The McClure and Weiss Models of Fe-O₂ Bonding for Oxyhemes, and the HbO₂ + NO Reaction

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Abstract:

For the Fe-O₂($S = 0$) linkages of oxyhemes, valence bond structures are re-presented for the McClure (Fe^{II}($S = 1$) + O₂($S = 1$)), Pauling-Coryell (Fe^{II}($S = 0$) + O₂^{*}($S = 0$)), and Weiss (Fe^{III}($S = \frac{1}{2}$) + O₂⁽⁻⁾($S = \frac{1}{2}$)) models of bonding. The valence bond structures for the McClure and Weiss models are of the increased-valence type, with more electrons participating in bonding than do occur in their component Lewis structures. The Fe-O bond number and O-O bond order for the McClure structure are correlated with measured Fe-O and O-O bond lengths for oxymyoglobin. **Back-bonding from the O₂⁽⁻⁾ to the Fe^{III} of the Weiss structure gives a restricted form of the McClure structure.**

The McClure and Weiss increased-valence structures are used to provide valence bond formulations of mechanisms for the HbO₂ + NO reaction with Hb = hemoglobin. The products of these two formulations are Hb⁽⁺⁾ + NO₃⁽⁻⁾ and Hb⁽⁺⁾ + OONO⁽⁻⁾, respectively. Because Hb⁽⁺⁾ + NO₃⁽⁻⁾ are the observed products, they provide an experimental procedure for distinguishing the McClure and Weiss models. It is also shown that the same type of agreement between McClure-type theory and experiment occurs for oxy-coboglobin + NO, cytochrome P-450 monooxygenases, and related hydrogen atom transfer reactions.

In the Appendices, the results of DFT and multireference MO calculations for oxyhemes are related to one formulation of the increased-valence wavefunction for the McClure model, and theory is presented for the calculation of approximate weights for the Lewis structures that are components of the McClure increased-valence structure.

Keywords Valence bond · Increased-valence · McClure · Weiss · Oxyheme · Nitric oxide

dioxygenation · Oxy-coboglobin · Cytochrome P-450 monooxygenases · Hydrogen atom transfer

Introduction:

The three primary models of the electronic structures for the Fe-O₂ linkages of oxyhemes, for example oxyhemoglobin (HbO₂) and oxymyoglobin (MbO₂), are those of eqs (1)-(3),

in which S is the total spin quantum number, and the Fe^{II} and Fe^{III} involve (3d)⁶ and (3d)⁵ atomic orbital (AO) configurations, respectively.

In this paper, initially we shall re-present the valence bond (VB) structures for the McClure, Pauling-Coryell and Weiss models. These VB structures will then be used to demonstrate that for nitric oxide dioxygenation reactions such as $\text{HbO}_2 + \text{NO} \rightarrow \text{Hb}^{(+)} + \text{NO}_3^{(-)}$, the McClure but not the Weiss VB formulation can accommodate the observed formation of the $\text{Hb}^{(+)} + \text{NO}_3^{(-)}$ products. Consideration will also be given to VB formulations for cytochrome P-450 monooxygenases and a related hydrogen atom transfer reaction. For them, the McClure but not the Weiss model also accommodates the observed formation of products.

Both the McClure Fe^{II}-O₂ and the Weiss Fe^{III}-O₂^{·-} VB structures (**2** and **11** in Schemes 2 and 6 below) are of the increased-valence type [5-8]; for them, without valence shell expansion, more electrons participate in bonding than do occur in Lewis-type VB structures. We shall show again that these structures are equivalent to resonance between at least either four or two Lewis-type VB structures, respectively [5g].

It is to be noted that the VB structures for the Pauling-Coryell model of Fe-O₂ bonding do not lend themselves easily to a VB formulation for the reaction of NO with HbO₂. However consideration will also be given to this model in order to relate it to a Lewis-type VB component of the increased-valence structure **2** (Scheme 2 below) for the McClure model.

It is not the primary intention to relate the increased-valence structures to the results of numerous quantum mechanical calculations that have been reported – for example those of refs [11,51,52,57-68] in ref [9]. Rather, it is to focus attention on the relevance of the Green-Linnett [10] type VB structures for the O₂ ground-states of O₂ and O₂^{·-} to obtain the compact increased-valence structure for the McClure and Weiss models of Fe-O₂ bonding. However using one type of wavefunction for the McClure increased-valence structure, in Appendix 1, a comment will be made on an interpretation of the results of DFT and multi-configurational molecular orbital (MO) calculations [9,11] for an Fe-O₂ linkage of oxyhemes. Publications [5a-c,g] were cited in refs [9,11].

To conclude this Introduction, it is noted that according to ref [5g], as stated in ref [12], “using MO configurations to distinguish between the bonding models of Pauling, Weiss, and McClure-

Goddard is not straight forward because those bonding models are based on VB structures and not on MO configurations”.

Valence Bond Structures for O₂

Scheme 1: Valence bond structures **A-D** for the generalized Pauling three-electron bond (with atomic formal charges omitted) and **E-J** for O₂. In refs [14,15], a VB structure of type **D**, as in **H**, is used to symbolize the three-electron bond, in which the top dot is the antibonding electron.

As well as an electron-pair σ bond, the $^3\Sigma_g^-$ O₂ ground-state has two Pauling three-electron π bonds (or diatomic three-electron two AO π -bonds) with MO configurations $(\pi_x)^2(\pi_x^*)^1$ and $(\pi_y)^2(\pi_y^*)^1$ and parallel spins for the antibonding π_x^* and π_y^* electrons. Green and Linnett deduced that each of these configurations is equivalent to using a VB structure of the general type seen in **Scheme 1A**, which is equivalent to **Scheme 1B** or **Scheme 1C** [5-8]) (for electron spin quantum numbers $S = M_S = +1/2$, in which the crosses and circles represent electrons with m_s spin quantum numbers of $+1/2$ and $-1/2$, [13] respectively). The resulting Green-Linnett ground-state VB structure for O₂ with a double bond, is **Scheme 1E** without electron spins, and **Scheme 1F** for $S = M_S = +1$. This VB structure, and the familiar $S = 0$ spin Lewis structure (**Scheme 1G**), will be used in the next Sections to discuss the McClure and Pauling-Coryell theories [5-7] of the Fe-O₂ bonding in oxyhemes.

