Comparison of the Initial and Final Stages of the Grignard Reduction Reaction[1]

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Methyl *t*-butyl ketone has been reduced with both the Grignard reagent and the dialkylmagnesium reagent from (+)-1-chloro-2-methylbutane in each case under two sets of conditions designed to isolate the initial and final stages of the reaction. The assumption was that the first alkyl group (in R_2Mg) would demonstrate different stereospecificity in the reduction than the second alkyl group (in $RMgOR'$). The per cents of asymmetric reduction from these four reactions were the same within experimental error. These results are interpreted as indicating that the same species is responsible for the reductions in each case and that indeed the first and second stages of the reaction have *not* been isolated due to a *relatively* rapid exchange reaction

$$2ROMgR \rightleftharpoons R_2Mg + (RO)_2Mg$$

Recent findings concerning the nature of the Grignard reagent[3] are best interpreted in terms of the formula $R_2Mg \cdot MgX_2$, in which the magnesium atoms retain their identity. If the Grignard reagent is indeed an etherate of $R_2Mg \cdot MgX_2$, then a difference might be expected in the reactivity of the first *vs.* the second R group attached to the magnesium atom. As the reaction proceeds, this predicted difference might be revealed in rates of reaction, relative proportions of products and/or in stereoselectivity. In the reaction of a Grignard reagent (I) with a carbonyl compound the initial product (II) should be that with both an akyl group (R) and an alkoxy group (OR′) attached to magnesium. The OR′ attached to the magnesium represents the alkoxy group resulting from either addition to (equation 1), or reduction of (equation 2),

$$\text{C=O} + R_2Mg \cdot MgX_2 \longrightarrow \text{R—C(—O—MgR}\cdot MgX_2\text{)} \quad \text{(addition)} \quad (1)$$

$$\text{C=O} + R_2Mg \cdot MgX_2 \longrightarrow \text{H—C(—O—Mg—R}\cdot MgX_2\text{)} + \text{olefin} \quad \text{(reduction)} \quad (2)$$

the carbonyl compound. Enolization and condensation products could also be formed in the initial reaction and, to the extent that they occur, there will be alkoxy groups, OR′, of still a different type. This "first stage" reaction can be abbreviated as in equation 3, where the OR′ group represents this multiple character.

$$\underset{\text{I}}{\text{C=O}} + R_2Mg \cdot MgX_2 \longrightarrow \underset{\text{II}}{R—Mg—OR'\cdot MgX_2} \quad (3)$$

When the remaining alkylmagnesium group reacts with a second molecule of carbonyl compound, addition and/or reduction can again occur. But from the different steric requirements and electronic environment of the R group in $R_2Mg \cdot MgX_2$ (I) *vs.* $RMgOR' \cdot MgX_2$ (II), one would predict different rates, different ratios of products, and altered stereoselectivity in this "second stage" reaction (equation 4).

$$\underset{\text{II}}{\text{C=O}} + R—MgOR'\cdot MgX_2 \longrightarrow \underset{\text{III}}{R''OMgOR'\cdot MgX_2} \quad (4)$$

We have already postulated a difference[4] in the relative ratios of products resulting from the "first stage" reaction (equation 3) and the "second stage" reaction (equation 4) to explain the results obtained in the reaction of diisopropyl ketone with ethylmagnesium bromide in a flowing stream system. To compare further these consecutive stages of the Grignard reaction we have chosen to study the stereoselective reduction of methyl *t*-butyl ketone by the Grignard reagent from (+)-2-methyl-1-chlorobutane[5] and by the corresponding dialkylmagnesium compound[6] under conditions designed to isolate these stages. An amount of ketone equivalent to only one half of the R groups in the Grignard (or dialkylmagnesium) reagent was first added and after stirring six hours at room temperature the remainder of the reagent was consumed by the addition of acetaldehyde. This procedure was then reversed. The results are recorded in Table I.

It is apparent that within rather minor experimental limits it made *no difference in stereoselectivity* whether the methyl *t*-butyl ketone was added for the "first stage" of the Grignard reaction or for the "second stage" of the Grignard reaction, and furthermore the same was true for the (+)-di-2-methylbutylmagnesium reagent. However, differences in yields were observed, especially in the amount of condensation product formed when acetaldehyde was first added to the dialkylmagnesium reagent. It is difficult to evaluate the meaning of this latter observation since considerable condensation of the ketone could have occurred while stirring the reaction mixture in the presence of the basic magnesium alkoxides.

