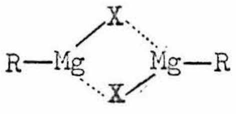


II

However, magnesium halides have also been shown to be associated in diethyl ether (6, 10), and this, of course, will cause difficulty in the interpretation of such results. Association of magnesium halides in tetrahydrofuran was not observed at low concentrations (7) and has not been studied at higher concentrations.

If the Schlenk equilibrium actually occurs, equivalent Grignard reagents should be obtained from either the alkyl halide and magnesium or magnesium halide and dialkylmagnesium. Dessy (11) has shown that the dielectric constant for mixtures of ethylmagnesium bromide is the same as that for a mixture of diethylmagnesium and magnesium bromide. Electrical conductivity studies (12) show that, above 0.4 M, the two kinds of solutions are similar, but below this concentration considerable differences were found. Possibly at low concentrations, association equilibria can be established between molecules of magnesium bromide before equilibrium is established between the magnesium bromide and diethylmagnesium. Product ratios, addition versus reduction versus enolization, for chemical reactions of Grignard reagents with hindered ketones (13) and infrared studies (14) also indicate that reaction mixtures are identical whether one starts from the alkyl halide or from dialkylmagnesium and magnesium halide.

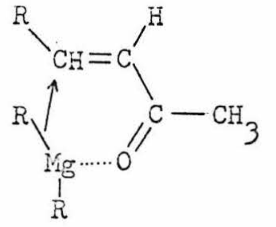
Smith and Becker (15) have recently studied the reaction between dialkylmagnesium and magnesium halide in ether by studying heats of mixing. Their data indicate that a rapid and nearly complete reaction between dialkylmagnesium and magnesium halide occurs until a 1:1 mixture has been mixed together. Incompleteness was attributed to the fact that at equilibrium, all reagents were not in the form of the alkylmagnesium halide.

The identity of the mixtures prepared from opposite sides of the proposed Schlenk equilibrium has been fairly well established. The equilibrium position is reached quite easily from either side, and, in general, at this position the predominant species apparently is the alkylmagnesium halide.

Isotopic labeling experiments have been used to try to study the course of the reaction in the Schlenk equilibrium. In an attempt to determine the existence of the proposed Schlenk equilibrium, Dessy (16) attempted to exchange the magnesium from magnesium bromide labeled with magnesium-28 with diethylmagnesium. Very little exchange was found in early experiments indicating that ethylmagnesium bromide was not formed. Later work (17) using magnesium-25 as a label demonstrated complete isotopic exchange. Cowan and co-workers (18), using magnesium-25 labeled magnesium bromide, showed that complete statistical exchange occurred when the magnesium bromide was added to ethylmagnesium bromide. For some unexplained reason the original work by Dessy did not show exchange. However, the later experiments have demonstrated that somehow magnesium from magnesium halide will be incorporated into the alkyl-containing species. Blomberg (19), using carbon-14 labeled ethyl bromide, has found complete exchange between the ethyl groups in a mixture of ethylmagnesium bromide and diethylmagnesium. This result, and the others, can be interpreted as proof of exchange due to the Schlenk equilibrium, but it can also be explained by a transmetalation process in which the ethyl groups are transferred from magnesium to magnesium without formation of magnesium bromide.

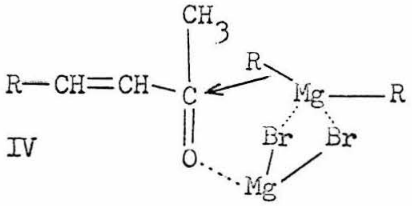
Many studies attempted to determine the kinetics of the addition reactions of Grignard reagents. A reaction which is second order in Grignard reagent could be explained as progressing through a dimer or dialkylmagnesium species; a reaction first order in Grignard reagent would be progressing through the alkylmagnesium halide. Anteunis (20) has studied the reaction of methylmagnesium bromide with pinacolone and benzophenone and found these additions to be second order in Grignard reagent. Mosher and co-workers (21) have found that similar reactions follow consecutive second-order kinetics for the addition of ethylmagnesium bromide to 2,4-dimethyl-3-pentanone; a magnesium species containing two alkyl groups first could add to the ketone and then the reacted half of the organometallic species could add again to another ketone molecule. Bikales and Becker (22) have shown that in tetrahydrofuran the reaction of methylmagnesium bromide with benzophenone is initially first order in each reactant. Apparently the solvent affects the nature of the reacting species. Although Mosher (13, 21) has attempted to explain many of his results by picturing a transition state containing a dimeric species, House (23) has shown that this approach may not be general and, therefore, probably neglects important aspects of the reaction. (It should be pointed out that many of the transition-state ideas are based on Dessy's first exchange experiments (16), although they are also influenced by the existence of asymmetric reduction of ketones by Grignard reagents.) Applying the ideas of a six-membered transition state to the 1,4-addition of Grignard reagents to *α,β*-unsaturated ketones, House reasoned that the presence of magnesium halide should reduce 1,4-addition and increase 1,2-addition, and conversely, the removal of magnesium halide should promote 1,4-addition. He discovered that the presence of magnesium halide slightly enhanced the normal 1,2-addition but the effect was extremely small. The following diagrams demonstrate the reasoning which led House to look for an effect on 1,4-addition by the presence of magnesium halide.

III



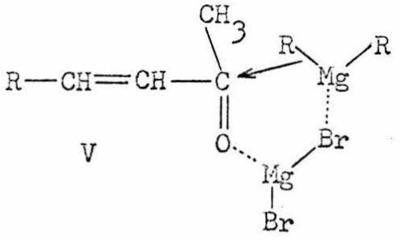
1,4-Addition

IV



1,2-Addition

V



1,2-Addition

Much of the kinetic work studying the addition to ketones may have been complicated by such things as complex formation between starting materials (22, 24) and formation of magnesium alkoxides (25). The formation of alkoxides as the addition reaction with ketones proceeds can explain the reduced activity of Grignard reagents. Because magnesium halide affects the ratio of reduction and addition products in adding ethyl Grignard reagents to ketones, Mosher has introduced magnesium halide into his picture of the transition state. However, as House explains, the effect can be attributed to reaction of magnesium halide with the active alkoxides formed upon addition, R'OMgR, thereby generating an inactive alkoxide, R'OMgX, and an active Grignard species, RMgX.

The work with ketones has demonstrated the problems in doing kinetic studies with Grignard reagents. The most reliable results are probably those which seem to be general throughout the systems studied. The rate of addition is slowed down by the presence of magnesium halide with the addition of dialkymagnesium to the ketone being the fastest reaction. After addition is 50% complete, the reaction slows down drastically or may even stop (26). Comparison of the studies in ether with those in tetrahydrofuran where the kinetic order of Grignard reagent changes from two to one shows that the mechanism of addition may be dependent on the solvent used. Reactions of alkylmagnesium halides prepared from dialkylmagnesium and magnesium halide seem to be identical to similar concentration solutions prepared from alkyl halide and magnesium.

Similar results have been found by studying other addition reactions of Grignard reagents (27), but the metalation of 1-alkynes has probably been most extensively studied because the reduced hydrocarbon can serve as the monitoring device for measuring the reaction rate and the reaction seems to be simple with few, if any, troublesome side reactions. Unlike the addition to ketones, the metalation reaction appears to be first order in Grignard reagent when diethyl ether is the solvent (28), but Hashimoto and co-workers (9) have found that the order varies with solvent. As in the ketone-addition studies, dialkylmagnesium reacts faster with 1-alkynes than the corresponding Grignard reagents (29). The presence of magnesium halide markedly reduces the reaction rate of dialkylmagnesium with 1-alkynes. From these results it appears that magnesium halide influences the reacting species the same way in both alkyne metalation and addition to the ketone; however, the kinetic orders seem to be different.

The effects of solvent on metalation reactions have been studied, and contradictory results are found in the literature. Zakharkin (30) has examined the nucleophilicity of the alkyl group in several reactions, one being the metalation of phenylacetylene by methylmagnesium bromide. He finds that the greater the "solvating power," a combination of coordinating ability and basicity, the faster the rate of metalation. Wotiz and Proffitt (29d) have found conflicting results when studying the metalation of 1-hexyne by ethylmagnesium bromide. In their studies, increasing basicity decreased the reaction rate. Addition of tertiary amines such as triethylamine to Grignard reagent solutions has been found to increase the rate of metalation of alkynes, but the rate was unaffected by amine when all the magnesium halide has been removed (31). Because of the different results on the solvent effects, little can be said about the nature of solvation and its influence on the character of the Grignard reagent from these studies. A change in solvent may produce a change in reaction mechanism; in two different reactions such as addition to ketones and metalation of alkynes, the Grignard reagent may work differently. The chemical reaction of a Grignard reagent with a substrate is complicated by many factors which make interpretation of results extremely difficult. Also, a possibility exists that the reacting species of the Grignard reagent is not one of the predominant species normally present in a Grignard reagent solution. All these studies do indicate that the reactions of Grignard reagents are dependent on many factors, and this may be because Grignard species equilibrate rapidly. This point will be discussed in more detail later.

From infrared studies carried out by Mosher and Salinger (14) the carbon-magnesium absorption frequencies have been assigned to both Grignard reagents and their corresponding dialkylmagnesium compounds. In tetrahydrofuran, the results support a Schlenk equilibrium of the type

$$R_2Mg + MgX_2 \rightleftharpoons 2\ RMgX \qquad (2)$$

with an equilibrium constant approximately equal to 4. When magnesium halide is added to these solutions, the absorption frequency is shifted away from that of the pure dialkylmagnesium species in such a way that would indicate that the above equilibrium is being shifted to the right.

Upon adding N-methylpyrrolidine to solutions of ethylmagnesium bromide in tetrahydrofuran or diethyl ether, a shift in the infrared absorption was noted with the diethyl ether solution but none with tetrahydrofuran (27c). A precipitate of magnesium bromide was obtained from the diethyl ether solution indicating a shift in the equilibrium to the left. However, the shift is away from the frequency assigned for diethylmagnesium. Changes in the character of the carbon-magnesium bond because of solvation changes (32) may produce variations in the infrared bands which cannot be explained by simple shifts in the Schlenk equilibrium. Identity of the classical Grignard reagents to mixtures of the corresponding dialkylmagnesium and magnesium halide has been demonstrated, but shifts in the bands may be from other complicated phenomena.

Nuclear magnetic resonance spectroscopy was applied by Maher and Evans (33) to structural problems presented by Grignard reagents in solution. When comparing methyl and ethyl Grignard reagents with dimethyl- and diethylmagnesium, little difference could be found between the different species. A simple interpretation of this was that the Grignard reagent was probably in the form of the dialkylmagnesium species. Roos and Zeil (34) also tried to use nuclear magnetic resonance to distinguish between dialkylmagnesium forms and alkylmagnesium halide forms, and they reached essentially the same conclusion. Very small changes in chemical shift are observed for protons in the organometallic reagents when magnesium halide concentrations are varied. At no time were major differences observed which could be attributed either to a dialkylmagnesium species or to classical alkylmagnesium halide species.

Studies by Roberts, Whitesides, and Witanowski on the conformational stability of organometallic reagents (35) have shown that several processes may be going on which average the resonances of the different species. Examination of 3,3-dimethylbutyl organometallic compounds has demonstrated the occurrence of an inversion process which causes conformational instability in these primary organometallic species. Although the exact nature of the inversion process is not known, it has also been confirmed in Grignard reagents in which the primary Grignard function is next to an asymmetric carbon (35b, 36). Rapid inversion at the primary carbon will cause the chemical shift of its two protons to average because the asymmetry of the adjacent carbon is no longer experienced.

Although the occurrence of an inversion process is well established, it may be a phenomenon apart from the Schlenk equilibrium, because it also occurs (albeit much more slowly) with no magnesium halide present. However, any attempts to observe the different species of the Schlenk equilibrium must allow for this inversion process with its possible averaging of the physical properties of the organometallic species on the nmr time scale. An attempt to slow down inversion would be a necessity if differences in chemical shift or proton-proton coupling constants were to be used to distinguish between the different forms of the Grignard reagent suggested by the Schlenk equilibrium.

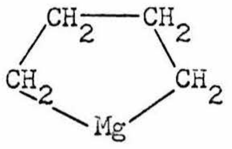
The pentafluorophenylmagnesium halide is a Grignard reagent in which inversion cannot occur. Evans and Kahn (37), knowing that other pentafluorophenylmetals undergo alkyl exchange slower than the corresponding hydrogen derivatives, observed the nuclear magnetic resonance spectrum of pentafluorophenylmagnesium bromide in diethyl ether and tetrahydrofuran. Two triplets are observed for the _para_ fluorine resonance which coalesces to one triplet at high temperature. One triplet is from the arylmagnesium halide; the other is from the diarylmagnesium species, since the ratio of the two is a function of magnesium halide concentration. This is the first observation of different organomagnesium forms in the Schlenk equilibrium by nuclear magnetic resonance. However, the perfluorophenyl Grignard reagents in some of their reactions have been shown to behave quite differently from the ordinary aliphatic or aryl Grignard reagents (38). For this reason the conclusion may not be generally extendable to other Grignard reagents.

In the research reported in this thesis an attempt was made to examine the Schlenk equilibrium by nuclear magnetic resonance spectroscopy. Several investigators had already shown that the dialkylmagnesium reagents and Grignard reagents are essentially indistinguishable in the nuclear magnetic resonance experiment. A method was required to make different forms give non-equivalent spectra.

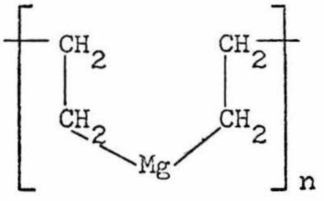
By using a difunctional Grignard reagent, a di-Grignard reagent, another species would be introduced into the Schlenk equilibrium since the di-Grignard reagent could form a cyclic intramolecular dialkylmagnesium species. The possible forms of the di-Grignard reagent are represented in the following diagram in which the di-Grignard reagent of 1,4-dihalobutane is the representative reagent.

$XMgCH_2CH_2CH_2CH_2MgX$

VI



VIII



VII

Species VI and VII would, by analogy to other Grignard reagent studies, give the same nmr spectrum. However, by introducing a third species VIII whose nmr spectrum might present different chemical shifts from those found with VI and VII, a Schlenk equilibrium among the species might be observed.

The problem then becomes one of detecting the cyclic magnesium species, _e. g._ tetramethylenemagnesium, and then using it to monitor the Schlenk equilibrium. Solvation changes produced by varying solvents, equilibrium changes produced by removing magnesium halide with dioxane, and concentration changes should all be influential in determining the nature and position of the Schlenk equilibrium with di-Grignard reagents.

The great solvation changes produced by adding N,N,N',N'-tetramethylethylenediamine to Grignard reagents have been studied using ethylmagnesium bromide as a sample Grignard reagent. The discussion of the results and conclusions are presented in Part I of this thesis. In Part II of this thesis the nature of the di-Grignard reagent is presented. The influence of N,N,N',N'-tetramethylethylenediamine on the nature of the di-Grignard reagent is also reported.

I. THE INFLUENCE OF N,N,N',N'-TETRAMETHYLETHYLENEDIAMINE ON THE SCHLENK EQUILIBRIUM

Results and Discussion

The proton magnetic resonance spectrum of ethylmagnesium bromide in tetrahydrofuran is a typical A_2X_3 type spectrum (Figure 1). The resonance of both the methyl (67 Hz*) and methylene (-47 Hz) protons are easily distinguished from the peaks of tetrahydrofuran. With good resolution, the second-order splitting is easily detected. However, suspended particles, paramagnetic impurities from magnesium, or operation of the spectrometer at some other probe temperature than its normal ambient temperature (~35°) causes reduction in resolution, and second-order splitting is not resolvable. Ethane (47 Hz) is a side product produced by trace amounts of moisture.

In tetrahydrofuran solutions, inversion of configuration of the carbon atom by making and breaking the carbon-magnesium bond is slower than in diethyl ether. Whitesides and Roberts (35b) showed how the inversion rate in 3,3-dimethylbutylmagnesium chloride decreases with tetrahydrofuran relative to diethyl ether. With diglyme, a bidentate solvent whose solvating power is much greater

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*In this thesis chemical shifts will be reported in Hertz from tetramethylsilane. Positive values denote shifts down-field from tetramethylsilane; negative values denote up-field shifts. Chemical shifts are reported with reference to external tetramethylsilane.

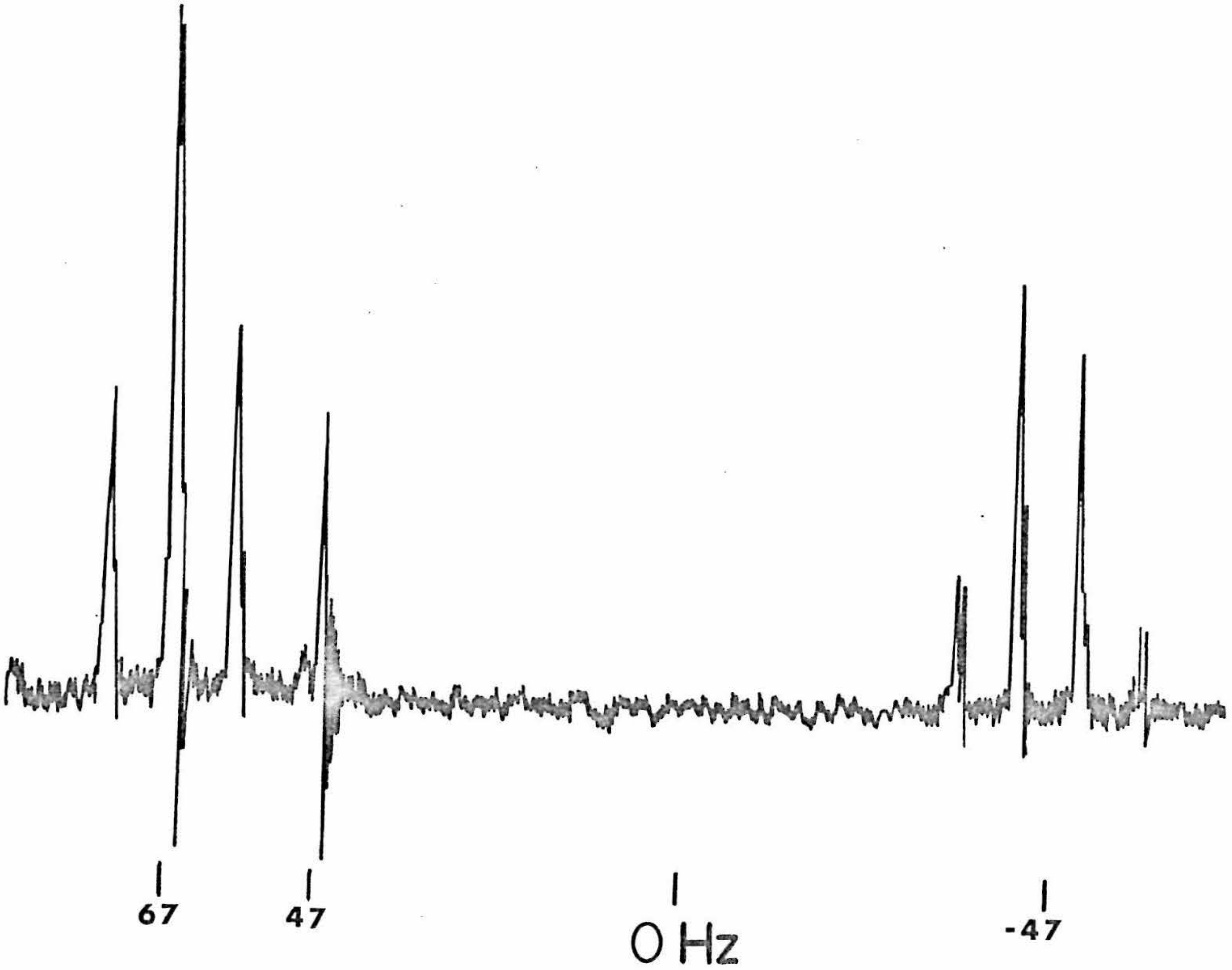


Figure 1. The nmr spectrum (60 MHz) of ethylmagnesium bromide prepared in tetrahydrofuran.

than diethyl ether or tetrahydrofuran, the inversion rate is reduced to a much greater extent.

Fraenkel and Dix (36) report that the rate of inversion of 2-methylbutylmagnesium bromide in tetrahydrofuran is more than 20 times slower than in diethyl ether at 25°. In figure 2a, the nmr spectra of a 1.0 M solution of 2-methylbutylmagnesium bromide in tetrahydrofuran is shown; Figure 2b shows nmr spectra of the same sample with 10% N,N,N',N'-tetramethylethylenediamine, a bidentate solvent. The inversion rate has been reduced by the presence of the amine, but the effect is small. The volume change produced is approximately 10%. Inversion rates are dependent on concentration effects, and possibly part of the reduction in inversion rate arises from this.

The same effect is seen in the nmr spectrum of 3,3-dimethylbutylmagnesium chloride. The $-CH_2Mg-$ protons are shown in Figure 3a without added diamine and in Figure 3b with approximately 10% by volume of added N,N,N',N'-tetramethylethylenediamine. A small change is again apparent which corresponds to slower inversion. The important result from these two comparisons is that the diamine has not completely stopped inversion.

N,N,N',N'-tetramethylethylenediamine seems to greatly change the solvation of Grignard reagents. Thus, samples of Grignard reagents in nmr tubes, which are sufficiently concentrated to have deposited crystals upon cooling to 0°, have shown no signs of crystallization when made approximately 5% by volume in diamine.

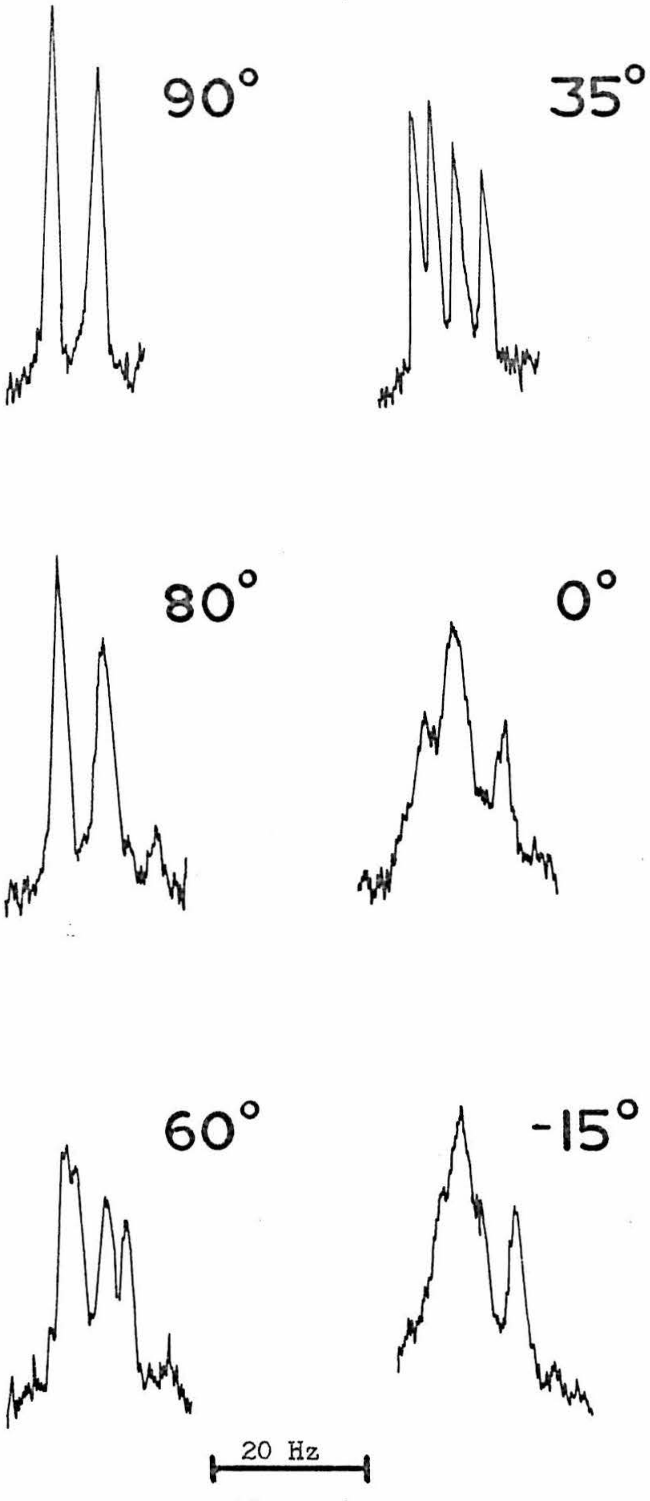


Figure 2a. The nmr spectra (60 MHz) of the $-CH_2Mg-$ protons in 2-methylbutylmagnesium bromide in tetrahydrofuran.

