[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

AN APPARATUS FOR DETERMINING BOTH THE QUANTITY OF GAS EVOLVED AND THE AMOUNT OF REAGENT CONSUMED IN REACTIONS WITH METHYL MAGNESIUM IODIDE

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Methyl magnesium iodide has long been used as a valuable and, in most cases, a reliable reagent for ascertaining the number of active hydrogen atoms in an organic compound.[1] This is accomplished by measuring the methane evolved when a known weight of substance reacts with excess of the reagent in an apparatus devised by Zerewitinoff[2] which admirably serves this purpose.

A number of Grignard reactions—notably those involving oxidation and reduction—are accompanied by evolution of gas which is not due to the presence of active hydrogen. In order to follow the course of these reactions it is necessary to know the quantity of reagent consumed as well as the amount of gas evolved. The apparatus herein described was designed for the study of such reactions. Once at hand it has been employed for getting information on the structure of a great variety of organic compounds, and has proved so useful that it seemed advisable to make it available to others with similar problems.

The Apparatus[3]

The apparatus is shown in Fig. 1. *A* is a 500cc. cylindrical reservoir used for storing the solution of the reagent. It is attached to the apparatus by a ground-glass joint and contains a glass tube *a* which connects it to the buret *B* through the by-pass in the special stopcock *C*. At the top the reservoir is connected by a glass tube *b* to the stopcock *c*. Stopcocks *c* and *d* are 120° three-way stopcocks whose use will be described below, *B* is a 10cc. buret graduated in twentieths of a cc. *D* is a 5cc. buret graduated in tenths of a cc. The special stopcock *C*[4] carries, in addition to the by-pass, an ordinary three-way stopcock arrangement for con-

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[1] Houben, "Die Methoden der Organischen Chemie," Georg Thieme, Leipzig, **1924**, second edition, Vol. 4, p. 732.

[2] Zerewitinoff, *Ber.*, **40**, 2026 (1907).

[3] An apparatus essentially like this was first designed by J. F. Stone, Jr., for the investigation of nitro compounds. After several years' experience it was redesigned and simplified by R. C. Fuson. The quantitative results published herewith were obtained with the new apparatus.

[4] Instead of this special stopcock the original apparatus had a rubber stopper with four holes through which passed inlet and outlet tubes, and the ends of the two burets. In that form the apparatus can be constructed from materials generally available. It gives satisfactory results with substances that react rapidly but when long heating is necessary the rubber stopper consumes reagent and evolves gas.

necting *B* and *D* in turn with the reaction chamber *E*. The reaction chamber consists of a 40cc. flat-bottomed flask attached by a ground-

