Antibacterial Activity of Polyoxometalates Against Moraxella catarrhalis

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The antibacterial activity of 29 different polyoxometalates (POMs) against Moraxella catarrhalis was investigated by determination of the minimum inhibitory concentration (MIC). The Preyssler type polyoxotungstate (POT) [NaP₉W₃O₁₁₀]¹⁴⁻ demonstrates the highest activity against M. catarrhalis (MIC = 1 μg/ml) among all tested POMs. Moreover, we show that the Dawson type based anions, [P₂W₁₈O₆₂]⁶⁻, ([P₂O₇]Mo₁₈O₅₄)¹⁴⁻, [As₂Mo₁₈O₆₂]⁶⁻, [H₅P₂W₁₁₅V₂O₆₂]⁶⁻, and [AsW₁₈O₆₀]⁷⁻ are selective on M. catarrhalis (MIC range of 2-8 μg/ml). Among the six tested Keggin type based POTs ([PW₁₂O₄₀]³⁻, [H₂PCoW₁₁O₄₀]⁵⁻, [H₂CoTiW₁₁O₄₀]⁶⁻, [SiW₁₀O₃₆]⁸⁻, [SbW₉O₃₃]⁹⁻, [AsW₉O₃₃]⁹⁻), only the mono-substituted [H₂CoTiW₁₁O₄₀]⁶⁻ showed MIC value comparable to those of the Dawson type group. Polyoxovanadates (POVs) and Anderson type POMs were inactive against M. catarrhalis within the tested concentration range (1-256 μg/ml). Four Dawson type POMs [P₂W₁₈O₆₂]⁶⁻, ([P₂O₇]Mo₁₈O₅₄)¹⁴⁻, [As₂Mo₁₈O₆₂]⁶⁻, [H₅P₂W₁₅V₂O₆₂]⁶⁻ and the Preyssler POT [NaP₉W₃O₁₁₀]¹⁴⁻ showed promising antibacterial activity against M. catarrhalis (MICs < 8 μg/ml) and were therefore tested against three additional bacteria, namely S. aureus, E. faecalis, and E. coli. The most potent antibacterial agent was [NaP₉W₃O₁₁₀]¹⁴⁻, exhibiting the lowest MIC values of 16 μg/ml against S. aureus and 8 μg/ml against E. faecalis. The three most active compounds ([NaP₉W₃O₁₁₀]¹⁴⁻, [P₂W₁₈O₆₂]⁶⁻, and [H₅P₂W₁₅V₂O₆₂]⁶⁻) show bacteriostatic effects in killing kinetics study against M. catarrhalis. We demonstrate, that POM activity is mainly depending on composition, shape, and size, but in the case of medium-size POTs (charge is more than −12 and number of addenda atoms is not being higher than 22) its activity correlates with the total net charge.

Keywords: bioactive polyoxometalates, metal-oxo clusters, Preyssler archetype, Dawson archetype, minimum inhibitory concentration, time-killing analysis, Gram-negative pathogen

INTRODUCTION

Moraxella catarrhalis is a Gram-negative human mucosal pathogen which causes middle ear infections in infants and children and lower respiratory tract infections in adults with chronic pulmonary disease (Karalus and Campagnari, 2000). M. catarrhalis is one of the three major causes of otitis media along with Streptococcus pneumoniae and Haemophilus influenzae.
Based on culture isolation and serological studies, *M. catarrhalis* has been implicated as a cause of sinusitis in both children and adults. In addition, *M. catarrhalis* occasionally causes severe infections such as septic arthritis, bacteremia, cellulitis, osteomyelitis, endocarditis, and pericarditis (Karalus and Campagnani, 2000). The fact that *M. catarrhalis* was not considered as an important human pathogen until recently has contributed to the limited research aimed to find vaccines for prevention or selective antibiotics for the treatment of respiratory tract infections (Karalus and Campagnani, 2000).

