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POLYOXOMETALATES: INTRODUCTION TO A CLASS OF INORGANIC COMPOUNDS AND THEIR BIOMEDICAL APPLICATIONS

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1. ABSTRACT

An increasing number of potential applications for polyoxometalates in human medicine have been reported in the literature. These inorganic complexes are composed of early transition metals (mainly molybdenum, tungsten and vanadium) and oxygen. The present review gives an introduction into the chemistry of these compounds, and an overview of the principal studies of their biological and biochemical effects and their therapeutic potential. The reported antitumoral and antibiotic properties of molybdates and tungstates *in vitro* and *in vivo* are compiled and discussed, as are their influences on the blood glucose level in diabetic animals. Aspects of antiviral activities and cell penetration are treated.

2. INTRODUCTION

Polyoxometalates (POMs) are a class of inorganic compounds which have fascinated chemists for almost two centuries. Indeed, the so called "molybdenum blues" were described by Berzelius as early as 1826, but only the last decades have witnessed the systematic synthesis and characterization of this ever growing family of compounds. (1) Polyoxometalates are negatively charged aggregates of transition metals (mainly Vanadium, Molybdenum and Tungsten) with oxygen. More precisely, they are typically composed of metal ions in their highest oxidation state bridged by oxo ligands (O^{2-}). Almost any other element can be incorporated into the POM framework, and this leads to a overwhelming diversity of structures and properties. (2-5) It is therefore not surprising that POMs have attracted interest from a variety of disciplines, and nowadays applications in the fields of chemical analysis, catalysis, material science, nuclear waste treatment and medicine are developped. (6, 7) The last point might appear surprising, as inorganic pharmaceuticals are still rare compared to the far more common organic compounds. (8) The aim of this review is therefore to introduce the field of POMs to researchers outside the (inorganic) chemist community and to survey some of the biomedical studies that have appeared today. We are convinced that a closer exchange between chemists and biologists will boost the developement of biomedical applications of POMs, giving rise to new possibilities in molecular biology and in diagnosis and therapy of diseases. Excellent reviews have been published on biological and medical applications of POMs. (9, 10) As each author emphasizes different aspects, the interested reader should refer also to those publications.

2.1. Structure drawings

POMs contain a fairly large number of atoms in a relatively compact, three-dimensional structure. The representation of all bonds of every atom is therefore very crowded and not always informative. Instead, chemists have adopted the polyhedral representation where each metal ion is in the center of a polyhedron with its ligands on the vertices. For instance, a hexacoordinated metal is represented by an octahedron and a tetracoordinated metal by a tetrahedron. In condensed structures with bridging ligands, the polyhedra share vertices and edges, or more rarely faces. Figure 1 gives an example for the representations of *alpha*-$[Mo_8O_{26}]^{4-}$.

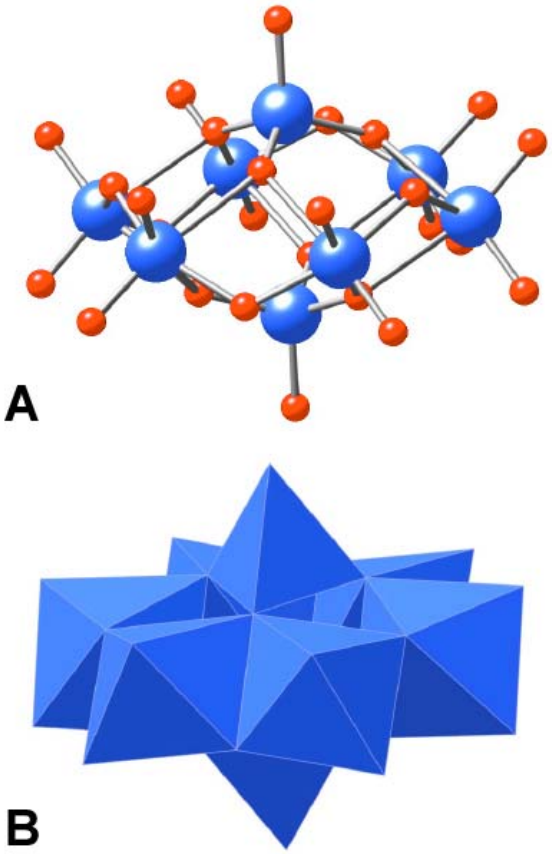

Figure 1. Structure drawings of *alpha*-$[Mo_8O_{26}]^{4-}$. a) Ball-and-Stick representation. b) Polyhedral representation.

