Iron Complexes of Triphenylphosphine and Triphenylarsine Oxides and their Antimicrobial Activities

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Antimicrobial activities of iron complexes of triphenylphosphine and triphenylarsine oxides are described. Synthesis, analytical data, as well as IR spectra are presented. The triphenylphosphine oxide complexes of the composition $[FeX_2(OPPh_3)_4][FeX_4]$, $[Fe(NCS)_3(OPPh_3)_3]$, $[Fe(CH_3CN)_2(OPPh_3)_4](I_3)_2 \cdot S$ are generally more antimicrobially effective than the triphenylarsine oxide complexes of the composition $[Fe_2^{III}O(OAsPh_3)_4X_3][Fe^{III}X_4] \cdot S$ (X = Cl or Br; S = CH_3CN).

Iron complexes of triphenylphosphine and triphenylarsine oxides ($OEPh_3$; E = P or As) have been studied from the catalytic activity point of view. The $OPPh_3$ complexes act as good oxidation catalysts and have much higher catalytic activity than $OAsPh_3$ complexes [1—3]. We have explored the biological activity of these complexes, too. It has been interesting to find out if the biological properties of $OEPh_3$ complexes are different.

Characteristic feature for both types of the complexes is their preparation by two principal ways:

I. Direct reaction of $OEPh_3$ with FeX_3 (X = Cl, Br or NCS) [4, 5] or $FeI_2(+ I_2)$ [3].

II. Autocatalytic oxidation of EPh_3 by dioxygen in the presence of appropriate iron compounds and corresponding anions [3, 6—8].

Main products of the reactions with $OPPh_3$ or PPh_3 are mononuclear complexes of the composition $[Fe^{III}X_2(OPPh_3)_4][Fe^{III}X_4]$ where X is Cl (*I*) or Br (*II*) [9, 10], $[Fe^{III}(NCS)_3(OPPh_3)_3]$ (*III*) [7], and $[Fe^{II}(CH_3CN)_2(OPPh_3)_4](I_3)_2 \cdot S$ (*IV*) (S = CH_3CN) [3], however, in the case of reactions with $AsPh_3$ or $OAsPh_3$ binuclear complexes of the composition $[Fe_2^{III}O(OAsPh_3)_4X_3][Fe^{III}X_4] \cdot S$, where X is Cl (*V*) or Br (*VI*) [8], are formed in a mixture with another two iron triphenylarsine oxide complexes.

Composition of the complexes *I*—*VI* has been found on the basis of elemental analysis (Table 1), X-ray analysis, and infrared spectra [1—10]. The chloro and bromo complexes *I* and *II* have a similar ionic structure. The coordination sphere of the cations $[FeX_2(OPPh_3)_4]^+$ is formed by distorted tetrahedral bipyramid and $[FeX_4]^-$ anions have gently distorted tetragonal structure. In the complex cation the coordination sphere is created by four $OPPh_3$ ligands which form a tetragonal plane, and two halogeno ligands occupy axial positions. The thiocyanate complex *III* has a nonionic structure. Fe(III) is octahedrally coordinated by three N atoms of NCS groups and by three O atoms of $OPPh_3$ ligands. The ferrous complex *IV* consists of cations $[Fe(CH_3CN)_2(OPPh_3)_4]^{2+}$, I_3^- anions, and acetonitrile solvate molecules. The Fe(II) atom is in a pseudooctahedral environment built up by two CH_3CN ligands bound through the N atoms and by four $OPPh_3$ ligands linked through the O atoms to the Fe(II) atom. The chloro- and bromo-$OAsPh_3$ complexes *V* and *VI* have a similar ionic structure with the binuclear cations $[Fe_2O(OAsPh_3)_4X_3]^+$, complex anions $[FeX_4]^-$, and acetonitrile solvate molecules. In the cation, one iron atom is pentacoordinated by four $OAsPh_3$ ligands and μ-oxo ligand which connects tetracoordinated iron atom in chromophore $FeCl_3O$.

These iron-$OEPh_3$ complexes evidently differ in their catalytic properties; mononuclear $OPPh_3$ complexes function as good oxidation catalysts [1, 3, 7] unlike the binuclear $OAsPh_3$ complexes.

