STUDIES OF GRIGNARD REAGENT REARRANGEMENTS BY MEANS OF NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

I. THE STRUCTURE OF ALLYLIC GRIGNARD REAGENTS

II. THE INTERCONVERSION OF CYCLOPROPYLCARBINYL AND ALLYLCARBINYL GRIGNARD REAGENTS

Thesis by

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Dick Shafer made this thesis possible through his skillfulness, and pleasurable through his enthusiastic and perceptive counsel; it is dedicated to him with gratitude and admiration.

ABSTRACT

I. THE STRUCTURE OF ALLYLIC GRIGNARD REAGENTS

The nuclear magnetic resonance (n.m.r.) spectra of several simple allylic Grignard reagents in diethyl ether solution, of benzylmagnesium chloride in ether, and of diallylmagnesium and dibutenylmagnesium in dioxane have been investigated. The results for the simple allylic systems are best interpreted in terms of an extremely mobile tautomeric exchange of magnesium between allylic positions, whereas the conventional structure is indicated for the benzyl Grignard reagent. The results are related to the rearrangements known to occur in the Grignard reactions of allylic halides.

II. THE INTERCONVERSION OF CYCLOPROPYLCARBINYL AND ALLYLCARBINYL GRIGNARD REAGENTS

The Grignard reagent, in ether solution, from either cyclopropylcarbinyl chloride or allylcarbinyl chloride has been shown by its n.m.r. spectrum to possess the allylcarbinyl structure. Nortricyclyl chloride and exo- or endo-5-dehydronorbornyl chloride also give a common Grignard reagent, whose n.m.r. spectrum seems best fitted to the nortricyclyl structure. The results explain the products formed in the Grignard reactions of these sets of isomeric halides. They are also discussed with respect to the recently discovered interchange between the 1- and 2-positions in allylcarbinylmagnesium halides.

ACKNOWLEDGMENTS

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More important than all else have been the encouragement and aid of my parents, which have always been beyond measure.

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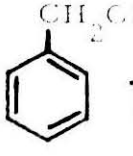
I. THE STRUCTURE OF ALLYLIC GRIGNARD REAGENTS

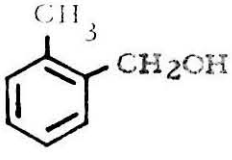
INTRODUCTION

Considerable research has been stimulated by the remarkable reactions of a variety of allylic-type Grignard reagents. Precise definition of this class of compounds still awaits more certain and thorough structural knowledge. For the present discussion, however, these reagents will be defined broadly as species in which a magnesium atom is attached to a position adjacent to carbon-carbon, or in some cases possibly carbon-nitrogen unsaturation. The most distinctive feature of allylic-type Grignard reagents is their propensity to form products by bonding at a position allylic to (conjugated with) that from which an atom was displaced in their preparation. The following known reactions illustrate the diverse systems which display such behavior

$$CH_3CH{=}CHCH_2Br \xrightarrow[Et_2O]{Mg} CH_2\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow{H_2O} HO{-}\overset{CH_3}{\overset{|}{C}}{-}\underset{CH_3}{\overset{|}{C}}H{-}CH{=}CH_2 \quad (1)$$



$$\xrightarrow[Et_2O]{Mg} \xrightarrow{(CH_2O)_3} \xrightarrow{H_2O} \quad (2)$$

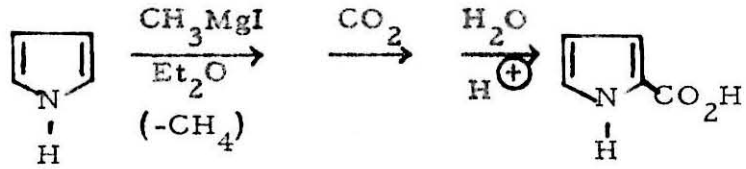


(Eq. 1)

$$CH_3(CH_2)_3C{\equiv}C{-}CH_2Br \xrightarrow[Et_2O]{Mg} \xrightarrow{CO_2} \xrightarrow[H^{\oplus}]{H_2O} \quad (3)$$

$CH_3(CH_2)_3C{\equiv}C{-}CH_2CO_2H$ 9%

\+ $CH_3(CH_2)_3\underset{CO_2H}{\overset{|}{C}}{=}C{=}CH_2$ 41%

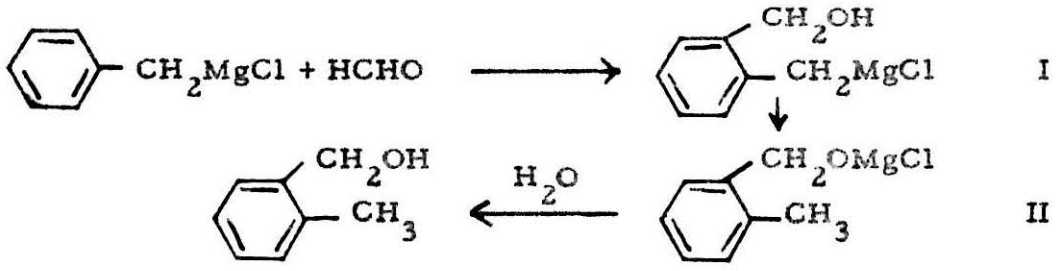


(4)

Such rearrangements have been studied for over fifty years and scores of papers dealing with this general subject have been published (5). Nonetheless, it is fair to state today that a thorough elucidation of an allylic Grignard reaction mechanism has not yet been achieved. The principal obstacle to a better understanding of these processes has been the failure of purely chemical experiments to determine unambiguously the structures of the Grignard reagents themselves. The objective in the present research was the determination of the structures of several important simple allylic Grignard reagents by nuclear magnetic resonance spectroscopy, a powerful physical technique made available in recent years. It was hoped that this approach, free from the ambiguities inherent in purely chemical investigations, would make possible a distinction between those mechanistic hypotheses which have been advanced on the basis of chemical evidence.

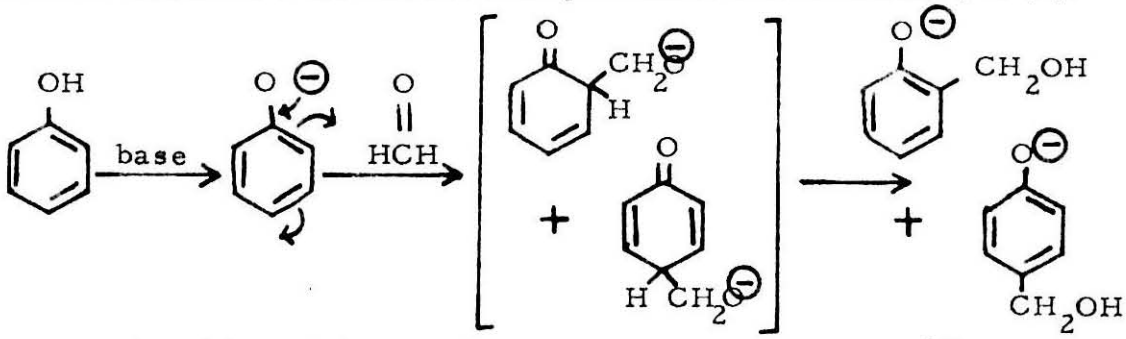
The earliest report of rearrangement in the reaction of an allylic Grignard reagent was provided in 1903 by Tiffeneau and Delange (2), who identified the sole product of the reaction between formaldehyde and the Grignard reagent from benzyl chloride as o-tolylcarbinol (Eq. 1), rather than β-phenylethanol. These workers contrasted this unusual reaction course with those of paraldehyde, acetone, and carbon dioxide, which under the same conditions proceeded "normally" to give 1-methyl-2-

phenylethanol, 1,1-dimethyl-2-phenylethanol, and phenylacetic acid, respectively. They concluded that the Grignard reagent in question had the benzylmagnesium chloride structure and suggested the following sequence as an explanation for the peculiar reaction with formaldehyde.

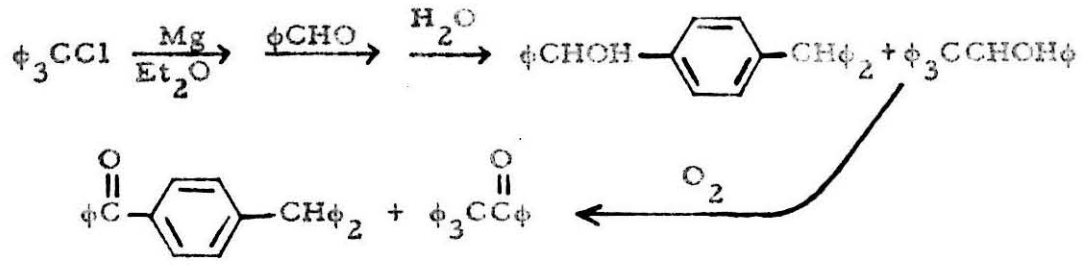


That the unhydrolyzed product mixture was inert toward carbon dioxide but reacted with acetic anhydride to give o-xylyl acetate was taken to indicate complete conversion of I to II.

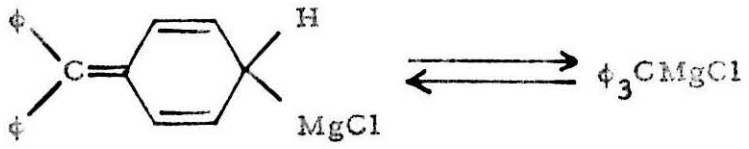
The proposed first step was pointed out to be analogous to the Lederer-Manasse reaction between phenoxide and formaldehyde (6),



Schmidlin and Garcia-Banus took a divergent view (7). They observed that triphenylmethylmagnesium chloride upon treatment with benzaldehyde produced, after air oxidation, p-benzoyltriphenylmethane as well as β-benzopinacolin (phenyl trityl ketone),

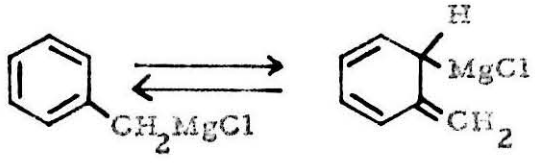


They asserted that two tautomeric molecules of the Grignard reagent were thereby indicated



α ρ

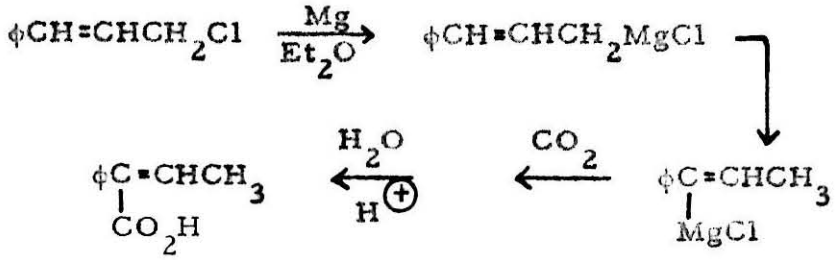
the metastable, quinonoid α-form giving rise to ρ-benzoyltriphenylmethane and the stable β-form leading to β-benzopinacolin. It was argued that facile tautomerism of this sort was consonant with the extraordinary reactivities of the phenyl-substituted methyl halides (although the relationship was not scrutinized) and that the rearrangement reactions of benzylmagnesium chloride ought similarly to be accounted for by two tautomeric Grignard reagent species



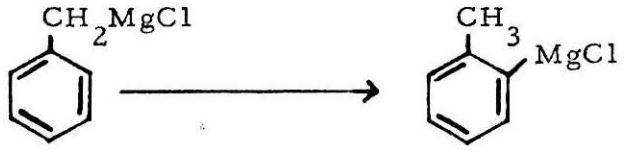
It was necessary to postulate that this equilibrium could be completely displaced in either direction by appropriate reactants, in order to accommodate diametric courses of reaction, for example with

formaldehyde, exclusively "abnormal" (rearranging) to give o-tolylcarbinol, and with carbon dioxide, exclusively normal to produce phenylacetic acid.

A third interpretation was offered by Gilman and Harris (8). These authors obtained only methylatropic acid from carbonation of the Grignard reagent of cinnamyl chloride. They concluded that the initially formed cinnamylmagnesium chloride had undergone rearrangement to the isomeric α-(β-methyl)-styrylmagnesium chloride.



It was concluded by analogy that a comparable rearrangement preceded reaction of benzylmagnesium chloride with formaldehyde



The discovery (9), however, that methylatropic acid was actually a rearrangement product of the initially formed phenylvinylacetic acid, $\phi\underset{\underset{CO_2H}{|}}{C}HCH{=}CH_2$, revealed the incorrectness of this theory, and it was abandoned. Gilman and Kirby demonstrated further (10) that only mechanisms involving allylic intermediates were at all likely to account for

the abnormal reactions of benzylic Grignard reagents, since no rearrangement accompanied the reactions with formaldehyde of cyclohexylmagnesium halides, β-phenylethylmagnesium bromide, styrylmagnesium bromide, or phenylethynylmagnesium bromide.

By 1932 a large number of reactions of benzylic Grignard reagents had become established. In that year Austin and Johnson (11) consolidated those data and classified the reactants as either normal or abnormal. Normal reactants were taken as those giving exclusively benzyl derivatives, while abnormal reactants were those leading to the formation of o- (and sometimes p-) tolyl products, generally in addition to some unrearranged counterparts. The results of this classification are listed in Table 1; these compounds which appear below the dividing spaces have been added in this writing together with references. In all cases listed by Austin and Johnson the ethereal Grignard reagent was added slowly to a solution of the reactant in excess. Inasmuch as abnormal reactions generally produced o-substituted derivatives, several reactions were studied of o-substituted benzylmagnesium chlorides. The results of the results of these experiments are summarized in Table 2. The data in Table 2 show that ortho-substitution can change the course of reaction with some reactants, but not with others. This demonstration taken together with the wide range of reactivities observed for a variety of reactants between completely normal (e.g. carbon dioxide) and completely abnormal (e.g. formaldehyde) pathways led Austin and Johnson to reject all theories which do not take into account the

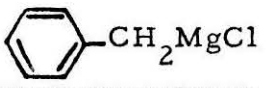
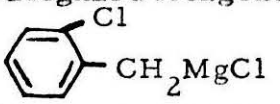
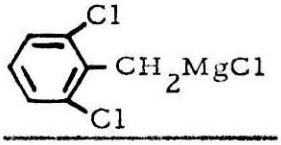
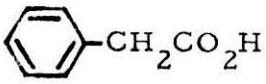
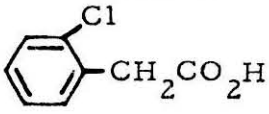
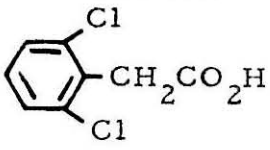
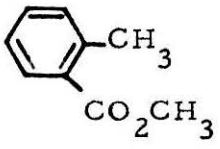
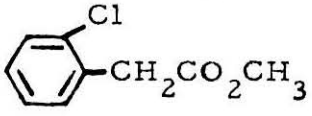
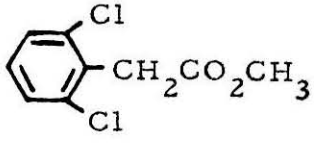
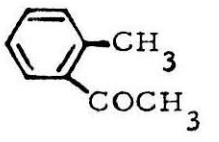
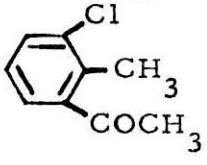
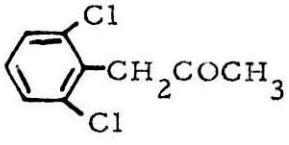
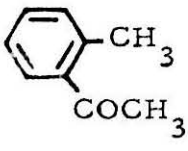
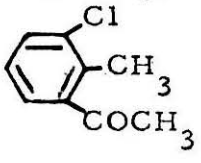
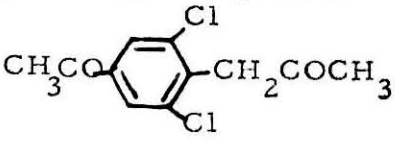
Table 1

Behavior toward Benzylmagnesium Chloride

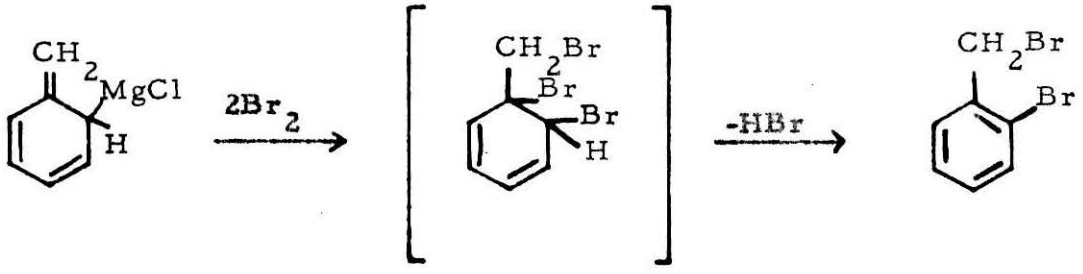
Abnormal Reactants	Normal Reactants
Formaldehyde	Paraldehyde
Benzaldehyde	Alkyl and aryl ketones
p-Methoxybenzaldehyde	Acetals and ethyl orthoformate
Ethylene oxide	Ethyl acetate, benzoate, and carbonate
Alkyl chloromethyl ethers	Carbon dioxide
Ethyl and methyl chloroformate	Epichlorohydrin and chloroacetone
Ethyl formate	Allyl iodide
Acetyl and benzoyl chloride	Mercuric chloride
Acetic and chloroacetic anhydride	Phenyl isocyanate
	Alkyl p-toluenesulfonates
Valeraldehyde (11)	Bromine (10)
Citronellal (18)	Benzyl chloride (10)
Diethyl sulfate (12)	Benzonitrile (10)
Trifluoroacetonitrile (21)	Chloroacetophenone (10)
Alkyl α-haloalkyl ethers (13)	N,N-Diphenylchloroformamide (10)
Aliphatic aldehydes (20)	Sulfur dioxide (22)
Cyanogen (21)	Cyanogen bromide (21)
	Hydrogen chloride (14)

Table 2

Behavior toward Benzyl- and ortho-Substituted Benzylmagnesium Chlorides

Reactant			
CO_2	Normal 	Normal 	Normal 
CH_3OCOCl	Rearrangement 	Normal 	Normal 
$(CH_3CO)_2O$	Rearrangement 	Rearrangement 	Normal 
CH_3COCl	Rearrangement 	Rearrangement 	Rearrangement 

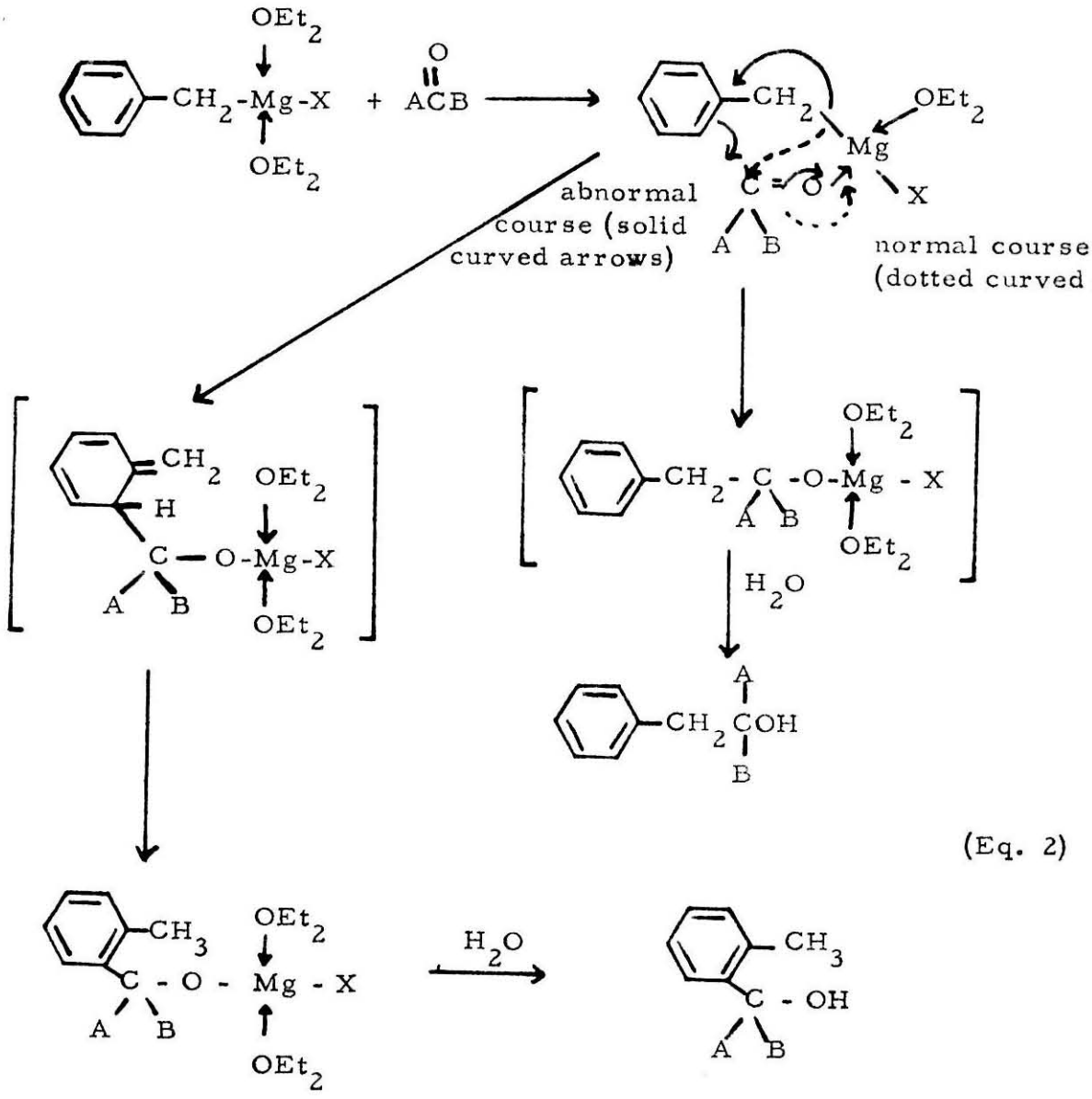
nature of the reactant in determining the balance between rearrangement and non-rearrangement. Thus the hypothesis of Schmidlin and Garcia-Banus, which postulates a rearrangement prior to intimate involvement of the reactant, was judged an unsatisfactory explanation of the abnormal reaction. This depreciation of Schmidlin's mechanism was supported by an investigation of Gilman and Kirby (10), who added bromine to benzylmagnesium chloride in ether in the hope that if the Grignard reagent were present in an ortho- (or para-) quinonoid form it might be intercepted by bromine according to the reaction



The only product obtained was pure benzyl bromide in 63% yield.

Austin and Johnson did not explicitly reject the mechanism of Tiffeneau and Delange, but in 1933 Johnson (15) proposed an alternative general mechanism to encompass both the normal and abnormal reactions of benzylic Grignard reagents. Johnson postulated that the reactant, if structurally capable, initially forms a coordination compound with benzylmagnesium chloride, and the products are then determined by the mode of decomposition of the complex. In the normal reaction there is an α-γ migration of the benzyl group essentially as an anion, without rearrangement, while the acidity (in the Lewis sense) of the

magnesium atom becomes satisfied by coordination with ether. The abnormal reaction proceeds via a cyclic six-membered transition state; attack upon the reactant's electrophilic center by the ortho ring position is accompanied by an allylic shift of electrons. This step leads to a quinonoid ring system which rearranges by an allylic hydrogen shift to an o-tolyl structure, either simultaneously with or subsequent to cyclic rearrangement of the initial coordination compound. The scheme is illustrated below for a generalized carbonyl reactant, ACOB.



(Eq. 2)

The factors that determine which of the two paths is followed are not completely delineated by Johnson. Inspection of Table 1 reveals no striking unity within either group of reactants. However, several generalizations have been pointed out which enable limited prediction to be made. Steric considerations are clearly important. The more hindered a carbonyl group within a comparable series of reactants the less is the tendency for abnormal reaction. Thus, the extent of rearrangement follows the order

HCH	>	$n\text{-}C_4H_9CH$	>	alkyl-C-alkyl
exclusively abnormal		partially normal and abnormal		exclusively normal

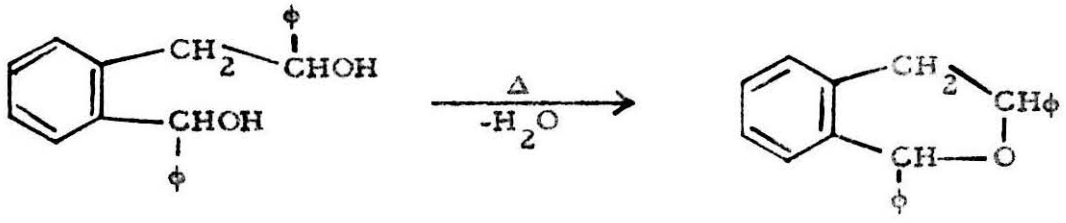
Also the extent of electronic polarization of the reactant carbonyl group seems to bear upon the mode of reaction; the more strongly polarized compounds favor abnormal behavior. For example, among simple acyl derivatives the order of rearrangement is

$$CH_3CCl > CH_3COCCH_3 > CH_3COC_2H_5 \quad \text{(exclusively normal).}$$

The Johnson mechanism is attractive in several respects. It provides a convenient cyclic six-membered transition state for the genesis of ortho-rearranged products, from an initial coordination complex whose formation would be expected by inductive effect to facilitate carbon-magnesium bond breaking. It postulates the Grignard reagent to

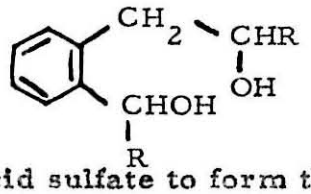
exist exclusively in its favored benzenoid form. It depicts the normal reaction as occurring by the same steps which have been suggested for saturated Grignard reagents (16). Its experimental basis, however, does not disprove either the Tiffeneau and Delange or the Schmidlin and Garcia-Banus mechanisms. It may only appear more reasonable than these alternatives. Furthermore, it fails to deal with at least two types of pertinent data in the literature at the time. The first of these is the p-tolyl rearrangement. A high proportion of abnormal benzyl Grignard reactions have been observed to give para- as well as ortho-rearrangement products. Gilman and Kirby (10) reported a trace of p-toluic aldehyde (among 88% phenylacetaldehyde and 12% o-toluic aldehyde) from the reaction of benzylmagnesium chloride with ethyl formate, and more para- than ortho-rearranged ether from benzylmagnesium chloride and chloromethyl ethyl ether; Bottomley, Lapworth, and Walton obtained the same results with chloromethyl methyl ether (17). Indeed, Gilman and Kirby (10) found that benzylmagnesium chloride and ethylene oxide produced γ-phenylpropanol and 2-p-tolylethanol in approximately equal amounts, with no detectable yield of 2-o-tolylethanol. The Johnson mechanism leaves untreated the question of the mode of formation of para-rearrangement products, and for steric reasons it is highly improbable that these are formed from the same coordination complex pictured as the precursor to both normal and ortho abnormal derivatives. Secondly, the hypothesis of Johnson makes no provision for the documented variation in proportions of normal and abnormal products as a function of the relative concentrations of

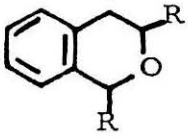
Grignard reagent and co-reactant during the course of reaction. An early and striking example of such behavior was furnished by Schmidlin and Garcia-Banus (7), who found that slow addition of benzaldehyde to benzylmagnesium chloride gave as much as 95% of the normal product (phenylbenzylcarbinol) whereas the reverse addition gave only 30% of the normal product and 70% of diphenylisochromane, formed by dehydration of an abnormal product incorporating two aldehyde residues, attached at the ortho and at the methylene positions,

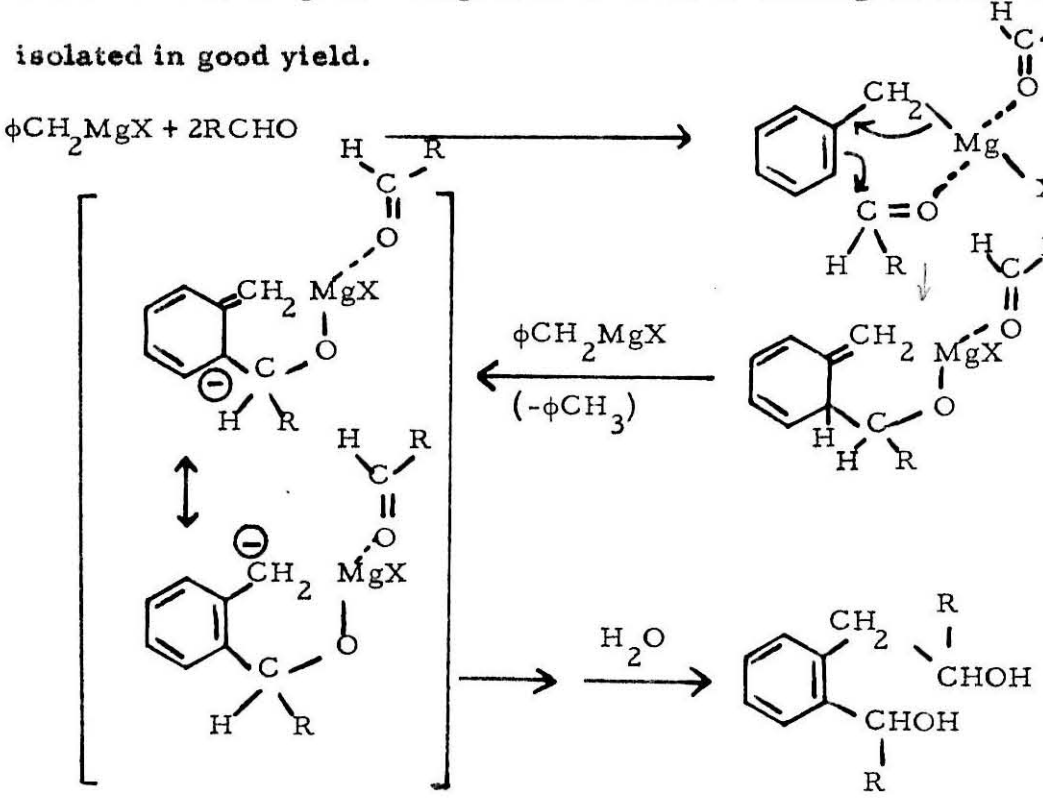


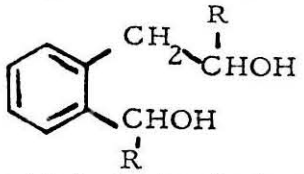
Gilman and Kirby (10) later reported (without details) similar fluctuations in the product composition with the mode of addition in the reactions of benzylmagnesium chloride with ethyl chloroformate and with ethyl formate.