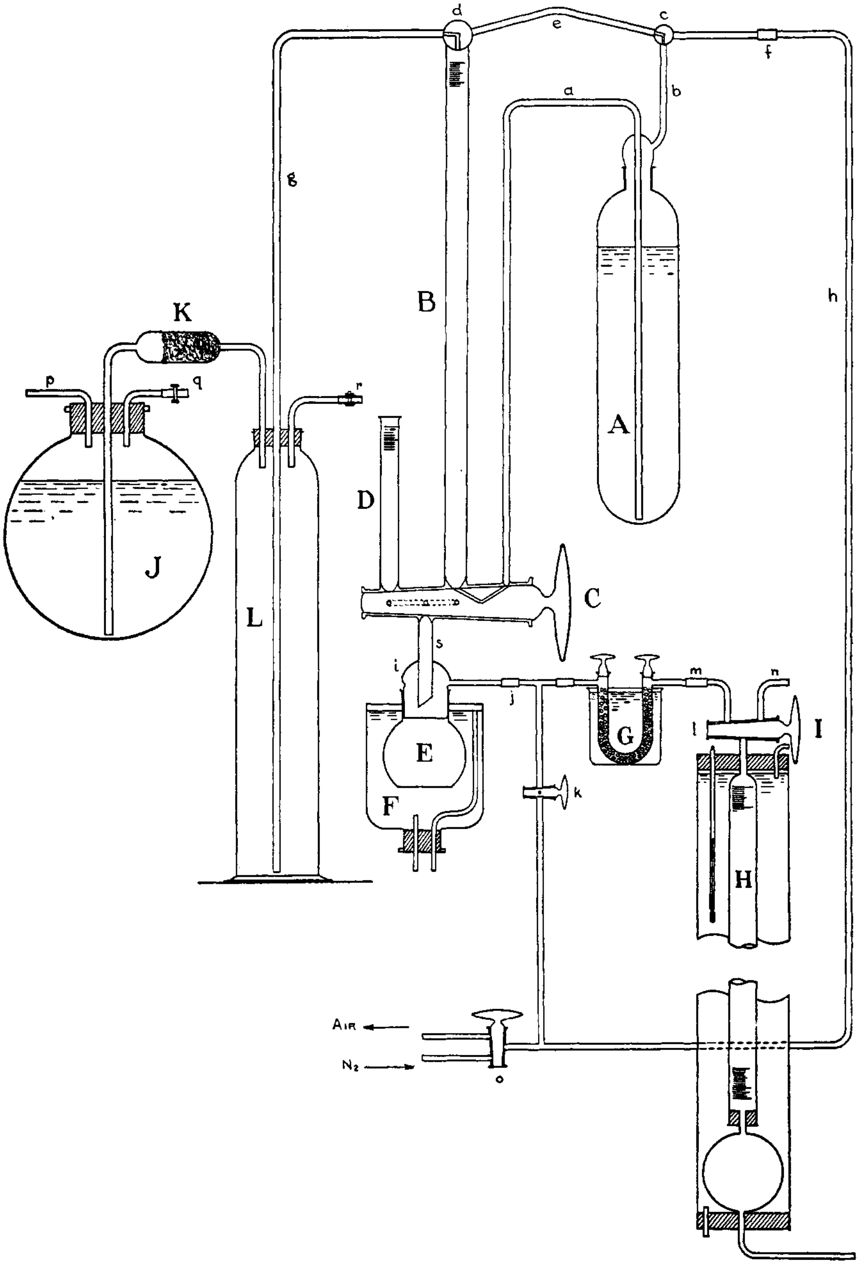

Fig. 1.

glass joint to the shoulder *i*. In the present work four such flasks were made, each being ground to fit *i*; this was done to allow for breakage and to avoid delays due to cleaning. *E* is immersed in a bath *F* which serves as a temperature regulator. From the shoulder *i* a tube for gas leads to a U-tube *G* packed with glass beads and phosphorus pentoxide. In order that its temperature may not undergo any sudden change, *G* is kept in a beaker of water at room temperature. The U-tube is connected to a gas buret *H*. This buret is an ordinary 50cc. gas buret graduated in tenths of a cc. and equipped with a special capillary stopcock *I* which serves not only to connect the buret in turn with the capillary arms *m* and *n* but has in addition a special vent *l* which serves to connect *m* with the air. The buret is filled with mercury and has at its base a 20cc. overflow bulb which is connected with a leveling bulb. It is enclosed in a Victor Meyer jacket filled with water and carrying a thermometer. The tube *g* serves ordinarily to connect to the air through *d* but during the process of filling it is attached to the system *J–K–L* which will be described later. *A*, *B*, *C*, *D* and *E* are made of Pyrex glass.

The Preparation of the Reagent

The Grignard reagent used is a solution of methyl magnesium iodide in *iso*-amyl ether containing approximately 0.8 mole of active reagent per liter. In preparing it pure dry materials are used and the operations are carried out as far as possible in an atmosphere of pure dry nitrogen.[5]

The following procedure is used. One hundred g. of *iso*-amyl ether and 8 g. of magnesium are placed in a 500cc. round-bottom welted-neck flask equipped with a stirrer, dropping funnel and a tube for introducing dry nitrogen. Forty g. of methyl iodide is dropped in during the course of an hour, the reaction flask being continually swept by a current of dry nitrogen and maintained at a temperature between 0 and 20°. The reagent is then diluted by the addition of 175 g. of *iso*-amyl ether. The flask is immersed in an oil-bath and heated for one and one-half hours at about 100°. After being allowed to stand overnight it is transferred to the apparatus.

Filling the Apparatus

For introducing the reagent solution into the reservoir *A* a special apparatus is attached to tube *g* as shown in Fig. 1. The flask *J* is the original vessel in which the

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[5] Purification of the Nitrogen.—Pure dry nitrogen was obtained by passing tank nitrogen successively through Fieser's solution, saturated lead acetate solution, concd. sulfuric acid and phosphorus pentoxide. The purification train consisted of the following ten parts connected in the order named: mercury trap (for pressure regulation), safety bottle, two wash bottles containing Fieser's solution,[6] safety bottle, wash bottle containing lead acetate solution, safety bottle, two sulfuric acid drying towers, a Liebig duck partially filled with phosphorus pentoxide.

