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ORIGINAL ARTICLE

Pyrazole Derived Cationic Surfactants and their Tin and Copper Complexes: Synthesis, Surface Activity, Antibacterial and Antifungal Efficacy

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Abstract Five membered heterocyclic cationic 3-pyrazolium surfactants namely: 2-[2-(alkyloxy)-2-oxoethyl]-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-3-pyrazolium bromide (decyl-; dodecyl-) and their copper and tin complexes were synthesized, their structures were confirmed using different spectroscopic tools. The IR spectra of the metal complexes showed that these compounds exhibit a tetrahedron structure with the transition metal ion (M^{2+}) at the center and the cationic ligands arranged in the apexes, while the halide ions in the center. The synthesized compounds were evaluated as biocides against different types of bacteria and fungi. The biological activity data showed that the cationic surfactants exhibit moderate to high efficacy against the tested microorganisms (either bacteria or fungi). While, complexation of these cationic surfactants with Cu (II) and Sn (II) ions the antimicrobial activity was strongly increased. The surface activity of these compounds were discussed and correlated to their chemical structure and the type of substituents on the heterocyclic moiety. Meanwhile, the antimicrobial assay was correlated to the surface activities of the synthesized compounds.

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Introduction

Heterocyclic compounds are considered the most effective active matters in about 70% of biocidal drugs, especially the antibacterial and antifungal medications. These heterocyclic compounds contain five or six membered rings or even fused rings. Some of these heterocyclic substances are the pyrazole derivatives which remain of great interest due to their wide applications in the pharmaceutical and agrochemical industry. Pyrazole derivatives were reported to possess significant antibacterial [1] and monoamine oxidase inhibitory activity [2] insecticide, anticancer, anti-HIV and herbicide properties. This gave a great impetus to the search for potential pharmacologically active drugs carrying pyrazole substituents. Pyrazolyl pyrazoline derivatives were found to possess therapeutic activities such as antiinflammatory [3] antimicrobial [4], antiallergic [5], antidiabetic [6] and cardiovascular [7]. The efficiency of the pyrazole derivatives was increased by introducing charged core in its structure either as a cationic (pyrazolium) or anionic center (carboxylate, sulfate …).

In this work, cationic surface active pyrazolium derivatives containing different substituents and their copper and tin complexes were synthesized. The surface activities of the parent cationic compounds were determined. The parent cationic compounds and the metal complexes were evaluated for their antimicrobial activity against gram positive, gram negative bacteria and fungi, and their effectiveness as antimicrobial agents was discussed using the data of their chemical structures and surface activities.

Experimental Technique

Synthesis of 1-Phenyl-3-Methyl-2-Pyrazolin-5-One and 3-Methyl-1*H*-Pyrazol-5(4*H*)-One ($P_{I,II}$)

To a suspension of 1-phenyl-3-methyl-2-pyrazolin-5-one (0.01 mol) in warm ethanol (50 mL) phenyl hydrazine or hydrazine hydrate (0.01 mol) was added. The reaction mixture was warmed on a water bath for one hour then the solvent was evaporated under vacuum. The resulting solid products were filtered off and washed by ethanol and then recrystallized from ethanol to produce I, II.

Synthesis of 1-Phenyl-3-Cyano-2-Pyrazolin-5-One and 3-Cyano-1*H*-Pyrazol-5(4*H*)-One ($P_{III,\ IV}$)

To a suspension of 3-cyano-1-phenyl-2-pyrazolin-5-one (0.01 mol) in warm ethanol (50 mL) phenyl hydrazine or hydrazine hydrate (0.01 mol) were added. The reaction mixture was warmed under controlled thermostated conditions for one hour. The solvent was evaporated in vacuum and the resulting solid products were filtered off and crystallized twice from ethanol to prepare III and IV.