Young and Siegel (18) pursued further this second inadequacy in the Johnson theory. They found for the reaction between benzylmagnesium chloride and citronellal ($RCHO, CH_2{=}C(CH_3)(CH_2)_3CH(CH_3)CH_2CHO$) behavior parallel to that observed by Schmidlin and Garcia-Banus for benzaldehyde. When the aldehyde was added slowly to an excess of the ethereal Grignard reagent the normal product, $\phi CH_2\underset{R}{C}HOH$, was obtained in 80% yield. Inverse addition produced in like yield the disubstituted abnormal product

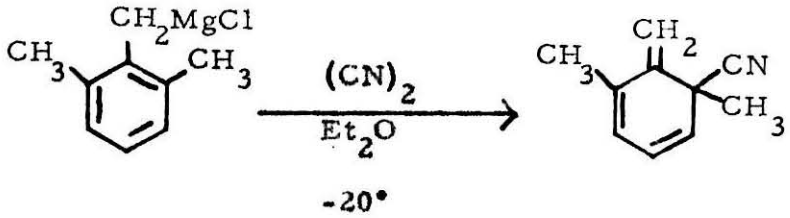


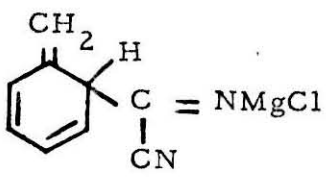
, which lost water upon treatment with potassium acid sulfate to form the isochromane  . The authors concluded that a revision in the Johnson mechanism was demanded by these results and offered a modified scheme for abnormal reaction in the presence of excess aldehyde. They postulated that initially two molecules of the aldehyde form a complex with one of the Grignard reagent. This step was thought to weaken the carbon-magnesium bond more than coordination by a single molecule of reactant, thereby increasing the electron density at the ortho position and so facilitating rearrangement. The second addition step was depicted as being prepared by the action of free Grignard reagent as a base, liberating toluene, which was isolated in good yield.



Siegel, Coburn, and Levering (19) reinvestigated the reaction with benzaldehyde and verified the findings of Schmidlin and Garcia-Banus. Siegel, Boyer, and Joy (20) discovered this behavior to be general for a series of aliphatic aldehydes. Both studies were cited as reinforcement for the hypothesis of Young and Siegel. With the aliphatic aldehydes all the abnormal products were of the structure  , no o-tolyl derivatives being detectable; only formaldehyde leads to an o-tolylcarbinol.

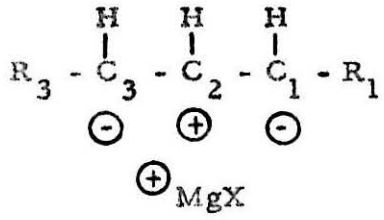
Raaen and Eastham (21) have recently provided definitive evidence on the nature of the intermediate in a rearrangement reaction of benzylmagnesium chloride. These workers discovered cyanogen to be extremely effective in inducing the ortho-abnormal benzylic Grignard reaction, and indeed were able to isolate in 45% yield the anticipated quinonoid product from the reaction between cyanogen and 2,6-dimethylmagnesium chloride.



Furthermore, these workers found that when the mixture from the reaction between benzylmagnesium chloride and cyanogen was hydrolyzed with tritium-labeled water, tritium-labeled o-tolunitrile was obtained. Thus tautomerization of the quinonoid intermediate 

to yield the benzenoid product was demonstrated to occur at least partially in the hydrolysis step. This evidence effectively disproves the mechanism originally offered by Tiffeneau and Delange, which envisages carbon-magnesium bond breaking after the product-forming step and predicts no quinonoid intermediate. It may be taken as support for the cyclic mechanism of Johnson, but still does not refute Schmidlin's early theory based on a quinonoid Grignard reagent.

Finally, Mousseron and Du (20) have proposed that allylic Grignard reagents be considered from the standpoint of the ion pair



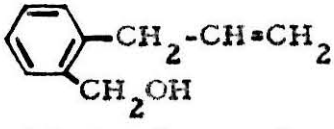
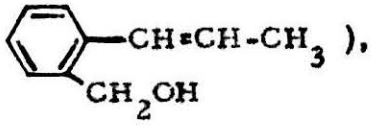
whose structure is determined by the preference of the ion $\oplus MgX$ for C_1 or C_3 depending on the nature of groups R_1 and R_3. The products formed with a reactant Z will depend upon the generally different positional preference of the first-formed complex ion $[ZMgX]^{\oplus}$, varying (in an undefined way) with the properties of molecule Z.

While ethereal Grignard solutions have measurable electrical conductivities, these are so low (23) (specific conductance of benzylmagnesium bromide 5.88×10^{-5} at 20° in 1N ether solution) that the extent of ionization must be very small (24). The carbon-magnesium bond is attributed only 34% ionic character by the Pauling electronegativity relationship (25). The absence of appreciable quantities of free carbanions in ethereal Grignard solutions is further supported by the stability of these

solutions to attack upon the solvent, in contrast to the ease with which organolithium, -sodium, and -potassium compounds remove a β-proton from ether to produce ethylene and ethoxide ion. Mousseron and Du's concept of the intermediate complex $[ZMgX]^{\oplus}$ may only be sustained by assuming that the rate of Grignard reagent dissociation is substantially greater than the rate of product formation. In the absence of empirical support for this view, however, most credence has been placed in hypotheses in which the carbon-magnesium bond is broken subsequent to coordination of the magnesium atom with the donor site of the reacting molecule.

Of all the allylic-type Grignard reagents which have been investigated, the most intensively studied group has been the magnesium derivatives of the simple monosubstituted allyl halides, $RCH{=}CHCH_2X$ and $RCHXCH{=}CH_2$, chiefly with $R{=}CH_3$ or C_6H_5. Here, as with the benzylic systems, research has revealed important synthetic utilities. But uncertainty about the structures of the Grignard reagents has blocked unequivocal establishment of the reaction mechanisms.

Gilman and Harris (9) first studied the Grignard reagent from cinnamyl chloride (26) and found that carbon dioxide, phenylisocyanate, and ethyl chloroformate all reacted to give α-phenylallyl products, namely phenylvinylacetic acid (originally misidentified (8)), phenylvinylacetanilide, and phenylvinylacetic acid, respectively. Inasmuch as Burton and Ingold previously had shown (27) by ozonolysis that cinnamyl bromide,

and therefore with assurance also the less mobile cinnamyl chloride, was uncontaminated with its secondary isomer (1-phenylallyl bromide), an allylic rearrangement accompanies the Grignard transformation of cinnamyl chloride to the products noted. Gilman and Harris interpreted this as probably a free-radical process occurring during preparation of the Grignard reagent and imparting to it the α-phenylallylmagnesium chloride structure, $\phi\underset{\underset{MgCl}{|}}{CH}\text{-}CH{=}CH_2$. The authors point out, however, that on this basis one might expect reaction with formaldehyde to yield some proportion of the carbinol  (or else ), by analogy with the abnormal reaction of formaldehyde with benzylmagnesium chloride; experimentally no ring substitution was found to occur with either formaldehyde or ethyl chloroformate. Gilman and Harris acknowledged the possibility of the primary, cinnamylmagnesium chloride structure, $\phi CH{=}CHCH_2MgCl$, giving rearranged products. Attempts to locate the point of attachment of the magnesium atom by catalytic reduction or by ozonolysis of the olefinic linkage in this and other unsaturated Grignard reagents were, and have continued to be, unsuccessful (9).

In 1939 Young, Ballou and Nozaki (28) proposed that the cinnamyl Grignard reagent was a mixture of primary and secondary allylic isomers, on the strength of an earlier observation (29) that monochloroamine reacts to form only (primary) cinnamylamine, $\phi CH{=}CHCH_2NH_2$, and their own

finding that dilute acid hydrolysis of ethereal cinnamylmagnesium chloride produces a mixture of olefins. The primary and secondary forms were judged to be present in the ratio of 27:73, corresponding to the proportions of propenylbenzene, $\phi CH{=}CHCH_3$, and allylbenzene, $\phi CH_2CH{=}CH_2$, formed on hydrolysis. It was implicit in their interpretation that tautomeric equilibration between isomers of the Grignard reagent is much slower than the rates of hydrolysis. An alternative formulation of the Grignard reagent as a resonant ionic species $[\phi CH{=}CH\text{-}CH_2^{\ominus} \leftrightarrow \phi\overset{\ominus}{C}H\text{-}CH{=}CH_2]^{\oplus}MgCl$ was disfavored. It was argued that such a structure should be susceptible to competition between magnesium and various added metallic ions, resulting in different product mixtures on hydrolysis; experimentally the presence of extraneous ions was found to be without effect (28).

Similar conclusions issued from early research on the allylic butenyl Grignard reagent. However, an additional complication attends this system, the mobile anion tautomerism which exists between the crotyl and α-methylallyl bromides used to prepare the reagent. This situation was studied quantitatively by Young and Winstein (30). The isomeric bromides are separable by careful distillation near 0° at reduced pressures. Their individual densities and refractive indices have been determined, and mixtures may be analyzed from these properties. Both of the pure bromides rearrange to an equilibrium mixture of 14% secondary (α-methylallyl) and 86% primary (crotyl) in a few days at room temperature and much more rapidly at elevated temperatures.

It was anticipated by Young, Prater, and Winstein (31) that the butenyl bromide equilibrium could also be measured by conversion of the isomeric bromide mixture to the corresponding Grignard reagents followed by analysis of the butenes generated on hydrolysis. Consequently it was remarkable that the proportions of butenes obtained (32) (56.4 ± 2.0% 1-butene, 26.5 ± 1.4% cis-2-butene, and 17.2 ± 3% trans-2-butene) were found to be independent of the composition of the starting bromide mixture (from 20 to 90% crotyl bromide). The butenyl chlorides were observed to behave in the same way (33) and to produce a mixture of butenes very nearly identical to that from the bromides. If it is assumed that the net rearrangement in the transformation of the halobutenes to butenes occurs entirely in the preparation of the Grignard reagent, then butenylmagnesium bromide exists as an equilibrium mixture corresponding to the butenes formed, i.e. 27% cis-primary, 17% trans-primary, and 56% secondary (34). This interpretation predicts a 65:35 ratio of primary and secondary butenyl groups in the octadienes from reaction of the Grignard reagent with the equilibrated butenyl bromides. The proportions found experimentally by Lespieau and Heitzmann (35), ca. 70:30, were noted to be in good agreement.

Young and co-workers provided further evidence on the nature of such butenyl rearrangements by reducing the halides to butenes in the presence of finely divided metals suspended in boiling 80% ethanol, conditions where very short-lived butenylmetallic compounds may be presumed to exist. Zinc (33,36), chromium, tin, cadmium, and amalgamated

aluminum (37) were employed. In all cases the proportions of butenes were insensitive to the proportions of isomeric butenyl halides taken and to the solvent composition (33) but were a function of the metal used. The results of this group of reductions make it clear that equilibration of the intermediate butenylmetallic compounds is a very rapid process indeed and probably takes place during their formation. It seems reasonable to assume the same conclusion valid for Grignard reagent formation in ether.

Young and Pokras (38) treated butenylmagnesium bromide in ether with dioxane and hydrolyzed separately the supernatant solution containing halogen-free dibutenylmagnesium and the precipitate containing, presumably, butenylmagnesium bromide and magnesium bromide as dioxane complexes. The latter phase was found to give the same butene mixture as had the Grignard reagent in ether, but the dibutenylmagnesium solution yielded a different butene mixture, 44.5% 1-butene, 32.2% cis-2-butene, and 23.2% trans-2-butene. It was judged therefrom that the formation of dibutenylmagnesium by dioxane-induced displacement of the Schlenk equilibrium

$$2RMgX \rightleftharpoons R_2Mg + MgX_2 \quad , \quad X = \text{halogen}$$

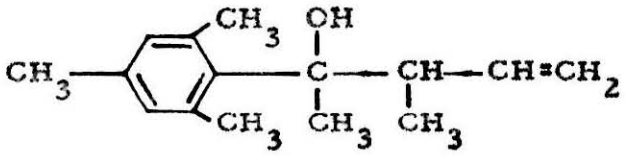
involves an allylic rearrangement in intermediate carbanions, which are therefore not the species responsible for the equilibration initially attending preparation of the Grignard reagent. Young and Pokras (38) offered further support for the postulated equilibrium composition of butenylmagnesium bromide in that reaction of the Grignard reagent with oxygen to

form alcohols or with allyl bromide to form heptadienes was found to lead to the same proportions of primary and secondary radicals as those produced by the action of water.

Interpretation of butenylmagnesium bromide as a mixture of allylic isomers, however, became increasingly challenged from 1944 on by the studies of Young and co-workers on the behavior of this reagent toward a variety of carbonyl compounds and in several new displacement reactions. Carbonation of the Grignard reagent (39) and of halogen-free dibutenylmagnesium (40) was discovered to produce exclusively methylvinylacetic acid. Likewise, butenylmagnesium bromide was found to add to formaldehyde, acetaldehyde, and acetone in excellent yields to give in each case products containing only the secondary butenyl radical (40). Thus, while carbon dioxide and acetone are normal reactants toward benzylmagnesium chloride, and formaldehyde, acetaldehyde, and propionaldehyde react with differing degrees of rearrangement, these molecules all lead solely to α-methylallyl products with butenylmagnesium bromide. The same exclusive behavior of the butenyl Grignard reagent was also noted (41) with phenyl isocyanate and ethyl formate, and ethyl orthoformate gave at least 96% secondary butenyl derivative.

The reactivity of butenylmagnesium bromide toward sterically hindered ketones is particularly remarkable in comparison with the behavior of saturated aliphatic Grignard reagents under the same conditions. Butenylmagnesium bromide adds in 89% yield to diisopropyl ketone, 85% as the α-methylallyl group (15% crotyl) (42); isopropylmagnesium bromide

gives only enolization (29% yield) and reduction (65% yield) products with this ketone (43). The butenyl Grignard reagent also adds to acetomesitylene to produce methyl-α-methylallylmesitylcarbinol (44, 45)



in 83% yield, whereas ethylmagnesium bromide forms no addition product. Butenylmagnesium bromide likewise reacts by addition with benzophenone, isobutyrylmesitylene, and pentamethylacetone to give principally, if not exclusively, α-methylallyl derivatives (46). Only with hexamethylacetone was crowding about the carbonyl group sufficiently severe to force the introduction of the butenyl group in exclusively its primary (crotyl) form (46).

Distinctive behavior has been discovered in the reactions of the butenyl Grignard reagent with α,β-unsaturated carbonyl compounds. Phenyl vinyl ketone and t-butyl cinnamate are known to react efficiently by 1,4-addition with alkyl and phenylmagnesium bromides (47, 48). Butenylmagnesium bromide also reacts completely with these compounds but yields no 1,4-addition products (41).

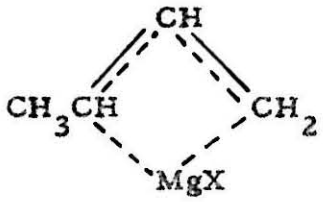
Young, Roberts, and Wax investigated in detail the coupling reactions of butenylmagnesium bromide with allylic halides (49). The results are complicated, owing to the several possibilities for rearrangement before and during reaction, but here again it is evident that the Grignard reagent strongly tends to introduce the (secondary) α-methylallyl radical. Koch has observed the same preference in the coupling reaction of cinnamyl chloride over magnesium in ether (50).

Finally, studies on the reactions of butenylmagnesium bromide with an assortment of active hydrogen compounds have contributed further to an understanding of this reagent. It will be recalled that the first reaction studied of butenylmagnesium bromide was cleavage with dilute acid. In 1946 Young and Roberts (45) reported that treatment of butenylmagnesium bromide in ether with phenylacetylene gave immediately a butene mixture of at least 93% 1-butene (in contrast to 56% 1-butene formed on hydrolysis). Wilson, Roberts, and Young (51) tested two alcohols, several carboxylic acids, hydrogen chloride, anhydrous ammonium iodide, benzhydryl mesityl ketone, and dibenzenesulfonylmethane. In each of these cases 1-butene predominated over cis- and trans-2-butenes in the product mixture, although the proportions were found to be markedly sensitive to the nature of the active hydrogen compound and the solvent (or its absence).

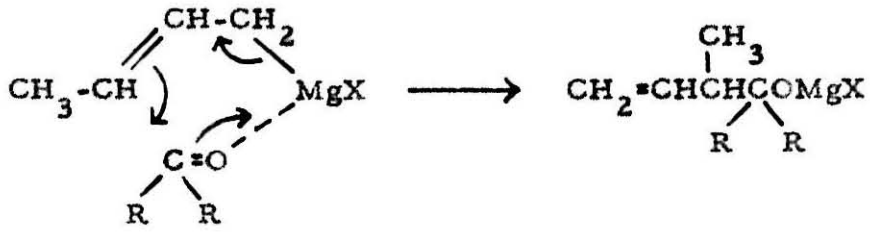
Thus a weighty and diverse body of evidence published between 1944 and 1950 rendered increasingly unsatisfactory the initially postulated constitution of the butenyl Grignard reagent as a mixture of crotyl (44%) and α-methylallyl (56%) magnesium bromides, equilibrated, following their preparation, less rapidly than their rates of subsequent reactions. The early view fails to account for 1) the striking specificity of the reagent in introducing the secondary butenyl group in carbonyl addition reactions, 2) the extraordinary capacity of butenylmagnesium bromide to add to sterically hindered ketones, where saturated aliphatic Grignard reagents are ineffective, 3) the pronounced driving force for 1,2- instead

of 1,4-addition to conjugated carbonyl compounds, and 4) the varying relative amounts of 1- and 2-butenes produced in reactions of butenylmagnesium bromide with different active hydrogen molecules.

In consideration of these facts Young and Roberts proposed an alternative theory for the nature of the butenyl Grignard reagent (41, 42, 45, 52). They asserted that the remarkable specificity exhibited by the reagent in addition reactions and in nucleophilic displacements upon allylic chlorides could not be accommodated either by a slowly or rapidly interconverting mixture of primary and secondary isomers, or by a static, resonance species in which both the α- and γ-carbon atoms were partially bonded to the magnesium atom.

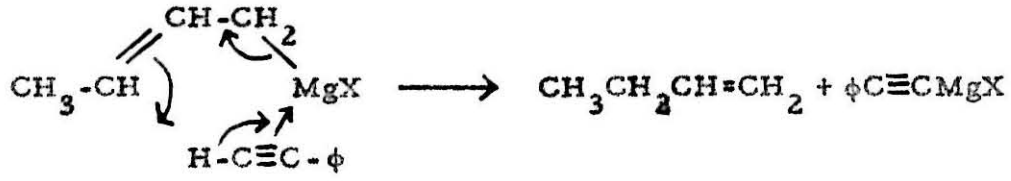


They argued further that the sharply divergent behavior of butenylmagnesium bromide from saturated aliphatic Grignard reagents toward sterically hindered and toward conjugated carbonyl compounds demonstrated the operation of a mechanism for the butenyl Grignard reagent which was not available to the latter. This they postulated to be initial coordination between the carbonyl oxygen and the magnesium atom of the crotyl Grignard reagent, followed by product formation through a six-membered cyclic transition state, giving rise to an α-methylallyl derivative.



(Eq. 3)

It will be recognized that Equation 3 is precisely analogous to the mechanism of Johnson for the formation of abnormal products from benzylmagnesium chloride (Eq. 2). Since the latter mechanism must proceed at the expense of the resonance stabilization of the benzene ring, the corresponding open-chain mode of reaction should be relatively more facile (and also does not require a subsequent allylic hydrogen shift to achieve product stability). Thus, the butenyl Grignard reagent is judged to exist solely in its primary form, and reactions which generate product mixtures are interpreted in terms of competing mechanisms. In general, the course of reaction is related to a reactant's ability to form initially a coordination complex with the Grignard reagent. Those compounds structurally well disposed toward such complex formation will demonstrate a preference for reaction by Equation 3. In this scheme, the basic center in the co-reactant molecule need not be a carbonyl oxygen atom. The π-electrons in a carbon-carbon triple bond, for example, may function to complex with the Grignard reagent's magnesium atom and initiate reaction by a cyclic course; at least 93% of the butenes resulting from the cleavage of butenylmagnesium bromide by phenylacetylene is 1-butene, as cited above, presumably formed by the preferred pathway (45)



In contrast, other reactants less suitable for initial complex formation may not exploit the mechanism of Equation 3 and are expected to react less discriminately at either the α- or γ-carbon atom; ammonium iodide, which has no unshared electrons available for complexing, cleaves butenylmagnesium bromide with the formation of 58% 2-butenes and 42% 1-butene (51).

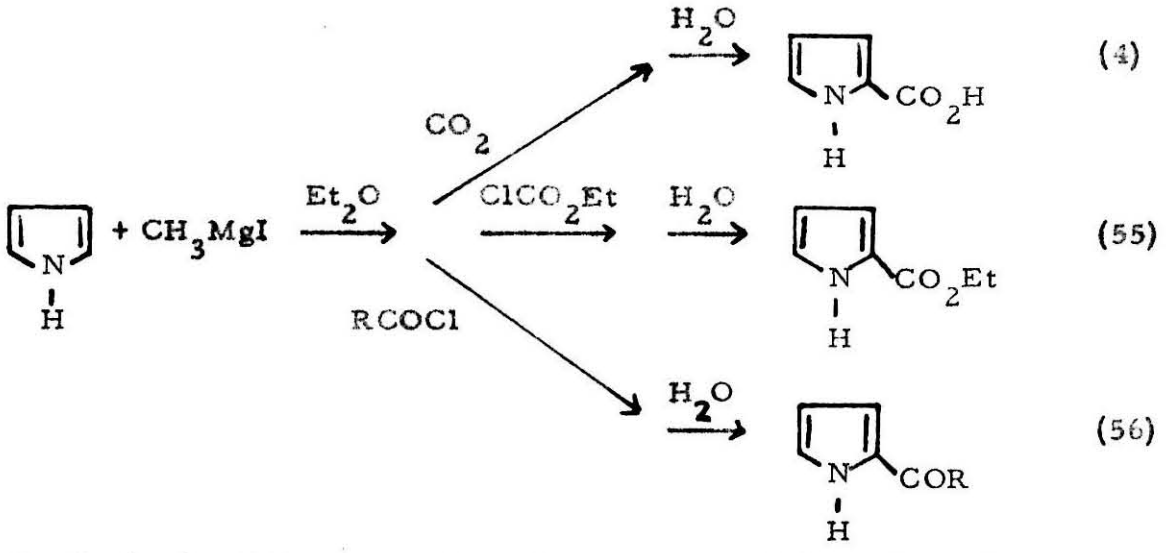
Thus, primary complex formation has been judged to be a determinant of reactive specificity in the above allylic Grignard reactions. Reactions of the highly ionic cinnamylsodium, however, would not be expected to require such an important role for coordination prior to product formation. Accordingly, it is not unreasonable that the reactions of cinnamylsodium in liquid ammonia with methanol, ammonium chloride powder, and phenylacetylene show no effect of the nature of the proton donor upon the isomeric composition of the product (53).

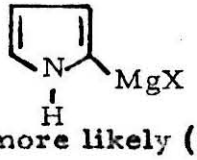
Recently DeWolfe, Hagmann, and Young (54) reported the ultraviolet absorption spectra of cinnamylmagnesium bromide and of dicinnamylmagnesium. Their close resemblance to those of trans-propenylbenzene and cinnamyl alcohol was taken as support for the formulation of the Grignard reagent in ether solution as the unionized primary isomer.

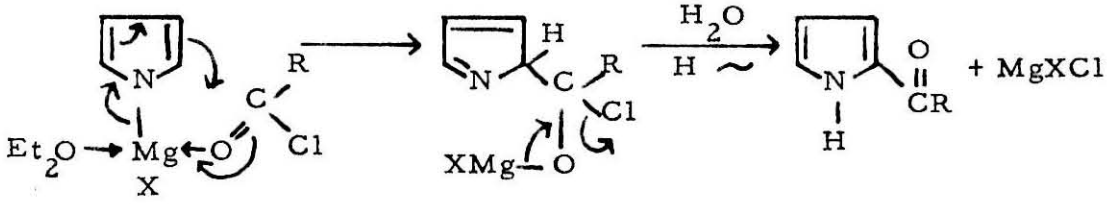
In summary, then, this physical evidence and the accumulation of chemical data have been found best interpreted in terms of the primary

benzyl, cinnamyl, and butenyl Grignard reagents, associated with a distinctive cyclic mechanism responsible for preferential introduction of the corresponding secondary allylic group in suitable cases.

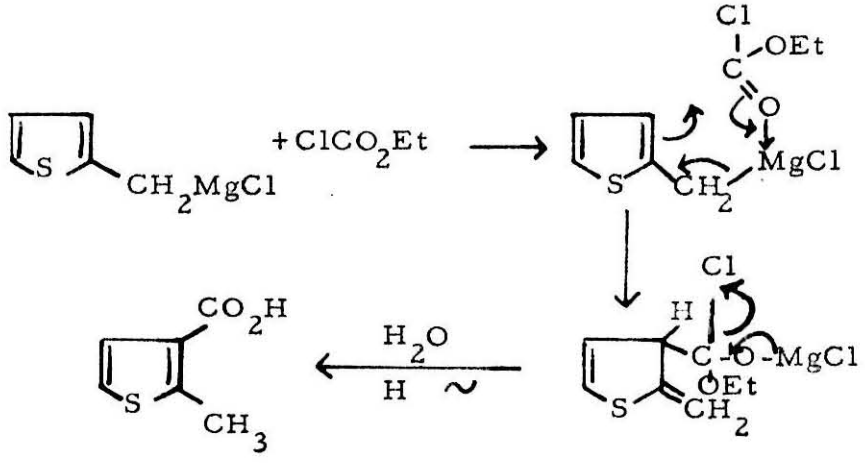
This theory seems additionally useful in application to the reactions of other allylic-type Grignard reagents whose mechanisms have received less study. For example, pyrrylmagnesium iodide demonstrates a general preference for the formation of 2-pyrryl derivatives.



