Novel molecular receptors capable of forming Cu_2–O_2 complexes. Effect of preorganization on O_2 binding

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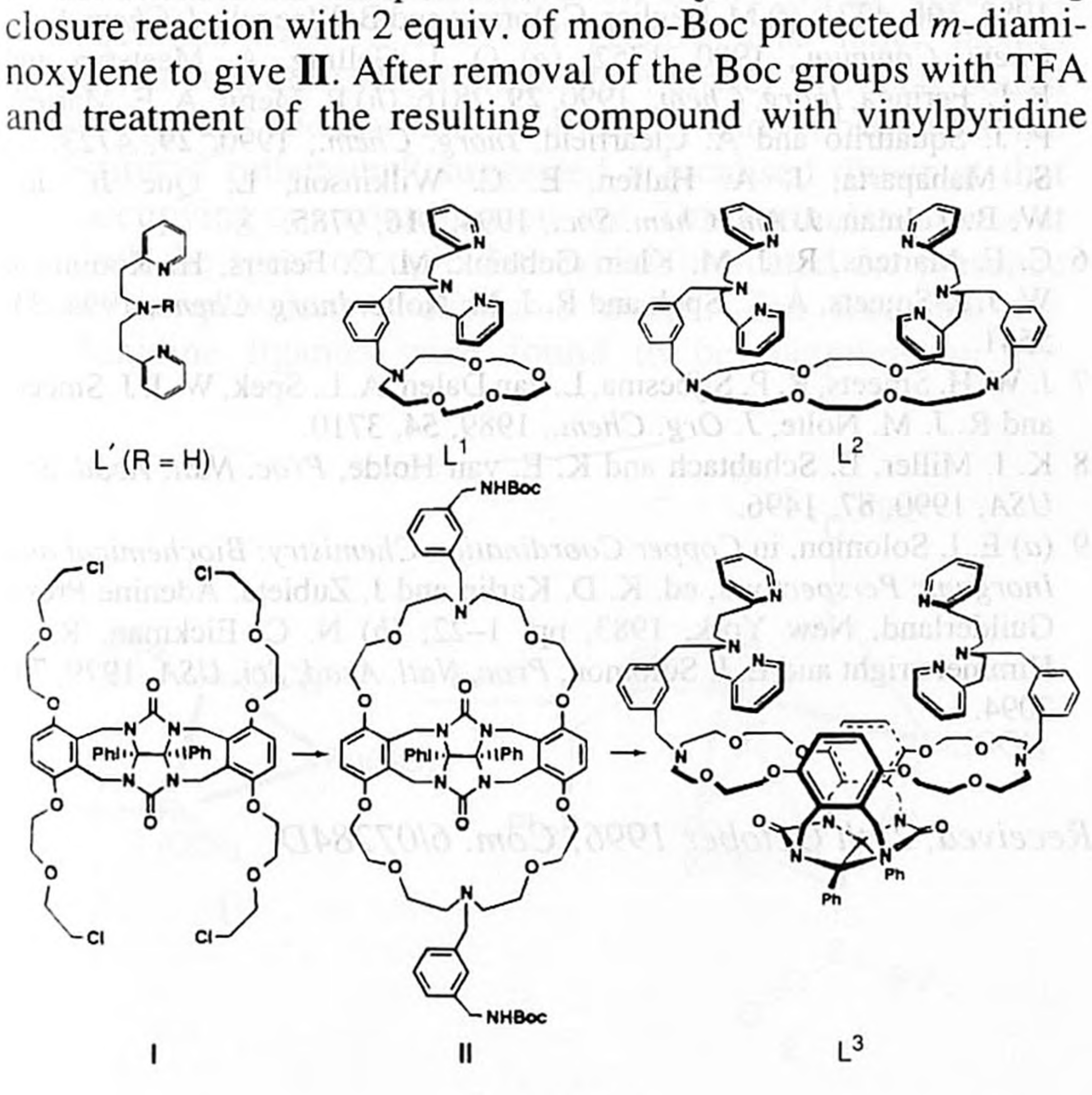
Novel biomimetic copper(I) receptors react with O_2 to form metastable O_2 complexes and the rate of these reactions depends on the preorganization of the ligands.