These results are in agreement with the interpretation that the Grignard structure is not RMgX, since the stereoselectivities observed in the reduction reaction were the same with either the Grignard or the dialkylmagnesium reagent. On the other hand, how can the previous discussion concerning the first and

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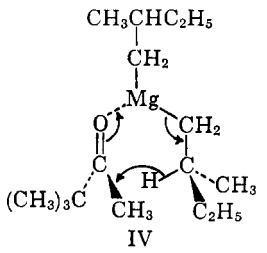
TABLE I

REACTION OF (+)-DI(2-METHYLBUTYL)MAGNESIUM OR CORRESPONDING GRIGNARD REAGENT WITH METHYL *t*-BUTYL KETONE

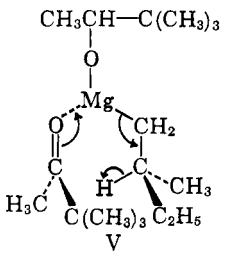
Organomagnesium		Pinacolone		Acetaldehyde		% yields pinacolone products[b]			Pinacolyl alcohol	Half phthalate	% excess dextro isomer	
Cpd.	Equiv.[a]	Order	Moles	Order	Moles	Enol.	Red.	Cond.	$[\alpha]^{24}D$	$[\alpha]D^{20}$	*c*	*d*
R_2Mg	0.205	First	0.10	Second	0.10	16	28	56	+0.93	+8.02	12.0	13.0
R_2Mg	.205	Second	.10	First	.10	63	26	11	+0.84	+7.98	10.9	12.9
"RMgX"	.17	First	.085	Second	.085	17	36	47	+0.88	+7.61	11.4	12.3
"RMgX"	.17	Second	.085	First	.085	12	39	49	+0.86	+7.84	11.1	12.7

[a] An equivalent of Grignard reagent is calculated as one formula weight of "RMgX" or one-half formula weight of $R_2Mg \cdot MgX_2$. [b] The distribution of products was determined by gas–liquid partition chromatography, the yield of pinacolone representing enolization, that of pinacolyl alcohol reduction, and that of the high boiling material condensation. [c] Corresponds to the per cent of asymmetric reduction based on the rotation of the gas chromatographically purified pinacolyl alcohol using the value of $[\alpha]^{20}D$ +7.71° of Pickard and Kenyon [*J. Chem. Soc.*, **105**, 1120 (1914)] for the pure carbinol. [d] Corresponds to the per cent of asymmetric reduction based on the rotation of the crystallized acid phthalate using the values $[\alpha]D$ 63.9° of the pure dextro isomer and takes into account the 97% optical purity of the (+)-1-chloro-2-methylbutane from which the optically active reducing agents were prepared.

second stages of the reaction of dialkylmagnesium compounds be reconciled with these results! Several possible explanations present themselves. It is barely possible that within experimental error the four reagents, R_2Mg, RMgOR′, $R_2Mg \cdot MgX_2$, and RMgOR′·MgX_2, exert the same stereoselectivity in this reduction reaction. This can be stated in terms of the differences in energies of activities, $\Delta\Delta F^*$ for IV and its diastereomeric transition state and V and its diastereomeric



IV



V

transition state. Although these two transition states and their diastereomeric forms, where the methyl and *t*-butyl groups on the ketone are interchanged, seem very similar, they do in fact differ considerably. The Grignard asymmetric reduction reaction is very sensitive to small changes; for instance, the difference between 13% asymmetric reduction and 11% asymmetric reduction at room temperature represents a difference of only 0.030 kcal./mole in the energies of activations between the *d* and *l* transition states. Substitution of an ethyl group for the methyl group in the *t*-butyl ketone causes such a change in asymmetric reduction.[5] Certainly structures IV and V should reflect larger differences than this. This same line of reasoning can be used to dismiss the assumption that the reactive species in the Grignard reduction reaction is RMgX, since it seems quite unlikely that RMgX would have the same stereoselectivity as R_2Mg or RMgOR′.