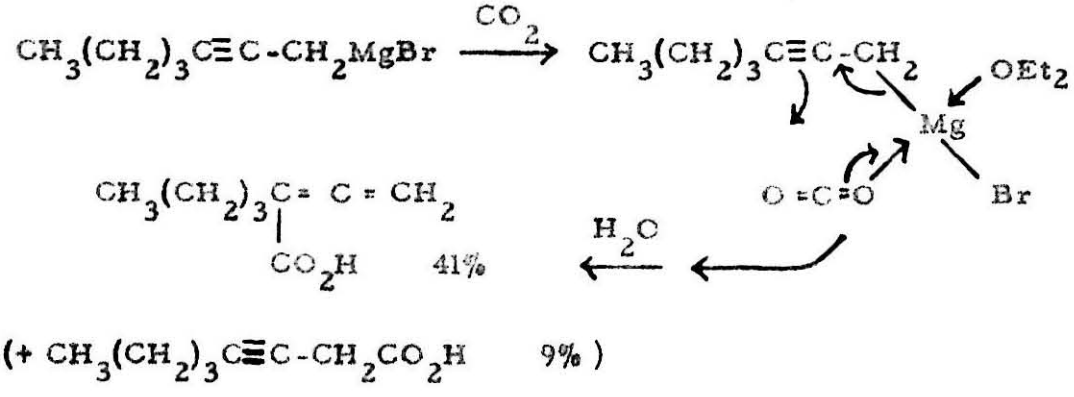
On the basis of these reactions the structure of the Grignard reagent has been argued to be (4, 55, 56, 57)  yet the structure  would seem much more likely (58) in consideration of the expected greater acidity of the nitrogen-bound proton in the starting material and the related greater ability of nitrogen to bear negative charge in the Grignard reagent. The latter structure can be readily accommodated by postulating for its reactions a cyclic transition state of five ring members accompanied by a double allylic electronic rearrangement, e.g.



An analogous mechanism has been suggested (59) to serve the rearrangement reactions of 2-thenylmagnesium chloride, e.g.



The preference of a number of propargylic Grignard reagents to form allenic acids upon carbonation (3, 60) may possibly also be due to the operation of a cyclic mechanism, such as the following.



(The linearity of the C≡C-C grouping, however, seems from models to prevent this sytem from assuming as favorable a geometry for formation of the new carbon-carbon bond as in other cases.)

Thus, one mechanism for the rearrangement reactions of a variety of allylic-type Grignard reagents seems highly attractive on chemical grounds. But it cannot be considered proved, nor its alternatives excluded with certainty, since the structures of these highly mobile Grignard reagents may not be assigned unambiguously from chemical evidence. The advent of high-resolution nuclear magnetic resonance spectroscopy now offers a solution to this problem, since herein lies a non-destructive, sensitive physical method for obtaining structural information from permanent samples, in ordinary glass tubing, of concentrated ethereal Grignard solutions.

EXPERIMENTAL RESULTS AND INTERPRETATION (61)

A study of the structures of Grignard reagents by nuclear magnetic resonance (n.m.r.) spectroscopy depended at the outset upon fulfillment of several experimental requisites. It was necessary to be able to prepare a clear solution of the Grignard reagent in high yield and in sufficiently high concentration to produce distinct n.m.r. signals from the protons in the solute. It was important to find a solvent both chemically suitable and as free as possible from n.m.r. absorption in regions of the spectrum containing critical solute peaks. It was essential to be able to identify any n.m.r. signals caused by impurities in the samples. When this work was undertaken no examples of Grignard reagent n.m.r. spectra were found in the literature.

A potential source of impurities in the preparation of any Grignard reagent is the coupling reaction which can take place between the freshly formed Grignard reagent and the starting halogen compound.

$$RMgX + RX \longrightarrow R\text{-}R + MgX_2$$

The occurrence of this side reaction is quite common, but in most cases it proceeds in negligibly low yield. It becomes a more severe problem for specially reactive halides, such as allylic bromides. Indeed, the predominance of the coupling reaction frustrated early attempts to

prepare allylmagnesium bromide. Gilman and McGlumphey (62) in 1928 reported the first successful preparation of this Grignard reagent, by means of a novel technique. Their procedure (based on the original version of Gilliland and Blanchard (63)) consisted of adding allyl bromide slowly to a column of stirred magnesium turnings while ether was being continuously distilled from an attached flask, condensed, and returned to the flask by way of the column of magnesium. In this manner the allyl bromide was highly diluted with fresh ether at the top of the column before reacting with the magnesium, while the resulting non-volatile Grignard reagent accumulated in the flask below. Yields of 90% were reported. Gilman and Harris (64) used a modified model of this "cyclic reactor" in the preparation of cinnamylmagnesium chloride. In 1950 Rowlands, Greenlee and Boord presented a paper, published only in abstract (65), on the construction and operation of a refined cyclic reactor. Several other workers have reported excellent yields of otherwise difficultly accessible Grignard reagents by the use of this apparatus (66) (although its details have never been published). In the present research, such a cyclic reactor was constructed and employed in the preparation of allylmagnesium bromide and several methyl-substituted homologs. Important features in its successful operation were the use of amalgamated magnesium turnings (prepared by treating the magnesium in situ with mercuric bromide dissolved in ether) and the incorporation of an upward loop in the return line from

the reaction column to the terminal flask, which kept the magnesium immersed in ether throughout. A thorough description of the cyclic reactor and its use are included in the Experimental Details section.

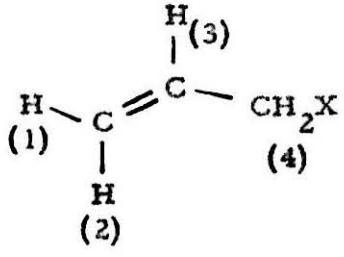
Ethyl ether was employed as the solvent for all the Grignard reagents reported. It allowed the preparation of clear, colorless viscous samples of up to ca. 15 mole-% Grignard reagent (as RMgBr). The n.m.r. spectra of these solutions were in general sharply resolved, and fortuitously there was no confounding overlap of solvent and solute absorption bands in any case.

The reagents were initially prepared in dilute ether solution and then pressure filtered through sintered glass to remove excess magnesium, salts, and other suspended solids. Finally the solutions were concentrated to saturation and decanted into attached n.m.r. sample tubes (5-mm. o.d. Pyrex), which were broken off and quickly sealed. Any solids which remained in the samples could be precipitated by centrifugation and the clear supernatant solutions decanted into fresh tubes. All operations were carried out under an atmosphere of purified nitrogen.

N.m.r. spectra were all taken at a resonant frequency of 60 Mc. Chemical shifts were measured by the audio-oscillator side-band-superimposition method (67) with the aid of a precise frequency counter; they are expressed throughout in cycles per second (c.p.s.) relative to tetramethylsilane as an internal standard. Chemical shifts so measured are judged to be accurate to $\pm$ 0.2 c.p.s. within each

sample. However, Grignard reagent chemical shifts relative to those of the solvent have been observed to vary with the sample concentration several c.p.s. over the range of concentrated solutions studied. Accordingly, absolute line positions will be discussed only to the nearest c.p.s.

Of principal interest in this study was the structure of butenylmagnesium bromide, since its reactions have been extensively studied. As an aid in interpreting the n.m.r. spectrum of the butenyl Grignard reagent, allylmagnesium bromide in ether was first prepared and its spectrum taken(Figure 1). The spectrum of this substance is amazingly more simple than expected. It may be compared with those of allylbenzene(Figure 2) and allyl bromide(Figure 3), both of which evince four magnetically (and chemically) distinct proton types in the allyl group.



X = C_6H_5, Br

The spectrum of allylmagnesium bromide has a simple two-band pattern characteristic of an AX_4 proton grouping (68), i.e., one in which the four terminal hydrogen atoms are all equivalent with respect to

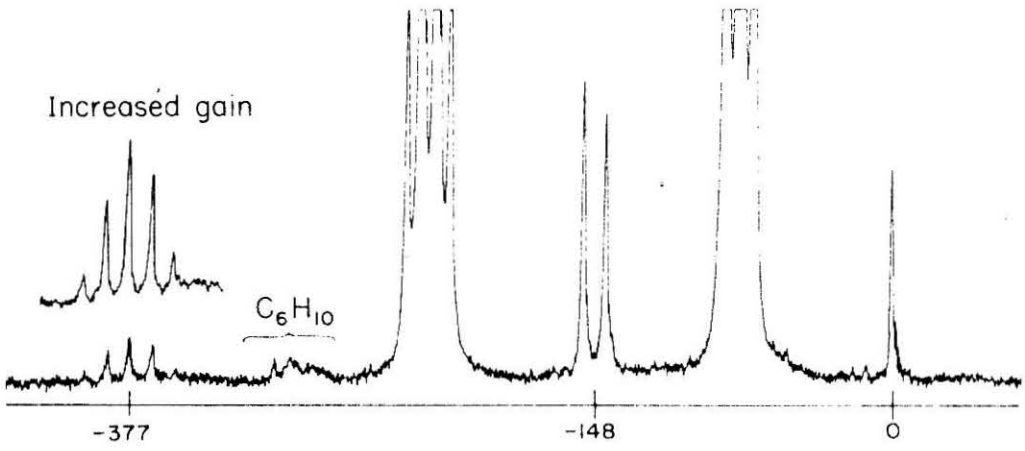


Fig. 1. - Proton magnetic resonance spectrum of allylmagnesium bromide in ether, plus tetramethylsilane as internal standard. Chemical shifts are in c.p.s. The off-scale bands are due to the ether, and the signals designated C_6H_{10} are due to diallyl (coupling product).

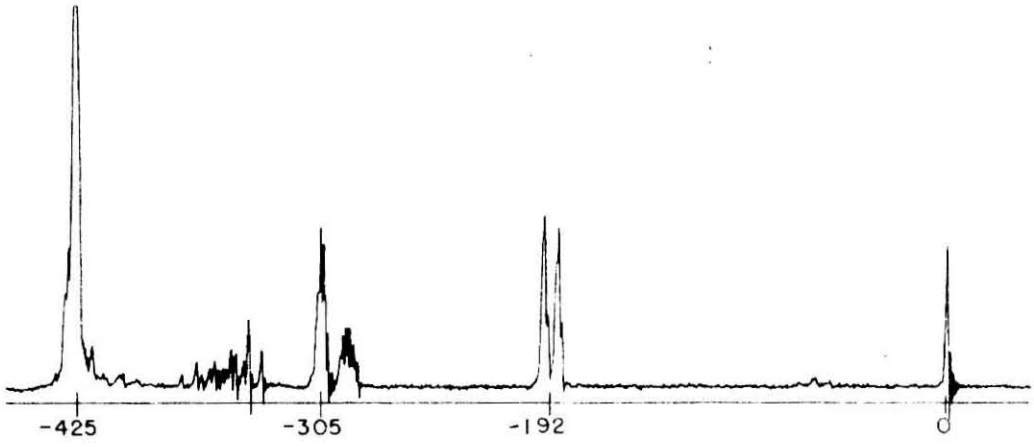


Fig. 2. - Proton magnetic resonance spectrum of allylbenzene, plus tetramethylsilane as internal standard. Chemical shifts are in c.p.s.

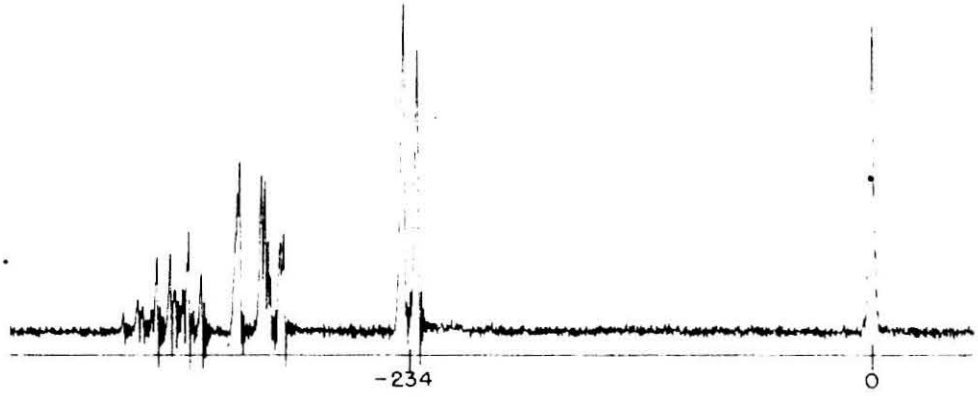
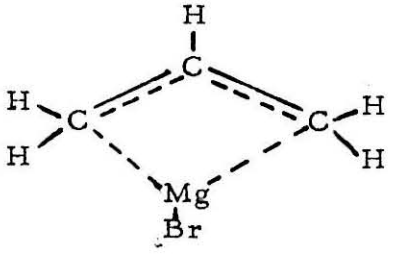


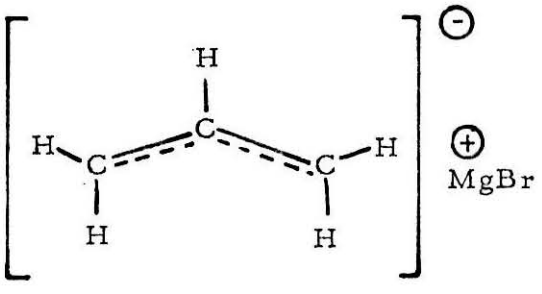
Fig. 3. - Proton magnetic resonance spectrum of allyl bromide, plus tetramethylsilane as internal standard. Chemical shifts are in c.p.s.

the tertiary hydrogen atom and each other. The chemical shift separating the A and X protons, 229 c.p.s., is much greater than the spin-spin coupling constant between them, J_{AX} = 10.7 c.p.s., resulting in a symmetrical quintet of resonance lines for A and a doublet, of four times the intensity, for the resonance of X. The signals designated C_6H_{10} are due to a small amount of diallyl formed by coupling during preparation of the Grignard reagent, as verified by the spectrum of a sample to which diallyl was added deliberately.

The coincident chemical shifts of the α and γ protons in allylmagnesium bromide might be rationalized in terms of (a) a symmetrical bridged structure such as III, (b) the completely ionic structure IV, or (c) a very rapid equilibrium, V, between conventional structures.



III

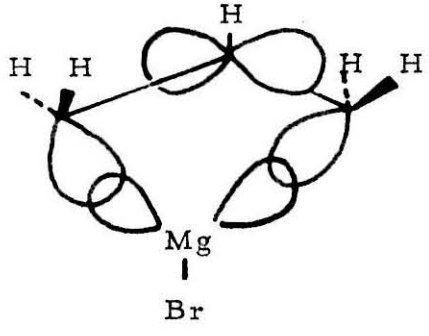


IV

$$\underset{\gamma\quad\beta\quad\alpha}{BrMg\text{-}CH_2\text{-}CH{=}CH_2} \rightleftharpoons \underset{\gamma\quad\beta\quad\alpha}{CH_2{=}CH\text{-}CH_2\text{-}MgBr}$$

V

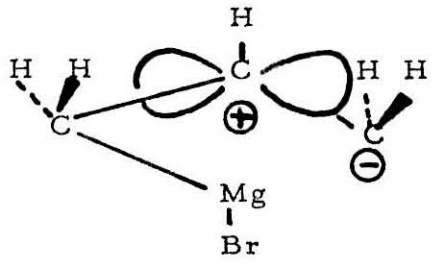
The spectrum requires, however, that there be no differentiation of the methylene protons into cis and trans types. Structure IV, in which all the carbon and hydrogen atoms are coplanar, is unsatisfactory on this count; rotation would certainly not be expected to occur with any rapidity about C-C bonds with 50% double-bond character. The same objection against III may be avoided by postulating a configuration such as IIIa, in which the β proton is staggered between the α and the γ protons. But in IIIa the adjacent atomic orbitals which must accommodate the unsaturation electrons lie in planes perpendicular to each other. Orbital overlap is thus minimal and least favorable for the formation of a stable molecular orbital to provide



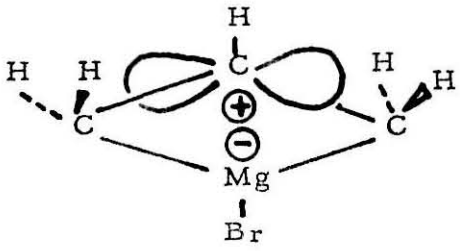
IIIa

for π-electron delocalization. It is apparent that significant contributions to the electronic structure of IIIa would have to be made by destabilized configurations in which charge is isolated at the central carbon atom, as in IIIb and IIIc.

Equilibrium V appears to be the most reasonable interpretation of the allylmagnesium bromide spectrum. If a proton undergoes



IIIb



IIIc

exchange between two chemical environments A and B, there will be a gradual coalescence of the separate resonance signals for protons at A and B as the respective mean lifetimes in these environments decrease. It has been shown (69) that if the mean lifetimes τ_A and τ_B (in seconds) are equal, the two resonance lines will just coalesce when

$$\tau_A = \sqrt{2}\ (\pi \delta_{AB}H)^{-1} \quad ,$$

where $\delta_{AB}H$ equals the chemical shift (in c.p.s.) between protons at A and B in the absence of exchange. Smaller values of τ_A lead to a sharper single peak. Most examples of such exchange processes involve the breaking and forming of bonds to hydrogen. In the present case environments A and B are the olefinic and primary methylene positions, which are equilibrated through tautomeric exchange of the magnesium atom. It is possible to calculate from the data presented in Table 3 a lower limit for the frequency of magnesium exchange

between the α and γ positions necessary to cause merging of the α- and γ-proton resonances.

Table 3

$\delta_\alpha H$, Chemical Shift of α Protons
(tetramethylsilane internal reference)

R	RCH_2Br	RCH_2MgBr in $(C_2H_5)_2O$	$\Delta(\delta_\alpha H)$ (RCH_2MgBr -RCH_2Br
CH_3-	-204 c.p.s.	+ 38 c.p.s.	242 c.p.s.
CH_2=CH-	-234	-148	86
CH_3CH=CH-	-234	- 43	191
$(CH_3)_2C$=CH-	-236	- 35	201

If the shift in α-methylene line position found between ethyl bromide and ethylmagnesium bromide in ether (242 c.p.s.) is taken also to separate the α resonance of allyl bromide from that of a hypothetical static molecule of allylmagnesium bromide in ether, then the latter would be expected to occur at +8 c.p.s. The observed methylene shift in the allyl Grignard reagent (-148 c.p.s.) represents an average between the α and γ values for a non-exchanging molecule, so

$$\frac{\delta_{\gamma}H + 8}{2} = -148$$

$$\delta_{\gamma}H = -304 \text{ c.p.s.}$$

and $$\delta_{a\gamma}H = 8-(-304) = 312 \text{ c.p.s.}$$

Therefore $$\tau_{a} = \tau_{\gamma} << \sqrt{2}\,(312\pi)^{-1}$$

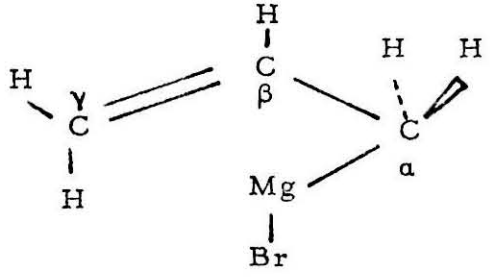
$$<< 0.001 \text{ sec.}$$

and the rate constant for tautomeric exchange (69c)

$$k >> (0.001)^{-1}$$

$$>> 10^{3} \text{ sec.}^{-1}$$

The conventional structure for each tautomer in V is Va.



Va

It is seen that in the C_{a}-C_{β} rotational conformer pictured, that in which the magnesium atom is in nearest proximity to C_{γ}, the α-methylene protons are in identical environments. The γ-methylene protons will, in addition, have identical average environments if it is

reasonably assumed that upon migration of the magnesium atom to the γ position the trans-γ hydrogen atom is displaced with equal probability either into or out from the plane of the diagram. From the resulting symmetrical conformation either hydrogen atom can, upon a second migration, assume either the cis or trans orientation with equal likelihood. The absorption lines for the cis- and trans-γ-protons will merge sharply if exchange between environments by partial rotation is such that

$$\tau_{cis} = \tau_{trans} \ll \sqrt{2} \quad (20\ \pi)^{-1}$$

$$\ll \quad 0.02 \text{ sec.},$$

since the cis-trans separation in the absence of interchange would be expected to be ca. 20 c.p.s. (70). This upper lifetime limit, however, is an order of magnitude larger than that already calculated to be imposed by equilibration between the α and γ positions. The latter, therefore, becomes the governing value, since the same exchange process is responsible for the merging of resonance lines in both cases. It is to be noted that rapid, complete rotation about the C-C single bond in species Va need not be postulated in order to explain the n.m.r. spectrum of allylmagnesium bromide. Furthermore, the total volume in space occupied by the exchanging magnesium atom may be pictured as quite closely confined between C_α and C_γ, conferring a low activation entropy upon the tautomerization. In the foregoing interpretation it has been assumed that V is an intramolecular process.

Although the experimental results presented up to this point cannot ascertain whether the equilibrium is established by intra- or intermolecular processes, evidence will be presented later which supports the assumption made.

The spectrum of β-methylallylmagnesium bromide in ether (Figure 4) is consistent with the proposed tautomerism and incompatible with alternatives analogous to III and IV . In this compound there are no protons on adjoining carbon atoms, and spin-spin splitting is not observed. The Grignard reagent spectrum thus consists of single lines for the methylene (relative intensity 4) and methyl (relative intensity 3) protons. Di-β-methylallyl peaks (C_8H_{14}) in the spectrum were easily identified from the spectrum of the independently prepared diene. (The formation of this impurity in amounts upwards of 10 mole-% of the Grignard reagent persisted through several preparations under varied conditions.)

The n.m.r. spectrum of butenylmagnesium bromide in ether is shown in Figure 5. The peaks due to the minor amounts of octadiene coupling products (C_8H_{14}) formed were again identified as reinforced signals in the spectrum of a sample containing added dibutenyls. Sidebands caused by the natural abundance (1.1%) of ^{13}C in the ether methylene and methyl groups (71) are also prominent in this spectrum and are designated ^{13}C. Because of the asymmetry introduced by the methyl group in this Grignard reagent its spectrum is more complex than that

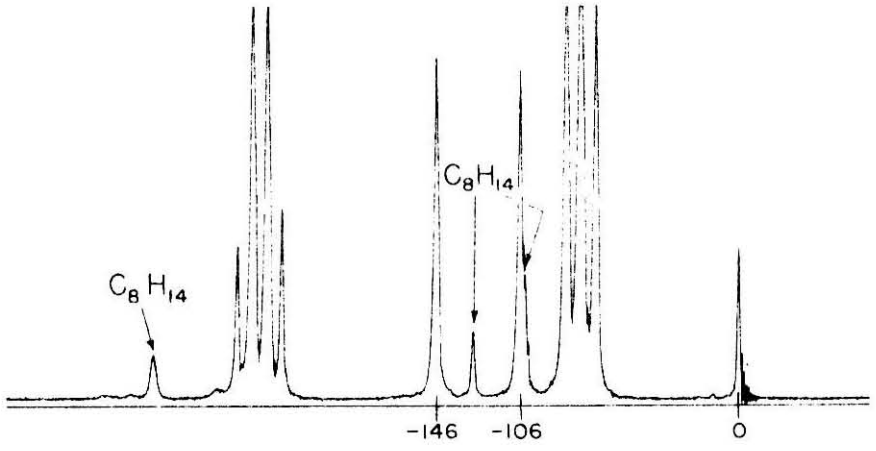


Fig. 4. - Proton magnetic resonance spectrum of β-methylallylmagnesium bromide in ether, plus tetramethylsilane as internal standard. Chemical shifts are in c.p.s. The signals designated C_8H_{14} are due to di-β-methylallyl (coupling product).

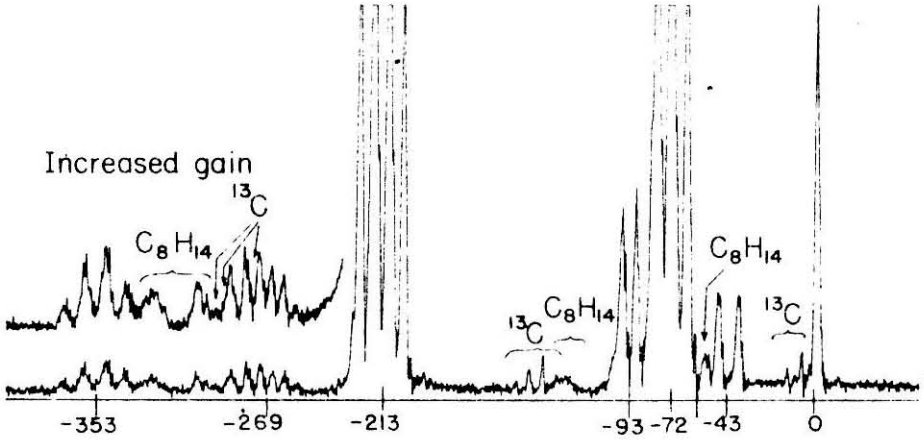
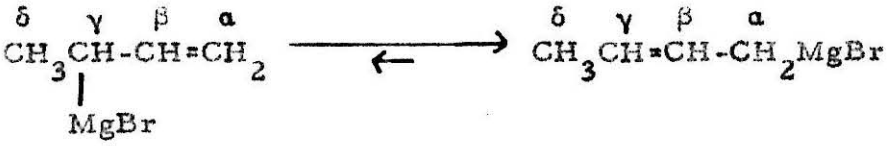


Fig. 5. - Proton magnetic resonance spectrum of butenylmagnesium bromide in ether, plus tetramethylsilane as internal standard. Chemical shifts are in c.p.s. The signals designated C_8H_{14} are due to octadiene coupling products, and those designated ^{13}C are sidebands due to naturally abundant ^{13}C in the ether.

of the parent allylmagnesium bromide. The spectrum of butenylmagnesium bromide may be explained reasonably by an analogous tautomeric model, VI, in which the primary (crotyl) isomer predominates in the equilibrium. This position of equilibrium is in accord with the



VI

well known greater stability of negative charge at a primary than at a secondary carbon atom (72) as well as the preference for a non-terminal over a terminal double bond (73).

The doublet at -43 c.p.s. (relative intensity 2) is thus due to the α-methylene protons, most highly shielded because of the greater statistical contribution of the primary tautomer to the composite structure "seen" by n.m.r. The β-proton resonance occurs as a quartet (relative intensity 1) at -353 c.p.s., split by equal, or very nearly equal, spin-spin interaction with the adjacent CH_{2_α} and CH_γ protons. The δ-methyl resonance is assigned to the doublet (relative intensity 3) at -93 c.p.s. The band remaining as the γ-methine absorption signal is a rather complicated pattern of six apparent lines. In order to demonstrate unambiguously the congruity of this pattern with the proposed rapid equilibrium VI, a mathematical analysis of the butenylmagnesium bromide spin system was carried out.

The quantum-mechanical analysis of an n.m.r. spectrum involves calculation for a suitable model spin system of the complete set of stationary-state spin wave functions, their respective energies, and the relative probabilities for induced transitions between the various levels (74). Chemical shift and spin-spin coupling parameters are adjusted empirically to achieve correspondence between the calculated and observed spectra. The butenyl group is a seven-spin system of low symmetry, whose exact analysis would require solution of a 7x7 determinant, a formidable algebraic problem. In the case at hand, however, a complete solution was not necessary, since the focus of attention was the γ-proton resonance pattern only. As a first approximation, therefore, interaction was assumed negligible between the α and γ protons, reducing the problem to one of five spins, an ABX_3 type (68).

$$\overset{\delta}{CH_3}\text{-}\overset{\gamma}{CH}\text{-}\overset{\beta}{CH}\text{-}\overset{\alpha}{CH_2}\text{-MgBr}$$

X_3 B A

The general calculation of energy levels and allowed transitions for the ABX_3 system has been published by Fessenden and Waugh (75), whose results may be used as the basis for analysis of specific cases. A further simplification was achieved, however, by treating the five-spin ensemble as the superimposition of two BX_3 systems, representing the two line positions for the B proton determined by interaction with the A proton. In other words, the spin-spin couplings of the B

proton with the A proton and with the X_3 protons were dealt with separately and then combined. The AB sub-system was considered first. This is the case for which two neighboring protons have a comparable chemical shift and spin-spin coupling constant. Here the n.m.r. spectrum is no longer simply the two symmetrical doublets which are observed when the chemical shift is much greater than the coupling constant (an AX system) (76). In mathematical terms, it is necessary to consider mixing between the spin states $\alpha\beta$ and $\beta\alpha$, which have the same total spin (0) but differ in the spins of the A and B protons (69b). General solution of the AB system (77) has shown that the splitting of the multiplets is still J_{AB}, but the distance between the multiplet centers is no longer $\delta_{AB}H$ but $\sqrt{J^2 + \delta_{AB}^2 H^2}$.

