Potential Oxygen-Carrying Complexes by Design

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Abstract
There are twenty four elements known to be necessary for human life, seven of which are transition metals. These seven elements; V, Cr, Mn, Fe, Co, Cu, and Zn have an important role in living systems due to their ability to form complexes with diverse donor groups present in biological systems. [Co(salen)] has been previously studied as a model compound for oxygen transport. In this work other metallic complexes, Ni(II), Zn(II), Cu(II) and Fe(II) with N,N'-bis(salicylaldehyde)ethylenediamine (salen-H_2) were synthesized. The active form of each complex was obtained by reaction with dimethylsulfoxide. The ability of these metallic complexes to act as O_2 carriers was determined. From the results, the complexes of the Co(II), Fe(II) and Cu(II) with salen are able to transport oxygen with an ordering of Co(II) > Fe(II) > Cu(II) regarding the capacity to carry O_2. We used the PM7 semiempirical hamiltonian to study the complexes of salen with Co(II), Cu(II), Fe(II) and Ni(II) and their potential as oxygen carriers. We performed full geometry optimizations in the gas phase for each complex, its active form with DMSO as ligand, and with dioxygen complexed with the active form. We discuss energetic features associated with the binding of dioxygen to the complexes.

1. Introduction

Transport and storage of molecular oxygen is an essential physiological function carried out by molecular species containing Fe(II) and Cu(II) which are found in blood and can have a variety of functions in the blood system. An important example is the hemoglobin which contains the porphyrin–Fe complex. This complex coordinates an oxygen molecule, forming the oxyhemoglobin, which is responsible for the red color of blood [1, 2]. Other porphyrin–metal complexes function as oxygen stores, such as myoglobin, the non-porphyrin metalloproteins hemerytrin and hemocyanin. The last two can store 2 moles of oxygen per mole of complex.

In hemoglobin there are four flat units of porphyrin, which are referred to as heme groups. Each heme group contains four nitrogen atoms coordinated with a Fe(II) cation in a square flat arrangement. Figure 1 shows a scheme of a heme group where iron is coordinated to the four nitrogen atoms from the porphyrin; it is additionally coordinated to one nitrogen belonging to a histidine from the surrounding protein (not shown) and the sixth position holding one oxygen molecule [3, 4], this bond is possible because an oxygen atom donates one of its electron pairs to the iron [5, 6].

This reaction can be reversible

$$\text{Carrier} + O_2 \rightleftarrows \text{Carrier}(O_2)$$
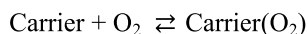
Equilibrium is displaced to the right when the free heme sites from hemoglobin encounter a high concentration of oxygen due to a high partial pressure of oxygen in the lungs. Equilibrium is displaced to the left when the oxyhemoglobin reaches a cell in which the partial pressure of oxygen is low, setting it free in the tissues as required for cellular metabolism [7, 8].
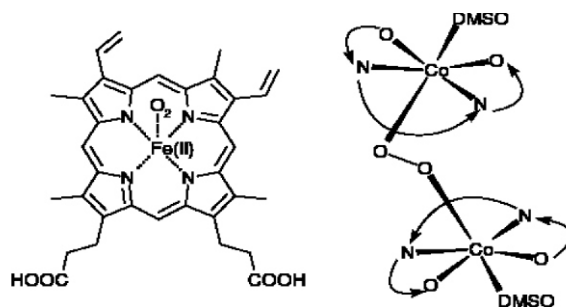

Figure 1. On the left, structure of basic backbone of a porphyrin, known as Heme b B, with O_2 coordinated to the iron. On the right: model compound in which the metallic ion Co(II) is coordinated with two nitrogen atoms and two oxygen atoms that belong to the ligand. The fifth position around the metallic ion is occupied by the oxygen atom from the DMSO, and its sixth position will be occupied by a bridging dioxygen molecule.

Seven out of the twenty four elements that are known to be necessary for human life are first row transition metals. These seven elements V, Cr, Mn,

Fe, Co, Cu, and Zn have an important role in live systems due to their ability to form complexes with diverse donor groups present in biological systems [9, 13]. [Co(salen)] is a species that has been studied previously as a model for oxygen transport [14-16] (see figure 1 for a schematic depiction). The metallic ion Co(II) is coordinated with two nitrogen atoms and two oxygen atoms that belong to the ligand. The fifth position around the metallic ion is occupied by the oxygen atom from the DMSO and its sixth position is occupied by a briding dioxygen molecule.