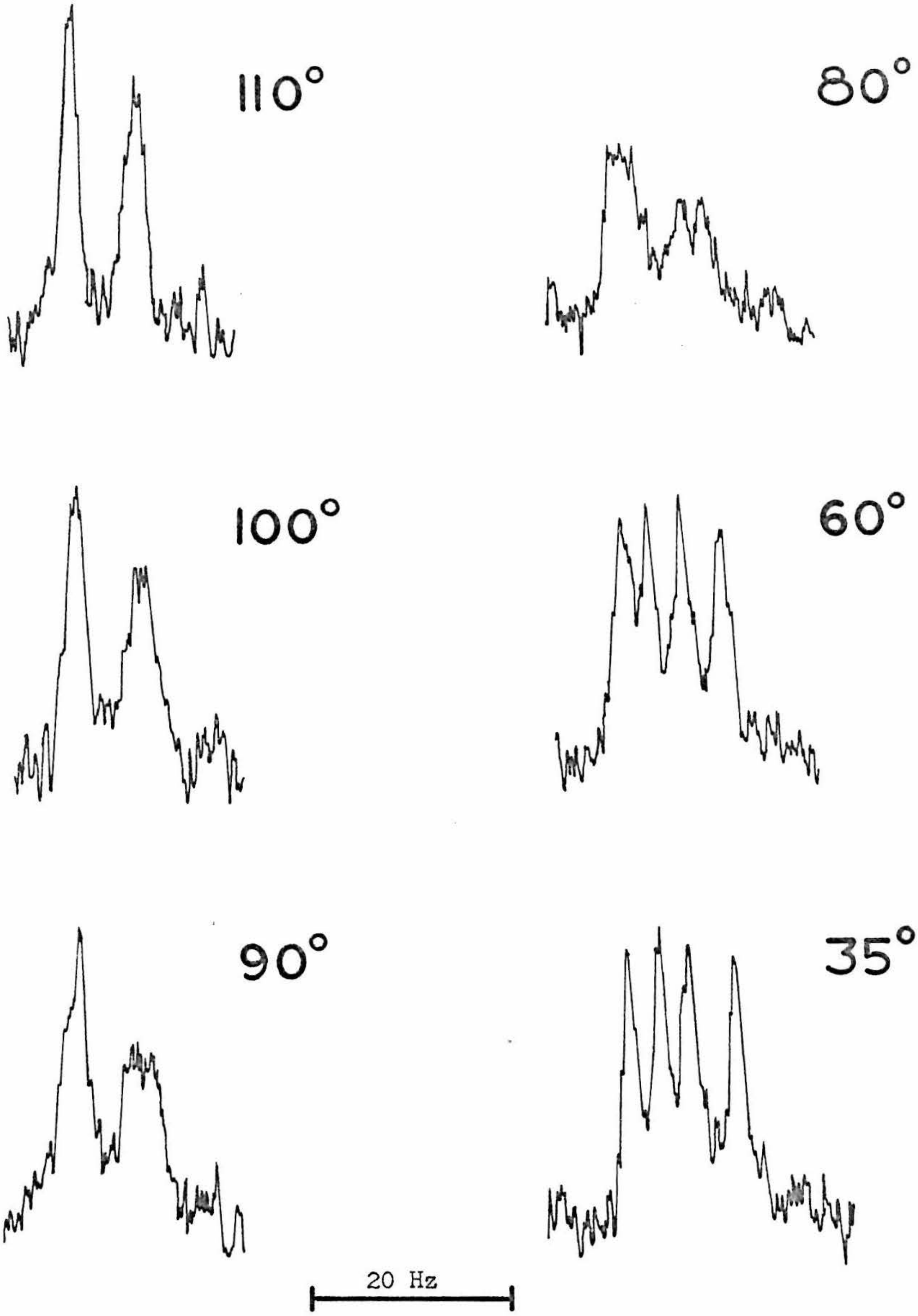
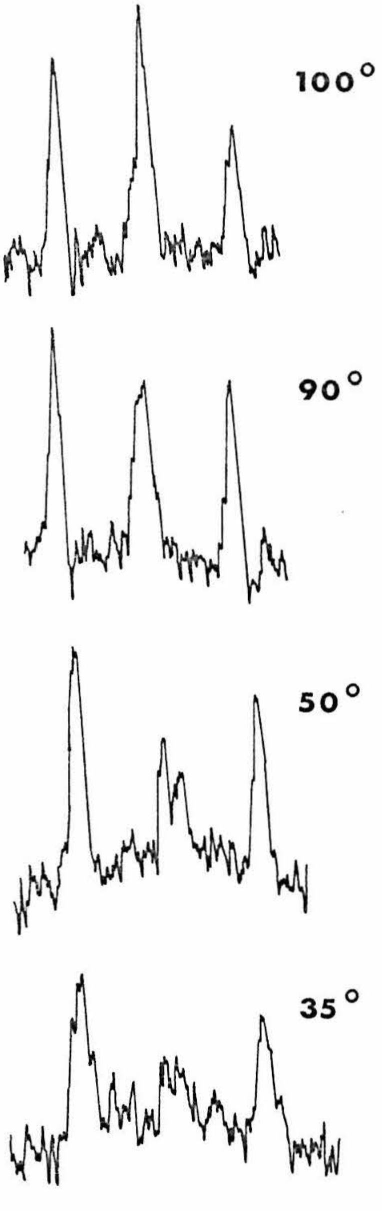


Figure 2b. The nmr spectra (60 MHz) of the $-CH_2Mg-$ protons in the same sample shown in Figure 2a with 10% by volume of N,N,N',N'-tetramethylethylenediamine.



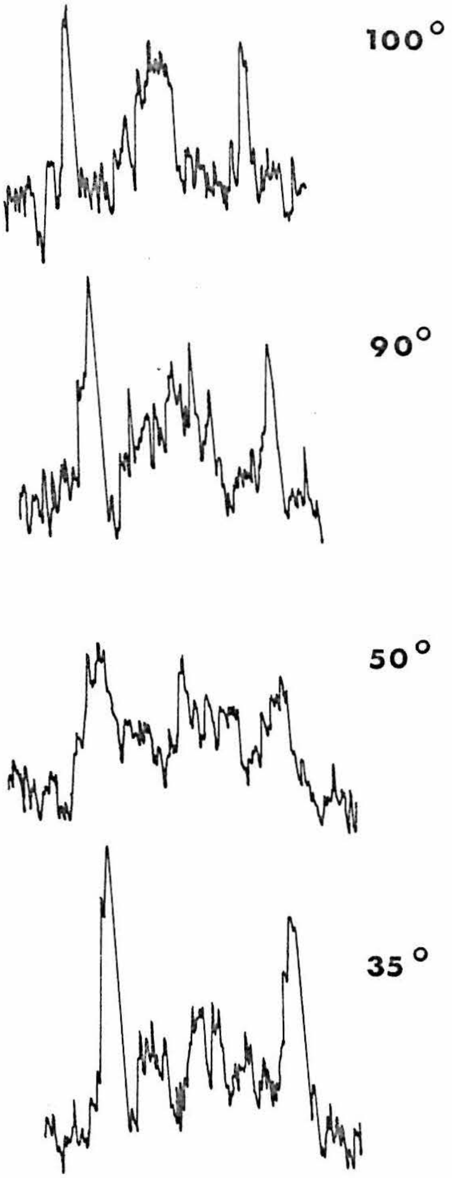


Figure 3a. The nmr spectra (60 MHz) of the -CH$_2$Mg- protons in 3,3-dimethylbutylmagnesium chloride prepared in tetrahydrofuran.

Figure 3b. The nmr spectra (60 MHz) of the -CH$_2$Mg- protons in 3,3-dimethylbutylmagnesium chloride prepared in tetrahydrofuran with diamine.

Also, a 2.6 M solution of ethylmagnesium bromide in tetrahydrofuran, which deposited crystals within 24 hours, deposited no crystals after 4 months with 16% by volume of added N,N,N',N'-tetramethylethylenediamine. However, many anomalous effects are observed and the concentration of Grignard reagent and magnesium bromide are clearly important. For example, when ethyl Grignard reagent is prepared from the halide and then N,N,N',N'-tetramethylethylenediamine is added to attain a molar ratio of Grignard reagent to diamine of 2.0, crystallization occurred at temperatures lower than room temperature when the concentration was greater than 0.33 M in Grignard reagent. These crystals would dissolve again upon warming to room temperature. However, when diethylmagnesium was prepared from diethylmercury, and the diamine was added and then magnesium bromide was generated in this mixture from ethylene bromide and magnesium, no precipitate formed even at temperatures as low as -60°. In this case also the mole ratio for the theoretical amount of ethylmagnesium bromide to diamine was 2.0, and solutions approximately 2 M in Grignard reagent could be prepared without crystal formation. The nmr spectra of the ethylmagnesium groups in these solutions were essentially indistinguishable from those of ethylmagnesium bromide prepared in the classical way (Figure 8). The exact nature of the amine in affecting the solubility of the Grignard reagent is not known. Clearly equilibrium is not easily approached from either side, and it may well be that the solutions are metastable — a characteristic which has been reported before for other kinds of Grignard solutions.

The nmr spectrum of the methylene protons of a tetrahydrofuran solution which is 0.33 M in ethylmagnesium bromide and 0.18 M in diamine is shown in Figure 5 as obtained with the aid of a Varian C-1024 Time Averaging Computer. Broadening of the resonances occurs when lowering the temperature, and at -50°, extra resonances are visible. As will be shown later, the methylene protons are actually seen as two overlapping quartets at low temperature.

High temperature

Low temperature

Figure 4

The coupling constants which can be obtained from the four central lines are equal. The outer lines are unresolved because of their lower intensity and the resultant difficulty in obtaining good spectra.

When a solution of ethylmagnesium bromide is prepared in tetrahydrofuran and dioxane added to remove most of the magnesium

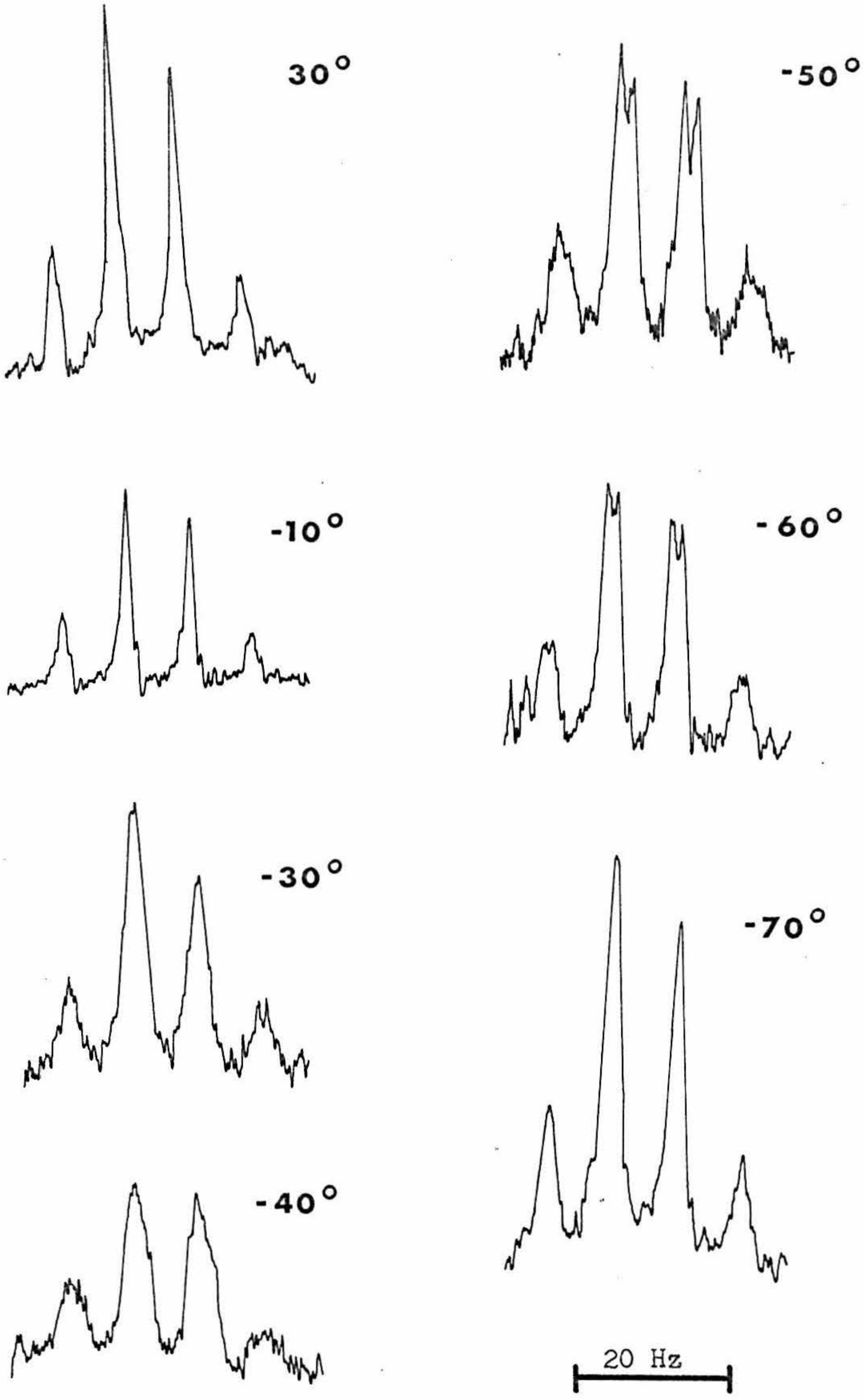


Figure 5. The nmr spectra (60 MHz) of the $-CH_2Mg-$ protons in ethylmagnesium bromide in tetrahydrofuran and N,N,N',N'-tetramethylethylenediamine. The amplitudes of the spectra differ.

halide, the methylene protons of diethylmagnesium give the nmr spectrum shown in Figure 6a. The second-order splitting disappears, but no broadening or extra peaks are visible down to -60°. The resolution remains fairly good at this low temperature as shown by the up-field tetrahydrofuran resonances at -60° in Figure 7 (the resolution at low temperatures was always judged by the spectrum of solvent tetrahydrofuran). When N,N,N',N'-tetramethylethylenediamine is added to this solution, the spectra remain the same at low temperature. Again no broadening is visible (Figure 6b).

Similar spectra were obtained for the methylene protons of diethylmagnesium prepared from diethylmercury. When N,N,N',N'-tetramethylethylenediamine was added to this sample, the methylene quartet did not change at low temperature. However, when magnesium bromide, in a concentration slightly greater than the diethylmagnesium, was prepared in this sample from magnesium bromide and ethylene bromide, the same changes were found in the low-temperature spectra of the methylene protons (Figure 8) as with the ethylmagnesium bromide spectra (Figure 3). Extra resonances are present at low temperatures which can be attributed to two overlapping quartets. Since the spectra did not change when magnesium bromide was not present, the changes in the presence of magnesium bromide can be explained by another species in equilibrium with the diethylmagnesium. This equilibrium presumably contains the magnesium bromide.

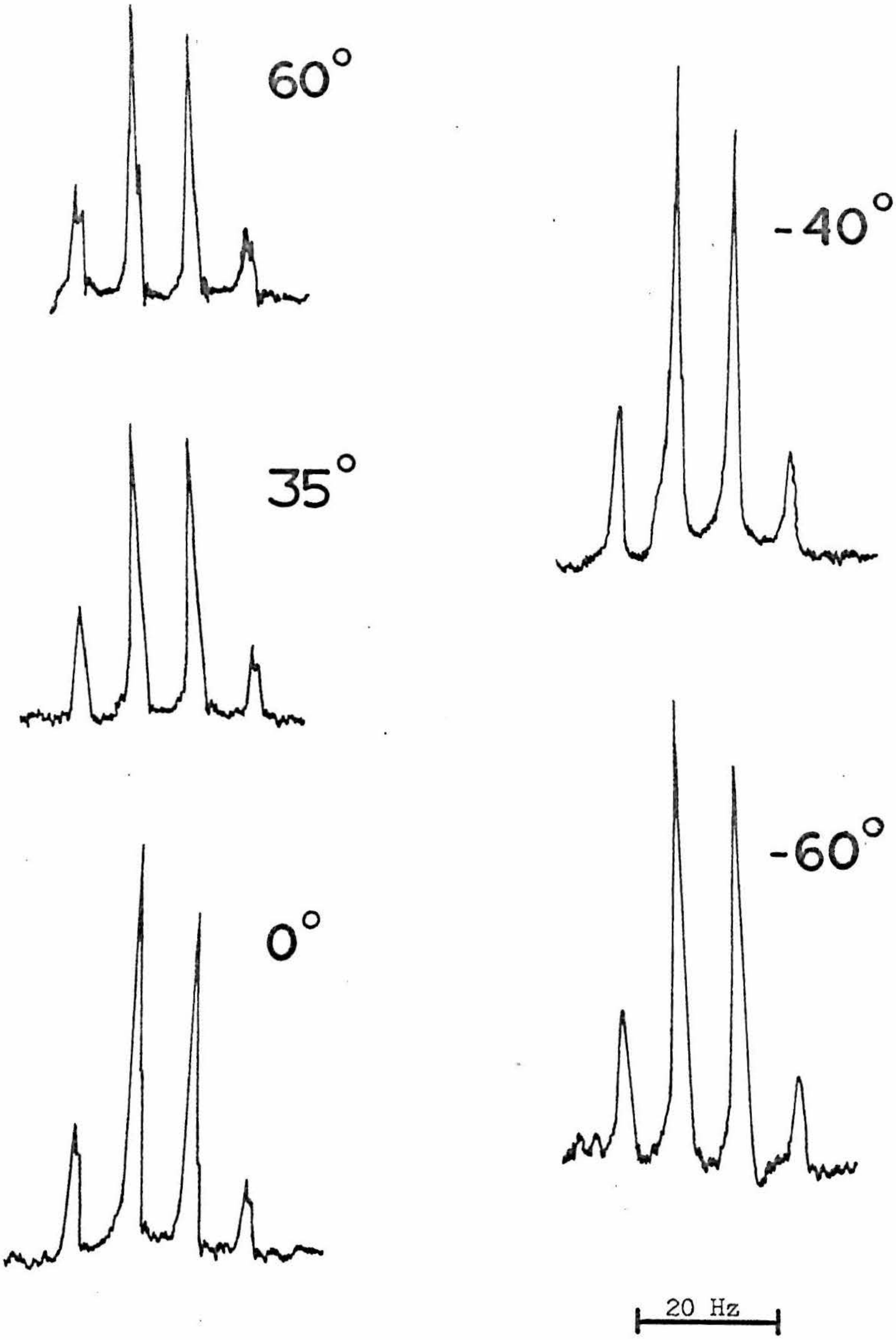


Figure 6a. The nmr spectra (60 MHz) of the $-CH_2Mg-$ of ethylmagnesium bromide in tetrahydrofuran to which dioxane had been added.

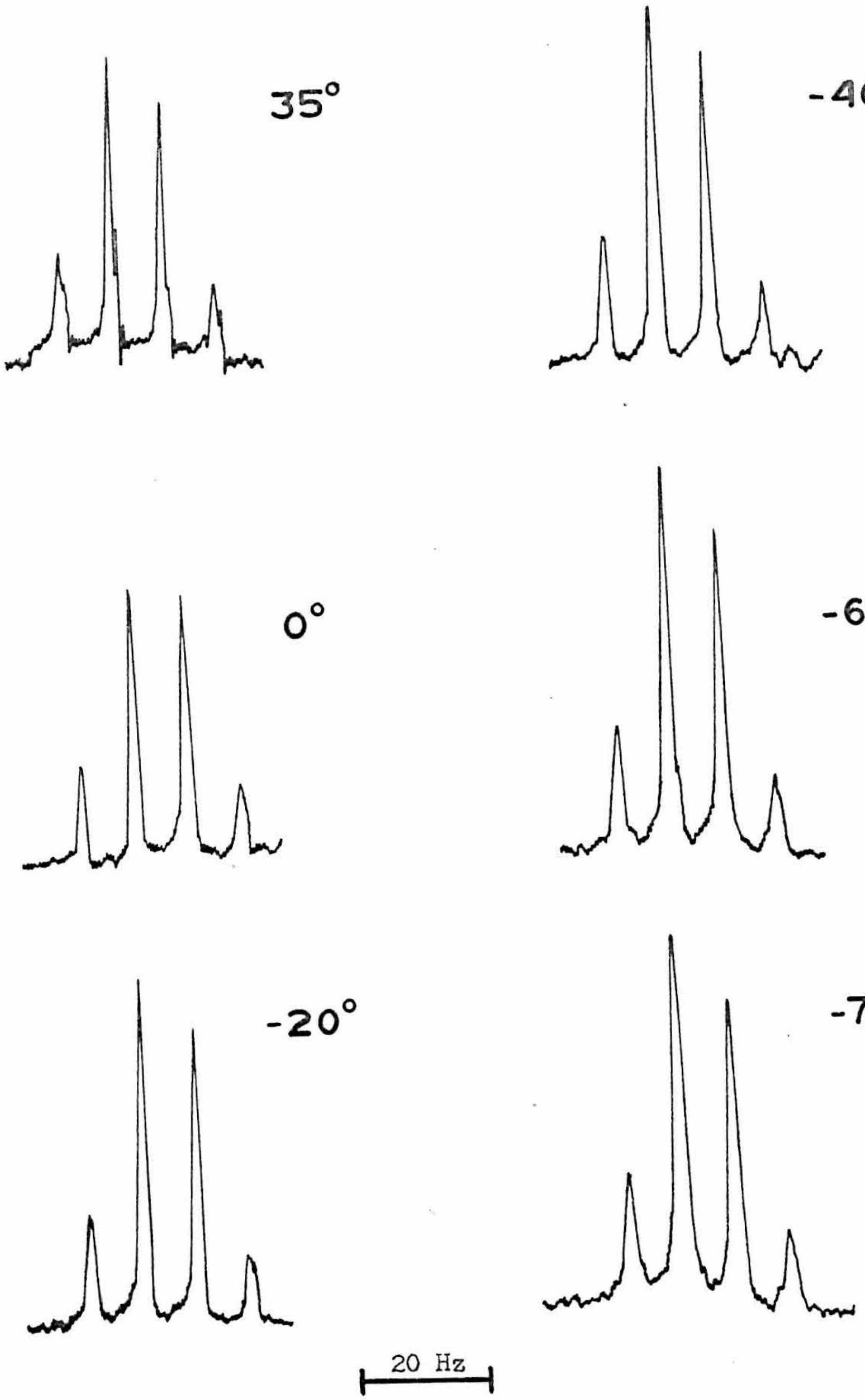


Figure 6b. The nmr spectra (60 MHz) of the $-CH_2Mg-$ protons of the same sample shown in Figure 6a diluted with N,N,N',N'-tetramethylethylenediamine.

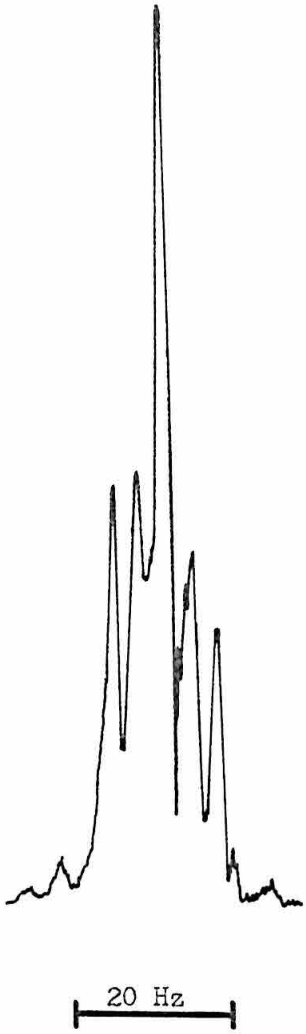


Figure 7. The nmr spectrum (60 MHz) of the protons *beta* to oxygen at -60° in solvent tetrahydrofuran containing diethylmagnesium.

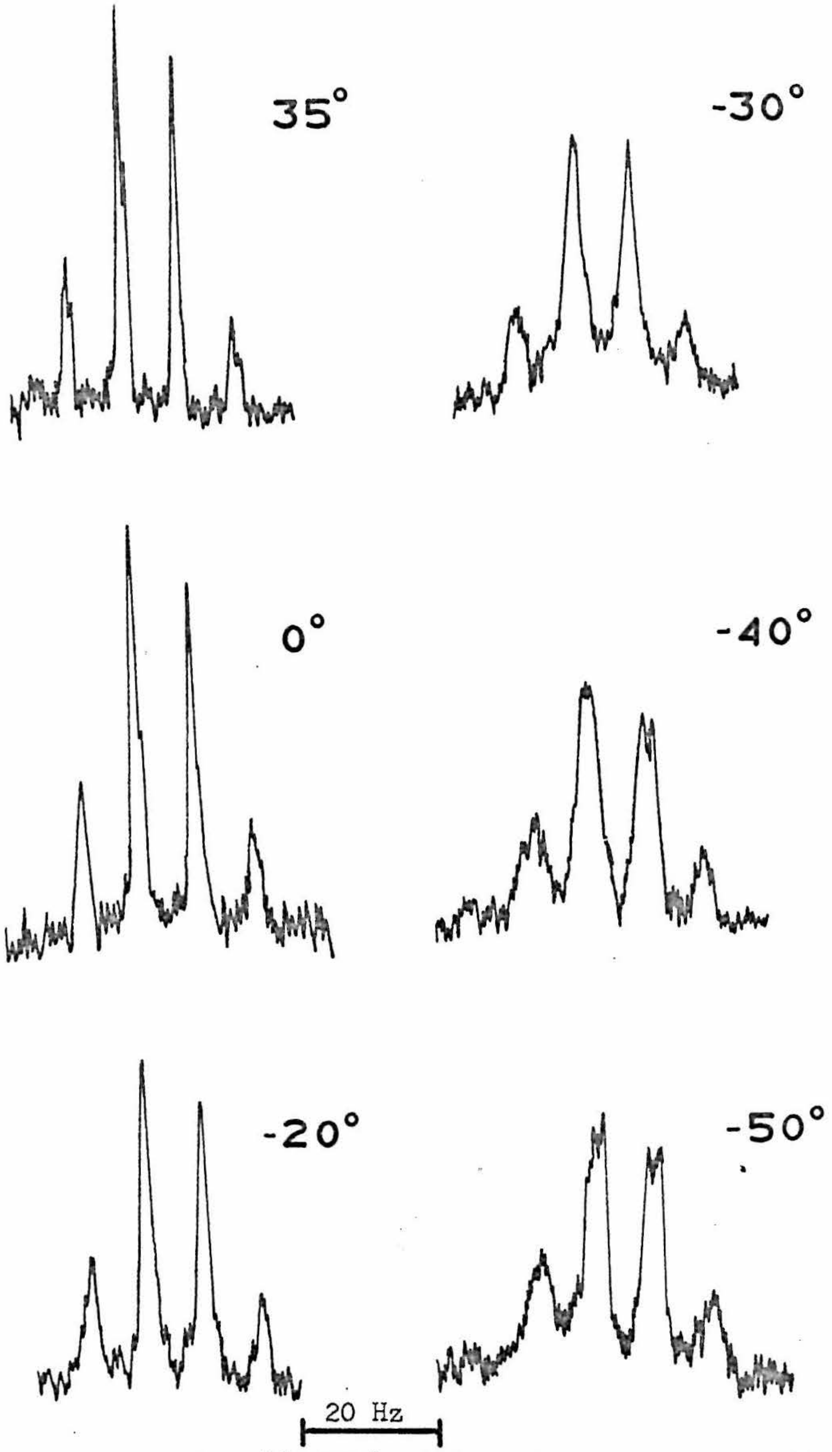


Figure 8. The nmr spectra (60 MHz) of the $-CH_2Mg-$ protons of diethylmagnesium prepared from diethylmercury with magnesium bromide prepared from ethylene bromide.

Diethylmagnesium was prepared from diethylmercury by transmetalation, and then ethyl bromide was treated with magnesium in the same solution to produce a mixture in which the molar ratio of diethylmagnesium to ethylmagnesium bromide was 1.0. The nmr spectra of the methylene protons in the ethyl groups do not change to two quartets at low temperature when diamine is added. This may be attributed to several factors. The amount of bromide in solution is possibly not great enough to produce enough halide-containing species to be detected by nmr spectroscopy. Another factor may be the concentration and temperature effects on the chemical shifts. In Figure 3 the two quartets which are fairly distinct at -50° are not visible at -70°. The rapid change of the spectra over 20° probably arises from temperature-dependent chemical shifts; a change in the equilibrium from approximately 50% of each species to 100% of one species over such a short temperature range is not reasonable. The possibility that concentration and solvation changes influence the chemical shifts will be discussed in the next several paragraphs.