The intensities of the four lines are given by

$$\frac{\text{Intensity of outer lines}}{\text{Intensity of inner lines}} = \left(\frac{1+Q}{1-Q}\right)^2$$

$$\text{where } Q = \frac{J_{AB}}{\delta_{AB}H + \sqrt{J_{AB}^2 + \delta_{AB}^2 H^2}}$$

The frequencies and intensities of the two B lines were determined according to these relationships. Next, the splitting of each of these lines by the X_3 group (the coupling constant being much smaller than the chemical shift) produced a simple symmetrical quartet with intensities in the ratio 1:3:3:1 (76). Finally, the results of the BX_3 and AB

calculations were combined to yield the desired B-proton spectrum. The coupling constant J_{AB} = 10.1 c.p.s. was obtained from the splitting observed in the A-proton quartet, and J_{BX} = 6.0 c.p.s. from the observed splitting of the X_3-group doublet. The chemical shift $\delta_{AB}H$ = 83.0 c.p.s. was calculated from the relationship cited above,

Observed separation of multiplet centers,	$=\sqrt{J_{AB}^2 + \delta_{AB}^2 H^2}$.
83.6 c.p.s.	

The calculated γ-proton spectrum is presented schematically in Figure 6. Line frequencies were calculated relative to the unsplit γ-proton (B-proton) absorption as zero and then related to tetramethylsilane. If lines 3+4 and 5+6 are combined (separations < 2.0 c.p.s. in each case) the calculated spectrum becomes a nearly symmetrical sextet whose three low-field peaks are uniformly reinforced relative to their high-field counterparts. In view of the approximations made, the close agreement with the observed spectrum is gratifying. (Care must be taken in inspecting the experimental γ-proton spectrum because of the proximity of sidebands due to naturally abundant ^{13}-CH_2- groups in the ether.) Thus the spectrum of butenylmagnesium bromide is consistent in all respects with the proposed tautomeric structure, VI.

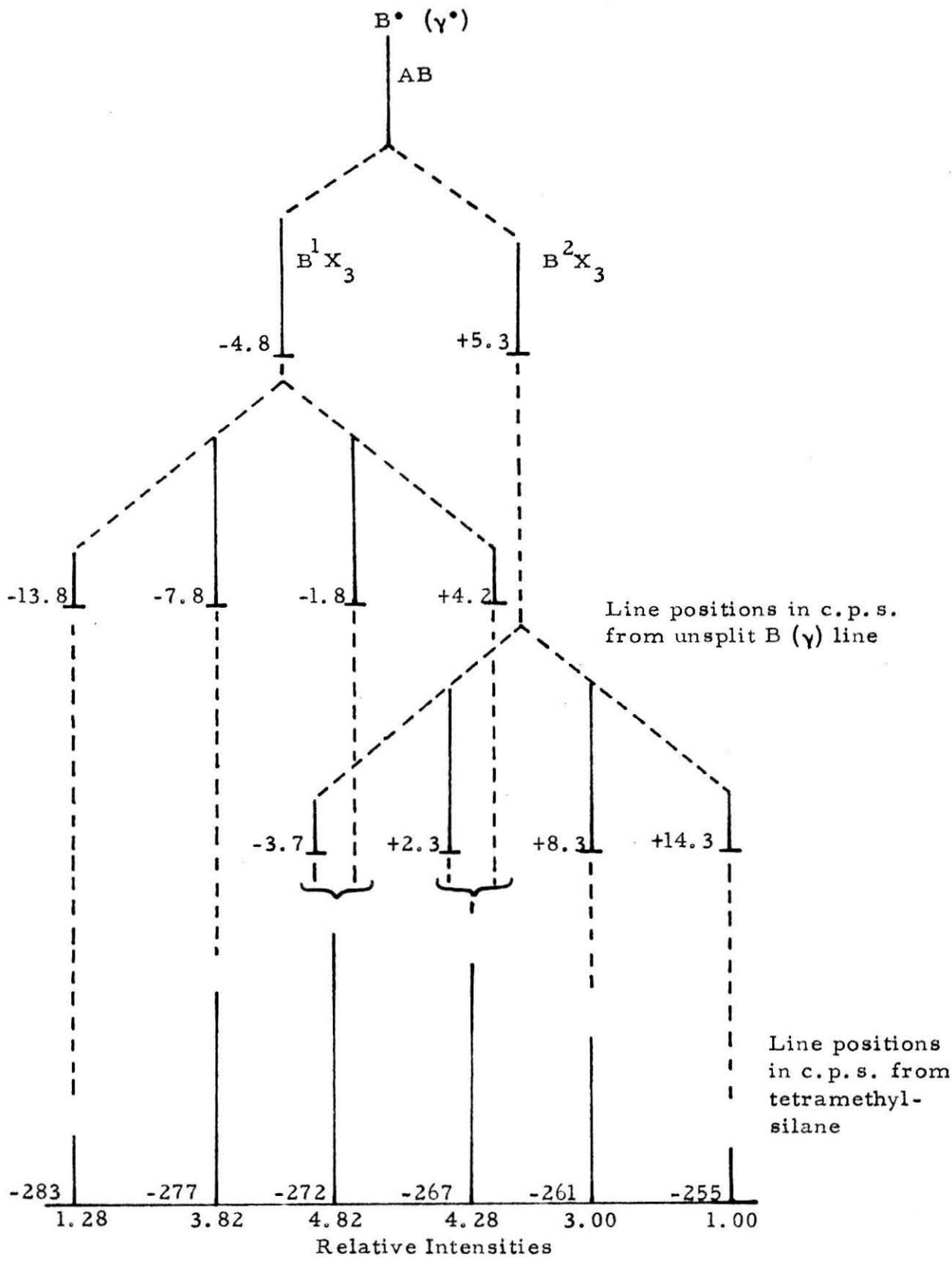


Fig. 6. - γ-Proton N.m.r. Spectrum Calculated for Butenylmagnesium Bromide as an ABX_3-Type Spin System

It was anticipated that a measure of the position of equilibrium VI might be gained by treating the observed α-methylene chemical shift as a weighted average of the estimated shifts for this proton group in the two structures contributing to the equilibrium. The analysis of water-acetic acid mixtures may be cited as an example of the determination of the relative concentrations of rapidly exchanging species by chemical shift measurements (78). In the spectra of solutions of the two substances only a single line for the hydroxyl protons is present, demonstrating that these hydrogens have their chemical shifts averaged by rapid exchange between acetic acid and water. Furthermore, the position of the hydroxyl peak has been found to be a linear function of the fraction of the hydroxyl protons in the form of acetic acid.

If a first-order proportionality is assumed also to exist between the α-methylene chemical shift in the butenyl Grignard reagent and the fractions of the interconverting species, then the equilibrium constant for the exchange process VI can be determined if two points relating α-methylene line position and tautomeric composition can be established. Such points may be derived from the data in Table 3. The α-methylene chemical shifts measured for allyl and crotyl bromides are seen to be identical, showing that methyl substitution at the γ position in the latter compound exerts a negligible effect on the α-proton resonance. For this reason the methylene group line positions for static models of crotyl- and α-methylallylmagnesium bromide in ether are predicted

to be the same as those calculated earlier (page 42) for the α (+8 c.p.s.) and γ (-304 c.p.s.) protons, respectively, in a hypothetical non-exchanging allylmagnesium bromide molecule. The assumed linearity between chemical shift and tautomeric composition leads to:

$$\left.\begin{array}{l}\text{Percent crotyl form}\\ \text{of butenylmagnesium}\\ \text{bromide in ether}\end{array}\right\} = \frac{-43-(-304)}{8-(-304)} \times 100$$

$$= 83.6\%,$$

whence:

$$K_{IV} = \frac{[\text{Crotyl form}]}{[\alpha\text{-Methylallyl form}]} = \frac{83.6}{16.4} = 5.10$$

and $\Delta F = -RT \ln K$ (Eq. 4)

$= -0.981$ kcal./mole $(T = 30°C)$

At this point it became of great interest to study the n.m.r. spectra of the ethereal allyl and butenyl Grignard reagents at reduced temperatures. One objective of such experiments was the possible retardation of tautomeric exchange rates to the point where the discrete structures in V and VI might become manifest in the spectra, replacing the average representations observed at room temperature. As calculated earlier, allylmagnesium bromide would be expected to exhibit the spectrum of its conventional structure if its mean lifetime in

one tautomeric form could be increased to substantially greater than 0.001 sec. If resolution of the discrete forms could be achieved, then it would be possible in principle to determine precise values for the interconversion rates from variations of the resonance line shapes with temperature (69a). A second anticipated application of low-temperature spectra was calculation of the enthalpy difference for the butenylmagnesium bromide exchange process, VI, from changes in the measured equilibrium constant, according to the well-known thermodynamic expression

$$\ln \frac{K_2}{K_1} = \frac{-\Delta H}{R} \left(\frac{1}{T_2} - \frac{1}{T_1} \right) , \qquad \text{(Eq. 5)}$$

ΔH being considered to be constant over the temperature range studied. The entropy change for a specified temperature would then follow from the relationship

$$\Delta F = \Delta H - T\Delta S . \qquad \text{(Eq. 6)}$$

The spectra of allylmagnesium bromide and butenylmagnesium bromide in ether were examined at several temperatures down to -66° and -59°, respectively, below which the solute peaks could not be distinguished due to viscosity broadening (79). In neither case did the spectra show any transition from the exchange-averaged structure to the separate contributing forms. Thus, the mean lifetime of a discrete

allylmagnesium bromide tautomer is indicated to be considerably less than 0.001 sec. even at -66°.

The butenylmagnesium bromide equilibrium constant, K_{VI}, was determined at -20° by measurement of the separation of prominent lines in the α- and γ-proton multiplets. Both line positions were measured relative to tetramethylsilane with an estimated accuracy of ± 0.5 c.p.s. at this temperature. These measurements showed the percentage of crotyl form of butenylmagnesium bromide at -20° to be unchanged from that at +30°, i.e., the equilibrium constants to be equal at the two temperatures. Application of Equation 4 to this result gives $\Delta H_{VI} = 0$, a most unreasonable conclusion. The crotyl form of the butenyl Grignard reagent should have a considerably lower enthalpy than the α-methylallyl isomer on two main counts. In the first place, the former, in which the double bond is internal, would be expected to be more stable than the latter, which has a terminal double bond, by perhaps as much as the difference in heats of hydrogenation of trans-2-butene and 1-butene, 2.7 kcal. per mole at 25° (80). Secondly, the crotyl form has negative charge concentration at a primary carbon atom, whereas the concentration of negative charge in the α-methylallyl form is at a secondary carbon atom. There is considerable published qualitative evidence in support of the stability order primary > secondary > tertiary for alkyl carbanions (72, 81). Unfortunately, however, the literature contains no quantitative data directly related to these differences. Precise measurement of the acidities of carbon

acids has been possible only for cases in which the conjugate base was stabilized by resonance delocalization of the negative charge, often largely on an electronegative atom (as in alkyl carbonyl compounds, aliphatic nitriles, and nitroalkanes). The electron affinities of organic radicals are known in too few cases and with insufficient accuracy to permit calculation of the desired energy differences among anions (82). Pertinent thermochemical measurements, such as the heats of neutralization of isomeric alkylmetallic compounds, have not been made.

It is possible to rationalize the anomalous experimental conclusion that $\Delta H_{VI} = 0$. It will be recalled that the equilibrium constant K_{VI} was determined by interpolation of the experimental α-proton line position in the butenyl Grignard reagent spectrum between hypothetical values predicted for the individual tautomers in VI. These values were based on chemical shift data measured for ethylmagnesium bromide. It is certainly conceivable that the saturated Grignard reagent is an unreliable basis for prediction in the allylic Grignard series. The former is unable to reflect the polarizability of the olefinic linkage in the latter and the contribution which delocalized ionic resonance forms may make to the electronic structure of the latter. Both of these effects would tend to decrease the concentration of negative charge at the carbon atom bound to magnesium in an allylic Grignard reagent and thereby shift the resonance of protons at this position to a lower field than that predicted by a saturated model. Thus the α-proton line

position estimated for crotylmagnesium bromide in VI may be substantially in error in the high-field direction, and the derived equilibrium constant, K_{VI}, a good deal lower than the true value. If such is the case to the extent that the butenyl Grignard reagent exists nearly completely in the crotyl form at room temperature, then lowering the temperature to -20° might not increase K_{VI} enough to be reflected in the n.m.r. spectrum as a measurable increase in the α-γ line separation. The apparent identity of equilibrium constants at the two temperatures would then lead to the observed spurious result, $\Delta H_{VI} = 0$.

The situation described may be illustrated and delimited quantitatively. Let it be arbitrarily assumed that the heat of isomerization ΔH_{VI} is composed of a contribution of -2.0 kcal. from the greater stability of a non-terminal over a terminal double bond and a contribution of -2.0 kcal. from the lower enthalpy of a primary, relative to a secondary, carbon-magnesium bond; $\Delta H_{VI} = -4.0$ kcal. For $T_1 = 303$ and $T_2 = 253°$ K, the right-hand side of Equation 5 becomes equal to 1.31. Therefore,

$$\ln \frac{K_2}{K_1} = 1.31 = 2.303 \log \frac{K_2}{K_1}$$

$$\log \frac{K_2}{K_1} = 0.568$$

$$\frac{K_2}{K_1} = 3.70$$

If, for example, the butenyl Grignard reagent were, in fact, 99% crotyl instead of 84% as previously derived, then $K_1 = 99.0$ and $K_2 = 366$, corresponding to 99.7% of the crotyl form at -20°. Now, again under the assumption that the α-methylene line position is linear with the tautomeric composition, the α-proton chemical shift for pure crotylmagnesium bromide is calculated to be (cf. Table 3)

$$-148 + [\,-43-(-148)\,] \times \frac{50}{49} = -41.0 \text{ c.p.s.}$$

relative to tetramethylsilane. The α-methylene line position would be expected to shift from -43.0 c.p.s. observed at room temperature to -41.6 c.p.s. at -20° for a mixture of 99.7% crotyl- and 0.3% α-methylallylmagnesium bromide. The observed position at -20° was -42 ± 0.5 c.p.s. Thus, if the equilibrium constant K_{VI} is already large (e.g., 99.0) at room temperature, an increase in K_{VI} of nearly four-fold at -20° is not perceptible from chemical shift measurements. From Equations 4 and 6, for 30°C, $\Delta F_{VI} = -2.77$ kcal. and $\Delta S_{VI} = -4.06$ e.u. The calculated entropy change is, of course, without precise significance because of the arbitrarily assumed value of ΔH_{VI}, but is at least not unreasonable.

It must be concluded, therefore, that the tautomeric butenyl Grignard reagent contains approximately 99% of the crotyl form, and that the hypotheses used earlier to derive a value of 84% are, as discussed, not valid.

This revised view of the composition of butenylmagnesium bromide suggests a new evaluation of the upper limit for the mean lifetime of a discrete allylmagnesium bromide tautomer. The separation of the α and γ resonances in a non-exchanging allylmagnesium bromide molecule are now calculated to be (<u>cf.</u> page 42)

$$2[-41-(-148)] = 214$$

so that

$$\tau \ll \sqrt{2} \quad (214\,\pi)^{-1}$$

$$\ll 0.002 \text{ sec.}$$

The order of magnitude of this value is seen not to differ from that calculated earlier.

The n.m.r. spectrum of γ,γ-dimethylallylmagnesium bromide in ether is shown in Figure 7. The formation of coupling products was particularly troublesome in the preparation of this Grignard reagent. The reaction of the bromide with amalgamated magnesium turnings in the cyclic reactor was carried out three times under widely varied concentrations of the starting material in ether and rates of addition to the magnesium; the extent of coupling was uniformly high in all cases. The peaks in the spectrum due to the decadiene impurities were identified by "titrating" a sample of the Grignard reagent with γ,γ-dimethylallyl bromide and following the reinforcement of the decadiene peaks and the diminution of the Grignard reagent peaks.

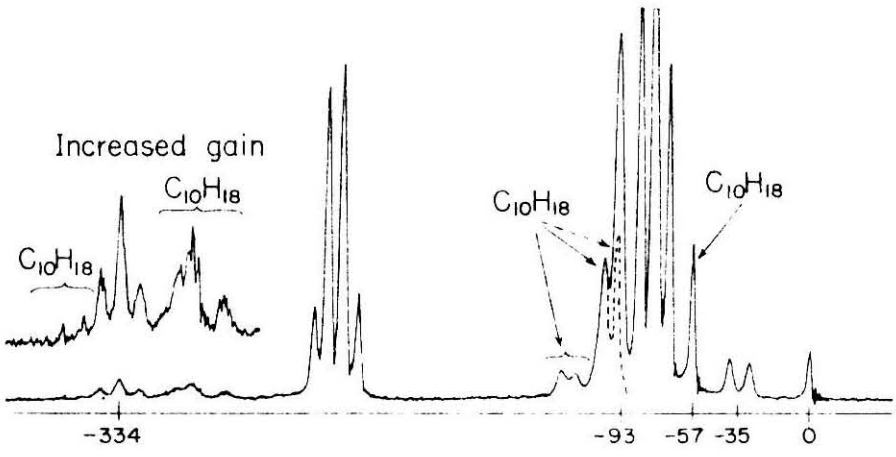


Fig. 7. - Proton magnetic resonance spectrum of the Grignard reagent, in ether, from γ, γ-dimethylallyl bromide, plus tetramethylsilane as internal standard. Chemical shifts are in c.p.s. The signals designated $C_{10}H_{18}$ are due to decadiene coupling products.

It is seen from Figure 7 and Table 3 that substitution of a second methyl group at the γ position in allylmagnesium bromide, making this position tertiary, has a much smaller incremental effect (+10 c.p.s.) on $\Delta(\delta_{\alpha}H)$, and hence on the position of tautomeric equilibrium, than a first methyl group substitution at the same position (+105 c.p.s.). It is also noteworthy that there is a variation in the coupling constant $J_{\alpha\beta}$ among the allylic Grignard reagents in the following order (Table 4):

allyl > butenyl > γ,γ-dimethylallyl

Table 4

α-β Spin-Spin Coupling Constants in Allylic Grignard Reagents

Grignard reagent from	$J_{\alpha\beta}$, c.p.s.
CH_2=CH-CH_2Br	10.7
CH_3CH=CH-CH_2Br	9.5
$(CH_3)_2$C=CH-CH_2Br	8.9

Proton coupling constants are generally greater across carbon-carbon double bonds than single bonds (83). The order of $J_{\alpha\beta}$ values observed is therefore consistent with a decreasing degree of α-β double-bond character from allyl- to γ,γ-dimethylallylmagnesium bromide brought about by an increasing predominance of the primary

($-(CH_2)_a-MgBr$) form in the tautomeric composition of the Grignard reagent. As with the change in $\Delta(\delta_a H)$ values in Table 3, the variation in $J_{a\beta}$ values in Table 4 is sharpest between the allyl and butenyl Grignard reagents.

Since the γ,γ-dimethylallyl Grignard reagent exhibits the greatest degree of β-γ double-bond character in the series studied, it would be predicted that this case would be the most favorable one for the observation of restricted β-γ rotation at low temperatures. The molecule is well suited to detection of this phenomenon in the n.m.r. spectrum, as retarded β-γ rotation should cause the δ-methyl-group singlets, superimposed at -93 c.p.s. at room temperature, to separate into two single lines for the cis and trans orientations at suitably low temperatures. The n.m.r. spectra of this region at -16°, -34°, and -38° are shown in Figure 8 (the spectrum at -43° was unchanged from that at -38°). There is the distinct appearance of an additional line near -93 c.p.s. as the temperature is decreased. Unfortunately, however, this result is ambiguous, owing to the presence of the decadiene coupling products in the sample. These impurities give rise to two peaks near -93 c.p.s., one of which (dotted line, Figure 7) lies directly under the signal of the methyl groups in the Grignard reagent at room temperature. It is entirely possible that the extra line seen at low temperatures is due to a relative shift between the decadiene lines and the Grignard reagent dimethyl singlet, instead of a separation of the lines of the Grignard reagent methyl groups. In fact, the former explanation would seem more likely in

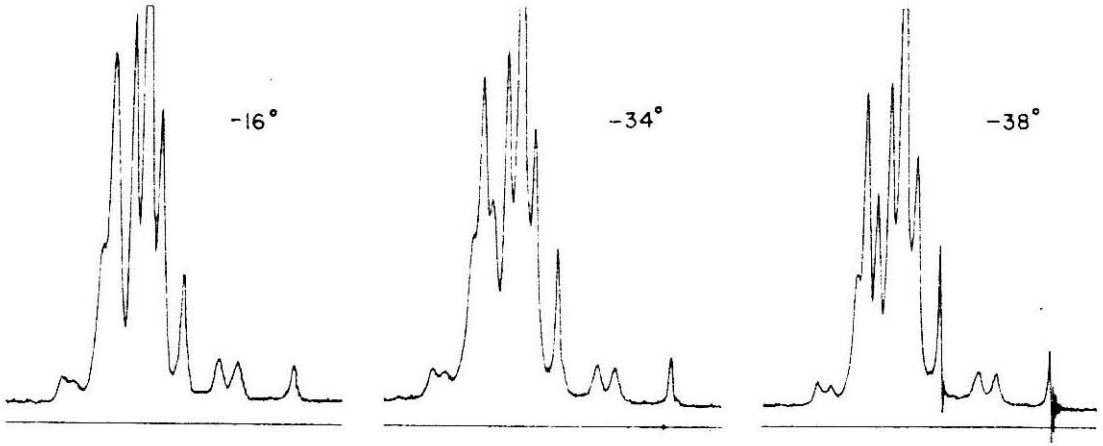


Fig. 8. - Low-temperature proton magnetic resonance spectra of the Grignard reagent, in ether, from γ,γ-dimethylallyl bromide, plus tetramethylsilane as internal standard. Only the region of the spectrum above -150 c.p.s. is shown in each case.

consideration of the relative intensities of the signals near -93 and -35 c.p.s. in the spectrum at -38° (Figure 8). Each of the two major peaks in the -93-c.p.s. region appears considerably more than three times as intense as each of the lines about -35 c.p.s.; the 3:1 ratio would be the case if the two δ-methyl groups in the Grignard reagent were separated.

The question of the intra- or intermolecular nature of the postulated mobile tautomerism in allylic Grignard reagents has been alluded to earlier (page 44). At that time the exchange was depicted as being intramolecular, but the presentation of experimental support for this choice was deferred.

The uncertainty which surrounds the question of the molecularity of the exchange process is part of the greater uncertainty which exists regarding the general constitution of Grignard reagents. Schlenk (84) in 1929 suggested that Grignard reagents consisted of a mixture of species represented by the equilibrium

$$2RMgX \rightleftharpoons R_2Mg + MgX_2 ,$$

X = Cl, Br, I.

Since then a great deal of work has been directed toward an evaluation of the "Schlenk equilibrium" (85). Physical measurements of the colligative, conductometric, and thermochemical properties of Grignard reagents and their solutions (85, 86) have produced most of our information on the nature of these systems. Complementary data have been

provided by chemical studies of steric and solvent effects upon products and rates (87). Thorough discussions of all but the most recent of these studies and their significance have been published elsewhere (85) and will not be reiterated here. The conclusions of such studies, however, have established Grignard reagents to be nonvolatile, infusible solids, quite insoluble in hydrocarbons, but very soluble in ether and other aprotic basic solvents. The heats of solvation in such cases are large and negative (exothermic);Grignard reagents form very tightly-bound etherates, whereas the etherates of dialkylmagnesium compounds are much more easily decomposed. Grignard reagents in ether solutions are associated to various extents, depending on the specific reagent, the concentration, and the temperature. Such solutions are weakly conducting, and the products of electrolysis indicate the presence of large, complex anions and cations (85). 1,4-Dioxane precipitates the halogen-containing species from an ethereal Grignard solution, leaving the dialkylmagnesium compound in solution. But this reaction is unsatisfactory as a method for determining the position of the Schlenk equilibrium, since the compositions of the resultant solid and liquid phases upon prolonged mixing slowly approach values independent of the composition of the original solution (85b). Recently Dessy and co-workers reported (88) that when the ethyl (or phenyl) Grignard reagent was prepared by dissolving together in ether diethylmagnesium (diphenylmagnesium) and magnesium bromide labeled with radioactive ^{28}Mg,

precipitation of the halogen-containing species with dioxane after 36 hours left virtually no radioactivity in the supernatant solution of diethylmagnesium (diphenylmagnesium). Only 4.5% of magnesium exchange occurred (7.0% for the phenyl case), irrespective of the lifetime of the solution before the addition of dioxane. These results were interpreted to negate the operation of the Schlenk equilibrium. However, there is no assurance that a Grignard solution prepared by mixing together a dialkylmagnesium and anhydrous magnesium halide in ether has the same constitution as one prepared by reacting the alkyl halide with magnesium in ether. Indeed a significant and reproducible difference has been observed (86a) in the equivalent conductance of ethyl Grignard solutions prepared by these two methods. In summary, the accumulated evidence is as yet inconclusive as to the constitution of the Grignard reagent but seems to favor the formulation $R_2Mg \cdot MgX_2$ more nearly than either RMgX or $R_2Mg + MgX_2$ (85a).

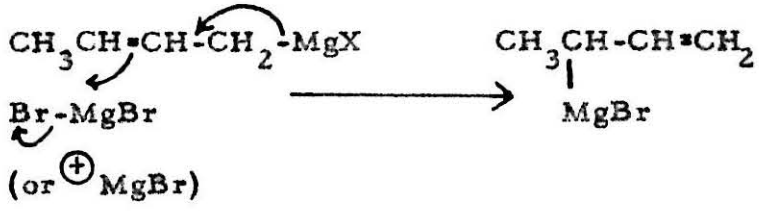
In the present discussion Grignard reagents have been represented sometimes by RMgBr and in other instances by RMgX. It should be understood that such formulations have been used solely for the sake of simplicity and convenience. They have not been intended to imply the identity of the second group bound to magnesium, nor has the nature of this group been pertinent to the presentation up to this point.

Some new information on this question, however, is provided by the Grignard reagent n.m.r. spectra obtained in the present study.

In every instance, the Grignard reagent solute signals have been as sharply resolved as those of the ether solvent, and no multiplicity has been observed in the α-proton resonance pattern beyond that clearly due to splitting by protons at the β (and occasionally also at the γ) position. Such would not be expected to be the case if appreciable amounts of structures of the types RMgBr and RMgR both existed separately or were interconverted slowly in solution by the Schlenk equilibrium. The α-proton chemical shift in a molecule RMgY should certainly be made detectably different as Y is changed from a halogen atom to a second alkyl group. In an analogous system, the methyl resonance frequency for tetramethylsilane was found to be 23.5 c.p.s. higher than that for chlorotrimethylsilane in an ether solution of the two. Many similar examples may be cited from the spectra of hydrocarbon derivatives, one being the difference in methyl group chemical shifts between propane (-54 c.p.s. from tetramethylsilane (89)) and ethyl bromide (-98 c.p.s., present work). In each case the comparison is between the effect of an alkyl group and a halogen atom upon the chemical shift of protons separated from these substituents by two atoms. It must be concluded, therefore, that either the Schlenk equilibrium functions as a very fast exchange process or else the Grignard reagent exists exclusively as RMgX or as RMgR associated with MgX_2 (X = halogen). The latter alternative seems favored by the additional observation that crystals, apparently of salt, formed slowly in the sealed Grignard reagent samples upon standing but no changes resulted

in the n.m.r. spectra of these samples.

