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SOME BIOLOGICAL APPLICATIONS OF ORGANOMETALLIC COMPOUNDS[1]

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ORGANOMETALLIC compounds are compounds which have a metal directly attached to carbon, and are conveniently designated by the formula RM where M is a metal. They fall into three broad groups: those which are highly reactive *chemically*, like organopotassium compounds; those of moderate reactivity, such as organolithium and organomagnesium compounds; and those of relatively low reactivity, like the organomercury and organobismuth types.

Only those organometallic compounds of low chemical reactivity find any immediate biological application. It is out of the question, for example, to use organopotassium compounds directly, for they are not only spontaneously inflammable but react violently with water and carbon dioxide; and both violently and indiscriminately with the organic materials that go to make up cells.

However, it is probable that reactive types like those of magnesium (the Grignard reagents) and those of lithium are of greatest biological significance not because of their effects on body cells and fluids but because of the uncommon service they give to an understanding of biologically active material. There is hardly a branch of biologically active organic compounds (like vitamins, hormones, carcinogens) wherein RM compounds have not been used in one way or another to throw light on reaction mechanisms and procedures concerned with the structure and preparation of such compounds. It is doubtful if any class of organic compounds exceeds the reactive

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[1] Address of the retiring vice-president and chairman of the Section on Chemistry, American Association for the Advancement of Science, December 27, 1940.

RM types in versatility of reaction, particularly from the viewpoint of synthesis. Interestingly enough, some of the methods of choice for synthesis of the immediately important, less reactive RM compounds involve the use of the more reactive RM types. As an illustration, many organomercury compounds are best prepared from organomagnesium or organolithium compounds.

Organometallic compounds have not been prepared from all the metals. It is highly probable, however, that all types of RM compounds will be prepared. The history of organometallic compounds shows that hypotheses postulating the non-formation of some RM types have undergone repeated revision necessitated by the preparation of organometallic compounds, the possible existence of which has been denied. At one time or another practically all the lesser reactive RM types have been examined for a great variety of biological action. Out of these studies have come some highly important applications, and promises of other significant biological uses.

The beneficial use of metals and their inorganic compounds in medicine dates back hundreds of years. Organometallic compounds, on the other hand, are relatively new. The biological action of metals and inorganic salts may differ markedly from organometallic compounds which are, in many respects, also salt-like in character. A bridge connecting inorganic materials with organometallic compounds is the class of compounds known as the metallic hydrides. Actually, these hydrides may be considered formally as the first members of the organometallic homologous series. For example, if one adds to sodium hydride (NaH) the constant of homology (CH_2) there results methylsodium (CH_3Na) or the simplest true organosodium compound in that homologous series.

The hydrides, such as arsine (AsH_3) and tin hydride (SnH_4), are characterized by general extreme toxicities. With the introduction of CH_2 groups the toxicity tends to decrease, but the simpler organometallic compounds are definitely and characteristically poisonous. The decrease in toxicity as one goes from the metallic hydrides to the simpler organometallic compounds points the way to the synthesis of organometallic compounds sufficiently toxic for invading organisms and adequately tolerated by the host. The various reactions at the disposal of the organic chemist now make it possible to convert a highly toxic, relatively simple organomercury compound, for example, to an organomercury compound which is relatively safe and effective. The necessary transformations are somewhat simple in character, and involve alterations in the architecture of a molecule by appropriate variations of the kind, number and arrangement of groups. The actual operations may initially be quite difficult because of the special chemistry involved with many organometallic compounds. However, when proper conditions have been devised, the possibilities of preparing large numbers of compounds are essentially unlimited. This is a fortunate circumstance, because the paucity of information correlating physiological action with chemical constitution demands a large amount of empirical work, and the synthesis of a great number of compounds. An historically important illustration is Ehrlich's "606" for the treatment of syphilis.

As a consequence of this necessary "trial and error" approach there have evolved the beginnings of some relatively amorphous generalizations on chemical constitution and physiological action. Biologists are peculiarly appreciative and sympathetic of the gropings of the chemist, because of the astonishing differences between animate and inanimate matter. Both, however, are moving in the idealistic direction of achieving formulations which will be so exact that accurate predictions can be made. The goal, however, is so very distantly removed that they don't waste time considering that with the ultimate fruition of their efforts they will have succeeded in transforming science to bookkeeping, by the simple process of making science extinct when there is no further need to devise and interpret experiments.