Although the methylene proton resonances of ethylmagnesium bromide to which dioxane and then N,N,N',N'-tetramethylethylenediamine had been added exhibited no change at low temperatures, addition of diamine and then dioxane produced a solution whose methylene proton resonances changed from one quartet to two at low temperature (Figure 9). Normally the dioxane would precipitate

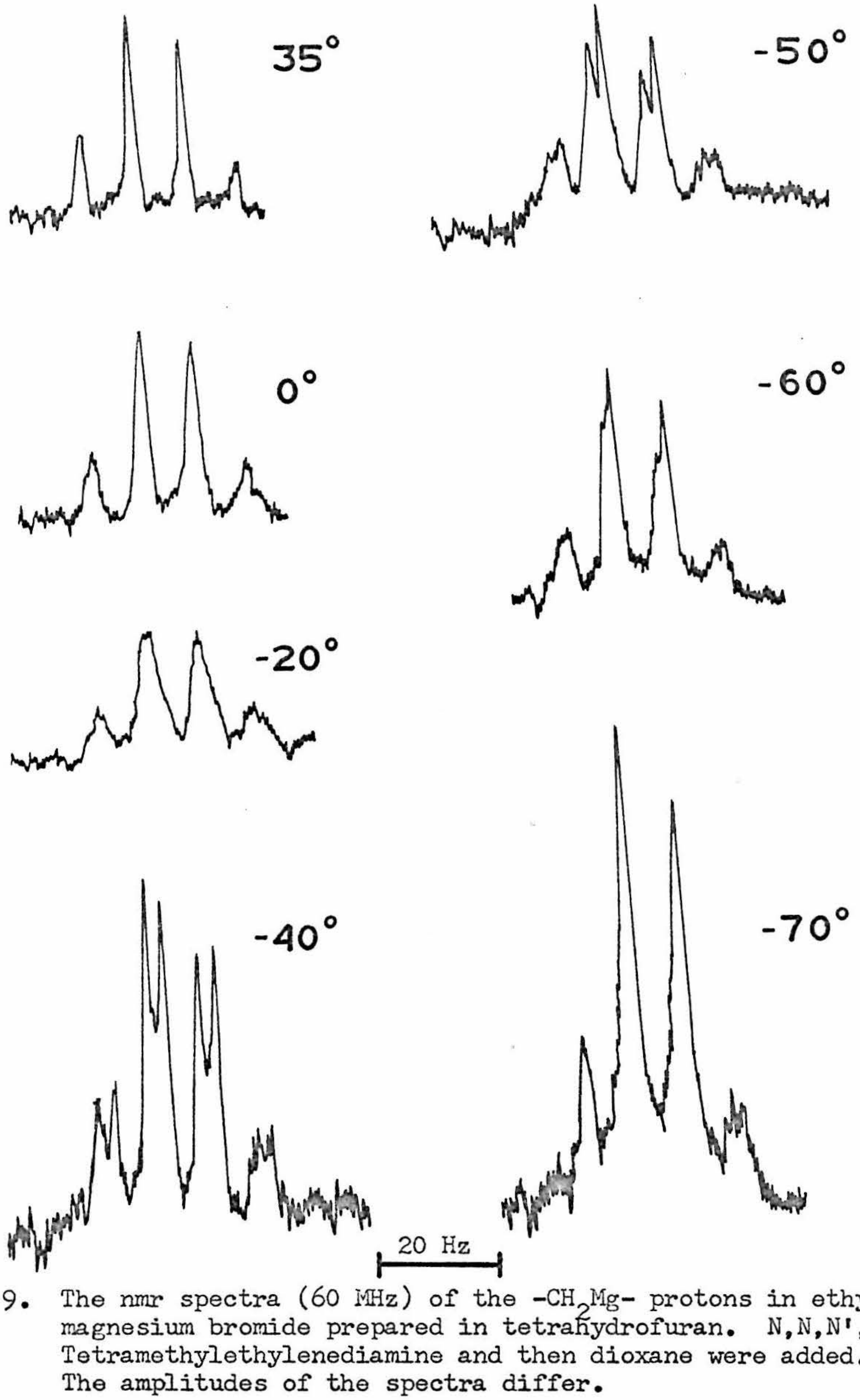


Figure 9. The nmr spectra (60 MHz) of the $-CH_2Mg-$ protons in ethylmagnesium bromide prepared in tetrahydrofuran. N,N,N',N'-Tetramethylethylenediamine and then dioxane were added. The amplitudes of the spectra differ.

the magnesium halide as a dioxanate complex. A large amount of precipitation occurred, and the amount of alkylmagnesium compound remaining in solution, as shown by the nmr spectrum, remained almost as great as before dioxane addition. Most of the precipitate, therefore, is magnesium bromide dioxanate, although some ethylmagnesium species or some of the diamine might be present in the precipitate. The nmr spectra of the methylene protons exhibit the same changes as those of the Grignard reagent (Figure 3), so that this experiment implies that the equilibrium observed does not involve magnesium bromide. However, quantitative analysis of the effectiveness of dioxane in forming precipitation complexes in the presence of N,N,',N'-tetramethylethylenediamine shows that the dioxane is not as effective as when no amine is present. Therefore, the equilibrium involved here can still be attributed to the combined effects of magnesium bromide and diethylmagnesium.

In this experiment with dioxane, the sample possessed a molar concentration ratio of magnesium halide to diethylmagnesium of considerably less than 1.0. However, in the experiment discussed earlier, the ratio was also quite low (magnesium bromide to diethylmagnesium ratio was 0.33) and no change in the nmr spectra was seen. Apparently dioxane precipitation of the magnesium halide is sufficiently ineffective in the presence of the amine and most of the halide remains in solution.

It is interesting that after heating the sample whose spectrum is shown in Figure 6b for 150 hours in a steam bath, the low temperature spectra were unchanged. Apparently once the dioxanate is formed, it cannot be redissolved by heating with N,N,N',N'-tetramethylethylenediamine. The amine apparently interacts with ethylmagnesium bromide in tetrahydrofuran to reduce the rate of dioxanate formation. The data presented in Table I support this. The Grignard reagent from ethyl bromide was prepared in tetrahydrofuran. Different tests were then conducted. When diamine was added to the solution before dioxane, more of the magnesium halide remained in solution then when no diamine was present. The diamine appears to retard the rate of magnesium bromide dioxanate formation. Less magnesium bromide was found in solution two hours after dioxane addition than 15 minutes after addition, both with and without diamine. Thus, when dioxane was added to ethyl Grignard reagent in an nmr tube after N,N,N',N'-tetramethylethylenediamine had been added, the methylene protons gave two quartets as their nmr spectrum at low temperatures. These nmr spectra were taken just several hours after dioxane addition, and a considerable amount of magnesium bromide remained in solution. Four months later, when all the magnesium bromide had precipitated, the nmr spectra of the methylene protons consisted of only one quartet at low temperature.

Magnesium bromide was generated from ethylene bromide and magnesium in the sample of ethylmagnesium bromide, diethylmagnesium, and diamine mentioned above which had shown no change at low temperature (the mole ratio of ethylmagnesium bromide to diethylmagnesium had been 1.0). With this extra magnesium bromide, the resonances of the methylene protons again changed from one quartet to two at low temperature. These methylene resonances are shown in Figure 10 as obtained at 100 MHz. The two quartets are now resolved so that all eight lines can be seen at -50°. As mentioned before, the coupling constants are equal in both quartets.

A sample of ethylmagnesium bromide was prepared in tetrahydrofuran and N,N,N',N'-tetramethylethylenediamine was added. Magnesium bromide was prepared in this solution so that the molar ratio of ethylmagnesium bromide to magnesium bromide was 1.0. At low temperature, two quartets were visible for the methylene protons of the ethyl group (Figure 11). By comparing these two quartets with those seen in other samples it is seen that the low-field quartet is more intense when more magnesium bromide is present. Intensities are difficult to interpret because of the overlapping of peaks, but in comparing the changes in different samples, the low-field quartet is the one which is favored by the addition of excess magnesium bromide. With a sample containing a low concentration of magnesium bromide relative to the diethylmagnesium (see Figure 9, -50°), the low-field quartet is less intense than the up-field quartet. With a sample containing a large excess of magnesium bromide (see Figure 11, -50°), the low-field quartet is larger than the up-field one (this sample partially crystallized

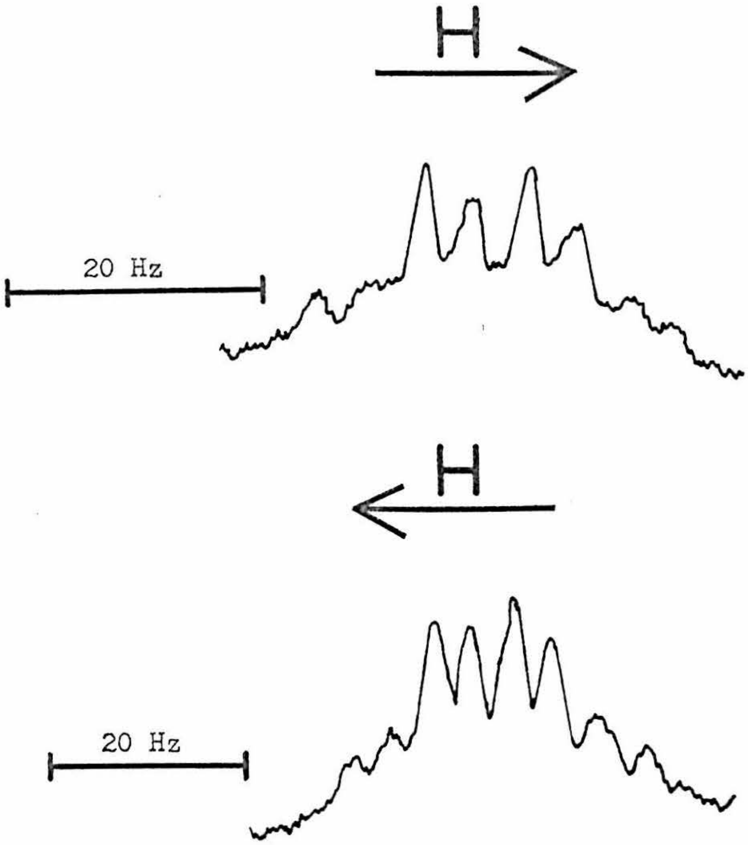


Figure 10. The nmr spectra (100 MHz) at -50° of $-CH_2Mg-$ protons of a sample prepared from ethylmagnesium bromide, diethylmagnesium, and magnesium bromide.

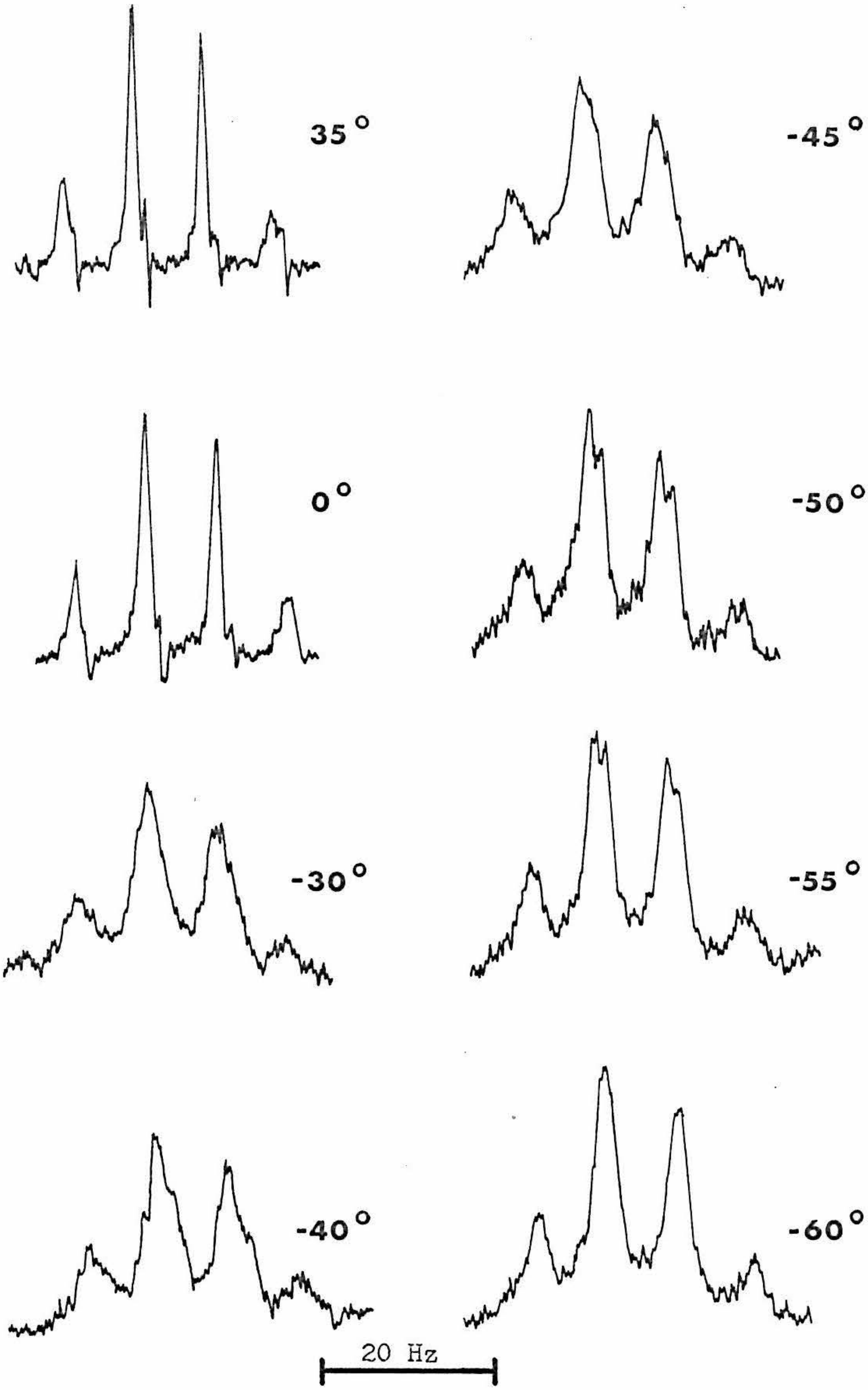


Figure 11. The nmr spectra (60 MHz) of $-CH_2Mg-$ protons of ethylmagnesium bromide in tetrahydrofuran. Magnesium bromide was added so that the molar ratio of ethylmagnesium bromide to magnesium bromide is 1.0.

at low temperatures).

The resonances of the methyl groups in all samples of ethylmagnesium compounds were triplets, but only one triplet was visible for the methyl protons even when two quartets were observed for the methylene protons. Even at 100 MHz only one triplet was resolved. One line superimposed on the up-field side of the center line of the triplet does appear when two quartets are present for the methylene protons at low temperature. This may be the center of one triplet, but the outer lines were never observed. Since the chemical shifts of the methylene protons in the two quartets only differ by approximately 2 cycles, it is not surprising that the chemical shift of the methyl protons are nearly the same. If the down-field quartet arises from ethylmagnesium bromide and the up-field one from diethylmagnesium, then the difference in methylene proton chemical shifts are caused by differences in -MgBr and $-MgCH_2CH_3$. The difference in chemical shifts of protons on carbons bound to magnesium is small, and the effect on protons one atom further removed from magnesium would be smaller. The assignment of the down-field quartet to ethylmagnesium bromide and the up-field quartet to diethylmagnesium is in agreement with what one would predict assuming the -MgBr group to be more electronegative than the $-MgCH_2CH_3$ group.

While the methylene protons of the Grignard reagents have been undergoing changes, the spectra of N,N,N',N'-tetramethylethylenediamine have also been seen to undergo changes with temperature. The spectra in Figure 12a provide examples of the spectral changes found for the diamine in a solution of the Grignard reagent of 1,4-dibromo-2,3-dimethylbutane in tetrahydrofuran with dioxane added. The diamine in tetrahydrofuran with magnesium bromide also broadens with extra resonances appearing at the lowest temperatures observed (Figure 12b). Another set of spectra (Figure 12c) of the diamine in a tetrahydrofuran solution of 3,3-dimethylbutylmagnesium chloride shows similar changes.

Complexes of N,N,N',N'-tetramethylethylenediamine with dialkylmagnesium compounds have been reported by several workers (39). These complexes are stable and can be sublimed easily. The changes in the nmr spectrum of N,N,N',N'-tetramethylethylenediamine indicate that the diamine in solution is in equilibrium with some complex. These changes have occurred in samples where the alkylmagnesium halide concentration is greater than or less than that of the diamine. The changes were not the same for all samples, because the concentrations were different. The diamine did not exhibit any spectral changes in solutions containing diethylmagnesium with no magnesium halide. The complex could be the dialkylmagnesium type previously reported. It also could be a complex of diamine and magnesium bromide, or diamine and alkylmagnesium bromide.

Although very stable complexes are found between diamine and

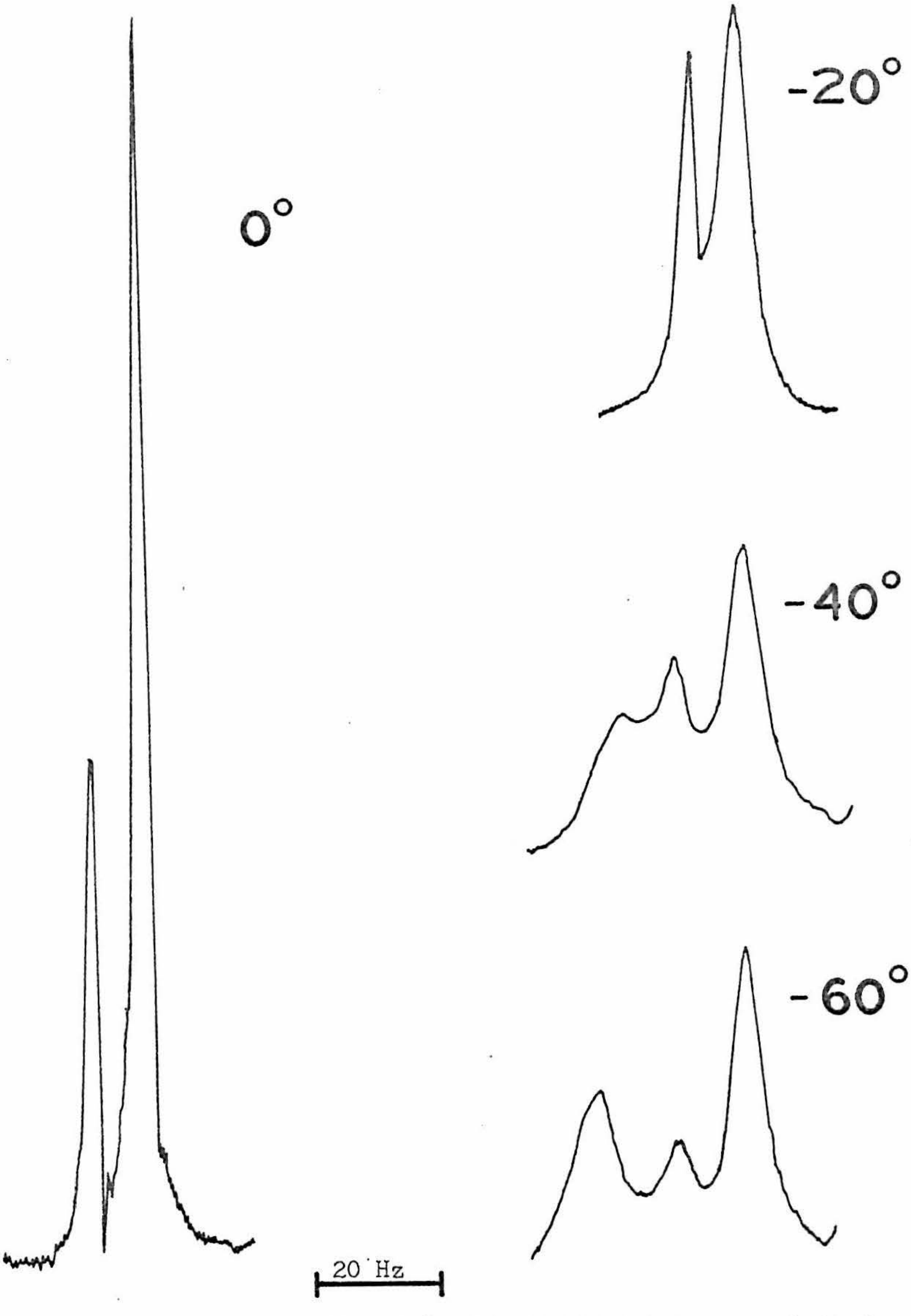


Figure 12a. The nmr spectra (60 MHz) of N,N,N',N'-tetramethylethylenediamine in a tetrahydrofuran solution of the di-Grignard reagent of 1,4-dibromo-2,3-dimethylbutane.

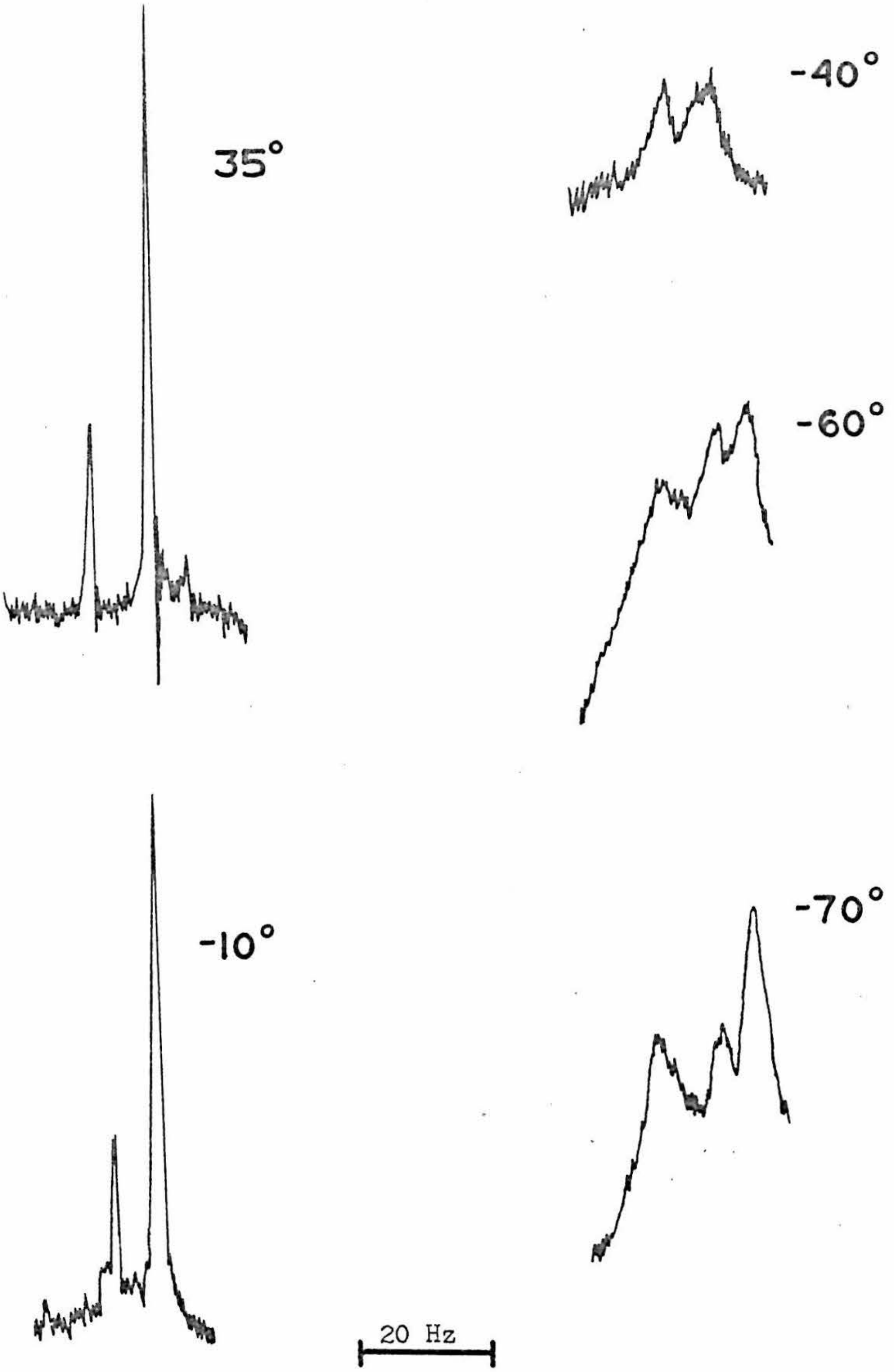


Figure 12b. The nmr spectra (60 MHz) of N,N,N',N'-tetramethylethylenediamine in a tetrahydrofuran solution of magnesium bromide. The amplitudes of the spectra differ. The spectra at -60° and -70° are on the side of one of the tetrahydrofuran resonances.

