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Metal ion-tetracycline interactions in biological fluids. 10. Structural investigations on copper(II) complexes of tetracycline, oxytetracycline, chlortetracycline, 4-(dedimethylamino)tetracycline, and 6-desoxy-6-demethyltetracycline and discussion of their binding modes.

Autorzy

Małgorzata Jeżowska-Bojczuk

L. Lambs

Henryk Kozłowski

Guy Berthon

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Streszczenie

The present work examines the different binding modes of the Cu2+ ion in its complexes with three bioactive tetracycline antibiotics: tetracycline, oxytetracycline, and chlortetracycline (similar studies with doxycline were prevented by precipitation problems). Spectroscopic investigations involving UV-visible absorption and circular dichroism techniques have been used under predetermined conditions of concentrations and pH so that species successively formed in each system could be selectively investigated. Copper interactions with structurally simpler analogs (4-(dedimethy1amino)tetracycline and 6-desoxy-6-demethyltetracycline)were also studied as references, which required the determination of corresponding complex formation constants. For all bioactive analogs including
6-desoxy-6-demethyltetracycline,it is shown that the first donor group to bind copper is the 0 3 atom, which starts deprotonating at relatively low pH, with MLH2 as the resulting species. When the pH is raised, MLH progressively substitutes for MLH2, chelation then taking place at the 010-012 system as the OH12 group dissociates. The ultimate ligand deprotonation at the C4 dimethylammonium group leads to the formation of ML, with a new change in the binding mode in favor of the N4-OH12, donor set. Concerning the 1:2 metal-to-ligand complexes which coexist with the above species, ML2H4 is logically bound in the MLH2 manner, whereas ML2H2, ML*H, and MLadopt an identical coordination scheme in which alternate bonds are presumed to be formed at both the 0 1 0 4 1 2 juncture and the N4-012, pinch. The present work further substantiates Albert's former view of a possible influence of metal ions on the pharmacological action of tetracyclines. Following the recent evidence of the important roles of calcium and magnesium in the transport of these drugs in blood plasma, it is now suggested here that copper can act as a cofactor of their antibiotic activity: first, the structural flexibility of copper binary complexes within the three distinct donor sites of bioactive tetracyclines is expected to favor mixed-ligand mixdination with bacterial nucleic acids; then, through the formation of such ternary complexes, copper may induce the attack of free radicals
known to damage these nucleic acids.

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