240. Cuprous Complexes and Dioxygen

Part X[1])

Influence of Ring Size on the Autoxidation of Cu(I) Complexes with *cis*- and *trans*-N_2S_2 Macrocyclic Ligands

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Summary

The autoxidation of the Cu^+ complexes with a series of six 12-, 14- and 16-membered macrocycles containing the N_2S_2 set of donor atoms has been studied with an oxygen electrode and with the stopped-flow technique. Inspite of the identical set of coordinating groups, the reactivity of the Cu^+ complexes towards O_2 varies by more than 5 orders of magnitude, with rate constants between < 0.1 and $2 \cdot 10^4$ $M^{-1}s^{-1}$. Simple bimolecular rate laws are obtained from initial rates of autoxidation, but successive one-electron transfers with intermediate formation of superoxide are implied from the analysis of complete reaction curves for the complexes with the 12-membered macrocycles. The kinetic parameters are compared with the redox potentials for the corresponding CuL^{2+}/CuL^+ couples. Only a rather rough correlation is found and steric factors must in addition be responsible for the observed reactivity pattern which shows a decrease of autoxidation rate with increasing size of the macrocyclic ring. No systematic effect was observed for the influence of *cis*- *vs.* *trans*-configuration of the donor atoms.

Introduction. – Because of the innate steric restrictions imposed by their structures, macrocyclic ligands would be good choices for the study of structure-reactivity relationships in the autoxidation of Cu(I) complexes. However, no such investigation seems to have been performed to this date. This finding can be rationalized on the basis that the bulk of the well-known macrocyclic ligands would not be ideal for this purpose. Tetraaza macrocycles lead to unstable Cu(I) complexes with CuL^{2+}/CuL^+ redox potentials around −400 mV [2]. Complexes with tetrathia ligands have redox potentials around +600 mV and are inert towards O_2 [3]. Polyoxa ligands are preferred for the binding of main group metal ions and have been little studied with transition metals [4].

Here we report on the autoxidation of Cu(I) complexes with a series of six macrocyclic ligands **1**–**6** containing the N_2S_2 set of donor atoms.

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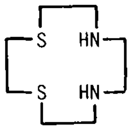
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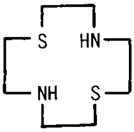
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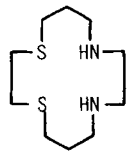
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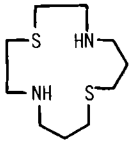
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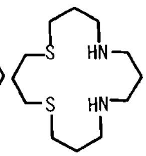
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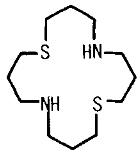
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For several reasons, these recently synthesized diaza-dithia macrocyclic ligands [5] would be obvious candidates for autoxidation studies: *i*) In line with interpolation between N_4- and S_4-macrocycles, both Cu^+ and Cu^{2+} complexes are reasonably stable with these ligands [6]. *ii*) Based on experience with more simple systems [7], we can expect reasonable rates of autoxidation for these complexes which have CuL^{2+}/CuL^+ redox potentials between 80 and 420 mV [6]. *iii*) The N_2S_2 set of donor atoms would be of specific interest with regard to its presence in plastocyanin [8] and related 'blue' copper proteins.

The following questions have been the specific subject of this study: *i*) Despite the identical set of two thiaether and two secondary aliphatic NH_2 groups, the redox potentials $E(CuL^{2+}/CuL^+)$ vary by almost 400 mV or six orders of relative complex stability. Will this be paralleled by a corresponding change in susceptibility to autoxidation? *ii*) From the inspection of molecular models we can safely imply differences in the stereochemistry of the complexes with the 12-, 14- and 16-membered ligands. What is the relative importance of direct *vs.* indirect (*via* influence on the redoxpotential) steric effects? *iii*) The macrocyclic ligands impose some, but by no means perfect, rigidity on the structure of the complexes and this may to some degree lower the *Frank-Condon* barrier to the electron transfer [3] [9]. Will this be reflected in an unusually high reactivity of some or all of the Cu(I) complexes? *iv*) Can we obtain any information on the detailed reaction mechanism, specifically the relative importance of one- and two-electron reduction paths for O_2?