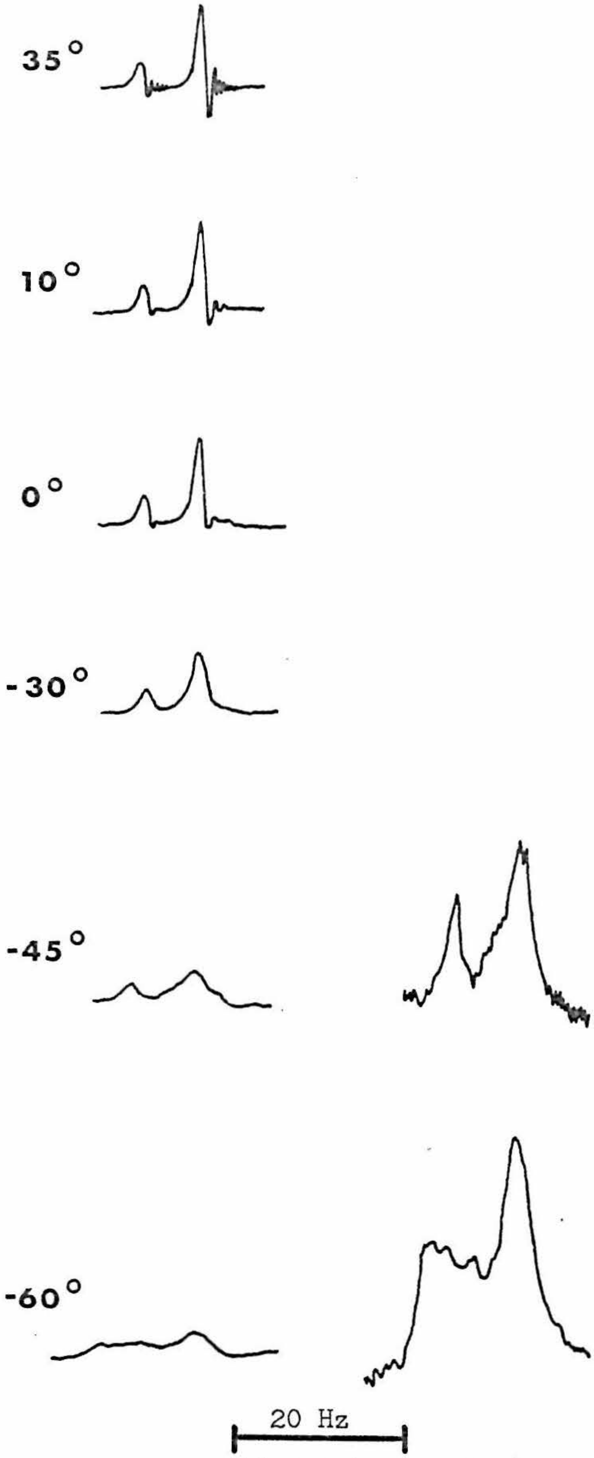
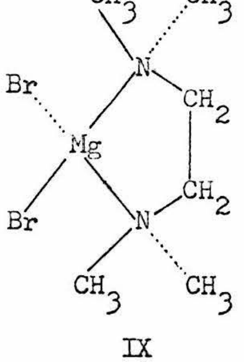
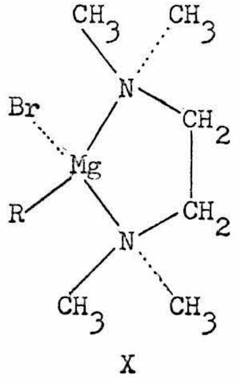


Figure 12c. The nmr spectra (60 MHz) of N,N,N',N'-tetramethylethylenediamine in a tetrahydrofuran solution of 3,3-dimethylbutylmagnesium chloride. The two spectra at right, -45° and -60°, were taken with increased spectrum amplitude.

several transition metal halides (40), little work has been carried out with the magnesium halides. The anomalous solubility effects of N,N,N',N'-tetramethylethylenediamine in Grignard reagents has already been discussed. In recent unpublished work on Grignard reagents of 3-chloronortricylene (41), magnesium chloride was found to precipitate from these Grignard solutions when the diamine was added. However, as already noted, the diamine sometimes confers solubility on all of the Grignard species. The effect on magnesium bromide alone was checked by preparing two identical samples of magnesium bromide in tetrahydrofuran from ethylene bromide and magnesium. To one sample was added N,N,N',N'-tetramethylethylenediamine. The samples were both 0.33 M in magnesium bromide, and one was 0.16 molar in diamine. Within one day, crystals of magnesium bromide were present in the tube without diamine. Cooling to -50° did not produce crystals in the tube with the diamine, but a white powder was present on the wall of the sample vessel. After one week



IX



X

at room temperature, considerable quantities of white powder collected which is undoubtedly the complex of the amine with the magnesium bromide IX. A very recent study of alkylzinc halide and N,N,N',N'-tetramethylethylenediamine has indicated that the diamine will form complexes with zinc halides or alkylzinc halides (42). The nature of the zinc species in the complex, whether zinc halide or alkylzinc halide, was a function of halide and solvent. This may be the reason why the analogous Grignard reagent systems also give variable results. The N,N,N',N'-tetramethylethylenediamine may be in equilibrium with different complexes. The chemical shifts of the protons in the different complexes are averaged at room temperature, but when the rate of exchange is reduced, the different chemical shifts can be seen. Another factor which may introduce additional chemical shift complications is the possibility of the alkylmagnesium halide complex X in which the diamine is unsymmetrical. The protons of the diamine can be divided into two groups by a plane in the five-membered ring, with the protons on one side having chemical shifts different from those of the corresponding protons on the other side. The nmr spectrum of this complex would be quite complicated. At low temperatures, the nmr spectrum of the diamine may be partly composed of this complicated spectrum.

Even though the diamine is unsymmetrical in X, the ethyl group would not experience any asymmetry. Therefore, its nmr spectrum is not expected to be further complicated by the existence of this complex.

The nmr spectra of the diamine prove that a definite equilibrium involving the amine and some magnesium species does exist. Because the spectral changes observed are not constant and because the solubility characteristics of the Grignard reagents with the amine vary to such a large extent, the complexes formed may differ from experiment to experiment. In no case discussed did any solid crystallize at low temperature except where magnesium bromide concentration was equal to the ethylmagnesium bromide concentration. The complex which separated from the solution of diamine and tetrahydrofuran was never found with solutions containing alkylmagnesium species. Therefore, the equilibria among the Grignard species was never influenced by selective removal of one of them. If complex formation is the mechanism for reducing the rates of interconversion, then the magnesium in the Grignard species must be in rapid equilibrium with both diamine and tetrahydrofuran, the diamine complexes, of course, having the greater equilibrium constants of formation.

Table I

Effectiveness of dioxane in complexing magnesium bromide in Grignard reagent solutions in tetrahydrofuran.

The samples were prepared from 2 ml. of ethyl bromide (0.0263 moles) and excess magnesium in 10 ml. of tetrahydrofuran. To test dioxane effectiveness, 2 ml. of dioxane (0.0236 moles) was added to precipitate magnesium halide. To test the influence of N,N,N',N'-tetramethylethylenediamine, 2 ml. of the diamine (0.013 moles) was added before dioxane. Aliquots of the supernatants were withdrawn and analyzed for halide concentration.

Trial	Time between dioxane addition and aliquot withdrawal	% Halide remaining when just dioxane added	% Halide remaining when diamine and then dioxane added
1	15 min.	21.0%	40.5%
2	120 min.	11.1%	26.9%

Table II

Characteristics of 5 samples of ethylmagnesium bromide in tetrahydrofuran which exhibited 2 quartets for the methylene protons at low temperature.

	Moles of ethyl groups	Moles of diamine	Moles of bromide ion	Coalescence temperature	Molar ratio* $RMgX/R_2Mg$	Chemical shift difference of quartets	General description of resolution
1	0.00131	0.00098	< 0.00131	-30°	< 2:1	2.3 Hz	Good
2	0.00016	0.00008	0.00016	-40°	2:1	1.8 Hz	Good
3	0.00094	0.00098	0.00230	-40°	2:1	1.5 Hz	Good
4	0.00049	0.00080	0.0011	-40°	> 2:1	1.3 Hz	Good
5	0.00016	0.00008	0.00048	-45°	> 2:1	1.1 Hz	Fair

1. Ethylmagnesium bromide prepared from ethyl bromide in tetrahydrofuran, amine added, then dioxane added.

2. Ethylmagnesium bromide prepared from ethyl bromide in tetrahydrofuran, diamine added.

3. Diethylmagnesium prepared from diethylmercury in tetrahydrofuran, diamine added, then magnesium bromide prepared from ethylene bromide.

4. Prepared as in 3.

5. Ethylmagnesium bromide from ethyl bromide in tetrahydrofuran and additional magnesium bromide from ethylene bromide.

* This ratio is the largest possible RMgX concentration to the largest possible R_2Mg concentration. The theoretical ratio for a Grignard reagent prepared from ethyl bromide would be 2:1.

I. THE INFLUENCE OF N,N,N',N'-TETRAMETHYLETHYLENEDIAMINE ON THE SCHLENK EQUILIBRIUM

Conclusions

House (43) has recently demonstrated that N,N,N',N'-tetramethylethylenediamine can markedly affect the rates of alkyl exchange of dialkylmagnesium compounds in ether solvents. By using two different alkyl groups and slowing down the rate of exchange at low temperature, the nmr spectrum of the unsymmetrical dialkylmagnesium compound was observed along with that of the symmetrical dialkylmagnesium. Although he was able to do this without the diamine by using dicyclopentadienylmagnesium as one species, the amine was necessary for observing the mixed dialkyl species from dimethylmagnesium and diphenylmagnesium. The diamine was needed to reduce the alkyl exchange rate for the methyl-phenyl system; the diamine was also shown to reduce exchange rates in the methylcyclopentadienyl system.

When small amounts of magnesium bromide were added to the dialkyldiarylmagnesium systems, the rate of alkyl exchange increased substantially. In the ethylmagnesium bromide system which has been studied, alkyl exchange would be increased by the presence of the halide; however, use of tetrahydrofuran and N,N,N',N'-tetramethylethylenediamine as the solvent system should slow down the rate. The rate of alkyl exchange is indeed reduced to that point where two different alkyl groups are observed. The halide ion is apparently involved in the equilibrium, because the two alkyl species are not observed when no halide is present.

The experimental results can be explained by the presence of two alkylmagnesium species, diethylmagnesium and ethylmagnesium bromide, which are equilibrating rapidly with each other.

$$CH_3CH_2MgBr \rightleftharpoons MgBr_2 + (CH_3CH_2)_2Mg \qquad (3)$$

This is the Schlenk equilibrium. Both tetrahydrofuran and N,N,N',N'-tetramethylethylenediamine slow down the rate of conversion from one side of the equilibrium to the other, but the diamine is the rate-retarding agent needed to make observation of the different species possible.

A possible mechanism for rate retardation is the formation of tight solvent complexes of the alkylmagnesium species with the diamine. The Grignard reagents are probably tetrahedral about magnesium with solvent occupying two of the four positions (44). One molecule of the diamine could occupy two of the solvent positions. The tendency for the diamine to do this is supported by the evidence of complex formation with dialkylmagnesium compounds, dialkylzinc compounds, or alkylzinc halides. The change observed for the nmr spectra of the diamine with the Grignard reagent indicates that a definite solvent complex is formed. Which species are complexed is not known; possibly all three of the magnesium species present in the Schlenk equilibrium are involved.

$$\begin{tikzcd}
C_2H_5MgBr \arrow[r, phantom, "\rightleftharpoons"] \arrow[d, phantom, "\upharpoonleft\downharpoonright"] & MgBr_2 \arrow[d, phantom, "\upharpoonleft\downharpoonright"] & + & (C_2H_5)_2Mg \arrow[d, phantom, "\upharpoonleft\downharpoonright"] \\
C_2H_5MgBr.diamine \arrow[r, phantom, "\rightleftharpoons"] & MgBr_2.diamine & + & (C_2H_5)_2Mg.diamine
\end{tikzcd} \qquad (4)$$

In the above equilibrium the species not coordinated with diamine would be solvated by tetrahydrofuran.

The existence of a dimeric type Grignard reagent can be disregarded. All carefully conducted association studies indicate that the Grignard reagent is monomeric in tetrahydrofuran.

The different species present do not form insoluble complexes with the diamine as shown by the solubility characteristics already discussed. In fact, N,N,N',N'-tetramethylethylenediamine can increase the solubility of both magnesium bromide and the Grignard reagent in tetrahydrofuran.

It is difficult to make any conclusions about the position of the equilibrium in these solvent mixtures, because of a shift which may be produced by the diamine. Also, the resonances of each species overlap and prevent a good measurement of the exact amount of each species. A crude approximation from the nmr spectra indicates that about 50% of the alkyl groups are in the dialkylmagnesium form with the remainder present as alkylmagnesium halide. This indicates an equilibrium constant of 4 for the reaction

$$(C_2H_5)_2Mg \quad + \quad MgBr_2 \rightleftharpoons 2\ C_2H_5MgBr \qquad (5)$$

This value is the same as that reported in a recent review article by E. C. Ashby (45). The value of 4 was obtained by Becker and Smith from heats of mixing of diethylmagnesium and magnesium bromide in tetrahydrofuran. This value is also very close to that value reported by Mosher and Salinger from infrared studies (14).

As expected, the presence of magnesium bromide, whether less or more than one halogen atom per magnesium atom, appears to influence the concentration of species present. However, the concentration of diamine does not appear to alter the equilibrium position, as one would expect if a very tight solvation complex of one of the magnesium species were formed. A fourfold change in the ratio of diamine to Grignard reagent had little, if any, effect on the position of the equilibrium. This, perhaps, is unexpected but need not be unsettling.

The work reported to this point in this thesis has been conducted in order to study the Schlenk equilibrium for Grignard reagents. The results indicate that the Schlenk equilibrium does occur for ethylmagnesium bromide in tetrahydrofuran, but that the rates of interconversion between the different species are very fast. By using N,N,N',N'-tetramethylethylenediamine as a co-solvent with tetrahydrofuran, this rate has been reduced so that two species, which appear to be diethylmagnesium and ethylmagnesium bromide, can be observed on the nmr time scale. House (43) has demonstrated that the alkyl-exchange reactions are extremely fast and even faster with magnesium halide in solution. Presumably this is the reason for the lack of proton-magnesium-25 coupling with alkylmagnesium compounds (46) and proton-carbon-13 coupling across magnesium in dimethylmagnesium and methylmagnesium iodide (47). With N,N,N',N'-tetramethylethylenediamine in solution, the rates of the exchange processes have been reduced and the different forms in which the alkyl Grignard reagents exist have been observed.

II. THE NATURE OF THE DI-GRIGNARD REAGENT

Results and Discussion

The di-Grignard reagents of dihalogen compounds are useful synthetically and give fairly good yields of cyclic addition products with di- or polyfunctional molecules. To study the nature of the di-Grignard reagent by the nuclear magnetic resonance method, the reagent has to be preparable without formation of side products which might interfere with the nmr spectra. For example, a side product such as _n_-butylmagnesium bromide would be expected to have peaks overlapping those of the di-Grignard reagent of 1,4-dibromobutane. Fortunately, the protons on the carbon _alpha_ to magnesium have a chemical shift which is up-field from tetramethylsilane. Therefore, only other Grignard reagents will interfere with these resonances.

Although the di-Grignard reagent of 1,4-dibromobutane and higher homologs can be prepared in good yield in diethyl ether (48), this ether is not very suitable because the di-Grignard reagent is almost completely insoluble—a two-phase liquid mixture being formed with the more dense phase containing almost all the desired di-Grignard reagent in ether. The less dense portion is mostly diethyl ether containing a small amount of magnesium bromide. Addition of co-solvents such as tetrahydrofuran, dioxane, or dimethoxyethane to the layer containing the di-Grignard reagent caused formation of copious amounts of white precipitate. The small amount of supernatant contained no di-Grignard reagent. In no case could the di-Grignard reagent be solubilized by ether-type co-solvents once the heavier oil had separated.

One method for obtaining solutions of the di-Grignard reagent in diethyl ether was found. Namely, after the reaction with magnesium was complete, miscibility could be achieved by adding 1,4-dibromobutane. However, coupling rapidly occurred in the resulting solutions to give octane Grignard reagents which interfered with the nmr spectra of the 1,4-di-Grignard reagents.

Somewhat better, but still not satisfactory, results were obtained by preparing the di-Grignard reagents in dimethyl ether. 1,4-Dibromobutane and 1,4-dichlorobutane reacted readily with magnesium in dimethyl ether when ethylene bromide was used as an initiator, but substantial crystallization occurred. The supernatant usually contained a rather low concentration of Grignard reagents, but its nmr spectrum was that expected for a solution of the di-Grignard reagent. However, 24 hours after the reaction with the excess magnesium, the spectrum was complicated with extra peaks. The majority of these were from the di-Grignard reagent of 1,8-dibromooctane. The formation of this coupling product comes about because the 1,4-dihalobutanes apparently do not react completely with magnesium, and some of the initially formed monofunctional Grignard reagent may crystallize and later couple with the 1,4-Grignard reagent. Some monofunctional Grignard reagent may also be present in solution when the initial nmr spectra were taken. The products from Wurtz-type coupling are the major side products when using dimethyl ether. Figure 13 shows the nmr spectrum of the di-Grignard reagent of 1-bromo-4-chlorobutane at 100 Mhz. The resonances at -60 Hz are from protons alpha to magnesium. Irradiation of these protons decouples the resonances at 155 Hz, the protons beta to magnesium. Irradiation at 155 Hz decouples the resonances at -60 Hz, but there is more than one singlet. Clearly, more than one species with protons on the carbons alpha to magnesium must be present. One of these is the Grignard reagent of the octane coupling product. The large peak at 132 Hz is from methylene protons of this product. The resonances slightly up-field are from mono-functional Grignard reagents such as n-butylmagnesium bromide, side products from partial hydrolysis of di-Grignard molecules. A third side product usually found, but not shown in Figure 13, is cyclobutane which is produced by intramolecular coupling.

The side products produced in dimethyl ether make this unsuitable as a solvent. Tetrahydrofuran, however, was found to be satisfactory for the study of di-Grignard reagents as are mixtures of dimethyl ether and tetrahydrofuran. To be sure, when the di-Grignard reagent of 1,4-dibromobutane is prepared in

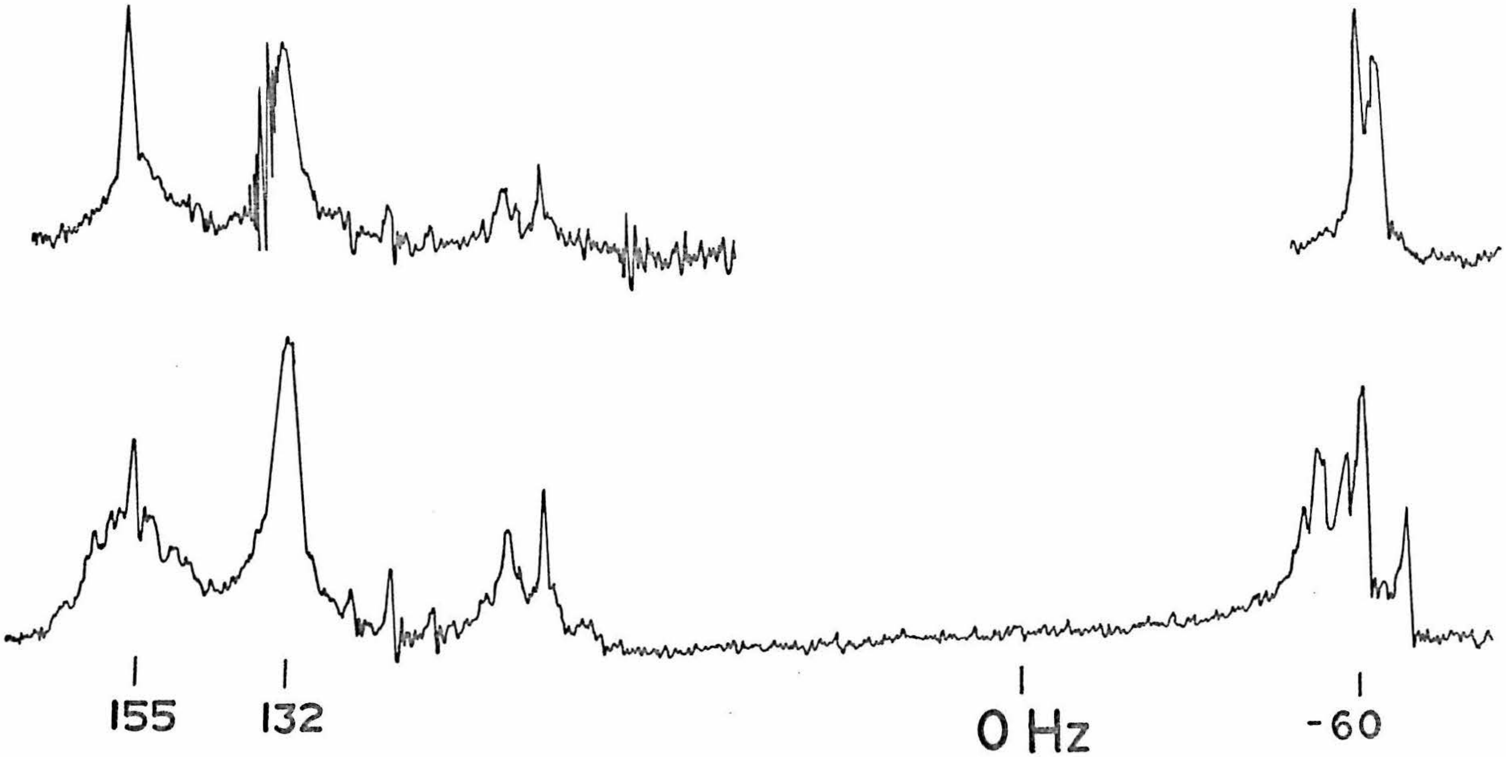


Figure 13. The nmr spectrum (100 MHz) of the di-Grignard reagent of 1-bromo-4-chlorobutane prepared in dimethyl ether. The left side of the upper spectrum is the result of irradiating at -60 Hz; the right side is the result of irradiating at 155 Hz.

tetrahydrofuran, crystallization occurs, but these crystals are certainly magnesium bromide because the intensities of resonances of the alkylmagnesium species remaining in solution are not diminished. Crystallization of magnesium chloride does not occur when the dichloro Grignard reagent is prepared at the concentrations normally used. However, the bromide reacts faster and more completely, and there are advantages to using mixtures of the two halides.

The spectrum of a mixture of di-Grignard reagents from 1,4-dibromobutane and 1,4-dichlorobutane prepared in dimethyl ether and perdeuterated tetrahydrofuran is shown in Figure 14. The singlet at 108 Hz is the resonance of cyclobutane, the amount of which appears to be a function of the temperature of the reaction. When the reaction of the dihalide with magnesium is carried out below 45°, the amount of this coupling product is quite small. Higher temperatures lead to larger quantities. The conversion at 45° was not usually complete, but after the initial rapid reaction had subsided, indicating that most of the dihalide had reacted, a short heating in a steam bath could be used to remove any remaining halide by reaction with magnesium or by coupling with another Grignard function. A product of this coupling is the di-Grignard reagent of 1,8-dihalooctane whose methylene protons on carbons <u>delta</u> and <u>gamma</u> to magnesium produce the resonance at 67 Hz. The less intense resonances slightly up-field are from partially

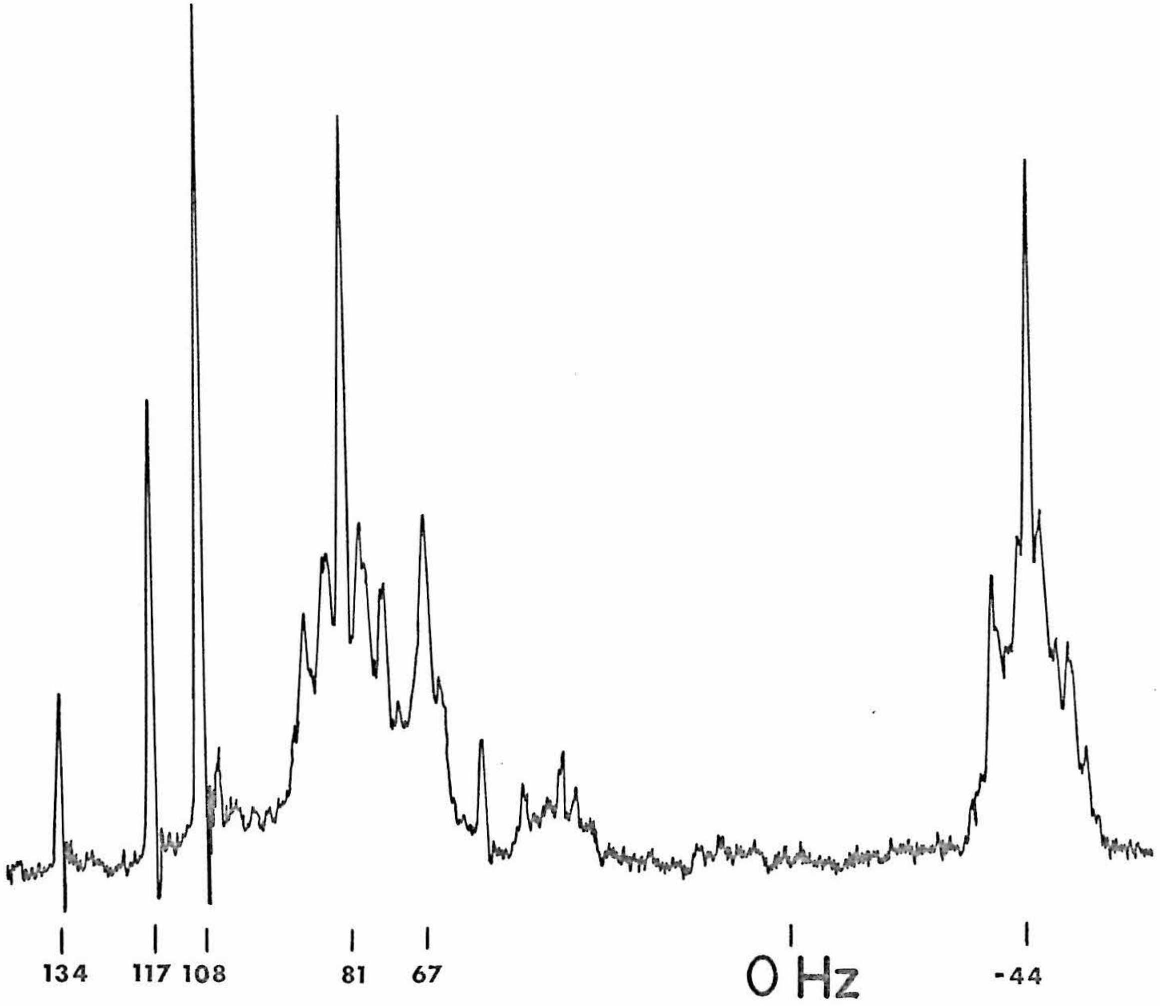


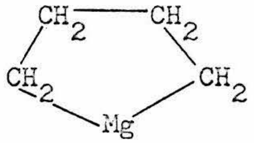
Figure 14. The nmr spectrum (60 MHz) of the di-Grignard reagent prepared from a mixture of 1,4-dibromobutane and 1,4-dichlorobutane in a mixture of diethyl ether and perdeuterated tetrahydrofuran.

hydrolyzed di-Grignard reagent and are expected to correspond to n-butyl- or n-octylmagnesium halide. The singlet for the carbon-13 satellite of dimethyl ether is found at 117 Hz while the singlet at 134 Hz is a spinning sideband of that solvent. The larger resonances at 81 and -44 Hz are from the protons beta and alpha to magnesium, respectively, of the desired di-Grignard reagent.

The complex spectrum of the di-Grignard reagent is similar to that of the methylene protons of 1,4-butanediol in water. The spectrum of the di-Grignard might be simplified by inversion of the terminal carbon atoms, a process which cannot occur in the diol. A spectrum which appears to be very similar to these is the AA'A''A'''XX'X''X''' (49) spectrum of tetrahydrofuran (50). These two compounds can be used as models for the difference in the two di-Grignard forms XI and XII.

$XMgCH_2CH_2CH_2CH_2MgX$

XI

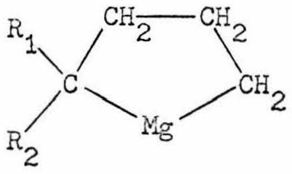


XII

To obtain anything significant with respect to coupling constants, the di-Grignards had to be selectively deuterated. This will be discussed later.