Excessive or improper use of antibiotics led to the development of antibacterial resistance worldwide during the last few decades, suggesting the incidence of these infections may continue to rise. Thus, new active classes of antibiotics are urgently needed for the most common community-acquired respiratory pathogens with emerging antimicrobial resistance. Along with new organic compounds, metal oxides have attracted significant interest over the past decade as they offer alternative modes of antimicrobial action (Dizaj et al., 2014). A particularly attractive sub-class of metal oxides is metal oxide anions, the so-called polyoxometalates (POMs) (Pope, 1983). POMs comprise an array of corner- and edge-sharing pseudo-octahedrally coordinated MO₆ (M most often V, Nb, Mo, W) units that form an ionic core and are amenable to a variety of chemical transformations (Figure 1). Alongside with applications of POMs in catalysis (Wang and Yang, 2015), nanotechnology (Yamase and Pope, 2006), electrochemistry (Sadakane and Steckhan, 1998), material sciences (Proust et al., 2008), and molecular magnetism (Clemente-Juan et al., 2012), POMs have also been proven to exhibit remarkable biological activity. Due to the highly negative charge, strong acidity, geometry, their use in macromolecular crystallography (Bijelic and Rompel, 2015, 2017; Molitor et al., 2017) and as antimicrobial (Yamase, 2005; Li et al., 2016; Bijelic et al., 2018), antiviral (Judd et al., 2001), antitumor (Fu et al., 2015), antidiabetes (Nomiya et al., 2001), and antiamyloid-fibril agents (related to Alzheimer’s disease) (Gao et al., 2014) has been reported so far and more attention should be given to the biological and therapeutic effect of POMs.

Polyoxotungstates (POTs), polyoxomolybdates (POMos) and polyoxovanadates (POVs) of different structural types have been shown to exhibit synergy with some conventional antibiotics (Yamase et al., 1996; Tajima, 2001) or direct antibacterial activity (Inoue et al., 2005; Bae et al., 2008) against both Gram-negative and Gram-positive bacteria. In general POTs, especially decavanadate, and large, highly negatively charged POMs exhibit a high activity, whereas for example the activity of Keggin type POMs is bacterial strain dependent (Bijelic et al., 2018).

Thus, in this paper, we determined the antibacterial activity of 18 POTs, seven POMos and four POVs. Mainly we focused on two the most common Keggin and Dawson archetypes with different type of addenda atom and number of lacunas. A few examples of isopolytungstates, -molybdates, and -vanadates, as well as Anderson type anions together with larger Preyssler POT were added to the tested group in order to estimate effect of size and charge of anions. The minimum inhibitory concentration (MIC) against *M. catarrhalis* for each POM was determined. The five most active compounds based on Dawson and Preyssler archetypes with MIC < 8 μg/ml were also tested on two Gram-positive organisms *Staphylococcus aureus* and *Enterococcus faecalis* and the Gram-negative bacterium *Escherichia coli*. In addition, time-kill assays were performed against *M. catarrhalis* to study the pharmacodynamics of the POMs of Preyssler and Dawson type with MIC = 1–2 μg/ml by examining the rate of bactericidal activity at varying POM concentrations over time.

### MATERIALS AND METHODS

#### Materials

The Preyssler POT (Figure 1A) (NH₄)₁₄[NaP₅W₅O₁₁₀]·30H₂O (Jeannin et al., 2007); heteropolyoxometalates with Dawson...
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**RESULTS AND DISCUSSION**

**Antibacterial Activity of Preyssler and Dawson Type POTS and POMos**

The antibacterial activity of the 29 POMs against the Gram-negative *M. catarrhalis* was evaluated by means of MIC (Table 1). The highest activity with a MIC range of 1-8 µg/mL was observed for POMs with Preyssler type (Figure 1A) and Dawson (Figure 1B) structure.

