100. Copper Catalysed Oxygenation of Bis(2-pyridyl)methane and 6-Methyl-bis(2-pyridyl)methane to the Corresponding Ketones

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Summary

The ligands (L) bis(2-pyridyl)methane (BPM) and 6-methyl-bis(2-pyridyl)methane (MBPM) form the three complexes CuL^{2+}, CuL_2^{2+}, and $Cu_2L_2H_{-2}^{+2}$ with Cu^{2+}. Stability constants are log $K_1 = 6.23 \pm 0.06$, log $K_2 = 4.83 \pm 0.01$, and log K $(Cu_2L_2H_{-2}^{2+} + 2\,H^+ \rightleftharpoons 2\ CuL^{2+}) = -10.99 \pm 0.03$ for BPM and 4.56 ± 0.02, 2.64 ± 0.02, and -11.17 ± 0.03 for MBPM, respectively. In the presence of catalytic amounts of Cu^{2+}, the ligands are oxygenated to the corresponding ketones at room temperature and neutral pH.

With BPM and 2,4,6-trimethylpyridine (TMP) as the substrate and the buffer base, respectively, the kinetics of the oxygenation can be described by the rate law

$$-d[O_2]/dt = k_1[CuL_2^{2+}]/[H^+] + k_2[CuL_2^{2+}][TMP] + k_3[CuL^{2+}]/[H^+] + k_4[Cu_2L_2H_{-2}^{2+}]/[H^+]$$

with $k_1 = (5.9 \pm 0.2) \cdot 10^{-13}$ mol l^{-1} s^{-1}, $k_2 = (4.0 \pm 0.6) \cdot 10^{-4}$ mol^{-1} l s^{-1}, $k_3 = (1.1 \pm 0.1) \cdot 10^{-12}$ mol l^{-1} s^{-1}, and $k_4 = (9 \pm 2) \cdot 10^{-14}$ mol l^{-1} s^{-1}.

In the course of our studies on the autoxidation of cuprous complexes [1] we have come across the internal monooxygenase behaviour (1) in the copper catalysed

$$SH_2 + O_2 \rightleftharpoons SO + H_2O \tag{1}$$

autoxidation of bis(1-methylbenzimidazol-2-yl)methane to bis(1-methylbenzimidazol-2-yl)ketone [2]. This seems to be the first system of low molecular weight fulfilling the basic requirements for internal monooxygenase activity: Dioxygen is used as the oxidant, one atom of O_2 is incorporated into the substrate, no external reducing agent is needed, and the oxygenation is absolutely dependent on the presence of a suitable catalyst. Independent of our work analogous oxidations of two unsaturated tetraazamacrocycles in the presence of Co^{2+} have been reported recently [3] [4]. The formation of the corresponding ketones has been shown by

IR. [3] or X-ray analysis [4] in these instances, but neither redox stoichiometry nor the origin of the carbonyl oxygen-atom have been determined. Also, due to oxidation of Co^{2+} to Co^{3+} and the kinetic inertness of the macrocyclic complexes formed, catalytic amounts of metal ion do not seem to be suitable for quantitative oxidation of the organic substrate.

In order to extend our work to aqueous systems we have studied the copper catalysed oxidation of bis(2-pyridyl)methane (BPM) and 6-methyl-bis(2-pyridyl)-methane (MBPM). Our results show that the reaction described in [2] is not limited to imidazole derivatives but may rather be a common property of the structural element $-N=CR-CH_2-CR=N-$.

Experimental part

Materials. - Bis(2-pyridyl)methane (BPM) [5] and 6-methyl-bis(2-pyridyl)methane (MBPM) [5] were purified by distillation i.V. (BPM: b.p. 101-106°/0.4 Torr (lit. [5]: 116-136°/2 Torr); MBPM: b.p. 110-112°/0.5 Torr (lit. [5]: 107-133°/1.2 Torr) and repeated crystallization from ethanol: BPM · 2HBr: m.p. 271-272° (275-276° [6]), MBPM · 2HCl: m.p. 235-237° (237° [5]). $CuSO_4$ solutions were standardized spectrophotometrically on a *Cary* 118 by titration of 2.5 ml samples with 0.1M EDTA using an AGLA micrometer syringe (1:1 acetate buffer 0.1M, $\lambda = 650$ nm, ε ($CuEDTA^{2-}$) = 44 mol^{-1} l cm^{-1}, ε ($Cuaq^{2+}$) ~ 3 mol^{-1} l cm^{-1}). Other reagents were of quality *p.a.* and used without further purification. Twice distilled water was used throughout.

