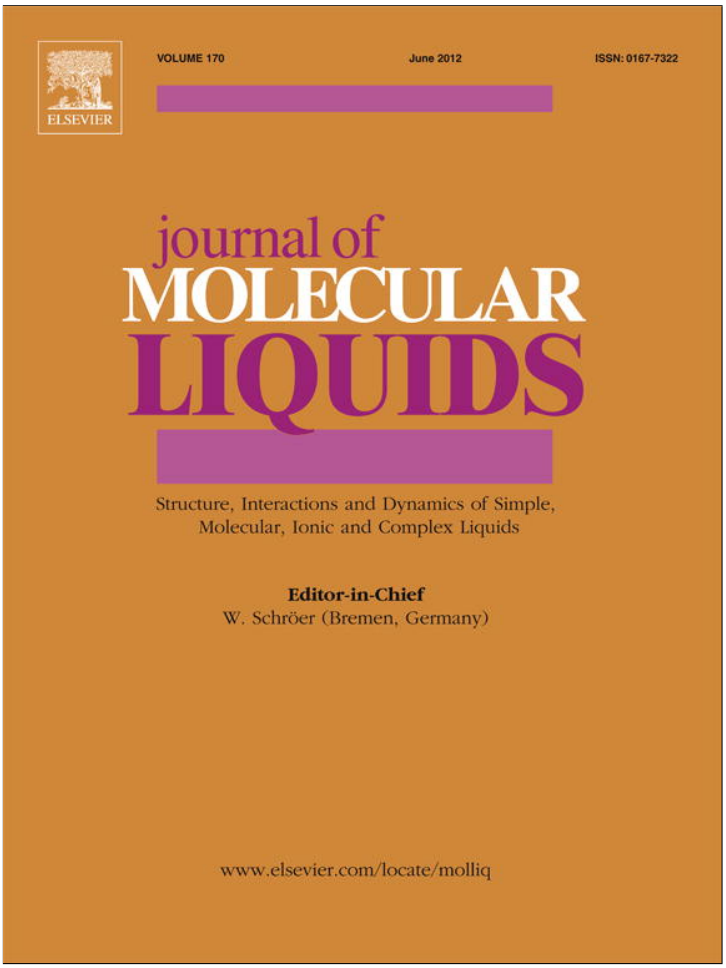

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Antimicrobial activity of the ionic liquids triethanolamine acetate and diethanolamine chloride, and their corresponding Pd(II) complexes

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ABSTRACT

The antimicrobial activity of the ionic liquids triethanolamine acetate [TEA][HOAc] and diethanolamine chloride [HDEA][Cl], as well as of their Pd(II) complexes *trans*-dichlorobis(triethanolamine-*N*)palladium(II) (*trans*-$[PdCl_2(TEA)_2]$) and diethanolammonium–tetrachloridopalladate(II) ($[HDEA]_2[PdCl_4]$), is presented. The investigated compounds showed low antibacterial activity. Better results were for antifungal activity. [TEA][HOAc] exhibited better activity than corresponding complex. *Aspergillus* species were especially sensitive to $[HDEA]_2[PdCl_4]$. The activity of this complex against *A. restrictus*, *A. fumigatus* was up to ten times higher than the activity of positive control, fluconazole.

1. Introduction

The term ionic liquids (ILs) refer to the compounds composed only of ions, and are liquid below 200 °C [1–4]. This relatively new class of substances is composed of an organic cation and an organic or inorganic anion, whose careful choice, provides their unique properties: *i*) good solvents for a wide range of organic, inorganic and organometallic compounds, *ii*) polar substances, *iii*) immiscible with a number of organic solvents, i*v)* ILs are thermally stable (are not explosive and flammable), and do not evaporate since they have very low vapor pressures. All these features significantly distinguish ILs from classical volatile and toxic organic solvents, and due to that are considered as environmentally friendly and more attractive and ecologically acceptable green solvents [5–12]. Ionic liquids attract much interest in the context of green chemistry, and they are one of the most exciting topics nowadays [13–15].