Moreover, the most active POM on *M. catarrhalis*, namely the Preyssler anion $\text{P}_{5}\text{W}_{10}^{6-}$ (Figure 1A) (MIC = 1 µg/mL), was additionally tested on the Gram-positive organisms *S. aureus* and *E. faecalis* and the Gram-negative *E. coli*, which are major human pathogens that cause a wide range of clinical infections (Table 2). $\text{P}_{5}\text{W}_{10}^{14-}$ exhibited good activity against *S. aureus* with MIC = 16 µg/mL and *E. faecalis* with MIC = 8 µg/mL, which is the same as for the clinically applied drug azithromycin (Lode et al., 1996), however, it performed inactive against the Gram-negative *E. coli*. The chitosan-$\text{P}_{5}\text{W}_{30}$ nanoscaffold has already demonstrated high anticancer activity, which is considered to arise due to high number of phosphorous and tungsten atoms (Shah et al., 2014). Remarkably, the Se-containing lacunary anion $\text{Se}_{2}\text{W}_{29}^{14-}$, which is of comparable size and equally charged, exhibited significantly lower MICs (64 µg/mL). This indicates the importance and the influence of the structure, shape, and composition for the antibacterial activity, justifying more detailed studies to elucidate the structure-activity relationship.

Except for $\text{P}_{2}\text{Mo}_{18}^{6-}$, $\text{S}_{2}\text{Mo}_{18}^{4-}$, and $\text{As}_{2}\text{W}_{18}^{6-}$, all Dawson type POMs (Figure 1B) tested in this study exhibited potential antibacterial activity exhibiting a MIC within the range of 2–8 µg/mL. Among the Dawson type group, $\text{P}_{2}\text{W}_{18}^{14-}$ and its
triple-protonated equally charged vanadium-substituted analog $P_2W_{15}V_6^{5−}$ (Figure 1B) have proven to be the most promising with a MIC of 2 μg/ml suggesting that VO$_6$ sites in Dawson type mixed polyoxovanadatotungstates (POVTs) lattice do not have any significant impact on the antibacterial activity, which was observed earlier for Keggin POVTs as they were remarkably more active against *S. pneumoniae* than their corresponding POTS (Fukuda and Yamase, 1997). In the Dawson pair $P_2W_{15}V_6^{5−}$ (MIC = 2 μg/ml) and $P_2Mo_{18}^{5−}$ (MIC > 256 μg/ml), the POMo is considered as inactive, whereas for $As_3W_{18}^{5−}$ (MIC > 256 μg/ml) and $As_3Mo_{18}^{5−}$ (MIC = 4 μg/ml) the opposite effect is observed. Dawson related compounds, namely $AsW_{18}^{7−}$ (Figure 2C), with
Jeannin and Martin-Frere, (1979), and P₂O₅Mo₆⁶⁻ (Figure 2B), which has a pyrophosphate anion enclosed (Kortz and Pope, 1994), demonstrated higher activity against bacteria (MIC values are 8 and 4 µg/ml, respectively) than classical As₂W₆⁶⁻ and P₂Mo₆¹⁸⁻ (Figure 2A). The presence of highly bioactive and toxic arsenic trioxide in the first case should play a significant role, but difference in the coordination of the heteroatoms in both cases leads to a change of the “ruby-ball-shaped” (Figure 2A) Dawson structure to a “hour-glass” shaped anion (Figures 2B,C), which also may be related to discrepancies in antibacterial activity. These anomalies in the activity of isostuctural POTS and POMos indicate that both the hetero- and addenda atoms play a significant role in the bioactivity and that the appropriate combination of these atoms must be decisive for the antibacterial activity.

The superiority of the Dawson structure among four different structural groups of polynuclear molybdates in the inhibition of a tartrate-resistant acid phosphatase (ACP) from Leishmania donovani and the tartrate-sensitive ACP from human seminal fluid (prostatic ACP) has been reported previously (Saha et al., 1991). As₂Mo₆⁶⁻ was the most potent inhibitor and exhibited the highest degree of selectivity against both ACPs. Here, As₂Mo₆¹⁸⁻ is proved to be a potent antibacterial agent with the third lowest MIC value of 4 µg/ml against M. catarrhalis.