Synthesis of Bromopropionic Esters ($E_{I,\ II}$)

To a solution of decyl- or dodecyl alcohol (0.1 mol) and bromopropionic acid (0.1 mol) in *p*-xylene (150 mL) were mixed, and then *p*-toluene sulfonic acid (0.0005 mol) was added as a catalyst [8]. The reaction mixture was refluxed for 3 h in a vessel until the theoretical amount of water was removed as an indication of the reaction completion. The products were purified by vacuum distillation and washed several times with hot solution of sodium carbonate (5%) and dissolved in petroleum ether (bp 40–60 °C); the organic layer containing the desired bromoesters (decyl bromopropionate: E_{10} or dodecyl bromo-propionate: E_{I2}) was separated and the solvent was distilled off.

Synthesis of the Cationic Pyrazolium Surfactants (CPS)

The procedures which are used to synthesize the quaternary pyrazolium derivatives are the general methods to synthesize quaternary cationic surfactants. Pyrazole derivatives ($\boldsymbol{P_{I\text{-}IV}}$, 0.02 mol) were refluxed with 0.02 mol of alkyl bromopropionate (E_{10}, E_{12}) in presence of acetone (50 mL) for 8 h and allowed to separate overnight. The produced salts were filtered off, washed twice with acetone and dried at 40 °C in vacuum oven [9].

Synthesis of Metal Complexes (CPS-M)

The desired transition metals were used in form of chlorides ($CuCl_2$ and $SnCl_2{\cdot}2H_2O$). The cationic pyrazolium derivatives ($CPS_{1\text{-}4}$) and the different metal ion solutions were mixed in absolute ethyl alcohol by the ratio of 2:1, respectively. The reaction mixture was refluxed for 16 h. On cooling, the different pyrazolium metal complexes were precipitated and filtered under suction. The produced crystals were washed with cold ethanol/petroleum ether (50:50 vol) and finally with diethyl ether and kept in a desiccator over fused $CaCl_2$ [10, 11].

Instrumentation

Microelemental analysis of the synthesized surfactants was performed using a Vario Elementar instrument. Infrared spectroscopic analysis of the synthesized surfactants was performed using a Fourier-transform infrared spectrophotometer. NMR spectroscopic analyses of the synthesized surfactants were performed using a Bruker model DRX-300 NMR spectrometer with TMS as an internal standard.

Surface and Interfacial Tension Measurements

The surface tension (γ) of the cationic surfactant solutions (in concentration range of 0.1 to 0.0001 M/L) was measured with a Krüss K-6 tensiometer (Hamburg, Germany) based on the Du Noüy platinum ring detachment method and was calibrated using deionized water at 25 °C. The platinum ring was cleaned before each measurement by flaming (Bunsen burner) to remove any residual deposit. The surface tension measurements were taken after 90 min. of pouring the surfactant solution in the measuring container to ensure the equilibrium. The readings were taken in triplicate for each solution to check repeatability and the surface tension values were within an error less than or equal to ± 1 mN/m. Interfacial tension measurements were carried out for 0.1 g/L surfactant solutions against paraffin oil [12–14] at 25 °C.

Antimicrobial Activity Measurements

The antimicrobial activity was tested against gram-positive and gram-negative *Staphylococcus aureus* and *Escherichia coli*, and the antifungal activity was tested against *Candida albicans* and *Aspergillus flavus*.

The cationic pyrazolium amphiphiles and their copper and tin complexes were screened for their antimicrobial activity against bacteria and fungi by the well diffusion method [14, 15] using 0.1 mL of the cationic pyrazolium inhibitors dissolved in DMF (1 mg/mL). The tested compounds were completely compatible with the medium of

agar and no turbidity was observed during the mixing process. The inhibition zone diameter produced by these compounds against the particular test bacterial strain determined the antibacterial activity of the compound. The mean value obtained for three individual replicates was used to calculate the zone of growth inhibition of each sample. The antimicrobial activities were calculated as a mean of three replicates.

