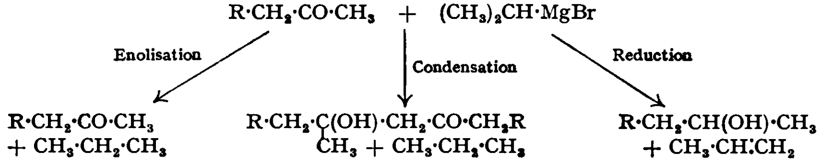
2. *The Anomalous Reactions of Grignard Reagents. Part II.*

By H. J. Shine.

Several methyl ketones, COMeR (R = Me, Et, $\mathrm{Pr^i}$, $\mathrm{Bu^i}$, $\mathrm{Bu^t}$), have been treated with $\mathrm{Pr^iMgX}$ and $\mathrm{Bu^sMgX}$ (X = Cl, Br, I) under controlled conditions. The gaseous products of reaction have been measured, and the percentage of saturated and unsaturated hydrocarbon components determined. It has been found that the proportion of enolisation and condensation to reduction caused by these Grignard reagents follows the order RMgCl > RMgBr > RMgI ; anomalous reaction is incomplete unless an excess of Grignard reagent is used. The rôle of an addition complex in anomalous reaction is discussed, and it is suggested that anomalous reaction involves the attack by other molecules on an addition complex, rather than various modes of rearrangement of a single complex.

Continuation of the investigation of anomalous reactions of Grignard reagents has shown the importance of the influence of the Grignard reagent halogen on anomalous reaction. Earlier studies by other workers on the effect of the halogen on anomalous reaction have shown conflicting results. Grignard and Savard (*Bull. Soc. chim. Belg.*, 1927, **36**, 97) found that, in the reaction of pulegone with alkylmagnesium halides, the extent of enolisation decreased with increasing atomic weight of the halogen atom. On the other hand, Grignard and Blanchon (*Bull. Soc. chim.*, 1931, **49**, 28), working with menthone and alkylmagnesium halides, concluded that, in general, the extent of enolisation is expressed by the order RMgCl < RMgBr > RMgI. Kharasch and Weinhouse (*J. Org. Chem.*, 1936, **1**, 220) reported that *n*-butylmagnesium bromide causes less reduction of benzophenone than does the chloride. Kharasch, Morrison, and Urry (*J. Amer. Chem. Soc.*, 1944, **66**, 368) found that methylmagnesium iodide causes the reduction of 2 : 4 : 6-trimethylbenzoyl chloride to the benzil, whereas the corresponding bromide does not. Shine and Turner (*J. Inst. Petroleum*, 1950, **36**, 73; Part I) have shown that pinacone undergoes condensation and reduction to 2 : 2 : 3 : 6 : 6-pentamethylheptane-3 : 5-diol in the presence of *iso*propyl- and *sec.*-butyl-magnesium bromides, but not in the presence of the corresponding chlorides.

In the present study a number of methyl ketones was treated with Grignard reagents that give saturated and unsaturated hydrocarbons as a consequence of anomalous reaction :



The effect of the halogen was determined by measuring the amount of gas evolved during reaction under controlled conditions, and determining the percentage constitution of the gas with respect to saturation and unsaturation. In Table I are given the results of these measurements. The volumes of the saturated gas are taken as a direct measure of the extent of enolisation and condensation, while those of the unsaturated gas are taken as that of reduction.

From Table I it can be seen that the total volume, representing total anomalous reaction, expresses the well-known effect of group size on extent of reaction; that is, $\mathrm{COMeBu^t}$ > $\mathrm{COMePr^i}$ > COMeEt > $\mathrm{COMe_2}$. This relation holds for all the Grignard reagents, RMgCl, RMgBr, RMgI, used. The Grignard reagents differ markedly, however, in the ratio saturated gas : unsaturated gas. For each of the ketones this ratio follows the order RMgCl > RMgBr > RMgI. (In Table I this ratio is expressed as percentage of unsaturated gas in the gaseous product.)