3. OVERVIEW OF POLYOXOMETALATES

3.1. Synthesis

In aqueous solution, transition metal cations are coordinated by aqua (H_2O), hydroxo (OH^-) and oxo (O^{2-}) ligands. The acidity of a coordinated ligand parallels the charge of the metal cation. The higher the positive charge of the metal, the easier the protons on the ligand dissociate. Therefore, the highly charged cations of fully oxidized metals of groups 5 and 6 (e.g. vanadium(V), molybdenum(VI), tungsten(VI)) form stable complexes with oxo ligands in aqueous alkaline solutions (VO_4^{3-}, MoO_4^{2-}, WO_4^{2-}). On acidification, a condensation reaction takes place, which yields M-O-M bridges (for details see inorganic textbooks (11-13)). This process can be repeated.

Furthermore, an expansion of the coordination number (i.e. the number of attached atoms to a given metal ion) occurs, and condensed structures result. (14) The precise nature of the POM thus formed depends on the boundary conditions, i. e. stoichiometry, solvent, pH, temperature, concentration, counterions, and many different compounds can be created by systematic variation of these factors. In addition, the formation of coordination bonds is reversible. As a consequence, the oxo bridges in POMs can be cleaved by the addition of base, and many more compounds are obtained by controlled degradation. These products are called lacunary POMs as opposed to plenary or saturated POMs. The derivatization of preformed POMs is now fairly well understood and rational syntheses of regiospecifically substituted Keggin and Dawson structures (see figure 2 below) have been developped. (15-17) In other respect, the linking of preorganized and transferable building blocks has afforded extremely large POMs. (18)

3.2. Classification

One can divide the family of POMs in several groups depending on their composition and structure. (2, 11, 12, 19) For the purpose of this review, it is sufficient to note the following classes. POMs of the general formula $[M_mO_y]^{n-}$ containing only a transition metal and oxygen are called isopolyoxometalates. Compounds including a small number of additional elements $[X_xM_mO_y]^{n-}$ (X = heteroelement, x smaller than m) belong to the sub-class of heteropolyoxometalates.

3.3. Common structures of iso- and heteropolyoxometalates

Among the different structures known for POMs, some are more common and are shown in Figure 2. The Lindqvist structure is adopted by hexametalates of the formula $[M_6O_{19}]^{n-}$. It consists of an octahedral arrangement of six octahedra. Each octahedron (which represents a metal ion with its coordination sphere, as explained above) is sharing four edges with four neighboring octahedra. This is a very compact arrangement, and the Lindqvist structure can indeed be seen as a fragment of a cubic closed packed metal oxide.

The structures in Figure 2b and c exemplify the structural diversity of compounds with the same general formula $[M_7O_{24}]^{n-}$. The bent structure in Figure 2b is adopted by the isopolymolybdate $[Mo_7O_{24}]^{6-}$, the so called paramolybdate. Heteropolyoxometalates $[XM_6O_{24}]^{n-}$ present the Anderson structure depicted in Figure 2c. Six edge-sharing octahedra are arranged into a planar hexagon around the central heteroatom. In this case, X is octahedrally coordinated. The most common structure with tetrahedrally coordinated heteroatoms is the Keggin ion of general formula $[XM_{12}O_{40}]^{n-}$ (Fig. 2d). Four trimetallic groups are arranged around a central tetrahedron. Finally, the Dawson structure of $[X_2M_{18}O_{62}]^{n-}$ (Fig. 2e) can be formally considered as the combination of the fragments of two Keggin ions. A trimetallic group is withdrawn on each Keggin ion, and the remaining fragments are associated.

