[CONTRIBUTION OF THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA]

The Oxygen-carrying Synthetic Chelate Compounds.[1a] I.

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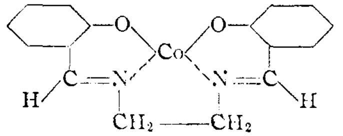
Introduction.—The importance of chelate compounds in biological oxidation–reduction systems needs no elaboration. Their widespread appearance in such systems led us to the study of synthetic chelate compounds in the hope of gaining an understanding of their nature and the properties which make them so indispensable to biological oxidation and reduction especially. The course of the work very soon led to the preparation in 1938[2] of chelates from *o*-hydroxy aldehydes and ethylenediamine following Pfeiffer.[3]

In 1933, Pfeiffer had described among other compounds, one having the composition of cobaltous bis-salicylaldehydethylenediimine, which he noted at that time turned from a reddish color to black upon exposure to air for several days. In 1938, Tsumaki,[4] a former collaborator of Pfeiffer, reported the results of further study of this particular compound. He showed that the blackening apparently was due to the absorption of oxygen from the air and that this oxygen could be driven off by heating the compound in a stream of carbon dioxide. The amount of oxygen absorbed by the compound as prepared by Tsumaki corresponds to one molecule of oxygen for each three atoms of cobalt. In 1940, we repeated and confirmed this experimental work. In addition to the form prepared by Tsumaki, we have prepared at least two other crystalline modifications of the compound, one of which is totally inactive toward oxygen and another which will carry reversibly one molecule of oxygen for each two atoms of cobalt. The work was then extended to include a search for other compounds which might exhibit this oxygen-carrier property, as well as a study of the mechanism of the reaction itself involving an examination of rates, equilibria, X-ray crystallography, magnetism, solutions, absorption spectra, cycling properties, etc. The present paper contains a very brief résumé of the general results of these investigations and will be followed by individual reports on each phase of the work.

Preparation of the Compounds.—The present work was done under the direction of three more or less simultaneous objectives: (1) to increase the weight per cent. of oxygen carried, (2) to increase the stability of the compound so as to allow it to be cycled a larger number of times, and (3) to increase the rate at which oxygen would be absorbed and released; all on the dry solid compound. We hope eventually to fill in the gaps and obviate the limitations imposed by these requirements.

Practically all of the compounds to be discussed here were made of three components: a metal atom usually cobalt, an aldehyde or ketone component, usually a salicylaldehyde derivative, or an *o*-hydroxyacetophenone derivative, and an amine component.[5] Two types of compounds emerged as being capable of carrying oxygen in the solid state as well as in solution in certain solvents. They can be represented by the following unsubstituted parent compounds.



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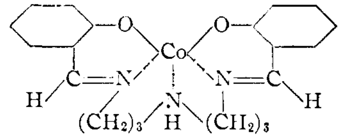

II

The compounds of type I, when in the proper form, were capable of carrying one molecule of oxygen for each two atoms of cobalt, while those of type II were capable of carrying one molecule of oxygen for each atom of cobalt.

In general, these chelate compounds can be prepared in one form or another by simply mixing their component parts in aqueous alcoholic solution and heating on a water-bath in the absence of air. While this procedure in conjunction perhaps with a recrystallization from some solvent generally sufficed to produce a clean crystalline product (frequently containing solvent of crystallization) suitable for analysis and solution work, the determination of the activity (oxygen-carrying qualities) of the solid, being very sharply dependent upon the crystal form and physical state, usually required that it be prepared under very carefully controlled conditions, and under as wide a variety of conditions as possible. The variety of crystal forms of the parent compound of type I have already been mentioned. Similar considerations hold for the derivatives of type I.[6] For example, the 3-fluoro derivative of type I exists not only in

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(2) Calvin, *Trans. Faraday Soc.*, **34**, 1181 (1938); THIS JOURNAL, **61**, 2230 (1939).

(3) Pfeiffer, Breith, Lübbe and Tsumaki, *Ann.*, **503**, 84 (1933).

(4) Tsumaki, *Bull. Chem. Soc. Japan*, **13**, 252 (1938).

(5) One of these amines, the γ,γ'-diaminodipropylamine used to prepare compounds of type II, was first prepared for us under the direction of Dr. T. A. Geissmann at U. C. L. A.

