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Interaction of Ribonucleosides With Copper(II) Acetate

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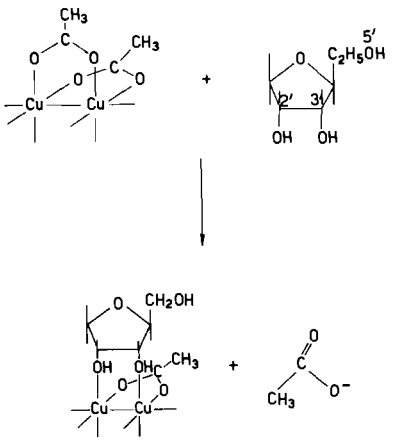
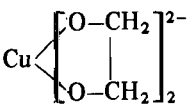
An argument commonly used to interpret the specificity of interaction between molecules is stereoselective fit. Bond distances, bond angles, and configurations determined from X-ray structures in the solid state are quite often used to explain the seemingly selective behavior of molecules or ions in solution. Recently, the rationale of stereoselectivity was used to explain the interaction of dimeric copper (II) acetate hydrate, $(Cu_2(CH_3COO)_4 \cdot 2H_2O)$, with the hydroxy groups of the sugar moieties in ribonucleosides and deoxyribonucleosides in the solvent, dimethylsulfoxide [1, 2]. In the proposed reaction scheme, one of the acetate groups in the copper(II) acetate is displaced by the ribose unit in the ribonucleoside.



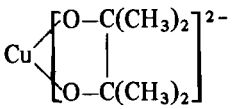
Copper(II) acetate dimer + ribonucleoside →
copper(II) complex + acetate ion

The average oxygen–oxygen distance between the oxygen atoms in the 2′ and 3′ hydroxy groups is 2.7 Å which matches the copper–copper distance of 2.63 Å in the copper(II) acetate [3]. The deoxynucleosides in which only one hydroxy group is present showed no significant interaction with copper (II) acetate. Additional evidence for the above stereoselective reaction schemes was the peak broadening that was observed in the ^1H nmr spectrum of the ribose protons in the presence of copper(II) acetate and the changes caused by ribonucleosides in the electronic spectrum of the copper(II) acetate in the dimethylsulfoxide [1]. Despite the attractiveness of the stereoselective fit of the 2′ and 3′ hydroxy groups in the ribose group with the copper–copper bond distance, the above reaction scheme does not explain all the experimental data. An alternative explanation that is more consistent with all the observed spectral data and the known solution chemistry of copper(II) carboxylates is given below.

Dimeric copper(II) acetate dissociates in the presence of water or other ligands that form strong complexes with copper(II). The intact dimeric structure, however, exists in certain non-aqueous solvents. In ethanol solutions, copper(II) acetate does not obey Beer's Law, but does so only in the presence of excess acetate ions [4]. This implies that the equilibrium, dimer ⇌ monomer + acetate ions, is set up in ethanol solution and the addition of an excess of acetate ions drives the equilibrium to the left. The driving force to the right is of course the ability of ethanol to solvate the monomeric species of copper(II). Further evidence that simple alcohols can act as monodentate ligands and form weak complexes with transition metal ions is provided by the spectral perturbations that have been observed in aqueous solutions of $Cu(NO_3)_2$ and $Cu(ClO_4)_2$ containing varying quantities of ethanol [5, 6]. In contrast to the simple monodentate alcohols, polyalcohols, especially *cis*-glycols, form strong complexes with transition metal ions [7]. Confirmation of this statement is provided by the isolation [8] of the deprotonated glycol complex



as well as the analogous pinacol derivative,



The formation of chelate rings has been demonstrated or proposed for several other metal–nucleoside complexes [9–11].