In refs [14,15], the VB structures for the $^3\Sigma_g^-$ ground-state of O₂ with two three-electron π -bonds are equivalent to that of **Scheme 1H**, with **Scheme 1D** used for each

three-electron bond. Structure **5** of Scheme 1 in refs [9,11] uses **Scheme 1I**, which becomes the VB structure **Scheme 1J** when the σ bond is included.

Heme-O₂ Bonding

Atomic formal charges in the VB structures to be discussed are assigned on the assumption that bonding electrons are shared equally by pairs of adjacent atoms [5-8]. Of course the variationally-best values for the formal charges need to be determined via calculation.

The Fe atomic formal charge in a VB structure is relative to a value of zero for Fe^{II}(3d⁶) (see for example Pauling [1,2]). The effects of the porphyrin (or cysteine) and proximal histidine on the Fe formal charge are therefore ignored. In the heme VB structures that follow, the two $\bullet$ electrons of each $\bullet|\bullet$ occupy the same d-electron AO.

(a) McClure Theory:

The McClure theory of the Fe-O₂ bonding for an oxyheme involves the promotion of each high-spin Fe^{II} of the heme, with four parallel-spin ($S = 2$) unpaired electrons, into an intermediate-spin Fe^{II} state with two parallel-spin ($S = 1$) unpaired electrons [3]. (An estimate of the promotion energy is 250 cm⁻¹ [16].) The latter two electrons are spin-paired with the two unpaired electrons of the $S = 1$ spin ground-state of O₂, to give an $S = 0$ spin Fe^{II}-O_B-O_A linkage. In ref [5g], it is indicated that other early workers such as those of refs [17-21] have also supported the Fe^{II}($S = 1$) + O₂($S = 1$) → Fe^{II}O₂($S = 0$) theory.

As shown above, the Green-Linnett VB structure for the $^3\Sigma_g^-$ O₂ ground-state with spin quantum numbers $S = M_s = 1$, is that of Scheme 1E. When its antibonding π^*_y and π^*_z electrons are singlet spin-paired with the two unpaired d_{yz} and d_{z²} electrons of intermediate-spin Fe^{II} with a (d_{xy})²(d_{x²-y²})²(d_{yz})¹(d_{z²})¹ configuration, as in VB structure **1** (Scheme 2), the VB structure **2** (Scheme 2) is obtained. This VB structure can also be generated [5,7,8] from the Pauling-Coryell Lewis structure **3** (Scheme 2) by means of the one-electron delocalizations from the O_A⁽⁻⁾ into O_B⁽⁻⁾-O_A⁽⁺⁾ bonding MOs.

Scheme 2: Construction of increased-valence structure **2** for the McClure model of oxyheme bonding.

With Heitler-London type formulations of the $d_{yz}-\pi^*_y$ and $d_{z^2}-\pi^*_z$ electron spin-pairings, (i.e. of the type $d(1)\pi^*(2) + \pi^*(1)d(2)$ - see Supplementary Information) with a d AO overlapping with its associated π^* MO, it has been deduced [5d,e,g,h] that VB structure **2** (Scheme 2) is equivalent to resonance between the Pauling-Coryell (Lewis) structure **3** (Schemes 2 and 3), and the singlet diradical (Lewis) structures **4-6** (Scheme 3).

Scheme 3: Component Lewis VB structures for the increased-valence structure **2** of Scheme 2.

The Pauling-Coryell structure **3** (Schemes 2 and 3), and the Goddard-Olafson structure **4** (Scheme 3) [22,23] correspond respectively to structures **3** and **6** in the Scheme 1 of refs [9,11].

The VB structure **2** (Scheme 2) and also the VB structures **9** (Scheme 3), **11** (Scheme 6), **15** (Scheme 6), (i)-(iii) of Figure 1 and those of Figures 2 and 3, are examples of increased-valence

structures. They involve more electrons in bonding [5-8,13] than do the Lewis VB structures from which they can be generated (for example **3** (Scheme 2) $\rightarrow$ **2** (Scheme 2), as discussed above). Only nearest-neighbour bonding is indicated in increased-valence structures [5-8,13].

Pauling-Coryell Lewis-type VB structure **3** (Scheme 2) with an Fe=O double bond has an Fe-O bond number of two. Because Fe=O double bonds are absent in the Lewis structures **4**, **5** and **6** (Scheme 3, the Fe-O bond number in the increased-valence structure **2** (Scheme 2) is less than two, i.e. its two Fe-O electron-pair bonds are fractional. Thin bond lines are used to represent fractional electron-pair bonds in increased-valence structures [5-8,13].

In refs [5a-f,h], it is indicated that because the electronegativities of the oxygen atoms O_A and O_B must differ in the non-symmetrical Fe- O_B - O_A linkage, the O-O bond order of increased-valence structure **2** (Scheme 2) is less than two. This bond order reduction is in accord with the reduced value of the O-O stretching frequency relative to that for unbound O_2 namely 1120-1200 cm^{-1} v. 1556 cm^{-1} (cf. Table 1 in each of refs [24,25]).

In ref [5e], it has also been noted that the presence of the fractional Fe-O double bond in increased-valence structure **2** (Scheme 2) is in accord with an estimate of 567 cm^{-1} for the Fe-O stretching frequency of HbO_2 [26] being smaller than frequencies of 832 and 790 cm^{-1} for the Fe-O double bond stretch of K_2FeO_4 [27].

(b) Pauling-Coryell Theory:

The Pauling-Coryell VB structure **8** (Scheme 3), binds the $S = 0$ spin O_2 Lewis structure **D** of Scheme 1, as in **7** (Scheme 4), to low-spin ($S = 0$) Fe^{II} [1,2]. The Lewis structures **3** (Scheme 2) and **8** (Scheme 4) participate in resonance in the Pauling-Coryell VB formulation [1,2]. Structure **8** (Scheme 4) can be stabilized via the one-electron delocalizations displayed in Scheme 4 to give increased-valence structure **9** (Scheme 4), which participates in resonance with increased-valence structure **2** (Scheme 2).