Measurements and equipment. - Temperature 25±0.2°, ionic strength 0.1 (KCl). Potentiometric titration curves were obtained using the instrumentation and according to the criteria described in [7] with 0.4M NaOH (Titrisol). Conditions: a) 25 ml, $[L]_{tot} = 0.0064$, $[Cu^{2+}]_{tot} = 0.0024$ or 0.0048, b) 40 ml, $[L]_{tot} = 0.004$, $[Cu^{2+}]_{tot} = 7.5 \cdot 10^{-4}$, c) 50 ml, $[L]_{tot} = 0.0032$, $[Cu^{2+}]_{tot} = 0$, 0.0024 or 0.0012 (L = BPM or MBPM). The activity coefficient of H^+ and the ion-product of H_2O were determined each day by titration of 50 ml samples of 0.005M HCl. The kinetics of the oxygenation reaction were followed amperometrically with an oxygen sensor coupled to a high-impedance millivolt recorder [8] under conditions where the organic substrates were present in large excess over O_2. The reactions were strictly zero order with respect to $[O_2]$ under most conditions and evaluated accordingly. If some deviation occurred at very low $[O_2]$, initial rates were used instead. The redox stoichiometry was determined with a gas burette. IR. spectra were obtained on a *Perkin Elmer* 157G, and GC./MS. on a *Pye Unicam* 104 (GC.) and *AEI* 30 (MS.) set-up with a SE 52 column 1.5 m long and ¼"⌀.

In analogy to the oxygenation of bis(1-methylbenzimidazol-2-yl)methane to bis(1-methylbenzimidazol-2-yl)ketone [2], bis(2-pyridyl)ketone (BPK) and 6-methyl-bis(2-pyridyl)ketone (MBPK) were the products expected from BPM and MBPM, respectively. These were prepared by treatment with O_2 (1 atm., 20°, **2d**) of solutions containing BPM (0.753 mmol) [11] or MBPM (0.972 mmol) and Cu^{2+} (0.075 or 0.194 mmol, resp.) in water (25 ml) at pH 9.8 or 7.3, resp., controlled by a potentiostat; Cu^{2+} was then sequestered by adding EDTA and the ketones were extracted into chloroform. The extracts were investigated by ^1H-NMR.: 7-9 ppm (aromatic H); 4.4 ppm (*s*, CH_2, corresponding to ~5% unreacted starting material); for MBPM only: 2.6 ppm (*s*, CH_3); all rel. to TMS. The residue from $CHCl_3$ evaporation was investigated by IR.: 1672 cm^{-1} (C=O) and GC./MS.: 184 (M^+, 60), 85 (100) for BPK; 198 (M^+, 73), 169 (100) for MBPK. The data for BPK agree with those of an authentic sample *(Fluka)*. No solid semicarbazone was directly isolated from aqueous reaction mixtures. In evaporation residues of these, no C=O band was detected in the IR. Finally, solutions of BPM or MBPM alone turned yellow on treatment with O_2. Potentiometric as well as kinetic data were treated numerically using the procedure suggested by *Marquardt* [9]. As best parameters were considered those which yielded the minimal error square sum in the degree of neutralization a [7] or log v for potentiometric and kinetic data, respectively. All parameters were tested for significance at 95 and 99% levels by using reduced trial functions and applying the F-test. The calculations were done on a *Hewlett Packard* HP 9821 with fully expanded memory and a 9862 calculator plotter for graphical output. The uncertainties of all parameters are indicated by twice their standard errors $\pm 2\,\sigma_k$, as obtained from the nonlinear least squares treatment of the data.

Results. - **Equilibria.** Log K^H values of 7.65, 6.93, and 6.11 were obtained for the buffer bases TMP, 2,6-dimethylpyridine (DMP), and 2-methylpyridine (PIC), respectively. CuL^{2+}, $Cu_2L_2H^{2+}_{-2}$, and CuL_2^{2+} (L = BPM or MBPM) were the species needed to explain the experimental data at moderate pH. In more strongly basic solutions polymerisation and eventually precipitation occurs. The stability constants of CuL^{2+} and CuL_2^{2+} (L = BPM) have been reported previously [10]. Ligand protonation constants were obtained from two different titration curves per ligand. Stability constants of the Cu^{2+} complexes were calculated from duplicate batches of 5 titration curves of different $[L]_{tot}$ and $[Cu^{2+}]_{tot}$. The results are compiled in *Table*, along with the ligand protonation constants. For all sets of data σ (ml), the standard deviation in ml of base consumed, was less than 0.006 or 0.6% of the total volume (1 ml) delivered. The inclusion of $CuLH^{+}_{-1}$ and/or $CuL_2H^{+}_{-1}$ as additional complex species was tried, but did not significantly decrease the overall error square sum. With the 6-methyl derivative MBPM the stability of the 2:1 complex is low and the value of the corresponding parameter was suspected to be relatively uncertain. Confirmation of this species was obtained by titration of 2 ml of a mixture containing 9.6 µmol Cu^{2+} and 12.8 µmol MBPM at pH 6.85 with 0.05 M MBPM which had been adjusted to the same pH. According to equ. (2), addition of excess ligand should lead to the consumption of protons if a 1:2 complex is formed.