As mentioned above, lacunary structures are obtained by the selective removal of one or more metal ions by addition of base. They present open coordination sites which can be occupied by other metal or non-metal atoms. This strategy is commonly used to modify the structure and properties of POMs.

3.4. Functionalized POMs

Although it is now a common practice to refer to functionalized POMs, there does not seem to be a general agreement on the scope of this expression which will be used here in the brodest sense. One can recognize four sub-classes of functionalized POMs. i) *Metal derivatives of lacunary POMs* can be properly viewed as functionalized

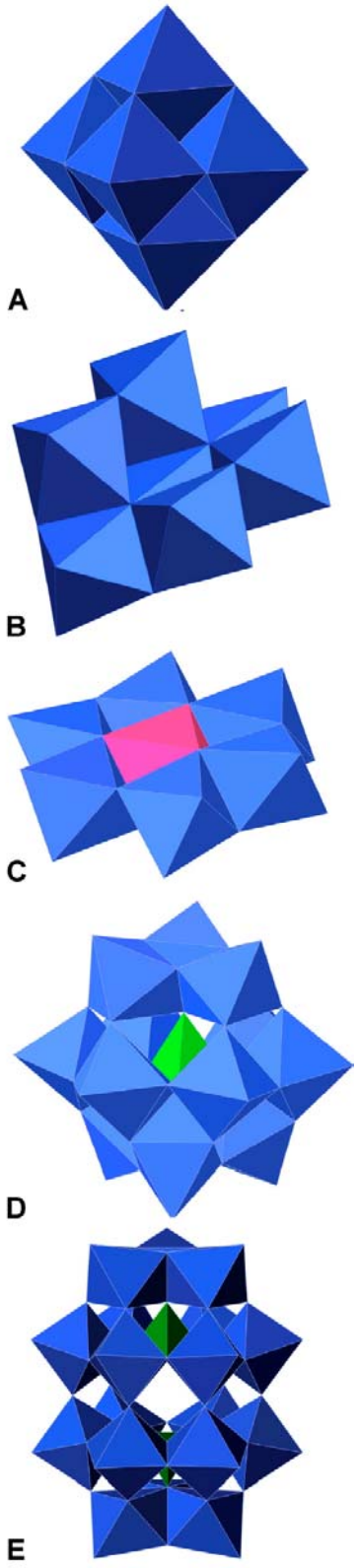

Figure 2. Polyhedral representations of some common polyoxometalate structures. a) $[M_6O_{19}]^{n-}$ (Lindqvist-structure), b) $[Mo_7O_{24}]^{6-}$, c) $[XM_6O_{24}]^{n-}$ (Anderson-structure), d) $[XM_{12}O_{40}]^{n-}$ (Keggin-structure), e) $[X_2M_{18}O_{62}]^{n-}$ (Dawson-structure).

POMs. Indeed several transition metal derivatives are catalytically active for epoxidations with various oxidants. (20) In other respect, derivatives such as $[PW_{11}O_{39}RhCH_2CO_2H]^{5-}$ (21) or [*alpha*$_2$-$P_2W_{17}O_{61}Sn(CH_2)_2CO_2H]^{7-}$ (22) cary a terminal functional group which can be further derivatized. ii) A sizable number of *organic derivatives of POMs* have been reported. Among others, these include alkoxo, organosilyl and organophosphoryl derivatives. (23) Alkoxo derivatives have been obtained by a variety of methods including O-alkylation and esterification of POMs, and self-assembly reactions. (24) Organosilyl and organophosphoryl derivatives have been obtained by reacting organochlorosilanes and organophosphonic acids, respectively, on lacunary POMs. (25, 26) Moreover a number of organophosphoryl and organoarsonyl derivatives have also been obtained by self-assembly reactions. (23, 27) iii) POMs where some terminal oxo ligands have been replaced by other *multiply-bonded ligands* form a third sub-class of derivatives. These compounds have been obtained via Wittig-like net [2+2] reactions of Mo=O bonds or by self-assembly reactions, including reductive nitrosylation and related reactions. (23, 28) iv) *Organometallic derivatives of POMs* are a sub-class of organometallic oxides. (29) Derivatization of POMs is of interest as it can lead to the immobilization of catalytically active POMs and might facilitate the recognition of biological targets.