Discussion.—The intention of this work was to obtain further knowledge of the way in which the nature and extent of the products formed in Grignard reactions depend on the halogen atom of the Grignard reagent, and to apply the results obtained to the currently accepted mechanisms of Grignard reactions. In discussing and so applying the results, it will be first assumed that these mechanisms are correct; later, however, it will be shown that the mechanisms are not entirely satisfactory, and modifications will be suggested.

The mechanisms by which are formed the several products of the reaction between a Grignard reagent and a carbonyl compound are currently believed to involve the breakdown and rearrangement of a complex consisting of Grignard reagent and carbonyl compound. Certain refinements have been made in the pictorial representations of the addition-complex mechanisms since Hess and Rheinboldt (*Ber.*, 1921, **54**, 2043) and Grignard *et al.* (*Compt. rend.*, 1923, **177**, 299; *Ann. Chim.*, 1928, **9**, 5; *Bull. Soc. chim. Belg.*, 1927, **36**, 97) first suggested that the products corresponding to normal addition, reduction, enolisation, and condensation arose from rearrangements and breakdown of an intermediate complex, but the necessity for the existence of such a complex is still generally accepted. This necessity has been recently claimed from work on asymmetric reduction of carbonyl compounds with Grignard reagents (Vavon, Rivière, and Angelo, *Compt. rend.*, 1946, **222**, 959; Vavon and Angelo, *ibid.*, 1947, **224**, 1435; Mosher, Foley, and LaCombe, Abstracts of Papers, 115th Meeting of the American Chemical Society, page 1L; *J. Amer. Chem. Soc.*, 1950, **72**, 3994), and has been demonstrated kinetically for the reaction of Grignard reagents with nitriles (Swain, *J. Amer. Chem. Soc.*, 1947, **69**, 2306).

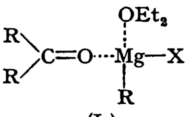
TABLE I.[a]

Volumes and percentage unsaturation of gaseous hydrocarbons evolved during Grignard reaction.

	COMe$_2$.			COMeEt.			COMePr^i.			COMeBu^t.			COMeBu^i.		
	b.	*c.*	*d.*	*b.*	*c.*	*d.*	*b.*	*c.*	*d.*	*b.*	*c.*	*d.*	*b.*	*c.*	*d.*
Pr^{i}MgCl	975	43·5	8·8	1440	64·2	12·2	1840	82·0	10·2	2130	95·0	13·8	1660	74·0	7·3
	—	—	—	1430	63·8	12·5	—	—	—	2060	92·0	13·3	1660	74·0	7·3
Pr^{i}MgBr	865	38·6	11·1	1250	55·8	16·5	1765	78·8	14·2	2130	95·0	18·7	1510	67·5	8·7
	885	39·2	12·1	1290	57·5	17·3	1855	83·0	15·0	—	—	—	1590	71·0	8·4
Pr^{i}MgI	725	32·4	26·7	1120	50·0	30·6	1735	77·5	26·1	2015	90·0	27·0	1425	63·5	13·7
	730	32·6	26·5	—	—	—	1675	74·7	25·7	1960	87·5	27·1	1410	63·0	13·7
Bu^{s}MgCl	1535	68·5	15·6	1610	71·8	17·8	1795	80·0	13·4	1900	84·8	20·0	—	—	—
	1480	66·0	15·8	1635	73·0	17·3	—	—	—	1900	84·8	20·0	—	—	—
Bu^{s}MgBr	1430	63·8	22·4	1730	77·2	27·1	1970	88·0	20·8	2060	92·0	28·1	—	—	—
	1360	60·6	22·3	—	—	—	1900	84·8	21·1	1860	83·0	27·7	—	—	—
Bu^{s}MgI	855	76·3	32·9	785	70·0	38·1	885	79·0	36·1	925	82·5	39·1	—	—	—
	715	63·8	31·0	800	71·5	37·8	830	78·0	34·5	835	74·0	40·0	—	—	—

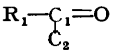
(*a*) This table represents reaction of 0·1 mole of ketone with 0·22 mole of Grignard reagent, except in the case of the Bu^{s}MgI reactions, in which 0·05 mole of ketone and 0·11 mole of Grignard reagent were used. (*b*) Total volume of gas obtained in ml. at N.T.P. (*c*) Percentage of theoretical yield of gas based on ketone. (*d*) Percentage of unsaturated gas in (*b*).