$$2\,H^+ + M_2L_2H^{2+}_{-2} + 2\,L \rightleftharpoons 2\,ML_2^{2+} \qquad (2)$$

The pH was kept constant by the addition of 0.05 M HCl. The experimental values compared well with those calculated using the equilibrium constants listed in *Table* and a total of 0.073 ml HCl (3.65 µmol, calculated 3.46 µmol) was needed.

Table. *Ligand protonation constants and stability constants of Cu^{2+} complexes with BPM and MBPM*[a]

Reaction	log K[b]	
	BPM	MBPM
$LH^+ + H^+ \overset{K_2^H}{\rightleftharpoons} LH_2^{2+}$	2.67 ± 0.07 (65) 2.69[c]	3.07 ± 0.02 (65)
$L + H^+ \overset{K_1^H}{\rightleftharpoons} LH^+$	5.23 ± 0.02 (65) 5.18[c]	5.81 ± 0.02 (65)
$Cu^{2+} + L \overset{K_1}{\rightleftharpoons} CuL^{2+}$	6.23 ± 0.06 (302) 6.1[c]	4.56 ± 0.02 (291)
$CuL^{2+} + L \overset{K_2}{\rightleftharpoons} CuL_2^{2+}$	4.83 ± 0.01 (302) 5.1[c]	2.64 ± 0.02 (291)
$2\,CuL_2^{2+} \rightleftharpoons Cu_2L_2H^{2+}_{-2} + 2\,H^+$	− 10.99 ± 0.03 (302)	− 11.17 ± 0.03 (291)

[a] Mixed constants, with $[H^+] = 10^{-pH}$, are given; [b] with $\pm 2\,\sigma_K$ and number of degrees of freedom; [c] see [10], $\mu = 0.1$ ($NaNO_3$), T = 20°.

Kinetics. - The rate of dioxygen uptake was studied under conditions where BPM or MBPM were present in large excess over $[O_2]_{tot}$. The influence of the following parameters was studied: $[Cu^{2+}]$, [L], $[O_2]$, pH, and [buffer]. 2,4,6-Trimethylpyridine (TMP), 2,6-dimethylpyridine (DMP), or 2-methylpyridine (PIC) were used as buffer bases. Most reactions were started with an initial concentration of O_2 near $2.5 \cdot 10^{-5}$ M. Since the rates of oxidation were independent of $[O_2]$, log v (3) was the most suitable entity to test the influence of the other parameters.

For *bis(2-pyridyl)methane* (BPM), the experimental rate law was obtained by numerical analysis of 95 data points where TMP was used as the buffer throughout. Some of the results are shown in *Figures 1-3*. All solid curves in *Figures 1-3* were calculated with the overall rate law (4) and $k_1 = (5.9 \pm 0.2) \cdot 10^{-13}$ mol l^{-1} s^{-1}, $k_2 =$