Recent studies have investigated the effects of ionic liquids on enzyme activity [16], mammalian cell lines [17], survivorship of the marine bacterium *Vibrio fischeri* [17], acute and chronic toxicity on *Daphnia magna* [18,19] and survivorship and life history of the freshwater snail, *Physa* acuta [20]. The effect of ionic liquids on microorganisms has been also studied. Scientists noted that antimicrobial activity is greatly affected by the alkyl chain length. Pernak et al. [21,22] and Roslonkiewicz et al. [23] have reported a trend of increasing toxicity towards a range of bacteria and fungi with increasing chain length of alkyl substituents in pyridinium, imidazolium and quaternary ammonium salts. The antimicrobial activities of five new groups of choline-like quaternary ammonium chloride ionic liquids were evaluated gainst a range of Gram positive and Gram negative bacteria [24]. The ionic liquids tested all showed good antimicrobial activity, and confirmed that lipophicity was the main factor in determining antimicrobial activity. Recently, the antimicrobial activity of six common ionic liquids with halogen anion was tested and the results indicate that the growth of *Escherichia coli*, *Staphylococcus aureus* and *Bacillus subtilis* was inhibited in the presence of ionic liquids [25]. Carson et al. [26] reported for the first time the *in vitro* antibiofilm activity of a 1-alkyl-3-methylimidazolium chloride ionic liquids while Busetti et al. [27] described the antimicrobial and antibiofilm activities of a range of 1-alkylquinolinium bromide ionic liquids. These ionic liquids exhibited potent antibiofilm activity which was also dependent on alkyl chain length.

The subject of numerous scientific papers relating to the palladium and its complexes is the examination of their biological activity. Some of these studies relate to the examination of their cytotoxicity [28–32] and cardiotoxicity [33–35]. Published data on effects of palladium on heart showed that palladium(II) complexes and palladium in the form of organic compounds, do not contribute significantly to cardiotoxicity, while inorganic compounds of palladium are more toxic to myocardium. The main reason for studying palladium(II) complexes as potential antitumor drugs is the significant similarity of the coordination chemistry between palladium(II) and platinum(II) compounds. It was shown that palladium complexes are not promising as anticancer drugs, but they are good models for the mechanistic study of the activity of the analogous Pt(II) complexes.

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Antimicrobial activity of the Pd(II) complexes [36–38] and the ability to hydrolyse peptide bond in peptides and proteins, as well as their behavior as artificial metallopeptidases [39–42] are studied, also. Many investigations of the antimicrobial activity of Pd(II) complexes and their ligands showed that the complexes are more active than the ligands, that they could possibly be used as broad spectrum antibiotics in the near future.

The aim of this study was to investigate *in vitro* antibacterial and antifungal activity of the ionic liquids triethanolamine acetate [TEA][HOAc] and diethanolamine chloride [HDEA][Cl], and their Pd(II) complexes *trans*-$[PdCl_2(TEA)_2]$ and $[HDEA]_2[PdCl_4]$, recently synthesized [43,44].

2. Experimental

Nutrient liquid medium, a Mueller–Hinton broth was from Liofilchem, Italy, while a Sabouraud dextrose broth was from Torlak, Belgrade. An antibiotic, doxycycline, was purchased from Galenika A.D., Belgrade, and antimycotic, fluconazole, was from Pfizer Inc., USA.

2.1. DFT studies

The geometrical parameters of all stationary points were optimized with Gaussian09 [45], using the CPCM model, and dimethyl sulfoxide as solvent ($\varepsilon = 46.83$). All calculations were performed using the M06 functional [46]. The triple split valence basis set 6-311 + G(d,p) was used for C, H, O, N, and Cl, whereas LANL2DZ + ECP [47] was employed for the Pd center. All calculated structures were confirmed to be local minima (all positive vibrational frequencies) for ground state structures by frequency calculations. The natural bond orbital analysis (Gaussian NBO version) was performed for all structures.