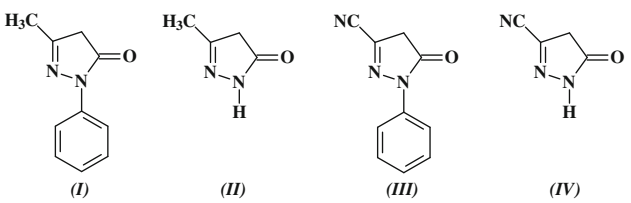
Results and Discussion

Chemical Structure

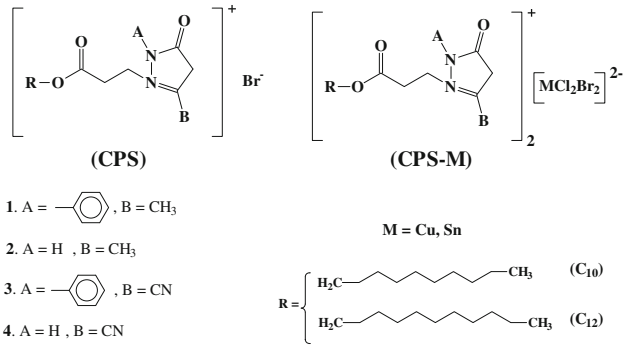
The elemental analyses showed the purity of the synthesized compounds (99.7%). The IR and ^{1}H-NMR spectra showed the chemical structures of the synthesized pyrazole ($P_{I\text{-}IV}$), fatty esters (E_{10}, E_{12}) are identically as represented in Scheme 1.

Compound I: mp 132 °C; yield 87%; 2200 and 1720 cm^{-1} corresponded to (CN, C=O stretching); ^{1}H-NMR: $\delta = 2.3$ ppm (s, 2H, CH_2), 0.9 ppm (s, 3H, CH_3) and 7–7.6 ppm (m, 5H, aromatic). ***Compound II***: mp 105 °C; yield 78%; 3300, 2200 and 1715 cm^{-1} (NH, CN and C=O stretching groups); ^{1}H-NMR: $\delta = 2.2$ ppm (s, 2H, CH_2), 0.9 ppm (s, 3H, CH_3) and 7 ppm (s, 1H, NH). ***Compound III***: mp 142°; yield 72%; IR: 3320, 2200, 1700 cm^{-1} corresponded to (NH, CN, C=O str.); ^{1}H-NMR: $\delta = 2.2$ ppm (s, 2H, CH_2), 2.1 ppm (s, 3H, CH_3) and 7.3 ppm (m, 5H, phenyl). ***Compound IV***: mp 110 °C; yield 82%; IR: 3100, 2200 and 1725 cm^{-1} corresponded to (NH, CN and C=O str.); ^{1}H-NMR: $\delta = 2.2$ ppm (s, 2H, CH_2), 2.1 ppm (s, 3H, CH_3) and 7–7.6 ppm (s, 1H, CH). ***Compound E_{I0}***: Waxy; yield 95%; IR: 2950, 2842, 1735 cm^{-1} corresponded to (CH_2, CH_3, C=O str.); ^{1}H-NMR: $\delta = 2.2$ ppm (q, 16H, CH_2), 2.1 ppm (t, 3H, CH_3) and 3.4 ppm (t, 2H, H_2CCO). ***Compound E_{I2}***: Waxy; yield 90%; IR: 2950, 2842, 1735 cm^{-1} corresponded to (CH_2, CH_3, C=O str.); ^{1}H-NMR: $\delta = 2.2$ ppm (q, 20H, CH_2), 2.1 ppm (t, 3H, CH_3) and 3.4 ppm (t, 2H, H_2CCO).

IR spectra of the synthesized cationic pyrazolium surfactants appeared identical absorption bands to the start materials $P_{I\text{-}IV}$ and $E_{I0,\ I2}$ with the appearance of a new band at 3040 cm^{-1} corresponded to (N^+) group, Scheme 2.



Scheme 1 The synthesized pyrazole derivatives $P_{I\text{-}IV}$



Scheme 2 Chemical structures of the parent cationic pyrazolium surfactants (CPS) and their metal complexes (CPS-M)

Dodecyl CPS-1: $\delta = 1.2$ ppm (d, 3H, CH_3), 1.3 ppm (t, 2H, CH_2), 1.2 ppm (t, 20H, CH_2) and 7–7.6 ppm (m, 4H, aromatic). ***Dodecyl CPS-2***: $\delta = 1.1$ ppm (d, 3H, CH_3), 1.3 (t, 2H, CH_2), 1.2 ppm (t, 20H, CH_2) and 5.6 ppm (NH). ***Dodecyl CPS-3***: $\delta = 1.1$ ppm (d, 3H, CH_3), 1.3 ppm (t, 2H, CH_2), 1.2 ppm (t, 20H, CH_2) and 7–7.6 ppm (m, 4H, aromatic). ***Dodecyl CPS-4***: $\delta = 1.1$ ppm (d, 3H, CH_3), 1.3 ppm (t, 2H, CH_2), 1.2 ppm (t, 20H, CH_2) and 5.9 ppm (NH).