The binding and activation of molecular oxygen by dinuclear copper enzymes has attracted much attention in recent years.[1,2] Using model studies it was proposed,[1d,3] and later confirmed,[4] that molecular oxygen is bound between the two copper centres in the active site of haemocyanin *via* an unusual μ-η²:η² binding mode.† Several groups have demonstrated that synthetically derived Cu_2–O_2 complexes can carry out oxygenation reactions,[5] in particular, upon the ligands of the complex. One aim of our research is to design systems which may be used in oxygenation reactions on exogeneous substrates. For this reason we have attached the previously studied ligand L′[5a–d] (Scheme 1) to particular crown ethers and to a known molecular receptor,‡ for the potential to bind substrates in close proximity of an Cu_2O_2 centre. Here, we describe initial studies with three new ligands L¹–L³ (Scheme 1) and their copper(I) complexes **1–3**, and characterization of their molecular oxygen binding ability.

Ligands L¹ and L² were synthesized from the commercially available crown ethers aza-15-crown-5 and diaza-18-crown-6. The secondary nitrogen atoms of the latter compounds were alkylated with 3-cyanobenzyl bromide, and the cyano groups were reduced with $LiAlH_4$. The resulting primary amines were alkylated with vinylpyridine under high-pressure conditions (15 kbar)[6] using acetic acid as a catalyst, providing pure L¹ and L² in 27 and 58% overall yield, respectively. For the preparation of L³ the tetrachloro compound **I**[7] was subjected to a double ring closure reaction with 2 equiv. of mono-Boc protected *m*-diaminoxylene to give **II**. After removal of the Boc groups with TFA and treatment of the resulting compound with vinylpyridine under high-pressure conditions compound L³ was obtained in 80% overall yield.§



Scheme 1

Copper(I) complexes **1–3** were synthesized by adding the ligands L¹–L³, dissolved in CH_2Cl_2, to the appropriate amount of $[Cu^I(MeCN)_4]ClO_4$ under strictly anaerobic conditions. After several precipitations with Et_2O the complexes were isolated as yellow–brown powders. Elemental analysis and spectral data were in agreement with the structures $[Cu^IL^1]ClO_4$ **1**, $[Cu^I_2L^2][ClO_4]_2$ **2** and $[Cu^I_2L^3][ClO_4]_2$ **3**.§

Complexes **1–3** all formed metastable O_2 adducts in CH_2Cl_2 at −85 °C (Scheme 2). The rates of formation of these adducts were quite different, whereas their UV–VIS spectra were very similar (Table 1). Complex **2**·O_2 was obtained within 1–2 min after bubbling pre-cooled O_2 through a CH_2Cl_2 solution of **2** at −85 °C. During the reaction the colour of the solution changed from yellow to purplish green. Under the same conditions the bright orange complex **3**·O_2 was formed in 10–20 min. In contrast, both the colour of a solution of **1** and the absorption spectrum of this solution remained initially unchanged. If, however, an O_2-saturated solution of this complex was allowed to stand for 3–5 h at −85 °C, an orange complex formulated as $\mathbf{1}_2$·O_2 was formed slowly; this diminished O_2-binding rate and stoichiometry is in keeping with that observed for other L′ (R = Me, $PhCH_2$, Ph) copper(I) mononuclear complexes.[5c] In view of the spectral and structural similarities with previously reported Cu_2–O_2 complexes[1c–e,3] we propose that complexes $\mathbf{1}_2$·O_2, **2**·O_2, and **3**·O_2 all contain a peroxo ligand in a (bent) μ-η²:η² binding mode; the distinctive absorption around 364 nm

$$2\,Cu^IL^1 + O_2 \xrightarrow{-85\,°C} (Cu^{II}L^1)_2O_2$$

$$Cu^I_2L^n + O_2 \xrightarrow{-85\,°C} Cu^{II}_2L^nO_2$$

(n = 2,3)

λ_{max} = 364 nm

orange-green

Scheme 2

Table 1 UV–VIS characteristics [λ/nm (ε/dm³ mol⁻¹ cm⁻¹)] of copper complexes **1–3** and haemocyanin