Scheme 4: Pauling-Coryell VB structures **7** and **8** and associated increased-valence structure **9** for oxyheme bonding. In refs [11,28,29] for example, VB structure **8** (without atomic formal charges) is used to represent the $\text{Fe}^{\text{II}}\text{-O}_2$ linkage.

Increased-valence structure **9** (Scheme 4) is equivalent to resonance between the Pauling-Coryell Lewis structure **8** (Scheme 4) and three (non-displayed) singlet diradical Lewis structures. Increased-valence structure **2** (Scheme 2) accommodates better than does structure **9** (Scheme 4) McClure's comment [3] that "since O_2 is absorbed rapidly and reversibly, it is not likely that it undergoes a great deal of electronic rearrangement upon adding to haemoglobin". Increased-valence structure **2** (Scheme 2) also lends itself readily to VB formulations for reactions of MbO_2 or HbO_2 with NO , as is shown later in this paper.

(c) Weiss theory

For Weiss's $\text{Fe}^{\text{III}}\text{-O}_2^{(\cdot)}$ model of oxyheme bonding [4], the Green-Linnett type VB structure for $\text{O}_2^{(\cdot)}$ is **Scheme 5K** (or for $S = M_s = +1/2$) **Scheme 5L** with a singly-occupied antibonding (π_z^*) MO. When the π_z^* electron is singlet spin-paired with the unpaired electron d_{z^2} of low-spin Fe^{III} , as in structure **10** (Scheme 6), increased-valence structure **11** (Scheme 6) is obtained, which is equivalent to the Scheme 6 **12** $\leftrightarrow$ **13** resonance. Structure **11** (Scheme 6) is an alternative to structure **3** in the Scheme 1 of refs [9,11,28], namely structure **R** of Scheme 5.

Scheme 5: Green-Linnett type VB structures **K** and **L** for $\text{O}_2^{\cdot-}$, **M** and **N** for $\text{Fe}^{\text{II}}\text{-O}^{\cdot-}$ and $\text{Fe}^{\text{II}}\text{-O}$, and **O** for NO . $\text{Fe}^{\text{III}}\text{-O}_2^{\cdot-}$ VB structure **R** and **S** are used in refs [9,11,28] and ref [52], respectively.

Scheme 6: VB structures for the Weiss (**10-13**) and restricted McClure (**14** and **15**) models of oxyheme bonding.

(d) Comparison of Weiss and McClure VB Structures

The Weiss model accommodates the similarity of the O-O stretching frequency (1107 cm^{-1} [24,25]) to the 1150-1200 cm^{-1} for $\text{O}_2^{(-)}$ [24,25], and the development of substantial net negative charge on the O_A and O_B atoms (cf. refs [9,11] for example). However as is discussed in Appendix 1, these effects can also be accommodated primarily via one type of formulation of the wavefunction for increased-valence structure **2** (Scheme 2). It is noted also that the results of the multi-configurational second-order perturbation calculations of ref [30] lead to the conclusion that the ground-state of oxyheme is dominated by Pauling and Weiss configurations. This Pauling configuration, with occupation of $\text{O}_2 \pi^* + \text{Fe } 3d_{z^2}$ and $\text{O}_2 \pi^* - \text{Fe } d_{yz}$ MOs (orbitals 74a and 46b of ref [30]) involves some characteristics of the McClure model with $\pi_z^* - d_{z^2}$ and $\pi_y^* - d_{yz}$ spin-pairings, as in increased-valence structure **2**, but this matter will not be pursued here.

If the O-O bond order HbO_2 is approximately 1.5 (as is implied by the value of the O-O stretching frequency), Lewis structures **12** and **13** (Scheme 6) contribute equally to the **12** $\leftrightarrow$ **13** $\equiv$ **11** resonance scheme. The Fe-O bond-number (n_{FeO}) for the $\text{Fe}^{\text{III}} - \text{O}_2^{(-)}$ increased-valence structure **11** is then 0.5, which implies that the Fe-O bond should be substantially longer than estimates of 1.86-1.92 Å for an Fe-O single bond [31,32]. (Calculated DFT lengths of the Fe-O single bonds for low-spin $[\text{Fe}(\text{H}_2\text{O})_6]^{2+}$ range from 1.912 Å to 2.077 Å [33].) Using the bond-length bond-number formulae $r_{\text{FeO}} = 1.86 - 0.70 \cdot \log(n_{\text{FeO}})$ and $r_{\text{FeO}} = 1.92 - 0.91 \cdot \log(n_{\text{FeO}})$ (see Appendix 2), $n_{\text{FeO}} = 0.5$ gives $r_{\text{FeO}} = 2.07$ Å and 2.19 Å.

Experimental estimates of the Fe-O bond-length for MbO_2 are 1.83 Å and 1.81 Å [34,35], which are shorter than the above estimates for an Fe-O single bond length. Therefore the Weiss $\text{Fe}^{\text{III}} - \text{O}_2^{(-)}$ formulation, (via VB structure **11** (Scheme 6)), provides an unsatisfactory representation of the electronic structure of the Fe-O bond. (It is recognized however that electrostatic attraction between the Fe^{III} and $\text{O}_2^{(-)}$ could shorten and strengthen the bond, and that use of the Fe-O bond number alone to calculate the bond length is incomplete.) It is noted also that the corresponding O-O bond lengths are 1.25 Å and 1.24 Å [34,35], which are closer to the O_2 double bond length of 1.21 Å, than to the $\text{O}_2^{(-)}$ bond length of 1.31 Å.