2.2. Microbiological assays

2.2.1. Test microorganisms

Antimicrobial activity of the complex and its precursors was tested against 29 microorganisms. The experiment involved 16 strains of pathogenic bacteria, including 7 standard strains (*E. coli* ATCC 25922, *Enterococcus faecalis* ATCC 29212, *Pseudomonas aeruginosa* ATCC 27853, *S. aureus ATCC* 25923, *Sarcina lutea* ATCC 9341, *Bacillus subtilis* ATCC 6633, *Proteus mirabilis ATCC12453*) and 9 clinical isolates (*E. coli*, *E. faecalis*, *P. aeruginosa*, *S. aureus*, *S. lutea*, *B. subtilis*, *P. mirabilis*, *Salmonella enterica, Salmonella typhymurium*). Also, five species of pathogenic fungi (*Aspergillus fumigatus* PMFKG-F23; *Aspergillus flavus* PMFKG-F24; *Aspergillus restrictus* PMFKG-F25; *Aspergillus niger* PMFKG-F26 and standard strain *A. niger* ATCC 16404); three yeast species (*Candida albicans* (clinical isolate), *C. albicans* ATCC 10231 and *Rhodotorula sp.* PMFKG-F27) and five species of probiotics (*Lactobacillus plantarium* PMFKG-P31, *B. subtilis* IP 5832 PMFKG-P32, *Bifidobacterium animalis subsp. lactis* PMFKG-P33, *Lactobacillus rhamnosus* PMFKG-P35 and *Saccharomyces boulardii* PMFKG-P34) were tested. All clinical isolates were generous gift from the Institute of Public Health, Kragujevac. The other microorganisms were provided from a collection held by the Microbiology Laboratory Faculty of Science, University of Kragujevac.

2.2.2. Suspension preparation

Bacterial and yeast suspensions were prepared by the direct colony method. The turbidity of initial suspension was adjusted by comparing with 0.5 McFarland's standard [48]. Initial bacterial suspension contains about 10^8 colony forming unites (CFU)/mL and suspension of yeast contains 10^6 CFU/mL. 1:100 dilutions of initial suspension were additionally prepared into sterile 0.85% saline. The suspensions of fungal spores were prepared by gentle stripping of spore from slopes with growing aspergilli. The resulting suspensions were 1:1000 diluted in sterile 0.85% saline.

2.2.3. Microdilution method

In vitro antimicrobial activity was tested by determining the minimum inhibitory concentration (MIC) and minimum microbicidal concentration (MMC) using microdilution method with resazurin [49]. Serial twofold dilutions of tested compounds were made in a concentration range from 1000 μg/mL to 7.81 μg/mL in sterile 96-well plates containing Mueller–Hinton broth for bacteria, and Sabouraud dextrose broth for fungi and yeasts. After that, 10 μL of diluted bacterial, yeast suspension and suspension of spores was added to each well to give a final concentration of 5×10^5 CFU/mL for bacteria, and 5×10^3 CFU/mL for fungi and yeast. Finally, 10 μL resazurin solution, as an indicator of microbial growth, was added to each well inoculated with bacteria and yeast. Resazurin is a blue non-fluorescent dye that becomes pink and fluorescent when reduced to resorufin by oxidoreductases within viable cells. The inoculated plates were incubated at 37 °C for 24 h for bacteria, 28 °C for 48 h for the yeast and 28 °C for 72 h for molds. MIC was defined as the lowest concentration of tested substance that prevented resazurin color change from blue to pink. For molds, MIC values of the tested substance were determined as the lowest concentration that visibly inhibited mycelia growth.

Doxycycline and fluconazole, dissolved in nutrient liquid medium, were used as a positive control. The tested compounds were dissolved in DMSO and then diluted into nutrient liquid medium to achieve a concentration of 10% DMSO. Solvent control test was performed to study an effect of 10% DMSO on the growth of microorganism. It was observed that 10% DMSO did not inhibit the growth of microorganism. Also, in the experiment, the concentration of DMSO was additionally decreased because of the twofold serial dilution assay (the working concentration was 5% and lower). Each test included growth control and sterility control. All tests were performed in duplicate and MICs were constant.

Minimum bactericidal and fungicidal concentration (MBC/MFC) was determined by plating 10 μL of samples from wells, where no indicator color change was recorded, on nutrient agar medium. At the end of the incubation period the lowest concentration with no growth (no colony) was defined as minimum microbicidal concentration.