If tautomeric exchange in allylic Grignard reagents were an intermolecular process, a likely mechanism would be electrophilic attack at the allylic position by magnesium bromide, or $BrMg^{\oplus}$ ion, accompanied by loss of $^{\oplus}MgX$ (X = Br or $-C_4H_7$)



In order to test this possibility, halogen-free solutions of diallylmagnesium and dibutenylmagnesium in dioxane were prepared from the Grignard reagents by the dioxane precipitation technique. Their n.m.r. spectra are shown in Figures 9 and 10, respectively. A first inspection shows these spectra to be qualitatively the same in all respects as those of the corresponding Grignard reagents in ether. The spectra of the diallylmagnesium compounds in dioxane are shifted upfield 4-6 c.p.s. from those of the Grignard reagents in ether. But the position of tautomeric equilibrium is seen to be very nearly the same in dibutenylmagnesium in dioxane as in butenylmagnesium bromide in ether, as measured by the separation of the α- and γ-proton band centers, 224.2 and 226.0 c.p.s., respectively. The spectra of the diallylmagnesium compounds, then, rule out a salt-catalyzed intermolecular mechanism for tautomerization of the allylic Grignard reagents, at least as the sole

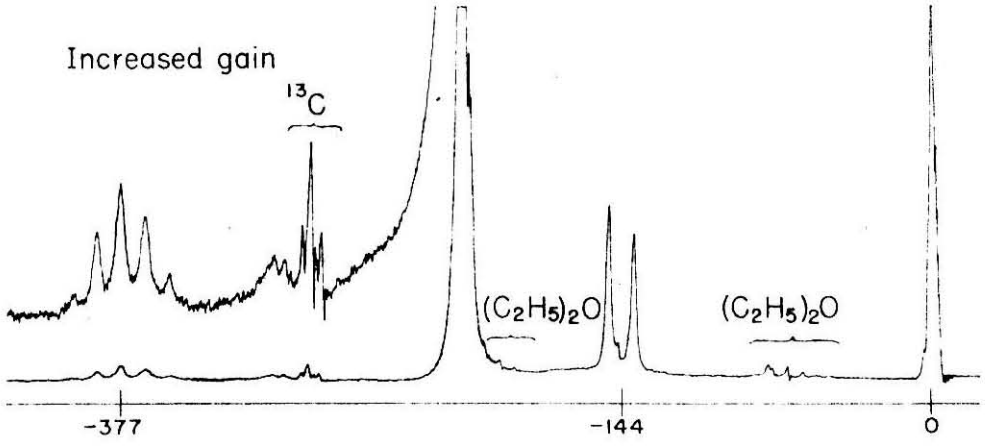


Fig. 9. - Proton magnetic resonance spectrum of diallylmagnesium in dioxane, plus tetramethylsilane as internal standard. Chemical shifts are in c.p.s. The off-scale peak is due to the dioxane. The signals designated ^{13}C are sidebands due to naturally abundant ^{13}C in the dioxane. Signals due to traces of ether are also labeled.

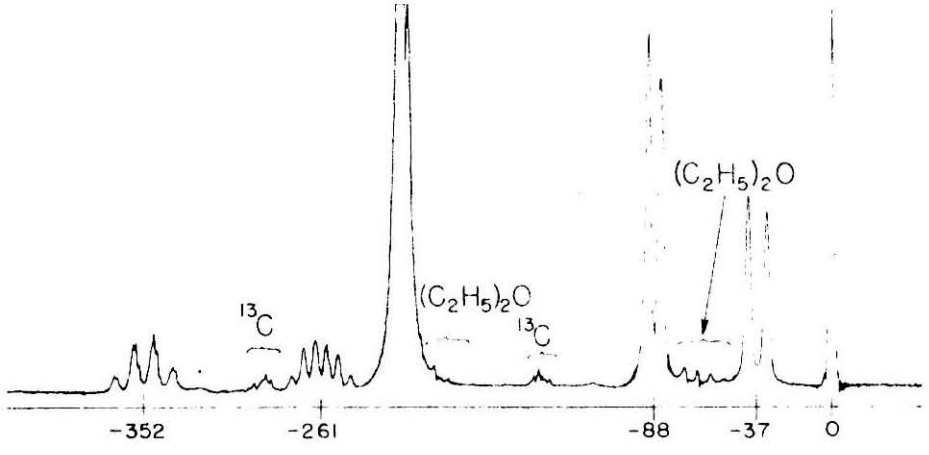
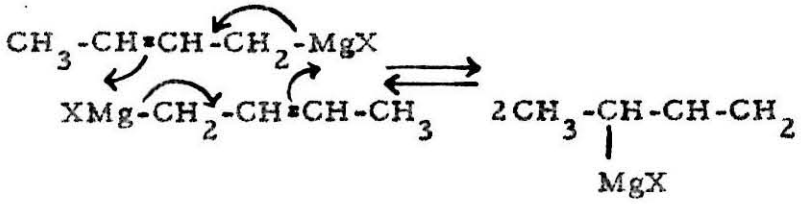


Fig. 10. - Proton magnetic resonance spectrum of dibutenylmagnesium in dioxane, plus tetramethylsilane as internal standard. Chemical shifts are in c.p.s. The signals designated ^{13}C are sidebands due to naturally abundant ^{13}C in the dioxane. Signals due to traces of ether are also labeled.

mechanism. Another possibility for intermolecular exchange would be a simultaneous interchange of magnesium atoms between two or more molecules of the original reagent, for example

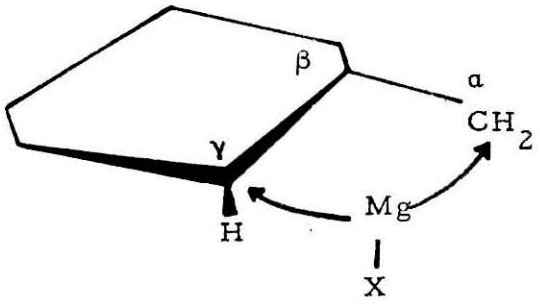


Such a process would be expected to require a very large negative entropy of activation; activation entropies of -20 to -25 cal. per deg. mole are commonly observed (90) for the Diels-Alder reaction, another four-center-type process. An activation entropy of this order of magnitude would seem to be difficultly compatible with an exchange process of the observed facility. Moreover, the n.m.r. evidence presented for the lack of significantly retarded exchange at temperatures in the neighborhood of -60°, where the Grignard solutions become extremely viscous, argues further against a four (or more)-center-type, simultaneous interchange mechanism. Any mechanism involving intermediate free carbanions is unlikely, for the reasons already discussed in the Introduction (pp. 16-17).

A simple intramolecular exchange mechanism, as originally postulated, is therefore the most attractive explanation of the experimental results.

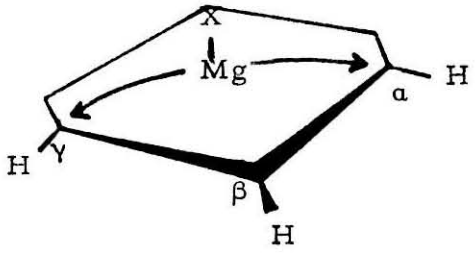
A brief investigation was made of the geometric constraints upon the tautomerization process postulated for allylic Grignard reagents.

Heretofore the position of the magnesium atom has been pictured as oscillating between the α and γ positions in the plane of the α, β, and γ carbon atoms. It was thought of interest to compare the reactions and possibly the n.m.r. spectra of ethereal solutions of the Grignard reagents from 1-bromomethylcyclohexene and 3-bromocyclohexene. In the former, VII, the three carbon atoms of the allylic system are fixed in the conformation presumed to be preferred in simpler, more flexible systems.



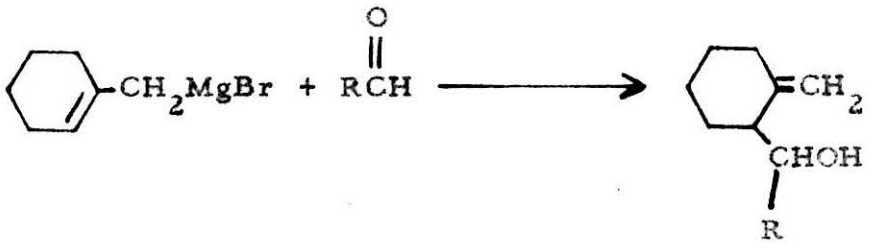
VII

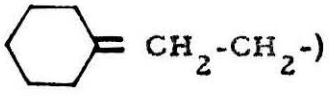
In the latter, VIII, this conformation is not possible, and the magnesium atom must occupy a position above or below the plane of the allylic system in shifting between the α and γ positions.



VIII

1-Cyclohexenylmethylmagnesium bromide, VII, has been reported (91) to react in benzene-ether with cyclohexylideneacetaldehyde to give the product of reaction at the γ position of the Grignard reagent.



(R =  CH_2-CH_2-)

Thus this Grignard reagent can react with the same type of rearrangement characteristic of the behavior of butenylmagnesium bromide.

The Grignard reagent from 3-bromocyclohexene has not been reported in the literature. 3-Bromocyclohexene was found to react readily with magnesium in the cyclic reactor. The ethereal product solution gave a positive Gilman color test (92) for the presence of Grignard reagent. The clear, colorless solution decomposed, however, during concentration by solvent removal in a stream of purified nitrogen. A green color appeared, which darkened deeply over several hours. The color of the solution, sealed under nitrogen in an n.m.r. tube, changed gradually through dark blue to dark brown, accompanied by the formation of amorphous solid material, which eventually grew to compose the entire sample. This behavior was reproduced in a second run. The initially-formed green color was observed to fade rapidly

upon exposure to air and instantly upon neutral hydrolysis. The n.m.r. spectrum of the freshly concentrated green product solution was moderately well resolved and contained strong peaks in the cyclohexyl- and olefinic-proton regions, but did not conform to any simple structure for the Grignard reagent. These signals were all severely broadened in the spectrum taken several hours later. The week-old dark blue sample showed no electron paramagnetic resonance absorption. The decomposition process was not investigated more thoroughly, but it is evident that 3-cyclohexenylmagnesium bromide exhibits a sharp departure in stability from the other allylic Grignard reagents studied. All of the latter are indefinitely stable at room temperature except for the very slow deposition of salt crystals, this process being without effect upon the n.m.r. spectra. A possible explanation for the observed decomposition of 3-cyclohexenylmagnesium bromide is the inability of this molecule to assume the stabilizing conformation of the other allylic Grignard reagents.

Benzylmagnesium chloride in ether was prepared in a conventional manner under high dilution and then concentrated. The n.m.r. spectrum of this Grignard reagent is shown in Figure 11. The peaks caused by impurities were identified from the spectra of samples to which the suspected impurities were deliberately added. The weak signal at -272 c.p.s. was not positively identified. It may perhaps be due to Mg(OH)Cl, insofar as it is soluble, formed, together with toluene,

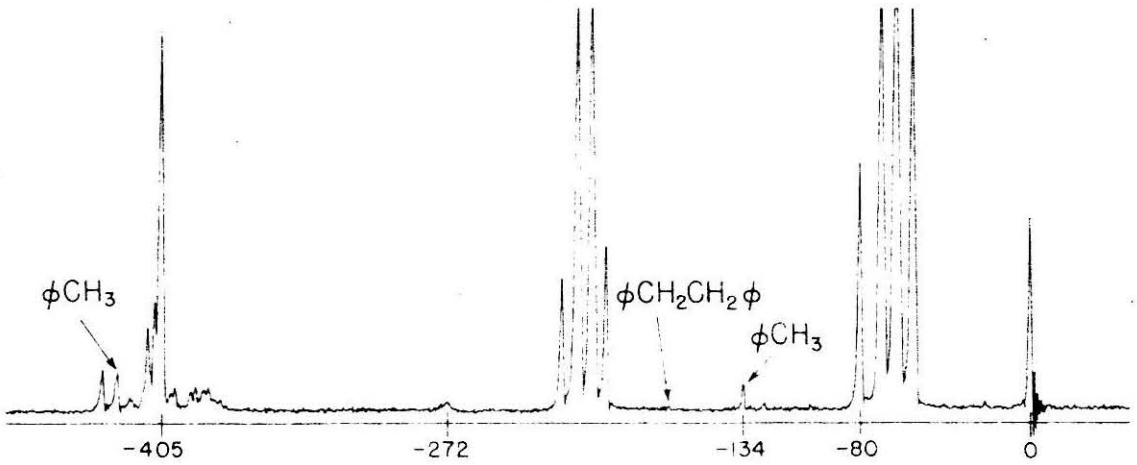
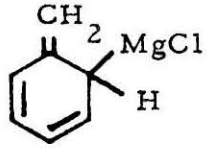


Fig. 11. - Proton magnetic resonance spectrum of benzylmagnesium chloride in ether, plus tetramethylsilane as internal standard. Chemical shifts are in c.p.s. Signals due to traces of toluene and dibenzyl are identified.

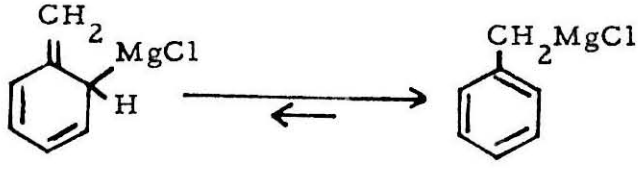
by adventitious traces of moisture,

$$\phi CH_2MgCl + H_2O \longrightarrow \phi CH_3 + Mg(OH)Cl \quad .$$

The signal in question was not affected by hydrolysis of the sample and therefore does not represent any Grignard reagent species. The spectrum of the Grignard reagent is seen to consist of a sharp singlet at -80 c.p.s., which is assigned to the $-CH_2-Mg-$ protons, and to a complex pattern of lines in the phenyl region, the most prominent one coming at -405 c.p.s. There are no signals in the olefinic-proton region of the spectrum, -275 to -355 c.p.s. (93). This piece of evidence rules out the presence of the quinonoid form of the Grignard reagent originally suggested by Schmidlin and Garcia-Banus (7) at least as a species



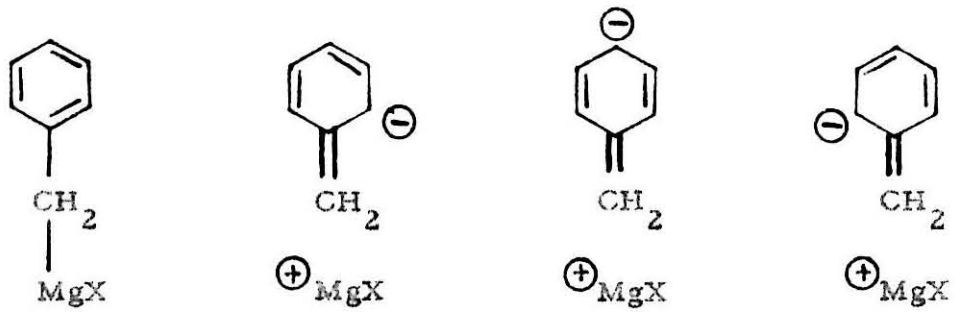
sufficiently long-lived to be recognized in the n.m.r. spectrum. It is true that a very rapid tautomeric exchange between the quinonoid and benzenoid forms, with the latter highly predominant, is not negated by



the spectrum. However, it has already been shown that the free energy difference between the α-methylallyl and γ-methylallyl (crotyl) Grignard reagents in such a process is enough to cause the latter to prevail as approximately 99% of the equilibrium mixture. A much larger difference would be expected to exist between the quinonoid and benzenoid forms of benzylmagnesium chloride, since the resonance stabilization of the benzene ring is sacrificed in the former. On this basis, the proportion of quinonoid form in tautomeric equilibrium with the benzyl form should be vanishingly small. The evidence strongly favors the conventional structure for the benzyl Grignard reagent.

The chemical shift and the multiplicity of the phenyl group absorption in this Grignard reagent are of interest. Whereas the ring protons in benzyl chloride produce a sharp, single line, those in the magnesium derivative give a considerable amount of fine structure. Furthermore, the phenyl resonance signals in the Grignard reagent are all shifted upfield, by 21 c.p.s. for the principal peak, relative to the phenyl peak in the starting material and also to unsubstituted benzene (the latter two being coincident (94)). The upfield chemical shift and the appearance of fine structure in going from benzyl chloride to benzylmagnesium chloride are probably due to a combination of resonance and inductive effects. Corio and Dailey (94) have studied the effects of a variety of single substituents on the chemical shifts of the protons in benzene and have been able in several cases to distinguish between

inductive and resonance interactions. The inductive effect by itself diminishes with the distance from the substituent, and so for an electron-donating group, such as $-CH_2 \overset{\delta-}{\longleftarrow} \overset{\delta+}{MgX}$, the order of the signals toward increasing field strength would be <u>para</u> < <u>meta</u> < <u>ortho</u>. Supply of electrons to the ring by a substituent through resonance interaction alone would give rise to the order of signals, <u>meta</u> < <u>ortho</u> = <u>para</u>. In benzylmagnesium chloride the contributions of resonance structures IX, X, and XI,



IX X XI

represent the partial ionic character of the carbon-magnesium bond. If this resonance effect dominates over the inductive effect of the $-CH_2MgX$ group, then the order of signals to be expected would be <u>meta</u> < <u>para</u> < <u>ortho</u>. This order has been observed for aniline and N-methylaniline (94). The question could be resolved in the present case by the n.m.r. spectra of benzylmagnesium chlorides containing deuterium substituted appropriately in ring positions.

DISCUSSION

The foregoing interpretation of the structures of simple allylic Grignard reagents as extremely mobile tautomeric systems should not be accepted without careful consideration of at least two main reservations. While the equilibrium model provides an explanation of the data obtained in this study, it certainly cannot be presented as a definitive theory.

The most weighty of these reservations is the marked insensitivity of the equilibrium constants estimated for unsymmetrical cases to temperature, solvent and the distinction between the Grignard reagent and the halogen-free diallylmagnesium compound. The insensitivity to solvent is in conspicuous contrast to the behavior of prototropic tautomeric systems. For example, the position of keto-enol equilibrium for ethyl acetoacetate varies strongly with the polarity of the solvent, from 0.4% enol in water to 46.4% enol in hexane (95). To be sure, solvent effects are doubtless very much more important for keto-enol tautomerism, where the two tautomeric forms have quite different structures, than for equilibration between primary and secondary or tertiary forms of an allylic Grignard reagent. Nonetheless, it is remarkable that (a) no measurable change in the equilibrium constant for butenylmagnesium bromide in ether accompanies an apparently considerable decrease in salt concentration as indicated by the formation of colorless crystals in the sample upon standing, and, perhaps more

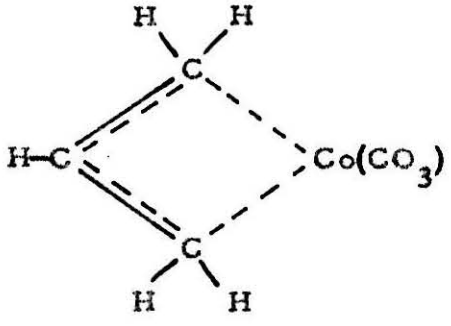
strikingly, (b) the position of equilibrium is virtually identical for dibutenylmagnesium in salt-free dioxane and butenylmagnesium bromide in ether. Winstein and co-workers (96) have recently furnished strong evidence for very large salt effects upon the rates of ionizing reactions in ether, to the extent that ether becomes a better ionizing medium than acetic acid at concentrations of lithium perchlorate above 0.036 M. The concentrated ether solutions of Grignard reagents used in the present work certainly contain considerable quantities of dissolved magnesium bromide and constitute much more highly polar media than those existing in salt-free dioxane solutions of diallylmagnesium compounds. It seems peculiar indeed that the contribution of solvation effects to the free energy difference between the primary and secondary forms of butenylmagnesium bromide and dibutenylmagnesium is apparently negligible.

It has been mentioned earlier that the lack of temperature dependence of the butenylmagnesium bromide equilibrium constant can be rationalized by assuming the equilibrium to lie nearly completely in favor of the primary isomer of the Grignard reagent at room temperature. This means that a static crotylmagnesium bromide molecule might have an α-proton chemical shift only ca. 2 c.p.s. toward higher field than that observed (-43 c.p.s.) for the tautomeric mixture (Table 3). However, if the butenyl Grignard reagent is virtually all primary isomer, it remains to be understood why the α-methylene line position for the Grignard reagent from γ,γ-dimethylallyl bromide is 10 c.p.s.

toward higher field relative to its starting bromide than that observed in the butenyl case (Table 3), i.e., why the former Grignard reagent appears to be appreciably more highly primary than the latter.

A second reservation to be considered with regard to the validity of the tautomeric model of allylic Grignard reagents is the seemingly extraordinary rates of tautomerization which must be postulated. The high mobility observed for the Grignard reagents is in special contrast to that of 1,3-prototropic systems, many of which undergo exchange slowly enough in the absence of catalysts to permit determination of the enol content by titration methods (97). However, comparisons with prototropic rearrangements are probably not apt, for there is recent evidence that highly facile rearrangements also occur in other organometallic compounds. Thus, rapid methyl group exchange in trimethylaluminum dimmer (98), in dimethylaluminum chloride dimer, and between methylaluminum chloride and dimethylaluminum chloride (99) has been established by n.m.r. Similarly, the methyl groups in a solution containing both dimethylzinc and dimethylcadmium give only a single n.m.r. line, showing them to be undergoing rapid chemical exchange (100). The degree of mobility in allylic Grignard reagents does not have to be much more than an order of magnitude greater than that found for these methyl group exchanges. Indeed, greater mobility would be expected for magnesium in place of the less electropositive aluminum, zinc, and cadmium and for allyl groups in place of methyl groups.

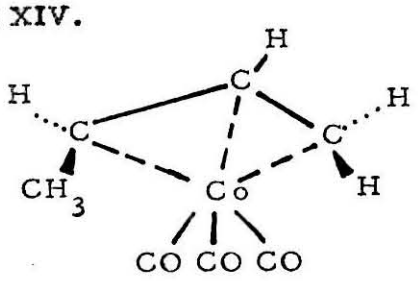
The results of some recent n.m.r. studies of allylcobalt tricarbonyls are of interest to the present discussion. Allylcobalt tricarbonyl, from allyl bromide and sodium cobalt tetracarbonyl in ether, was found by Heck and Breslow (101) to be diamagnetic and to possess an n.m.r. spectrum containing three peaks, of relative intensities 2:2:1. They postulated XII as the most likely structure for the molecule, the pairs of equivalent protons being those cis and trans to the β-proton, respectively.



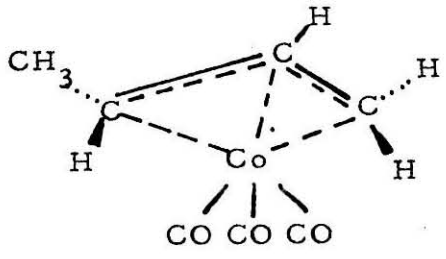
XII

Jonassen and Moore have studied butenylcobalt tricarbonyl (102) and have found by n.m.r. that two modifications exist, one of which is converted to the other as the temperature is raised from -80° to 0°. They have assigned the cis and trans structures XIII and XIV to the thermodynamically less stable and more stable forms, respectively. The fact that the β-proton signal was observed to come some 60 c.p.s. upfield from the corresponding band in the butenylmagnesium bromide spectrum suggests that the cobalt might be bonded to the butenyl group

partially through the p-orbital on the β-carbon atom, as shown in XIII and XIV.



XIII



XIV

It seems quite possible that structures like XIII and XIV may also be of significance for allylic Grignard reagents, by providing an excellent low-energy intramolecular path for rearrangement between the classical forms.

The results of the present research unfortunately do not permit definitive conclusions to be drawn on the mechanisms of the reactions of allylic Grignard reagents. In view of the highly unconventional and still incompletely understood structural nature of these compounds, it must be considered possible that their reactions take place in an unknown manner from some non-classical configuration. However, the n.m.r. data for the butenyl Grignard reagent can be completely reconciled with the cyclic reaction mechanism founded on chemical evidence (discussed at length in the Introduction). It need only be assumed that the first step in additions to carbonyl compounds (and in other reactions served by the cyclic mechanism) is coördination of the carbonyl oxygen with magnesium in such a way as to slow greatly the rate of

isomerization between the forms relative to the rate of addition. From the fact that the Grignard reagent is very predominantly primary in character, such coördination would give largely and indeed perhaps exclusively the crotyl form of the initial complex, and hence α-methylallyl products. In the event that such an addition were unusually slow, as would be expected in the case of di-t-butyl ketone, then isomerization to the α-methylallyl form of the complex might well occur, facilitating more rapid cyclic addition to give the less sterically congested crotyl adduct. Those reactions of butenylmagnesium bromide which are not associated with complex formation and which give mixtures of isomeric products find obvious interpretation in terms of the rapidly exchanging Grignard species. The predominance of α-methylallyl products in these reactions may be related to the more nearly trigonal nature of the γ-carbon atom as against a less accessible tetrahedral α-carbon atom. Finally, it should be remarked that the n.m.r. results obtained in this work immediately explain the recent finding of Nystrom and co-workers (103) that the Grignard reagent from allyl-1-^{14}C chloride upon hydrolysis gave propylene with the label distributed equally between the 1- and 3-positions.

EXPERIMENTAL DETAILS

N.m.r. Spectra. - All n.m.r. spectra were taken at 60 Mc. on a Varian Model V4300B spectrometer equipped with Super Stabilizer, constant-temperature magnet cooling, and field homogeneity control coils. Chemical shifts were measured by means of a Hewlett-Packard Model 200AB audio oscillator and Model 521C frequency counter. For low-temperature spectra, the samples were cooled by nitrogen bubbled through liquid nitrogen and passed via insulated pipes through a vacuum-jacketed probe insert (104); temperatures were measured using a calibrated copper-constantan thermocouple together with a Leeds and Northrup precision potentiometer.

Magnesium. - Magnesium turnings from a bar of the resublimed, highly pure metal were used in preparation of the Grignard reagents in this study.

Ethyl Ether. - Freshly opened Mallinckrodt anhydrous ether was used without further purification. The solvent was always transferred by means of dried pipettes.

β-Methallyl Bromide. - β-Methyallyl bromide was prepared from the corresponding chloride by reaction with sodium bromide in refluxing methanol. The procedure followed was that of Nichols et al. (105), as modified by Teuscher (106). An optimum reaction time of 4.5 hours was determined by monitoring the course of the reaction by vapor-phase chromatography (v.p.c.). The product was obtained as a

clear, colorless liquid, b.p. 90.5-93.0°, in 35.5% yield. A center cut, b.p. 93°, completely pure by v.p.c., was used for conversion to the Grignard reagent.

Butenyl Bromides. - The mixture of butenyl bromides used was prepared by the addition of hydrogen bromide to 1,3-butadiene in acetic acid, in the same manner as that used for 3-methyl-1-bromo-2-butene (vide infra). Distillation of the product through a 60-cm. Podbielniak column under reduced pressure yielded a clear, colorless liquid of b.p. 54-64° (200 mm.), whose vapor phase chromatogram was consistent with a mixture of principally trans-crotyl bromide plus cis-crotyl and α-methylallyl bromide. The n.m.r. spectrum of butenylmagnesium bromide prepared from this bromide mixture was the same as that from the bromides synthesized from α-methylallyl alcohol, 48% hydrobromic acid, and sulfuric acid (107).

3-Methyl-1-bromo-2-butene. - This bromide was prepared by the hydrobromination of isoprene in acetic acid at 0°, following the procedure of Staudinger et al. (108). The product, a clear, colorless liquid, had b.p. 93.5-94.0° (37 mm.); the yield was 68.5%.

3-Bromocyclohexene. - Cyclohexene was brominated with N-bromosuccinimide in carbon tetrachloride, according to the original directions of Ziegler et al. (109). The yield was 64%. A center cut, b.p. 64-65° (13 mm.) was used for reaction with magnesium.