4. BIOLOGICAL AND MEDICAL ACTIVITIES

4.1. Antiviral activities

In 1970, a group in Paris around Chermann noticed an inhibitory effect of "silicotungstic acid supernatants (STAS)", a cell culture supernatant obtained in a procedure where silicotungstic acid was employed. (30, 31) They subsequently recognized that the inhibitor was the silicotungstate ion, (32) and this led to a systematic study of the antiviral activities of this and other polyanions.(33-38) A particular effective compound was the tungstoantimonate $(NH_4)_{19}[Sb_9W_{21}O_{86}]$ (HPA-23). (39-45)

The advent of AIDS has increased the search for antiviral agents, and encouraged many studies also with polyoxometalates. In particular the groups of Hill and Yamase are very active in this area. This work is beyond the scope of this paper, and the interested reader should refer to the pertinent literature. (10, 45-50)

4.2. Antitumoral activities

4.2.1. Polyoxomolybdates

Yamase and his coworkers recognized the antitumor activities of Anderson-type polyoxomolybdates and of heptamolybdates. (51, 52) They investigated in particular the compound $(NH_3{}^iPr)_6[Mo_7O_{24}]$ (named PM-8 by the authors) *in vivo*. This compound significantly suppressed the tumor growth in mice bearing subcontaneously or intraperitoneally implanted methylcholanthrene-induced tumor (Meth A sarcoma) or MM-46 adenocarcinoma. (53) The compound $(NH_3{}^iPr)_6[Mo_7O_{24}]$ was administered intraperitoneally daily for nine days following the implantation of the tumor cells. For instance, a dose of 100 mg/kg produced an Increase-in-Life Span

(ILS [footnote 1]) of 63 % for mice with subcontaneous implants of Meth A sarcoma, and of 167 % for those with MM-46 adenocarcinoma. Similarly, a dose of 50 mg/kg led to a remarquable ILS of 111% for intraperitoneal implants of Meth A sarcoma. The parallel comparative study with approved drugs 5-fluorouracil (5-FU) and 1-(4-amino-2-methylpyrimidin-5-yl)methyl-3-(2-chloroethyl)-3-nitrosourea (ACNU) indicated that $(NH_3{}^{i}Pr)_6[Mo_7O_{24}]$ has a higher antitumor activity and is less toxic to mice.

Furthermore, the effectiveness of $(NH_3{}^{i}Pr)_6[Mo_7O_{24}]$ against the progressive growth of small human cancer xenografts (MX-1, OAT, CO-4) has been evaluated. (53, 54) Daily treatment started 17 days after the implant of a 2x2 mm graft. Ten intraperitoneal injections of 200 mg/kg $(NH_3{}^{i}Pr)_6[Mo_7O_{24}]$ slowed down the tumor growth of human breast cancer MX-1 so that the average size of the tumor was only 27% of that of the control group after 46 days. No special risks to the mice were detected.