The use of addition complexes in reaction mechanisms connotes geometrical influences of the molecules involved. This connotation has been used in the cases of asymmetric reduction above, and also, earlier, in explaining the change in the types of products accompanying alterations in the constituent groups of the Grignard reagents and carbonyl compound, in the sense that these geometrical influences are exerted *within* the complex. In view of this it would be of interest to construct scale models of such complexes, the examination of which would show how great geometric influences really are. This is not possible, however, since some of the bond distances involved may be anything between those of covalent bonding and the unknown minima for co-ordination. Nevertheless, since the steric effects within a complex such as (I) will be greatest when the groups are as closely bonded as possible, one can obtain some idea of the magnitude of these effects by constructing models in which the atomic radius and bond angles of tetrahedral magnesium are used (Pauling, " The Nature of the Chemical Bond," 2nd edn., Cornell Univ. Press, Ithaca, N.Y., 1944, p. 179), and in which all bonds are single covalent.



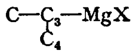
$\mathrm{R_2C{=}O\cdots Mg(\cdots OEt_2)(R){-}X}$

(I.)



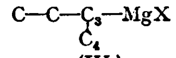
$R_1-C_1(C_2)=O$

(II.)



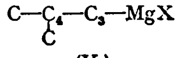
$C-C_3(C_4)-MgX$

(III.)



$C-C-C_3(C_4)-MgX$

(IV.)



$C-C_4(C)-C_3-MgX$

(V.)

In this way, for example, it is found that, in the four complexes (I) constructed from a methyl ketone (II) and the Grignard reagents (III), (IV), and (V), the alkyl groups R (denoted in skeletal form in III, IV, and V) can be brought into positions such that the least distance between the carbon atom C_1 and a hydrogen atom H_4 is the same for each complex, and similarly the least distance between a hydrogen atom H_2 and a carbon atom C_3 is the same for each complex. H_2 designates a hydrogen atom attached to the carbon atom C_2, and H_4 designates a hydrogen atom attached to a carbon atom C_4. The C_1–H_4 distance is that associated with bond formation during reduction, while the H_2–C_3 distance is that associated with enolisation. In the rigid models described, these distances, measured between atomic centres, are respectively 2·04 A. and 1·76 A. The C–H distance in alkanes is approximately 1·09 A., so that if one may draw a conclusion from the measurements in the models, it is that one would expect enolisation to occur always in greater proportion than reduction. The Grignard reagents (III), (IV), and (V), are respectively *iso*propyl-, *sec.*-butyl-, and *iso*butyl-magnesium halide, and it has been shown (Shine and Turner, *loc. cit.*) that in reactions of these reagents with ketones the extent of enolisation is generally greater than that of reduction for *iso*propyl-, approximately equal to that of reduction for *sec.*-butyl-, and much less than that of reduction for *iso*butyl-magnesium halides. Results of a similar nature are well known in the literature. Thus the influence of the alkyl groups on the formation of reaction products must be largely other than steric : that is, apart from the fact that steric hindrance may prevent normal addition and thus enhance anomalous reaction. That the formation of reaction products depends more on the bond making and breaking contributions of the constituent groups than on their size is even more apparent from the halogen variation. Geometrically, as found in the models, the halogen in the complex is intramolecularly entirely without influence, and this situation is not to be altered by the fact that the bond lengths in the complex are likely to be different from those used in its model. The results summarized in Table I, however, show that there is an ordered change in both the nature and the extent of reaction products in going from chloride to iodide; the extent of total anomalous reaction decreases, and the extent of reduction increases. This change can be due only to electronic contributions of the halogen atom. Since these contributions are an inherent character of the Grignard reagent, it become necessary to decide whether the effects they cause in reaction are due to their operation before reaction occurs or after the formation of a complex. Thus it has been argued by Kharasch, Morrison, and Urry (*loc. cit.*) that, in the presence of cobaltous chloride, methylmagnesium bromide behaves like the corresponding iodide, since that tendency possessed by the iodide to operate as a free radical, when the occasion is suitable, is created in the bromide by the cobaltous chloride; and the argument is continued that alkylmagnesium iodides may react either as ions or as free radicals according to the suitability of the situation. In this way the electronic contributions of the halogen atom are in operation before the reaction takes place. Now, while it is an attractive hypothesis that reduction by Grignard reagents is due to free-radical reactions (see also Blicke and Powers, *J. Amer. Chem. Soc.*, 1929, **51**, 3380), and enolisation and condensation are due to ionic reactions (see Arnold and Liggett, *ibid.*, 1941, **63**, 3444; Evans and Pearson, *ibid.*, 1942, **64**, 2875), there is still doubt whether either of these particle processes can occur. The Mg–X bond is undoubtedly partly polar, but it is not so certain that alkyl carbanions exist and react as such in the ethereal solution. (It should be noted that the electrolyte property of ethereal Grignard reagent solutions is thought to be due to complex carbanions such as $[R_2MgX_2]^=$; the useful reactions of Grignard reagents, however, are also considered by Hammett, " Physical Organic Chemistry," McGraw-Hill Book Co., Inc., 1940, pp. 146, 329, 382, to be those of a carbanion.) And while Kharasch, Morrison, and Urry have given consideration to the reaction of free radicals with the ether solvent, one cannot overcome the fact that the solvent molecules should be sufficient inducement to free-radical formation should the formation of free radicals need induction. Yet, one can store ethereal solutions of Grignard reagents for long periods without serious loss in activity; one can boil under reflux ethereal solutions of alkylmagnesium iodides, provided that the solutions are free from excess of alkyl halide, also without serious loss in activity; Whitmore and George (*J. Amer. Chem. Soc.*, 1942, **64**, 1241) have shown the gaseous products of reaction to be quantitatively equivalent to anomalous reaction; the results of the present paper indicate a reproducibility that would be unlikely if solvent decomposition was not inconsiderable; and if solvent–free radical interaction was taking place, one would expect the amount of gaseous hydrocarbon to increase in going from chloride to iodide, whereas it decreases.