The variations that have been reported in the electronic spectrum of copper(II) acetate in dimethylsulfoxide upon the addition of a ribonucleoside [1, 2] is consistent with the disruption of the dimeric structure. Ligands that form strong complexes, *e.g.* water, ethylene glycol, ribose, deoxy-

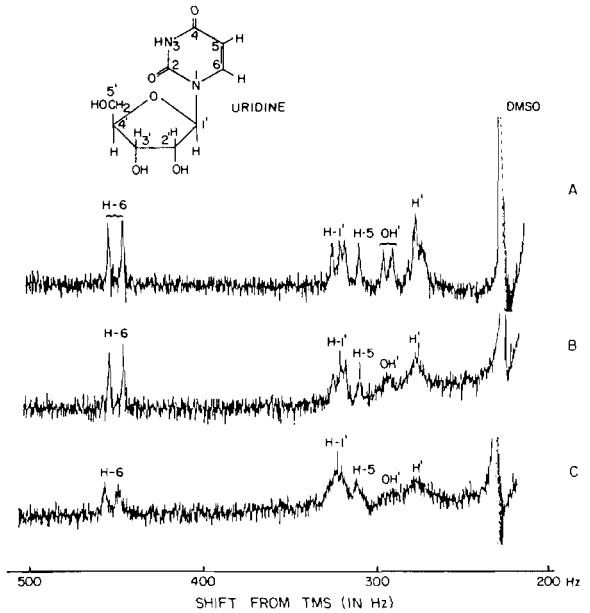


Fig. 1. Effect of copper(II) on the ^1H nmr spectrum (60 MHz) of 1.10 *M* uridine in $(CH_3)_2SO$, (DMSO). A. Uridine in DMSO. B. Uridine and 1.0×10^{-3} *M* hydrated copper(II) acetate in DMSO. C. Uridine and 1.0×10^{-3} *M* copper(II) nitrate dihydrate in DMSO. The protons in positions 2', 3', 4' and 5' are designated as H'. The protons on the hydroxy groups in positions 2', 3' and 5' are designated as OH'.

ribose and all ribonucleosides disrupt the dimeric structure of copper(II) acetate in dimethylsulfoxide and change the color of the solution from green to blue. Ligands that form weak complexes, *e.g.* ethanol and deoxynucleosides do not disrupt the dimeric structure as readily as the ligands that form strong complexes. A slow color change from green to blue occurs over a period of several hours and indicates that there is a weak interaction between these monodentate ligands and the monomeric copper(II) species.

The strongest argument that has been employed to substantiate the stereoselective reaction scheme is the broadening of the hydroxy proton peaks in 2' and 3' positions of the ribonucleosides in the ^1H nmr spectrum of the postulated copper(II) dimer–ribonucleoside complex. A careful examination of the ^1H nmr spectrum, however, shows that *all* the hydroxy proton peaks in the ribonucleosides as well as the deoxyribonucleosides are broadened. This peak broadening occurs not only in the presence of copper (II) acetate but also in the presence of copper(II) nitrate which is unquestionably monomeric (Fig. 1). The peak broadening, therefore, occurs as a result of the interaction of the hydroxy groups of the sugar moieties with the monomeric copper species in solution. Additional evidence for this statement was provided by the ^1H nmr study reported by Berger and Eichhorn [12] in which the ^1H nmr spectrum of uridine was compared with the spectra obtained in the presence of 1×10^{-3} *M* Cu^{2+} and 2.5×10^{-3} *M* Cu^{2+} in DMSO-d_6. It is evident that *all* the hydroxy peak protons were broadened by the addition of the paramagnetic Cu^{2+} species. Hence, the inescapable conclusion is that the existence of intact copper–copper bonds is not a necessary condition for peak broadening of the hydroxy proton peaks as claimed by Eichhorn and coworkers [1, 2].

We have shown that it is unnecessary to invoke a stereoselective reaction mechanism for the complex formation between dimeric copper(II) acetate and a ribonucleoside in dimethylsulfoxide. All the experimental observations can be explained on the basis of the disruption of the dimers to form monomeric copper(II) species upon the addition of monodentate or bidentate ligands with hydroxy groups. *All* the spectral data can be interpreted on the basis of weak or strong interactions of the hydroxy groups with the monomeric copper(II) species.

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