The aim of the present paper is to study and to compare the antibacterial and antifungal efficiency of the iron triphenylphosphine and triphenylarsine oxides complexes with the activity of uncoordinated ligands, *i.e.* $OPPh_3$ (*VII*) and $OAsPh_3$ (*VIII*).

Antimicrobial activity of the iron complexes characterized by IC_{50} and MIC values is summarized in Table 2.

Table 1. Characterization Data for the Iron-$OEPh_3$ Complexes

Compound	Formula	M_r	w_i(calc.)/% w_i(found)/%					Colour	Yield
			C	H	N	X^a	Fe		%
I	$C_{72}H_{60}Cl_6O_4P_4Fe_2$	1437.5	60.16	4.21		14.79	7.77	yellow	80
			60.25	4.15		14.83	7.82		
II	$C_{72}H_{60}Br_6O_4P_4Fe_2$	1704.2	50.74	3.55		28.13	7.77	red-brown	80
			50.90	3.62		28.00	7.53		
III	$C_{57}H_{45}N_3S_3O_3P_3Fe$	1064.9	64.29	4.26	3.95	9.03	5.24	dark-red	85
			63.85	4.33	4.20	9.27	5.72		
IV	$C_{78}H_{69}N_3O_4P_4I_6Fe$	2053.6	45.62	3.39	2.05	37.08	2.72	brown	80
			45.23	3.39	1.87	36.96	2.80		
V	$C_{74}H_{63}NO_5Cl_7As_4Fe_3$	1761.7	50.45	3.60	0.80	14.09	9.51	yellow	60
			50.78	3.56	0.77	14.20	9.47		
VI	$C_{74}H_{63}NO_5Br_7As_4Fe_3$	2072.9	42.88	3.06	0.68	26.98	8.22	orange	60
			42.33	2.97	0.48	26.50	8.08		

a) For *I* X = Cl; for *II* X = Br; for *III* X = S; for *IV* X = I; for *V* X = Cl, and for *VI* X = Br.

Table 2. Antimicrobial Activity ($IC_{50}/(\mu g\ cm^{-3})$ and $MIC/(\mu g\ cm^{-3})$) of Iron Compounds

Compound	Bacteria^a		Filamentous fungi													
	1		2		3		4		5		6		7		8	
	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC
I	320	500^c	500	>1000	100	1000^d	130	>1000	400	500^c	750	>1000	110	250^c	135	250^b
II	160	250^c	900	>1000	500	1000^d	120	>1000	150	250^b	800	>1000	150	250^b	150	250^b
III	160	250^c	600	>1000	100	1000^d	130	>1000	500	1000^d	750	>1000	130	250^c	135	250^b
IV	370	500^c	700	>1000	180	1000^d	100	>1000	510	1000^d	900	>1000	150	>500	135	250^b
V	>500	>500^c	>1000	>1000	800	>1000	550	>1000	>1000	>1000	>1000	>1000	700	>1000	250	>500^d
VI	>500	>500^c	>1000	>1000	720	>1000	600	>1000	>1000	>1000	>1000	>1000	800	>1000	230	250^b
VII	200	500^c	600	1000^e	80	>100	500	1000^d	120	>1000	500	>1000	100	1000^d	100	500^b
VIII	500	>500	>1000	>1000	600	1000^d	>1000	>1000	>1000	>1000	>1000	>1000	1000	>1000	500	>1000

1 – ***B. subtilis***, 2 – ***R. nigricans***, 3 – ***A. alternata***, 4 – ***B. cinerea***, 5 - ***F. nivale***, 6 – ***A. flavus***, 7 – ***M. gypseum***, 8 – ***T. terrestre***. *a*) All tested compounds were inactive against bacteria ***S. aureus***, ***E. coli***, ***P. fluorescens*** and against yeasts ***C. albicans***, ***C. parapsilosis***; *b*) MMC = 500 $\mu g\ cm^{-3}$; *c*) MMC > 500 $\mu g\ cm^{-3}$; *d*) MMC = 1000 $\mu g\ cm^{-3}$; *e*) MMC > 1000 $\mu g\ cm^{-3}$.