Complex	Cu^I	Cu_2O_2	Cu^II
1	340 (2150)	364 (4900)	346 (3900)
		428 (960)	616 (600)
		656 (450)	
2	344 (5800)	364 (12800)	344 (4000)
		526 (1000)	628 (300)
		642 (800)	768 (100)
3	340 (5000)	364 (13100)	358 (3400)
		418 (2900)	630 (500)
		524 (150)	
		650 (100)	
Haemocyanin[a]		345 (20000)	700 (200)
		570 (1000)	

[a] Taken from ref. 9(*b*).

points to this type of binding.¶ The low absorption coefficients observed, particularly in $1_2 \cdot O_2$, are ascribed to lack of complete formation of O_2 adducts, and with concurrent temperature dependent decomposition (*vide infra*).

We found that the formation of complex $1_2 \cdot O_2$ can be accelerated if $KClO_4$ is added to the solution containing **1**, before O_2 is bubbled through it. In the presence of $KClO_4$ the O_2 complex reached its maximum concentration after 30–45 min, whereas without $KClO_4$ it took approximately 5 h for the complex to be formed completely. For 15-crown-5 and related compounds it is known that K^+ ions induce the formation of sandwich complexes, as these cations are too large to fit in the crown ether rings. Apparently, K^+ ions have the same effect on complex **1**: two mononuclear complexes are brought together and are pre-organized in order to bind one molecule of O_2. The proposed structure of such a sandwich complex, as shown in Fig. 1, may represent an intermediate state, more than it represents the final product. The enhanced oxygen affinity of complex **1** in the presence of K^+ cations mimics to some extent the allosteric effect of Mg^{2+} ions on the oxygen binding by molluscan haemocyanin.[8] For the formation of $2 \cdot O_2$, and $3 \cdot O_2$ no acceleration effect of K^+ ions was observed.

Purging solutions $2 \cdot O_2$ with argon at −85 °C did not result in the decolourization of these solutions. When a solution of $2 \cdot O_2$ was rapidly heated under vacuum a green solution was obtained. These results indicate that the formation of the O_2 adducts is an irreversible process. As mentioned above the oxygen complexes are metastable; at −85 °C the loss in absorption intensity in the UV–VIS region was 5–10% after 1 h. Upon warming to room temperature the solutions of the complexes turned green within minutes. The resulting products could all be isolated as pale green powders in reasonable yields. IR and mass spectroscopy indicated that dinuclear copper(II) hydroxide complexes were formed. The starting ligands L^1–L^3 could be isolated from the corresponding copper(II) complexes after removal of the Cu^{II} ions with aqueous ammonia. Yields were above 70% for L^1 and L^3, whereas L^2 was recovered in approximately 50% yield, indicating that some ligand degradation had occurred.

In summary, we have shown that the new complexes **1–3** all form stable O_2 complexes, which after warming yield copper(II) complexes in which the ligand remains intact to a major extent. This opens the possibility to use these complexes as oxygenation catalysts for exogeneous substrates, which is currently under study. The O_2 affinity and rate of formation of the copper(I) complexes is determined by the degree of pre-organization present in the starting complex.

The authors are grateful to NATO for a grant in their Supramolecular Chemistry Programme (CRG950904). R. K. G. and R. N. would like to thank SON–NWO for financial support and K. D. K. in addition acknowledges the National Institutes of Health.