Experimental. – The macrocyclic ligands **1–6** were synthesized by high-dilution cyclization [5] and used in the form of their dihydrobromides (**1**, **2**) or dihydrochlorides (**3–6**). $[Cu(CH_3CN)_4]BF_4$, prepared as published in [10], was the source of Cu^+ ion. Other chemicals were of analytical grade and used without further purification. The ionic strength was adjusted to $I = 0.2$ by Na_2SO_4.

The redox stoichiometry, moles of O_2 consumed per mole of Cu(I) added, and the kinetics of autoxidation of the Cu(I) complexes with ligands **4–6** were followed at 20° by an oxygen electrode coupled to a high-impedance millivolt recorder as described in [11]. For some experiments, data were digitally collected on-line with a *Dolphin* microprocessor system, stored on magnetic tape, and subjected to numerical analysis on an *Apple II* (*cf.* below). The autoxidation of the complexes with ligands **1–3** proved to be too fast for the oxygen sensor. Stopped-flow measurements were done at 25° on a *Durrum D 110* spectrometer connected to a *Datalab Dl 901* transient recorder and controlled by a *Rockwell AIM 65* microprocessor for digital data acquisition and storage. The formation of CuL^{2+} (L = **1–3**) was generally followed at 650 nm. Longer wavelengths were used if necessary to avoid absorption of more than 10% of the incident light. The kinetics of autoxidation were independent of the wavelength in the range of 500–750 nm.

Data were transferred to an *Apple II* desk top computer and stored on floppy-disk. Numerical treatment of the data on the *Apple II* was carried out using a modified version of ELORMA [12] which equally allows the fitting of overlapping exponentials and of second-order reaction curves. Experimental data and calculated curves were plotted on a *Watanabe WX 4671 Miplot* plotter driven by the *Apple II*. The final analysis of the results from the individual experiments was done on a *Hewlett-Packard HP 9835A* calculator equipped with a *HP 7225A* plotter.

Results and Discussion. – Exploratory experiments were done at pH 5, 7 and 9 in 2% aq. CH_3CN with the oxygen electrode. Despite their identical N_2S_2 donor set the Cu(I) complexes showed dramatic differences in their reactivity with O_2. At pH 7 and 9 the kinetics were too fast to be followed by the oxygen electrode for *cis*-[12]aneN_2S_2 (**1**), *trans*-[12]aneN_2S_2 (**2**) and *cis*-[14]aneN_2S_2 (**3**). The complex with *trans*-[14]aneN_2S_2 (4) gave a pH-independent rate which could be easily studied. The two 16-membered macrocycles **5** and **6** again gave much slower rates of autoxidation, no significant O_2 uptake could in fact be observed with *cis*-[16]aneN_2S_2 (**5**). At pH 5, the reactivity was strongly influenced by complexation equilibria, *i.e.* formation of protonated complexes $CuLH^{2+}$ and $Cu(CH_3CN)LH^{2+}$ or dissociation [6]. For ligands **1**–**4** and **6** the kinetics of autoxidation were subsequently studied in more detail in phosphate buffer. Parameters were $[CuL^+]$, $[O_2]$, $[CH_2CN]$, [buffer] and pH with standard conditions of $[CuL^+] = 7.5\cdot10^{-5}$M, $[O_2] = 6\cdot10^{-5}$M (oxygen electrode) or $6\cdot10^{-4}$M (stopped flow spectrophotometry), $[CH_3CN] = 2\%$ *v/v* (0.38M), [buffer] $= 10^{-3}$M, pH = 7.0. Most of the experiments with the oxygen electrode were analyzed by the method of initial rates,

Table 1. *Second-Order Rate Constants Obtained by Variation of $[CuL^+]$, $[O_2]$, pH, $[CH_3CN]$, and [buffer]*