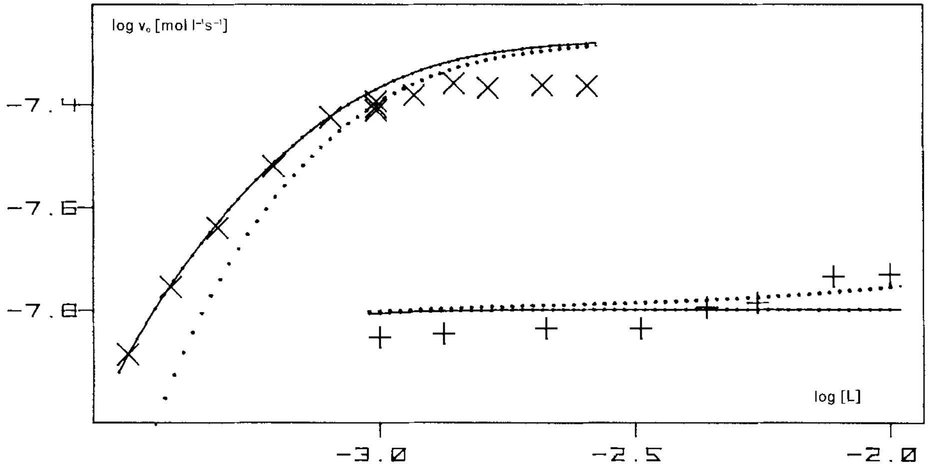


Fig. 1. *Ligand-dependence of the rate of oxygenation of BPM.*
A: $[Cu^{2+}] = 0.25$ mM, pH 8.53, [TMP] = 40 mM, × : experimental points, - calculated with (4), · · · calculated with $Cu(BPM)_2^{2+}$ as the only reactive species (k_1, k_2).
B: $[Cu^{2+}] = 0.15$ mM, pH 8.2, [TMP] = 40 mM, + : experimental points, – calculated with (4), · · · calculated with (4) and $k_5[Cu(BPM)_2^{2+}][BPM]$ ($k_5 = 1.2 \cdot 10^{-3}$ mol^{-1} l s^{-1}).

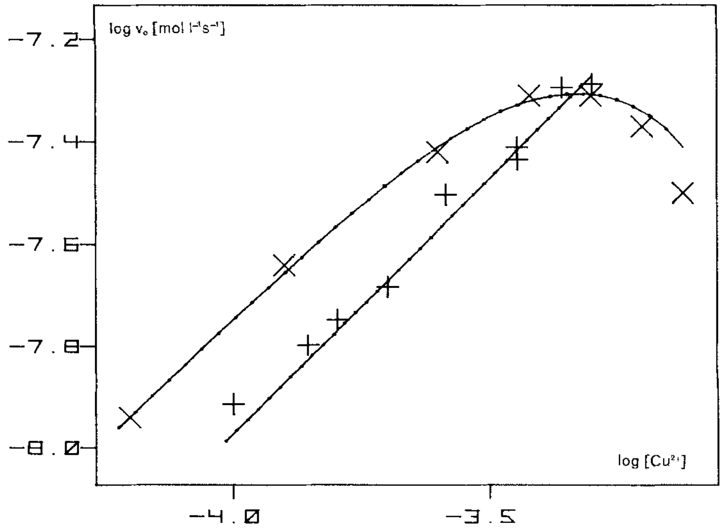


Fig. 2. *Dependence of BPM oxygenation on [Cu^{2+}].*
C: +, [BPM] = 10 mM, pH 8.2, [TMP] = 40 mM;
D: x, [BPM] = 1 mM, pH 8.46, [TMP] = 40 mM; – calculated with (4).

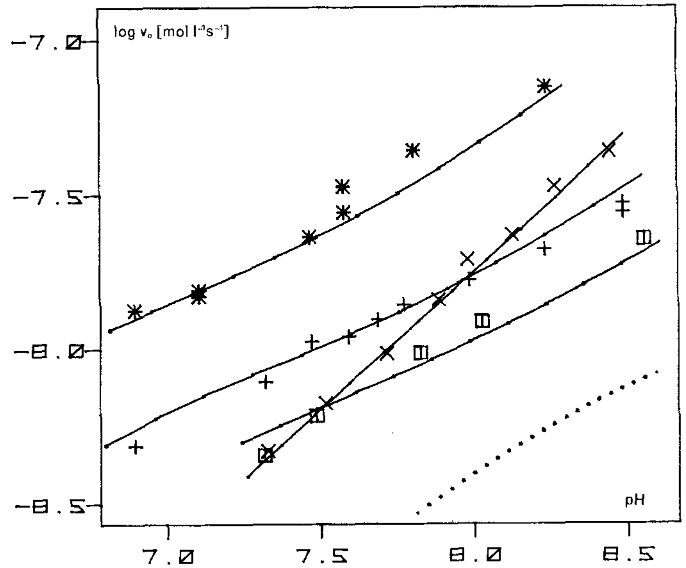


Fig. 3. *pH-dependence of the copper catalysed oxygenation of BPM.*
E: ×, [BPM] = 4 mM, $[Cu^{2+}] = 0.25$ mM [TMP] = 40 mM;
G: *, [BPM] = 3.33 mM, $[Cu^{2+}] = 3$ mM, [TMP] = 40 mM;
H: +, [BPM] = 1.11 mM, $[Cu^{2+}] = 1$ mM, [TMP] = 40 mM;
I: ◫, [BPM] = 0.555 mM, $[Cu^{2+}] = 0.5$ mM, [TMP] = 40 mM; ··· calculated without reactivity of 1:1 complexes; – calculated with (4).