Promising antitumor activity of $(NH_3{}^{i}Pr)_6[Mo_7O_{24}]$ was also reported against CO-4 human colon cancer and OAT human lung cancer xenografts. It is often difficult to cure completely patients with human breast, lung and colon cancer by chemotherapy because of their slow growth. The potency of $(NH_3{}^{i}Pr)_6[Mo_7O_{24}]$ is therefore promising and deserves further investigations. In order to explore the structure-activity relationship of $(NH_3{}^{i}Pr)_6[Mo_7O_{24}]$, chemical derivatives were tested for Meth A sarcoma inhibiting activity. $(NH_3{}^{i}Pr)Cl$ was ineffective, whereas the activities of $(NH_4)_6[Mo_7O_{24}]$ and $K_6[Mo_7O_{24}]$ are comparable to that of $(NH_3{}^{i}Pr)_6[Mo_7O_{24}]$. This shows that the antitumor activity is associated with the polyoxomolybdate anion, and the cation possibly determines the solubility of the compound, hence its bioavailability. A mixture of reduced species $[H_xMo_7O_{24}]^{6-}$ (x = 1 or 2) with one or two Mo^V atoms can be obtained by photoreduction of $(NH_3{}^{i}Pr)_6[Mo_7O_{24}]$ in aqueous solution. The reduced mixture showed the same cancerostatic potency against MX-1 human breast xenografts as the fully oxidized precursor $(NH_3{}^{i}Pr)_6[Mo_7O_{24}]$. However, it had a far higher toxicity to the host and resulted in the death of the mice during the experiment. Based on the strong toxic effect of reduced heptamolybdate, the authors have proposed a mechanism for the antitumor action of $(NH_3{}^{i}Pr)_6[Mo_7O_{24}]$. The $[Mo_7O_{24}]^{6-}$ species would be reduced to $[H_xMo_7O_{24}]^{6-}$ after thermal activation of a oxygen-to-molybdenum-charge-transfer. The reduced species would then be reoxidized by reduction of the tumor cell, causing cell lysis. This hypothesis can be correlated with the study of DNA binding of $(NH_3{}^{i}Pr)_6[Mo_7O_{24}]$. It was shown that the heptamolybdate binds non-specifically to single and double-stranded DNA with little recognizable modifications of the DNA structure. (55) The cytotoxicity should therefore not result from interaction with DNA.

4.2.2. Polyoxotungstates

Antitumor activities of a variety of polyoxotungstates are mentioned in the scientific literature or in patents. (56-60) In the last few years, Liu, Pope and their co-workers have investigated the cytotoxic properties of many heteropolyoxotungstates against cancer cell lines *in vitro*. In order to allow a comparison of their separately published work, the reported IC_{50} [footnote 2] values have been recalculated in μM (micromolar) and compiled in Table 1. The authors focused mainly on organic derivatives of heteropolyoxotungstates containing RSn or CpTi (Cp = cyclopentadienyl) groups.

Attempts have been made to correlate the cytotoxicity of the compounds with the potential of the first reduction process. Within several series of closely related compounds, it was found that the sequence of IC_{50} values is consistent with the order of the reduction potential: the higher the reduction potential, the higher their cytotoxicity. (65) However, this correlation cannot be generalized. Indeed, structure and composition clearly also play an important role in determining the activity. Furthermore, the encapsulation of $[CoW_{11}TiO_{40}]^{8-}$ in starch nanoparticles enhances considerably its activity against tumor cells. (64) It was shown that encapsulation increases the cell penetration of $[CoW_{11}TiO_{40}]^{8-}$, and it can therefore be assumed that the higher efficiency is due to a higher concentration of the heteropolytungstate inside the cell. Organic substituents on the polyoxometalate core might have the same effect, (10, 65) but this hypothesis still needs to be verified. Obviously, further investigations are necessary to elucidate the mechanism of the cytotoxicity of polyoxotungstates *in vitro*, and to establish a structure-activity relationship. Few data are available on the antitumor activity of polyoxotungstates *in vivo*. Yamase reported in his patent applications the growth inhibition of Meth A tumors in mice by rare earth-containing decatungstates. (56, 58) For instance, the intraperitoneal uptake of $Na_9[EuW_{10}O_{36}]$ resulted in a slower tumor growth. After administration of 100 mg/kg/day for 9 days, the tumor weight was only 44% of that of the control group. Liu found inhibitory rates in the same order of magnitude for $[CoW_{11}TiO_{40}]^{8-}$ taken orally against subcutaneous implants of SSMC-7721 (liver), HL-60 (leukemia) and HLC (colon) cancer cells in rats. (65) Thus, the *in vivo* activity of $[CoW_{11}TiO_{40}]^{8-}$ resembles that of antitumor drugs CP (cyclophosphamide) and 5-FU (5-fluorouracil), but its toxicity was found to be much lower. The LD_{50} of $[CoW_{11}TiO_{40}]^{8-}$ is 2898 mg/kg, as compared to 94 mg/kg and 230 mg/kg for CP and 5-FU respectively by oral uptake in rats. (69)