It seems much more reasonable to assume that the great similarities in stereoselectivities, in spite of the apparent different reagents and differences in orders of addition, is a result of reduction by the same reducing species. Three mechanisms whereby this is possible suggest themselves. *First:* If we assume that the active reducing species in the Grignard reagent is R_2Mg and that the first stage of the reaction is slow compared to the second stage reaction, *i.e.*,

$$\text{C=O} + R_2Mg \xrightarrow{k_1} RMgOR' \qquad (5)$$

$$\text{C=O} + RMgOR' \xrightarrow{k_2} R'OMgOR' \qquad (6)$$

where $k_1 \ll k_2$

so that, regardless of the order of addition of reagents, each R_2Mg is completely consumed by conversion to R′OMgOR′ without the accumulation of RMgOR′ then the observed stereoselectivity would be the cumulative results of equations 5 and 6. However, the assumption that R′OMgR reacts much faster than R_2Mg seems unlikely on the basis of the reaction of other known metalloörganic compounds. Thus Ziegler[7] reports that only one of the three alkyl groups in triethylaluminum will add to a carbonyl compound. The alkoxy group on magnesium would decrease the electrophilic character of the magnesium atom and thereby reduce its tendency to react with carbonyl compounds. This is shown in the much slower rate of the Meerwein–Ponndorf reaction *vs.* the Grignard reduction reaction.

Second: The same stereoselectivity would be observed if only one of the R groups in R_2Mg or only the R group in RMgOR′ *but not both* were responsible for the reduction. In the present experiments the yields of reduction products did not exceed 50% and so this would be theoretically possible. However, the yields of reduction products did not vary greatly from the "first stage" as compared to the "second stage" of the reaction, and furthermore, many Grignard reduction reactions exceed 50% yields; thus this simple alternative is inadmissable.

Third: The conditions for one reducing agent with constant stereoselectivity, but yields in excess of 50%, can be met by assuming that either R_2Mg or RMgOR′ (but not both) is the active reducing agent and that a rapid disproportionation reaction replenishes the active reducing species as the reaction progresses. This reducing species could be either R_2Mg or RMgOR′ produced by one of the other of the following disproportionation reactions.

$$2RMgOR' \xrightarrow{k_3} R_2Mg + Mg(OR')_2 \qquad (7)$$

$$R_2Mg + Mg(OR')_2 \longrightarrow 2RMgOR' \qquad (8)$$

where $k_1 \gg k_2$ and k_3 is the same order of magnitude or larger than k_2.

As discussed above, RMgOR′ should be less reactive than R_2Mg and thus equation 7 is favored as the key

(7) K. Ziegler, *Experientia*, Suppl. 2, **14**[e], 279 (1955).

disproportionation reaction and R_2Mg as the active reducing agent. Under these assumptions, reduction by RMgOR′ is minor under the usual preparative conditions for the Grignard reaction. If the rate of the "first stage" reaction (equation 5) is very rapid with respect to the "second stage" reaction (equation 6), then the speed of the disproportionation reaction needs to be fast only with respect to the over-all time of the reaction in order to explain the data in Table I.

The present conclusions apply only to the *reduction reaction* of the Grignard and dialkylmagnesium reagents and are in accord with our previous finding[8] that the nature of the halogen atom in the Grignard reagent has only a slight effect on the reduction reaction. The extent to which these ideas apply to the Grignard *addition reaction* is not known. Anteunis[9] has concluded that R_2Mg cannot be the active species in the addition reaction of the methyl Grignard reagent to benzophenone because of the observed kinetics and because only one of the two methyl groups in the dimethylmagnesium reacted. Because of the variations in the yields of addition products with different halogens of the Grignard reagent, we had previous postulated[8] that the Grignard addition reaction involved the halogen atom in the transition state. Addition takes place with pure dialkylmagnesium even more rapidly than with the Grignard reagent[9,10] and thus it would appear that there may be more than one mechanism for the addition reaction. In any event prior conclusions must be re-evaluated in the light of this postulated disproportionation reaction (equation 7).

This postulated disproportionation reaction (equation 7) adds another parameter to the variables in the Grignard reaction. It is possible that magnesium halide acts as a catalyst for this reaction which probably varies widely with the nature of the Grignard reagent. An application of this disproportionation concept may be able to rationalize the $R_2Mg \cdot MgX_2$ structure for the Grignard reaction with the many facts of the Grignard reaction now known.