[6] Fieser, This Journal, **46**, 2639 (1924).

reagent was made and is transferred to the position shown in Fig. 1 in such a way as to admit as little air as possible. *K* is a glass tube packed with glass wool for filtering the reagent. It leads into the settling tower *L* which carries the tube *g* leading to the apparatus.

Before *J* is placed in position the entire apparatus is cleaned, dried and filled with dry nitrogen. This is accomplished by washing successively with water, alcohol, ether and absolute ether. A rapid current of dry nitrogen is then passed through the apparatus for several hours. For this purpose *J* is replaced by an empty flask *J′* of the same size and stopcocks *c*, *d*, *C* and *o* are turned so that the nitrogen passes through the various parts of the apparatus in the following order: *J–K–L–g–B–a–A–b–h*. Stopcock *o* is turned so as to allow the nitrogen to escape into the air. In order to sweep the tube *e*, stopcocks *c* and *d* are turned so as to lead the gas directly from *g* to *h* through *e*. From time to time *o* is closed and *k* is opened so as to allow the gas to escape through the shoulder, the flask *E* being removed.

When the sweeping is complete *o*, *c*, *d* and *k* are closed and *J′* is replaced by *J* (containing the reagent). The reagent is then filtered through *K* into *L* by allowing nitrogen under suitable pressure to flow in at *p* and by opening *r* to the air. The reagent is allowed to settle in *L* and when clear or nearly so it is driven into the reservoir *A* by closing *r*, opening *o* to the air and turning *c* and *d* so that the solution flows from *g* into *B* and thence through the by-pass in *C* to the reservoir.

After the solution has been driven into *A*, stopcocks *c*, *d* and *C* are closed. *J*, *K* and *L* are then removed and *g* and *B* are cleaned by blowing successively dilute acid, water, alcohol and ether through the circuit *g-B-s* established by properly adjusting *d* and *C*. This circuit is then swept with dry nitrogen and the apparatus is ready for use.

Standardization of the Reagent Solution

Before the reagent solution can be used it must be standardized, that is, its strength in moles of active methyl magnesium iodide per liter must be determined. This is done in the following manner.

The reaction flask *E*, after being carefully cleaned, is heated in a free flame and allowed to cool in a vacuum desiccator. It is then placed in position, the ground-glass joint being lubricated with a small amount of good stopcock grease. If the grinding has been properly done, there will be little tendency for the flask to drop off and in case this seems likely the flask can be conveniently supported by a block placed in *F*. The bath *F* is now placed in the position shown in Fig. 1 such that *E* is almost entirely immersed. *C* is then turned so as to connect *D* and *s*, *k* is opened and nitrogen admitted at *o*. With *I* turned so as to connect *H* with *m*, the mercury level in *H* is raised until it stands a little above *I* in *m*. *I* is then closed. After the nitrogen has been passed through *D* and *E* for about twenty minutes *C* is turned so as to disconnect *s* and *D* and to connect *A* and *B* through the by-pass. *I* is now turned to connect *m* with the air through the vent *l*. The small amount of mercury in *m* is driven out and the circuit *G-m* is swept for a minute or two. *I* is then turned to connect *m* with *H* and *k* is closed after enough nitrogen has been allowed to flow into *H* to bring the mercury level down to the scale of the buret.

The Grignard reagent is now introduced. Stopcocks *o* and *c* are turned so as to admit nitrogen under pressure to *A*. *B* is then connected to *g* through *d*. The pressure of the nitrogen causes the solution to flow into *B*. When sufficient solution has been introduced into *B* the by-pass is closed by giving *C* an eighth of a turn in a clockwise direction; *c* and *d* are then closed. The level of the solution in *B* is now read as accurately as possible, by estimating to hundredths of a cc. With *d* still closed *C* is given a quarter turn in a clockwise direction. This brings the stopcock just beyond the position for connecting *B* to *s* and must be done quickly. With *h* connected to *B* through *c*, *C* is turned back (in a counter-clockwise direction) far enough to allow the solution to run into *E*. In this way the desired volume of solution is introduced into *E*, and *C* is closed by a slight clockwise turn. It is well to keep the mercury level in *H* so adjusted that the pressure in *E* is always less than atmospheric. After a minute or two the level of the solution is read as before; the difference between this and the initial reading gives the volume of solution used. A measured volume of water is now introduced from *D* by turning *C* (clockwise direction) to connect *s* and *D*. To complete the reaction *F* is replaced by a beaker of water kept boiling by a small flame and the reaction flask is heated at 100° for at least five minutes. *F* is now replaced and brought to its initial temperature. After allowing at least fifteen minutes for the system to reach equilibrium the level in *H* is again read. The difference between this and the initial reading gives the total increase in volume of the system. To get the volume of gas produced by the reaction it is necessary to subtract from this the volume of reagent solution and of water introduced. We now have the total volume of gas obtained from a measured volume of Grignard reagent; from this the strength of the latter can be calculated. This may be conveniently expressed in terms of the amount of gas obtained per cc. of solution used. Thus a solution made up according to the directions given above will have a strength of about 16 cc. of gas per cc. of solution.