IR spectra showed identical absorption bands as the cationic surfactants and also a shift of the absorption band at 3040 cm^{-1} by about 12 units, which confirms the participation of this group in the formation of the metal complexes. The atomic absorption spectra of the copper and tin complexes showed that the two elements are participating in the metal complexes by an identical ratio of 1:2. The chemical structures of the cationic metal complexes of copper and tin were represented in Scheme 2.

The crystal structure of the metal complexes of the type ML_2X_4 are shown in several publications to be in the tetrahedron structure and the metal ion located in the center of the structure while the two ligands are in the apexes and the four halide ions are occupied the four identical summits of the tetrahedron and the angle between the bonds is 120°.

Surface Activity

Figure 1 represents the variation for the surface tension vs. log conc. of the pyrazolium cationic surfactants (decyl-CPS) at 25 °C. The profile showed sharp break points corresponding to the critical micelle concentration values of the different surfactants [16]. The values of the surface tension appeared relatively high. That may be due to the presence of the heterocyclic nucleus. The critical micelle concentration values of the cationic surfactants were extracted from these profiles and listed in Table 1. It is clear that the chemical structure of these amphiphiles has a significant influence on their surface activities. Increasing the hydrophobic chain length (nonpolar tail) decreases the

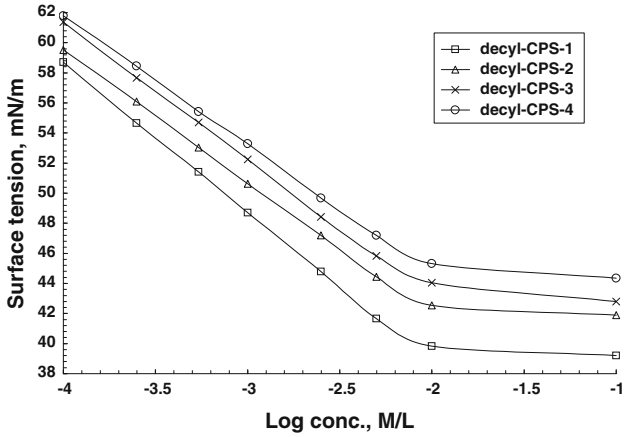


Fig. 1 Surface tension-log Conc. of the pyrazolium decyl derivatives at 25 °C

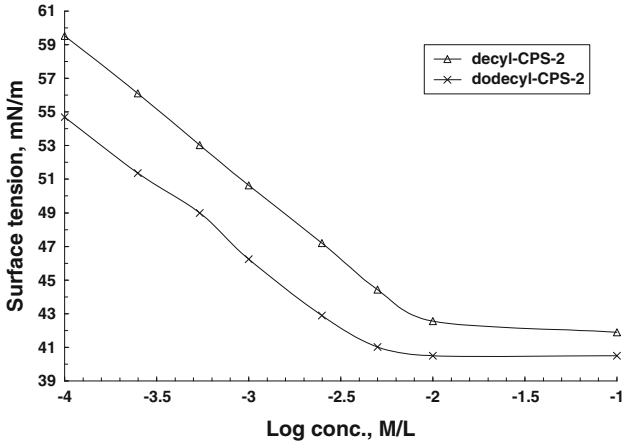


Fig. 2 Effect of the hydrophobic chain length on the surface tension of the synthesized surfactants

Table 1 Surface tension (ST), critical micelle concentration (CMC) and interfacial tension (IT) of the cationic pyrazolium derivatives decyl- and dodecyl CPS-(1-4)