Hence, it would appear more reasonable that the electronic contributions of the halogen atom are operative in a complex during reaction, and not before reaction takes place. However, although this may be so, and although, similarly, the electronic contributions of the other groups in the reactants are to be manifested in a complex, there is, nevertheless, a number of observations that does not support the second part of the currently accepted addition-complex reaction sequence, namely, that the products of reaction result from the breakdown and rearrangement of the complex.

Numerous examples are known in which the action of water on unheated solutions of Grignard reagent plus carbonyl compound, or on the dry residues obtained by the evaporation of such solutions, gave back the unchanged carbonyl compound. Pfeiffer and Blank (*J. pr. Chem.*, 1939,

153, 243) clarified this part of Grignard chemistry with their work on benzophenone and some substituted benzophenones, in which they showed, first, that equimolar proportions of ketone and phenylmagnesium bromide give precipitates of complexes, which, when treated with water, regenerate the respective ketones; and secondly, that excesses of 100—300% of phenyl magnesium bromide are required to prepare the desired tertiary carbinols.

In the same way it can be seen from Table II that anomalous reaction is also incomplete if an excess of Grignard reagent is not used. Indeed, the sensitive colour test with Michler's ketone was not positive at the end of those reactions in which equimolar proportions of reagents were used, and in those in which a 10% excess of Grignard reagent was used, but it was positive when 100—120% excess of Grignard reagent was used.

TABLE II.