After a determination has been made *E* is removed and *D* is connected to *s*. Dilute acid, water, alcohol and ether are poured successively into *D* and allowed to run out through *s*. To clean the shoulder *i* it is sufficient to spray it with suitable solvents, usually alcohol followed by ether.

Use of the Apparatus

The apparatus is designed for the purpose of determining simultaneously two things—the amount of gas given off and the amount of Grignard reagent consumed by a given reaction. These ends are accomplished by the following procedure.

A weighed sample, usually about 0.2 g. of the compound to be studied, is placed in the reaction flask *E* which is then put in place and swept with nitrogen as described above. A measured volume of the Grignard reagent solution is now introduced, care being taken to use an amount in considerable excess of that required by theory. The reaction chamber is heated until the reaction ceases and the increase in volume is measured and the volume of evolved gas calculated in the manner previously described.

To find the amount of reagent consumed it is necessary only to determine the amount remaining unchanged at the end of the reaction and to subtract this from the total amount used. This is done by introducing a measured volume of water from *D* and determining the amount of Grignard reagent remaining by the procedure used in standardizing the solution. Thus in the case of acetanilide, for example, a sample weighing 0.2648 g. (0.00196 mole) was treated with 4.01 cc. of methyl magnesium iodide solution containing 0.7143 mole per liter or 0.00286 mole of Grignard reagent. The volume of evolved gas corrected to 0° and 760 mm. was 44.2 cc. or 0.00198 mole. By treating the excess Grignard reagent with water 20.8 cc. or 0.00093 mole of gas was obtained. The amount of reagent consumed in the reaction is, therefore, 0.00286 − 0.00093 = 0.00193 mole.

TABLE OF RESULTS

ALL QUANTITIES ARE EXPRESSED IN THOUSANDTHS OF A MOLE

Compound	Amt. of compd.	Amt. of reagent used	Gas from reaction	Gas from excess of reagent	Amt. of reagent consumed
Benzhydrol..................	0.99	1.80	1.01	0.82	0.98
Benzhydrol..................	1.00	1.80	1.03	.83	.97
Diphenylamine................	0.98	2.25	1.05	1.26	.99
Benzophenone................	1.77	2.90	0.03	1.16	1.74
Benzil.......................	0.97	2.85	.09	0.90	1.95
Benzoin......................	1.08	2.82	1.10	.67	2.15
Dibenzoylmethane.............	0.50	1.80	0.53	.76	1.04*
Dibenzoylmethylmethane......	.50	1.80	.08	.75	1.05*
Dibenzoylbromomethane.......	.50	1.80	.03	.78	1.02*
Acetanilide..................	1.96	2.86	1.98	.93	1.93
Benzyl benzamide.............	1.01	2.90	1.01	1.87	1.03
Acetophenone.................	2.28	2.90	0.33	0.63	2.27
Acetophenone.................	2.31	2.86	.36	.56	2.30
Desoxybenzoin................	1.76	2.77	.10	.98	1.79
Triphenylethanone............	1.15	2.79	.16	1.63	1.16
Acetomesitylene..............	0.95	1.35	.94	0.43	0.92*

The first two compounds contain only active hydrogen, the following two only carbonyl groups. The values obtained with these four substances indicate that under favorable conditions the apparatus makes it possible to determine both the gas evolved and the reagent consumed with an accuracy of about 3%. Benzoin and dibenzoylmethane, representing substances which contain both hydroxyl and carbonyl groups, give almost equally good results. In all these cases the reaction, including the escape of most of the gas from the solution, is rapid—most of the gas being collected within a few minutes.

The values obtained for the succeeding two compounds show that solutions of methyl- and bromodibenzoylmethane contain little if any enolic modification. Neither of these substances gives a copper compound when its ethereal solution is shaken with copper acetate, but the former is capable of forming a sodium compound while the latter apparently is not.[7] The sodium compound of the methyl derivative may be formed as a result of progressive enolization but the ratios between the quantities of reagent consumed and gas evolved show that in these cases addition to carbonyl is far more rapid than enolization. It seems quite as probable therefore that the sodium compound is formed by addition of sodium alcoholate and elimination of alcohol.