If $\text{O}_2^{(-)}$ coordinates to Fe^{III} as $\text{Fe}^{\text{III}} \leftarrow \text{O}_2^{(-)}$ via the O_B p_z (with some s character) and Fe d_{z^2} AOs, to produce an electron-pair Fe-O σ bond, the resulting VB structure is **14** (Scheme 6). In this structure, the $\text{O}_2^{(-)}$ odd electron now occupies the antibonding π_y^* MO, and is spin-paired with the

d_{yz} electron of the $\text{Fe}^{\text{III}} \leftarrow \text{O}_2^{(-)}$ coordinated Fe^{III} . VB structure **14** is a restricted form of the McClure $\text{Fe}^{\text{II}}\text{-O}_2$ increased-valence structure **2** (Scheme 2) and is equivalent to resonance between the Lewis structures **3** and **4** of Scheme 2. With a fractional Fe-O double bond, **14** accommodates the shortening of the Fe-O bond relative to a single bond better than does the Weiss $\text{Fe}^{\text{III}}\text{-O}_2^{(-)}$ structure **11**. (A similar result is obtained via resonance between the Pauling-Coryell structures **3** and **8**, which are Lewis components of the increased-valence structures **2** and **9**.) Figure 6 of ref [36] uses VB structures **3**, **4** and **8**. Structure **14** as well as structure **2** can be used to establish the VB mechanism of Figure 1 below.

A second restricted form of the $\text{Fe}^{\text{II}}\text{-O}_2$ increased-valence structure **2**, namely VB structure **15**, is equivalent to resonance between the Lewis structures **3** and **5** (Scheme 3).

Using the Fe-O and O-O bond lengths of 1.83 Å and 1.25 Å for MbO_2 [34], an O-O bond order of 1.8 (Appendix 2), and the $r_{\text{FeO}} = 1.86 - 0.70 \cdot \log(n_{\text{FeO}})$ and $r_{\text{FeO}} = 1.92 - 0.91 \cdot \log(n_{\text{FeO}})$ formulae to obtain estimates of the Fe-O bond number (n_{FeO}), empirical values of 0.22, 0.63, 0.04 and 0.12, and 0.33, 0.55, 0.04 and 0.07 are calculated (Appendix 2) for the weights of the Lewis structures **3-6** (Scheme 3), which are components of the increased-valence structure **2** (Scheme 2). These weights give a net negative charge of either -0.1e or -0.26e for the terminal O_A oxygen atom. Resonance between the McClure and Weiss increased-valence structures **2** and **11**, (with **2** dominant [5b]), can associate negative charge also with the O_B oxygen atom. As discussed in ref [9], the results of CASSCF(g), CASSCF/MM, and DFT/MM calculations yield an O_2 charge close to -0.2e in the gas phase and close to -0.5e in the protein.

To conclude this section, it is to be noted that for the **2** $\leftrightarrow$ **11** resonance, an equivalent VB structure can be constructed by replacing the fractional electron-pair $\text{O}_B\text{—Fe}$ ($p_y\text{-}d_{yz}$) bond in VB structure **2** by $(-\frac{1}{2}) \bullet \text{O}_B \bullet \text{Fe}(+\frac{1}{2}) = \text{O}_B\text{—Fe} \leftrightarrow (-):\text{O}_B \text{ Fe}(+)$.

MetHb (or $\text{Hb}^{(+)}$) + $\text{NO}_3^{(-)}$ are the products (see for example refs [37-43]) of the reaction of NO with HbO_2 via the transient intermediate [40] $\text{HbFe}^{\text{II}}\text{OONO}$ or $(\text{HbFe}^{\text{III}} \leftarrow (\text{OONO})^{(-)})$. Both heme and non-heme oxygenases produce analogous products when they react with NO [37-43].

Figure 1: $\text{HbO}_2 + \text{NO} \rightarrow \text{HbFe}^{\text{II}}\text{OONO} \rightarrow \text{Hb}^{(+)} + \text{NO}_3^{(-)}$. The Green-Linnett VB structure for the ($S = M_S = +\frac{1}{2}$ spin) ground-state of NO, with one antibonding π^* electron is structure Scheme 5O of Scheme 5. Without electron spins, structure Scheme 5Q is the dominant Lewis structure [44], and for convenience, it is used here and in Figure 2 and Scheme 7 below.

As discussed by Kurtikyan and Ford [39], the rapid reaction of NO with HbO₂, leading to the formation of NO₃⁽⁻⁾ and metHb is generally thought to proceed via an $\text{Fe}^{\text{III}} \leftarrow (\text{OONO})^{(-)}$

intermediate. Kurtikyan and Ford also wrote that ambiguity remains regarding the lifetime of such intermediates, and whether isomerization to nitrate is initiated by homolytic O-O cleavage or concerted. Their low temperature spectroscopic study of the reaction of $\text{Fe}(\text{Por})(\text{NH}_3)(\text{O}_2)$ implies that “peroxynitrite intermediates, if formed, must undergo very facile isomerization to the nitrate analogue.”

In Figure 1, we show how increased-valence structures can be used to formulate either an initial O-O cleavage or a concerted isomerization. Using VB structures **2** (Scheme 2) for HbO_2 and the dominant Lewis structure (Scheme 5Q) for NO, we obtain initially VB structure (ii) when NO binds to HbO_2 . In (ii) (and (iii)), peroxynitrite $\text{ONOO}^{(-)}$ is coordinated to the Fe^{III} of the metHb. The electronic reorganization indicated in (ii) leads to the weakening of the O-O bond, as in (iii), from which the $\text{HbFe}^{\text{II}}\text{ONO}_2$ of (iv) is obtained via the electronic reorganization indicated in (iii). H_2O displaces the coordinated $\text{NO}_3^{(-)}$ of (iv) to give the products of (v) (in which only one of six equivalent $\text{NO}_3^{(-)}$ increased-valence structures is displayed). If O-O bond cleavage occurs in (iii) to form $\text{HbFe}^{\text{II}}\text{O} + \text{NO}_2$ prior to the formation of the fractional O- NO_2 bond in (iv), the NO_2 can then bond to the $\text{HbFe}^{\text{II}}\text{O}$ to give the $\text{HbFe}^{\text{II}}\text{ONO}_2$ structure (iv).