### Antibacterial Activity of Keggin- and Anderson Based Type POTS

Keggin type POTS are known to exhibit antibacterial activities, for example, by increasing the susceptibility of certain bacteria strains toward beta-lactam antibiotics (Yamase et al., 1996). In this study the strongest activity was shown for the Keggin based CoTiW⁸⁻ (Figure 1D) exhibiting a MIC value of 16 µg/ml. Interestingly, despite consisting of the same isomer of Keggin unit, the classical PW¹₂⁻ (Figure 1C) and the two mono-substituted PCoW⁵⁻ and CoTiW⁶⁻ (Figure 1D) showed completely different activities. The most negatively charged CoTiW⁶⁻ is the most active compound; however, the charge dependency is not observed in the case of the other two Keggin anions-PW¹₂⁻ with a total charge of -3 exhibited a MIC of 128 µg/ml and PCoW⁵⁻ with a total charge of -5 exhibited a value >256 µg/ml. Thus, we assume a decisive role for the accessible TiO₆ unit in CoTiW⁸⁻ (Figure 1D) in the activity against M. catarrhalis. CoTiW⁸⁻ was previously also shown as the most potent NTPDase inhibitor among six different POTS, (Müller et al., 2006).

The dilacunary SiW⁸⁻ (Figure 1E) showed much higher activity than the trilacunary anions SbW⁹⁻ and AsW⁹⁻ (Figure 1F; 32 µg/ml for SiW⁸⁻ against >256 µg/ml for SbW⁹⁻ and AsW⁹⁻). Nevertheless, the Keggin and Dawson P₂W¹₁⁸⁻ lacunary anions did not meet the expectation that more negatively charged compounds exhibit higher antibacterial activity.

The inorganic and organically functionalized Anderson type POTS and POMos (Figure 11) are inactive against M. catarrhalis (Table 1). The inactivity of this type of POM was previously observed for Helicobacter pylori, which as well as M. catarrhalis is most sensitive to larger POMs (Yamase et al., 1996). It is tempting to speculate that the combination of compact size and small charge of Anderson type anion (Blazevic and Rompel, 2016) is the reason of its antibacterial inactivity.

### Antibacterial Activity of Isopolymetalates

Among the investigated isopolymetalions only two POTS (W¹⁺⁻ (Figure 1H) and W¹⁺⁻) and octamolybdate Mo₈⁶⁻ (Figure 1G) showed a MIC value >256 µg/ml. It should be noted, that decavanadate tested in this study (V⁵⁻) did not show antibacterial activity (MIC >256 µg/ml), which confirms the selective activity of the most common vanadates V⁵⁻ and V⁴⁻ against Streptococcus pneumoniae with MIC values in the range of 4–32 µg/ml (positive control with conventional antibiotics: 2–32 µg/ml; Fukuda and Yamase, 1997). We also included tetranuclear vanadium tartrates (V⁴⁻L-tart⁴⁻ and V⁴⁻D-tart⁴⁻) in our study as they, similarly to V⁵⁻, are one of the few vanadate species with proved stability and hydrolytic immunity in aqueous solutions over time (Schwendt et al., 2007). However, both POVs were inactive toward M. catarrhalis.