(6) The first active derivative of type I, namely, the 3-NO$_2$ derivative, was first prepared by Dr. H. C. Diehl and collaborators at the Iowa State College.

an active and two inactive forms, but has two different monohydrates as well. The compounds of type II also exhibit a variety of crystal forms, some active and some inactive.

In solution, under the proper conditions, most of the compounds of both types have the property of combining reversibly with molecular oxygen.

Thermodynamics of the Reaction on the Solid Chelates.—The equilibrium oxygen pressure over the solid chelates of type I has been measured as a function of the degree of oxygenation and of the temperature. From these measurements, it appears that the system is not a simple three-phase one (*i.e.*, original chelate, oxygenated chelate, gaseous oxygen) but rather that at the higher degrees of oxygenation (in the vicinity of 75% of complete oxygenation, the actual value depending upon temperature), the unoxygenated phase disappears entirely and a solid solution is formed. The order of magnitude of the pressures at 50% oxygenation are, for the parent compound (type I) at 25° approximately 5 cm. of mercury and at 0° somewhat less than 5 mm. For the 3-fluoro compound at 0° it is ~0.4 mm. and at 25° it is ~2 mm.

The pressures over the solid compounds of type II are much higher. They cannot be estimated very accurately because of the slowness of the reaction; all we can say at present is that they may reach 50 or 60% at atmospheric pressure of oxygen (room temperature), and can be made to approach >90% (~8% by weight) at 200 p.s.i. of oxygen pressure.

X-Ray Examination.—The compounds of type I appear to be coplanar molecules arranged in layers. In the active (2 to 1) crystal form they are so arranged as to leave holes in the lattice large enough to accommodate oxygen molecules and the passage between holes is only slightly smaller so that the oxygen molecules may pass completely through the lattice by passing over relatively low potential barriers between the holes. In the inactive form, no such holes are found.

That the steric factor is not the only determinant is demonstrated by an examination of the type I compound formed from *o*-hydroxyacetophenone. Here also there are large holes in the lattice, but the compound is very slow in its reaction with oxygen.

A study of the powder patterns as a function of oxygen content confirms the suggestion that the unoxygenated phase disappears completely around 75% oxygenation (at room temperature).

Magnetic Measurements.—The magnetic susceptibilities of all of the active compounds of type I correspond to one unpaired electron per cobalt atom, with a rather large orbital contribution, the actual molal susceptibilities lying in the range 2000–3000 $\times 10^{-6}$ at 25°. When oxygen is absorbed by these compounds the paramagnetic susceptibility decreases linearly with the amount of oxygen absorbed and practically vanished when the full complement of oxygen (*i.e.*, one oxygen for each 2 cobalt atoms) has been absorbed. The active compounds of type II have a susceptibility corresponding to three unpaired electrons per cobalt atom. This decreases to one unpaired electron per cobalt atom when the compound has absorbed one molecule of oxygen per cobalt atom.

Kinetics of the Oxygenation Reaction on the Solid Compounds.—In the studies on the rates of oxygen absorption there were two primary variables: the temperature, and the oxygen pressure. Because of the high heat of reaction, precautions were taken to insure good heat transfer from the reaction bed and thus attain isothermal conditions. Only compounds of type I were studied in detail in the solid phase. Each of them showed a temperature at which the rate of oxygen absorption is a maximum. This is due to the fact that as the temperature is raised, the reverse reaction (desorption of oxygen) begins to play an important part; *i.e.*, the rate measurements are approaching the region of equilibrium. At temperatures well below the optimum, an analysis of the rate curves at constant pressure of oxygen shows that the reaction is first order with respect to the active chelate in the cases of the parent compound and the 3-ethoxy compound, while in the case of the 3-fluoro compound, the reaction is second order. In all cases, these rate constants are first order with respect to oxygen pressure.

Of all the compounds measured, the 3-fluoro has the fastest rate of oxygenation, it being such that at 25° and 15.1 cm. pressure of oxygen, the compound is 80% saturated in ~3.5 minutes. For the 3-ethoxy compound, the rate is such that it is 80% saturated in ~5.5 minutes, at 25° and 15.1 cm. of oxygen pressure, while the parent compound reaches 80% saturation in 6.5 minutes at 25° and 76 cm. of oxygen pressure which if extrapolated to 15.1 cm. of oxygen for comparison with the previous two compounds would require a time of the order of 30–35 minutes.