Compound	ST (mN/m) at CMC	CMC × 10^{-3} (mol/L)	IT (mN/m)
Decyl CPS-1	40.0	6.76	6
Decyl CPS-2	41.5	8.13	9
Decyl CPS-3	43.0	10.2	6.5
Decyl CPS-4	44.5	9.55	3
Dodecyl CPS-1	38.0	4.14	5.5
Dodecyl CPS-2	40.5	4.79	9
Dodecyl CPS-3	41.9	6.31	6
Dodecyl CPS-4	43.5	7.90	2.5

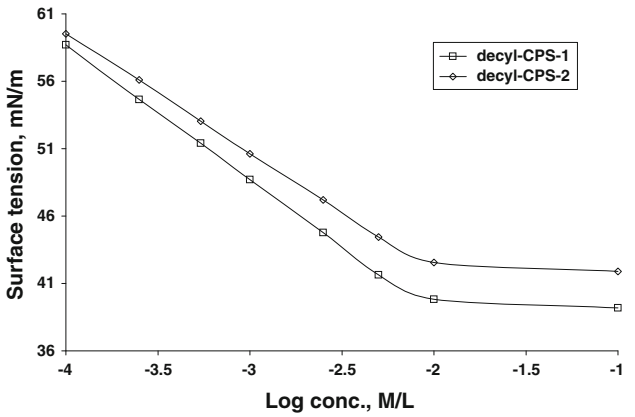


Fig. 3 Influence of phenyl groups on the surface tension of the synthesized pyrazolium cationic surfactants

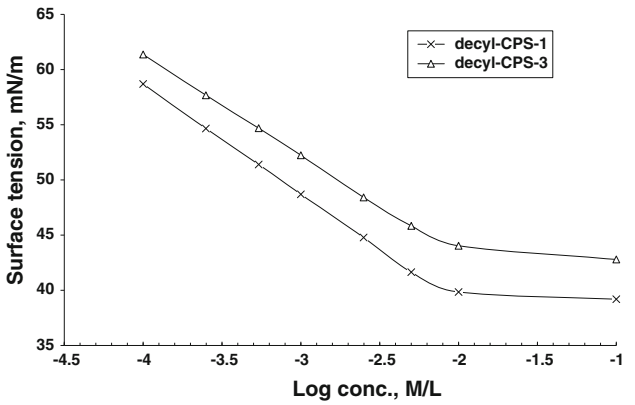


Fig. 4 Influence of cyano groups on the surface tension of the synthesized pyrazolium cationic surfactants

critical micelle concentrations of the investigated surfactant at 25 °C (Fig. 2) which referred to increase the hydrophobicity as the result of increasing the methylene groups [17, 18] and consequently the micellization process enhanced. Table 1 represents the surface active parameters of the pyrazolium cationic amphiphiles. It is clear that increasing the hydrophobic chain length from 10 to 12 methyl groups (–CH_2–) improves the surface activities for all the synthesized surfactants. On the other hand, the substituents on the heterocyclic nucleus have a considerable role in their surface activity. Derivatives which contain phenyl groups (CPS-1) have a higher surface depression than those containing hydrogen protons (CPS-2), (Fig. 3). That can be referred to the change of the hydrophobicity of the molecules under consideration by the type of substituents [19, 20]. In order to determine the effect of the cyano-substituents on the surface activity of these surfactants, surface tension profiles of both decyl-CPS-1 and decyl-CPS-3 were drawn in Fig. 4. It is clear that cyano-substituents increase the surface tension values more than the methyl derivative. The cyano group is characterized by the presence of the triple bond in addition to its ability to attract electrons from the neighboring atoms. That decreases the hydrophobicity of the surfactant molecules and their surface activity

Table 2 The antibacterial activities of the cationic pyrazolium surfactants at 5 mg/mL

Compound	Inhibition zone diameter (mm)	
	Escherichia coli	*Staphylococcus aureus*
Decyl CPS-1	16	15
Decyl CPS-2	17	18
Decyl CPS-3	15	16
Decyl CPS-4	22	17
Dodecyl CPS-1	14	14
Dodecyl CPS-2	16	17
Dodecyl CPS-3	15	15
Dodecyl CPS-4	14	19
Tetracycline	21	19

compared with the more hydrophobic molecules containing methyl groups.