$(4.0 \pm 0.6) \cdot 10^{-4}$ mol⁻¹ l s⁻¹, $k_3 = (1.1 \pm 0.1) \cdot 10^{-12}$ mol l⁻¹ s⁻¹ and $k_4 = (9 \pm 2) \cdot 10^{-14}$ mol l⁻¹ s⁻¹ as parameters.

$$v = -d[O_2]/dt \ (\text{mol l}^{-1}\,\text{s}^{-1}) \tag{3}$$

$$v = -d[O_2]/dt = k_1[CuL_2^{2+}]/[H^+] + k_2[CuL_2^{2+}][TMP] + k_3[CuL^{2+}]/[H^+] + k_4[Cu_2L_2H_{-2}^{2+}]/[H^+] \tag{4}$$

It follows from *Figure 1* that 1:1 and 1:2 complexes both take up dioxygen in this system. If the data of set A (x: $[Cu^{2+}] = 0.25$ mM, $[TMP]_{tot} = 40$ mM, pH = 8.53) are calculated with CuL_2^{2+} as the only reactive species, a rather poor fit results, as is indicated by the dotted line. Further, at pH 8.2 and [L] 3 mM (set B), some data suggesting an additional term $k_5[CuL_2^{2+}]$ [L] were obtained (+, dotted line). Since this term ($k_5 = [1.2 \pm 0.6] \cdot 10^{-3}$ mol⁻¹ l s⁻¹) was not significant at the 90% level as judged by the F-test, it was dropped for the final calculations.

In *Figure 2*, log v is plotted against log $[Cu^{2+}]$. At high ligand to metal ratios (pH 8.2, set C, +) the rate of dioxygen consumption is essentially proportional to the concentration of the catalyst. As $[Cu^{2+}]/[L]$ approaches 1:2 (pH 8.46, set D, ×) we obtain a maximum and at still higher metal concentrations the rate decreases again.

In *Figure 3*, the effect of varying pH is given. When the substrate is present in large excess (x: $[BMP]_{tot} = 4$ mM, $[Cu^{2+}]_{tot} = 0.25$ mM, set E), $-d[O_2]/dt$ approaches proportionality to $1/[H^+]$. Evaluation of log v *vs.* pH as a straight line yields a slope of 0.92 ± 0.06. Decreasing $[L]_{tot}$ to 2 mM under otherwise identical conditions (set F, 6 points, not shown) gives a somewhat lower slope of 0.84 ± 0.04, but otherwise the results are very similar to those of set E. The reactivity of the 1:1 complexes was studied in experiments at substrate to metal ratios of 1:0.9 and 3 different concentrations: $[Cu^{2+}]_{tot} = 3$ mM (set G, *), 1 mM (set H, +), and 0.5 mM (set I, ☐), respectively. In each series the reactivity increases with pH, but slopes of 1 in a logarithmic plot are not obtained at all for the corresponding best straight lines. If no reactivity is assigned to 1:1 complexes and the data of sets G–I are evaluated with k_1 and k_2 alone, a very poor fit results as indicated for the lowest curve in *Figure 3* (I, dotted line). It follows from the data in *Figures 1–3* that in the presence of a large excess of substrate over catalyst the most prominent term in the rate law must be $k_1[CuL_2^{2+}]/H^+]$. In order to explain the data of sets G–I and to obtain agreement between experimental and calculated points of set A *(Fig. 1)*, the following terms besides $k_1[CuL_2^{2+}]/[H^+]$ were considered: $k_3[CuL^{2+}]/[H^+]$, $k'_3[CuL^{2+}]$, $k'_3[CuL^{2+}]/[H^+]^2$, $k_4[Cu_2L_2H_{-2}^{2+}]/[H^+]$, and $k'_4[Cu_2L_2H_{-2}^{2+}]$. Of all possible combinations only the one containing k_3 and k_4 proved satisfactory. Inclusion of an additional term on top of k_3 and k_4 did not significantly lower the overall standard deviation of $\sigma_{\log v}$.