If the NO bonds to the HbO_2 as shown in (vi), electronic reorganization can proceed initially according to (vi) $\rightarrow$ (vii) $\rightarrow$ (viii). Rotation around the (fractional) O-O bond of (viii) gives a VB structure analogous to (iii), to generate the $\text{Hb}^{(+)} + \text{NO}_3^{(-)}$ via further electronic reorganization analogous to that used (iii) $\rightarrow$ (iv) $\rightarrow$ (v).

Figure 2. $\text{HbFe}^{\text{III}}-\text{O}_2^{(-)} + \text{NO} \rightarrow \text{HbFe}^{\text{III}} + \text{OONO}^{(-)}$. (The more-stable *cis* $\text{OONO}^{(-)}$ isomer [45] rather than the *trans* $\text{OONO}^{(-)}$ isomer displayed in (iii) can be obtained by rotation around the OO-NO bond of VB structure (ii).)

Increased-valence structure **11** (Scheme 6) (or (i) of Figure 2), is the VB structure for the Weiss $\text{Fe}^{\text{III}}(S = 1/2) + \text{O}_2^{(-)}(S = 1/2)$ formulation of HbO_2 bonding. As shown in Figure 2, reaction of

NO with HbO₂ via Fe^{III}-O₂⁽⁻⁾ would give the HbFe^{III} + OONO⁽⁻⁾ as products. As shown in Figure 1, increased-valence structure **2** (Scheme 2) (or (i) of Figure 2) for the McClure Fe^{II}(S = 1) + O₂(S = 1) formulation of HbO₂ bonding can accommodate the formation of the MetHb + NO₃⁽⁻⁾ products. Therefore, the McClure rather than the Weiss formulation of Fe-O₂ bonding provides the appropriate model for the bonding of O₂ to Hb. However if the OONO⁽⁻⁾ of (iii) of Figure 2 can coordinate to the HbFe^{III} of Figure 2, to give either (iii) or (viii) of Figure 1, the Hb⁽⁺⁾ + NO₃⁽⁻⁾ products can then be obtained.

Co^{II}(S = 1/2)-O₂(S = 1) + NO and Co^{III}(S = 1)-O₂⁽⁻⁾(S = 1/2) + NO Reactions

Figure 3: Starting VB structures **16** and **17** for Co^{II}-O₂ + NO → Co^{II}OONO → Co^{III} + NO₃⁽⁻⁾ and Co^{III}-O₂⁽⁻⁾ + NO → Co^{III}OONO → Co^{III} + OONO⁽⁻⁾. If O₂⁽⁻⁾ coordinates with Co^{III}(S = 0), a restricted form of the Co^{II}(S = 1/2)-O₂(S = 1) VB structure in **16**, namely **18**, is obtained [5b],

The reactions of the oxy-coboglobin systems (NH₃)Co(Por)(O₂) (Por = meso-tetra-phenyl and meso-tetra-p-tolylporphyrinato dianions) with NO also generate NO₃⁽⁻⁾ [40] rather than OONO⁽⁻⁾ as products. The increased-valence structures **16** and **17** displayed in Figure 3 are the starting structures for the VB formulations of the Co^{II}(S = 1/2)-O₂(S = 1) + NO and Co^{III}(S = 1)-O₂⁽⁻⁾(S = 1/2) + NO reactions. Subsequent electronic reorganizations are similar to those of Figures 1 and 2 and lead to the formation of NO₃⁽⁻⁾ and OONO⁽⁻⁾ products, respectively.

Cytochrome P-450 Mono-Oxygenases and a Hydrogen Atom Abstraction Reaction

Figure 4 provides a variation on the ref [5e] concerted or stepwise VB formulation for the cytochrome P450 catalysis of the hydroxylation of a substrate R-H. The Fe^I-O₂ of VB structure (i)

1 is the isoelectronic analogue of the $\text{Co}^{\text{II}}\text{-O}_2$ VB structure **16** (Scheme 6), and is obtained by
 2 adding an electron to the $\text{Fe}^{\text{II}} d_{yz}$ AO of VB structure **1** (Scheme 2).

Figure 4: $\text{Fe}^{\text{I}}\text{-O}_2 + 2\text{H}^{(+)} + \text{RH} \rightarrow \text{Fe}^{\text{III}}\text{-OH}_2^+ + \text{ROH}$. Diprotonation of oxygen atom O_A to give (iv) could occur either as shown in (ii) and (iii), or only after the ROH of (iv) has been formed [5e].

The $(\pi_y)^2(\pi_y^*)^1$ radical character of the $\text{Fe}^{\text{I}}\text{-O}_2$ VB structure (i) is exploited to extract the hydrogen atom of the RH substrate [5e]. In refs [46-51] for example, $\text{Fe}^{\text{III}}\text{-O}_2^{(2-)}$ (or $\text{Fe}^{\text{II}}\text{-O}_2^{(-)}$) replaces $\text{Fe}^{\text{I}}\text{-O}_2$, and the $\text{O}_B^{(-)}$ acts as a nucleophile for reaction with a proton. If breaking of the $\text{O}_A\text{-O}_B$ bond occurs prior to any protonation of O_A , it would yield $\text{Fe}^{\text{II}}\text{-O}^-$ (or $\text{Fe}^{\text{III}}\text{-O}^{(2-)}$) whose VB structure Scheme 5M possesses one three-electron bond as in Compound II [46-48] (cf. VB structures 5K and 5L of Scheme 5 for $\text{O}_2^{(-)}$). The $S = 1/2$ spin Compound I as $\text{Fe}^{\text{II}}\text{O}$ (or $\text{Fe}^{\text{IV}}\text{-O}^{(2-)}$) with two three-electron bonds in its VB structure Scheme 5N (cf. VB structure Scheme 1E for O_2) and an odd electron associated with the porphyrin, manifests itself in the mechanism of refs [46-48]. Release of H_2O from (iv) generates the Fe^{III} of the resting state for cytochrome P-450.

The three-electron bond VB symbolisms used here for the $\text{Fe}^{\text{II}}\text{-O}$ and $\text{Fe}^{\text{II}}\text{-O}^{(-)}$ components of Compounds I and II differ from the Lewis-type VB symbolisms used in refs [46-51].