Although tetrahydrofuran was a good solvent for the di-Grignard reagent, dioxane could not be added without obtaining a large amount of white precipitate containing most or all of the alkylmagnesium compounds besides the magnesium halide. However, dioxane could be added to the di-Grignard solution when prepared in a dimethyl ether-tetrahydrofuran solvent mixture. The results with such mixtures will be discussed later.

By using a di-Grignard reagent prepared from dihalides with a primary and tertiary halide, asymmetry could be introduced into the cyclic dialkylmagnesium form, as in XIII.



XIII

4-bromo-1-chloro-4-methylpentane was synthesized, and its di-Grignard reagent was prepared. This compound could not give an asymmetrical form because R_1 and R_2 are both methyl groups, but it did serve as a trial sample for preparing the mixed di-Grignard reagent. The nmr spectrum of the Grignard reagent showed that alkenic protons had been produced when the halide reacted with magnesium. The spectrum of the protons <u>alpha</u> to magnesium in the primary Grignard function showed that more than one Grignard reagent had been formed. Elimination had occurred at the tertiary carbon producing possibly two alkenes. Because this dihalide did not give a single product, dihalides of this type were deemed unsuitable for the study of di-Grignard reagents.

The nmr spectrum of the di-Grignard reagent of the dibromo- and dichlorobutane in Figure 14 indicates that only one type of di-Grignard reagent is present or that all existing forms are in rapid equilibrium on the nmr time scale. This is the same result obtained for all monofunctional Grignard reagents in solutions containing magnesium halide. The equilibrium between the alkylmagnesium halide and dialkylmagnesium has not been reported as observable by nmr spectroscopy except for the work described in the first part of this thesis in which N,N,N',N'-tetramethylethylenediamine was present and the work reported by Evans and Kahn (37) on the pentafluorophenylmagnesium halides. Because only one set of resonances is visible at 35°, the cyclic di-Grignard species XII, if it is present, is rapidly equilibrating with the other forms of the di-Grignard reagent. At low temperatures where these rates might have been reduced, viscous broadening of all the resonance lines in the spectra occurs and the resolution was so poor that no information could be obtained.

To simplify the nmr spectra of the di-Grignard reagent of 1,4-dibromobutane and 1,4-dichlorobutane, 1,4-dibromo-1,1,2,2-tetradeuteriobutane and 1,4-dichloro-1,1,2,2-tetradeuteriobutane were synthesized. The nmr spectra of these tetradeuterated dihalides are much less complex than those of the undeuterated dihalides. The resonances of the protons alpha to halogen are well-resolved triplets, while the resonances of the beta protons are triplets with lines broadened considerably by coupling to deuterium. Figure 15 is the nmr spectrum of the di-Grignard reagent prepared from a mixture of the tetradeuterated dihalides. The solvent is a mixture of dimethyl ether and tetrahydrofuran. The resonances at -46 Hz are the protons alpha to magnesium, and the broadened triplet at 77 Hz is from the protons beta to magnesium. Considerable viscous broadening of all the resonance lines occurred so that resolution at low temperatures was extremely poor. Even with the considerable simplification of the spectrum by selective deuteration, all fine-structure changes with temperature were masked by loss of resolution.

To obtain information about the inversion rates at carbons bound to magnesium in di-Grignard reagents, three dihalides having structural features analogous to halides which give mono-Grignard reagents especially suitable for studying inversion were synthesized. For example, Whitesides, Witanowski, and Roberts (35) had studied inversion in 3,3-dimethylbutylmagnesium chloride. The analogous dihalide is 1,5-dichloro-3,3-dimethylpentane. The nmr spectrum of this compound is shown in Figure 16; the protons alpha and beta to chlorine give the typical AA'XX' nmr spectrum characteristic of a

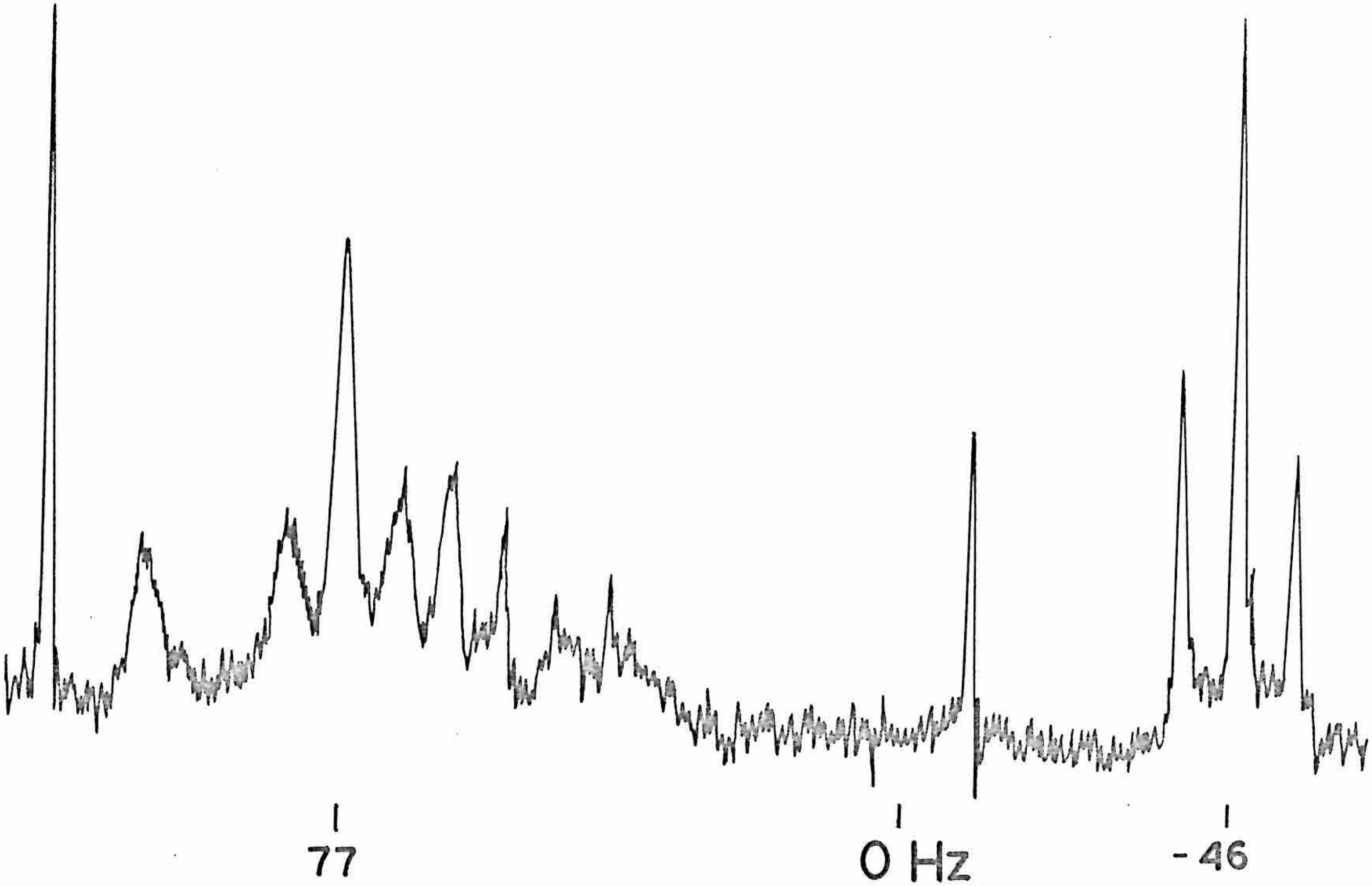


Figure 15. The nmr spectrum (60 MHz) of the di-Grignard reagent prepared from 1,4-dibromo- and 1,4-dichloro-1,1,2,2-tetradeuterio-butane in dimethyl ether and perdeuterated tetrahydrofuran. Singlet near 0 Hz is impurity.

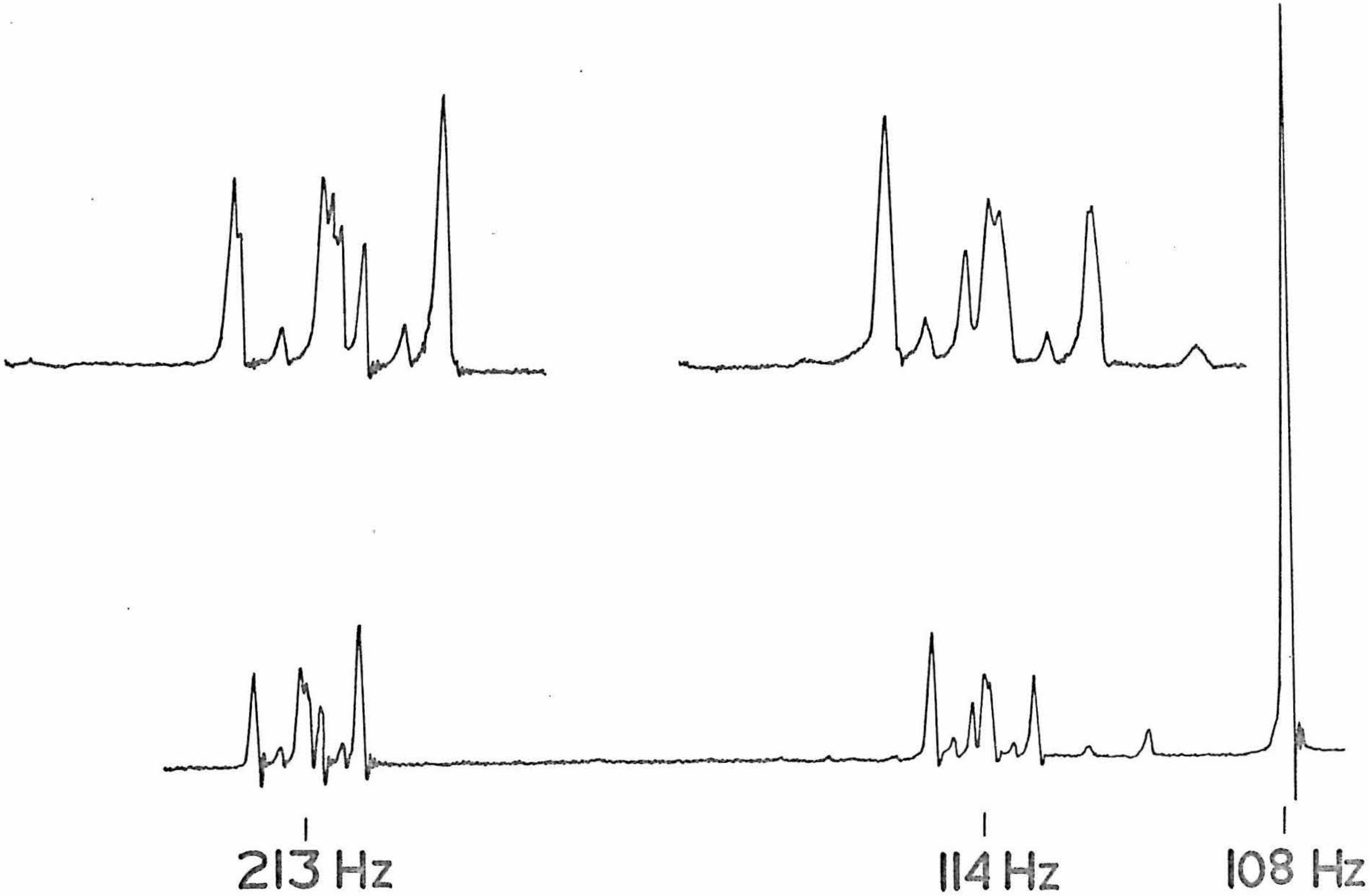


Figure 16. The nmr spectrum (60 MHz) of 1,5-dichloro-3,3-dimethylpentane.

disubstituted ethane with a marked preference for one of the possible conformations involved in rotation about the ethane carbon-carbon bond. The spectrum is very similar to that obtained for 3,3-dimethylbutyl chloride (35a). The compounds analogous to the 2-methylbutyl bromide studied by Fraenkel and Dix (36) are 1,5-dichloro-2,4-dimethylpentane and 1,6-dibromo-2,5-dimethylhexane. Both of these halides were prepared; the dihalopentane was clearly a mixture of diastereoisomers as shown by the nmr spectrum, but the dihalohexane appeared to be one diastereoisomer.

In order to compare the rates of inversion of the monofunctional Grignard reagents with the difunctional Grignard reagents, samples with identical concentrations of Grignard functionality were prepared in tetrahydrofuran, and nmr spectra obtained as a function of temperature. Figure 17 shows the spectral changes occurring at various temperatures for the protons alpha to magnesium in 3,3-dimethylbutylmagnesium chloride. When compared with the protons alpha to the magnesium in the di-Grignard reagent of 1,5-dichloro-3,3-dimethylpentane (Figure 18), it is easily seen that inversion is much faster in the di-Grignard reagent. The nmr spectrum of the monofunctional reagent possesses characteristics of an AA'XX' spectrum at 35°, and the limiting low-temperature spectrum is visible at 0°. In contrast, the di-Grignard reagent gives an A_2X_2 spectrum, a triplet, at 35°. At -10°, the central line has become less intense relative to the outside lines, but AA'XX' characteristics are not clearly

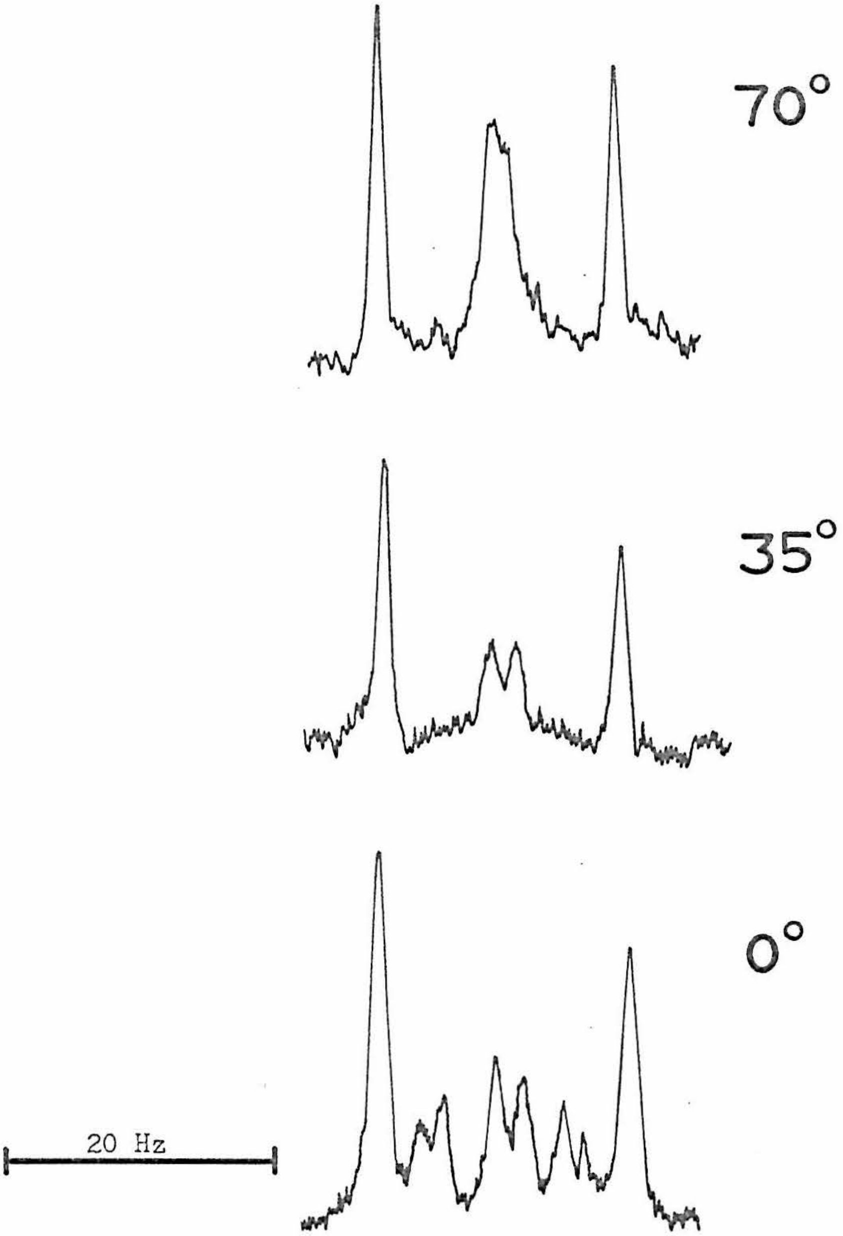


Figure 17. The nmr spectra (60 MHz) of the $-CH_2Mg-$ protons in 3,3-dimethylbutylmagnesium chloride (0.8 M) in tetrahydrofuran.

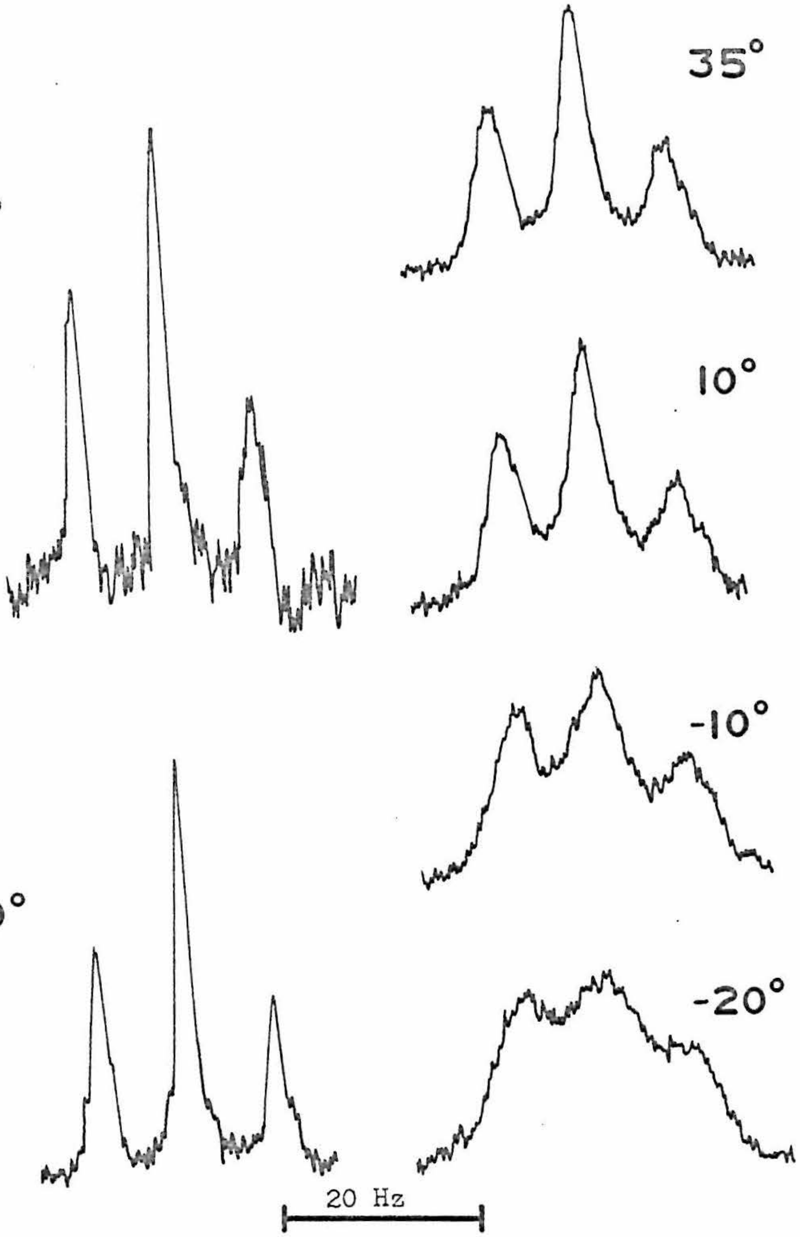


Figure 18. The nmr spectra (60 MHz) of the $-CH_2Mg-$ protons of the di-Grignard reagent of 1,5-dichloro-3,3-dimethylpentane (0.8 M in Grignard function) in tetrahydrofuran.

visible, and at lower temperatures, the resolution becomes extremely poor.

The spectra of the Grignard reagents from the dihalides with asymmetric centers <u>beta</u> to magnesium give the same results with respect to relative inversion rates. The protons <u>alpha</u> to magnesium should give resonances typical of the A_2 part of an A_2X spectrum if inversion is rapid. With slow inversion, these same protons should give the resonances of the AB part of an ABX spectrum. This is the case for 2-methylbutylmagnesium bromide (Figure 19); the protons <u>alpha</u> to magnesium give an A_2 part at 90°, and at 35°, the characteristic AB pattern is present. In the di-Grignard reagents of 1,5-dichloro-2,4-dimethylpentane (Figure 20) and 1,6-dichloro-2,5-dimethylhexane (Figure 21), the nmr spectra are the A_2 type at 35°, and at 0° they appear to be starting to change. The inversion process is, therefore, faster in the di-Grignard reagent than in the corresponding monofunctional Grignard reagent.

The inversion rate is clearly faster with di-Grignard reagents than with mono-Grignard reagents, and therefore, any attempts to obtain coupling constants for these reagents is made difficult because inversion results in averaging of the coupling constants in the different species of interest. The purpose of preparing 1,4-dihalo-1,1,2,2-tetradeuteriobutane was to simplify the nmr spectra so that coupling constants could be used to indicate the nature of

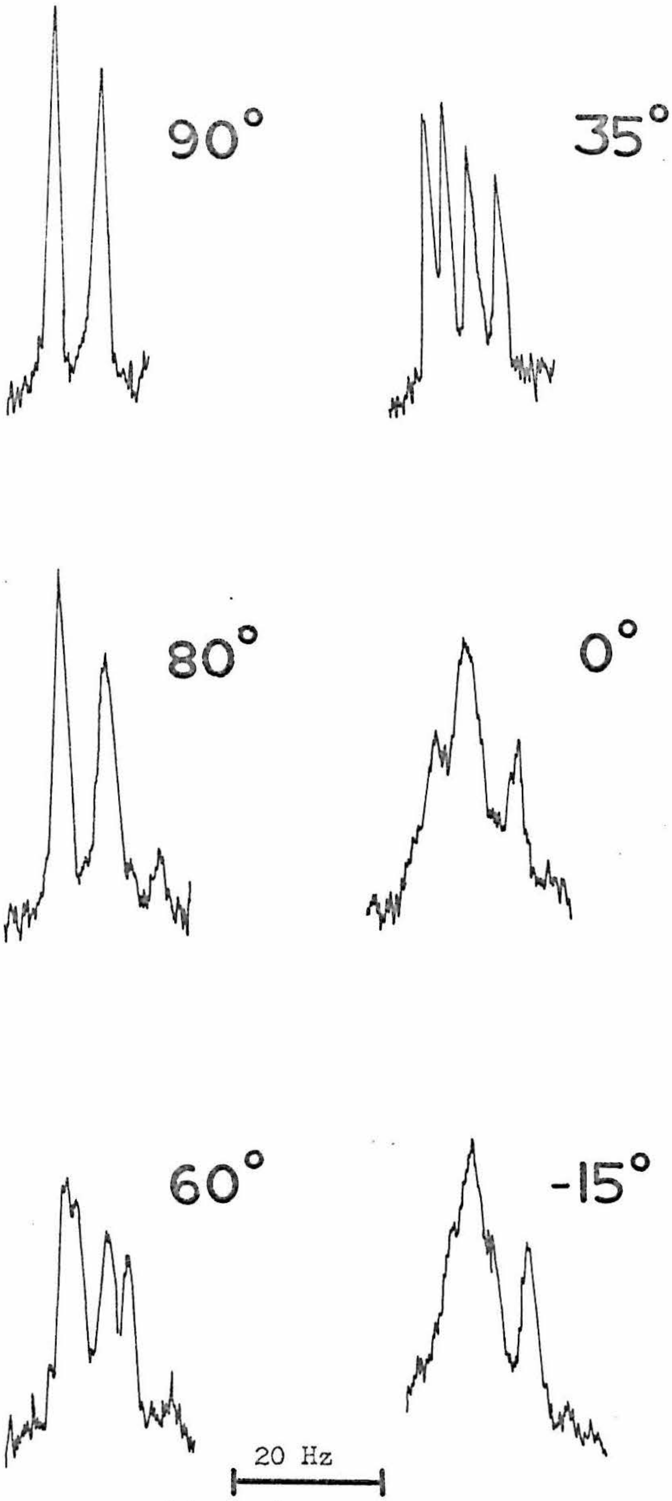


Figure 19. The nmr spectra (60 MHz) of the $-CH_2Mg-$ protons in 2-methylbutylmagnesium bromide (1.0 M) in tetrahydrofuran.

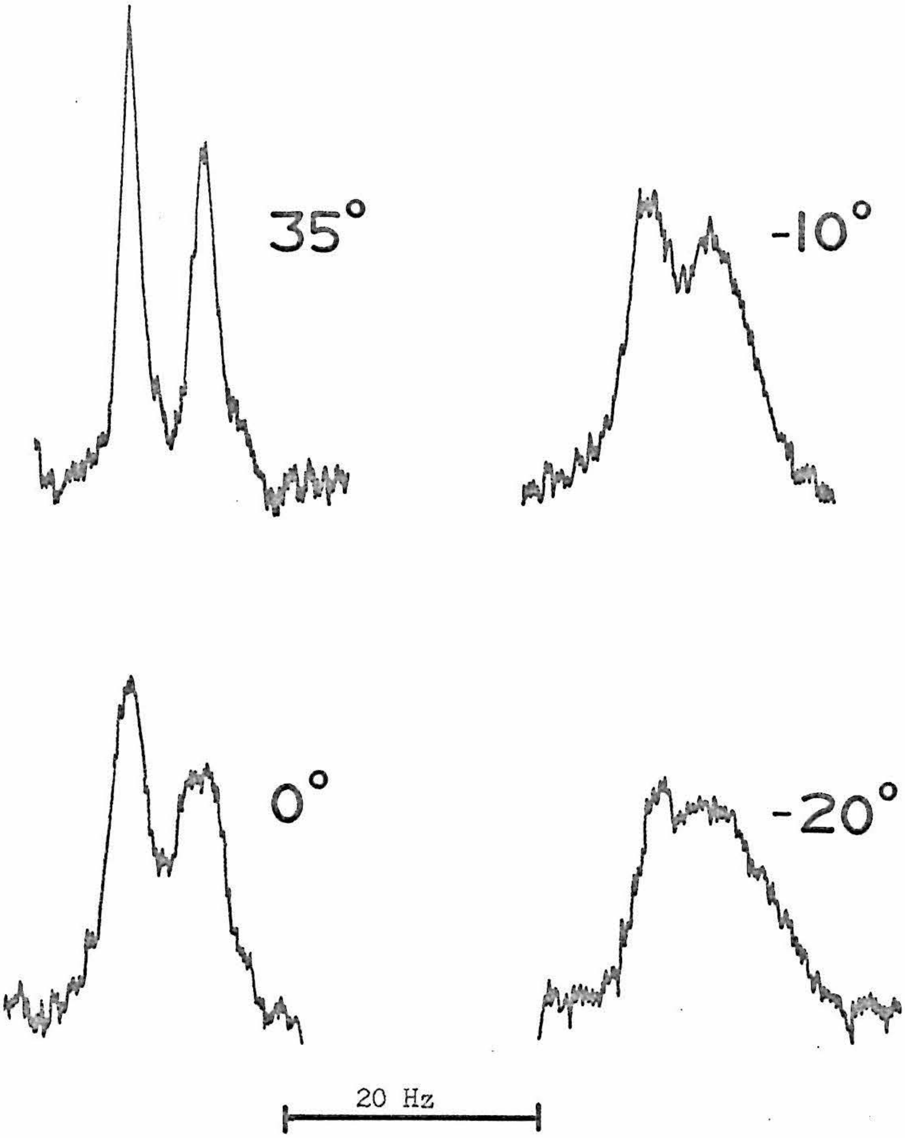


Figure 20. The nmr spectra (60 MHz) of the $-CH_2Mg-$ protons in the di-Grignard reagent of 1,5-dichloro-2,4-dimethylpentane (1.0 M in Grignard function) in tetrahydrofuran.