Ligand	Parameter varied[a]	Range	k_2 $[M^{-1}s^{-1}]$[b]	No. of points
cis-[12]aneN_2S_2 (**1**)	$[CuL^+]$	37.5–150 μM	$(2.7 \pm 0.3)\cdot10^3$	16
	$[O_2]$	0.125–0.6 mM	$(2.8 \pm 0.1)\cdot10^3$	6
	pH	6.20–7.91	$(2.9 \pm 0.4)\cdot10^3$	27
	$[CH_3CN]$	0.075–1.0M	–[c]	20
	[buffer]	1–10 mM	$(2.8 \pm 0.3)\cdot10^3$	16
	[buffer]	1–10 mM	$(2.2 \pm 0.2)\cdot10^3$	12[d]
trans-[12]aneN_2S_2 (**2**)	$[CuL^+]$	37.5–150 μM	$(6.7 \pm 0.5)\cdot10^3$	16
	$[O_2]$	0.125–0.6 mM	$(9.4 \pm 0.5)\cdot10^3$	6
	pH	6.18–7.85	–[e]	23
	$[CH_3CN]$	0.075–1.0M	–[c]	18
	[buffer]	1–10 mM	$(7.9 \pm 0.5)\cdot10^3$	16
	[buffer]	1–10 mM	$(7.6 \pm 1.3)\cdot10^3$	12[d]
cis-[14]aneN_2S_2 (**3**)	$[CuL^+]$	25–100 μM	$(4.6 \pm 0.2)\cdot10^3$	14
	$[O_2]$	0.125–0.6 mM	$(5.4 \pm 0.6)\cdot10^3$	10
	pH	6.25–7.93	$(4.1 \pm 0.3)\cdot10^3$	32
	$[CH_3CN]$	0.27–1.5M	$(4.1 \pm 0.3)\cdot10^3$	25
	[buffer]	1–10 mM	$(4.1 \pm 0.5)\cdot10^3$	16
	[buffer]	1–10 mM	$(4.2 \pm 0.2)\cdot10^3$	12[d]
trans-[14]aneN_2S_2 (**4**)	$[CuL^+]$	7.5–100 μM	(38 ± 9)	12
	$[O_2]$	9.7–92 μM	(44 ± 4)	16
	pH	6.5–8.3	(43 ± 4)	19
	$[CH_3CN]$	0.12–0.79M	(47 ± 4)	12
	[buffer]	1–10 mM	(45 ± 4)	14
trans-[16]aneN_2S_2 (**6**)	$[CuL^+]$	60–180 μM[f]	(1.9 ± 0.3)	6
	$[O_2]$	48–110 μM[f]	(1.8 ± 0.2)	4
	pH	7.9–8.1	(2.4 ± 0.2)	4
	$[CH_3CN]$	0.19–0.57M[f]	(1.9 ± 0.2)	6
	[buffer]	1–3 mM[f]	(2.5 ± 0.1)	4

[a] Other conditions *cf. Experimental.* [b] Defined according to *Eqn. 2,* with standard errors. [c] Dependent on $[CH_3CN]$, *cf. Fig. 1.* [d] Stopped-flow measurements at 20°. [e] Decrease of reactivity below pH 7. [f] Measurements at pH 8, contribution of Cu^+_{aq} to O_2-consumption at pH 7.

while the complete reaction curves were evaluated in the case of stopped-flow measurements. The main results are summarized in *Table 1*.

In all five systems, the weak phosphate buffer (10^{-3}–10^{-2}M) did not influence the rate of autoxidation. In general, no pH-dependence was observed for pH > 7 and the decrease of the reactivity at higher acidities could be ascribed to the formation of the monoprotonated complexes $Cu(CH_3CN)LH^{2+}$ (L = **1** or **2**, *cf. Eqn. 1*) or $CuLH^{2+}$ (L = **3**, **4**, **6**) [6]. In fact, the autoxidation of the complexes with ligands **3**, **4**, and **6** could be described by a simple bimolecular rate law *(Eqn. 2)*.

$$CuL^+ + H^+ + CH_3CN \rightleftharpoons Cu(CH_3CN)LH^{2+} \tag{1}$$

$$v = -d[O_2]/dt = \tfrac{1}{2}\, d[CuL^{2+}]/dt = k_2[CuL^+][O_2] \tag{2}$$

Over the whole range of experimental conditions given in *Table 1*, complete reaction curves could be satisfactorily analyzed as second-order reactions of the same type for ligands **3** and **4**, while **6** only was studied by the method of initial rates because of the slowness of reaction.