Time does not permit a detailed accounting of the immediate biological applications of organometallic compounds. In human medicine, organometallic compounds of mercury have been used as antiseptics, for the treatment of syphilis, and as diuretics. The arsenic, antimony and bismuth compounds have found wide applications in a variety of protozoan diseases. Organogold compounds have been used, with indifferent success, in the treatment of tuberculosis; but with greater promise in the treatment of some forms of arthritis. Recent studies indicate that organolead compounds following the earlier and somewhat abortive work on the use of colloidal lead, may be beneficial in the treatment of cancer. Currently, germanium compounds are being examined in studies on pernicious anemia.

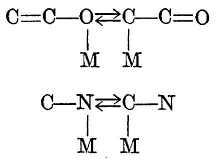
In veterinary medicine it is now being established that, among other applications, organic compounds of arsenic and bismuth are effective in the treatment of some forms of coccidiosis. In botany, organomercury compounds are used extensively as seed disinfectants to prevent smut diseases of cereals. Little work has been done with organometallic compounds in entomology, partly because of a trend to avoid the use of metals and partly because of cost. Neither of these objections may be serious with future developments. Practically nothing has been done directly in genetics. However, some studies indicate that mutations have been effected, in very low rates, with Drosophila by means of salts of metals. The highly selective and preferential reactions of organometallic compounds may make possible mutations by chemical agents.

The pronounced effects of very small quantities of metals and their derivatives have given rise to the expression "oligodynamic action." For example, 1 part of copper in 100,000,000 parts of distilled water will kill algae. Metals or their salts are widely distributed in plants and animals, and the importance of traces of metals in nutrition is common knowledge. Some metals like copper and zinc are normal constituents of the human brain, and are perhaps necessary for normal functioning. Traces of copper and cobalt assist iron in maintaining a steady formation of haemoglobin in the cure of anemia; and copper appears to be particularly necessary for the formation and maintenance of cytochrome oxidase activity of some tissues.

The pronounced effect of small amounts of metals is initmately associated with enzymes. A case can be made for the concept that any substance which is present in traces in the cell *and* which is apparently necessary in the diet or medium must either be an essential part of some enzyme or the enzyme itself. The trace metals which may be necessary for normal functioning of cells are copper, cobalt, zinc and manganese; and these metallic combinations appear to function as prosthetic groups in enzymes. It may be attractive, speculatively, to pursue the idea of enzyme-like action of certain synthetic drugs, minute amounts of which are profoundly effective. We refer here to synthetics which are not normal constituents of cells but which may become transitorily prosthetic groups of enzymes. One may expect confidently that the expanding use of the tracer element technique, particularly with radioactive metal combinations, will throw new light on the biological transformations of metallic substances.

It may properly be asked: "What relationship exists between metals and their inorganic salts and organometallic compounds?" We know that it is possible to convert some inorganic materials biologically to organometallic types. Tellurium is methylated in the body and exhaled as the offensive dimethyltellurium. Molds will also methylate inorganic compounds of arsenic and tellurium to the corresponding organometallic compounds. Relatively little is known of the mechanism of biological action of metallic types. There may or may not be an intermediary and transitory formation of organometallic or pseudo-organometallic compounds, although it is possible, in the laboratory, to prepare organometallic compounds by interaction of organic compounds with metals or their inorganic salts. Even if true organometallic compounds are not involved in biological transformations, there are good reasons for believing that in a number of cases organic compounds are formed in which the metal is bound not necessarily to carbon (to give a true organometallic compound) but to oxygen, sulfur or nitrogen. The type of metal linkage in such cases may be coordinate.

Recent studies have shown that numerous organic compounds having a metal attached to oxygen or nitrogen behave in many respects as though the metal were attached to carbon. The rearrangements involved may be illustrated simply by the following:



$$\mathrm{C{=}C{-}\underset{M}{O}\rightleftarrows\underset{M}{C}{-}C{=}O}$$

$$\mathrm{C{-}\underset{M}{N}\rightleftarrows\underset{M}{C}{-}N}$$

The extent of these and other equilibria varies with the particular system of elements involved. However, the observations that some organic compounds having a metal attached presumably to an element other than carbon may function as a true organometallic compound in which the metal is attached to carbon are of paramount importance. The applicability of this concept is significant not only from a strictly chemical aspect but also from the viewpoint of two of the most important biological materials; chlorophyll and haemoglobin.

Willstätter has suggested that the magnesium linkage in chlorophyll may resemble that present in Grignard reagents and be a significant point of reaction with carbon dioxide in photosynthesis. One may then speculate that some of the subsequently necessary reductions and condensations leading to carbohydrates may also involve known Grignard-like transformations. It is interesting to recall that quite recent studies show the formation of carboxylic acids in photosynthesis, for a primary reaction between Grignard reagents and carbon dioxide is the formation of carboxylic acids. To continue speculatively, the other biologically important catalyst, haemoglobin, may function as an oxygen carrier, possibly by means of peroxide formation due to an organoiron complex or its equivalent.