### The Relationship Between the Composition of POMs and Its Activity Against M. catarrhalis

By analyzing the data in Table 1, it becomes clear that POMs despite having the same or very close charge and size can demonstrate absolutely different activities (e.g. compare Dawson-based P₂W⁶⁻ and P₂Mo₆¹⁸⁻ or Keggin-based PCoW¹₁⁻ and CoTiW⁸⁻). As already noted above, there are at least three factors affecting the antibacterial activity: size, charge, chemical composition, and their combination. In order to understand the structure-activity-relationship (SAR) we minimized the influence of one of these factors and compared the main characteristics for phosphorus-containing Keggin PW¹₂⁻ (Figure 1C), Dawson P₂W⁶⁻ (Figure 1B), and Preyssler P₃W¹₃⁻ (Figure 1A) POTS (Table 2). Leastways for these fully saturated (not lacunary) POTS with the same heteroatom PW¹₂⁻, P₂W⁶⁻, and P₃W¹₃⁻ there is a clear dependence in the increase in antibacterial activity with an

| TABLE 2 | Minimum inhibitory concentration (MIC) of Dawson and Preyssler type POMs against the M. catarrhalis strains. |
| --- | --- |
| Compound | S. aureus | E. faecalis | E. coli |
| | (ATCC 29213) | (ATCC29212) | (ECM1556) |
| PREYSSLER ANION |  |  |  |
| P₃W¹₃⁻ | 16 | 8 | >256 |
| DAWSON-BASED ANIONS |  |  |  |
| P₂O₂Mo₆¹⁸⁻ | >256 | >256 | >256 |
| As₂Mo₆¹⁸⁻ | 256 | >256 | >256 |
| P₂W₁₀V⁶⁻ | >256 | >256 | >256 |
| AsW₁₈⁻ | >256 | >256 | >256 |
| Azithromycin (positive control)* | 1 | 8 | 0.25 |

*MCIs for azithromycin were obtained in this study.

Antibacterial Activity of Isopolymetalates Against Moraxella catarrhalis strains.
FIGURE 2 | Ball and stick representation of (A) classical Dawson type anion $P_2Mo_{6}^{6-}$ (Briand et al., 2002); (B) anion in $P_2O_7Mo_{18}^{18-}$ (Kortz and Pope, 1994); (C) anion in $AsW_{7}^{7-}$ (Jeannin and Martin-Frere, 1979). Color code: addenda atom Mo (B) or W (C), dark blue spheres; heteroatom P (B) or As (C), yellow spheres; O, red spheres.

TABLE 3 | Dimension and redox characteristics for phosphorus-containing Keggin, Dawson, and Preyssler POTs.

| POT               | Charge number ($z$) | Volume/10$^{-22}$ cm$^3$** | Volume charge density/cm$^{-3}$** | $z/m$* | Reduction potential, V** | MIC, µg/ml |
|-------------------|---------------------|-----------------------------|-----------------------------------|--------|--------------------------|------------|
| $P_2W_{14}^{12-}$ (Preyssler) | −14 | 18.48 | 1,213 | 0.47 | −0.43 | 1 |
| $P_2W_{15}^{16-}$ (Dawson) | −6 | 9.995 | 961.8 | 0.33 | +0.06 | 2 |
| $PW_{3}^{3-}$ (Keggin) | −3 | 6.234 | 771.0 | 0.25 | −0.023 | 128 |

*m-number of addenda atoms.
**were taken from López et al. (2006).

increase in charge and size and no correlation with respect to the redox potential.

No simple SAR was found for all tested POMs, however, narrowing the data set only to the largest tested group, namely POTs with a charge $< −12$ and with a number of addenda atoms not being higher than 22 it became possible to correlate the antibacterial activity and the charge of the POT (Figure 3). The presented dependence may indicate for medium-sized POTs (but not for POTs with number of addenda atoms more than 22) a stronger effect against *M. catarrhalis* of anions exhibiting a charge of $−8$ to $−6$.

Cells of *M. catarrhalis* have on their surface low molecular weight lipopolysaccharides (LPS), also called lipoooligosaccharides (LOS), which contribute to the increased hydrophobicity of its outer membrane and to the high susceptibility to hydrophobic antimicrobial agents such as macrolides (Gotoh et al., 1989; Tsujimoto et al., 1999). However, *M. catarrhalis* shows susceptibility not only to hydrophobic agents, but also to hydrophilic agents such as β-lactam antibiotics (Gotoh et al., 1992). The increased susceptibility of these strains toward β-lactams is probably due to the higher permeability of the outer membrane toward these agents. POMs, as examples of super chaotropic anions, can adsorb onto lipid monolayers via electrostatic and/or hydrophobic interaction depending on the charge of the lipid layer (Kobayashi et al., 2017). The model experiments with three differently charged Keggin anions show that dominant interaction equally depends both on the charge density of POMs and on the lipid density (Kobayashi et al., 2017).