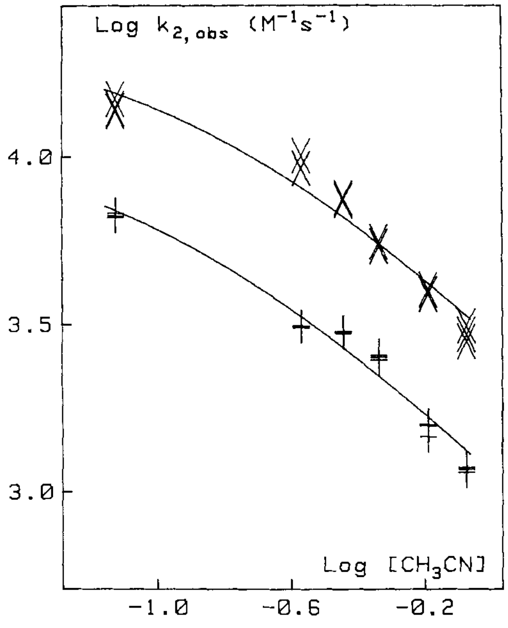

Fig. 1. *CH_3CN-dependence of autoxidation of CuL^+*. [L] = 10^{-4}M, [Cu(I)] = $7.5\cdot10^{-5}$M, [O_2] = $6\cdot10^{-4}$M, pH = 7.0. —— Curves calculated with *Eqn. 2'*; +: L = *cis*-[12]aneN_2S_2 (**1**), $k_2' = (1.2 \pm 0.1)\cdot 10^4$ $M^{-1}s^{-1}$, $k_2' = 9.3 \pm 1.5M^{-1}$; ×: L = *trans*-[12]aneN_2S_2 (**2**), $k_2' = (2.4 \pm 0.3)\cdot 10^4$ $M^{-1}s^{-1}$, $k_2' = 7.3 \pm 1.2M^{-1}$.

The situation proved to be somewhat more complicated for the complexes with the 12-membered macrocycles **1** and **2**. As shown in *Fig. 1*, the reaction is inhibited by CH_3CN, reaching limiting values only for [CH_3CN] < 0.1M. Numerical analysis indicates that formation of $Cu(CH_3CN)LH^{2+}$ according to *Eqn. 1* is not sufficient to explain the observed effect, since the influence persists at pH 8, where the protonated complexes are irrelevant. Weak association of CH_3CN with the neutral complexes CuL^+

(L = **1** or **2**) has to be postulated. As is also shown in *Fig. 1*, the influence of CH_3CN can be described by *Eqn. 2'* with $K'_2 = K(CuL^+ + CH_3CN \rightleftharpoons Cu(CH_3CN)L^+) = 9 \pm 2 M^{-1}$ and $7 \pm 1 M^{-1}$ for **1** and **2**, respectively.

$$k_{2,\mathrm{obs}} = k'_2/(1 + k'_2[CH_3CN]) \qquad (2')$$

It may be noted that the formation of $Cu(CH_3CN)L^+$ had not been revealed by the equilibrium studies [6]. This can be ascribed to the weakness of the complexes and/or to the fact that complexation of Cu(I) by LH^+ starts at very low pH with **1** and **2** [6].

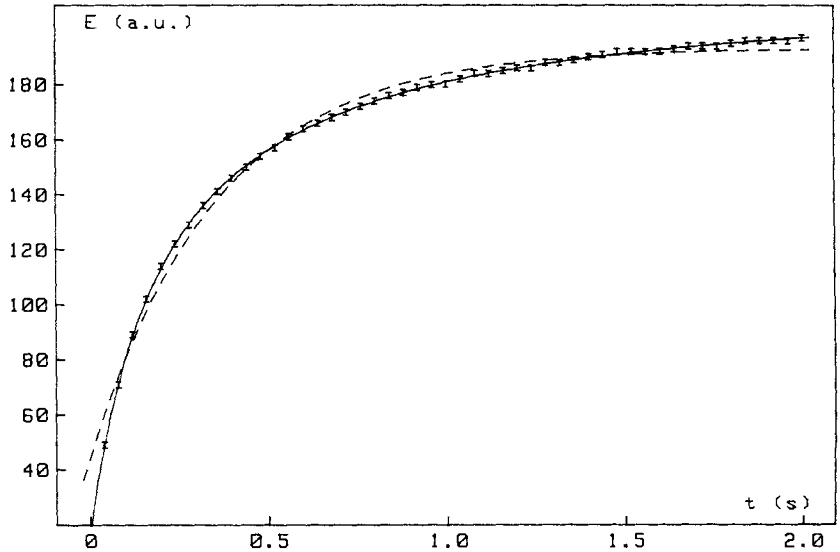

Fig. 2. *Analysis of stopped-flow experiment with* trans-*[12]aneN$_2$S$_2$* (**2**). Conditions as in *Fig. 1*, $[CH_3CN] = 0.38 M$. I: experimental points. ---- Calculated with *Eqn. 2*, $\sigma_E = 3.9$ bit. —— Calculated with *Eqn. 3*, $\sigma_E = 0.5$ bit.