3. Results and discussion

The ionic liquids [TEA][HOAc] and [HDEA][Cl] were prepared by dropping the stoichiometric amount of acetic acid or hydrochloric acid to the dichlorometane solution of corresponding amino alcohol (TEA or DEA) [43,44]. The reactions of $PdCl_2$ with these ionic liquids, in molar radio 1:2, afford the complexes *trans*-dichlorobis(triethanolamine-N)palladium(II) (*trans*-$[PdCl_2(TEA)_2]$) and diethanolammonium–tetrachloridopalladate(II) ($[HDEA]_2[PdCl_4]$), respectively [43,44].

The structures of ionic liquids [TEA][HOAc] and [HDEA][Cl], and of complexes *trans*-$[PdCl_2(TEA)_2]$ and $[HDEA]_2[PdCl_4]$ were examined using DFT method. Since the biological evaluation was performed in DMSO as solvent, the optimization of the investigated compounds was done in DMSO as solvent, Fig. 1. The NBO analysis reveals N–H bonds in both ionic liquids, implying that they consist of acetate and chloride anion, and triethanolammonium and diethanolammonium cations, respectively. Bond distances reveal strong hydrogen bonding in all ILs, Table S1 of Supplementary data. The NBO analysis is in accordance with this finding. Namely, there is strong donation of density from the p orbitals on O to the σ^* antibonding N – H orbital of [TEA][HOAc]. Similarly, the p orbitals on Cl delocalize into the σ^* antibonding N – H orbital of [HDEA][Cl]. Owing to hydrogen bonding, it is obvious that molecular association is present. In addition, the molecules are polar (nitrogen, oxygen and chlorine bear partial negative charge, whereas H is partially positively charged). These properties are characteristic for molecular liquids.

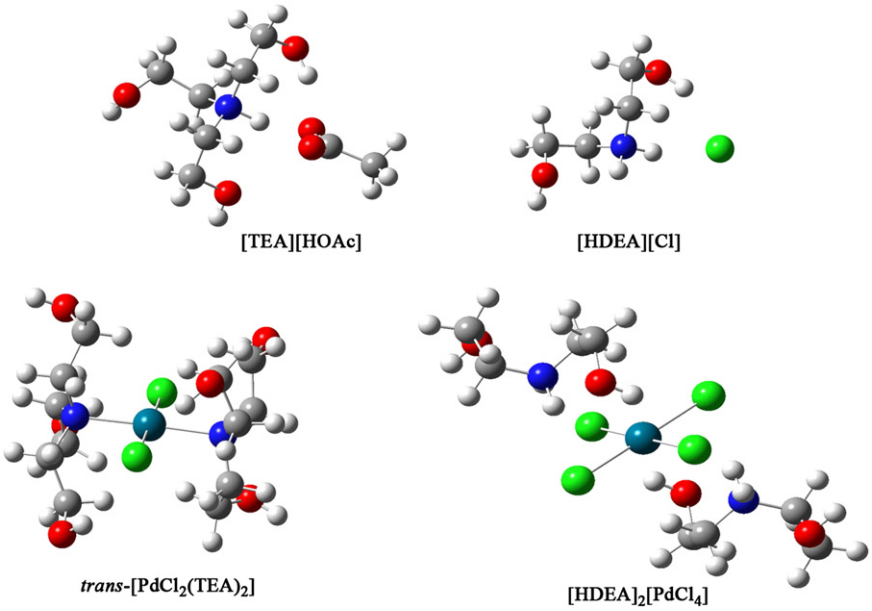

Fig. 1. The optimized structures of [TEA][HOAc] and [HDEA][Cl] ionic liquids, and of *trans*-$[PdCl_2(TEA)_2]$ and $[HDEA]_2[PdCl_4]$ complexes.

The *trans*-$[PdCl_2(TEA)_2]$ complex exhibits a square planar coordination. According to the NBO analysis, palladium is sp^2d hybridized, and builds covalent bonds with both nitrogens and both chlorines. The sp^3 orbitals of the Cl atoms and almost pure p orbitals of the N atoms participate with about 88% in the bonds around palladium. There is strong donation of density from each Pd – N bond to the adjacent σ* antibonding Pd – N orbital. As a consequence, the occupancies in the Pd – N orbitals are noticeable low (1.83).