Cyclic Reactor. - The cyclic reactor and the accessory apparatus used in the preparation of the allylic Grignard reagents are illustrated in Figure 12. A plug of glass wool was first inserted at the bottom of the reaction column, to prevent carry-over of the magnesium turnings during reaction. The column was then packed with magnesium turnings to just below the upper bend in the return line; thus the magnesium was kept immersed in ether throughout the reaction. The charged reactor and the rest of the glassware were oven dried (120°, $\geq$ 3 hours) and then assembled quickly under an atmosphere of nitrogen, purified by passage through Fieser's solution and concentrated sulfuric acid (110). The nitrogen atmosphere was maintained throughout all subsequent operations. The rotary selector at the base of the reactor was initially positioned away from the 50-ml. flask with the sintered glass disc; a 100-ml. round-bottomed flask was attached at the other outlet. The magnesium turnings were amalgamated in the cyclic reactor by treatment, in four or five portions over 40 minutes, with 0.30 g. of mercuric bromide dissolved in 15 ml. of ether. The magnesium was washed between portions with 10 ml. of ether and after the last one with 50 ml. of ether. The flask containing the washings was replaced by a fresh 50-ml., round-bottomed flask. Ether (ca. 30 ml.) was added to the new flask and heated to reflux at a rate of approximately 60 drops per minute. Addition of the freshly distilled allylic bromide (1.5 ml.) dissolved in ether (15 ml.) was begun, at a rate of approximately 6 drops

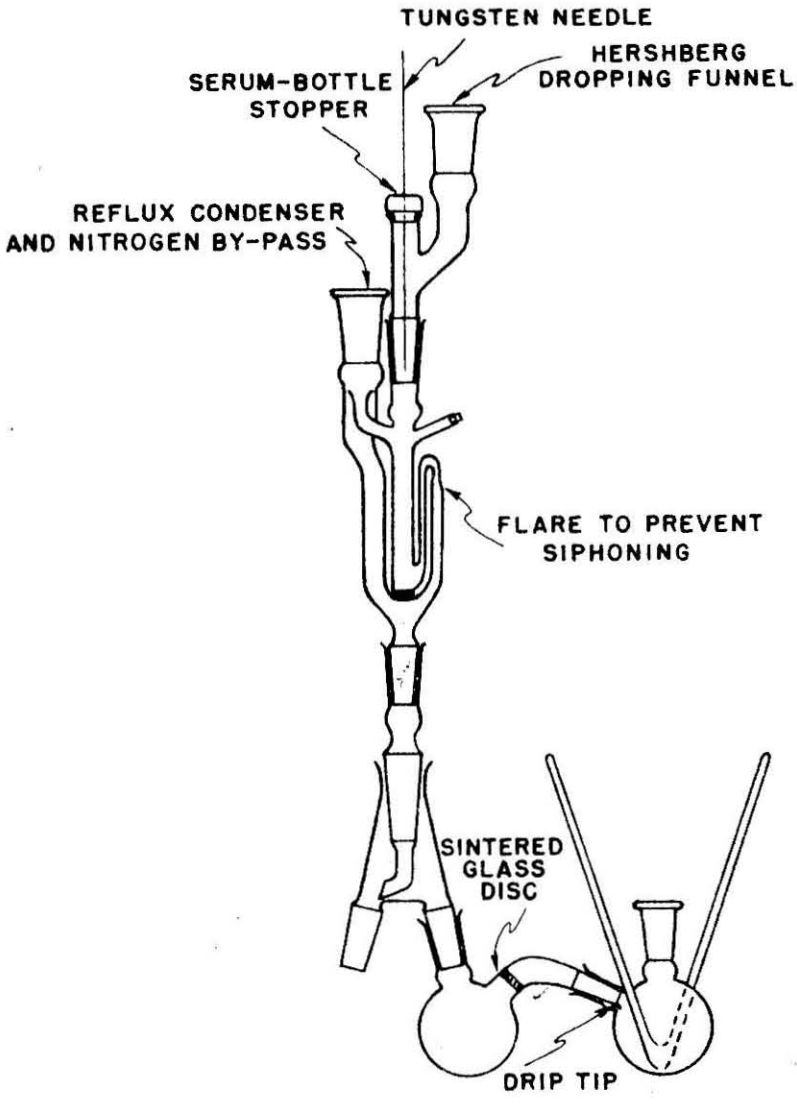


Fig. 12. - Cyclic reactor and accessory apparatus used in the preparation of the allylic Grignard reagents. (Scale = 1/4).

per minute, and the topmost pieces of magnesium were punctured with the tungsten needle to aid initiation of the reaction. An induction period of several minutes was generally observed, followed by very vigorous reaction and the formation of a milky white suspension in the ether. Gradually the intensity of reaction subsided to the point of moderate ebullition, and the product solution became clear and colorless. When these conditions were reached, the return flow was directed into the second terminal flask, where the product accumulated. The resulting Grignard solution was filtered under nitrogen pressure through the sintered glass disc into a 50-ml., round-bottomed flask equipped with n.m.r.-tube sidearms. Here the magnetically stirred and gently warmed solution was concentrated by solvent removal in a stream of nitrogen to a final volume of 2-3 ml. The viscous concentrate was decanted into the n.m.r. tubes, which were broken off, and temporarily capped. Each tube was suspended near its top in a stemless funnel filled with Dry Ice, charged with 3-4 drops of tetramethylsilane, cleaned thoroughly at the point for sealing (using pipe cleaner), and sealed.

Diallylmagnesium. - Allylmagnesium bromide in ether was prepared in the cyclic reactor, as described above, using 2.0 ml. of allyl bromide; the Grignard reagent was collected in a 50-ml. centrifuge bottle, and fresh ether was added to make the final volume approximately 35 ml. An atmosphere of purified nitrogen was maintained throughout. To the allylmagnesium bromide solution, cooled in an ice-water bath, was added dropwise 14 ml. of freshly purified (111) dioxane; a copious

white precipitate formed instantly. The mixture was stirred vigorously at room temperature for 15 minutes and then thoroughly centrifuged to precipitate the suspended solids. The clear, colorless supernatant solution was transferred by forced siphon to a 50-ml., round-bottomed flask equipped with two n.m.r.-tube sidearms. A Gilman color test (92) for the presence of an organometallic compound was strikingly positive, as with all the Grignard reagents prepared. The dilute nitric acid hydrolysate of a sample of the solution gave an absolutely negative test for halogen with silver nitrate. Solvent was removed in a stream of nitrogen from the magnetically stirred solution, which was heated by an oil bath gradually up to 80°; the volume was reduced to 1-2 ml. N.m.r. samples were prepared by decanting the concentrate into the attached tubes, which were broken off and quickly sealed.

Dibutenylmagnesium. - N.m.r. samples of dibutenylmagnesium in concentrated dioxane solution were prepared as described above for diallylmagnesium.

Benzylmagnesium Chloride. - The preparation was carried out in the same flask used with the cyclic reactor to collect the Grignard reagent, as illustrated above. All apparatus was first oven dried, and an atmosphere of purified nitrogen was maintained throughout. The temperature of the reaction mixture was kept at $20 \pm 2°$ by a water bath. To 0.636 g. (0.0262 gram-atom) of oven-dried magnesium turnings, magnetically stirred under 10 ml. of ether, was added dropwise over 4.0 hours 1.5 ml. (1.66 g., 0.0131 mole) of freshly distilled benzyl

chloride in 20 ml. of ether. The mixture was stirred at room temperature overnight. The product solution was filtered and concentrated, and n.m.r. samples made up in the manner described above for use of the cyclic reactor. Traces of toluene were found by n.m.r. spectra to be present in each of three separate preparations, indicating the entrance of adventitious moisture. It is suspected that the tetramethylsilane used was somewhat wet.

Ethylmagnesium Bromide. - Samples of this Grignard reagent in concentrated ether solution for n.m.r. study were prepared in essentially the same manner as those of benzylmagnesium chloride, described above.

Di-β-methylallyl. - β-Methylallyl chloride (18.3 g., 0.202 mole) was coupled over 2.52 g. (0.110 mole) of magnesium in 40 ml. of ether, according to the method of Tamele et al. (112). The product (4.54 g., 0.0414 mole, 41%) had b.p. 110-111°; the fraction taken for n.m.r. work, b.p. 111°, was very pure by v.p.c.

Octadienes from the Coupling of Butenylmagnesium Bromide with Butenyl Bromides. - The procedure employed was that of Young, Roberts, and Wax (49), modified by the use of amalgamated magnesium turnings, as in the cyclic reactor. The product mixture of 3,4-dimethyl-1,5-hexadiene, 3-methyl-1,5-heptadiene, and 2,6-octadiene was distilled through a 60-cm. Podbielniak column, b.p. 100-120°; the yield was 87.2%.

Allylbenzene. - Allylbenzene was prepared by coupling phenylmagnesium bromide with allyl bromide in ether solution, according to

the method of Herschberg (113).

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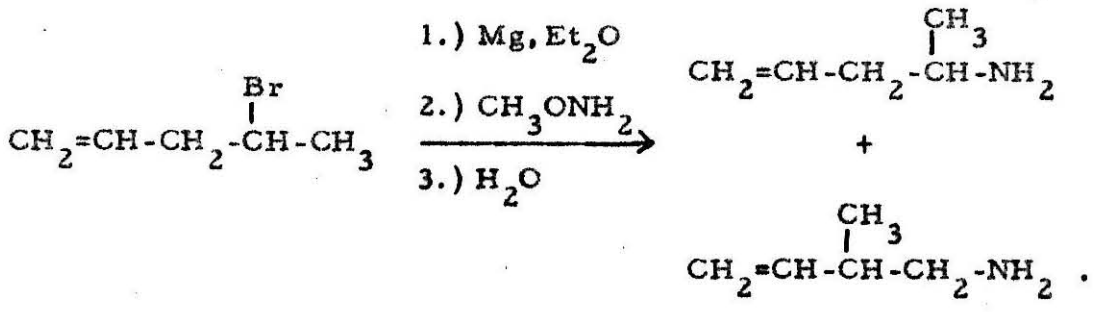
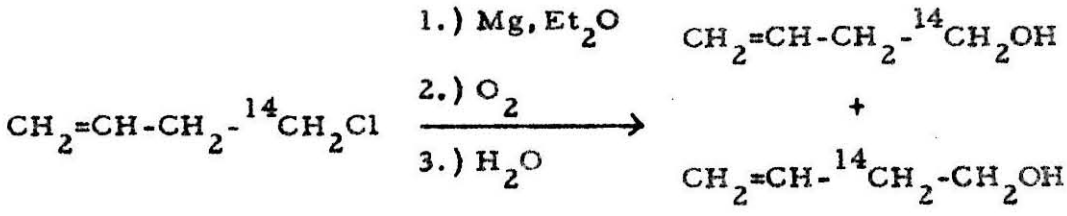
II. THE INTERCONVERSION OF CYCLOPROPYLCARBINYL AND ALLYLCARBINYL GRIGNARD REAGENTS

INTRODUCTION

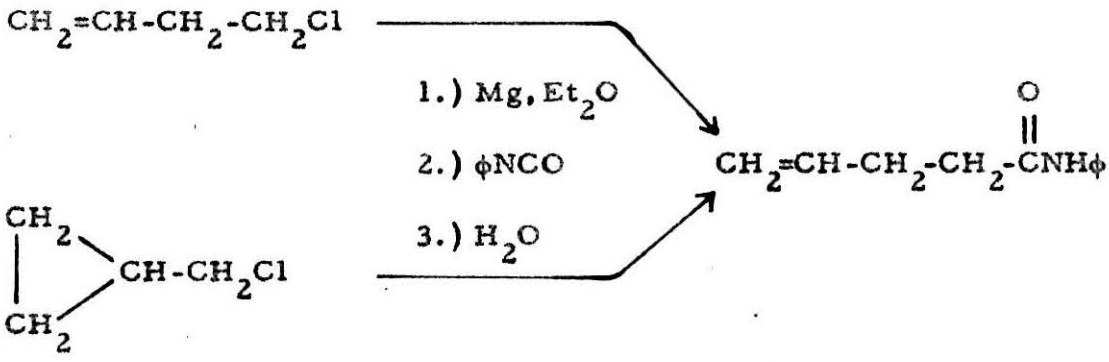
In 1959 Silver (1) discovered an unexpected rearrangement in preparing allylmethylcarbinylamine from allylmethylcarbinylmagnesium bromide and methoxylamine. The vapor-phase chromatogram of the main distillation fraction of the amine product, b.p. 107-110°, indicated the formation of two products in addition to a principal amount of the desired compound. Direct identification of the by-products was not made. But oxygenation of the allylmethylcarbinyl Grignard reagent also yielded a mixture of three products, and the largest and second-largest components were identified as allylmethylcarbinol and α-methylallylcarbinol. It was therefore concluded that the major by-product in the Grignard reaction with methoxylamine was probably α-methylallylcarbinylamine, i.e.,



These results suggested that analogous rearrangements might be observed in the Grignard reactions of isotope-labeled allylcarbinyl halides. Indeed, when the Grignard reagent prepared from allylcarbinyl-1-^{14}C chloride was oxygenated some 24 hours after its preparation, equal amounts of allylcarbinyl-1- and -2-^{14}C alcohols were formed (1).

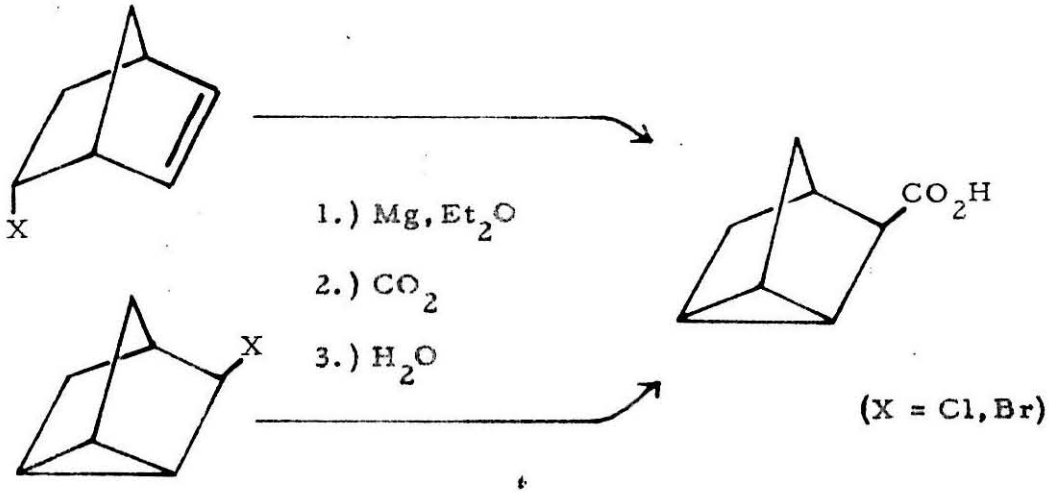


These two rearrangements were the first such cases to be reported (1) for the Grignard reactions of open-chain allylcarbinyl halides, but they were not without precedents in closely related systems. In 1951 Roberts and Mazur (2) found that the Grignard reagents derived from allylcarbinyl chloride and cyclopropylcarbinyl chloride both gave upon treatment with phenyl isocyanate only the open-chain product, allylacetanilide. It could not be determined at which stage rearrangement occurred starting with cyclopropylcarbinyl chloride, but the results certainly suggested a common intermediate in the transformation of the isomeric chlorides to the same product.



Roberts and co-workers (3) discovered the converse relationship to hold in the Grignard reactions of 5-<u>endo-</u> dehydronorbornyl and nortricyclyl halides. The former incorporate the allylcarbinyl system, and the latter the cyclopropylcarbinyl system, within a rigid framework. But here,

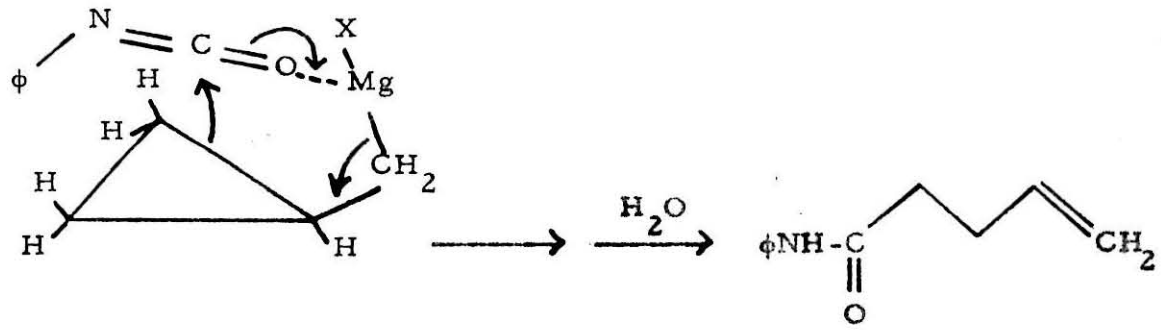
conversion to the Grignard reagents followed by either hydrolysis or carbonation gave exclusively nortricyclyl products from both isomeric starting materials, e.g.,



Several hypotheses may be offered to explain both the formation of the same Grignard-reaction products from isomeric allylcarbinyl- and cyclopropylcarbinyl-type halides and the rearrangements observed in the Grignard reactions of substituent- and of isotope-labeled allylcarbinyl halides. It may be postulated that (a) both isomeric halides form only the cyclopropylcarbinyl Grignard reagent, (b) both halides form only the allylcarbinyl Grignard reagent, (c) the cyclopropylcarbinyl and allylcarbinyl Grignard reagents exist together in equilibrium, or (d) a single Grignard reagent is formed from both isomeric halides, whose structure is intermediate between those of the starting materials. Of course, the same explanation need not be valid for both the simple allylcarbinyl-cyclopropylcarbinyl case and the analogous bicyclic case.

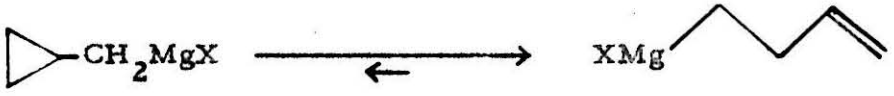
If (a) were correct, then the cyclopropylcarbinyl Grignard reagent would react exclusively at the ring methylene positions (at least with the

reactants studied thus far) to yield allylcarbinyl products, perhaps by a cyclic mechanism such as



The analogous nortricyclyl Grignard reagent, however, would react, without rearrangement, at its magnesium-bearing carbon atom. If (b) were correct, then either two equally occurring modes of reaction, at the 1- and 2-positions, would be necessary for the oxygenation of allylcarbinyl-1-^{14}C-magnesium bromide, which seems exceedingly unlikely, or else a mechanism would have to be operative for equilibration of the 1- and 2-positions before reaction of the Grignard reagent. If (c) were the case, a number of possible conditions might obtain. Firstly, the equilibrium might lie very greatly in favor of the Grignard reagent corresponding to the product obtained, so that non-rearranging reaction would lead to an undetected amount of the minor product. Secondly, reaction of one form of the Grignard reagent might proceed with complete, or virtually complete, rearrangement to give the observed product isomer, regardless of the position of Grignard reagent equilibrium. Thirdly, one Grignard reagent isomer might react much more rapidly than the other, with equilibration taking place faster than product formation.

Possibility (c) has a particularly interesting aspect. If it is reasonably assumed that interconversion of the isomeric Grignard reagents involves ionization of the carbon-magnesium bond as the first step, then the process shown in equation 1 would appear to be a carbanion analog of the intensively studied rearrangements which occur in carbonium-ion reactions of cyclopropylcarbinyl derivatives (2, 4).



(Eq. 1)

The analogy holds to the extent that when the cyclopropylcarbinyl cation is generated reversibly by treating the chloride with Lucas reagent (a solution of zinc chloride in concentrated hydrochloric acid), the starting material is completely converted to allylcarbinylchloride (2). There is, however, a fundamental difference in the rearrangement reactions of the oppositely charged intermediates, in that the cyclobutyl structure is intimately involved in the carbonium-ion series but excluded in the carbanion series. Most carbonium-ion reactions of cyclopropylcarbinyl and cyclobutyl derivatives give mixtures of cyclopropylcarbinyl, cyclobutyl, and allylcarbinyl products, whose compositions are essentially independent of the isomeric structure of the starting materials (4c). On the other hand, no cyclobutyl products have been detected in the Grignard reactions of cyclopropylcarbinyl halides (2), and the Grignard reagents from cyclobutyl chloride (2) and bromide (5) react to give only cyclobutyl products.

It was anticipated that valuable information on the nature of cyclopropylcarbinyl- and allylcarbinyl-type Grignard reactions could be gained from the nuclear magnetic resonance (n.m.r.) spectra of solutions of the Grignard reagents prepared from various sets of isomeric halides in this series.

EXPERIMENTAL RESULTS

The Grignard reagents from allylcarbinyl chloride and cyclopropylcarbinyl chloride (at least 99% pure by vapor phase chromatography (v.p.c.)) were prepared in ether under conventional conditions, filtered free from suspended solids, concentrated, and made up into n.m.r. samples. The n.m.r. spectra of the two Grignard reagents were identical in all respects. The spectrum of the common Grignard reagent is shown in Figure 1, together with the spectra of the isomeric chlorides. It is clear from the spectra that the Grignard reagent possesses fundamentally the allylcarbinyl structure(6). Thus,the triplet at + 28 cycles per second (c.p.s.) (all chemical shifts are relative to tetramethylsilane as an internal standard) belongs to the α-methylene protons (which absorb at -209 c.p.s. in allylcarbinyl chloride), split by the β-methylene protons and highly shielded by the adjacent magnesium atom. The quartet at -135 c.p.s. in the Grignard reagent spectrum is assigned to the β-methylene hydrogens and corresponds to the quartet at -148 c.p.s. in the allylcarbinyl chloride spectrum. The fine structure in the Grignard reagent γ-proton band (centered at -353 c.p.s.) is virtually identical to that in the allylcarbinyl chloride spectrum. There are seen to be distinct differences in the δ-methylene resonance pattern between the Grignard reagent (at -285 c.p.s.)

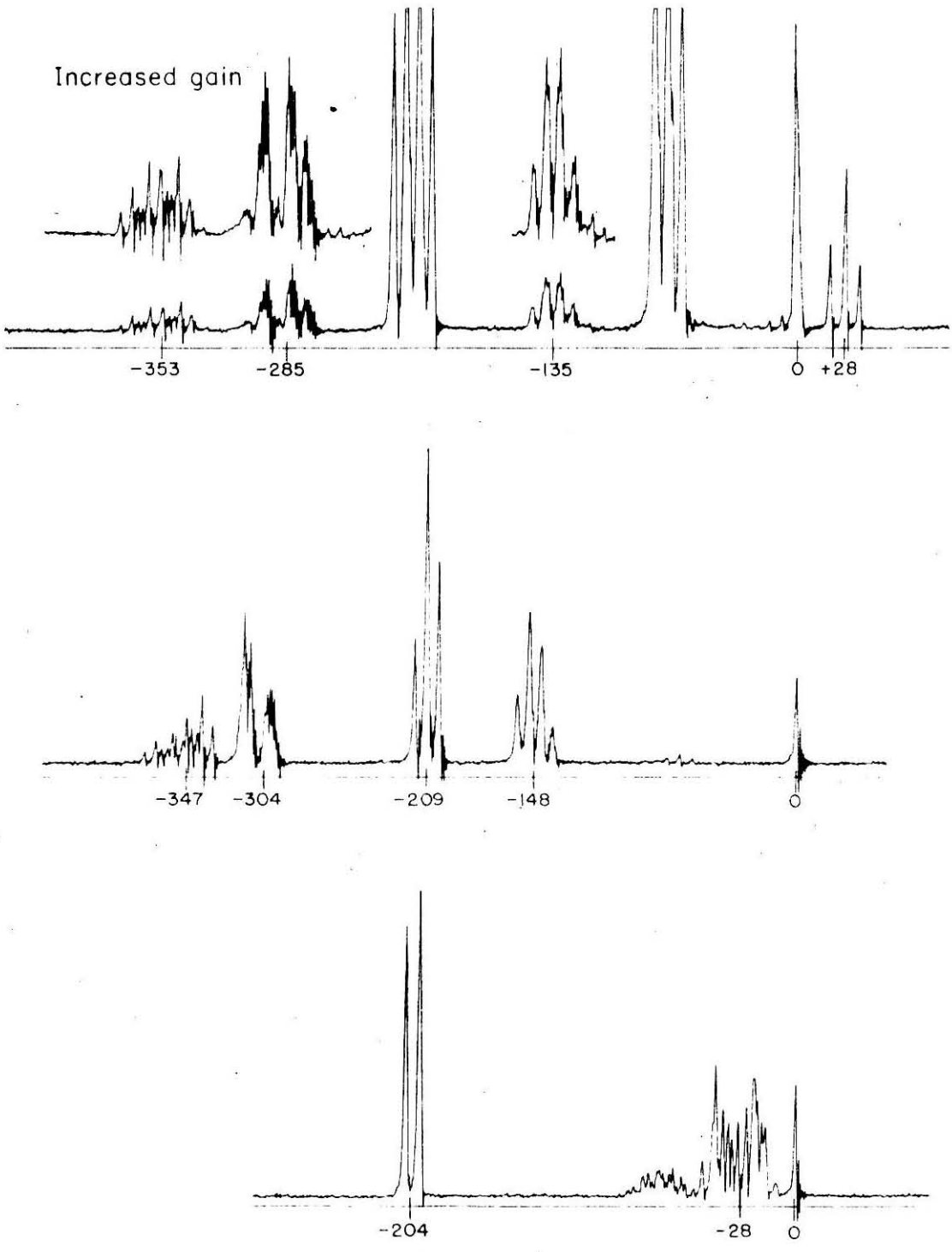


Fig. 1. - Upper: Proton magnetic resonance spectrum of the Grignard reagent, in ether, from either allylcarbinyl chloride or cyclopropylcarbinyl chloride, plus tetramethylsilane as internal standard. Middle: Spectrum of allylcarbinyl chloride, plus tetramethylsilane. Lower: Spectrum of cyclopropylcarbinyl chloride, plus tetramethylsilane. Chemical shifts are in c.p.s.

and allylcarbinyl chloride (at -304 c.p.s.). This dissimilarity might well be due to a field-effect shift in the relative line positions for the cis- and trans-δ-protons in going from the chloride to the Grignard reagent.

The n.m.r. spectrum of the Grignard reagent from cyclobutyl chloride is shown in Figure 2, together with that of cyclobutyl chloride (at least 95% pure by v.p.c.). The cyclobutylmagnesium chloride structure is clearly indicated by the single band for the ring-methylene protons at -124 c.p.s., in the same region as the band for the methylene protons in the cyclobutyl chloride spectrum. The α-proton signal of the Grignard reagent appears to be mainly hidden under the ether $-CH_3$ band.

Next, the Grignard reagents from endo-5-dehydronorbornyl chloride, exo-5-dehydronorbornyl chloride, and nortricyclyl chloride were investigated. Careful distillation of the Diels-Alder adduct of cyclopentadiene and vinyl chloride yielded a fraction whose composition by v.p.c. was ~ 84% endo- and ~ 16% exo-5-dehydronorbornyl chloride (Chloride A). A sample of nortricyclyl chloride from the chlorination of norbornene was found to be $\gtrsim$ 99% pure by v.p.c. (Chloride B). endo-5-Dehydronorborneol was treated with thionyl chloride in ether to give a mixture (Chloride C) of ~ 40% exo-5-dehydronorbornyl chloride and ~ 60% nortricyclyl chloride (by v.p.c.). Chlorides A, B, and C were converted to their respective Grignard reagents in ether solution

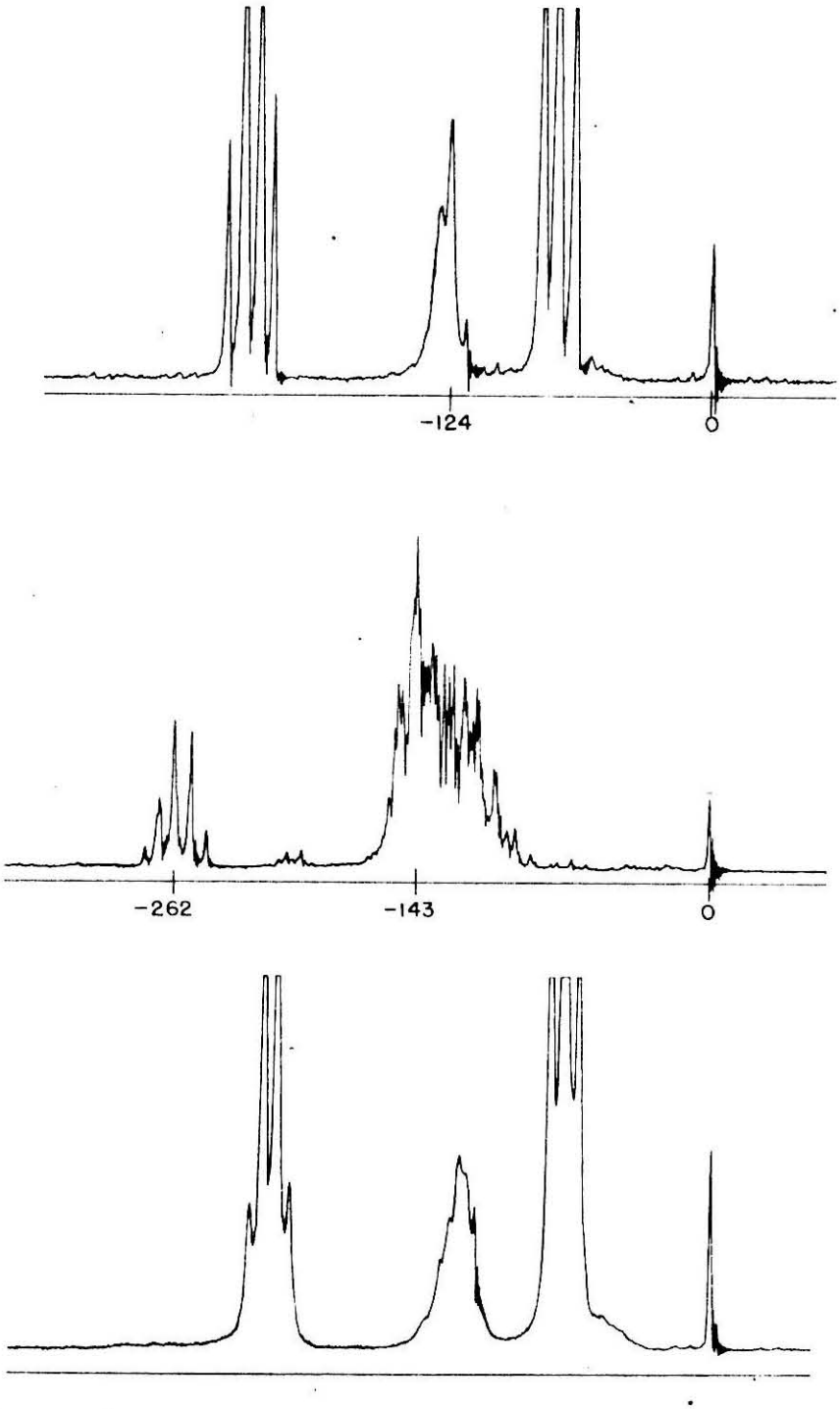


Fig. 2. - Upper: Proton magnetic resonance spectrum of cyclobutylmagnesium chloride in ether, plus tetramethylsilane as internal standard (room temperature). Middle: Spectrum of cyclobutyl chloride, plus tetramethylsilane. Lower: Spectrum of cyclobutylmagnesium chloride in ether, plus tetramethylsilane, at -37°. Chemical shifts are in c.p.s.

and concentrated. The n.m.r. spectra of all three Grignard reagents were identical. The common spectrum is shown in Figure 3, along with those of chlorides A and B.