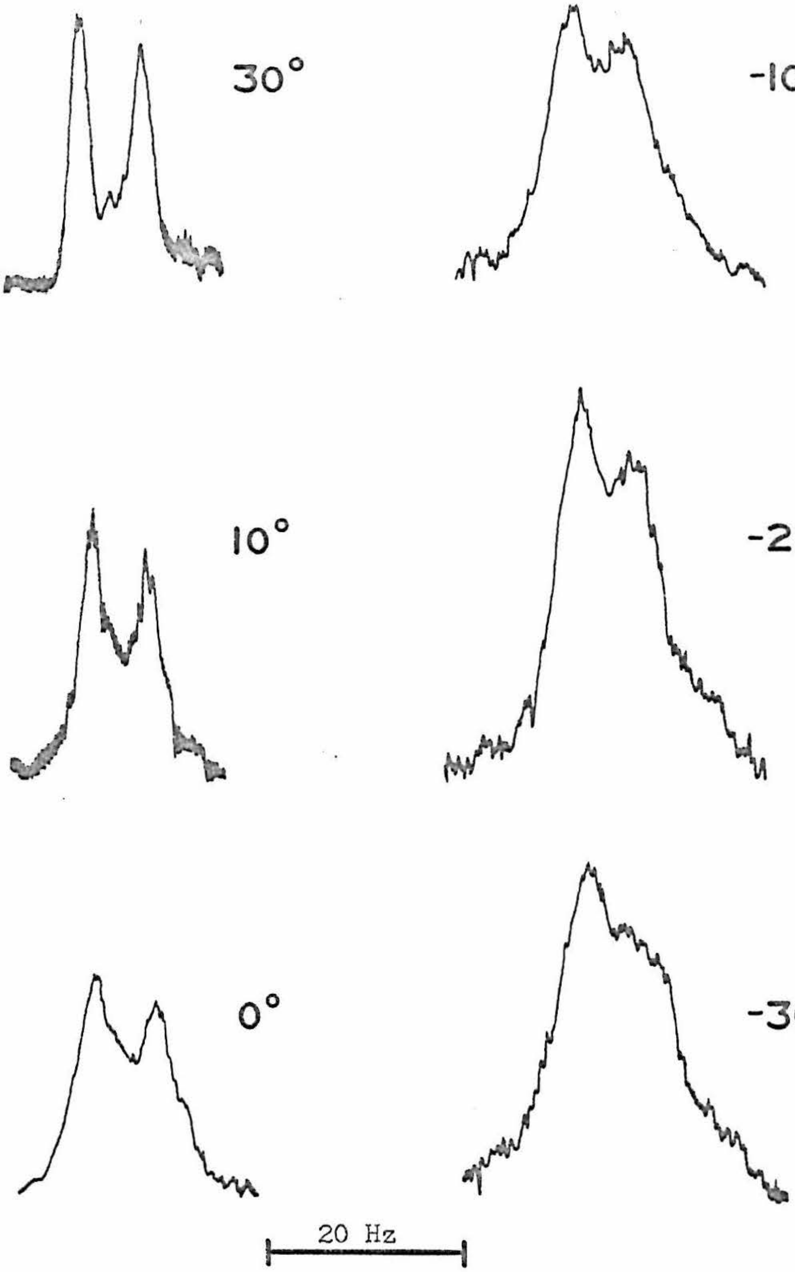
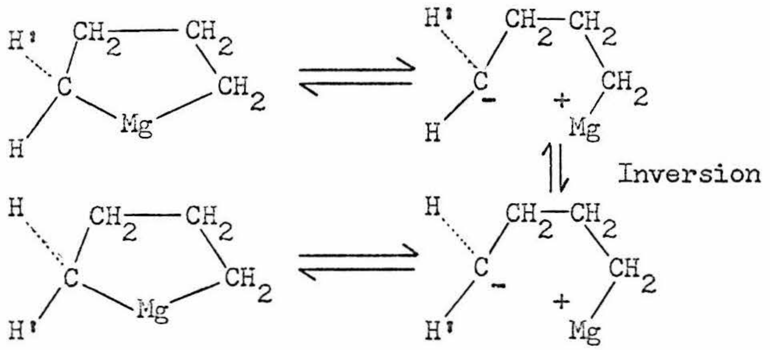


Figure 21. The nmr spectra (60 MHz) of the -CH$_2$Mg- protons of the di-Grignard reagent of 1,6-dichloro-2,5-dimethylhexane (1.0 M in Grignard function) in tetrahydrofuran. The amplitudes of the spectra differ.

the di-Grignard reagent. Thus, if the cyclic species tetramethylenemagnesium were present in a solution of the di-Grignard reagent of the tetradeuterated dihalide, its nmr spectrum would be of the AA'XX' type provided inversion were slow. However, if inversion can occur within the cyclic form so that the cyclic species does not lose its identity, an A_2X_2 spectrum would be obtained. Such inversion might proceed by a dissociation-inversion-recombination mechanism.



(6)

If the spectrum were of the AA'XX' type, two vicinal coupling constants could be found, and conclusions might be drawn about the presence of the cyclic species.

However, there is still the possibility, even if inversion and exchange were both slow, that the alpha protons of the cyclic species might appear as a triplet. Abraham and Bernstein (51) have delineated the conditions whereby AA'XX' spectra will appear as a triplet. This condition is

$$J_{AX} - J_{AX'} < [2\Delta\nu_{1/2}(J_{AA'} - J_{XX'})]^{1/2} \tag{7}$$

where J_{AX} and $J_{AX'}$ are the vicinal coupling constants, $J_{AA'}$ and $J_{XX'}$ are the geminal coupling constants, and $\Delta\nu_{1/2}$ is the line width at half-height of the component lines. It is important for our system here that this condition appears to be satisfied in tetrahydrofuran for the protons alpha and beta to oxygen. Thus the proton spectrum of 2,2,3,3-tetradeuteriotetrahydrofuran must be of the AA'XX' type because there is restricted rotation about the carbon-carbon bond. Nevertheless, the spectrum shows only two triplets. The complex spectrum of tetrahydrofuran itself is due to couplings between the β, β' hydrogens, and not markedly different α, β vicinal couplings. Obviously, if the cyclic magnesium species tetramethylenemagnesium is analogous to tetrahydrofuran, the spectrum of the tetradeuterated species may not provide the information needed for obtaining the vicinal coupling constants.

A sample of the di-Grignard reagent from a mixture of 1,4-dichlorobutane and 1,4-dibromobutane was prepared in a dimethyl ether-tetrahydrofuran solvent mixture. As already pointed out, the low-temperature spectra below -25° of these di-Grignard reagents provide no information because resolution is poor because of viscous broadening. Dioxane was added to the sample separating most of the magnesium halide from the alkylmagnesium compounds. The low-temperature nmr spectra of alkylmagnesium species were then obtained, but again loss of resolution from viscous broadening occurred. This same experiment was conducted with the di-Grignard reagent from a mixture of 1,5-dichloropentane and 1,5-dibromopentane. The results were the same as with the other di-Grignard reagent. Even though some of the halide could be removed, the resolution was too poor to establish anything about an equilibrium among all the possible forms for the alkylmagnesium species.

The effect of N,N,N',N'-tetramethylethylenediamine on the rates of equilibration of the Grignard species has been discussed extensively in Part I of this section. When the diamine was added to a di-Grignard reagent solution and then dioxane added, a white precipitate was formed. However, the nmr spectrum of the supernatant indicated that most of the di-Grignard reagent was left in solution. Some halide probably remained in solution because of the inefficiency of dioxane in precipitating magnesium halide in the presence of N,N,N',N'-tetramethylethylenediamine (52). The low-temperature nmr spectra of di-Grignard reagents in tetrahydrofuran with the diamine and dioxane added were obtained. However, viscous line broadening was so great below -30° that all resolution was lost. It was necessary to use the deuterated halides where the spectra were not so complex.

The following type of experiment indicates that the viscous broadening observed in the solutions made as described above is probably due to magnesium halide remaining in solution. Thus, when N,N-diethylaniline or N,N,N',N'-tetramethylethylenediamine was added to solutions of mono— or di-Grignard reagents from which the bulk of the magnesium halides were precipitated with dioxane, low-temperature spectra with good resolution were obtained.

The di-Grignard reagent from a mixture of 1,4-dichloro-1,1,2,2-tetradeuteriobutane and 1,4-dibromo-1,1,2,2-tetradeuteriobutane was prepared in tetrahydrofuran. The low-temperature nmr spectra of the protons alpha to magnesium are shown in Figure 22 (53). The lines are fairly broad, but some extra lines, possibly from another species, are evident, especially at -20°. The low-temperature nmr spectra of the same sample with 5% by volume of N,N,N',N-tetramethylethylenediamine are displayed in Figure 23. Again extra lines are present. At -35° and -40°, two lines appear to be present in the central resonance. Possibly two triplets are overlapping with each triplet being characterized by the same coupling constant (Figure 24). In Part I, it was demonstrated how N,N,N',N'-tetramethylethylenediamine slowed down the equilibrium between the diethylmagnesium and ethylmagnesium halide forms of the Grignard reagent. Both forms of the ethyl Grignard reagent were found to have the same

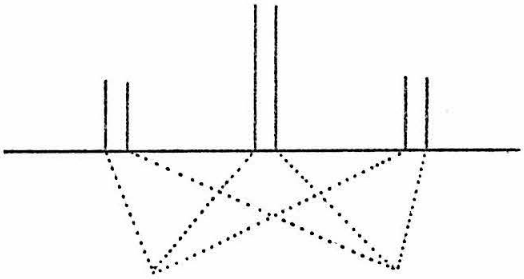


Figure 24

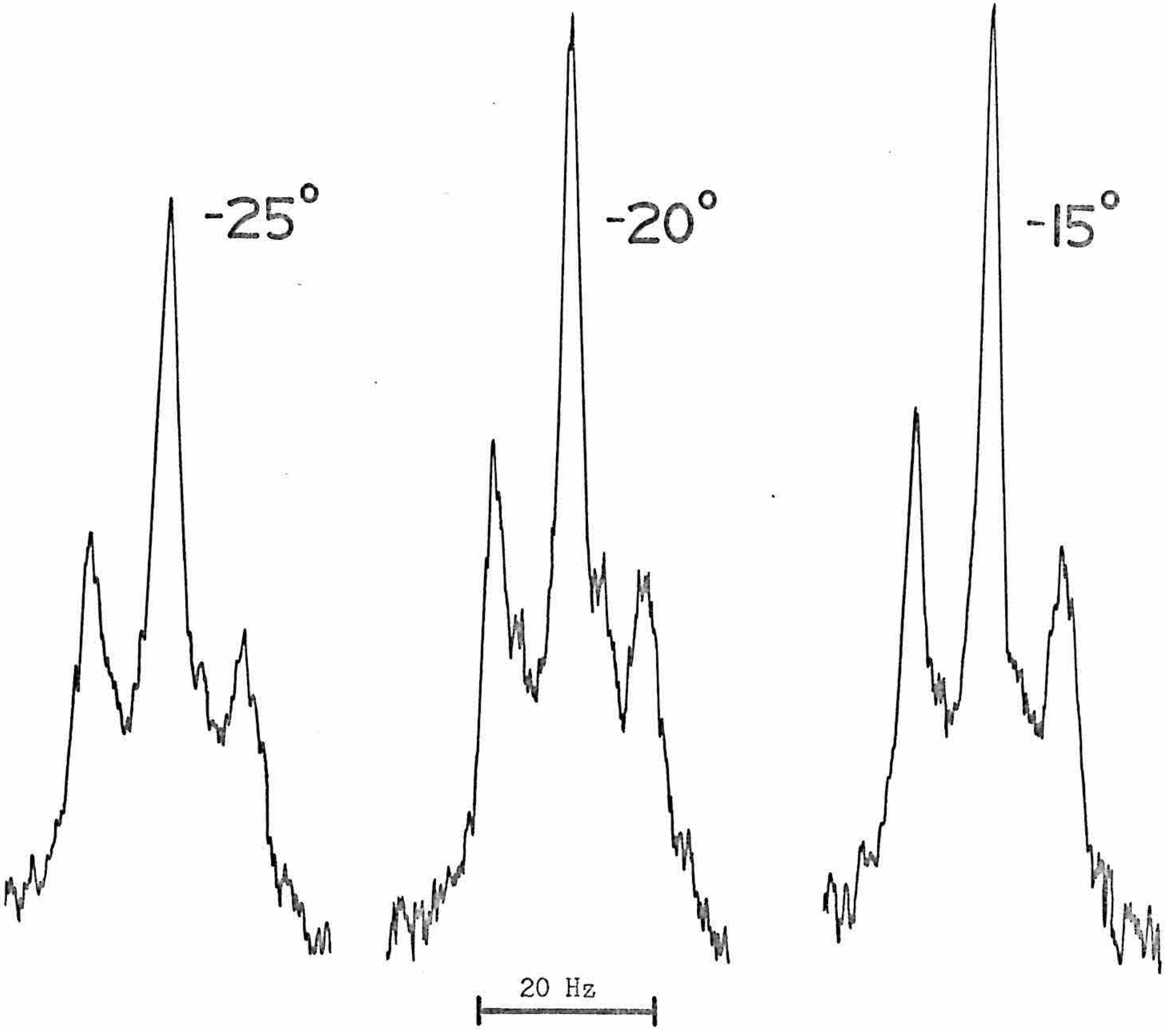


Figure 22. The nmr spectra (60 MHz) of the -CH_2Mg- protons of the di-Grignard reagent from 1,4-dibromo- and 1,4-dichloro-1,1,2,2-tetradeuteriobutane in tetrahydrofuran.

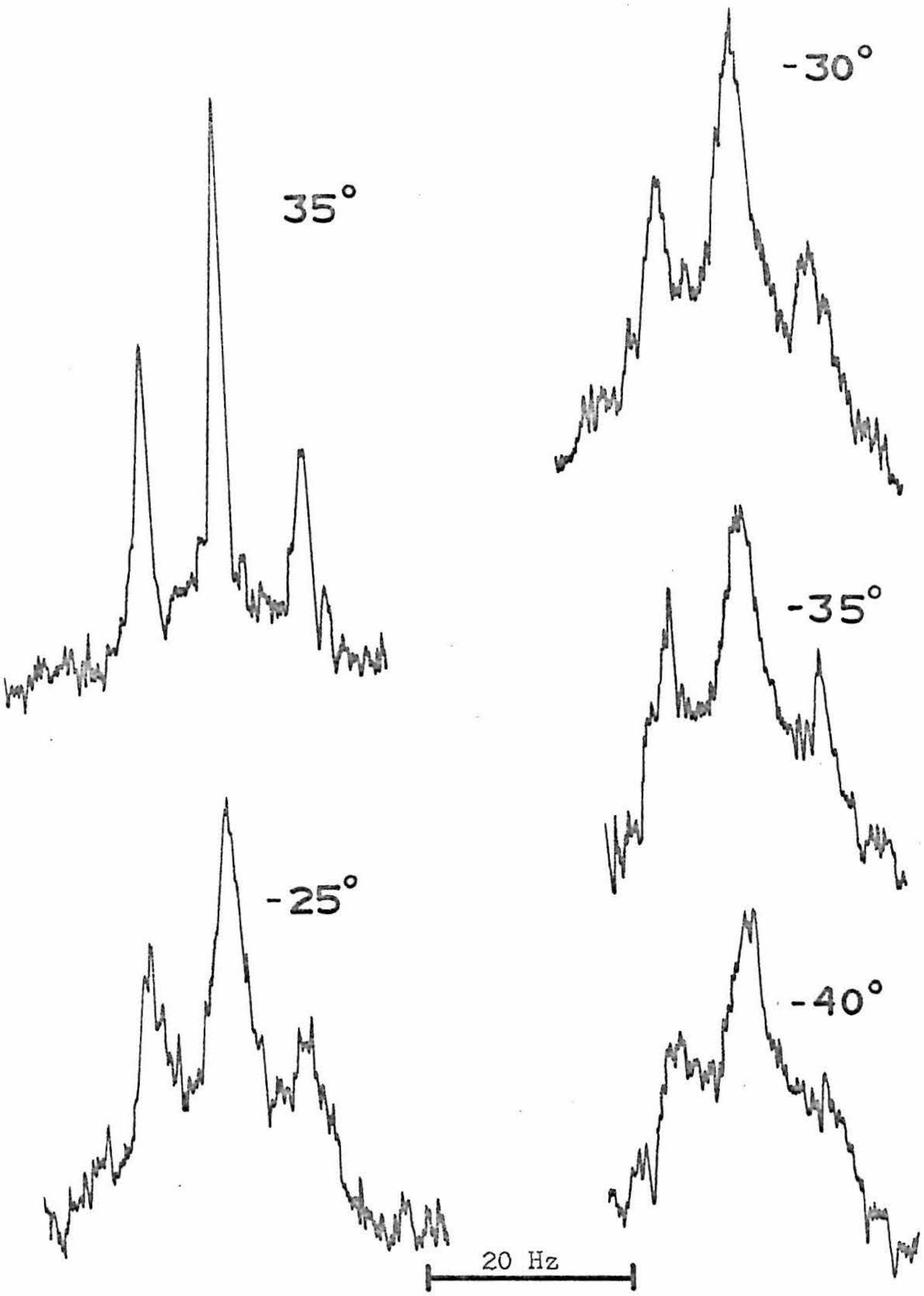


Figure 23. The nmr spectra (60 MHz) of the -CH_2Mg- protons of the di-Grignard reagent prepared from 1,4-dibromo- and 1,4-dichloro-1,1,2,2-tetradeuteriobutane in tetrahydrofuran and N,N,N',N'-tetramethylethylenediamine.

coupling constants. Possibly this is the situation for species giving the spectra shown in Figure 23 (53). One of the triplets may be from the cyclic tetramethylenemagnesium. In this case it is half of an AA'XX' spectrum with characteristics satisfying equation (7), or it is half of an A_2X_2 spectrum because carbon inversion is occurring within the cyclic form. The information available does not permit a definite distinction between these possibilities.

In order to add dioxane to the di-Grignard reagent of the 1,4-dihalo-1,1,2,2-tetradeuteriobutane without precipitating the alkylmagnesium species, this Grignard reagent was prepared in a mixture of dimethyl ether and perdeuterated tetrahydrofuran. The spectrum of the resulting solution has already been shown in Figure 15. To this sample was added N,N,N',N'-tetramethylethylenediamine and then dioxane. The low-temperature spectra of the protons alpha to magnesium are shown in Figure 25 (53). At low-temperature, two triplets are seen with unequal coupling constants. From the spectrum taken at -35°, the values of the sums of the vicinal coupling constants are 15.8 and 18.0 Hz. Figure 26 shows how two triplets with approximately equal intensities and unequal coupling constants can overlap to give the spectra obtained at -35° and -45°. In the first part of this thesis, ethylmagnesium halide and diethylmagnesium were shown to have identical coupling constants. The difference in vicinal coupling constants found here

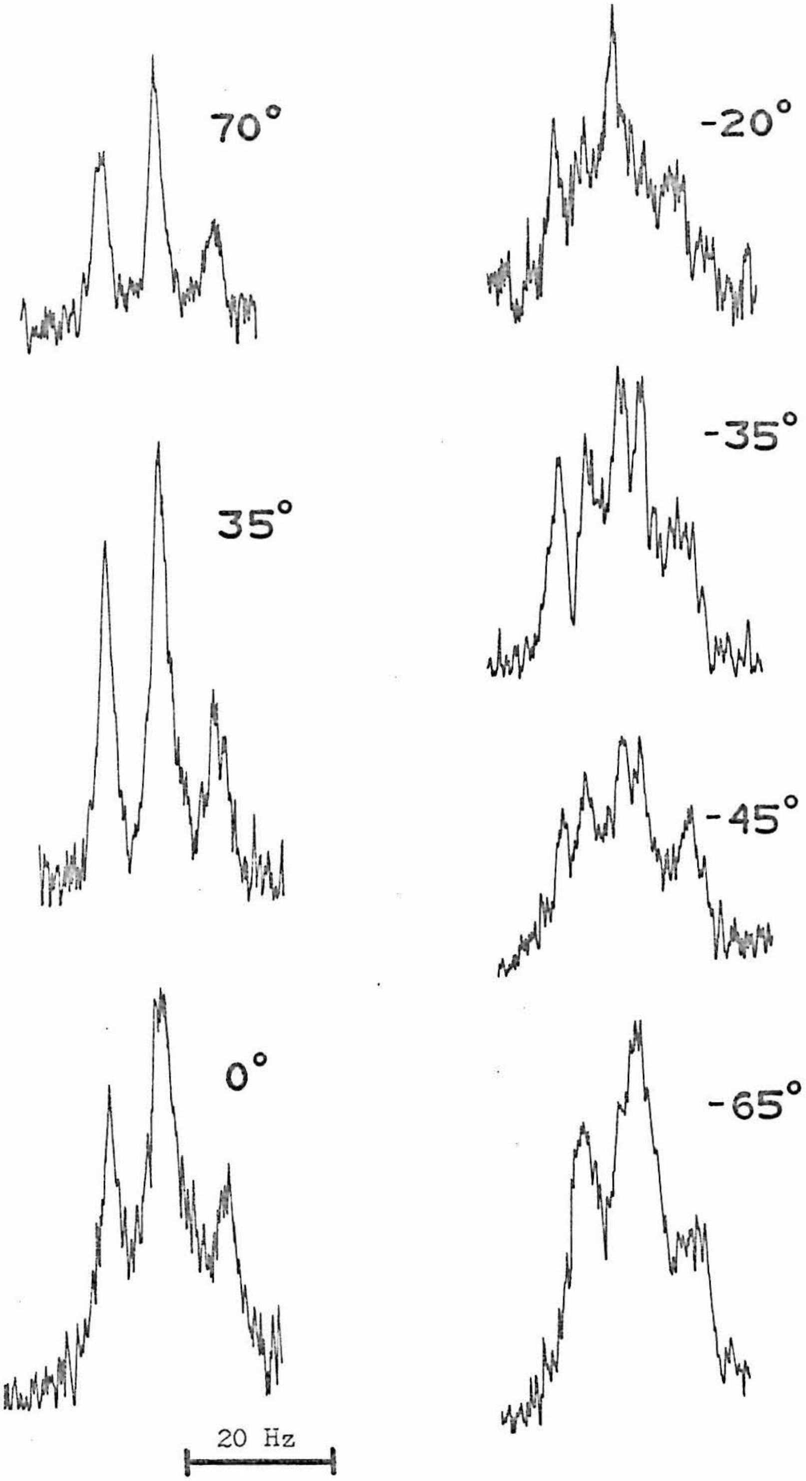


Figure 25. The nmr spectra (60 MHz) of the -CH$_2$Mg- of the di-Grignard reagent of 1,4-dibromo- and 1,4-dichloro-1,1,2,2-tetradeuteriobutane prepared in dimethyl ether and perdeuterated tetrahydrofuran. N,N,N',N'-tetramethylethylenediamine and dioxane have been added. Spectrum amplitudes differ.

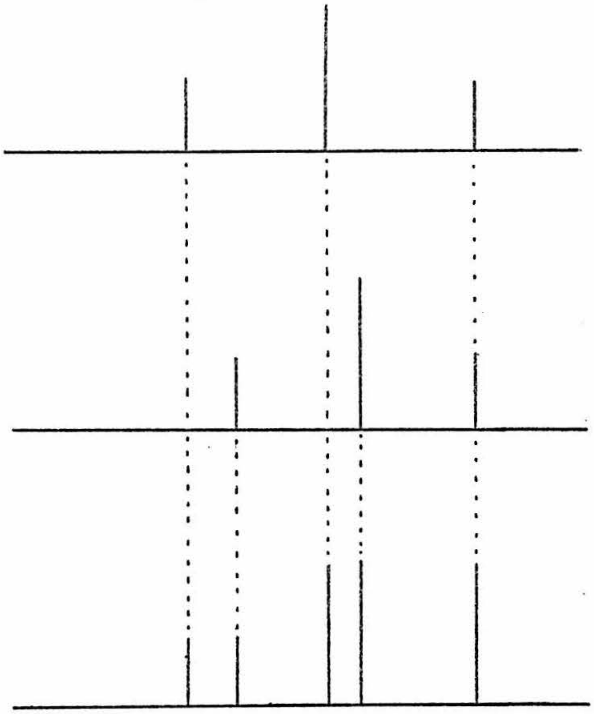


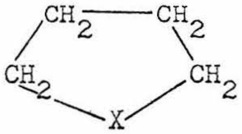
Figure 26

must be due to some other factor, and the best assumption seems to be that one triplet be attributed to the cyclic tetramethylenemagnesium form.

It is of interest to compare the relative magnitudes of the vicinal coupling constants in systems of the following types:

$YXCH_2CH_2CH_2CH_2XY$

XIV



XV

In 1,4-butanediol, the sum of the vicinal coupling constants between the protons alpha and beta to oxygen is 12.2 ± 0.3 Hz. The corresponding sum in 1,4-dimethoxybutane is 12.0 ± 0.3 Hz. The cyclic analog tetrahydrofuran has 13.3 ± 0.3 for the sum of the vicinal coupling constants. This sum in tetrahydrothiophene, the analogous sulfur compound, is 12.5 Hz (54), while 1,4-butanedithiol has the value 13.4 ± 0.3 Hz for the sum of its corresponding vicinal coupling constants. These sulfur and oxygen systems demonstrate that, as expected, the sums of the vicinal coupling constants are different in 1,4-disubstituted butanes and analogously constituted five-membered ring compounds. However, the differences are not large. The diol and dimethoxybutane give approximately the same value, and closing the ring increases the sum by slightly more than 1 Hz. The sulfur analogs change in the opposite direction, but the change is again approximately 1 Hz.