The autoxidation with complexes **1** and **2** indeed cannot be described by a simple bimolecular reaction according to *Eqn. 2* even for individual kinetic runs. While initial rates gave the same first-order dependence on $[CuL^+]$ and on $[O_2]$ as observed for the other ligands, the analysis of complete reaction curves gave a rather different and also at first puzzling result. As exemplified in *Fig. 2*, individual curves could be perfectly analyzed assuming second-order dependence on $[CuL^+]$, while first-order dependence proved completely unsatisfactory. Nevertheless, and in line with the results from initial rates, the half-lives of the reaction where independent of the initial concentration of CuL^+. In other words, the values of the second-order rate constants calculated according to *Eqn. 3* were inversely proportional to the total complex concentration, $[CuL^+]_{tot}$, *cf. Fig. 3*. Since O_2 was present in a twentyfold excess on an equivalent basis, the consumption of O_2 did not have to be taken into account in these calculations.

$$v_3 = d[CuL^{2+}]/dt = k_3[CuL^+]^2 \qquad (3)$$

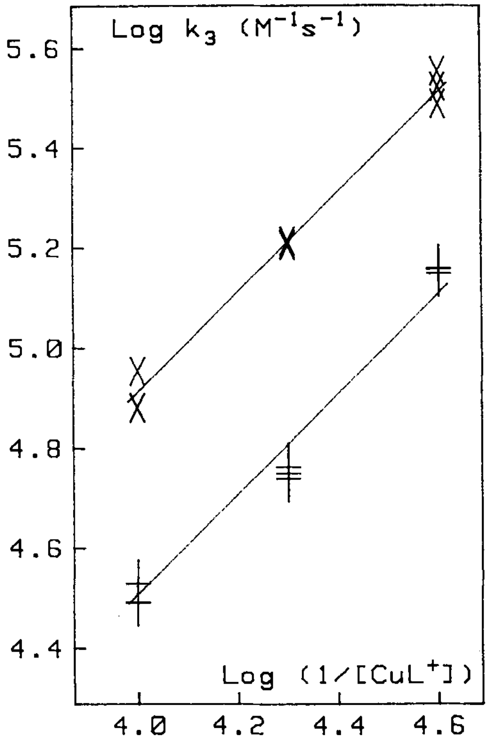

Fig. 3. *Copper dependence of autoxidation of CuL$^+$.* $[O_2] = 6 \cdot 10^{-4}$M, pH = 7.0, $[CH_3CN] = 0.38$M, [Cu(I)]/[L] = 0.75. +: L = *cis*-[12]aneN_2S_2 (**1**), ×: L = *trans*-[12]aneN_2S_2 (**2**). ——— Curves calculated assuming inverse proportionality between k_3 and $[CuL^+]_{tot}$.

As will be discussed elsewhere in more detail [13], second-order reaction curves with concentration independent relaxation times can indeed be obtained with a simple set (*4*), (*5*) of elementary steps:

$$\text{E(duct)} \underset{k_{-4}}{\overset{k_{+4}}{\rightleftharpoons}} \text{I(ntermediate)} + \text{P(roduct)} \tag{4}$$

$$\text{E} + \text{I} \xrightarrow{k_5} \text{P} + \text{P}' \tag{5}$$

Steady-state approximation to the intermediate I easily gives the rate law (*6*) in integrated form:

$$k_{-4}/k_5([\text{E}]_0/[\text{E}] - 1) + (1 - k_{-4}/k_5)\ln([\text{E}]_0/[\text{E}]) = 2k_{+4}t \tag{6}$$

$$t_{1/2} = [k_{-4}/k_5(1 - \ln 2) + \ln 2]/2k_{+4} \tag{7}$$

$$[\text{E}] = [\text{E}]_0/(1 + 2k_{+4}t) \tag{8}$$

As indicated in *Eqn. 7*, the half-time of such a reaction does not depend on the initial concentration of the educt $[\text{E}]_0$ and perfect hyperbolic functions are obtained for $k_{-4}/k_5 = 1$, *Eqn. 8*.