There are, then, three important classes of biological applications of organometallic compounds: (1) The almost indispensable use of organometallic compounds in the determination of structure and the synthesis of biologically significant materials like vitamins and hormones. (2) The direct application of organometallic compounds in the treatment of infections and diseases of both plants and animals. (3) The apparent organometallic characteristics of two basically important materials in plant and animal transformations: chlorophyll and haemoglobin. It seems altogether reasonable to predict that expanding knowledge in the relatively young field of organometallic chemistry will assist materially in advancing our understanding of biological processes and in further controlling various plant and animal diseases.

THE MOTIONS OF THE STARS[1]

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THE first observational evidence of stellar motions was given by Sir Edmund Halley[2] in 1718. Comparing the positions of the Almagest with recent observations to determine the precession, he found large changes in the latitudes of Sirius, Arcturus, Aldebaran and Betelguese; he considered these too great to be attributed to errors of observation or reduction and decided that these stars had a motion of their own.

The proper motion is an angle and we need the distance of the star to convert it into linear motion at right angles to the line of sight. The radial velocity is also needed to give the motion with reference to the sun.

If we accept the estimate that errors of observation did not exceed 15′ at the time of Copernicus; that Tycho reduced this limit to 2′ or 3′ and that Flamsted reduced it to 5″, we see how difficult it was to detect any small proper motions in less than a century.

By the end of the eighteenth century we have some proper motions in Maskelyne's "Catalogue of 36 Fundamental Stars" and in Mayer's "Catalogue of 80 Stars." Mayer obtained his motions by comparing his observations with those made by Roemer fifty years earlier.

Sir William Herschel[3] in 1783 used seven of these motions to determine the motion of the sun. He based his method on the fact that the solar motion would impart a parallactic component to each star, in a great circle passing through the star and the apex of the sun's motion. Drawing these great circles, he found that their intersections clustered in and around the constellation Hercules, with the mean point near λ Herculis; this he adopted as the solar apex. He checked this position with Mayer's motions and found 32 favorable and 12 unfavorable to his hypothesis.

Herschel[4] again considered the problem in 1805; he found a provisional apex from six stars of Maskelyne's Catalogue; then modified it by comparison with the other stars of that catalogue. This new value differed from the other by 16° in right ascension and 23° in declination.

Bessel increased the number of known proper motions by reducing the observations of Bradley and comparing them with the results of Piazzi and himself. With the better determined of these motions, he tested the hypothesis of Herschel by a different method. He[5] plotted the poles of the great circles in which these motions took place and found they were scattered all over the sky. Were they largely parallactic, they should have been concentrated along the great circle whose pole was the solar apex. His results did not agree with Herschel's.

Argelander was the first to observe a list of stars, limited to those suspected of having proper motions. His Abo Catalogue of 560 stars contained 390 whose centennial motions exceeded 10″. From these he determined the apex[6]; 259° = A, 32° = D. His method was to compute the position angle of each motion and compare it with the position angle of the parallactic motion with respect to an assumed apex. His equations were based on the assumption that directions of motion were at random. His result confirmed Herschel's and convinced astronomers that the solar motion was real.

Airy[7] published his method in 1859; he resolved the stellar motions along three rectangular axes. When the components were summed he assumed the peculiar motions would cancel, leaving the parallactic components to sum up into those of the solar motion. In Airy's method it was also necessary to make some assumption concerning the distance of the stars. In general the amount of proper motion was assumed to be a better criterion of distance than the visual magnitude.

Thus Stumpe[8] divided his 1,054 proper motions into four groups according to the size of the proper motions; in the first group of 551 stars, he took $.''16 < \mu < .''32$; in the next group of 340 stars, the limits were .″32 and .″64; in group 3 (105 stars) the limits were .″64 and 1.″28; and the last group had 58

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[1] Address of the retiring vice-president and chairman of the section of astronomy of the American Association for the Advancement of Science, Philadelphia, December 31, 1940.

[2] *Phil. Trans.*, 6, 329–330.

[3] Scientific Papers of Sir William Herschel, 1, 108–130.

[4] *Idem,* 2, 317–337.

[5] "Fundamenta Astronomiae," 308–313.

[6] A.N., 16, 45.

[7] *Mem. Royal Astron. Soc.*, 28, 143.

[8] A.N., 125, 385–430.