In this work, other metallic complexes derived from salen were synthesized to be studied as model compounds of biological systems. The potential of these metallic complexes as O_2 carriers was determined and compared to Fe-porphyrin.

2. Experimental

All the substances used were Aldrich Chemical Co. analytical grade.

2.1 Synthesis of Salen [9]

Ethanol (34.1 ml) was added to 2-hydroxybenzaldehyde (3.5 ml), then ethylendiamine (2.2 ml) was added slowly to the warm mixture. The compound formed was filtered off, and washed with ethanol. The yellow solid obtained was recrystallised from ethanol. Yield 64.3 %; IR (KBr disc) 3440 cm^{-1} (O-H), 1636 cm^{-1} (C=N); UV-Vis $\lambda_{max.}$ 332 nm.

2.2 Synthesis of the Complexes

Scheme I

salen-H$_2$ M(II)(salen)
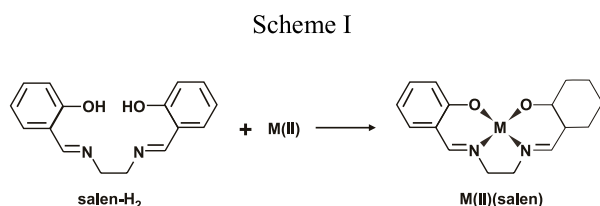
To a refluxing solution of salen-H$_2$ in ethanol, was slowly added an aqueous solution of corresponding metal acetate according to the desired complex. The reflux was maintained for one hour under an inert atmosphere at 80-90 °C. The solid products obtained were filtered off, washed, and purified with an adequate solvent. Yields = 61.2-88 %; IR (KBr disc) 1625-1635 cm^{-1} (C=N); to see UV-Vis λ_{max} for each complex refer to Table 1.

2.3 Synthesis of the Active Form of the Complexes

Scheme II

$2[M^{2+}(salen)]$ + 2DMSO + O_2 $\rightleftarrows$ $[(DMSO)M^{2+}(salen)]_2 O_2$
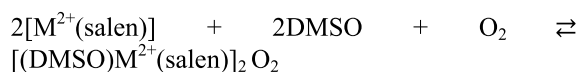
The reaction depicted in Scheme II, using the apparatus depicted in Figure 2, was performed as follows: 0.05 g of the complex M(salen) (M= Co^{2+}, Cu^{2+}, Zn^{2+}, Ni^{2+}, Fe^{2+}) was placed in the test tube 1. Then 5 ml of DMSO were introduced into test tube 2. Water was added to addition funnel 4 and the stopcock opened to allow levelling of the water between pipette 3 and addition funnel 4.

The DMSO was spilled over the complex and shaken for fifteen minutes. The displaced water volume was read in the pipette at STP, and the transported moles of oxygen were calculated using equation (1):

$$n = (P\text{-}f)V/(RT) \qquad (1)$$

where n is number of moles of oxygen, P is pressure (in mmHg), f is the pressure difference before and after adding the DMSO to the complex, as read from the burette, V is volume, R is the gas constant and T is the temperature. To test for the reversibility of the oxygen absorption, a few drops of chloroform were added to the formed product, to check for the release of oxygen.
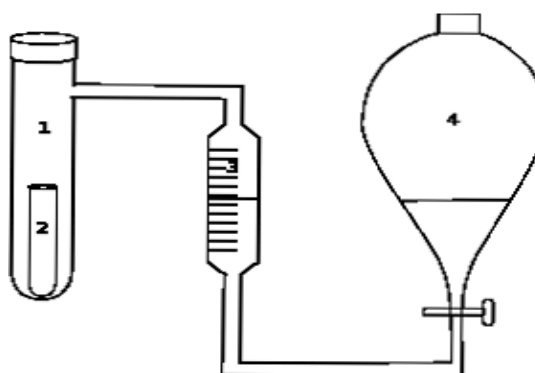

Figure 2. Apparatus for preparation of active form of M(salen) and its dioxygen uptake.

2.4 Computational studies

All the complexes and the salen structures were built and optimized using MOPAC2012 [17]. The

PM7 [17] Hamiltonian was used in all calculations. After optimization, vibrational analyses of all the stationary points obtained were calculated to identify and keep only true energetic minima.