The optimized structure of $[HDEA]_2[PdCl_4]$ complex is presented in Fig. 1. $[PdCl_4]^{2-}$ anion exhibits a square planar coordination, where the four chlorine anions lie in the equatorial plane, whereas the two protonated diethanolamine cations form hydrogen bonding with chlorido ligands. Cis- and trans-chlorido ligands form with palladium bond angles of 90° and 180°, respectively. The Pd – Cl bond length is equal to 2.38 Å, whereas the distances between chlorido ligands and hydrogens bonded to nitrogen lie in the range of 2.33–2.48 Å. The NBO analysis of the complex reveals covalent Pd – Cl bonds, with hybrid compositions of $0.41(sp^2d)Pd + 0.91(sp^3)Cl$. Lower occupancy in all σ Pd – Cl orbitals (1.90) is due to donation of density from each σ bonding orbital to the trans-σ* Pd – Cl antibonding orbital, in accord with the usual chemical picture of delocalized chemical systems.

In vitro antibacterial and antifungal activity of the ionic liquids, [TEA][HOAc] and [HDEA][Cl], and their corresponding Pd(II) complexes, *trans*-$[PdCl_2(TEA)_2$ and $[HDEA]_2[PdCl_4]$, were tested in relation to considerable number of microorganisms, including human pathogenic bacteria, probiotics, yeasts, molds, in order to evaluate broad-spectrum antimicrobial activity. The tested compounds showed low antimicrobial activity or no activity at tested concentrations (Tables 1 and 2). There was no significant difference in activity between corresponding complexes and its precursors. Detectable MIC values were in range from 15.6 μg/ml to 1000 μg/ml, while MMC were at 125 μg/ml and 1000 μg/ml. The most sensitive bacterium was probiotic *B. subtilis* IP 5832 in case of *trans*-$[PdCl_2(TEA)_2]$ and

Table 1
Antibacterial activity of [TEA][HOAc], [HDEA][Cl] and corresponding complex (μg/mL).

Species	*trans*-$[PdCl_2(TEA)_2]$		[TEA][HOAc]		$[HDEA]_2[PdCl_4]$		[HDEA][Cl]		Doxycicline	
	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC
Sarcina lutea ATCC 9341	>1000	>1000	1000	>1000	500	1000	500	1000	<0.448	7.81
Sarcina lutea	>1000	>1000	1000	>1000	500	1000	500	>1000	<0.448	3.75
Enterococcus faecalis ATCC 29212	>1000	>1000	1000	>1000	250	1000	250	>1000	7.81	62.5
Enterococcus faecalis	>1000	>1000	>1000	>1000	1000	1000	>1000	>1000	7.81	62.5
Bacillus subtilis ATCC 6633	1000	>1000	>1000	>1000	62.5	125	125	500	1.953	31.25
Bacillus subtilis	1000	>1000	>1000	>1000	250	1000	1000	>1000	0.112	1.95
Staphylococcus aureus ATCC 25923	>1000	>1000	>1000	>1000	62.5	>1000	250	>1000	0.224	3.75
Staphylococcus aureus	>1000	>1000	>1000	>1000	1000	1000	>1000	>1000	0.448	7.81
Escherichia coli ATCC 25922	>1000	>1000	>1000	>1000	1000	1000	>1000	>1000	15.625	31.25
Escherichia coli	>1000	>1000	>1000	>1000	1000	1000	>1000	>1000	7.81	15.63
Pseudomonas aeruginosa ATCC 27853	1000	>1000	>1000	>1000	500	1000	>1000	>1000	62.5	125
Pseudomonas aeruginosa	500	>1000	>1000	>1000	1000	1000	>1000	>1000	250	>250
Proteus mirabilis ATCC 12453	>1000	>1000	>1000	>1000	500	1000	>1000	>1000	15.625	62.5
Proteus mirabilis	>1000	>1000	>1000	>1000	1000	1000	>1000	>1000	250	>250
Salmonella enterica	>1000	>1000	>1000	>1000	1000	1000	>1000	>1000	15.625	31.25
Salmonella typhymurium	>1000	>1000	>1000	>1000	1000	1000	>1000	>1000	15.625	125
Lactobacillus rhamnosus	1000	>1000	500	>1000	N.T.	N.T.	N.T.	N.T.	7.81	31.25
Lactobacillus plantarum	>1000	>1000	>1000	>1000	500	>1000	1000	>1000	0.448	7.81
Bifidobacterium animalis subsp. lactis	>1000	>1000	>1000	>1000	N.T.	N.T.	N.T.	N.T.	31.25	62.5
Bacillus subtilis IP 5832	125	>1000	>1000	>1000	250	>1000	500	>1000	1.95	15.63

N.T. — not tested.