When the Figure 5 VB structure (i) for $\text{Fe}^{\text{II}}\text{-O}_2^{(-)}$ replaces the Figure 4 VB structure (i) for $\text{Fe}^{\text{I}}\text{-O}_2$, the H-atom transfer from H-R leads to the formation of $\text{Fe}^{\text{II}} + \text{HOO}^{(-)} + \text{R}\cdot$ in (ii) of Figure 5 as products.

Figure 5: $\text{Fe}^{\text{II}}\text{-O}_2^{(-)} + \text{H-R} \rightarrow \text{Fe}^{\text{II}} + \text{HOO}^{(-)} + \text{R}\bullet$. If the peroxide anion $\text{O}_2^{(2-)}$ of (iii) coordinates to low-spin Fe^{III} , to give $\text{Fe}^{\text{III}}\leftarrow\text{O}_2^{(2-)}$ or $\text{Fe}^{\text{II}}\text{-O}_\text{A}\text{-O}_\text{B}^{(-)}$ as in (iv) and a non-bonding $\text{O}_\text{B}^{(-)}$ electron is then delocalized into an $\text{O}_\text{A}\text{-O}_\text{B}$ bonding MO to stabilize (iv), increased-valence structure (i) for $\text{Fe}^{\text{II}}\text{-O}_2^{(-)}$ is obtained.

In Figure 6, the VB formulation of the hydrogen atom transfer reaction uses the $\text{Fe}^{\text{II}}\text{-O}_2$ increased-valence structure **2** (Scheme 2). This formulation provides an alternative to the $\text{Fe}^{\text{III}}\text{-O}_2^{(-)}$ formulation of ref [52] for example, whose $\text{Fe}^{\text{III}}\text{-O}_2^{(-)}$ VB structure in ref [52] is **Scheme 5S**. The (non-displayed) Weiss $\text{Fe}^{\text{III}}\text{-O}_2^{(-)} + \text{H-R}$ VB formulation generates $\text{Fe}^{\text{III}} + \text{HOO}^{(-)} + \text{R}\bullet$ as products.

Figure 6: H-atom transfer via McClure $\text{Fe}^{\text{II}}\text{-O}_2 + \text{H-R}$.

Conclusions:

We agree with Shaik and Hiberty that qualitative VB theory can provide ‘insight, and the ability to think, reason and predict chemical patterns’ [53]. To help do this for electron-rich

systems, it is necessary to exploit more fully the Green-Linnett VB symbolism for the so-called Pauling three-electron bond. The present paper shows how this has been done for Fe-O₂ linkages of oxyhemes, and then used, without computation, to deduce that only the McClure model of the heme-O₂ bonding can account qualitatively for the bond lengths of both the Fe-O and O-O bonds, and also provide a VB mechanism that generates the observed products for reactions such as HbO₂ + NO → Hb⁽⁺⁾ + NO₃⁽⁻⁾. This qualitative VB approach to electronic structure and mechanism formulation is therefore in accord with Coulson's admonition to 'Give me insight, not numbers', as cited by Shaik and Hiberty [53].

Note: Increased-valence structures for the Fe-NO linkages of nitrosylhemes are provided in ref [5b].

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APPENDIX 1 Comment on the Results of DFT and Multireference MO calculations

As discussed in ref [5g], an Fe-O₂ MO configuration can be expressed as a linear combination of Fe⁰-O₂⁽²⁺⁾, Fe^I-O₂⁽⁺⁾, Fe^{II}-O₂, Fe^{III}-O₂⁽⁻⁾ and Fe^{IV}-O₂⁽²⁻⁾ orbital configurations. Two of them correspond to the Fe^{II}(*S* = 1)-O₂(*S* = 1) and Fe^{II}(*S* = 0)-O₂(*S* = 0) configurations for the McClure and Pauling-Coryell models. Configuration interaction increases the importance of Fe^{II}(*S* = 1)-O₂(*S* = 1) relative to Fe^{II}(*S* = 0)-O₂(*S* = 0).

In refs [9,11], the results of DFT and multi-reference MO calculations have been interpreted to favour the Weiss Fe^{III}(*S* = ½)-O₂⁽⁻⁾(*S* = ½) mode of bonding. It involves a fractional Fe=O double bond, which is formed via a weakly-coupled π_y^* -d_{yz} and a dative σ (Fe-O_A) bond (cf. increased-valence structure **14** (Scheme 6)). The latter bond must involve two electrons occupying primarily the Fe-O σ bonding MO $p_z + \kappa d_{z^2}$, for which the p_z (with some s-AO hybridization) and the d_{z²} AOs are located on the oxygen atom O_B and the Fe^{III}, respectively, and $0 < \kappa < \infty$ when the AO overlap $\langle p_z | d_{z^2} \rangle$ is greater than zero.

If the $p_z + \kappa d_{z^2}$ MO is used to accommodate the two Fe-O_A σ -bonding electrons in increased-valence structure **14** (Scheme 6), then the DFT and multi-reference MO Fe^{III}(*S* = ½)-O₂⁽⁻⁾(*S* = ½) model can correspond to a restricted form of the McClure Fe^{II}(*S* = 1)-O₂(*S* = 1) model. It occurs for $\kappa < 1$ in $p_z + \kappa d_{z^2}$ (to generate negative charge on the O_A), with as indicated previously, a value of less than two for the O_A-O_B bond order because of the differences in the electronegativities of the two oxygen atoms.

Thus, with a MO formulation of the wavefunction for the dative Fe-O σ -bond, the McClure model via increased-valence structure **2** (Scheme 2) can accommodate the DFT version of the Weiss model via structure **14** (Scheme 6). There are then only two types of VB structures that require consideration, namely increased-valence structures **2** (Scheme 2) for Fe^{II}(*S* = 1) + O₂(*S* = 1) and (the less important) **9** (Scheme 4) for Fe^{II}(*S* = 0) + O₂(*S* = 0), both of which correspond to the development of increased-valence from the Pauling-Coryell structures **3** (Scheme 2) and **8** (Scheme 4). Of course this is not the case when Heitler-London AO wavefunctions (such as $d_{z^2}(1)p_{zA}(2) + p_{zA}(1).d_{z^2}(2)$) are used for electron-pair bonds. As discussed above, each of the Fe⁰-

$O_2^{(2+)}$, $Fe^I-O_2^{(+)}$, $Fe^{II}-O_2$, $Fe^{III}-O_2^{(-)}$ and $Fe^{IV}-O_2^{(2-)}$ configurations will then contribute to the MO-CI wavefunction.