The second order rate on the fluoro compound can bear further comment. It requires that the process involve two steps, the first of which is an equilibrium involving an activated oxygen molecule and a single chelate molecule in such a way that this oxygen has available to it the entire crystal mass, much as though it were in a solution.

Cycling Properties.—One of the primary purposes of this work was to develop compounds which could be used to prepare pure oxygen from air. In order to do this, the compound was prepared in the form of pellets or granules (1 to 5 mm. in size) and placed in the tubes of a heat exchanger. The tubes were usually 0.5 inch in diameter. The cycle then consists of passing air at a suitable pressure through these tubes while coolant (usually tap water) is flowing around the outside of the tubes (the absorption period); after the absorption has proceeded for the desired time (from two to fifteen minutes depending upon the compound, the air pressure, the temperature, the efficiency of heat exchange, and the rate of flow) the air is interrupted and the coolant is replaced by a heating medium usually 5 p.s.i. steam; during the first few seconds of the heating the evolved gases are allowed to escape through the same channel as the effluent air did during the absorption period, thus removing any remaining nitrogen from the tubes; after a purging period of several seconds (~20–30) the valving system is shifted so that the effluent gas (now substantially pure oxygen) is collected in a storage tank; this desorption period may last from five to ten minutes depending upon temperature and pressure of desorption. The cycle is thus completed and another absorption period may commence.

When the parent compound of type I is subjected to such cycling (90 lb. gage air, 13 min. absorption, $6^2/_3$ min. desorption at atmospheric pressure), it is found to deteriorate to 70% of its original productivity after 300 cycles. This would correspond to the production of ~15 lb. of oxygen per lb. of compound deteriorated to one-half its initial productivity. When the 3-fluoro compound of type I is subjected to cycling (20 lb. gage air, 3.5 min. absorption, 6 min. desorption), it deteriorates to 60% of its initial productivity after 1500 cycles, corresponding to the production of ~65 lb. of oxygen per lb. of chelate deteriorated to one-half its initial value. Neither of these cycling conditions are optimum and the production of oxygen can be raised above these figures.

This decrease in activity is not due to a recrystallization into the more stable inactive modification, but rather to an irreversible oxidation of part of the compound, the oxidation products acting as poisons for the remaining material. Thus, considerably more than one-half the chelate can be recovered from a sample which has deteriorated to one-half activity by cycling.

Oxygenation in Solution.—Very nearly all of the cobalt compounds of both type I and type II, as well as certain others (*o*-hydroxyacetophenone derivative, and compounds involving certain other diamines), were capable of absorbing oxygen reversibly when dissolved in the proper solvent. A series of measurements of the degree of oxygenation as a function of oxygen pressure at various temperatures, has been made on compounds of type II. They could not, however, withstand very many cycles since there was a very appreciable fraction of irreversible oxidation at each cycle. This irreversible oxidation was greater at the higher temperatures (20–30°), while at 0° and lower it was negligible over a period of half an hour, while the reversible uptake was complete in a few minutes (~5 min.). Thus only at the higher temperatures was any correction for irreversible oxidation necessary. The temperature range investigated was −10 to +30°; the solvent used in most of the measurements was quinoline, with exploratory runs in methyl benzoate, in pyridine, and in α-methylnaphthalene; the pressure range was from a few mm. to about one atmosphere of oxygen.

The saturation curves obtained are similar to those of hemoglobin, especially in that they are not representative of a simple equilibrium between one chelate molecule and one oxygen molecule. They reach a value as high as 0.9 mole of oxygen per mole of chelate at the higher pressures and lower temperatures. Each compound, of course, has a different range.

Although this solution work has only just begun, it already seems apparent that compounds having almost any desired saturation curve in the non-aqueous solvents can be synthesized and, further, that the synthesis of compounds capable of functioning as oxygen-carriers in aqueous solution is possible.

Acknowledgments.—The details of each of the above observations will appear in future publications with the men most concerned in each piece of work: Dr. Chandler H. Barkalew, Dr. Lloyd N. Ferguson, Dr. E. W. Hughes, Dr. Warren Miller, Dr. W. J. Taylor, Dr. S. Aranoff, Mr. Richard Holmes, Dr. J. C. Reid and Dr. O. L. Harle.

Summary

The general physical and chemical properties of the oxygen-carrying synthetic chelate compounds are described.

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