4.3. Antibacterial activities

Beta-lactam antibiotics such as penicillins and cephalosporins hinder the construction of the cell wall in bacteria. They are by far the largest class of antibiotic drugs used. Therefore the increasing resistance of bacteria to these drugs represents a major health problem today. Many bacteria produce beta-lactamases. These enzymes hydrolyse the beta-lactam ring of the antibiotics, which makes the drug ineffective. The combination of beta-lactam antibiotics with a beta-lactamase inhibitor such as

Table 1. IC_{50} values in *micro*M for different heteropolyoxotungstates on tumor cells *in vitro*

Compound	Cancer Cell Line		Reference
	SSMC-7721	HeLa	
alpha-$[(CpTi)_3Si_3W_9O_{37}]^{7-}$	7.8	14.0	61
beta-$[(CpTi)_3Si_3W_9O_{37}]^{7-}$	6.7	12.1	61
alpha-$[(CpTi)_3Ge_3W_9O_{37}]^{7-}$	4.0	7.6	61
beta-$[(CpTi)_3Ge_3W_9O_{37}]^{7-}$	8.4	9.1	61
gamma-$[(CH_3OOCCH_2CH_2Sn)_2SiW_{10}O_{38}]^{6-}$	20.2	24.5	62
gamma-$[(CH_3OOCCH(CH_3)CH_2Sn)_2SiW_{10}O_{38}]^{6-}$	19.0	23.2	62
gamma-$[(NCCH_2CH_2Sn)_2SiW_{10}O_{38}]^{6-}$	15.7	17.8	62
gamma-$[(C_5H_5Ti)_2SiW_{10}O_{38}]^{6-}$	4.4	8.8	62
gamma-$[(C_5H_5Zr)_2SiW_{10}O_{38}]^{6-}$	13.2	20.5	62
$[(CH_3OOCCH_2CH_2Sn)_2PW_{10}O_{38}]^{5-}$	17.2	21.7	63
$[(CH_3OOCCH(CH_3)CH_2Sn)_2PW_{10}O_{38}]^{5-}$	16.7	21.1	63
$[(NCCH_2CH_2Sn)_2PW_{10}O_{38}]^{5-}$	10.4	15.5	63
$[CoW_{11}TiO_{40}]^{8-}$	7.1	6.1, 14.1	64, 65
$[CoW_{11}TiO_{40}]^{8-}$ starch encapsulated	-	1.2	64
$[(C_5H_5Ti)CoW_{11}O_{39}]^{7-}$	3.2	11.5	65
$[(CH_3OOCCH_2CH_2Sn)_3(PW_9O_{34})_2]^{9-}$	8.7	9.1	66
$[(CH_3OOCCH(CH_3)CH_2Sn)_3(PW_9O_{34})_2]^{9-}$	7.3	8.3	66
$[(CH_3OOCCH_2CH_2Sn)PW_{11}O_{39}]^{4-}$	21.5	25.4	66
$[(CH_3OOCCH(CH_3)CH_2Sn)PW_{11}O_{39}]^{4-}$	20.8	24.9	66
$[(CH_3OOCCH_2CH_2Sn)P_2W_{17}O_{61}]^{7-}$	18.3	19.1	66
$[(CH_3OOCCH(CH_3)CH_2Sn)P_2W_{17}O_{61}]^{7-}$	16.7	18.3	66
alpha-$[(CH_3OOCCH_2CH_2Sn)_3SiW_9O_{37}]^{7-}$	28.1	28.8	67
beta-$[(CH_3OOCCH_2CH_2Sn)_3SiW_9O_{37}]^{7-}$	19.1	24.9	67
alpha-$[(CH_3OOCCH(CH_3)CH_2Sn)_3SiW_9O_{37}]^{7-}$	27.5	28.4	67
beta-$[(CH_3OOCCH(CH_3)CH_2Sn)_3SiW_9O_{37}]^{7-}$	18.7	24.2	67
alpha-$[(NCCH_2CH_2Sn)_3SiW_9O_{37}]^{7-}$	13.8	24.3	67
beta-$[(NCCH_2CH_2Sn)_3SiW_9O_{37}]^{7-}$	9.5	21.7	67
alpha-$[(CH_3OOCCH_2CH_2Sn)_3(SiW_9O_{34})_2]^{11-}$	10.8	15.6	67
beta-$[(CH_3OOCCH_2CH_2Sn)_3(SiW_9O_{34})_2]^{11-}$	9.4	14.0	67
alpha-$[(NCCH_2CH_2Sn)_3(SiW_9O_{34})_2]^{11-}$	5.2	11.1	67
beta-$[(NCCH_2CH_2Sn)_3(SiW_9O_{34})_2]^{11-}$	3.6	10.0	67
$[(C_5H_5Ti)CoW_{11}O_{39}]^{7-}$	3.2	11.5	65
$[(C_5H_5Ti)GeW_{11}O_{39}]^{5-}$	15.7	17.8	68
$[(C_5H_5Ti)GaW_{11}O_{39}]^{5-}$	14.0	15.8	68
$[(C_5H_5Ti)BW_{11}O_{39}]^{6-}$	12.9	14.6	68

