Copper(II) Carboxylates and their Antimicrobial Effect

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The antibacterial and antifungal efficiency of copper(II) carboxylates was studied. The antibacterial action was studied on Staphylococcus aureus, Escherichia coli and Pseudomonas aeruginosa, the antifungal on Trichophyton mentagrophytes var. granulosa, Trichophyton mentagrophytes var. interdigitale, Microsporum gypseum and Epidermophyton floccosum. Alkylcarboxylatocopper(II) compounds showed comparatively weak antimicrobial actions. An impressive increase of antimicrobial activity was observed in the case of copper(II) monohalogenoacetates. The activity increased in the order: $Cu(FCH_2COO)_2 < Cu(ClCH_2COO)_2 < Cu(BrCH_2COO)_2 < Cu(ICH_2COO)_2$. *In the case of copper(II) arylcarboxylates the action is increase in the order:* $Cu(C_6H_5COO)_2 \cdot 3H_2O > Cu(2\text{-}FC_6H_4COO)_2 \cdot H_2O > Cu(2\text{-}ClC_6H_4COO)_2 \cdot H_2O > Cu(2\text{-}BrC_6H_4COO)_2 \cdot H_2O \sim Cu(2\text{-}IC_6H_4COO)_2 \cdot H_2O$.

Introduction

Metals are known to display antimicrobial activity. The activity of metallic ions has been examined from various points of view. Generally, toxicity of metals increased with atomic weight [1]. In addition to atomic weight, toxicity of metals to various organisms has been shown to be related to electronegativity of metallic ions [2] and stability of metal chelates [3]. In recent years, inorganic compounds and organometals have again come to the forefront of interest from the biological point of view. As Horsfall [2] found, the fungicidal properties of $CuSO_4 \cdot 5H_2O$ were known a very long time ago. Sprowls and Poe [4] studied the inhibiting effect of copper(II) chloride, nitrate and sulphate on Staphyloccocus aureus and Salmonella typhi. Bacteriostatic activity of some copper(II) carboxylates with azachalcones were tested on bacterial strains of Staphylococcus pyogenes aureus Oxford, Escherichia coli and Bacillus subtilis [5]. It was found that a lowering or complete loss of antibacterial activity of azachalcones took place [6, 7]. Gupta *et al.* [8] studied the effect of metal ions on the antimicrobial activity of tetracycline hydrochloride. An antimicrobial effect was observed for copper(II) 8-hydroxyquinolinate [9]. In order to eliminate the negative part (high production costs) several authors have tried to replace 8-hydroxyquinoline with another suitable ligand.

Therefore the present work was aimed at the study of antibacterial and antifungal efficiency of carboxylatocopper(II) compounds.

Experimental

The following alkylcarboxylatocopper(II) compounds were studied: $Cu(HCOO)_2 \cdot 4H_2O$ [10], $Cu(CH_3COO)_2 \cdot H_2O$ [11], $Cu(CH_3CH_2COO)_2 \cdot H_2O$ [12], $Cu(CH_3CH_2CH_2COO)_2 \cdot H_2O$ [12], $Cu((CH_3)_2CHCOO)_2$ [13] and $Cu(XCH_2COO)_2L$, where X = F, Cl, Br, or I, and L = H_2O or 1-phenyl-2,3-dimethyl-5-pyrazolone [14, 15]. And from arylcarboxylatocopper(II) compounds it were: $Cu(C_6H_5COO)_2 \cdot 3H_2O$ [16] and $Cu(2\text{-}XC_6H_4COO)_2L$; where X = F, Cl, Br, or I and L = H_2O or 1-phenyl-2,3-dimethyl-5-pyrazolone [17].

The antimicrobial action of the compounds under investigation was studied on three bacteria species: Staphylococcus aureus (S. aureus), Escherichia coli (E. coli) and Pseudomonas aeruginosa. The dermatophytes were presented by Trichophyton mentagrophytes var. granulosa (T. gypseum), Trichophyton mentagrophytes var. interdigitale (TKW), Microsporum gypseum (M. gypseum) and Epidermophyton floccosum (E. floccosum). Minimum inhibitory concentration (MIC) in μg/ml determination of the bacteria races was performed in liquid medium: for S. aureus in Mueller-Hinton's bouillon, for E. coli in minimum substrate according to Drobnica [18], for P. aeruginosa in minimum substrate according to Eagon and Philbs [19]. The MIC determination of dermatophytes was made on Sabourd's agar. For dermatophytes the coefficient of inhibition was determined by measuring the increase of vegetative hyfa using the method published by Jesenska [20]. The method was chosen not only to obtain

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TABLE I. Antimicrobial Activity of Copper(II) Alkylcarboxylates.