Effect of variation in concentration of iso*propylmagnesium bromide on extent of anomalous reaction.*

Ketone.	Gas, ml. at N.T.P.	Unsat. gas, %.	RMgX, mole.	Ketone.	Gas, ml. at N.T.P.	Unsat. gas, %.	RMgX, mole.	Ketone.	Gas, ml. at N.T.P.	Unsat. gas, %.	RMgX mole.
COMeEt	840	18·9	0·10	COMeBu^i	1180	10·3	0·11	COMeBu^t	1620	17·1	0·10
	885	19·9	0·11		1175	10·7	0·11		1750	18·4	0·11
	885	19·3	0·11		1420	8·7	0·22		1860	18·2	0·11
	1160	16·5	0·22		1500	8·4	0·22		2040	18·7	0·22
	1200	17·3	0·22								

The indications are, therefore, that Grignard reactions, at least with carbonyl compounds, involve more than one molecule of Grignard reagent per molecule of second reactant. Further evidence that points in this direction is given perhaps by the formation of " coupling " products in many Grignard reactions. Particularly pertinent are the observations that in the reactions of *tert.*-butylmagnesium halide with allyl bromide, acetaldehyde, butyraldehyde, and *iso*-butyraldehyde (Whitmore, Stehman, and Hendron, *J. Amer. Chem. Soc.*, 1933, **55**, 3807), methyl ethyl ketone, and methyl *iso*butyl ketone (Shine and Turner, unpublished data), and various amides (private communication from Prof. E. E. Turner and Miss G. M. Owen, Bedford College, London), appreciable amounts of hexamethylethane are formed. It is well known that from reactions between *tert.*-butylmagnesium halide and *tert.*-butyl halide hardly any hexamethylethane is obtained, while attempts to prepare the latter by these reactions in the presence of cuprous chloride and cobaltous chloride were also without success (Shine and Turner, unpublished data). One would conclude, therefore, that the hexamethylethane is formed in the Grignard reactions, not by free-radical coupling, but by the attack of Grignard reagent on an addition complex of Grignard reagent and second reactant.

Thus, it appears from the evidence cited above that, although an addition complex is involved in Grignard reactions, the products of reaction are formed, not by various modes of rearrangement of this complex, but by the attack of other molecules on it. Where the geometric and electronic contributions of the constituent groups have their effect would then be in the manner in which a third molecule can approach and react with the complex. It is possible, in this collision mechanism, that the decrease observed in the extent of anomalous reaction in going from chloride to iodide may be due sterically to the increasing size of the halogen atom.

EXPERIMENTAL.

Reagents.—The halides and ketones used were fractionated through a column packed to a length of 4 ft. with Fenske helices, and fitted with a total-reflux, variable-take-off still head. A 1° range in b. p. was allowed in each case.

Preparation of the Grignard Solutions.—The following procedure was used for each halide except *sec.*-butyl iodide. 10 G. (0·41 g.-atom) of magnesium were covered with 50 ml. of dry ether in the usual three-necked flask set-up. To this was added 0·3 mole of the halide as a 10% solution in ether during 90 minutes, during which a further 150 ml. of ether were added in 50-ml. portions. When all the halide was added, the flask contents were boiled under reflux for 30 minutes, and the apparatus was flushed with nitrogen and then allowed to cool. The Grignard solution was then filtered by pumping it out of the flask, under nitrogen pressure, through a sintered-glass filter and into a graduated dropping-funnel. In later experiments the sintered-glass filter was replaced by a steel and glass filtration chamber, containing as the filter one of the conventional bacteria filter discs. The latter was found to be very rapid and efficient, and virtually unreactive toward the Grignard solutions. The graduated dropping-funnel was constructed so as to enable connection, by glass joints, to a gasometric analysis apparatus similar to that described by Gilman and his co-workers (*J. Amer. Chem. Soc.*, 1923, **45**, 155). The present apparatus was modified to enable the measurement of gas volume without making disconnections in the apparatus. After this apparatus had been used for determining the Grignard solution concentration, and parallel acid back-titrations had been run for the same purpose, the latter method was found sufficiently accurate for its continued use in the present study, and hence the gasometric method was eventually discarded. A measured volume of the standardised Grignard solution was then drawn from the dropping-funnel into the nitrogen-flushed reaction flask.