clavulanic acid (for example Augmentin®) can restore the antibiotic effectiveness. On the other hand, hydrolytically stable penicillins such as methicillin and oxacillin have been developped. Bacteria were developing resistance against these antibiotics by modifying their Penicillin-Binding-Proteins (PBP). For instance Methicillin-Resistant-Staphylococcus Aureus (MRSA) strains produce the PBP variant PBP 2', which plays the same role in the construction of the cell wall as PBP, but is insensitive to beta-lactams. These penicillin-resistant bacteria represent a very serious threat to humans, in particular in intensive care units, and much effort is devoted to find effective antibiotics against MRSA infections.

In 1993, Tajima reported the effect of an aged mixture of tungstate and phosphate in combination with beta-lactam antibiotics. (70) He discovered that a factor (named "Factor T" for Tungstate) greatly enhanced the antibacterial effect of the drug in MRSA strains, but there was no synergism of factor T with other classes of antibiotics, nor any effect on other groups of bacteria. He subsequently studied the mechanism of action of Factor T, and found that it reduced the amount of PBP 2', and thus sensitized the MRSA strains to beta-lactams. (71) Factor T was finally identified as the lacunary Keggin polyoxotungstate $[PW_{11}O_{39}]^{7-}$, (72) and an extended investigation together with Yamase on the synergistic effect of more than 70 polyoxometalates in combination with beta-lactam antibiotics followed. (73, 74) Whereas almost no polyoxomolybdate, nor polyoxovanadate exhibited a significant effect in combination with oxacillin on MRSA strains SR3605 and ATCC43300, almost all polyoxotungstates

Table 2. The antibacterial effects of polyoxotungstates alone (MIC) and in combination with oxacillin (FIC) against two different MRSA strains (73, 74)