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Experimental

Grignard from (+)-2-Methylbutyl Chloride.—The Grignard reagent from 123 g. (1.2 moles) of (+)-2-methyl-1-chlorobutane, $\alpha^{25}D$ +1.40° (1 dm., neat, 97% optically pure) and 31.6 g. (1.3 moles) of magnesium was prepared in 1 l. of anhydrous ether. The solution was allowed to settle and then decanted under nitrogen into a storage flask; titration indicated at 94% yield.

(+)-Di(2-methylbutyl)magnesium.—To 600 ml. (0.66 mole) of the Grignard reagent, prepared from the same (+)-2-methylbutyl chloride in ether, was added with stirring 76 g. (0.86 mole) of dioxane over a period of 4 hr. under a nitrogen atmosphere. After stirring for 24 hr. the mixture was transferred under nitrogen to centrifuge tubes which were capped and centrifuged. The supernatant solution was transferred to a graduated storage vessel; titration indicated an 80% yield of dialkylmagnesium compound.

Reaction of (+)-Di(2-methylbutyl)mgnesium with Methyl *t*-Butyl Ketone and Acetaldehyde.—To 275 ml. of an ether solution containing 0.205 equivalent (0.75 *N*) of (+)-di(2-methylbutyl)-magnesium was added over a 45-min. period 10 g. (0.1 mole) of methyl *t*-butyl ketone in 45 ml. of ether. After stirring for 6 hr. at room temperature 4.4 g. (0.1 mole) of freshly distilled acetaldehyde dissolved in 45 ml. of ether was added over a 45-min. period. After standing overnight the slightly turbid reaction mixture was hydrolyzed by the slow addition of a minimum amount of water. The ether solution was decanted from the crystalline precipitate of magnesium salts[11] and most of the ether removed by distillation through a 15-plate column. The residue was chromatographed using an Aerograph A-90-C gas chromatograph. The 150-cm. column was packed with Ucon Polar on firebrick. Each component was identified by comparison of retention times with authentic samples and by infrared spectrometric analysis of fractions trapped at the proper time from the effluent of the chromatograph. The percentage yields, 16% enolization, 28% reduction, and 56% condensation, were calculated from weight per cent as determined from the chromatogram.[12]

The reduction and condensation products were isolated using a Beckman Megachrome preparative gas chromatograph. The high boiling material proved to be the condensation product, 2,2,5,6,6-pentamethyl-4-hepten-3-one, $n^{20}D$ 1.4469, 2,4-dinitrophenylhydrazone; m.p. 147–148.5°. 2,2,5,6,6-Pentamethyl-4-hepten-3-one is reported to have the following properties, $n^{23}D$ 1.4500, 2,4-DNP, m.p. 147–148°.[13] The reduction product, methyl-*t*-butylcarbinol had the properties, $\alpha^{20}D$ +0.70 (1 dm., neat), acid phthalate $[\alpha]^{20}D$ 8.02° ($\alpha^{20}D$ +0.80°, *c* 9.97, $CHCl_3$, l = 1 dm.), m.p. 84.1–85.8°.

A second reaction, conducted exactly as the first except that the order of adding methyl *t*-butyl ketone and acetaldehyde was reversed, gave the results summarized in Table I. A third and fourth reaction using the Grignard reagent instead of the dialkylmagnesium compound, were carried out in the same manner with the results shown in Table I.

(13) P. D. Bartlett, *ibid.*, **76**, 2349 (1954).

Ambelline

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Degradative evidence is presented to show that ambelline possesses the stereo structure III (R = OH, R′ = H).

In one of our earliest isolation studies, we reported the occurrence of ambelline in *Amaryllis belladonna*.[2] Since that time, it has been detected in several other genera of the Amaryllidaceae, particularly in the *Nerine* spp.[3–5] Ambelline was characterized as a tertiary base, $C_{18}H_{21}NO_5$, with the oxygen atoms contained in two methoxyl groups, one methylenedioxy group, and one hydroxyl. Catalytic hydrogenation provided a single dihydro derivative.[2,6] One

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(6) An identical characterization was reported by J. Renz, D. Stauffacher, and E. Seebeck, *Helv. Chim. Acta*, **38**, 1209 (1955), for traces of ambelline isolated from *Buphane fischeri* Baker.