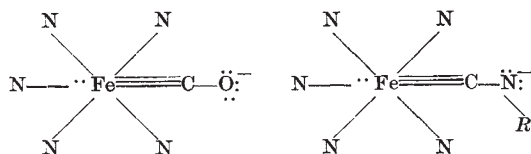


In this structural formula the iron atom is shown as forming a double bond with the first oxygen atom, which forms a single bond also with the second oxygen atom. (The iron atom then has two unshared electron pairs in its outer d^5sp^3 shell.) There is a formal charge +1 on the first oxygen atom and a formal charge -1 on the second oxygen atom. The difference in electronegativity of iron and oxygen is 1.7, which corresponds to 51 per cent of ionic character⁹. The electric charge assigned to the first oxygen atom is accordingly reduced to 0, whereas that of the outer oxygen atom remains -1. Except for the outer oxygen atom, the assigned structure is accordingly in good agreement with the principle of electroneutrality¹⁰.

The negative charge assigned to the outer oxygen atom of oxyhaemoglobin can now be accounted for by the structure of myoglobin, as determined by Kendrew⁷. In the myoglobin molecule there is a residue of histidine adjacent to the iron atom on one side of the haem group, and another residue of histidine constrained by the configuration of the polypeptide chain to a position a few Ångströms removed from the iron atom on the other side of the haem. These two residues of histidine are those that were proposed originally by Conant¹¹, in order to account for the observed haem-linked acid groups of haemoglobin, and their positions relative to the iron atom are those postulated by Coryell and Pauling¹² in their detailed discussion of the mechanism of change in acid strength of haemoglobin on oxygenation. It has been pointed out that the positive electric charge of the imidazolium side-chain of the second histidine residue probably serves, through its electrostatic interaction with the iron atom, to stabilize the bipoisitive state and assist in preventing oxidation of haemoglobin to ferrihaemoglobin¹³. We see, also, that for oxyhaemoglobin the structure assigned above places an oxygen atom with a negative charge in close approximation to the positively charged imidazolium group and, indeed, in such a position as to permit hydrogen bonding with the negatively charged oxygen atom, thus further stabilizing the structure.

Similar structures, involving iron-carbon double bonds, were formerly assigned to carbonmonoxyhaemoglobin and the ferrihaemoglobin alkylisocyanides^{4,5}. We may now recognize, however, that the arguments of the preceding paragraph strongly suggest that these molecules have structures in which the iron atom forms a triple bond with the carbon atom, and the outer oxygen atom or nitrogen atom has a negative electric charge:



I conclude that oxyhaemoglobin and related haemoglobin compounds are properly described as containing ferrous iron, rather than ferric iron, that their electronic structure involves essentially the formation of a double bond between the iron atom and the near-by oxygen atom in oxyhaemoglobin (with the iron-oxygen-oxygen bond angle about 120°) and a triple bond to the carbon atom in carbonmonoxyhaemoglobin and the haemoglobin alkylisocyanides (with iron-carbon-oxygen or nitrogen bond angle 180°). The iron-oxygen and iron-carbon interatomic distances in these compounds are predicted to have the values corresponding to these multiple bonds.

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¹ Weiss, J. J., *Nature*, **202**, 83 (1964).

² Pauling, L., and Coryell, C. D., *Proc. U.S. Nat. Acad. Sci.*, **22**, 210 (1936).

³ Pauling, L., *General Chemistry*, second ed. (W. H. Freeman and Co., San Francisco, 1954).

⁴ Pauling, L., *Stanford Med. Bull.*, **6**, 215 (1948).

⁵ Pauling, L., *Hemoglobin*, 57 (Butterworths Sci. Publ., London, 1949).

⁶ Pauling, L., *The Nature of the Chemical Bond* (Cornell Univ. Press, Ithaca, 1960).

⁷ Kendrew, J. C., "Myoglobin and the Structure of Proteins", in *Les Prix Nobel en 1962*, Stockholm, 1963, and references quoted there.

⁸ Perutz, M., "X-ray Analysis of Haemoglobin", in *Les Prix Nobel en 1962*, and references quoted there.

⁹ Ref. 6, Chap. 3.

¹⁰ Pauling, L., *J. Chem. Soc.*, 1461 (1948); ref. 6, 172.

¹¹ Conant, J. B., *Harvey Lectures*, **28**, 159 (1932-33).

¹² Coryell, C. D., and Pauling, L., *Biol. Chem.*, **132**, 769 (1940).

¹³ Zuckerkandl, E., and Pauling, L., in Kasha, M., and Pullman, B., *Horizons in Biochemistry* (Academic Press, New York and London, 1962).

THE essence of my suggestion was that there is a charge transfer from the haemoglobin to the oxygen molecule, that is, some delocalization of one of the d -electrons of the ferrous towards the oxygen. This was meant as a starting approximation, the details to be settled by some physical measurements concerning the electronic structure. There are no obvious grounds why the resulting structure could not be diamagnetic. If this would not agree with a certain conventional definition of oxidation number then this would only show that this definition is no longer useful in this case. This is perhaps not surprising, because the O_2^- ion has itself an unpaired spin unlike the common anions such as OH^- , CN^- , which are all diamagnetic. This does, therefore, involve the more complicated problem of the interaction of the two magnetic ions when they come close together.

The charge-transfer complex and the structure proposed by Prof. Pauling have two prominent features in common as, according to Pauling, there also is (1) a charge of -1 on the oxygen, and (2) the iron-oxygen bond has a large percentage of ionic character. The difference lies essentially in the disposition of the third positive charge, which Pauling does not associate explicitly with the iron. It might be expected, in any event, that there will be some delocalization of the positive charge over the porphyrin ring. It will be of interest to see whether Prof. Pauling's much more specific proposals can be confirmed.

The reasons for my suggestion were given previously¹, one of these being the observation that oxyhaemoglobin can act as a strong oxidizing agent; for this it would be difficult to give a simple explanation on the basis of the conventional structure.

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¹ Weiss, J. J., *Nature*, **202**, 83 (1964).

Molecular Orbital Evidence for Weiss's Oxyhaemoglobin Structure

WE have read with interest the recent paper by Weiss¹ concerning the electronic structure of oxygenated haemoglobin. From a consideration of: (1) magnetic properties, (2) absorption spectrum and (3) acid dissociation constant of oxygenated haemoglobin, Weiss has proposed that the iron has a +3 charge. Therefore, iron is essentially in the ferric state. His paper has prompted us to give additional evidence in support of his idea.

The charge on the iron atom can be derived from the coefficients of the molecular orbitals of the complex. The molecular orbitals used were calculated for a general examination of the structures and properties of oxygen metal complexes. The calculations included a total of 17 atomic orbitals with 18 electrons in these orbitals. The orbitals considered were the $2s$ and three $2p$ on each oxygen atom and the five $3d$, one $4s$ and three $4p$ orbitals on iron. The general method of the calculation is that of Ballhausen², but the details and a discussion of the results