The structure of this Grignard reagent may not be as readily deduced from its spectrum and those of the chlorides leading to it as was possible in the allylcarbinyl-cyclopropylcarbinyl case. The characteristics of the Grignard reagent spectrum, however, strongly favor the nortricyclyl- over the dehydronorbornylmagnesium chloride formulation. To be sure, the features of the spectrum of the magnesium derivative are decidedly different from those of nortricyclyl chloride. But the general complexities of the two spectra are quite comparable, indicating a similar order of symmetry for the two compounds. The spectrum of the dehydronorbornyl chlorides, in contrast, is vastly more complicated. In addition, the same singlet character of (a) the signal at -230 c.p.s. in the nortricyclyl chloride spectrum due to the deshielded proton at the chlorine-substituted position and (b) the signal at +17 c.p.s. in the Grignard reagent spectrum due to the shielded proton at the magnesium-substituted position supports the judgment that nortricyclyl chloride is converted to its Grignard reagent without a change in carbon structure. The proton at the chlorine-substituted position in endo-5-dehydronorbornyl chloride is seen to give rise to a pair of triplets, at -260 c.p.s. Furthermore, the difference in positions of lines (a) and (b) (247 c.p.s.) was found to be exactly equal to the chemical shift difference between the α-protons in ethyl chloride

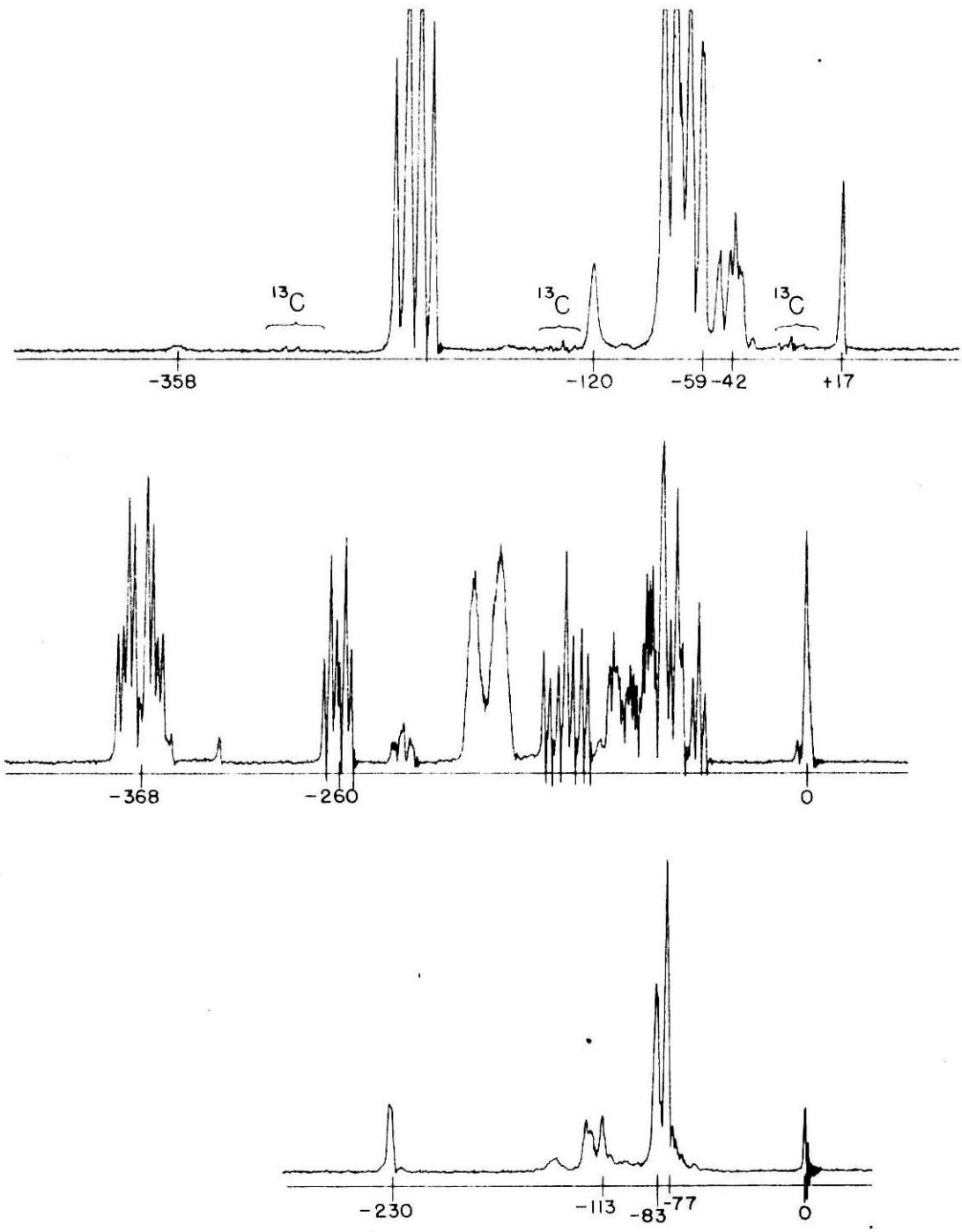


Fig. 3. - Upper: Proton magnetic resonance spectrum of the Grignard reagent, in ether, from either exo- or endo-5-dehydronorbornyl chloride or nortricyclyl chloride. Middle: Spectrum of Chloride A. Lower: Spectrum of Chloride B. Chemical shifts are in c.p.s. from tetramethylsilane as internal standard, not shown in the Grignard reagent spectrum. Sidebands in the Grignard reagent spectrum due to naturally abundant ^{13}C in the ether are identified.

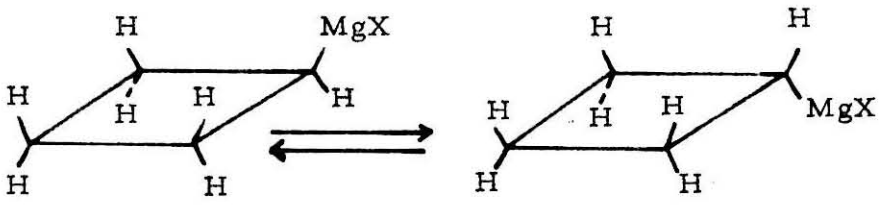
(-211 c.p.s.) and ethylmagnesium chloride in ether (+ 36 c.p.s.), further indicating that the reaction of nortricyclyl chloride with magnesium in ether, as that of ethyl chloride, effects simply the substitution of magnesium for chlorine.

It was suspected that the very weak band in the Grignard reagent spectrum at -358 c.p.s. might possibly be due to the olefinic protons in a small proportion of dehydronorbornylmagnesium chloride in slow equilibrium with nortricyclylmagnesium chloride. Partial hydrolysis of a sample of the Grignard reagent, however, resulted in an intensification of the band at -358 c.p.s. and a diminution of all other peaks due to the Grignard reagent. The low-field signal in question was thus concluded to be caused by a minor impurity (perhaps the basic salt Mg(OH)Cl) instead of any Grignard reagent species.

Some further attention was paid to an interesting facet of the n.m.r. spectrum of cyclobutylmagnesium chloride in ether (Figure 2). It is conspicuous that the band due to the methylene protons in this Grignard reagent is much less broad and less complex than the corresponding band in the cyclobutyl chloride spectrum. Thus, the substitution of magnesium for chlorine has brought about a high degree of coalescence of the line positions for the various methylene hydrogens in the ring. It is very likely that the electron-donating inductive effect of the magnesium atom is in part responsible for the observed narrowing. It has been found by deuterium labeling that in cyclobutanol the

2,4-hydrogens resonate at slightly lower field strength than the 3-hydrogens (4a). In all probability the same relationship obtains in cyclobutyl chloride, whose ring-proton resonance pattern is very similar to that of cyclobutanol (4a). The inductive effect of magnesium at the 1-position should shift the absorption of the 2,4-hydrogens upfield more strongly than that of the 3-hydrogens and so would be predicted to cause these groups of lines to merge to some extent in the Grignard reagent.

An additional possibility exists, however, to help explain the band-narrowing in the cyclobutyl Grignard reagent and is of considerable theoretical interest. The high multiplicity of the principal band in the cyclobutyl chloride spectrum is doubtless due in some measure to the non-identical environments of gem-protons cis and trans to the chlorine substituent. A distinct simplification of the Grignard reagent spectrum would be expected if rapid inversion about the 1-carbon atom in cyclobutylmagnesium chloride were able to take place, thereby averaging environments above and below the plane of the ring.



(7) (Eq. 2)

It is a rule thus far without verified exception that Grignard reactions take place with complete loss of stereochemical integrity at the

position bearing the halogen atom in the starting material (8). (Partial preservation of stereochemistry at saturated carbon has been reported, however, for optically active 2-octyllithium prepared and carbonated at -70° (9), optically active sec-butyllithium at -1° (10), and optically active 1-methyl-2,2-diphenylcyclopropyllithium at 6° (11), while stereospecific conversions of cis- and trans-2-methylcyclopropyllithium to the corresponding carboxylic acids have recently been observed (12). Also cis- and trans-vinyllithium compounds have been found to be configurationally stable, in some cases above 0° (13). Carbonation of the Grignard reagent from syn-7-bromonorbornene produces twice as much anti- as syn-carboxylic acid (14), but the behavior of the anti-7-bromide in this sequence has not been reported.) It has not been possible to decide, however, whether (a) racemization or equilibration takes place exclusively during reaction of the starting halide with magnesium at the metallic surface or (b) rapid inversion of configuration at the 1-carbon atom of the Grignard reagent after its formation can also account for the loss of geometric identity. Evidence has previously been cited (15) for the absence of appreciable concentrations of free carbanions in Grignard reagent solutions, but inversion could proceed through ionization to form ion pairs.

Such an inversion process in the cyclobutyl Grignard reagent (Equation 2) should be temperature dependent and lead to an increase in the fine structure of the n.m.r. spectrum as the temperature is

lowered and the inversion retarded. The spectrum of cyclobutylmagnesium chloride in ether at -37° is shown in Figure 2. It is seen that the multiplicity of the band due to the ring methylene protons is indeed somewhat greater at -37° than at room temperature. Although the difference is not sufficiently pronounced to be considered a conclusive demonstration of the operation of Equation 2, the results obtained would surely seem to justify further investigation of this question.

DISCUSSION

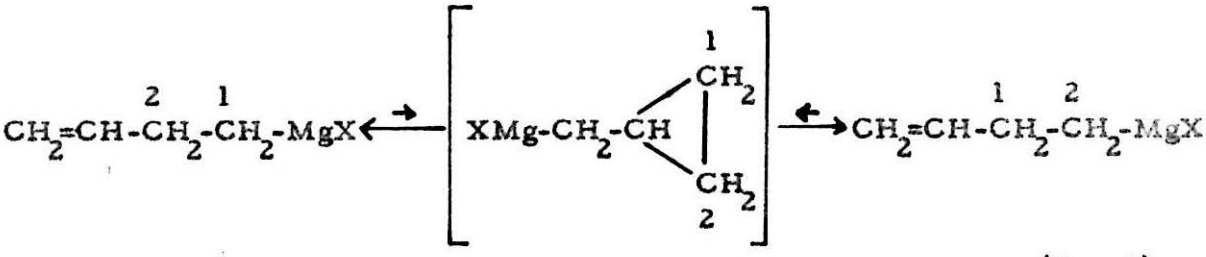
The assignment of (a) the allylcarbinyl structure to the Grignard reagent from either allylcarbinyl chloride or cyclopropylcarbinyl chloride and (b) the nortricyclyl structure to the Grignard reagent from either exo- or endo-5-dehydronorbornyl chloride or nortricyclyl chloride is in both cases in keeping with the relative thermodynamic stabilities of the isomeric forms involved. From heats of combustion the heat of isomerization of cyclopropane to propylene has been determined to be -7.68 kcal. per mole (16). Isomerization of either norbornene or nortricyclene over a silica-alumina catalyst has been found to give a mixture of 77% nortricyclene and 23% norbornene, corresponding to a free energy difference of 0.91 kcal. per mole at 105° (17). The reversal of the order of stabilities for related structures in going from the simple four-carbon case to the bridged bicyclic case has been attributed to angle strain and non-bonded interactions in norbornene (17). Actually the free energy difference between the nortricyclyl and dehydronorbornyl Grignard reagents must be considerably greater than that between the respective hydrocarbons, since the n.m.r. evidence indicates that none of the latter Grignard reagent is present in equilibrium with the former.

The reactions with magnesium of the isomeric halides in these related series proceed in the same respective directions as other

reactions whose natures are governed by the stabilities of the products formed. The isomerization of cyclopropylcarbinyl chloride to allylcarbinyl chloride with Lucas reagent (carbonium-ion conditions) has already been referred to. A similar rearrangement also occurs under free-radical conditions in the vapor-phase chlorination of methylcyclopropane, where the principal products are allylcarbinyl chloride and cyclopropylcarbinyl chloride in equal amounts (2). In the bicyclic series, the reactions of norbornene with N-bromosuccinimide and with bromine both yield only nortricyclyl bromide, and the reactions of endo-5-dehydronorborneol with thionyl chloride and with phosphorous tribromide give mainly nortricyclyl chloride and bromide, respectively (3).

Both the allylcarbinyl and nortricyclyl Grignard reagents are judged to exist exclusively (within the present limits of experimental detection) in one isomeric form and to react to form products without rearrangement.

There remains to be explained the mechanism whereby the 1- and 2-positions in the allylcarbinylmagnesium halides become interconverted. If it is assumed for the moment that the interconversion process takes placed continuously in solution after the formation of the Grignard reagent (evidence validating this assumption will be cited shortly), the simplest explanation would be the intervention of a transitory intermediate with the symmetry characteristics of cyclopropylcarbinylmagnesium halide; this species could then reopen in either of two directions, as shown in Equation 3.

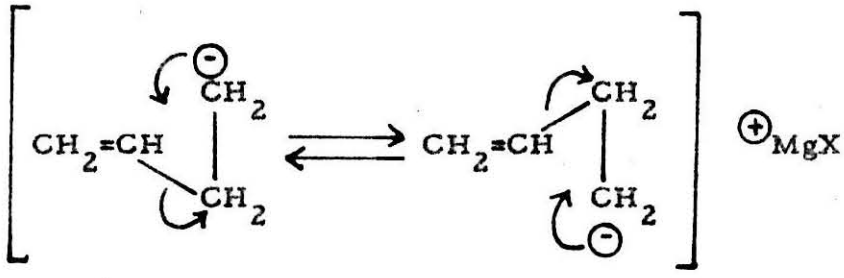


(Eq. 3)

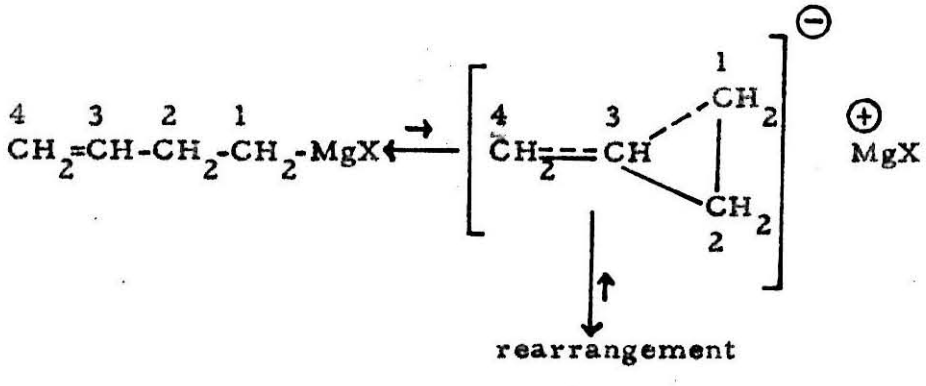
Recently Shafer (1) has found it possible to measure the overall rate of this rearrangement by following the changing intensities of the peaks due to the 1- and 2-protons in the n.m.r. spectrum of the Grignard reagent prepared from allylcarbinyl-1,1-$^{2}H_2$ bromide. In this manner, the half-time for equilibration was determined to be 30 hours at 27° and 40 minutes at 55.5°, corresponding to an activation energy of approximately 23 kcal. per mole. In addition, it was demonstrated that negligible rearrangement takes place either during formation of the Grignard reagent or in the course of its reaction with oxygen or carbon dioxide.

It is not possible to affirm whether the cyclopropylcarbinyl Grignard reagent exists as a discrete intermediate in Equation 3. It is estimated that roughly 2% of this form of the Grignard reagent could be detected in the n.m.r. spectrum, Figure 1. The steady-state concentration of cyclopropylcarbinylmagnesium chloride could, of course, be well below such a value, but only with a concomitant loss in the importance of this species as a "stable intermediate" facilitating the rearrangement process. It is alternatively possible that the cyclopropylcarbinyl configuration has significance only as a transition state in Equation 3.

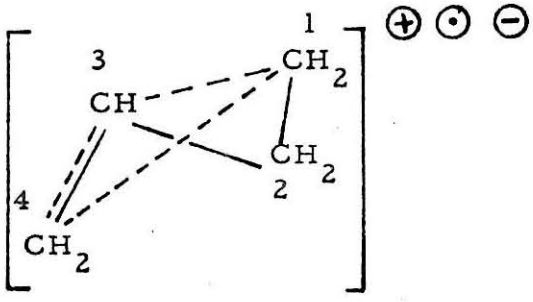
Another important aspect of the rearrangement which cannot be settled by the available data is the nature of the initiating step. Several possibilities may be considered. The first step might be ionization of the carbon-magnesium bond to form the simple allylcarbinyl anion, probably within an ion pair, $CH_2{=}CH{-}CH_2{-}\overset{\ominus}{C}H_2\,\overset{\oplus}{M}gX$. This carbanion could then undergo concerted transposition of its 1- and 2-carbon atoms



or else rearrange by way of an intermediate cyclopropylcarbinyl anion, with or without internal return to the corresponding Grignard reagent. As a related possibility, the initial ionization might proceed directly to a delocalized homoallylic carbanion, as part of an ion pair, whence one- or two-step rearrangement could follow.

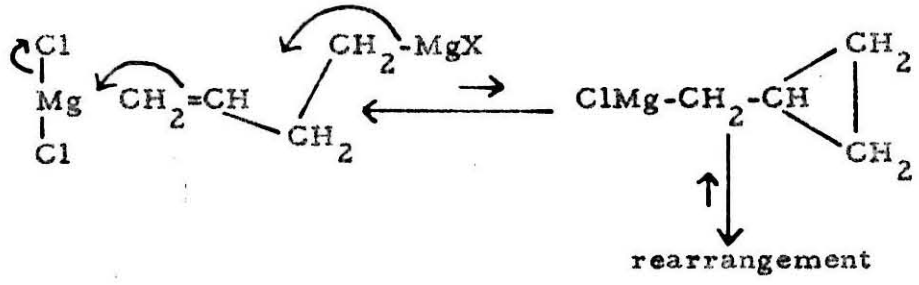


The homoallylic structure has been demonstrated to be important for a number of carbonium-ion intermediates (18). Simple LCAO molecular orbital calculations (19) show that the homoallylic structure possesses one bonding, one non-bonding, and one anti-bonding π-electron molecular orbital, so that the carbonium ion, radical, and carbanion all have the same delocalization energy if interelectronic repulsion is neglected (20). It is of further interest that similar calculations for the bicyclobutyl structure,



which takes into account 1-4 as well as 3-4 and 1-3 electronic interaction, lead to one strongly bonding orbital and two anti-bonding orbitals, so that the carbonium ion is predicted to be stabilized relative to the radical and anion (20). The bicyclobutonium ion offers the most reasonable interpretation of the interconversion in carbonium-ion reactions of a variety of cyclopropylcarbinyl and cyclobutyl derivatives (4). Since the bicyclobutonium-type intermediates in general might be expected to be transformed into cyclobutyl as well as cyclopropylcarbinyl and allylcarbinyl products, the calculated instability of the carbanion is consistent with the findings, cited previously, that cyclobutyl products are not formed in the Grignard reactions of cyclopropylcarbinyl chloride, and vice versa.

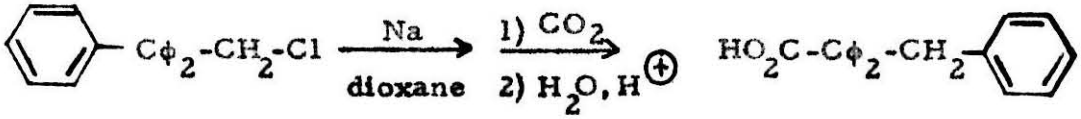
As an alternative first step distinct from the previous two suggestions, which involve ionization of the carbon-magnesium bond, the rearrangement might be initiated by attack of magnesium halide at the terminal vinylic carbon atom, leading directly to the cyclopropylcarbinyl Grignard reagent.



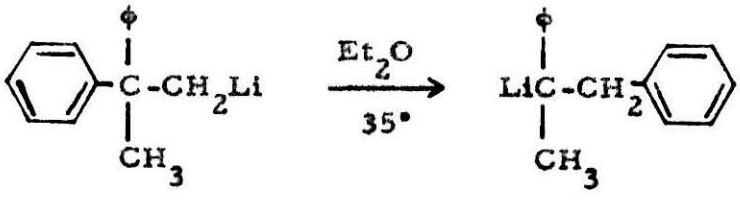
In view of this third possibility and in order to gain an understanding of the role of the solvent medium upon the rearrangement process of Equation 3, it would be of interest to study the rearrangement, by the deuterium labeling-n.m.r. technique, of di-(allylcarbinyl)-magnesium in salt-free dioxane. The recent report by Winstein and coworkers (21) of enormous salt effects upon the rates of ionizing reactions in ether adds relevance to such a projected experiment.

It is noteworthy that rearrangements analogous to that of Equation 3 do not seem to occur for Grignard reagents in which formation of an intermediate cyclopropylcarbinyl anion would require the disruption of benzenoid resonance. The Grignard reagent from tritylmethyl

chloride is reported to give only 1,1,1-triphenylethane upon hydrolysis (22), and completely unrearranged hydrocinnamic acid was obtained from carbonation of the Grignard reagent from 2-phenylethyl-1-^{14}C chloride some 46 hours after its preparation (23). However, such rearrangements do occur in systems where the magnesium is replaced by a univalent, more electropositive metal. When tritylmethyl chloride is treated with sodium in boiling dioxane and the mixture carbonated, the acid obtained (in 43% yield) is 2,2,3-triphenylpropionic acid (29).



Also, the rearrangement of 2,2-diphenylpropyllithium to 1,2-diphenyl-2-propyllithium in ether has recently been reported (25).



EXPERIMENTAL DETAILS

N.m.r. Spectra. - The instrumentation and accessory apparatus used to obtain the n.m.r. spectra have been described earlier (26).

Preparation of the Grignard Reagents. - The magnesium and ether used were the same as those previously described (26). The Grignard reagents were prepared and made up into n.m.r. samples in the same manner as that employed earlier in the preparation of benzylmagnesium chloride (27).

Allylcarbinyl Chloride. - The allylcarbinyl chloride used was prepared by the reaction of allylcarbinol with thionyl chloride, as described by Roberts and Mazur (2).

Cyclopropylcarbinyl Chloride. - The cyclopropylcarbinyl chloride used was a sample from the original material obtained by Mazur (2) by careful fractionation of the products of the vapor-phase chlorination of methylcyclopropane. V.p.c. has recently shown this cyclopropylcarbinyl chloride to be > 99% pure (4a).

Cyclobutyl Chloride. - The sample of cyclobutyl chloride used was also from material prepared by Mazur (2), by the vapor-phase chlorination of cyclobutane. Its vapor-phase chromatogram indicated the presence of < 2% allylcarbinyl chloride and < 3% cyclopropylcarbinyl chloride as impurities.

endo-5-Dehydronorbornyl Chloride. - Dicyclopentadiene and vinyl chloride were heated together in a sealed tube under the conditions

prescribed by Roberts et al. (3). The product mixture was carefully distilled through an efficient center-rod column under reduced pressure, and six fractions were collected. Of the fractions shown by v.p.c. to be practically free from dicyclopentadiene, that richest in endo- (relative to exo-) 5-dehydronorbornyl chloride had b.p. 123.5-124.0° (310 mm.). The peaks in the v.p.c. spectrum due to the endo and exo chlorides had areas in the ratio of 84:16, respectively. This material was designated Chloride A.

Nortricyclyl Chloride. - The nortricyclyl chloride used was obtained by Johnson (28) as one of the products of the liquid-phase chlorination of norbornene. Its purity was judged from its v.p.c. spectrum to be at least 99%. This material was designated Chloride B.

exo-5-Dehydronorbornyl Chloride. - endo-5-Dehydronorborneol, from saponification of the Diels-Alder adduct of cyclopentadiene and vinyl acetate (29), was allowed to react with thionyl chloride in ether containing a trace of pyridine, according to the method of Roberts, Bennett, and Armstrong (29). The resulting mixture of chlorides was distilled through an efficient center-rod column under reduced pressure. The main fraction had b.p. 51.0-53.0° (19 mm.). The peaks in the v.p.c. spectrum due to exo-5-dehydronorbornyl chloride and nortricyclyl chloride had areas in the ratio of 40:60, respectively. This material was designated Chloride C.

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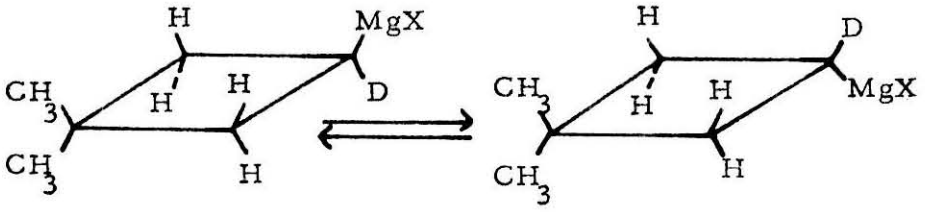
PROPOSITIONS

1. It is an experimental rule without verified exception that Grignard reactions (Eq. 1) take place with complete loss of stereo-

$$RX + Mg \xrightarrow{\text{Ether}} RMgX \xrightarrow{\text{Co-reactant}} \text{Products} \qquad (X = Cl, Br, I) \qquad \text{(Eq. 1)}$$

chemical integrity at the carbon atom bearing the halogen in the starting material (1). Evidence is not available, however, to allow one to decide whether (a) racemization or equilibration occurs exclusively during formation of the Grignard reagent, or (b) rapid inversion of configuration at the 1-carbon atom of the Grignard reagent occurs, after its formation.

It is proposed that this question could be resolved by the nuclear magnetic resonance (n.m.r.) spectrum of 3,3-dimethylcyclobutyl-1-^{2}H-magnesium bromide. If inversion of configuration at the 1-position (Eq. 2) takes place rapidly (discrete lifetimes << 0.01 sec.), the ring



(Eq. 2)

hydrogen atoms and the two methyl groups will have their respective environments averaged, and the n.m.r. spectrum will show single lines for the methyl protons and the methylene protons (assuming ^{1}H-^{2}H coupling to be negligible). If inversion is slow or nonexistent, then

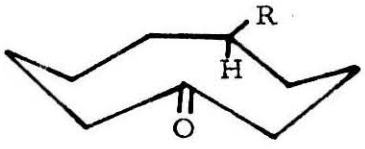
protons cis and trans to the magnesium atom would be expected to show a chemical shift separation.