Compound	Conc. (μg/ml)	Microbial Species[a]						
		1	2	3	4	5	6	7
$Cu(HCOO)_2 \cdot 4H_2O$	1000	+	–	+	+	+	+	–
	500	+	+	+	+	+	+	+
	250	+	+	+	+	+	+	+
$Cu(CH_3COO)_2 \cdot H_2O$	1000	+	–	–	–	–	–	–
	500	+	–	+	+	+	+	+
	250	+	+	+	+	+	+	+
$Cu(CH_3CH_2COO)_2 \cdot H_2O$	1000	–	–	–	–	–	–	–
	500	–	–	+	+	+	+	+
	250	+	+	+	+	+	+	+
$Cu(CH_3(CH_2)_2COO)_2 \cdot H_2O$	1000	–	–	–	–	–	–	–
	500	–	–	+	–	–	+	–
	250	+	+	+	+	+	+	+
$Cu((CH_3)_2CHCOO)_2$	1000	+	–	–	+	+	+	+
	500	+	+	+	+	+	+	+
	250	+	+	+	+	+	+	+

[a]1 – Staphylococcus aureus; 2 – Escherichia coli; 3 – Pseudomonas aeruginosa; 4 – Trichophyton mentagrophytes var. granulosa; 5 – Trichophyton mentagrophytes var. interdigitale; 6 – Microsporum gypseum; 7 – Epidermophyton floccosum. – inhibition; + growth.

TABLE II. Antimicrobial Activity of Copper(II) Monohalogenoacetates.

Compound	Conc. (μg/ml)	Microbial Species						
		1	2	3	4	5	6	7
$Cu(FCH_2COO)_2 \cdot H_2O$	1000	+	–	–	–	–	–	–
	500	+	+	+	+	+	+	+
	250	+	+	+	+	+	+	+
	100	+	+	+	+	+	+	+
$Cu(ClCH_2COO)_2 \cdot 2H_2O$	1000	–	–	–	–	–	–	–
	500	+	–	–	+	+	+	–
	250	+	+	+	+	+	+	+
	100	+	+	+	+	+	+	+
$Cu(BrCH_2COO)_2 \cdot H_2O$	1000	–	–	–	–	–	–	–
	500	–	–	–	–	–	–	–
	250	–	–	–	∓	∓	+	+
	100	+	+	+	+	+	+	+
$Cu(ICH_2COO)_2 \cdot H_2O$	1000	–	–	–	–	–	–	–
	500	–	–	–	–	–	–	–
	250	–	–	–	–	–	–	–
	100	–	–	∓	∓	+	+	+

– inhibition; + growth.

TABLE III. Antimicrobial Activity of Copper(II) Arylcarboxylates.

Compound	Conc. (μg/ml)	Microbial Species						
		1	2	3	4	5	6	7
$Cu(C_6H_5COO)_2 \cdot 3H_2O$	1000	–	–	–	–	–	–	–
	500	+	+	+	–	–	–	–
	250	+	+	+	+	+	+	+
$Cu(2\text{-}FC_6H_4COO)_2 \cdot H_2O$	1000	–	–	–	+	+	∓	–
	500	+	+	+	+	+	+	–
	250	+	+	+	+	+	+	+
$Cu(2\text{-}ClC_6H_4COO)_2 \cdot H_2O$	1000	∓	–	–	+	+	+	–
	500	+	+	+	+	+	+	+
	250	+	+	+	+	+	+	+
$Cu(2BrC_6H_4COO)_2 \cdot H_2O$	1000	+	∓	–	+	+	+	+
	500	+	+	+	+	+	+	+
	250	+	+	+	+	+	+	+
$Cu(2\text{-}IC_6H_4COO)_2 \cdot H_2O$	1000	+	–	–	+	+	+	+
	500	+	+	+	+	+	+	+
	250	+	+	+	+	+	+	+

– inhibition; + growth.

objective information of the increase and inhibition of the size of the colony, but also because in the pathogenesis of mycotic epidermis diseases hyfies play the most important part.