Besides the factors already discussed, the buffer bases used for pH control also have an effect on the rate of this copper catalysed autoxidation. The buffer dependence was studied at pH 7.2 ($[L]_{tot} = 1.2$ mM, $[Cu^{2+}]_{tot} = 0.4$ mM, set K, 12 data points) and pH 7.76 ($[L]_{tot} = 2.5$ mM, $[Cu^{2+}]_{tot} = 0.5$ mM, set L, 11 points). After inclusion of a term $k_2[CuL_2^{2+}]$ [TMP] with $k_2 = (4.0 \pm 0.06) \cdot 10^{-4}$ $mol^{-1} l s^{-1}$, the overall rate law (4) and satisfactory agreement between experimental and calculated points ($\sigma_{\log v} = 0.04$) is obtained. The influence of buffer bases is not restricted to TMP. If DMP is used instead, a similar effect of [DMP] is observed. In a series with $[L]_{tot} = 1.2$ mM, $[Cu^{2+}]_{tot} = 0.3$ mM, pH = 7.16, 0.01 M ≦ [DMP] ≦ 0.1 M, the results could be described by an analogous term $k_{2,DMP} \cdot [CuL_2^{2+}]$ [DMP]: $k_{2,DMP} = (5.5 \pm 1.2) \cdot 10^{-5}$ $mol^{-1} l s^{-1}$. Since no other dependences were done with bis(2-pyridyl)-methane and DMP as buffer, this value should be considered as tentative only.

The *oxidation of MBPM* was studied in somewhat less detail and no general rate law can yet be presented. $[Cu^{2+}]$, [MBPM], and [buffer] were varied at pH 6.8 or 6.2 with DMP or PIC (pH 6.2 only) as buffer bases. Between pH 5.8 and 7 the rate of autoxidation was essentially independent of $[H^+]$ after taking account of its direct influence on the concentrations of free ligand, complex species, and buffer base. For high $[MBPM]/[Cu^{2+}]$ ratios $-d[O_2]/dt$ was always directly proportional to [MBPM]. As indicated by the solid line in *Figure 4*, such data can be explained satisfactorily by a single second order rate constant $k_{MBPM} = 0.082$ $mol^{-1} l s^{-1}$ (5).

$$v_o = -d[O_2]/dt = k_{MBPM}[Cu(MBPM)_2^{2+}][MBPM] \qquad (5)$$

However, the rate of autoxidation unexpectedly reaches a maximum value at $[Cu^{2+}]/[MBPM]$ ratios well below 1:2, followed by a moderate but significant decrease in series with DMP as the buffer base (*Fig. 4*, ×, +, *). This observation

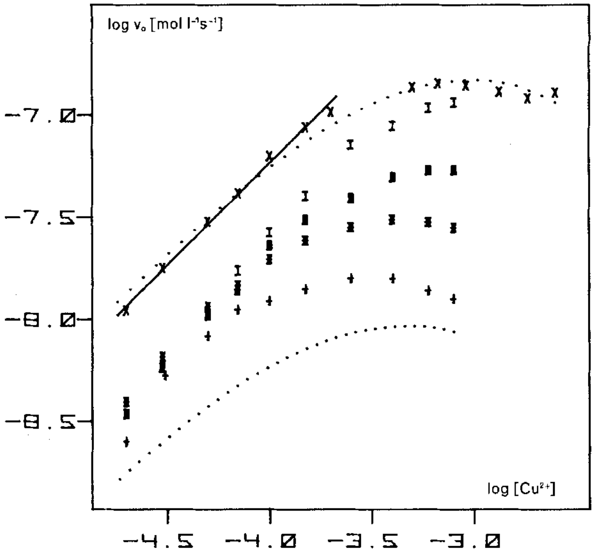


Fig. 4. *Oxygenation of 6-methyl-bis(2-pyridyl)methane at pH 6.2.*
×: [MBPM] = 10 mM, [DMP] = 25 mM, – calculated with (5), $k_{MBPM} = 0.082\ mol^{-1}\ l\ s^{-1}$, ··· calculated with (6), $k_6 = 0.129\ mol^{-1}\ l\ s^{-1}$, $k_6' = 1.1 \cdot 10^4\ mol^{-1}\ l$, $k_6'' = 0.0055\ mol^{-1}\ l\ s^{-1}$;
*: [MBPM] = 2.5 mM, [DMP] = 106 mM;
+: [MBPM] = 2.5 mM, [DMP] = 25 mM, ··· calculated with (6);
I: [MBPM] = 2.5 mM, [PIC] = 220 mM;
■: [MBPM] = 2.5 mM, [PIC] = 50 mM.