In order for the AA'XX' spectrum to be a triplet, the condition of equation (7) must be satisfied. With 1.2 Hz for $J_{AA'} - J_{XX'}$ (which was found for 3,3-dimethylbutylmagnesium (35a)), and the line width at half-height of the component lines as 2 Hz (a rather large estimate), $J_{AX} - J_{AX'}$ must be less than 2.2 Hz. This implies that J_{AX} and $J_{AX'}$ are about equal since the sum of the two coupling constants must be equal to 15.8 Hz or 18.0 Hz. Maximum variation for the pairs of J_{AX} and $J_{AX'}$ would be 9.0 and 6.8 Hz from the 15.8 Hz value and 10.1 and 7.9 Hz from the 18.0 Hz value. Although correlation of dihedral angles with vicinal constants in five-membered rings is rather uncertain (55), the values for coupling constants for small dihedral angles all fall in the ranges given from the crude calculations above.

As mentioned earlier, the tetradeuterated tetrahydrofuran gives two triplets for its nmr spectrum. It does not seem unreasonable that the corresponding tetradeuterated tetramethylenemagnesium should also give two triplets. However, the possibility of rapid inversion within the cyclic form which would lead to an A_2X_2 spectrum cannot be ruled out.

The spectral changes observed at low-temperatures must be attributed to a reduction in the rate of interconversion among the different species by processes related to the Schlenk equilibrium. One of these species is certainly the open form of the di-Grignard reagent or the corresponding intermolecular dialkylmagnesium compound. These two forms of the di-Grignard reagent are in equilibrium with the cyclic species. The two triplets from the protons <u>alpha</u> to magnesium have approximately equal intensities, but conclusions about the position of the Schlenk equilibrium cannot be made because a large amount of magnesium halide was removed from the solution by dioxanate precipitation. This was necessary in order to obtain well-resolved spectra at temperatures near -50°. Whether or not inversion in the di-Grignard reagent is slower than interconversion of the different species cannot be determined from the results on the 1,4-di-Grignard reagent. If this reagent behaves similarly to the unsymmetrical dialkylmagnesium compounds studied by House (43), then inversion most certainly has stopped before the different species can be observed. Because the nmr spectrum of the tetramethylenemagnesium is a triplet, there is no evidence for slow inversion. Any conclusion that inversion has stopped and the spectrum is a deceptively simple spectrum must be based on previous work with monofunctional alkylmagnesium compounds.

Di-Grignard reagents of 1,5-dichloro-3,3-dimethylpentane, 1,5-dichloro-2,4-dimethylpentane, and 1,6-dichloro-2,5-dimethylpentane have been examined in tetrahydrofuran solutions with diamine and dioxane added. The nmr spectra of the protons alpha to magnesium have been obtained down to -60°. The lines broaden considerably below -10°. This broadening is probably caused both by viscosity changes and rate changes in either inversion or interconversion of the possible species. The tetrahydrofuran resonances remain fairly well-resolved down to -60° indicating that viscosity changes are probably not the major source for the line broadening in the di-Grignard reagent. In all cases, the resolution was so poor below -10° that no information could be obtained from the spectra of these samples.

II. THE NATURE OF THE DI-GRIGNARD REAGENT

Conclusions

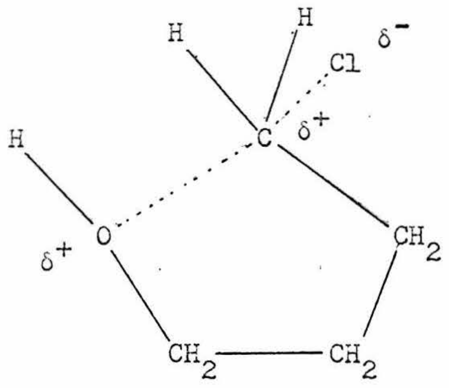
Inversion at the carbon-magnesium bond proceeds much faster in di-Grignard reagents than in the corresponding monofunctional reagents. As a consequence, detection of differences in coupling constants for the various forms in which the di-Grignard reagent can exist is difficult. Rapid inversion can lead to loss of the information which might be present in an AA'XX' spectrum of tetramethylenemagnesium prepared from the di-Grignard reagent of 1,4-dihalo-1,1,2,2-tetradeuteriobutane. With a solvent system of tetrahydrofuran, dimethyl ether, and N,N,N',N'-tetramethylethylenediamine, the rate of interconversion of the species in the Schlenk equilibrium has been reduced. At least two different species have been observed with the implications being that one is the cyclic tetramethylenemagnesium. The Schlenk equilibrium for di-Grignard reagents can, therefore, be represented as follows:

$$2\ \text{RMgX} \rightleftharpoons \text{R}_2\text{Mg} + \text{MgX}_2 \tag{8}$$

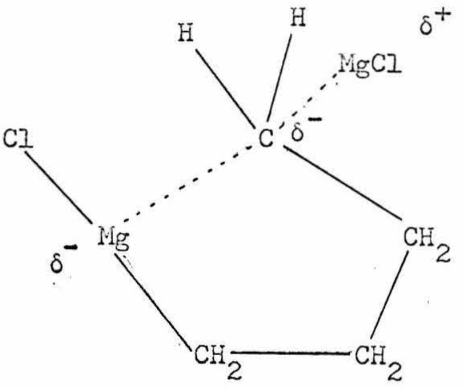
$$2\ \text{RMgX} = \text{XMgCH}_2(\text{CH}_2)_n\text{CH}_2\text{MgX}$$

$$\text{R}_2\text{Mg} = -(\text{CH}_2)_n\text{CH}_2\text{MgCH}_2(\text{CH}_2)_n- \quad \text{or} \quad \overline{\text{CH}_2\text{MgCH}_2(\text{CH}_2)_n}$$

The rapid inversion rate can be explained by an $\text{S}_\text{N}2$-type mechanism, or S_E2 mechanism, similar to that proposed for the formation of tetrahydrofuran from tetramethylene chlorohydrin (56)



XVI



XVII

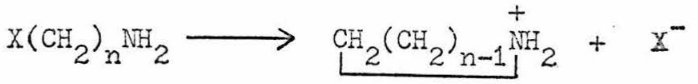
This type mechanism results in inversion of the reacting carbon atom (57) which would explain why the nmr spectra of 2-methylbutylmagnesium bromide and the analogous di-Grignard reagents show the A_2 part of an A_2X spectrum. If free rotation were the only averaging mechanism, the spectra should be the AB part of an ABX system. Fraenkel and Dix (36) found the rate law

$$\text{rate} = k\,[\text{RMgX}]^{2.5} \qquad (9)$$

for the inversion mechanism in diethyl ether and the concentration studies of Whitesides and Roberts (35b) indicate that the order is greater than one in Grignard reagent. The mechanism pictured in

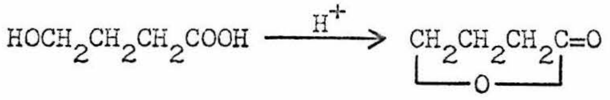
XVII would require a second-order rate law.

Perhaps the most convincing evidence for the proposed mechanism XVII is the rates measured for inversion. The inversion rates for 2-methylbutylmagnesium bromide and 3,3-dimethylbutylmagnesium chloride can easily be measured by the nmr method. However, in the corresponding di-Grignard reagents, the inversion rates were only slightly decreased at low temperature, and rate values could not be obtained. How much faster inversion is in the di-Grignard reagents was not established, but qualitatively it is obvious that the di-Grignard reagents invert much faster. By comparing the spectra shown in Figures 17 and 18 with the AA'XX' spectra calculated for changing inversion rates (35a), one obtains rates for the di-Grignard reagents which are 100 to 1000 times greater than for the monofunctional reagent. It is to be expected that a unimolecular reaction occurs much faster than the same bimolecular reaction (57b). The reactions of halides with amines (57b, 58) such as



$$X(CH_2)_nNH_2 \longrightarrow \underbrace{CH_2(CH_2)_{n-1}\overset{+}{N}}H_2 + X^- \qquad (10)$$

and the esterification of acids (59) such as



$$HOCH_2CH_2CH_2COOH \xrightarrow{H^+} \underbrace{CH_2CH_2CH_2C}_{O}{=}O \qquad (11)$$

have been shown to occur much faster intramolecularly than intermolecularly. In the hydrolysis of tetramethylene chlorohydrin (60), the intramolecular formation of tetrahydrofuran occurs almost exclusively with little diol being formed. When the inversion of di-Grignard reagents is interpreted in the light of Fraenkel's rate studies (36) and the other intramolecular versus intermolecular rate studies, the most probable mechanism for inversion of Grignard reagents is an S_E2 mechanism with XVII being the transition state for the di-Grignard reagent inversion.

The probable existence of cyclic polymethylenemagnesium species for di-Grignard reagents has been demonstrated. It may be derived from the transition state XVII in the same manner as diethylmagnesium and magnesium bromide might be produced from two molecules of ethylmagnesium bromide. The original purpose of using the di-Grignard reagent was to observe the Schlenk equilibrium by the nmr method. This was achieved separately with ethylmagnesium halides as reported in the first part of this thesis. The study of di-Grignard reagents also confirms the existence of the Schlenk equilibrium.

House (43) has demonstrated that inversion in 3,3-dimethylbutylcyclopentadienylmagnesium is not necessarily equivalent to the process of alkyl exchange. His work with unsymmetrical systems has shown that alkyl exchange can proceed without inversion. These studies, however, have not demonstrated that alkyl exchange cannot occur during the inversion process, but only that alkyl exchange can occur without inversion.

In the S_E2 inversion mechanism proposed in this thesis for di-Grignard reagents, alkyl exchange can occur when the cyclic transition state XVII or tetramethylenemagnesium is reopened by magnesium halide. This implies that there may be two methods of alkyl exchange; one proceeding with inversion and one proceeding with retention of configuration at the carbon atom.

I. THE INFLUENCE OF N,N,N',N'-TETRAMETHYLETHYLENEDIAMINE ON THE SCHLENK EQUILIBRIUM

Experimental

Melting points and boiling points are uncorrected. The melting points were taken with a Büchi apparatus.

Proton magnetic resonance spectra were obtained with a Varian Associates A-56/60A spectrometer equipped with a Varian C-1024 Time Averaging Computer. The probe contained a dewar-jacketed insert which could maintain stable temperatures as low as -100°; low-temperature time-averaged spectra could be taken at low temperature with no difficulty.

The starting halides for the Grignard reagents were used as received from the manufacturer. No further purification was required.

Tetrahydrofuran from Matheson Coleman and Bell was distilled from lithium aluminum hydride before use and stored over Linde 13X molecular sieves. The material was never used after more than three days of storage without being redistilled from lithium aluminum hydride.

N,N,N',N'-Tetramethylethylenediamine from Matheson Coleman and Bell was dried over potassium hydroxide and then distilled from sodium immediately before being added to Grignard reagents.

Magnesium was in the form of shavings ground from blocks of triply sublimed magnesium (61). Broad resonances characteristic of Grignard reagents prepared from Grignard-grade magnesium (which have been shown by House (43) to arise from traces of manganese) were never observed in the nmr spectra of Grignard reagents prepared from this triply sublimed magnesium.

Dioxane from Eastman Organic Chemicals was always distilled from lithium aluminum hydride directly before use.

Preparation of Grignard Reagents for Nmr Analysis.- To a 5-mm. nmr tube, precision ground by Wilmad Glass Company to a wall thickness of 0.30 mm., was added magnesium shavings to a depth of 2 cm. The tube was then flamed with a Bunsen burner and corked. When cool, the tube was uncorked, and 0.5 ml. of tetrahydrofuran and the desired amount of halide were added by means of a syringe. The tube was again corked and cooled in a Dry Ice-acetone bath. The tube was sealed as quickly as possible, and if the sealing was efficient, either end of the nmr tube could be placed downward in the probe when obtaining the spectrum.

No effort was made to exclude oxygen from the reaction tube.

After the tube was sealed, agitation of the mixture by shaking and/or warming in a steam bath would initiate the reaction. After the initial reaction subsided, the tube was heated in a steam bath for 1 hr. An excess of magnesium shavings was always used and along with any other solid material present was centrifuged to one end of the nmr tube. Careful decantation of the liquid to the other end of the tube provided a clear sample suitable for nmr spectroscopy.

To add N,N,N',N'-tetramethylethylenediamine to the Grignard reagent, the nmr tubes were cooled in Dry Ice-acetone, and approximately 1 cm. cut off from the top of the tubes. The desired amount of diamine was added by means of a syringe, and the tubes were immediately sealed and centrifuged as before. Other reagents were added in the same way.

In preparing the Grignard reagent of 3,3-dimethylbutyl chloride, two drops of ethylene bromide were added to the solution to initiate reaction. With the other halides no initiator was necessary.

Diethylmagnesium was prepared in two ways. The first was to prepare the Grignard reagent from ethyl bromide as noted above. Addition of dioxane would then produce the diethylmagnesium. However, this sample was not completely halogen free, and preparation from diethylmercury was effected.

To an nmr tube was added, to a height of 2 cm., triply sublimed magnesium, 0.05 ml. of diethylmercury (Eastman Organic Chemicals), a very small drop of mercury, and 0.5 ml. of tetrahydrofuran. The tube was sealed and heated overnight in a steam bath. An nmr spectrum of the centrifuged solution showed that the organomercury compound was completely converted to diethylmagnesium except for formation of a small amount of ethane ($\sim$ 5%).

Analysis of halide remaining in a solution of ethylmagnesium bromide in tetrahydrofuran to which dioxane or N,N,N',N'-tetramethylethylenediamine and dioxane had been added was determined by silver-halide precipitation. Ethyl bromide (2 ml.) was treated with excess Grignard-grade magnesium in 10 ml. of tetrahydrofuran. After the reaction was complete, 2 ml. of dioxane was added, and 15 min. later, 2 ml. of the remaining clear solution was withdrawn with a syringe and added to 5 ml. of water. Then 1 ml. of conc. nitric acid (shown to be halide free) was added to the solution, followed by addition of 5 ml. of a silver nitrate solution (20 g. silver nitrate in 20 ml. water). After 30 min. the entire solution was filtered through a fritted glass crucible, and the precipitate was washed with water. The crucible with its light green precipitate of silver nitrate was then dried in an oven at 115° for several hours before weighing.

A duplicate run was made in which 2 ml. of N,N,N',N-tetramethylethylenediamine was added to the solution before the dioxane was added. After 15 minutes, 2 ml. was withdrawn and analyzed as above.

Another duplicate set was measured in which the solution was allowed to stand for 2 hrs. before aliquots were withdrawn for analysis.

II. THE NATURE OF DI-GRIGNARD REAGENTS

Experimental

Melting points and boiling points are uncorrected. Melting points were taken with a Büchi apparatus. The micro boiling point measurements were obtained with a Mettler FP1 boiling point apparatus. Gas chromatographic analyses were carried out with a Varian Aerograph Autoprep. Microanalyses were performed by Elek Microanalytical Laboratories, Torrance, California.

Proton magnetic resonance spectra were obtained with four different spectrometers: 1) Varian Associates Model A-60A for room-temperature spectra; 2) Varian Associates Model HA-100; 3) Varian Associates Model A-56/60A operated at 60 MHz and equipped with a Varian C-1024 Time Averaging Computer and a probe with a dewar-jacketed insert which could maintain stable temperatures as low as -100°; 4) Varian Associates Model HA-60il, converted from a Varian V-4300B spectrometer.

The Grignard reagents were prepared in nmr tubes as described in the Experimental, Part I. In some preparations where the Grignard reagent was prepared in extremely dilute concentration, only a fraction of the solvent would be used initially, the nmr tube would be sealed with a cork, and the reaction of the halide with magnesium started. When the reaction seemed to be progressing rapidly, the tube would be cooled in Dry Ice-acetone, the remainder of the solvent would be added, and the tube would then be sealed in the gas-oxygen flame.

When using dimethyl ether as a solvent or co-solvent, all other reagents were added to the nmr tube first. Then dimethyl ether vapor (Matheson) was passed through a U-tube containing Drierite and potassium hydroxide pellets and directed into the nmr tube by means of a long syringe needle. While the dimethyl ether was flushing out the nmr tube, the bottom end of the tube was immersed in a Dry Ice-acetone bath. After the desired amount of dimethyl ether had condensed, the needle was withdrawn, and the nmr tube closed with a cork. The tube would then be sealed in a gas-oxygen flame. When the sealed end cooled to room temperature, the nmr tube could be removed from the Dry-Ice-acetone bath and handled like any other sample.

The magnesium used for preparing Grignard reagent samples for nmr spectra has been described in Part I (62). For large-scale reactions not intended for nmr analysis, the magnesium used was Grignard-grade magnesium turnings, 99.8% pure.

All solvents were carefully dried before use. The procedures for tetrahydrofuran, N,N,N',N'-tetramethylethylenediamine, and dioxane have been described elsewhere (63). When diethyl ether was the solvent, it was used directly from a newly-opened can (Mallinckrodt, analytical reagent) or distilled from lithium aluminum hydride directly before use.

All halides obtained from the manufacturer reacted easily with magnesium or with magnesium and a drop of ethylene bromide initiator. They were not redistilled unless they appeared to be colored from decomposition. All synthesized halides were distilled from phosphorus pentoxide before use as noted below.

4-Bromo-1-chloro-4-methylpentane. - Methyl Grignard reagent was prepared from 22.2 g. of methyl iodide (0.156 moles) and excess magnesium in 200 ml. of diethyl ether. The solution was filtered through glass wool into 50 ml. of diethyl ether containing 9.0 g. of 5-chloro-2-pentanone (0.083 moles). The reaction mixture was treated with saturated aqueous ammonium chloride solution to coagulate the salts, and the ethereal layer decanted, dried over magnesium sulfate, filtered, and the ether removed. The residual crude oil was added to an equal volume of phosphorus tribromide at 0°. The mixture was stirred for an hour at room temperature and poured onto ice. The organic layer was washed with aqueous sodium bicarbonate and water and dried over magnesium sulfate. After filtration and removal of the ether, the crude oil was distilled from phosphorus pentoxide under vacuum to give 7.2 g. of the desired dihalide, b.p. 95-96° (30 mm.); lit. (64) b.p. 90-91.5° (30 mm.). The nmr spectrum (60 MHz) gave a singlet at 125 Hz corresponding to the methyl groups, a multiplet at 215 Hz corresponding to the methylene protons alpha to chlorine, and a multiplet between 90 and 130 Hz for the remaining protons.

Anal. Calcd. for $C_6H_{12}BrCl$: C, 36.13; H, 6.02. Found: C, 36.12; H, 6.14.

1,1,2,2-Tetradeuterio-1,4-butanediol.- The following method of preparation was carried out satisfactorily with undeuterated samples. To a thick-walled Carius tube containing 5.0 g. of γ-butyrolactone, which had been dried over sodium sulfate and distilled, was added 20 ml. of methanol-O-d (65) and then 100 mg. of sodium. After the sodium had stopped reacting, the tube was degassed three times by the usual freeze-thaw method. The tube was sealed and heated in an oven at 180° for 8 hrs. The tube was allowed to cool, opened, and the methanol removed by distillation at atmospheric pressure. The lactone was then distilled at reduced pressure. A second and third exchange were carried out, each with 12 ml. of methanol-O-d. Approximately 3-4 ml. of deuterated lactone was obtained. The nmr spectrum showed that some of the lactone had possibly been converted to the methyl ester (10% by vpc), but it also showed that the deuterium exchange had proceeded well. The theoretical exchange was 98% for the protons alpha to the carbonyl. The entire higher boiling distillate was added to 15 ml. of ether which was then slowly added dropwise to 1 g. of lithium aluminum deuteride (Metal Hydrides Incorporated) in 15 ml. of ether. After the addition was complete, the reaction mixture was refluxed for 3 hrs. Then 10 ml. of water was slowly added followed by 10 ml. of 6 N hydrochloric acid. After all the salts had dissolved, 5 g. of sodium chloride was added to the aqueous layer, and it was extracted continuously with ether for 21 days. Removal of ether left 3.0 g. of crude oil containing the tetradeuteriobutanediol. The nmr spectrum (60 MHz) of the crude diol gave methylene resonances at 213 Hz and 90 Hz corresponding to the methylene protons alpha and beta to oxygen, respectively. The resonances were broad as the solution was extremely viscous. Diethyl ether was present. The crude diol was used without further purification.

2,2,3,3-Tetradeuteriotetrahydrofuran.- The following method of preparing the deuterated tetrahydrofuran was found to be satisfactory when using undeuterated 1,4-butanediol. To 1.0 g. of the crude 1,1,2,2-tetradeuterio-1,4-butanediol obtained above was added 0.2 ml. of concentrated sulfuric acid. The mixture was heated to 160°, and the tetrahydrofuran was collected as it distilled. As the product contained diethyl ether which was present in the crude diol, the deuterated tetrahydrofuran was purified by preparative vapor-phase chromatography. The nmr spectrum (60 MHz) of the deuterated tetrahydrofuran gave a well-resolved triplet at 221 Hz corresponding to the protons alpha to oxygen and a triplet broadened by deuterium coupling at 107 Hz which corresponds to the beta protons.

1,4-Dichloro-1,1,2,2-tetradeuteriobutane.- The following method for preparing 1,4-dichlorobutane was found to be satisfactory when using undeuterated samples. To 1.0 g. of the crude 1,1,2,2-tetradeuterio-1,4-butanediol was added 0.5 ml. of pyridine. Then 4.0 ml. of thionyl chloride was added slowly with stirring to the cooled mixture. After the addition was complete, the reaction mixture was heated at 75° for 2 hrs. and then poured over ice. The organic fraction was extracted with ether; the ether extract was then washed with 25 ml. of 2 N hydrochloric acid, water, and aqueous sodium bicarbonate, and then water. The ether extracts were dried over calcium chloride, the ether evaporated on a steam bath, and the dichloride distilled from phosphorus pentoxide at reduced pressure. The yield was 0.2 ml. of the desired deuterated dichloride, b.p. 30° (0.25 mm.). The nmr spectrum (60 MHz) showed a well-resolved triplet at 211 Hz corresponding to the protons *alpha* to chlorine and a triplet broadened by deuterium coupling at 113 Hz which corresponds to the *beta* protons.

1,4-Dibromo-1,1,2,2-tetradeuteriobutane.- The following method of preparing 1,4-dibromobutane was found to be satisfactory when using undeuterated samples. To 1.0 g. of the crude 1,1,2,2-tetradeuterio-1,4-butanediol prepared above was added 0.5 ml. of pyridine. After cooling this mixture in an ice bath, 1.8 ml. of phosphorus tribromide was added slowly and with stirring. The mixture was heated at 75° for 2 hrs., poured over ice, and the organic layer was extracted with ether. The ether extract was washed with 25 ml. of 2 N hydrochloric acid, water, aqueous sodium bicarbonate, and then water. The ether solution was dried over calcium chloride, and the ether was removed by evaporation. The residue was distilled from phosphorus pentoxide under vacuum, and

0.3 ml. of the desired deuterated dibromide was obtained, b.p. 35° (0.25 mm.). The nmr spectrum gave a well-resolved triplet at 205 Hz corresponding to the protons alpha to bromine and a triplet broadened by deuterium coupling at 118 Hz which corresponds to the beta protons.

1,5-Dichloro-3,3-dimethylpentane. - The method of preparation was a slight modification of that of Reid and Gompf (66). The method used for preparing the diethyl ester of 3,3-dimethylpentanedioic acid was essentially that described by Vogel for preparing diethyl adipate (67). To 35 ml. of absolute ethanol, 20 ml. of toluene, and 1 ml. concentrated sulfuric acid was added 10 g. of 3,3-dimethylpentanedioic acid (Aldrich). Water separation was accomplished by means of a modified Dean-Stark trap. During the first two hours of refluxing, approximately 20 ml. of distillate were removed through the trap. Then 20 ml. more of absolute ethanol and 10 ml. more of toluene were added to the reaction mixture, and the refluxing was continued for 24 hrs. The excess toluene and ethanol were then removed by distillation. The ester was distilled from the residue, 11.2 g., b.p. 60° (0.25 mm.); lit. (66) 90-91° (3 mm.).

To 1.2 g. of lithium aluminum hydride in 30 ml. of ether was added 5 g. of the diethyl 3,3-dimethylpentanedioate. After the addition, the mixture was refluxed for 1 hr. The excess hydride and salts were decomposed with 20 ml. of water and 20 ml. of 6 N hydrochloric acid. The two-phase reaction mixture was set up for continous extraction by ether. After three days, the ether was evaporated on a steam bath leaving several milliliters of high boiling residue, the crude diol. The crude diol was used in the next step without further purification.

To the crude 3,3-dimethyl-1,5-pentanediol was added 2 ml. of pyridine, and while cooling this mixture, 10 ml. of thionyl chloride was added with stirring in a 0.5-hr. period. After having been stirred overnight at room temperature, the mixture was refluxed for 6 hrs. It was then poured over ice, and the organic layer was extracted with ether. The ether extract was washed with 25 ml. of 2 N hydrochloric acid, water, aqueous sodium carbonate, and water, and then it was dried over sodium sulfate. The solution was filtered, the ether removed, and the dichloride distilled under vacuum from phosphorus pentoxide; 1.2 g. of the dichloride was obtained, b.p. 214° (760 mm.) on a Mettler FP1 boiling point apparatus; lit. (66) 135° (80 mm.). The nmr spectrum is shown in Figure 16.

1,5-Dichloro-2,4-dimethylpentane.- This dichloride was prepared by the same method used for preparing 1,5-dichloro-3,3-dimethylpentane. Starting with 5.0 g. of the diethyl ester of 2,4-dimethylpentanedioic acid (Aldrich), 2.3 g. of the dichloride was obtained, b.p. 203° (760 mm.) on a Mettler FP1 boiling point apparatus.

Anal. Calcd. for $C_7H_{14}Cl_2$: C, 49.75; H, 8.29. Found: C, 49.69; H, 8.32.

1,6-Dichloro-2,5-dimethylhexane.- This dichloride was prepared by the same method used for preparing 1,5-dichloro-3,3-dimethylpentane. From 5.0 g. of the diethyl ester of 2,5-dimethylhexanedioic acid (Aldrich), 2.5 g. of the dichloride was obtained, b.p. 222° (760 mm.) on a Mettler FP1 boiling point apparatus.

Anal. Calcd. for $C_8H_{16}Cl_2$: C, 52.49; H, 8.75. Found: C, 52.54; H, 8.84.

