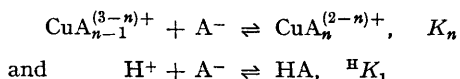


The Location of Binding Sites for Cu^{II} in Carboxylate Ligands by Differential Proton Relaxation

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CORRELATIONS of the equilibrium constants¹ for the series of reactions



suggest that α -hydroxy- and α -alkoxy-, and possibly also β -hydroxy-carboxylates may chelate Cu^{II}. However, the values of K_1 for these systems are only slightly higher in relation to those of ${}^{\text{H}}K_1$ and the differences in the ratios K_1/K_2 , which should be larger for bidentate ligands on statistical grounds, are also small. In an attempt to obtain more direct information about the binding sites, the differential paramagnetic broadening of high-resolution proton magnetic resonance signals of a wide variety of carboxylate ligands in H₂O or D₂O at 37° has been studied. The Perkin-Elmer 60 Mc./sec. spectrometer was operated by Mrs. E. Richards.

Widths $\Delta\nu$ at half-height of ¹H n.m.r. signals of alkali-metal carboxylate or buffer solutions (concentration $0.4 \leq A \leq 0.8$ M) containing small concentrations ($B \leq 2$ mM) of Cu^{II} perchlorate have been measured as a function of B . Under these conditions most of the Cu^{II} was co-ordinated, but free ligand was in considerable excess of bound ligand. On the reasonable assumption that the mean life-times of the ligands in the complexes are much shorter than the various spin-spin relaxation times, then $R = 10^{-3}\pi A \delta(\Delta\nu)/\delta B$ (in 10³ sec.⁻¹) is a measure of the proximity of a proton in bound ligand to the metal ion. Some typical values of R are given in the Table.

For unsubstituted, α - and β -halogenocarboxylates, R indeed decreases with the distance of the protons from the unique (carboxyl) binding site. Similar sequences are found for β -methoxypropionate, β -ethoxypropionate, γ -hydroxybutyrate

TABLE
R-Values for protons in positions relative to the carboxyl group

Ligand	R				
	α	β	γ	δ	
Propionate	4.3	1.9	—	—	
α -Bromobutyrate	5.2	1.8	0.37	—	
α -Hydroxybutyrate	5.2	2.7	3.3	—	
β -Hydroxypropionate	2.8	1.5	—	—	
γ -Hydroxybutyrate	4.6	3.8	1.9	—	
Methoxyacetate	2.8	—	6.7	—	
β -Methoxypropionate	2.7	1.0	—	—	0.17

and γ -hydroxyvalerate, which are therefore assumed to be predominantly unidentate with respect to Cu^{II} .

However, the sequence is disturbed for α -alkoxy- and β -hydroxy-carboxylates. R for the CH_2^β triplet of β -hydroxypropionate is greater than that for the CH_2^α triplet. Moreover, the former triplet collapses at a lower Cu^{II} concentration than the latter without destroying the spin-spin coupling. This ligand is therefore assumed to be mainly bidentate with respect to Cu^{II} . Similarly, chelation by β -hydroxybutyrate may be inferred from the R sequence $\text{CH} > \text{CH}_2 > \text{Me}$, by methoxyacetate from the sequence $\text{Me} > \text{CH}_2$ and by ethoxyacetate from the sequence $\text{CH}_2^\gamma > \text{CH}_2^\alpha > \text{Me}$.

The sequence of R values will be the same for α -hydroxycarboxylates, whether the ligand be unidentate or bidentate. However, R -values for α -protons in these ligands are at least ten times larger than those of corresponding protons in α -halogeno-analogues (*e.g.*, glycollate 70 and chloroacetate 1.2) and are usually larger than the value of 2.3 for malonate, which may be assumed to form a six-membered ring on thermodynamic grounds.

This approach indicates that, amongst others, glycollate, lactate, α -hydroxyisobutyrate, α -hydroxybutyrate, glyoxylate and mandelate are bidentate ligands. Conversely, cyanoacetate ($R = 1.0$) appears to be unidentate.

It is concluded that α -hydroxy-, α -alkoxy-, and β -hydroxy-carboxylates are predominantly bidentate with respect to Cu^{II} and β -alkoxy- and γ -hydroxy-carboxylates unidentate. Some confirmatory evidence of chelation in solution by the α -hydroxy-carboxylates may be adduced from infrared spectra,² circular dichroism of the lactate system,³ and calorimetric measurements.¹ In the solid state, Cu^{II} glycollate and methoxyacetate have now been shown to be chelates.⁴ The discrimination between β -hydroxy- and β -alkoxy-carboxylates is not altogether surprising. Our thermodynamic data¹ show that the α -alkoxy-complexes are less stable than the α -hydroxy-species. Moreover, in carbon tetrachloride solution, α -alkoxy-acids form intramolecular hydrogen bonds, whereas β -alkoxy-acids do not.⁵

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