cannot be explained by the decreasing concentration of free substrate with increasing [Cu^{2+}] but requires inhibition by some cupric species. While k_{MBPM} seems to be little influenced by the buffer concentration, the maximum rate of autoxidation increases with that quantity. For the curve with the highest (0.22 M) 2-methyl-pyridine concentration the inhibitory effect of Cu^{2+} has disappeared almost completely. The most simple logical trial functions consistent with these observations would be of the forms (6) or (7). In fact, as shown in *Figure 4*,

$$-d[O_2]/dt = \frac{k_6[CuL_2^{2+}][L]}{1+k_6'[CuL^{2+}]} + k_6''[CuL_2^{2+}][buffer] \qquad (6)$$

$$-d[O_2]/dt = \frac{k_7[CuL_2^{2+}][L]}{1+k_7'[CuL_2^{2+}]} + k_7''[CuL_2^{2+}][buffer] \qquad (7)$$

data belonging to a single series can be at least acceptably explained by (6) with $k_6 = 0.129\ mol^{-1}\ l\ s^{-1}$, $k_6' = 1.1 \cdot 10^4\ mol^{-1}\ l$, and $k_6'' = 0.0055\ mol^{-1}\ l\ s^{-1}$ (*Fig. 4:* ×, dotted line). If the parameters thus obtained are used to calculate theoretical values of other series, the result is rather poor, however (*Fig. 4:* +, dotted line). Obviously the complete rate law would be even more complicated than that for

BPM (4), including reactivities of both $[Cu(MBPM)]^{2+}$ and $[Cu_2(MBPM)_2H_{-2}]^{2+}$, most likely with their own buffer dependences and inhibitory terms.

Occasionally a slow uptake of dioxygen was observed before the addition of Cu^{2+} to the reaction mixture for both BPM and MBPM as substrates. This reaction could always be completely blocked by the addition of some EDTA and is ascribed to trace amounts of metal ion impurities. Also, the copper catalysed reaction could be abruptly stopped by a small excess of EDTA.

Catalysis by other transition metal ions. - For both substrates L, the catalytic oxygenation was tested with Mn^{2+}, Fe^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+} (M^{n+}) under the following conditions: $[O_2] = 0.12$ mM, $[M^{n+}] = 0.1$ mM, $[L] = 4$ mM, [buffer] = 20 mM. TMP at pH 8.0 and DMP at pH 6.2 were used for bis(2-pyridyl)methane and MBPM, respectively. As in the experiments with Cu^{2+}, a significant consumption of O_2 was observed for the combinations BPM/Co^{2+} and BPM/Fe^{2+}. No reactivity was observed with MBPM. Co^{2+} was less effective than Cu^{2+} by a factor of 5. With Fe^{2+}, the total decrease of $[O_2]$ was roughly 0.025 mmol l^{-1} corresponding to a 1:4 (O_2:Fe^{2+})-stoichiometry and indicating autoxidation of the metal ion rather than the organic substrate. Thus none of the metal ions tested was truly able to replace Cu^{2+} in its catalytic role.

Discussion. - In a copper catalysed reaction bis(2-pyridyl)methane (BPM) and 6-methyl-bis(2-pyridyl)methane (MBPM) are oxidized to the corresponding ketones BPK and MBPK in aqueous solution and neutral pH. The nature of the primary oxidation products must be left open (see exper. part) but the corresponding gem-diols seem to be the most likely precursors since BPK has been reported to hydrate very easily in the presence of metal ions [12]. Because of this hydration reaction the origin of the oxygen atom in BPK and MBPK could not be studied [12], contrary to the situation with bis(1-methylbenzimidazol-2-yl)ketone where the solvent does not interfere and where the carbonyl oxygen-atom was shown to be derived directly from O_2 [2]. In line with recent results for some benzimidazole derivatives [2] and two unsaturated macrocyclic complexes with Co^{2+} [3] [4] we suggest that the sequence $-N{=}CR{-}CH_2{-}CR{=}N-$ or perhaps more generally $-N{=}CR{-}CH_2{-}X$, X representing an unsaturated, electron withdrawing group [2], is responsible for this type of reaction. Here the kinetics of such a system are described for the first time. The oxygenation is absolutely dependent on the presence of a suitable catalyst suggesting analogies to enzyme controlled biological oxidations with O_2 as the oxidant. Since no external reducing agent is needed and the substrate undergoes a 4-electron oxidation with the incorporation of one oxygen atom, the reaction seems to be akin to that of internal monooxygenases [13] and can be described by the overall reaction (1).