Complete degeneracy of k_{-4} and k_5 is a mathematical construct not likely to be of much practical relevance. Model calculations have, however, shown that the hyperbolic shape of individual reaction curves is quite well preserved over a rather wide range of values for k_{-4}/k_5 [13]. In fact, unless $k_{-4}/k_5 \ll 1$, discrimination between *Eqn. 6* and *8* is not possible for data of normal (8 bit) stopped-flow quality.

We recall that $[O_2]_0 \gg [CuL^+]_0$ in our stopped-flow experiments and thus $[O_2]$ is essentially constant in a kinetic run. It is, therefore, logical to explain the hyperbolic reaction curves with concentration independent relaxation times by a mechanism with stepwise one-electron reduction of O_2 and superoxide as the intermediate (*Eqn. 9* and *10*).

$$CuL^+ + O_2 \underset{k_{-9}}{\overset{k_{+9}}{\rightleftharpoons}} {}^{\cdot}O_2^- + CuL^{2+} \qquad (9)$$

$$CuL^+ + {}^{\cdot}O_2^- \xrightarrow{k_{10},\ 2H^+} CuL^{2+} + H_2O_2 \qquad (10)$$

It should be added that *Eqn. 9* and *10* just give the most simple set of elementary steps necessary to describe the experimental facts. These results do not preclude at all the formation of unstable dioxygen adducts prior to electron transfer as has been established for the autoxidation of substituted imidazoles [11] [14] and other Cu(I) complexes. In fact, in view of the general preference of copper for inner-sphere electron transfer reactions [15] such dioxygen adducts would indeed be likely additional intermediates in the detailled reaction mechanism.

All rate constants collected in *Table 1* are recalculated to conform to the second-order rate law, *Eqn. 2*. It is not possible to decide on the basis of the present results, if the autoxidation of the complexes with ligands **3**, **4** and **6** also proceeds through one-electron reduction.

Table 2. *Second-Order Rate Constants, Redox Potentials and Redox Stoichiometries*

Ligand	k_2 [$M^{-1}s^{-1}$][a])	E_{CuL^{2+}/CuL^+} [mV]	$\Delta[CuL^+]/\Delta[O_2]$
cis-[12]aneN_2S_2 (**1**)	$(2.8 \pm 0.1) \cdot 10^3$ $(1.2 \pm 0.1) \cdot 10^4$ [c])	116[b])	2.18
trans-[12]aneN_2S_2 (**2**)	$(8.0 \pm 0.8) \cdot 10^3$ $(2.4 \pm 0.3) \cdot 10^4$ [c])	172	2.72
cis-[14]aneN_2S_2 (**3**)	$(4.4 \pm 0.2) \cdot 10^3$	84	2.24
trans-[14]aneN_2S_2 (**4**)	44 ± 2	262	2.61
cis-[16]aneN_2S_2 (**5**)	< 0.1	424	
trans-[16]aneN_2S_2 (**6**)	2.2 ± 0.1	396	

[a]) Weighted means with standard errors, *cf. Table 1.* [b]) Results from [6]. [c]) Limiting values calculated from CH_3CN dependences, *cf. Fig. 1.*

In *Table 2*, the redox stoichiometries and the second-order rate constants of the different complexes are summarized. Between 2.2 and 2.7 moles of CuL^+ are oxidized per mole of O_2, indicating preferential reduction of O_2 to H_2O_2 with some formation of H_2O. Due to the slowness of the reaction, no stoichiometry was obtained for *trans*-[16]aneN_2S_2 (**6**) and of course its *cis*-analogue **5**.

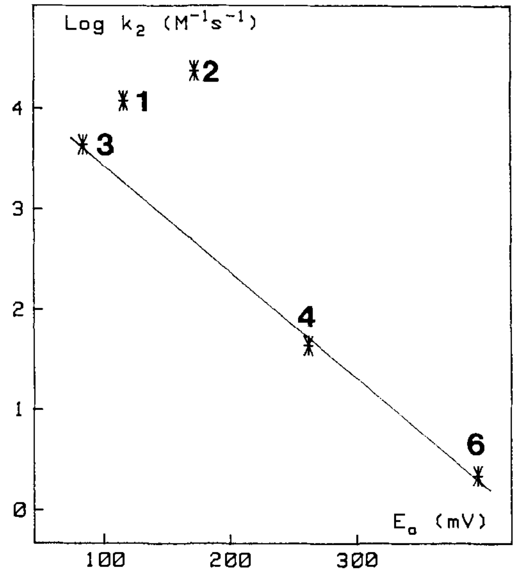

Fig. 4. *Correlation between second-order rate constants of autoxidation and CuL^{2+}/CuL^{+} redox potentials*