It is noted that the wavefunction for the $Fe-O_A$ electron-pair σ -bond can be formulated [5a] more generally using two singly-occupied Coulson-Fischer [54] type orbitals, $p_z + \kappa_1 d_{z^2}$ and $d_{z^2} + \kappa_2 p_z$. A value of zero for each of κ_1 and κ_2 gives the Heitler-London AO formulation for the increased-valence structure **2** (Scheme 2) as the **3** $\leftrightarrow$ **4** $\leftrightarrow$ **5** $\leftrightarrow$ **6** (Scheme 3) resonance. Non-zero values for κ_1 and/or κ_2 introduce additional Lewis-type VB structures into the resonance scheme. With $\kappa_2 > \kappa_1$, some negative charge is transferred from the Fe to the O_A atom.

APPENDIX 2:

Estimates of Weights for the Lewis VB Structures that contribute to the Weiss and McClure Models of the $Fe-O_B-O_A$ linkage

With **a** and **b** as the oxygen p_z AOs, **c** as the Fe d_{z^2} AO and $\phi_{ab} = \mathbf{a} + k\mathbf{b}$, the $S = 0$ spin Slater determinantal wavefunction for the four electrons that occupy these orbitals in the $Fe-O_B-O_A$ linkage of increased-valence structure **11** (Scheme 6) is given by eqs (1)-(4).

$$\Psi_{11} = |\mathbf{a}^\alpha \phi_{ab}^\beta \mathbf{b}^\alpha \mathbf{c}^\beta| + |\mathbf{a}^\beta \phi_{ab}^\alpha \mathbf{b}^\beta \mathbf{c}^\alpha| \quad (1)$$

$$= |\mathbf{a}^\alpha \mathbf{a}^\beta \mathbf{b}^\alpha \mathbf{c}^\beta| + |\mathbf{a}^\beta \mathbf{a}^\alpha \mathbf{b}^\beta \mathbf{c}^\alpha| + k(|\mathbf{a}^\alpha \mathbf{b}^\beta \mathbf{b}^\alpha \mathbf{c}^\beta| + |\mathbf{a}^\beta \mathbf{b}^\alpha \mathbf{b}^\beta \mathbf{c}^\alpha|) \quad (2)$$

$$= |\mathbf{a}^\alpha \mathbf{a}^\beta \mathbf{b}^\alpha \mathbf{c}^\beta| + |\mathbf{a}^\alpha \mathbf{a}^\beta \mathbf{c}^\alpha \mathbf{b}^\beta| - k(|\mathbf{b}^\alpha \mathbf{b}^\beta \mathbf{a}^\alpha \mathbf{c}^\beta| + |\mathbf{b}^\alpha \mathbf{b}^\beta \mathbf{c}^\alpha \mathbf{a}^\beta|) \quad (3)$$

$$= \Psi_{12} - k\Psi_{13}. \quad (4)$$

In the Slater determinants, α and β are the $m_s = +1/2$ and $m_s = -1/2$ electron spin wavefunctions. Non-displayed doubly-occupied orbitals are assumed to accommodate the remaining electrons in the VB structures. With the AO overlap integral $S_{ab} > 0$ and $0 < k < \infty$, $\phi_{ab} = \mathbf{a} + k\mathbf{b}$ is the bonding MO which accommodates the electron that forms the one-electron O-O bond in **11**. (Some s-p hybridization occurs for the **b** AO.)

To simplify the discussions below, AO overlap integrals will be omitted.

When each of Ψ_{11} , Ψ_{12} and Ψ_{13} is normalized (ⁿ), the resulting wavefunction is given by eq (5)

$$\Psi^n_{11} = (\Psi^n_{12} - k\Psi^n_{13})/(1 + k^2)^{1/2}. \quad (5)$$

The weight for Lewis structure **12** (Scheme 6) $W_{12} = 1/(1 + k^2)$, corresponds to the Fe-O_B bond number, n_{FeO} , for the Weiss increased-valence structure **11** (Scheme 6) The O-O bond order is given by $p_{\text{OO}} = 1 + k/(1 + k^2)$.

A similar type of 4-electron 3-centre theory applies to the overlapping oxygen p_y and Fe d_{yz} orbitals of increased-valence structure **14** (Scheme 6) with a fractional Fe-O double bond. With **d** and **e** as the oxygen p_y AOs, **f** as the Fe d_{yz} AO, and $\phi_{\text{de}} = \text{d} + l\text{e}$ as the bonding MO to accommodate the electron that forms the one-electron O-O bond, the $S = 0$ spin Slater determinantal wavefunction for the four electrons that occupy these orbitals in **14** is given by eqs (6)-(8)

$$\Psi_{14} = |\text{d}^\alpha \phi_{\text{de}}^\beta \text{e}^\alpha \text{f}^\beta| + |\text{d}^\beta \phi_{\text{de}}^\alpha \text{e}^\beta \text{f}^\alpha| \quad (6)$$

$$= |\text{d}^\alpha \text{d}^\beta \text{e}^\alpha \text{f}^\beta| + |\text{d}^\alpha \text{d}^\beta \text{f}^\alpha \text{e}^\beta| - l(|\text{e}^\alpha \text{e}^\beta \text{d}^\alpha \text{f}^\beta| + |\text{e}^\alpha \text{e}^\beta \text{f}^\alpha \text{e}^\beta|) \quad (7)$$

$$= \Psi_3 - l\Psi_4. \quad (8)$$

With normalized Ψ_{14} , Ψ_3 and Ψ_4 and one normal Fe-O σ -bond, the Fe-O bond number for the increased-valence structure **14** is $n_{\text{FeO}} = 1 + 1/(1 + l^2)$. The O-O bond order is given by $p_{\text{OO}} = 1 + l/(1 + l^2)$.