All tested compounds were inactive against G^+ bacteria *Staphylococcus aureus*, G^- bacteria *Escherichia coli*, *Pseudomonas fluorescens* and against pathogenic yeasts *Candida albicans* and *C. parapsilosis* (IC_{50} and MIC values are higher than 500 $\mu g\ cm^{-3}$). The antibacterial effect with G^+ *Bacillus subtilis* was found against $OPPh_3$ (*VII*) (IC_{50} = 200 $\mu g\ cm^{-3}$) and $OAsPh_3$ (*VIII*), which was less active (IC_{50} = 500 $\mu g\ cm^{-3}$). Growth of *B. subtilis* was inhibited by iron $OPPh_3$ complexes *I*—*IV*, too. The activity of complexes decreases in the sequence *II* ≈ *III*, *I*, *IV* (IC_{50} = 160 $\mu g\ cm^{-3}$, 320 $\mu g\ cm^{-3}$, and 370 $\mu g\ cm^{-3}$, respectively). Iron $OAsPh_3$ complexes (*V*, *VI*) were inactive in this case (IC_{50} > 500 $\mu g\ cm^{-3}$).

There are three iron compounds *I*, *III*, and *IV* (IC_{50} = 100 $\mu g\ cm^{-3}$ or 180 $\mu g\ cm^{-3}$, respectively) which were active against phytopathogenic fungus *Alternaria alternata*. The compound *II* showed the highest activity against *Fusarium nivale* (IC_{50} = 150 $\mu g\ cm^{-3}$). The effect of tested compounds on growth of phytopathogenic *Botrytis cinerea* decreases in the order: *IV*, *II*, *III* ≈ *I*, *V*, *VI*. Antifungal activities were found for all tested iron complexes, especially against dermatophytic fungi *Trichophyton terrestre* (IC_{50} = 135 $\mu g\ cm^{-3}$—250 $\mu g\ cm^{-3}$) and against *Microsporum gypseum* where they decrease in the order: *I*, *III*, *II* ≈ *IV*, *V*, *VI*. Compounds *I*—*IV* have manifested weak activity with mycotoxinogenic fungus *Aspergillus flavus*. The activity of uncoordinated $OPPh_3$ (*VII*) on filamentous fungi is generally higher than activity of triphenylphosphine oxide complexes (*I*—*IV*). The triphenylphosphine oxide and its iron complexes *I*—*IV* are generally more effective than the triphenylarsine oxide and its iron complexes *V* and *VI*. The coordination of $OEPh_3$ to the iron atom causes a decrease of its antimicrobial activity.

The complexes presented in this paper showed totally higher antimicrobial activity than iron—nicotinamide complexes which have been tested in our laboratory [11].

EXPERIMENTAL

Iron triphenylphosphine oxide complexes are possible to prepare by various methods [3, 6, 7], however, very comfortable with good results method is established on the reaction of $Fe_2(SO_4)_3 \cdot 9H_2O$ with KX (X = Cl, Br, NCS or I with I_2), PPh_3 and O_2 in acetonitrile in the mole ratio of reactants corresponding to the composition of the individual complexes. Iron triphenylarsine oxide complexes are the best to prepare from FeX_3 (X = Cl or Br), $AsPh_3$ and O_2 in acetonitrile because of their lower solubility [8]. Triphenylphosphine oxide and triphenylarsine oxide were commercial products.

$[FeX_2(OPPh_3)_4][FeX_4]$ (X = Cl or Br). A mixture of 1 mmol of $Fe_2(SO_4)_3 \cdot 9H_2O$, 4 mmol of PPh_3, and 6 mmol of KX in acetonitrile (40 cm^3) was stirred and dioxygen was supplied till all PPh_3 was oxidized. The reaction took place at 50 °C about 4 d for the chloro complex and about 1 d for the bromo complex. Then K_2SO_4 as a by-product was filtered off and a crystalline solid was gradually crystallized.

IR spectrum of *I*, $\tilde{\nu}/cm^{-1}$: 1149 ν(P—O); 414 ν(Fe—O); 380 $\nu(FeCl_4^-)$.

IR spectrum of *II*, $\tilde{\nu}/cm^{-1}$: 1140, 1118 ν(P—O); 416 ν(Fe—O); 290 $\nu(FeBr_4^-)$.

$[Fe(NCS)_3(OPPh_3)_3]$. A mixture of 1 mmol of $Fe_2(SO_4)_3 \cdot 9H_2O$, 6 mmol of PPh_3, and 6 mmol of KSCN in acetonitrile (40 cm^3) was stirred and dioxygen was supplied till all PPh_3 was oxidized. The reaction took place under a reflux condenser about 2 days. The crystalline complex was obtained by the procedures described above.