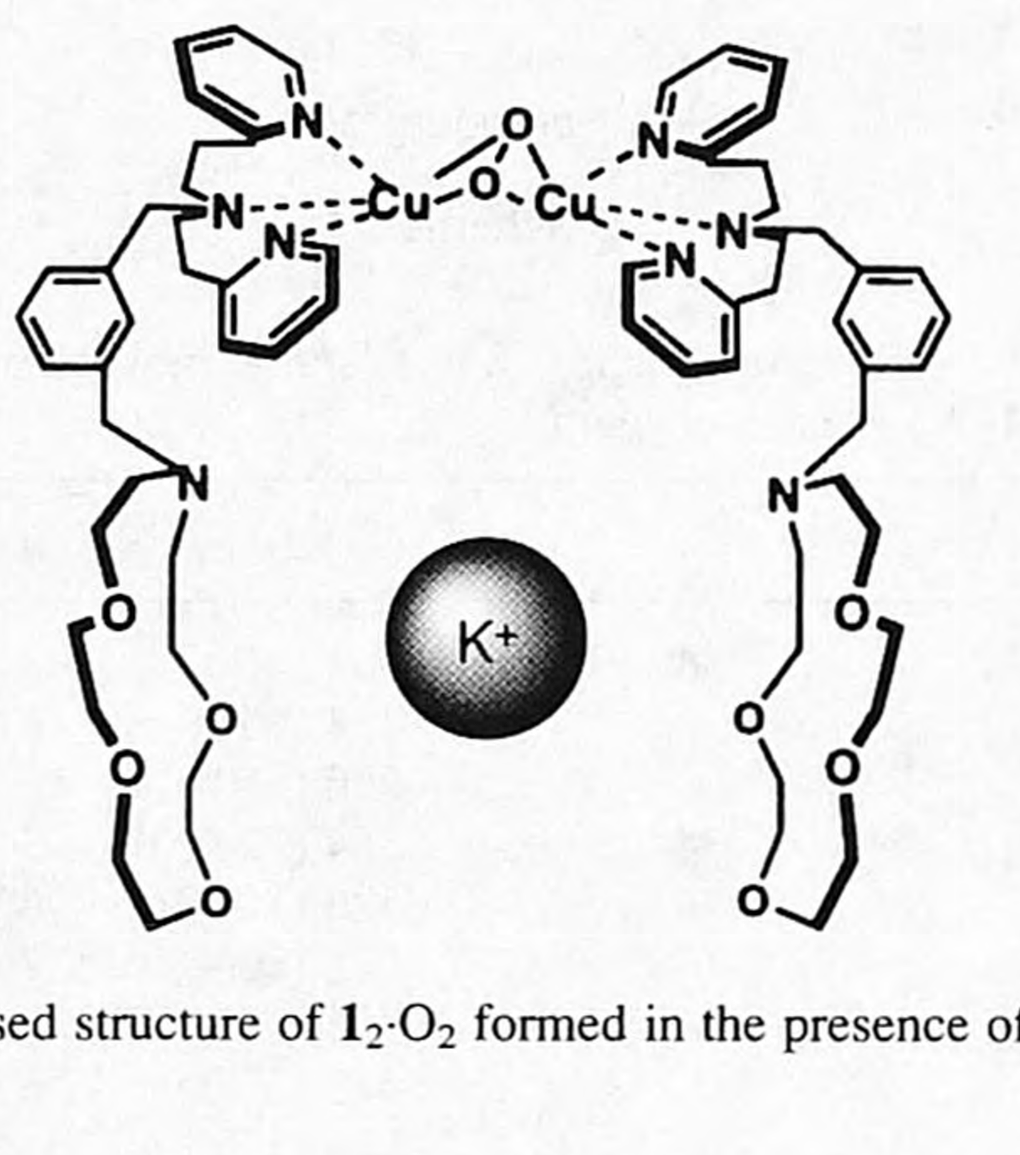


Fig. 1 Proposed structure of $1_2 \cdot O_2$ formed in the presence of K^+ ions

Footnotes

† Tolman and co-workers have recently demonstrated that interconversion of a $Cu_2(\mu\text{-}\eta^2:\eta^2\text{-}O_2)$ complex and a $Cu_2(\mu\text{-}O)_2$ complex is possible: J. A. Halfen, S. Mahaparta, E. C. Wilkinson, S. Kaderli, V. G. Young Jr., l. Que Jr., A. D. Zuberbühler and W. B. Tolman, *Science*, 1996, **271**, 1397.

‡ We have shown before that a similar complex with pyrazole instead of pyridine ligands, is capable of selectively oxidizing alcohols that are complexed in its cavity. C. F. Martens, R. J. M. Klein Gebbink, M. C. Feiters and R. J. M. Nolte, *J. Am. Chem. Soc.*, 1994, **116**, 5667.

§ Compounds L′–L^3 and **1–3** were fully characterized by spectroscopic methods; data were made available for the reviewers.

¶ Cu : O_2 stoichiometries of the novel complexes are based on spectral similarities with structurally related systems [see refs. 1(*c*)–(*e*) and 3].

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Received, 25th October 1996; Com. 6/07284D