Interfacial Tension (γ_{int})

The interfacial tension values of the cationic pyrazolium surfactants against paraffin oil at 25 °C were listed in Table 1. The data showed that the interfacial tension of these compounds is in the range 2.5–9.0 mN/m. That confirms the amphipathic characters of the cationic surfactant.

Biological Activities of the Pyrazolium Cationic Surfactants and their Copper and Tin Complexes

Antibacterial Activity

The antibacterial activities of the synthesized cationic pyrazolium surfactants (decyl and dodecyl derivatives of CPS-1, CPS-2, CPS-3 and CPS-4) were tested against two bacterial strains: *Staphylococcus aureus* and *Escherichia coli*, the results were listed in Table 2.

The antibacterial activities of the cationic pyrazolium surfactants were ranged between 14.0 and 22.0 mm for *Escherichia coli* and 14.0 to 19.0 mm for *Staphylococcus aureus* which may be considered as a moderate antibacterial activity compared with the standard used (tetracycline, 21 mm for *Escherichia coli* and 19.0 mm for *Staphylococcus aureus*). The highest antibacterial activities were observed for (decyl- and dodecyl-) derivatives of CPS-2 and CPS-4 which are characterized by the smallest substitutions (hydrogen and methyl groups). While, the derivatives containing phenyl groups showed low antibacterial activities with the inhibition zone diameters ranged between 17.0 and 19.0 mm. On the other hand, the antibacterial activities were independent on the hydrophobic chain length of the studied compounds. But some few exceptions were observed in the case of CPS-2, Table 2.

On complexation of the pyrazolium cationic compounds with Cu^{++} and Sn^{++} ions, the antibacterial activity was considerably increased. Some of the produced metal complexes exhibited a higher activity than their parent cationic surfactants. The variation of the efficiency by complexation with transition metals has been described in several works and attributed to the change in the total charge of the produced complexes [21, 22]. Complexes which have a high positive charge on the nitrogen atoms show a lower activity against the tested microorganisms and vice versa. This seems to depend on the electropositivity of the metal ions. Complexation of the synthesized surfactants using Sn^{++} increased their antimicrobial efficacy, while Cu complexes showed no change as expected from the electronegativity of Sn^{++} and Cu^{++} ions (−2.21, −1.49). More electronegative transition metals produce a higher positive charge on the nitrogen atom. Hence, the substituents on the nitrogen atoms play a vital role in the potency of the produced metal complexes [23, 24] and electronegative substituents decrease the complex potency Table 3.

Table 3 The antibacterial activities of the cationic pyrazolium metal complexes at 5 mg/mL

Compound	Inhibition zone diameter (mm)			
	Copper complex		Tin complex	
	Escherichia coli	*Staphylococcus aureus*	*Escherichia coli*	*Staphylococcus aureus*
Decyl CPS-1	20	19	19	20
Decyl CPS-2	21	19	19	21
Decyl CPS-3	19	20	17	20
Decyl CPS-4	17	18	18	19
Dodecyl CPS-1	19	19	18	18
Dodecyl CPS-2	18	19	18	18
Dodecyl CPS-3	18	19	19	19
Dodecyl CPS-4	18	18	18	20

Table 4 The antifungal activities of the cationic pyrazolium surfactants at 5 mg/mL

Compound	Inhibition zone diameter (mm)	
	Aspergillus flavus	*Candida albicans*
Decyl CPS-1	–	17
Decyl CPS-2	–	16
Decyl CPS-3	–	18
Decyl CPS-4	–	22
Dodecyl CPS-1	–	19
Dodecyl CPS-2	–	18
Dodecyl CPS-3	–	18
Dodecyl CPS-4	–	19
Amphotricine	5	20

Table 5 The antifungal activities of the cationic pyrazolium metal complexes at 5 mg/mL

Compound	Inhibition zone diameter (mm)			
	Copper complex		Tin complex	
	Aspergillus flavus	*Candida albicans*	*Aspergillus flavus*	*Candida albicans*
Decyl CPS-1	5	20	6	19
Decyl CPS-2	6	20	5	19
Decyl CPS-3	6	20	7	16
Decyl CPS-4	5	18	7	18
Dodecyl CPS-1	6	18	5	18
Dodecyl CPS-2	6	20	6	18
Dodecyl CPS-3	5	19	6	17
Dodecyl CPS-4	6	18	6	18

Antifungal Activity

The antifungal activities of the targeted compounds were tested against *Aspergillus flavus* and *Candida albicans* using Amphotricine™ as antifungal reference. From the results listed in Table 4, it is obvious that the synthesized pyrazolium cationic surfactants have a good antifungal activity against *Candida albicans*, but not against *Aspergillus flavus*. That resistance may be attributed to the high rigidity of the outer membrane of that fungus.