IR spectrum of *III*, $\tilde{\nu}/cm^{-1}$: 1180, 1121, 1144 ν(P—O); 422 ν(Fe—O); 2081, 2041 ν(CN); 855 ν(CS).

$[Fe(CH_3CN)_2(OPPh_3)_4](I_3)_2 \cdot CH_3CN$. A mixture of 1 mmol of $Fe_2(SO_4)_3 \cdot 9H_2O$, 8 mmol of PPh_3, 6 mmol of KI, and 3 mmol of I_2 in acetonitrile (30 cm^3) was stirred at 60 °C and dioxygen was supplied till all PPh_3 was oxidized (4 h). The crystalline complex was obtained by the procedures described above.

IR spectrum of *IV*, $\tilde{\nu}/cm^{-1}$: 1154 ν(P—O); 440, 305 ν(Fe—O); 137 $\nu(I_3^-)$.

$[Fe_2O(OAsPh_3)_4X_3][FeX_4] \cdot CH_3CN$ (X = Cl or Br). A mixture of 1 mmol of FeX_3 and 2 mmol of $AsPh_3$ in acetonitrile (40 cm^3) was stirred at 60 °C and dioxygen was supplied till all $AsPh_3$ was oxidized (2 d). The individual complexes were separated by fractional crystallization using acetonitrile from the obtained mixture of $OAsPh_3$.

IR spectrum of *V*, $\tilde{\nu}/cm^{-1}$: 860, 828 ν(As—O); 841, 411 ν(Fe—O—Fe); 382 $\nu(FeCl_4^-)$.

IR spectrum of *VI*, $\tilde{\nu}/cm^{-1}$: 874, 862 ν(As—O); 839, 409 ν(Fe—O—Fe); 293 $\nu(FeBr_4^-)$.

The analytical data are listed in Table 1.

The antimicrobial activity of the iron complexes and uncoordinated ligands under investigation was evaluated using G^+ bacterial strains *Bacillus subtilis CCM 1718, Staphylococcus aureus CCM 3824* and G^- bacteria *Escherichia coli CCM 5172* and *Pseudomonas fluorescens* (isolated from patients); the yeasts *Candida albicans CCY 29391* and *Candida parapsilosis* (isolated from patients); the filamentous fungi *Rhisopus nigricans, Aspergillus flavus, Alternaria alternata, Botrytis cinerea, Fusarium nivale* (obtained from the Collection of Microorganisms of the Slovak University of Technology), and *Microsporum gypseum* and *Trichophyton terrestre* (both isolated from patients).

The compounds under investigation were tested at concentration ranging from 10 to 500 $\mu g\ cm^{-3}$ for bacteria and yeasts and from 50 to 1000 $\mu g\ cm^{-3}$ for filamentous fungi. Chromatographically pure compounds were dissolved in dimethyl sulfoxide (DMSO); its final concentration never exceeded 1.0 vol. % either in the control or treatment samples. The final concentration of DMSO being 1.0 vol. % was not inhibitory to the tested microorganisms. Inhibitory concentration IC_{50} (concentration of a compound which in comparison to the control inhibits microbial growth by 50 %) and MIC (minimal inhibitory concentration of a compound which inhibits microbial growth by 100 %) were determined by the microdilution technique in Mueller-Hinton liquid medium in 96 well microtitration plates (bacteria) [12] and in Sabouraud liquid medium in L-shaped tubes (yeasts) [13] with vigorous shaking. The time course of absorbance (A(630 nm)) was determined in three parallels (reference $\alpha = 0$ nm). IC_{50} and MIC determination of filamentous fungi was made on Sabouraud's (dermatophytes) and malt agar (other tested fungi) by dilution method during static culturing [14]. The IC_{50} and MIC values were read from toxicity curves.

MIC experiments on subculture dishes were used to assess the minimal microbicidal concentration (MMC) values. Subcultures were prepared separately into Petri dishes containing competent agar medium and incubated at 30 °C for 48 h (bacteria, yeasts); and at 25 °C for 96 h (filamentous fungi). The MMC value was taken as the lowest concentration which showed no visible growth of microbial colonies in the subculture dishes. The data of the microbial activity are given in Table 2.

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