Acetanilide and benzyl benzamide behave exactly like benzhydrol and diphenylamine; the liberated gas is equivalent to the reagent consumed.

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[7] Wislicenus, *Ann.*, **308**, 247 (1899).

The resulting magnesium compounds are, doubtless, derived from the enolic modifications.

The last four substances constitute an interesting series. Acetophenone, however carefully dried and purified, always gives at least ten times as much gas as is normally obtained from substances which contain no active hydrogen, but the total amount of reagent consumed is one mole per mole of ketone. Phenyl acetophenone and diphenyl acetophenone also yield an excessive quantity of gas, the former three times, the latter five times the normal amount. In acetomesitylene, finally, the liberated gas is equivalent to the reagent consumed: one mole per mole of ketone.

The explanation of these peculiar results is as follows. In acetomesitylene the hindrance to addition of the Grignard reagent to the di-ortho substituted carbonyl group is prohibitive; the sole products of the reaction are, therefore, methane and the magnesium derivative $(CH_3)_3C_6H_2C(OMgI):CH_2$. In acetophenone the hindrance is comparatively small but the amount of enolization is still appreciable. The substitution of phenyl for hydrogen in the methyl group of acetophenone has a twofold effect: it increases the hindrance to addition and thereby favors the formation of the metallic derivative, but it also, like the introduction of methyl into dibenzoylmethane, diminishes the tendency to enolize. The result of these opposing influences appears to be a slight diminution in the amount of enolization. The work of Grignard and others[8] shows that in the reactions between ketones and organic magnesium compounds addition to carbonyl and enolization occur as competing processes far more frequently than we are aware. Grignard and Savard in a recent paper[9] have described the action of 22 Grignard reagents on pulegone. They obtained the most extensive enolization when the alkyl group was secondary or tertiary and contained 3 or 4 carbon atoms. The series under consideration presents another factor of importance. Here the hindrance to addition is not due to the complexity of the magnesium compounds; it lies in the structure of the ketone and in acetomesitylene it is so great that even the simplest Grignard reagent leads to complete enolization.

Use and Limitations

The foregoing list of compounds was selected from more than a hundred that have been examined, because they are well known, present no complications, and show both the nature of the results and the accuracy attainable. It is evident that the reaction with methyl magnesium iodide can be used for learning much more about the structure and properties of an organic compound than merely the number of active hydrogen atoms it

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[8] (a) Dupont, *Compt. rend.*, **154**, 599 (1912); (b) Grignard and Savard, *Bull. soc. chim.*, **35**, 1081 (1924).

[9] Grignard and Savard, *Bull. soc. chim. Belg.*, **36**, 97 (1927).

contains. For this reason an examination of its behavior in the new apparatus has in this Laboratory become a part of the systematic investigation of almost every new compound. Such an examination consumes but little time, once the apparatus is set up and charged, because a single charge of reagent serves for more than a hundred determinations. Analyses of the reagent immediately after its preparation and after it had remained in its receptacle, exposed to light for months, show that its composition is invariable. When the apparatus is thus permanently set up it can be used with advantage in all cases in which it is possible to determine active hydrogen by the Zerewitinoff method; but since it is more complicated and more liable to injury than that devised by Zerewitinoff, and also requires more experience for its successful operation, it would not be worth while to construct it merely for the purpose of an occasional determination of active hydrogen.

We have found that while an examination of the behavior of a substance toward methyl magnesium iodide is helpful in many—perhaps most—cases, there are others in which it is quite unprofitable. In some of these the substance is not sufficiently soluble in the reagent, a difficulty which can usually be overcome by first dissolving it in some indifferent solvent. We have used dry xylene which was added to the substance after it had been weighed into the flask. The values marked with an asterisk were obtained in this manner.

A much more frequent complication is due to the formation of insoluble intermediate addition products. These rarely interfere with the determination of active hydrogen, and sometimes disappear on prolonged heating, but not infrequently make it impossible to complete the reaction.

A third difficulty arises from the occurrence of successive reactions. These appear most frequently in cases involving oxidation and reduction, and reveal themselves by a slowly diminishing evolution of gas. In these cases it is impossible to determine when the reaction is complete.

Summary

This paper contains:

1. A description of an apparatus for determining the gas evolved and the reagent consumed in reactions between methyl magnesium iodide and organic compounds.
2. A list of values showing the degree of accuracy obtainable.
3. A discussion intended to indicate the use of the apparatus.

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