Complexation with Sn^{++} and Cu^{++} showed an increased antifungal activity compared with their parents, and corroborate the improvement produced by the metal complexes on the biological reactions with these microorganisms (Table 5). It can be observed also that the resistance of *Aspergillus flavus* fungus starts to decay, which reflects the high potency of the tested metal complexes.

Action Mode of the Cationic Pyrazolium Derivatives and their Metal Complexes

Several works have described the action mode of the cationic surfactants as biocides. The aim of the complexation of the cationic compounds is to increase their potency against microorganisms. Nevertheless, some cationic metal complexes exhibit a lower biocidal activity than their parent cationic surfactants. This is attributed to the formation of charges on the metal complex formed. In some cases, the formed metal complex acquires a higher positive charge than the parent cationic. This increases the sensitivity of the cellular membranes towards these complexes, which decreases their adsorption at these membranes and consequently their antimicrobial activity, while in other cases, the formed metal complexes lose their large charge by complexation, and thus adsorb more on the membrane and are more active. The action mode of the cationic biocides on the microorganisms is originally focused on their adsorption tendency on the cellular membranes [25, 26]. In gram-positive bacteria (Fig. 5), the adsorption is occurring in the lipoteichonic acid layer which is characterized by the charged nature and the ability to interact with the positively

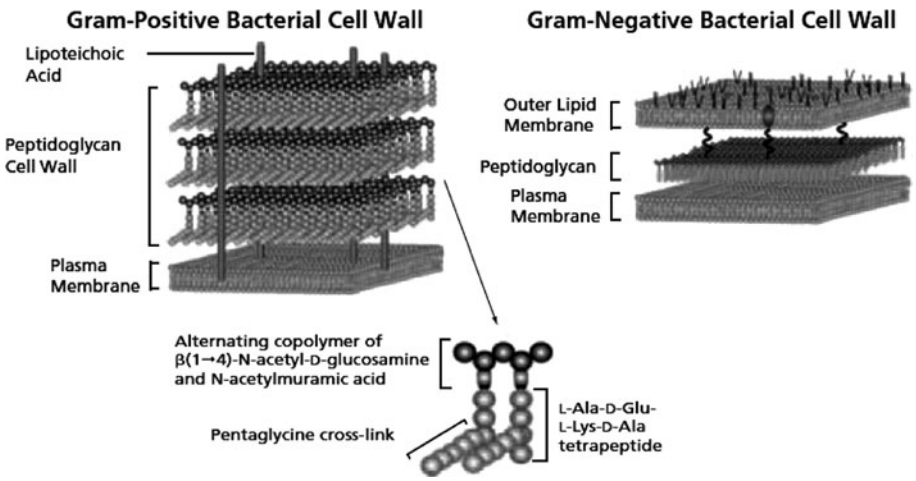


Fig. 5 Structure of the bacterial cell walls

charged molecules. On the other hand in the gram-negative bacteria (Fig. 5), the lipid layer (highly nonpolar layer) is the target of the positively charged biocide molecules. The adsorption disturbs the selective permeability of these membranes, and causes a severe disturbance of the biological reactions inside the cells due to the diffusion of several compounds from the environment due to the absence of the selective permeability [27]. Also, the presence of the halogen atoms (Cl^-) as counter ions increases the activity when they penetrate into the cells. The complexation of the synthesized cationic surfactants by Sn^{++} metal ions produces less positive charge on the nitrogen atom which facilitate its adsorption at the cellular membrane. The action mode of the synthesized pyrazolium biocides is seemed to be identical in the cases of fungi and bacteria [14, 26].

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