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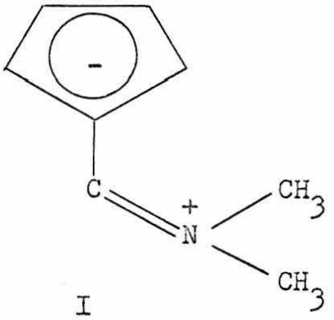
PROPOSITIONS

Proposition I

A study of the effect of salts upon the rate of rotation about the carbon-nitrogen bond in certain enamines is proposed. An extension to the study of the solvation of the same salts by various ethers is a possibility.

In the past year nuclear magnetic resonance spectroscopy has demonstrated the occurrence of cis-trans isomerism in certain enamines. Downing and co-workers (1) have studied 6-dimethylaminofulvenes and find that below -17° two resonances can be seen for the methyl groups. This can be explained by the existence of species I.



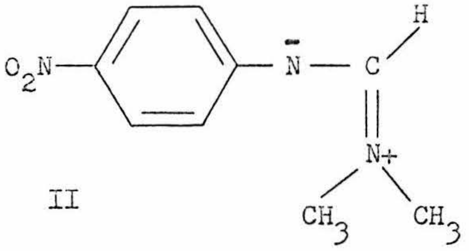
I

The same phenomenon is observed with other enamines and hydrazones (2). The presence of an electron-withdrawing formyl group in the 6-dimethylaminofulvene raises the coalescence temperature from -17° to above 50°. The barrier to rotation is increased by 3-4 kcal.

mole^{-1}. The benzofulvene derivatives have rotational barriers 2-3 kcal. mole^{-1} less than the corresponding fulvene derivatives.

The interaction of tertiary amines with metal halides has been shown to influence the reactions and nature of Grignard reagents (3,4,5,6) and analogous alkylzinc compounds (7). However, the interaction, probably from solvation changes, of tertiary amines with these organometallic reagents has not been studied extensively. The use of tertiary enamines to study this solvation interaction with metal salts is proposed. The experimental procedure would be to dissolve the enamine in some solvent which will also dissolve the metal salt. Ethers would probably be suitable. The variable temperature nmr spectra would then yield information about the interaction of the salt with the enamine by affecting the barrier to rotation about the carbon-nitrogen bond.

Bertelli and Gerig (8) have recently demonstrated that solvent effects in formamidines can influence the barrier to rotation about the carbon-nitrogen bonds. The nature of the solvent interaction is not known, but the result of the interaction is assumed to produce a change in the double bond character of the carbon-nitrogen bonds. Two methyl groups can be observed indicating slow rotation on the nmr time scale in the following compound. The barrier changes from 10.3 kcal. to 22.2 kcal in going from chloroform to benzene.



II

The effect of salts should produce a change in the magnitude of the rotational barrier. The differences produced by the various salts would be of interest. If the enamines interact with the salts at the nitrogen, the barrier to rotation should be reduced. This interaction would be similar to that of tertiary amines with organometallic halides. In studies of alkylzinc halides, Abraham and Rolfe (7) find that N,N,N',N'-tetramethylethylenediamine precipitates different forms of zinc, either the alkylzinc halide or the zinc halide, depending on which halogen is involved. Therefore, the difference in the association of the enamines with zinc chloride, bromide, or iodide would be of interest in showing whether the different diamine complexes found by Abraham and Rolfe are actually caused by the tendency of the tertiary amines to solvate each halide differently, or from an actual difference in the position of the equilibrium

$$2\ RZnX \rightleftharpoons R_2Zn + MgX_2$$

which may be influenced by the halide. Comparison of the rotational barrier in 6-dimethylaminofulvene when the different zinc halides are present would give some idea about the variation in solvation by tertiary amines when changing the halogen. This same study can be extended to other metal halides, such as the magnesium salts.

In order for this study to work, the metal halides must not reduce the energy barrier to that point where two methyl groups cannot be observed at low temperature. A variety of enamines are available with 6-dimethylaminofulvene being the best because of the lack of other functional groups. Enamines with nitrile or nitro substituents have larger rotational barriers and might be more satisfactory, because after a very large reduction in the rotational barrier, the magnitude might remain large enough so that two methyl groups could be observed at low temperature. However, with the enamines with large barriers, interaction of the metal salts with other parts of the molecule might become important.

Even with 6-dimethylaminofulvene the interaction of the salt with other parts of the molecule might occur. The salts might interact with the beta carbon or the ring and increase the barrier to rotation in the carbon-nitrogen bond. Protonation of $\Delta^{1(10)}$-quinolizidine occurs at the beta carbon when forming the perchlorate salt (9). These cyclic enamines appear to be more basic than the corresponding saturated amines (10). However, acyclic enamines are generally less basic than tertiary amines (11, 12). The question of interaction, similar to the amide protonation problem (13), cannot definitely be answered until the experiment is conducted.

If the metal halides do produce changes in the rotational barrier of enamines, then the influence of ethers on this system may be of considerable interest. For example, the change in the effect of magnesium bromide on the rotational barrier when varying the solvent from tetrohydrofuran to dimethyl ether to diethyl ether would give an indication of the solvation differences of the ethers for the metal halides.

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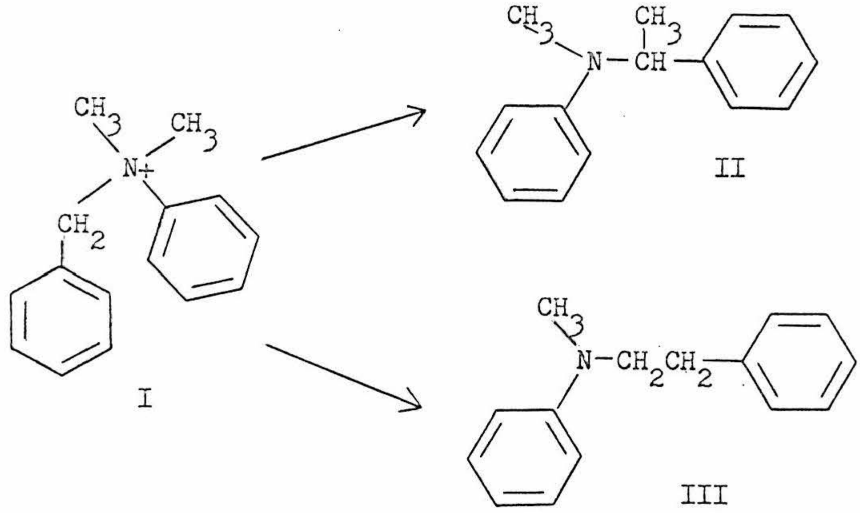
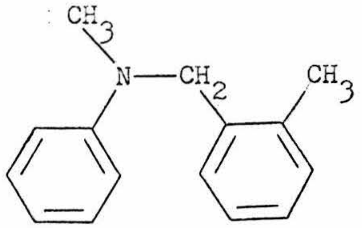
Proposition II

Experiments are proposed for studying the rearrangement of benzyldimethylanilinium chloride when fused with potassium hydroxide.

Several products have been isolated in fairly substantial yield when heating benzyldimethylanilinium chloride with solid potassium hydroxide (1). Two tertiary amines are produced as the major rearrangement product, N-methyl-N-(α-phenethyl)aniline II, 23%, and

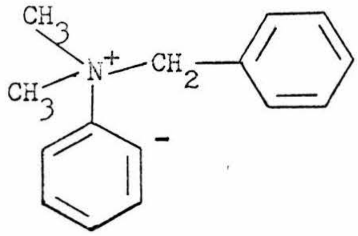


N-methyl-N-(β-phenethyl)aniline III, 4%. Giumanini has proposed that abstraction of a benzyl proton followed by methyl migration leads to II; abstraction of a methyl proton followed by benzyl migration would give III. No Sommelet rearrangement product IV was found indicating that no addition to the <u>ortho</u> position of the benzyl ring system occurred. However, abstraction of <u>ortho</u> protons in

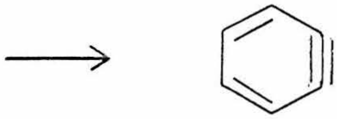


IV

the aniline system has been postulated to explain products such as anisole and benzyl phenyl ether which apparently arise from benzyne. The benzyne can be formed from V. The species V is analagous to



V

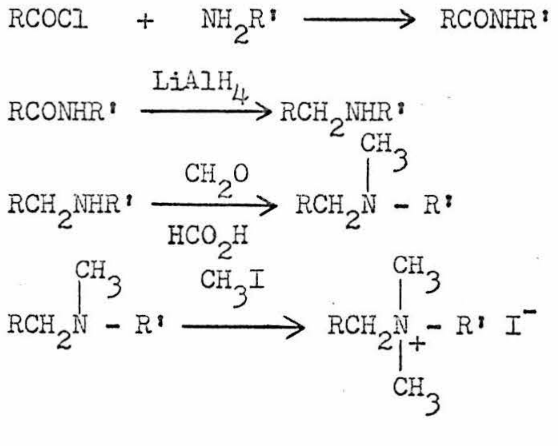


VI

that species which is proposed by Wittig and Benz as an intermediate in the addition of tertiary amines to benzyne (2). The phenyl anion abstracts a proton from one of the carbons in the alkyl groups on nitrogen. When triethylamine was added to benzyne, N,N-diethylaniline and ethylene were one set of products resulting from abstraction of a methyl proton. Abstraction of a methylene proton followed by ethyl migration gave N-ethyl-N-(α-methylpropyl)aniline. Since V is analogous to that intermediate proposed by Wittig, and Benz, it seems likely that proton abstraction within structure V may be occurring. Puterbaugh and Hauser (3) have shown that an equilibrium exists between the methyl and benzyl ylides of benzyltrimethylammonium iodide. This equilibrium may exist in the benzyldimethylanilinium chloride after abstraction of a proton by base.

To study the effects of proton abstraction or migration in these systems, several experiments are proposed. Instead of potassium hydroxide as the base, potassium deuteroxide should be used. Analysis of the products for deuterium would indicate whether or not complete scrambling of protons can occur. With no exchange of protons with the base, II and III should be deuterium free. The benzyne products should incorporate deuterium in positions <u>ortho</u> to the ether substituents.

If no random scrambling of protons occurs, then deuterium labeling experiments can be conducted. Deuterium can be placed into any of the reactive positions. Lepley and Becker (4) have a general synthesis for these ammonium salts.



$$\begin{gathered}
\mathrm{RCOCl} \quad + \quad \mathrm{NH_2R'} \longrightarrow \mathrm{RCONHR'} \\
\mathrm{RCONHR'} \xrightarrow{\mathrm{LiAlH_4}} \mathrm{RCH_2NHR'} \\
\mathrm{RCH_2NHR'} \xrightarrow[\mathrm{HCO_2H}]{\mathrm{CH_2O}} \mathrm{RCH_2}\overset{\mathrm{CH_3}}{\overset{|}{\mathrm{N}}} - \mathrm{R'} \\
\mathrm{RCH_2}\overset{\mathrm{CH_3}}{\overset{|}{\mathrm{N}}} - \mathrm{R'} \xrightarrow{\mathrm{CH_3I}} \mathrm{RCH_2}\underset{\mathrm{CH_3}}{\underset{|}{\overset{\mathrm{CH_3}}{\overset{|}{\mathrm{N}^+}}}} - \mathrm{R'}\ \mathrm{I^-}
\end{gathered}$$

Deuterium can be placed into the benzyl group by substituting lithium aluminum deuteride for the hydride. Deuterium can be placed in the methyl groups by using deuterated methyl iodide. By using the three differently labeled compounds and running the reaction as usual with potassium hydroxide, the method of proton abstraction from the three different sites should be made clear.

There remains one experimental difficulty. Hydrogen abstraction forming the benzyl and methyl ylides should easily be observed by examining the products which are collected. In order to observe intramolecular deuterium abstraction from the phenyl ring, anisole and benzyl phenyl ether can be examined for deuterium incorporation. It may also be necessary to collect benzyldimethylamine, one of the products produced upon benzyne formation from V. The author (1) does not report finding this amine in his reaction products, so it may be necessary to establish its existence.

All products may be derived from V. The benzyl and methyl ylides may be formed from this initial species. In this case, all products derived from the starting material with deuterated phenyl ring will have a proton _ortho_ to nitrogen. This should also be demonstrated by the presence of deuterium on the phenyl ring when using starting material with methyl and benzyl deuteration.

Methods of elucidating the possible interconversion of the methyl ylide, benzyl ylide and V when fusing benzyldimethylanilinium chloride with potassium hydroxide have been proposed. If complete deuterium scrambling should occur during the reaction, it may be possible to apply the proposed study to rearrangements induced with n-butyllithium or phenyllithium, reagents which have been used in similar reactions (4, 6).

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Proposition III

The study of the effect of a second Grignard reagent on the rate of inversion at the $-CH_2Mg-$ center in 3,3-dimethybutylmagnesium chloride or 2-methylbutylmagnesium bromide is proposed. If inversion proceeds by a bimolecular mechanism, then the nature of the second Grignard reagent, such as the size of the alkyl groups around magnesium, should influence the inversion rate in the Grignard reagent whose inversion rate can be measured.

Whitesides and co-workers (1, 2) have examined the configurational stability of primary Grignard reagents by nuclear magnetic resonance spectroscopy. The inversion rate at the $-CH_2Mg-$ center is a function of the concentration of the reagent. The higher the concentration, the greater the inversion rate. Fraenkel and Dix (3) studied the inversion rate in 2-methylbutylmagnesium bromide. They found a kinetic order of 2.5 in alkylmagnesium halide for the inversion process in diethyl ether. This indicates at least a bimolecular mechanism. Di-Grignard reagents have been found to invert much faster than corresponding monofunctional Grignard reagents (4). This may be because the inversion is occurring by a second-order intramolecular process.

The effect on the inversion rate upon adding a second Grignard reagent to a solution of 3,3-dimethylbutylmagnesium chloride or 2-methylbutylmagnesium bromide has never been determined. In unpublished results from this laboratory, the rate of inversion in 3-methyl-2-phenylbutylmagnesium bromide was found to increase when neopentylmagnesium bromide was added (5). The inversion rate probably increased because of the higher concentration of alkylmagnesium halide.

The concentration of Grignard reagents must be kept constant at all times in order to eliminate rate changes which can arise from concentration variations. To the Grignard reagent of 3,3-dimethylbutyl chloride or 2-methylbutyl bromide prepared in an nmr tube would be added the halide for preparing the second Grignard reagent. The concentration of the Grignard reagent whose inversion rate is to be measured must always be the same from sample to sample. The concentration of the second Grignard reagent must also be the same. After the samples are prepared, the inversion rates of the 3,3-dimethylbutylmagnesium chloride or 2-methylbutylmagnesium bromide can be determined from the variable temperature nmr spectra.

The protons _alpha_ to magnesium in Grignard reagents give resonances up-field from tetramethylsilane. Usually these resonances are uncomplicated by resonances from other compounds. However, with two Grignard reagents in solution, this may not be the case. The methyl Grignard reagent peak is up-field from the peaks of other primary Grignard reagents, so overlapping is no problem. Tertiary Grignard reagents have no protons _alpha_ to magnesium. Primary Grignard reagents with alkyl groups larger than methyl and secondary Grignard reagents may have to be deuterated in positions _alpha_ to magnesium in order to prevent complication of the resonances of the Grignard reagents whose inversion rates are being measured.

This study of solutions with two Grignard reagents may be extendable to the study of inversion in secondary Grignard reagents, which have been shown to invert slowly on the nmr time scale (2). Possibly with a second Grignard reagent present, even secondary Grignard reagents can be induced to invert rapidly.

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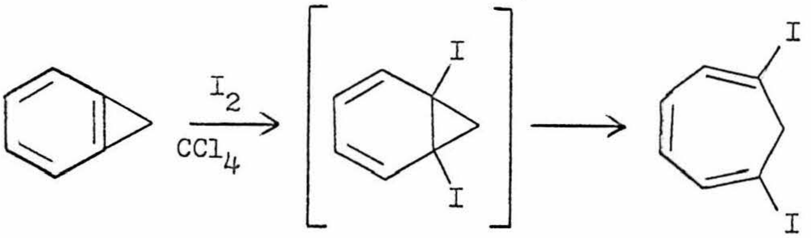
Proposition IV

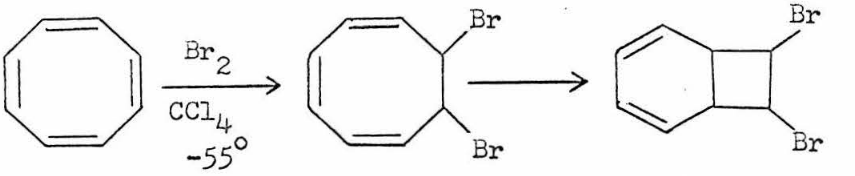
A method is proposed for proving the existence of 1,6-diiodonorcaradiene as an intermediate in the iodination of benzocyclopropene.

The synthesis of benzocyclopropene (I) has recently been reported by Vogel, Grimme, and Korte (1). The product obtained upon iodination of this compound in carbon tetrachloride was 1,6-diiodocycloheptatriene (III) with a possible intermediate being 1,6-diiodonorcaradiene (II).



I II III

The experiment which is proposed for detecting the norcaradiene intermediate is the same one used by Huisgen and Boche to study the bromination of cyclooctatetraene (IV) (2). Bromine was added to cyclooctatetraene at -55°, and a nuclear magnetic resonance spectrum was taken at this temperature. At these low temperatures the spectrum was that of 7,8-dibromocycloocta-1,3,5-triene (V), and at higher temperatures near 0° the spectrum observed was that of 7,8-dibromobicyclo(4,2,0)octa-2,4-diene (VI).

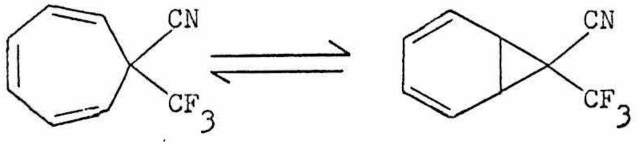


IV V VI

In order to observe 1,6-diiodonorcaradiene as an intermediate, iodine in carbon tetrachloride would be added to a -80° solution of benzocyclopropene in carbon tetrachloride in an n.m.r. tube. The n.m.r. spectra of benzocyclopropene and 1,6-diiodocycloheptatriene are reported by Vogel (1), and the n.m.r. spectrum of the intermediate should be considerably different. The chemical shift of the C-7 protons should be different in the three cases; this should be the simplest way of detecting the different species. The ^{13}C-proton coupling constant of C-7 can be used as another criterion for proving the structure of any intermediate. The analysis of the spectra of 7,7-dicyanonorcaradiene (3) and 7,7-bistrifluoromethylcycloheptatriene (4) have been completed, so any analysis needed with the diiodo intermediate would be an extension of these.

In recent years derivatives of the norcaradiene structure have been found, although low temperature n.m.r. experiments of cycloheptatriene and some of its derivatives showed no norcaradiene structure (5,6,7). Ciganek first prepared a simple norcaradiene system as a 7,7-dicyano derivative (8). Later he showed that an equilibrium exists between 7-cyano-7-trifluoromethylcycloheptatriene (VII) and

7-cyano-7-trifluoromethylnorcaradiene (VIII) (9).



VII VIII

Ciganek's work has shown that the norcaradiene system can exist other than by bridging C-1 and C-6 with more than one atom (10) or by incorporation of a double bond into an aromatic system (11). Therefore, the intermediate proposed by Vogel is certainly a possibility. It is realized that if the opening of the diiodo intermediate cannot be stopped by using low temperatures, nothing may be determined by the experiment. However, because Ciganek has shown the existence of norcaradiene derivatives and equilibria and because the similar experiment has worked with cyclooctatetraene bromination, there seems to be a definite chance of observing the intermediate. Because of the opportunity of demonstrating the norcaradiene derivative, the experiment is definitely worth doing (12).

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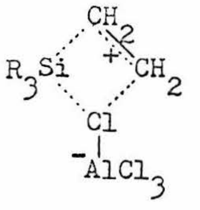
Proposition V

The use of an optically active, chlorine labeled silicon compound is proposed for determining the mechanism of the elimination of ethylene by aluminum chloride in reactions of the following type:

$$R_3SiCH_2CH_2Cl \xrightarrow{AlCl_3} R_3SiCl \quad + \quad CH_2{=}CH_2$$

In a recent paper on the rearrangement of aryldimethyl(chloromethyl)silanes, Bott, Eaborn, and Rushton propose a cyclic intramolecular chlorine transfer in one of two forms (1).



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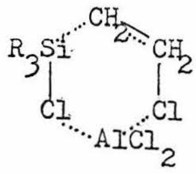
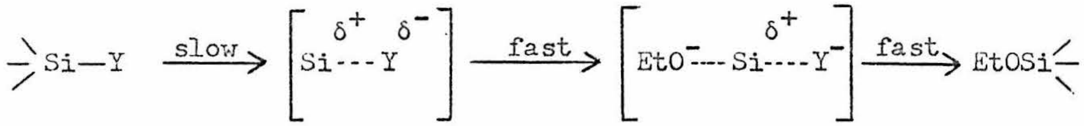


II

Their proposal is based on previously reported gas phase decomposition studies of (β-chloroalkyl)silicon compounds which supported an intramolecular chlorine transfer (2) and on their belief that Sommer's previous work (3) did not prove the existence of a partial siliconium ion.

Sommer had studied the solvolysis of trimethyl(β-chloroethyl)silane in ethanol and water. The products are ethylene and trimethylsilanol. Sommer's conclusions from kinetic studies were that a partial siliconium ion was formed in a slow reaction followed by attack of an ethoxide ion in a second fast reaction.



Rate studies showed that the rate of solvolysis was dependent on the ionizing power of the solvent but not its nucleophilic character. The rates were also retarded by electron-withdrawing groups on aryl substituents on silicon.

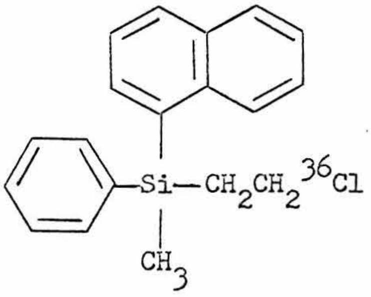
Bott believes that Sommer's solvolysis reaction undergoes an intramolecular chloride transfer followed by rapid solvolysis of the chlorosilane. It is true that chlorosilanes do undergo rapid solvolysis in aqueous solutions (4), and possibly Sommer's solvolysis study might involve two different reactions.

$$R_3SiCH_2CH_2Cl \longrightarrow R_3SiCl \xrightarrow{-OR^-} R_3SiOR$$

The above sequence is only possible with a direct intramolecular transfer of chlorine to silicon.

A mechanism proposed earlier by Eaborn (5) suggested an abstraction of chlorine from the alkyl group and attack by the tetrachloroaluminum anion upon silicon with displacement of ethylene. A completely free anion could attack silicon in the same way that Sommer proposes.

Although Bott, Eaborn, and Rushton have proposed an intramolecular chlorine transfer based on gas phase studies, this concept has not been proven for the aluminum chloride reactions. To what extent the chlorine stays bound to the original reactant and to what extent aluminum chloride plays a role in the chlorination of the silicon is not known. By running the reaction on an optically active silicon compound (III) in which the chlorine is labeled with chlorine-36, the role of aluminum chloride in this reaction would be further clarified.



III

If the reaction proceeds through I, then the optically active site should retain its configuration and the chlorine transferred should be the labeling isotope. If the reaction proceeds through II, then the optically active site should retain its configuration and the chlorine transferred would be low in labeling isotope--the only chlorine-36 coming from aluminum chloride to which it would have been transferred earlier. If the tetrachloroaluminum anion is the attacking species and is free from the silicon as in a mechanism similar to that of Sommer's or possibly an intermolecular mechanism similar to II exists, then inversion of configuration would occur with scrambling of the chlorine label. The mechanism path through I or II must proceed with retention of configuration. By Sommer's postulate of "least motion" (6) in which the alkyl groups are not allowed to enter a plane, the configuration of the silicon cannot be changed. Any mechanism which allows any inversion to occur must involve a siliconium ion which is more independent from the chlorine within the molecule than that proposed by Bott, or it must involve a displacement like the type proposed by Sommer.

The synthesis of the silicon compound should not be difficult. The procedure for making the optically active R_3SiOMe has been worked out previously by Sommer (7). Addition of vinylmagnesium bromide to form $R_3SiCH{=}CH_2$ with retention of configuration followed by addition of dry hydrogen chloride (8) labeled with chlorine-36 should give the desired product with known configuration at the silicon. Experimental procedures for obtaining the products have been worked out by Bott and co-workers (1). Indications from their work and that of Sommer's (9) are that this reaction will be slow enough to enable stopping the reaction before completion for analysis of products. This will enable following the reaction as it proceeds to completion.

One more reaction must be studied for completeness of this proposition. That is the reaction of an optically active silicon halide with aluminum chloride under the reaction conditions for the elimination of ethylene from the β-chloroethyl silicon compound. If any inversion occurs, then dissociation of the silicon chloride must take place with the formation of at least an ion pair if not a siliconium ion. This, in itself, would be some evidence against the mechanism proposed by Bott, Eaborn, and Rushton, since their mechanism is actually based on the idea that not even a partial siliconium ion can form. This experiment would best be conducted by using chlorine-36 in the silicon compound, because possible chlorine exchange could conceivably take place without inversion, if the aluminum chloride forms a complex with the silicon compound without the formation of any kind of siliconium ion.

Another factor which could lead to loss of information from the chlorine label is the possible occurrence of chlorine exchange without ethylene elimination. An analysis of starting material at some point in the reaction would tell if this exchange were occurring. If starting material were recovered which had lost some chlorine-36, then chlorine labeling of the starting material would be of no value. Therefore, if chlorine exchange occurs with the starting material before elimination occurs or if chlorine exchange occurs with the final product, the silicon chloride, before it can be analyzed, the use of chlorine-36 would tell nothing about the mechanism. In that case only the inversion studies would give any desired information.

Now the complete plan is established. Chlorine exchange must be studied in the silicon chloride which would be the product from ethylene elimination. Exchange with inversion would indicate that the original idea for proposing I and II has no real foundation. Chlorine exchange without inversion would indicate a complex between the silicon chloride and aluminum chloride. If inversion occurred, but not slower than ethylene elimination, the testing of the ethylene elimination reaction could not be done, but the conclusion could be made that I and II are probably not good pictures for the mechanism. If chlorine exchange in the silicon halide occurs without inversion but not slower than ethylene elimination, the ethylene elimination reaction could be studied but only as to whether retention or inversion occurred. This would not distinguish between I and II, however. If no chlorine exchange occurred or if the exchange reactions were slow compared to ethylene elimination, then the study using the proposed $\underline{\beta}$-chloroethyl compound will tell the difference between I or II or another mechanism.

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