Further information on the rate of inversion might be gained from high- or low-temperature spectra. The n.m.r. lines of protons located in two exchanging environments, where the average lifetimes in each environment are equal, will just coalesce when this lifetime is equal to $\sqrt{2}\ (\pi \delta H)^{-1}$ sec., where δH is the chemical shift, in c.p.s., between the lines in the absence of exchange (2). The proposed Grignard reagent has two such structural "probes" for observing the effect of temperature upon the inversion rate. In the absence of exchange the chemical shift differences between the two methyl groups and between the gem ring protons would be expected to be non-identical, and so the two sets of lines should coalesce separately, i.e., at different inversion frequencies and temperatures.

2. The very great importance of transannular migrations in the course of a variety of reactions of cyclooctyl, cyclononyl, cyclodecyl, and cycloundecyl derivatives has been forcefully demonstrated (3) by Prelog, Cope, Blomquist (and their respective co-workers), and others. This type of rearrangement seems to be quite strictly confined to cyclic systems of 8 to 11 ring members (medium-sized rings) (3c), and is due to the special proximity which positions on opposite sides of these rings can assume.

The knowledge of such rearrangements suggests that other types of cross-ring interactions might well be observed in this series of compounds. One such effect might be transannular stereochemical control of additions to suitably substituted cyclanones. The steric effects of α-substituents on the direction of additions to acyclic ketones has been intensively studied and has led to the establishment of Cram's Rule of asymmetric induction (4). Asymmetric induction by substituents γ to a carbonyl group undergoing addition has also been demonstrated, for phenylglyoxylic esters of optically active carbinols (5). Substituent steric effects on product geometry are often pronounced in the cyclohexane series. For substituents beyond the α-positions, however, ring-conformational effects are more important than direct interaction with the attacking species (6).

It is proposed that the stereochemistry of the carbonyl addition reactions of a series of 5-substituted cyclononanones (I) and 6-substituted cyclodecanones (II) be investigated. If R is a bulky group, transannular interference with the approach of a Grignard reagent or complex metal hydride, for example, should lead to alcoholic products from I and II in which the hydroxyl and R groups are predominantly cis. Compounds of type I may be prepared optically active and might lead to the observation of transannular asymmetric induction.



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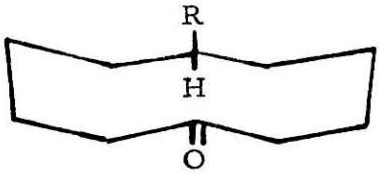
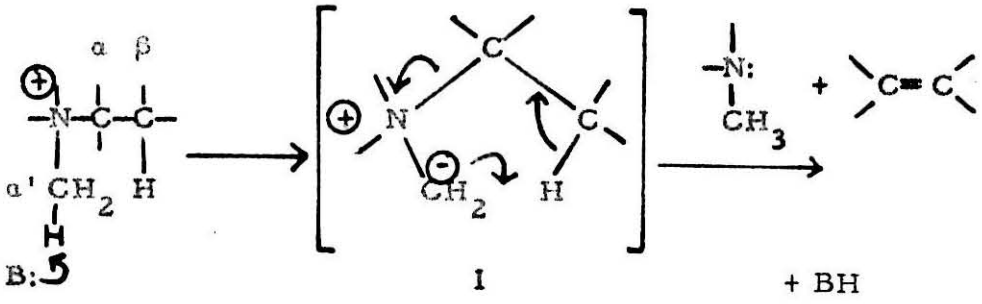


II

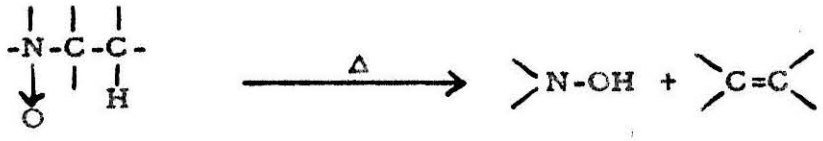
3. Until quite recently the thermal decomposition of quaternary ammonium hydroxides into tertiary amines, olefins, and water, the Hofmann elimination reaction, has been considered to take place unexceptionally by the E2 mechanism (7), in which a β-proton is removed by base simultaneously with the departure of tertiary amine from the other side of the incipient double bond.

Since 1956, however, an alternative mechanism for this reaction has been established by Wittig and Polster (8) and Weygand and coworkers (9). The newly proposed pathway involves initial abstraction of an α'-proton to form an ylid intermediate, I, which subsequently decomposes by removal of a β-proton via a quasi-five-membered cyclic transition state.



(B: = $^{\ominus}OH$, $^{\ominus}OR$, ϕLi, ...)

This ylid mechanism is completely analogous to that shown by Cope and co-workers (10) to be operative in the thermal decomposition of tertiary amine oxides, II (which are isoelectronic with primary ylids), wherein cis-elimination is highly favored.



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Since the E2 mechanism shows a strong preference for trans-elimination (7), the two possible pathways for the Hofmann elimination have a fundamental stereochemical distinction.

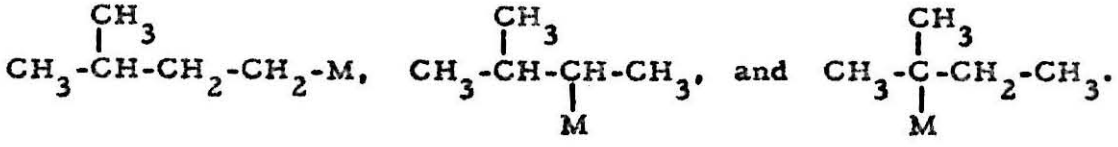
The recognition of a second possible mechanism for the Hofmann elimination suggests that in some cases earlier conclusions based on the assumed operation of the E2 mechanism for this reaction may be in error. It particularly suggests that explanations of parallel results of amine oxide pyrolyses and corresponding Hofmann elimination reactions may gratifyingly be sought in terms of an ylid intermediate for the latter process.

Two homologous cases in which such parallel behavior has been observed are the cyclononyl- and cyclodecyldimethylamines. Amine oxide pyrolysis (11) and Hofmann elimination (12) both produce exclusively the trans cycloölefin in both cases, the cis cycloölefins being the more stable isomers (11). It is proposed that the Hofmann elimination of cyclononyl- and cyclodecyl-α,α'-$^{2}H_{4}$-trimethylammonium hydroxide be studied. If reaction proceeds by way of the ylid, then the trimethylamine liberated will contain deuterium (1.0 atom of deuterium per molecule of trimethylamine, in the absence of

possible deuterium exchange in the starting material). Deuterium-free trimethylamine will be obtained if the elimination follows the E2 mechanism (again discounting deuterium exchange effects).

4. There is a large fund of qualitative evidence supporting the stability order primary > secondary > tertiary for alkyl carbanions (13). Unfortunately, however, the literature contains no quantitative data directly related to these differences. Precise measurement of the acidities of carbon acids has been possible only for cases in which the conjugate base was stabilized by resonance delocalization of the negative charge (14), often largely on an electronegative atom (as in alkyl carbonyl compounds, aliphatic nitriles, and nitroalkanes). The electron affinities of organic radicals are known in too few cases and with insufficient accuracy to permit calculation of the desired energy differences among anions (15). Pertinent thermochemical measurements have not been made.

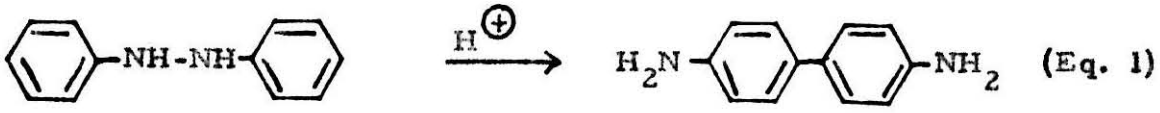
It is proposed that the heats of neutralization (protolysis) be measured for a series of isomeric primary, secondary, and tertiary alkylmetallic compounds, e.g.,



The differences in the experimental ΔH values would be a measure of the relative stabilities of negative charge concentration at primary, secondary, and tertiary carbon atoms, respectively.

It would be necessary to work with organometallic compounds of convenient stability, i.e., with a large degree of covalent character. It might be possible, however, to relate the differences in heats of neutralization for isomeric compounds with the electropositivity of the metal (16) and extrapolate to obtain the corresponding differences for more active metals, i.e., for more nearly pure carbanions.

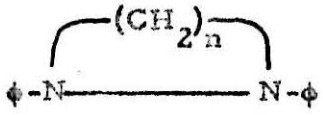
5. A fundamental uncertainty about the mechanism of the benzidine rearrangement (Eq. 1) is the question of whether N-N bond breaking



(Eq. 1)

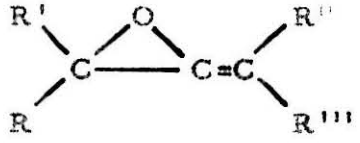
occurs during, prior to, or perhaps even subsequent to the rate-determining step. Dewar (17) has proposed that homolytic N-N bond fission accompanied by the formation of a π-complex usually precedes the rate-determining step. Hammond (18), on the other hand, prefers a mechanism in which the slow step is homolytic fission of the N-N bond of doubly-protonated hydrazobenzene. It has been suggested earlier (19) that the slow step is the second protonation itself.

It is proposed that new information on the mechanism of this reaction could be obtained by a study of the products, rates, and acid-concentration dependences of the rearrangements of a series of N-alkyl substituted hydrazobenzenes, ϕ-NR-NR'-ϕ . Steric effects between groups R and R' should influence the rates if N-N bond breaking is rate determining. It would be relevant also to investigate the reactions of hydrazobenzenes in which the two nitrogen atoms were joined together in a ring.



Models of members of this series indicate interesting geometric properties with respect to the formation of the products and intermediates normally associated with the benzidine rearrangement (17).

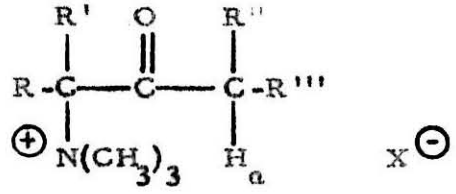
6. The literature contains very few, if any, examples of the formation of allene oxides,



I

which is not surprising, as such compounds would be expected to be very unstable. It is proposed that an investigation be made of the possible synthesis of allene oxides (with R and R' $\neq$ H) by the reaction of quaternary

ammonium salts of type II with a strong base, such as phenyllithium or sodium triphenylmethyl, in an aprotic solvent.



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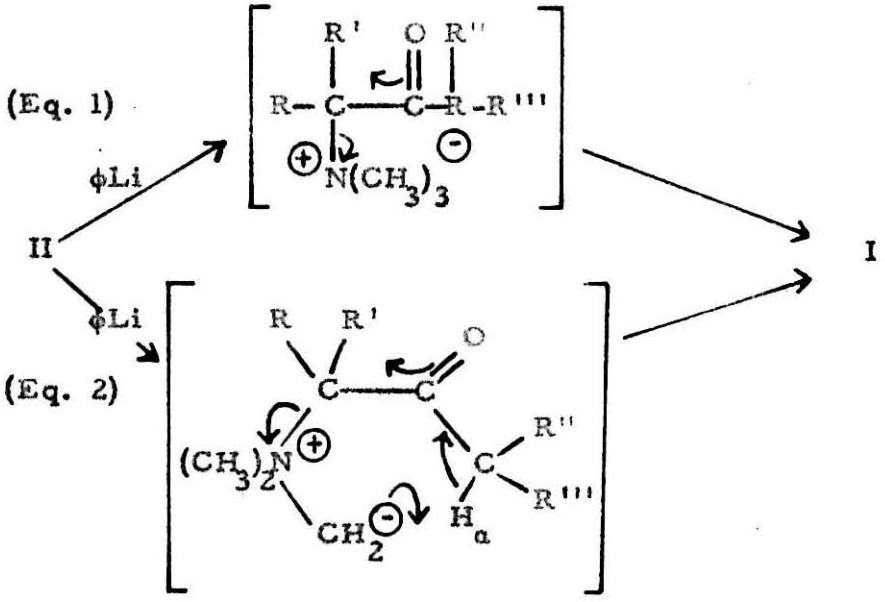
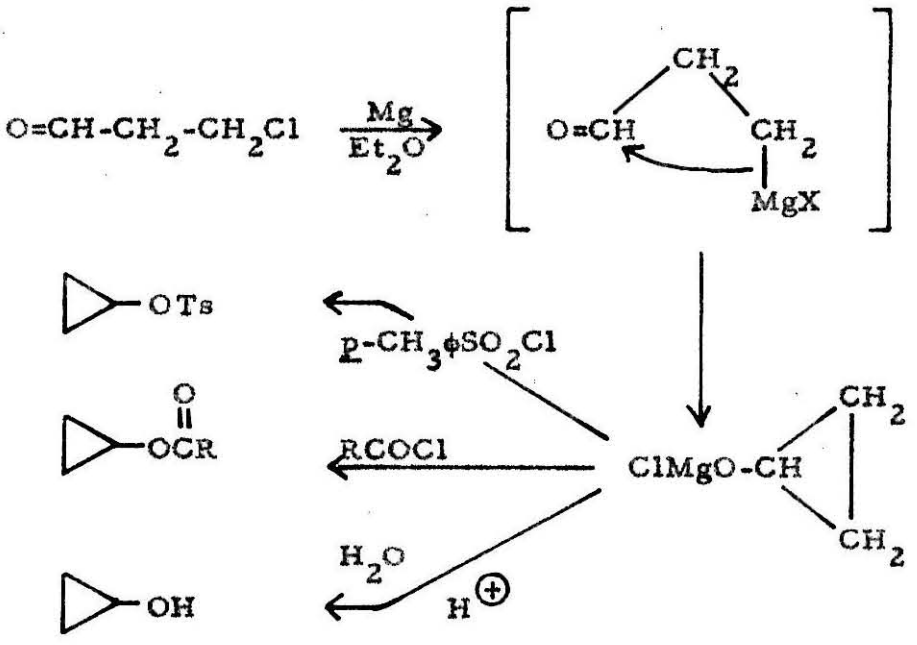
Two alternative mechanisms seem reasonable for the proposed transformation. The base might abstract proton H_a directly, followed by oxirane cyclization with the ejection of trimethylamine (Eq. 1), or else the first step might be ylid formation, followed by internal H_a-shift and synchronous or subsequent oxirane ring formation (Eq. 2).



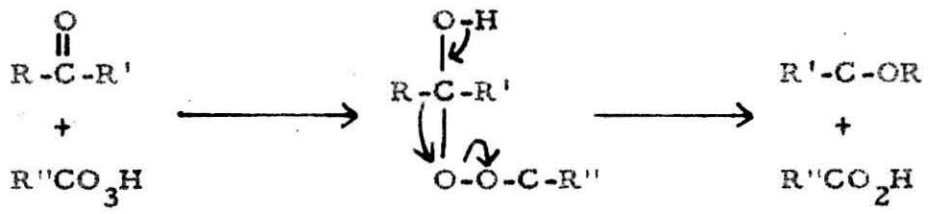
7. To date the method of choice for the preparation of a derivative of cyclopropanol is the Baeyer-Villiger oxidation of methyl cyclopropyl ketone to cyclopropyl acetate, using peroxytrifluoroacetic acid (20).

The reaction of cyclopropyl chloride with magnesium followed by oxidation and hydrolysis gives cyclopropanol in only 9% yield (21). Cyclopropanol has been obtained in yields up to 46% from the reaction of epichlorohydrin with ethylmagnesium bromide (21, 22), but the reaction is catalyzed by metallic halides, either added or present as impurities, gives impure product, and is difficult to reproduce and control (22).

It is proposed that the reactions of β-chloro- and β-bromopropionaldehyde with magnesium in ether under high dilution be investigated as a route to cyclopropanol and its esters, according to the scheme shown.



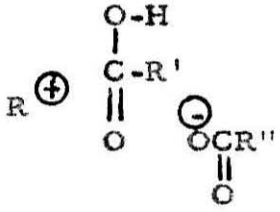
8. The relative migratory aptitudes of alkyl groups, R, in the Baeyer-Villiger reaction of ketones (Eq. 1) has been established to be generally tertiary > secondary > primary > methyl (23, 24).



(R'' = e.g. CF_3, CH_3)

(Eq. 1)

This order has been interpreted (23b, 24) as being most probably dictated by the relative abilities of alkyl groups to accommodate positive charge in the transition state for rearrangement, as represented by the canonical form I.



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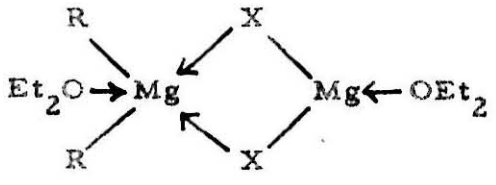
Hyperconjugation in $R^{\oplus}$ has been assumed to be important in stabilizing I, but without direct experimental support.

It is proposed that an investigation of the importance of hyperconjugation in determining relative migratory aptitudes in the Baeyer-Villiger reaction be made by treating 3-pentanone-1,1,1-$^2H_3$, II, with

II

peroxytrifluoroacetic acid (24). On the basis of a secondary deuterium isotope effect (25), hyperconjugation would be expected to be less effective in $CD_3CH_2^{\oplus}$ than in $CH_3CH_2^{\oplus}$. Its importance in facilitating the rearrangement, then, could be measured by the extent to which $CD_3CH_2CO_2CH_2CH_3$ might predominate over $CH_3CH_2CO_2CH_2CD_3$ in the product of the reaction.

9. The accumulated evidence on the constitution of simple aliphatic Grignard reagents seems to support best the formulation of these species as $R_2Mg \cdot MgX_2$ (R = Alkyl, X = Cl, Br, I) (26). Grignard reagents are intimately solvated by diethyl ether and form remarkably stable solid dietherates (27). A large number of possible structures can be written for these complexes, the two chlorine atoms being in identical environments in some of these descriptions and in dissimilar environments in others, e.g., I and II.



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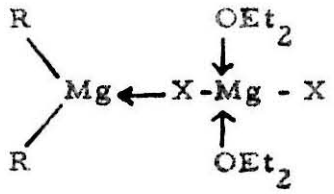
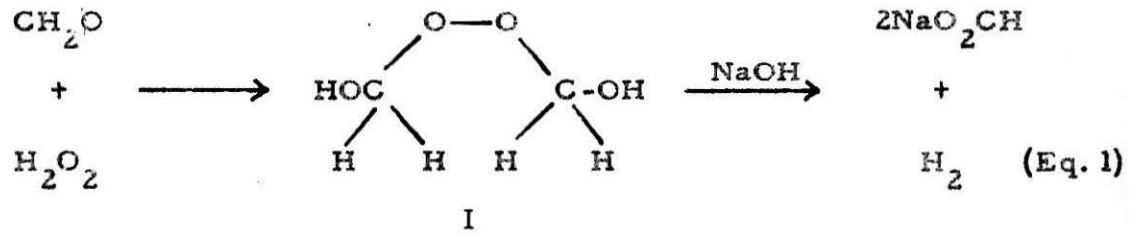


II

It is proposed that the ^{35}Cl nuclear quadripole resonance spectrum (28) of the solid dietherate of ethylmagnesium chloride be investigated in order to gain information on the environments of the halogen atoms in Grignard reagents.

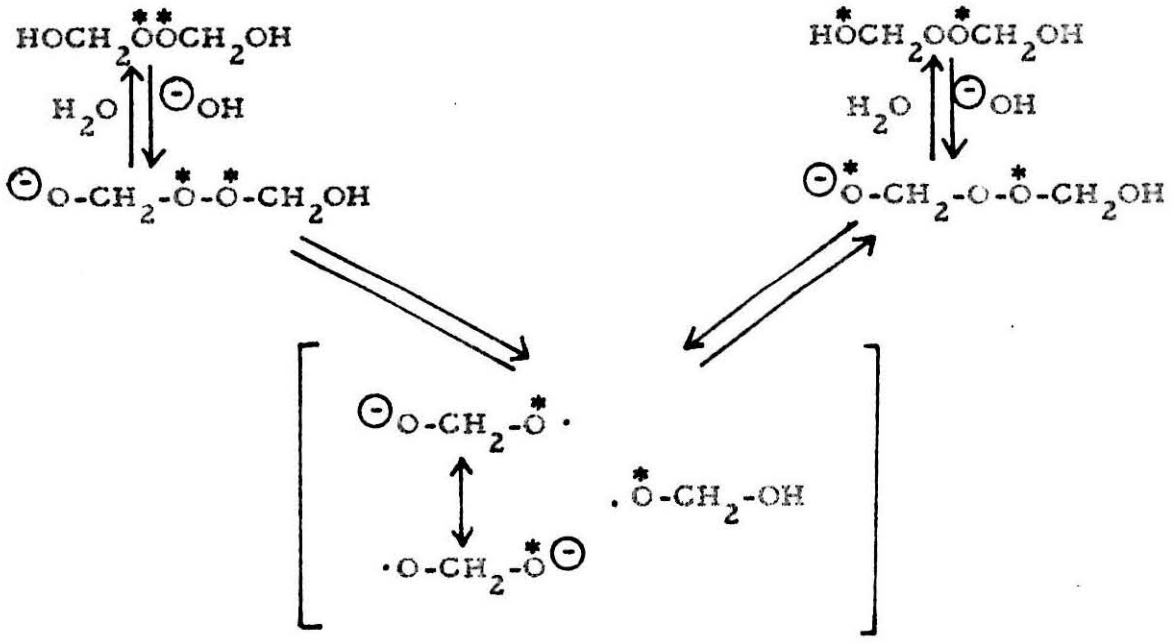
10. Jaillet and Ouellet (29) have studied the interesting base-catalyzed decomposition of bis-hydroxymethyl peroxide, I, in which molecular hydrogen is formed (Eq. 1). Kinetic measurements showed



I (Eq. 1)

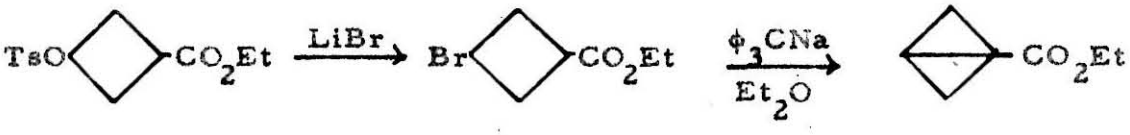
the reaction to be a complex one, and it was not possible to establish firm mechanistic conclusions. The presence of hydroquinone did not affect the course of reaction, however, allowing a radical chain mechanism to be discounted.

It would be of fundamental interest to determine whether (a) the formation of hydrogen takes place simultaneously with O-O bond fission, in a four-center-type process, or (b) the latter step occurs alone and is followed by hydrogen formation. Since (a) but not (b) predicts a primary deuterium kinetic isotope effect, it is proposed that the decomposition rates of I and I-C, C'-$^{2}H_{4}$ be compared. In the event that the rates are the same, I labeled with ^{18}O in the -O-O- positions should be partially decomposed and the recovered starting material analyzed for ^{18}O in the HO- and -O-O- positions to determine the possible operation of a rearranging dissociation-recombination process such as that of Equation 2.



(Eq. 2)

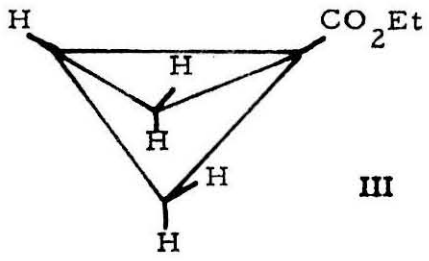
11. In 1959 Wiberg and Ciula (30) reported the synthesis of ethyl bicyclo[1.1.0]butane-1-carboxylate (II), the first authentic example of a bicyclobutane derivative, by the sequence of reactions shown.



I II

The assigned structure was based on the elemental analysis, molecular weight, and n.m.r. spectrum of the product.

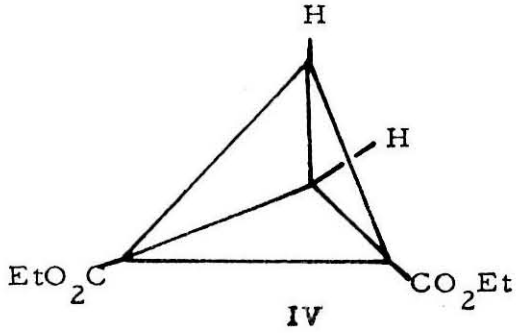
The geometry of II must be approximately represented by structure III. Although there is a great deal of apparent C-C-C bond angle



III

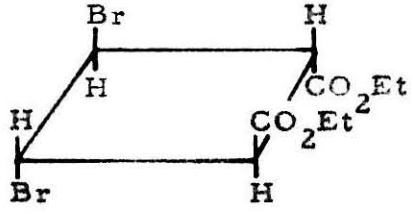
strain in III, II is a moderately stable compound, which was distilled near 60° (b.p. 56-58° (15 mm.)) and was observed to polymerize slowly upon standing.

It is proposed that the synthesis of a tricyclobutane, diethyl tricyclobutanedicarboxylate (IV), now be attempted.



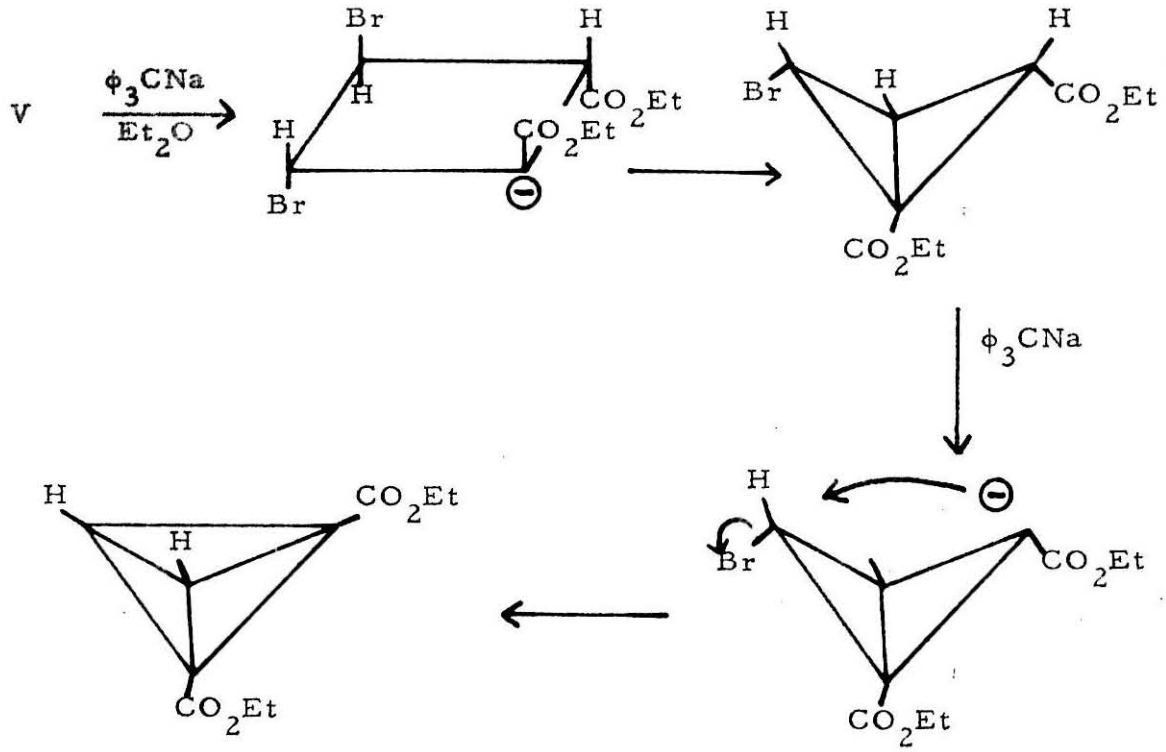
IV

Simple models indicate considerably less drastic change in molecular geometry and less incremental strain in going from III to IV than from I to III. Also, the strain in IV is shared equally among six C-C bonds, compared with five in III. A convenient starting material for the synthesis of IV would be the all-trans dibromodicarbethoxycyclobutane V.



V

This precursor has the proper geometry for successive internal S_N2 displacements, as shown in Equation 1.



(Eq. 1)

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