VB structure **14**, with a normal Fe-O σ -bond and a fractional Fe-O π - bond, is a restricted form of increased-valence structure **2** (Scheme 2) for the McClure model of Fe^{II}-O₂ bonding, with fractional Fe-O σ - and π - bonds. The VB structure **2** involves single occupation of the O-O bonding MOs $\phi_{\text{ab}} = \text{a} + k\text{b}$, $\phi_{\text{de}} = \text{d} + l\text{e}$. The resulting $S = 0$ spin wavefunction can then be expressed as eq (9),

$$\Psi_2 = \Psi_3 - l\Psi_4 - k\Psi_5 + kl\Psi_6 \quad (9)$$

(cf. ref [55] for an analogous approach to wavefunctions for the $\text{N}_3^{(-)}$ anion and N_3 radical), from which $\Psi_{14} = \Psi_3 - l\Psi_4$ is obtained by setting $k = 0$.

To determine empirical values for k and l , we relate as follows the Fe-O bond number $n_{\text{FeO}} = 1/(1 + k^2) + 1/(1 + l^2)$ and O-O π -electron bond order $p_{\text{OO}}^\pi = k/(1 + k^2) + l/(1 + l^2)$ for VB structure **2** to the Fe-O and O-O bond lengths of $r_{\text{FeO}} = 1.83 \text{ \AA}$ and $r_{\text{OO}} = 1.25 \text{ \AA}$ for MbO_2 [34].

1. Estimates of $1.65 \text{ \AA}$ [56] for the length of an Fe-O double bond and either $1.86 \text{ \AA}$ [31] or $1.92 \text{ \AA}$ [32] for the length of an Fe-O single bond give the Fe-O bond-length r_{FeO} ($\text{\AA}$), bond-number n_{FeO} equations $r_{\text{FeO}} = 1.86 - 0.70 \cdot \log(n_{\text{FeO}})$ and $r_{\text{FeO}} = 1.92 - 0.91 \cdot \log(n_{\text{FeO}})$. A value of $r_{\text{FeO}} = 1.83 \text{ \AA}$ for MbO_2 [34] gives an Fe-O bond-number of either 1.10 or 1.26.

An O-O bond-length bond-order equation $r_{\text{OO}} = 1.48 - 0.90 \cdot \log(p_{\text{OO}})$ is obtained from lengths of 1.48 Å and 1.21 Å for O-O single and double bonds. For MbO_2 , $r_{\text{OO}} = 1.25$ Å [34] gives an O-O bond order of 1.80. The resulting π -electron contribution to this bond order from the two one-electron O-O π bonds of increased-valence structure **2** of Scheme 2 is 0.80.

With $n_{\text{FeO}} = 1/(1 + k^2) + 1/(1 + l^2) = 1.26$ and $p_{\text{OO}}^{\pi} = k/(1 + k^2) + l/(1 + l^2) = 0.80$ respectively, one obtains $k = 0.36$ and $l = 1.29$ (or $k = 1.29$ and $l = 0.36$). With $k = 0.36$ and $l = 1.29$, (non variationally-best) weights for the Lewis structures **3-6** (Scheme 3) are $N^2 = 0.332$, $N^2 l^2 = 0.553$, $N^2 k^2 = 0.043$ and $N^2 k^2 l^2 = 0.072$. Because the electron-pair Fe-O σ bond of **4** should be substantially stronger than the electron-pair Fe-O π bond of **5**, $k = 0.36$ and $l = 1.29$ associates a larger weight for structure **4** than it does for structure **5**.

Via $n_{\text{FeO}} = 1.10$ from $r_{\text{FeO}} = 1.86 - 0.70 \cdot \log(n_{\text{FeO}})$ and $p_{\text{OO}}^{\pi} = 0.80$, one obtains $k = 0.43$ and $l = 1.7$ (or $k = 1.7$ and $l = 0.43$) and weights of 0.22, 0.63, 0.04 and 0.12 for the Lewis structures **3-6**.

Three parameters are needed to give the variationally-best energy for resonance between the Lewis structures **3-6**. Two such parameters (k and l) obtain for $\Psi_2 = \Psi_3 - l\Psi_4 - k\Psi_5 + kl\Psi_6$. Following the procedure used in ref [55], a third parameter μ could be introduced (see for example eq (19) in ref [55] for the N_3 radical), and another measured property is then needed to determine its value. Here, partly because the parameter k has a small value (with a value of zero, one obtains $\Psi_{14} \approx \Psi_2 = \Psi_3 - l\Psi_4$), the primary estimates of the weights are obtained by using the k and l parameters that correlate with the Fe-O and O-O bond lengths.

To conclude, we note that for the increased-valence structure **9** (Scheme 4) which binds an O_2 excited state to Fe^{II} , we have $p_{\text{FeO}}^{\pi} = k/(1 + k^2) + l/(1 + l^2) = 0.26$ (via $r_{\text{FeO}} = 1.92 - 0.91 \cdot \log(p_{\text{FeO}})$) and $n_{\text{OO}} = 1/(1 + k^2) + 1/(1 + l^2) = 1.80$. The resulting values for k and l are either -0.19 and 0.61 or 0.61 and -0.19, i.e. one of the Fe-O electrons in **9** is antibonding, not bonding.

Supplementary Material

Heitler-London singlet spin-pairing schemes for $\text{Fe}^{\text{II}}(S=1) + \text{O}_2(S=1) \rightarrow \text{Fe}^{\text{II}}\text{O}_2(S=0)$, delocalizations into antibonding MOs to generate increased-valence structure **2** (Scheme 2) and an $\text{Fe}^{\text{II}}\text{-O}_2$ interaction with the distal histidine are provided in the Supplementary Material available online. Distal histidine interactions on the O_2 binding to heme enlongate the Fe-O and O-O bonds by $\sim 0.01\text{-}0.02$ Å [57].

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