The compounds under investigation were tested at concentrations of 100, 250, 500 and 1000 μg/ml. Dimethylsulphoxide was used as the solvent, its final concentration being 0.01 ml/10 ml in the culture medium. Sodium salts of the respective acids showed no antimicrobial action at concentrations of 1000 μg/ml.

Results and Discussion

Alkylcarboxylatocopper(II) compounds showed a comparatively weak antimicrobial action. A certain dependence as to an increasing effect could be observed in connection with the branching of the carbon chain (Table I). While the initial $Cu(HCOO)_2 \cdot 4H_2O$ and $Cu((CH_3)_2CHCOO)_2$ in the concentration of 1000 μg/ml showed almost no inhibiting effect, for $Cu(CH_3CH_2COO)_2 \cdot H_2O$ and $Cu(CH_3CH_2CH_2\text{-}COO)_2 \cdot H_2O$ the MIC of the tested microbial races was about 500 μg/ml.

An expressive increase of antimicrobial activity was attained by substitution of hydrogen in the methyl group of copper(II) acetate with halogen (Table II). The efficiency increases linearly with the substituting halogen in the order of $F < Cl < Br < I$. Copper(II) iodoacetate exhibited MIC of the tested microbes in the concentration of 250–100 μg/ml. It appears interesting that the antipyrine adducts of the copper(II) monohalogenoacetates did not exhibit any higher efficiency compared with the basic Cu(II) compounds, even though antipyrine itself has already a healing action. Several correlations between the magnetic and spectral data of the copper(II) monohalogenoacetates, as well as the acidity of the respective acids, has been found [14, 15]. In the series of $Cu(XCH_2COO)_2L$, (X = F, Cl, Br, or I; and L = H_2O or antipyrine) the maximum for the d–d transitions fluoroacetate compound appears at higher energy than that of the corresponding iodoacetate compound, and the band positions of chloro- and bromoacetate compounds lie between them. The value of the exchange antiferromagnetic interaction increased in the same order, but the antimicrobial effect decreased: $Cu(ICH_2COO)_2L > Cu(BrCH_2\text{-}COO)_2L > Cu(ClCH_2COO)_2L > Cu(FCH_2COO)_2L$.

A contrary dependence was found for arylcarboxylatocopper(II) compounds (Table III). Though the effect achieved in this group was not so expressive as for halogen-substituted alkyl compounds, it is apparent that the lowest MIC value was found for $Cu(C_6H_5COO)_2 \cdot 3H_2O$ *i.e.* for the

TABLE IV. Percentage of Inhibition of Copper(II) Bromo- and Iodoacetate Compounds on Dermatophytes.

Compound	Conc. (μg/ml)	Dermatophyte group (% inhib.)			
		T.G.	TKV	M.G.	E.fl.
$Cu(BrCH_2COO)_2 \cdot H_2O$	500	100	100	100	100
	250	50	50	29	34
	100	0	0	8	25
$Cu(BrCH_2COO)_2 \cdot APY^*$	500	100	100	100	100
	250	50	50	25	66
	100	20	25	0	13
$Cu(ICH_2COO)_2 \cdot H_2O$	500	100	100	100	100
	250	100	100	34	100
	100	40	10	22	25
$Cu(ICH_2COO)_2 \cdot APY^*$	500	100	100	100	100
	250	50	50	34	34
	100	0	0	0	25

*APY, 1-phenyl-2,3-dimethyl-5-pyrazolone(antipyrine).

the unsubstituted benzoic acid, while it gradually increases in the order: $Cu(2\text{-}FC_6H_4COO)_2 \cdot H_2O > Cu(2\text{-}ClC_6H_4COO)_2 \cdot H_2O > Cu(2\text{-}BrC_6H_4COO)_2 \cdot H_2O \sim Cu(2\text{-}IC_6H_4COO)_2 \cdot H_2O$. The antipyrine adducts of the Cu(II) arylcarboxylates also did not exhibit any higher antimicrobial effect compared with the hydrates of Cu(II) arylcarboxylates.

Further testing showed (as well as low MIC) significant values of percentage of inhibition in the respective limiting concentration of the compound (Table IV). Since testing of the copper(II) bromo- and iodoacetate compounds was performed with races of the dermatophyte group, it may be assumed that their application would not be limited by selective effectiveness. The applicability of copper(II) bromo- and iodoacetates as antimicrobial drugs is still enhanced by their comparatively unpretentious preparation and by their stability.

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