The mechanism of this metal ion catalysed reaction must be rather complicated. Both 1:1 and 1:2 complexes are reactive. No dramatic differences in analogous rate constants were observed for BPM: $k_3 = 1.1 \cdot 10^{-12}$ mol l^{-1} s^{-1} for $CuL^{2+}/[H^+]$, $k_1 = 5.9 \cdot 10^{-13}$ mol l^{-1} s^{-1} for $CuL_2^{2+}/[H^+]$. Reduction of the average charge per metal ion decreases the reactivity ($k_4 = 9 \cdot 10^{-14}$ mol l^{-1} s^{-1} for $Cu_2L_2H_{-2}^{2+}$) by roughly 1 order of magnitude. Reaction with base prior to attack by dioxygen seems to be a prerequisite of the oxygenation. In all terms established for both ligands the rate of autoxidation is proportional to the concentration of either free ligand, buffer base, or hydroxyl ions. Most likely this reflects the need for primary deprotonation of the active methylene group.

The results with MBPM indicate that oxygenation may not directly follow the reaction with base since the first part of (6) requires the formation of an intermediate X (equ. (8) and (9)). If this intermediate would be attacked directly by O_2(10),

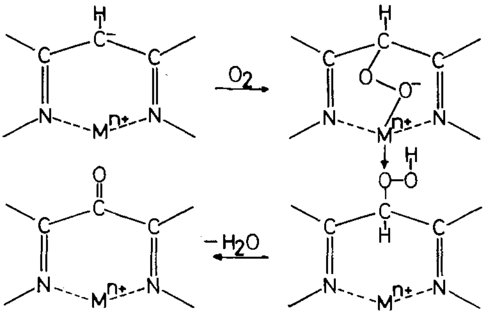
$$\mathrm{CuL_2^{2+}} + \mathrm{L} \xrightarrow{k_8} \mathrm{X} \tag{8}$$

$$\mathrm{X} + \mathrm{CuL^{2+}} \xrightarrow{k_9} 2\,\mathrm{CuL_2^{2+}} \tag{9}$$

$$\mathrm{X} + \mathrm{O_2} \xrightarrow{k_{10}} \mathrm{P} \tag{10}$$

then $[O_2]$ would appear in the rate law, at least under the 'limiting conditions' of copper catalysis discussed in a previous section ($k_9[\mathrm{X}][\mathrm{CuL^{2+}}] > k_{10}[\mathrm{X}][\mathrm{O_2}]$). It thus seems likely that (8) is followed by a rate determining rearrangement preceding interaction with O_2.

Since O_2 does not appear in the rate law, relatively little information is available about further steps in the reaction mechanism. *Weiss & Goedken* [3] suggested the formation of an O_2-bridged intermediate, which would be protonated and finally decompose into H_2O and the ketone, as indicated by the following scheme.



Primary attack of O_2 at the metallic center, while easily imagined of Co(II) in view of the numerous dioxygen adducts with this metal ion [14], does not seem likely with Cu^{2+} as the central atom. An intramolecular redox reaction leading to a Cu(I) radical complex may be invoked (11), but keeping our systems under N_2 before the

$$\mathrm{Cu^{2+}} \cdot \mathrm{L} \cdot \mathrm{LH_{-1}^{-}} \rightleftharpoons \mathrm{Cu^{+}} \cdot \mathrm{L} \cdot \mathrm{LH_{-1}^{\cdot}} \tag{11}$$

addition of air did not result in any increased reactivity. Formation of an organic hydroperoxide by direct oxygenation of the deprotonated methylene group must be considered to be equally likely at present. O_2 does react directly with carbanions derived from a weakly acidic methylene group in the extremely basic media of lithium diisopropylamide in ether [15] yielding reasonably stable hydroperoxides, which can be reduced to the corresponding alcohols. It is not yet clear if these uncatalysed reactions are directly related to those described in this study.

Our results show that the metal ion catalysed oxygenation (1) is not restricted to benzimidazoles and unsaturated macrocyclic ligands. This new type of reaction may well be a frequent feature for the sequence $-N{=}CR{-}CH_2CR{=}N-$. Certainly transition metal ions will promote deprotonation of the active methylene groups but their intimate role is not yet understood. While Cu^{2+} was the most active catalyst in [2], and could not be replaced effectively by any other metal ion in the present study, the copper analog to the cobalt complex described in [4] is inert towards O_2. Further study will be needed to explore the full scope and possible use in organic syntheses of this reaction.

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