3. Results and discussion

A series of metal complexes of salen having 1:1 (Metal:Ligand) stoichiometries have been isolated from alcohol solutions in good yield and data concerning their characterization are summarized in Table 1.

The experimental IR spectra of the complexes show imine stretch frequencies in the region 1625-1635 cm^{-1}, which are split and/or shifted relative to that of the corresponding free ligand (1636 cm^{-1}) due to complexation. In the individual spectra the absence of a band attributable to the O-H stretching vibration (3440 cm^{-1} in salen) was also evident, suggesting that the metal ions were also bound to the oxygen atoms of the hydroxyl groups. The computational results are qualitatively consistent with the shift of the C=N band when going from free salen to the complex, although the shift is overestimated.

Table 1. IR and UV-VIS spectral data for the ligand and complexes. The computational results were obtained from the M(salen) complex.

Compound	$\lambda_{max.}$ (nm)	C=N ν cm^{-1} (exp.)	ν cm^{-1} (by PM7)
Salen-H_2	332	1636	1837, 1853
Fe^{II}(salen)	487	1625	1691, 1698
Co^{II}(salen)	492	1630	1665, 1695
Ni^{II}(salen)	420	1630	1438*
Cu^{II}(salen)	430	1635	1733, 1765
Zn^{II}(salen)	317	1632	1776, 1789

*PM7 predicts tetrahedral geometry around the metal center.

Table 2 shows that the complexes of Co(II), Fe(II) and Cu(II) with salen in its active form are able to transport oxygen. In these model systems the oxygen molecule may be as O_2^{-} or O_2^{2-}. Ni(II) and Zn(II) complexes are unable to absorb oxygen so they are not active.

From the results the complexes of the Co(II), Fe(II) and Cu(II) with Salen are able to transport oxygen. The order of capacity to carry O_2 for the complexes studied here is Co(II) > Fe(II) > Cu(II).

The salen complex of Co is very well known experimentally as a dioxygen transporter [18]. The PM7 results for the complexes (see Table 3) agree qualitatively with the experimental findings. First of all, PM7 predicts that DMSO does not bind to the

Table 2. Metallic complexes with *N,N'*-bis(salicylaldehyde)ethylenediamine (salen) and their ability to carry oxygen.

Complexes	Yield (%)	Color		Moles of O_2/mole of complex
		Inactive Form	Active Form	
Fe^{II}(salen)	84.7	Red-brown	Wine red	0.313
Co^{II}(salen)	61.2	Purple	Brown	1.132
Ni^{II}(salen)	83.7	Orange	-	-
Cu^{II}(salen)	88.0	Green	Blue	0.272
Zn^{II}(salen)	82.7	Pale yellow	-	-

Ni(salen) nor the Zn(salen) complexes, thus preventing the formation of the activated complex. The dioxygenated Cu complex could not be calculated, because of repeated failures to achieve self-consistent field, but the relative energies found for Fe and Co are in qualitative agreement with the experimental finding that Co is a better oxygen carrier than Fe as the dioxygenated complex is more stable, but stability is not clearly related to capacity.

Table 3. PM7 energies of the salen complexes, their active form with DMSO and the active form before and after binding dioxygen. Relative energies in kcal/mole are in parentheses. Where appropriate, we have included the values of the S^2 operator. PM7 energy of dioxygen: 25.67333 kcal/mole.

Metal (M)	PM7 energies (kcal/mol)			
	M(salen)	M(salen) (DMSO)	M(salen) (DMSO)(O_2)	M(salen) (DMSO)(O_2) relative energy*
Fe	-20.42729	-94.9073	-117.79307	27.3729
Co	70.59573	-3.88354	-41.86107	-139.58286
Ni	62.48193	Does not form	---	---
Cu	69.61649	-43.10015	Not converged	---
Zn	-19.79771	Does not form	---	---

*considering M(salen)(DMSO) + O_2 as reagents.

4. Conclusions

We have shown that salen reacts with Fe, Co, Ni and Cu to form the corresponding complex. For the complexes studied here, only Co(II), Fe(II) and Cu(II) formed complexes able to transport oxygen. The ordering with respect to the capacity to carry O_2 for the mentioned complexes is Co(II) > Fe(II) > Cu(II) which is qualitatively followed by the theoretically determined reaction energies. The computations reveal that, in the case of Ni(II) and Zn(II), the lack of ability to transport dioxygen is due to inability to coordinate with DMSO and thus form the active complex.

5. Acknowledgements

6. Bibliography

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