Table 2
Antifungal activity of [TEA][HOAc], [HDEA][Cl] and corresponding complex (μg/mL).

Species	*trans*-$[PdCl_2(TEA)_2]$		[TEA][HOAc]		$[HDEA]_2[PdCl_4]$		[HDEA][Cl]		Fluconazole	
	MIC	MFC	MIC	MFC	MIC	MFC	MIC	MFC	MIC	MFC
Candida albicans ATCC 10231	>1000	>1000	>1000	>1000	>1000	>1000	1000	>1000	31.25	1000
Candida albicans	>1000	>1000	>1000	>1000	>1000	>1000	1000	>1000	62.5	1000
Rhodotorula sp.	1000	1000	1000	1000	>1000	>1000	500	1000	62.5	1000
Saccharomyces boulardii	1000	>1000	>1000	>1000	>1000	>1000	1000	>1000	31.25	1000
Aspergillus niger ATCC 16404	1000	>1000	500	>1000	125	250	>1000	>1000	62.5	62.5
Aspergillus niger	1000	>1000	250	500	125	250	>1000	>1000	500	1000
Aspergillus restrictus	>1000	>1000	1000	1000	62.5	125	>1000	>1000	500	1000
Aspergillus fumigatus	>1000	>1000	500	1000	15.6	15.6	>1000	>1000	500	1000
Aspergillus flavus	1000	>1000	500	500	1000	1000	>1000	>1000	1000	1000

B. subtilis ATCC 6633, *S. aureus* ATCC 25923 in case of $[PdCl_4(DEAH)_2]$. It is known that certain bacteria can utilize ethanolamines as source of carbon and/or nitrogen. This process, encoded by genes located together on the chromosome in the *e*thanolamine *u*tilization operon (*eut*), is characteristic for species of *Salmonella*, *Enterococcus*, *Klebsiella*, *Mycobacterium*, *Pseudomonas, Escherichia* [50]. This could be explaining the low antibacterial activity of tested compounds. Antifungal activity was better against molds than yeasts. *C. albicans*, clinical and standard strain, was resistant. Better results were for *Aspergillus* species, MIC values were between 15.6 and 1000 μg/ml. [TEA][HOAc] exhibited better activity than corresponding complex with MIC values from 250 μg/ml to 1000 μg/ml. Sensitivity of *Aspergillus* species were increased especially to $[HDEA]_2[PdCl_4]$. The activity of $[HDEA]_2[PdCl_4]$ against *A. restrictus*, *A. fumigatus* was up to ten times higher than the activity of positive control, fluconazole.

4. Conclusion

The structures of ionic liquids [TEA][HOAc] and [HDEA][Cl], and of complexes *trans*-$[PdCl_2(TEA)_2]$ and $[HDEA][PdCl_4]$ are investigated using DFT method. These compounds were tested for their *in vitro* antibacterial and antifungal activity. It was shown that complexes and their precursors showed low antimicrobial activity. Antibacterial activity was recorded against certain G^+ bacteria (*S. lutea*, *E. faecalis*, *B. subtilis*), probiotics (*L. rhamnosus*, *B. subtilis* IP 5832) and strains of *P. aeruginosa*. Antifungal activity was better against molds than yeasts. *Aspergillus* species were affected by tested compounds while *C. albicans*, clinical and standard strain, was resistant. The ionic liquid [TEA][HOAc], and especially complex $[HDEA][PdCl_4]$, with their high activity against *Aspergillus* species, can be considered as agents with potential antifungal activity, and therefore candidates for further stages of screening *in vitro* and/or *in vivo*.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.molliq.2012.03.009.

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