The rate constants compiled in *Table 2* are the limiting values obtained at low [CH_3CN] and high pH, where CuL^+ is the only reactive species. The rate of autoxidation decreases with the ring size of the macrocyclic ligands, the reactivities following the order **1**, **2** > **3**, **4** > **5**, **6**. No consistent preference for *cis*- or for *trans*-configuration is observed, *cis*-[14]aneN_2S_2 (**3**) being faster than **4**, while the reverse relation is true for the 12- and the 16-membered rings. Redox potentials are not exclusively responsible for the observed order of reactivities. As shown in *Fig. 3*, there is a rather good correlation for ligands **3**, **4** and **6**, but the two 12-membered rings are obviously off, reacting one to two orders of magnitude faster than expected. It is at least tempting to relate this observation to steric factors. The 12-membered rings are too small to surround the metal ion and some kind of pyramidal structure with a considerable opening on the apex must be assumed, allowing easy access of additional ligands. Almost perfectly tetrahedral models with effective shielding of the metal ion can be constructed with the larger ligands. This is of course well in line with the observed inhibition of the autoxidation by CH_3CN with *cis*- and *trans*-[12]aneN_2S_2, compared to the complete independence of [CH_3CN] with the larger macrocycles. Whether access of O_2 is completely blocked in these latter cases and the autoxidation thus proceeds by outer-sphere electron transfer cannot be decided at present, but would conform to the good correlation between redox potential and rate of autoxidation with ligands **3**, **4** and **6**.

Besides the experiments compiled in *Table 1* a few additional data were collected at pH 3–5, *i.e.* under conditions where any reactivity of the protonated species $CuLH^{2+}$ [6] would be most prominent. No such reactivity was observed for any system, the rates of autoxidation always being equal to or less than the ones calculated from the contributions of Cu^+_{aq} and CuL^+ present in the equilibrium mixtures. Less than calculated reactivity was most clearly observed for *cis*-[14]aneN_2S_2. Formation of $CuLH_2^{3+}$ with exclusive thioether coordination, which could not be observed by the potentiometric titrations [6], is made responsible for this reduced reactivity, but the phenomenon was not studied in further detail.

Conclusions. – Despite the identical N_2S_2 set of coordinating atoms the Cu(I) complexes with the 12- to 16-membered macrocyclic ligands **1**–**6** differ by more than five orders of magnitude in their relative reactivity towards O_2. The range of second-order rate constants is thus roughly the same as the range in the relative stability of the Cu(I) and Cu(II) complexes, $K_{CuL^+}/K_{CuL^{2+}}$, or the range of redox potentials between 80 and 420 mV [6]. The correlation between redox potentials and rates of autoxidation is not very good, however. Based on their positions in the order of redox potentials, the rates of the autoxidation of the complexes with *cis*- and *trans*-[12]aneN_2S_2 are increased by one to two orders of magnitude relative to that of those with the larger ligands. Steric factors, namely easier access of O_2 to a more pyramidal structure imposed by the small 12-membered macrocycles are made responsible. Whether an actual switch from inner-sphere to outer-sphere electron transfer takes place on increasing the chain length cannot be decided presently. No dramatic rate enhancement by the lowering of *Frank-Condon* barriers because of structural rigidity has been observed in this study. In fact, *cis*- and *trans*-[12]aneN_2S_2 have reactivities and redox potentials which compare very well with the extremely labile aquo ion Cu^+_{aq} ($k_2 = 3.5 \cdot 10^4 M^{-1}s^{-1}$ [16], $E_0 = 160$ mV [17]).

Three of the six ligands gave simple bimolecular rate laws without much clue to the actual reaction mechanism. For the complexes with 12-membered macrocycles successive one-electron transfers with intermediate formation of superoxide has been implied, however, from unexpected hyperbolic reaction curves with concentration-independent relaxation times. No evidence for a binuclear transition state $(CuL)_2O_2^{2+}$ has been obtained for any of the systems studied. The lack of data for analogous open-chain ligands precludes the discussion of any specific 'macrocyclic effect' regarding Cu(I) redox activity.

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