With *sec.*-butyl iodide it was found that the Grignard reagent can be prepared in reasonable concentration only by using (*a*) slow addition of the halide solution to the magnesium, (*b*) vigorous stirring with a Hershberg stirrer, and (*c*) temperatures between —15° and 15°. At temperatures below —15° reaction of the halide with magnesium becomes very slow, and it tends to become uncontrollable if a large concentration of halide is allowed to build up and get warmer. Complementary to these requirements is that of not refluxing the solution until after filtration. Hence, in preparing *sec.*-butylmagnesium iodide, the solution was stirred at —15° for 2 hours after the addition of the halide solution, filtered, and refluxed for one hour, the apparatus flushed with nitrogen and allowed to cool, and then analysis was carried out. Good agreement was always obtained between the amount of halide used, the starting amount of magnesium, the magnesium undissolved, the amount of Grignard reagent formed, and the calculated amount of coupling that had taken place. The table below indicates this agreement, the halide used in coupling being calculated from the amount of magnesium consumed and the amount of Grignard reagent formed, all data being in g.-moles :

Halide used.	RMgX.	RX in coupling.	Accounted RX.
0·275	0·137	0·138	0·274
0·275	0·138	0·144	0·282
0·275	0·138	0·149	0·287
0·275	0·134	0·151	0·285

The reactions between *sec.*-butylmagnesium iodide and the ketones did not give the same consistency of results as was obtained with the other halides, however, and the total amount of anomalous reaction accompanying the former reactions seems inconsistently large. The *sec.*-butylmagnesium iodide solutions were always pale yellow, whereas the other Grignard solutions were colourless.

Reactions and Gas Measurements.—In each reaction, except those involving *sec.*-butylmagnesium iodide, 0·1 mole of ketone was added as a 10% solution in dry ether to 0·22 mole of Grignard solution at room temperature. The times of addition (in minutes) were 35 for $COMe_2$, 45 for COMeEt, 60 for $COMePr^i$, and 75 for $COMeBu^t$ and $COMeBu^i$. In the reactions with *sec.*-butylmagnesium iodide, 0·05 mole of ketone and 0·11 mole of Grignard reagent were used, the times of addition being half those of the above times. After addition of the ketone solution the mixture was boiled under reflux for one hour in the case of the *iso*propylmagnesium halides, and 2½ hours in the case of the *sec.*-butylmagnesium halides.

The method of analysing the gaseous products from the *sec.*-butyl Grignard reactions differed from that of the *iso*propyl Grignard reactions. In the latter case the gases were freed from ether by first passing through a water condenser, and then by passing up an 18″ jacketed tower packed with glass beads, and kept at —5° by alcohol–carbon dioxide. The gas was then collected in traps of known volume immersed in alcohol–carbon dioxide at —76°. At the end of the reaction time the traps were connected to a calibrated aspirator in a brine tank. The gas was allowed to boil into the brine-filled aspirator, the residual gas in the traps being expelled by filling them with water. After measurement of the volume of the gas in the aspirator at room temperature and pressure, samples were analyzed for olefin in an Orsat apparatus containing 83·5% sulphuric acid. In this way, after allowance for the known volume of dead-space air in the gas, the percentage of saturated and unsaturated gas could be calculated. The consistency of the results, and the earlier work of Whitmore (*loc. cit.*), justifies the assumption that the gas components were paraffin and olefin corresponding to the Grignard reagent used.

In the case of the *sec.*-butyl Grignard reactions, the scrubber was used at room temperature, and the amount of ether vapour in the gas mixture was determined in an Orsat apparatus containing 5% sulphuric acid. The olefin was determined as above, 87·5% sulphuric acid being used. Most of the experiments were repeated at least twice.

At least two blanks were run for each Grignard reagent in the manner described above, but with the exclusion of ketone. It was found, as is to be expected if unreacted halide is absent from the solution, that the effect of refluxing the Grignard solution is virtually negligible.

The financial support which made this research possible was obtained in part from a Parke-Davis Research Fellowship, and in part from the Industrial Science Research Institute of Iowa State College. In connection with the latter the author expresses his appreciation to Dean Ralph M. Hixon. The author is much indebted to Dr. George S. Hammond and Mr. William J. Meikle for their many discussions and suggestions.

Iowa State College, Ames, Iowa, U.S.A.
Present address : Gates and Crellin Laboratories of Chemistry,
California Institute of Technology, Pasadena, Calif.

[*Received, May 2nd*, 1950.]