**Time-Killing Studies**

In order to assess whether the tested compounds kill the bacteria (bactericidal effect) or prevent its growth (bacteriostatic effect), time-kill study was performed. Killing kinetics for three the most active compounds: Preyssler $P_5W_{30}^{30-}$ (Figure 1A) and two Dawson $P_2W_{16}^{6-}$ and $P_2W_{15}V_6^{6-}$ (Figure 1B) POTs were
determined against *M. catarrhalis*. POTs were tested at three concentrations, corresponding to 1×, 5×, and 10×MIC. The bacteriocidal activity of the agents was defined for at least a 3 log₁₀ reduction in viable colony counts. In the control (sample without antibiotic), the numbers of the viable strain were kept within the cultivation of 24 h relative to those at 0 h. Figure 4 represents time-killing curves for compounds P₂W₁₅⁻, P₂W₁₈V₆⁻, and P₂O₇Mo₄⁻₁₈⁻. All tested POMs show bacteriostatic effects, resulting from a little change in viable colony numbers within 24 h despite the concentration being equal to 10-fold MIC (Figure 4). Although it would seem preferable for an antibiotic to kill the offending bacteria rather than to merely inhibit it, the clinical importance of an *in vitro* bactericidal action being better than a bacteriostatic action has rarely been documented. The superiority of bactericidal over bacteriostatic action in the treatment of gram-positive bacterial infections is intuitive rather than based on rigorous scientific research (Pankey and Sabath, 2004).

**CONCLUSIONS**

An important investigation in exploring biological effects of POMs was performed. The antibacterial activity of 29 POTs, POMs, and POVs against *M. catarrhalis* was investigated by determination of their minimum inhibitory concentrations (MIC) and time-killing kinetics. The following important conclusions were drawn:

1) According to their MIC values, Preyssler P₂W₁₅⁻ (Figure 1A) and five Dawson-based P₂W₁₈⁻, P₂W₁₈V₆⁻, P₂O₂Mo₁₈⁻, As₂Mo₁₈⁻, AsW₇⁻ (Figures 1B, 2) POMs are promising antibacterial agents against *M. catarrhalis*.

2) The Preyssler type POT P₂W₁₅⁻ (Figure 1A) showed the highest antibacterial activity against *M. catarrhalis* (MIC = 1 µg/ml) and further MIC investigation against *S. aureus* and *E. faecalis* proved its antibacterial potential.

3) Based on MIC values, Dawson-type POMs (see Figure 1B) exhibited highest activity and selectivity against *M. catarrhalis*.

4) Among Keggin-type POMs (see Figures 1C-E), only the mono-substituted CoTiW⁶⁻¹₁⁻ (Figure 1D) showed MIC comparable to that of the Dawson-type group.

5) POVs and Anderson type POMs (Figure 1I) were inactive (MIC > 256 µg/ml) against *M. catarrhalis* strain.

6) According to time-killing studies three the most active POTs (Preyssler P₂W₁₅⁻ and Dawson P₂W₁₈⁻...
and $P_2W_{15}V_{13}^{4-}$ showed bacteriostatic effect against *M. catarrhalis*.

7) POM activity mainly depends on composition, shape and size, but in the case of medium-size POTs correlates with the total net charge.

### AUTHOR CONTRIBUTIONS

NG and AR contributed toward the study design, wrote the manuscript. NG, EA-S, and LK synthesized and characterized POMs. HC-P and DV performed all antibacterial study. All authors read and approved the final version of the manuscript.

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