Complex	MIC (*micro*g/mL)		FIC	
	SR3605	**ATCC43300**	**SR3605**	**ATCC43300**
Keggin Ions				
$Na_3[PW_{12}O_{40}]\cdot n\ H_2O$	3200	3200	0.156	0.062
$Na_4[SiW_{12}O_{40}]\cdot n\ H_2O$	3200	3200	0.094	0.019
$K_5[BW_{12}O_{40}]\cdot 15\ H_2O$	800	800	0.156	0.094
$K_7[PTi_2W_{10}O_{40}]\cdot 6\ H_2O$	12800	3200	0.047	0.063
$K_5[PVW_{11}O_{40}]\cdot 6\ H_2O$	800	400	0.156	0.094
$K_6[BVW_{11}O_{40}]\cdot n\ H_2O$	800	200	0.094	0.156
$K_6[PV_3W_9O_{40}]\cdot n\ H_2O$	3200	1600	0.094	0.094
$K_6[CoW_{12}O_{40}]\cdot n\ H_2O$	3200	1600	0.078	0.094
$(^iPr_2NH_2)_5[PTiW_{11}O_{40}]\cdot 4\ H_2O$	12800	3200	0.039	0.031
$K_5[PV_2W_{10}O_{40}]\cdot n\ H_2O$	3200	1600	0.156	0.063
$K_5[SiVW_{11}O_{40}]\cdot n\ H_2O$	3200	800	0.125	0.031
$K_6H[SiV_3W_9O_{40}]\cdot 3\ H_2O$	6400	1600	0.125	0.020
$K_6[H_2SiNiW_{11}O_{40}]\cdot n\ H_2O$	6400	3200	0.078	0.012
Monovacant Keggin Ions				
alpha-$K_7[PW_{11}O_{39}]\cdot n\ H_2O$ (Fator T)	12800	6400	0.063	0.035
Trivacant Keggin Ions				
alpha-B-$Na_9[PW_9O_{34}]\cdot n\ H_2O$	12800	12800	0.047	0.031
beta-A-$Na_9[HSiW_9O_{34}]\cdot 23\ H_2O$	12800	6400	0.094	0.018
alpha-B-$Na_9[SbW_9O_{33}]\cdot 19.5\ H_2O$	3200	1600	0.156	0.156
Decatungstometalates				
$Na_9[EuW_{10}O_{36}]\cdot 32\ H_2O$	3200	1600	0.188	0.313
$K_6[GdW_{10}O_{36}]\cdot 20\ H_2O$	3200	1600	0.313	0.281
Anderson Ions				
$K_{5.5}H_{1.5}[SbW_6O_{24}]\cdot 6\ H_2O$	12800	12800	0.156	0.063
$K_6Na_2[MnW_6O_{24}]\cdot 12\ H_2O$	6400	3200	0.281	0.281
Giant Polyoxotungstates				
$Na_{27}[NaAs_4W_{40}O_{140}]\cdot n\ H_2O$	400	400	0.281	0.156
$K_{18}[KSb_9W_{21}O_{86}]\cdot n\ H_2O$	200	400	0.313	0.281
Wells-Dawson Ions				
$K_6[P_2W_{18}O_{62}]\cdot 14\ H_2O$	200	200	0.070	0.023
$Na_9[P_2W_{15}Nb_3O_{62}]\cdot 23\ H_2O$	800	800	0.141	0.023
$Na_{12}[P_2W_{15}O_{56}]\cdot 18\ H_2O$	200	100	0.133	0.039
$K_{10}[P_2W_{17}O_{61}]\cdot 15\ H_2O$	200	100	0.141	0.063

showed synergism. This result can be correlated with the amount of polyoxometalates found inside the cells of MRSA strains MRS394-1. (74) When these cells grown to a stationary phase were treated with 100 *micro*g/mL of $Na_3[PW_{12}O_{40}]$ for 20 min, the amount of tungsten found inside the cells (mainly in the cell membrane) was 1.05±0.18 mg/g dry weight of cell (6 *micro*mol/g). With the isostructural molybdate $Na_3[PMo_{12}O_{40}]$, only 0.05±0.02 mg/g dry weight of cell (0.5 *micro*mol/g) of molybdenum are incorporated into the cell. Metavanadate and hexaniobiate are also absorbed to a lesser extent by the cells than the examined polyoxotungstates. However, there are too few studies of isostructural polyoxometalates to draw conclusions about the relationship between composition and activity.

The synergistic potency of polyoxotungstates is decreased in the presence of polycations such as polylysine or protamine sulfate, which are likely to form ion pairs with the negatively charged polyoxotungstates. None of the factors charge, size or structure correlates with the FIC [footonote 3] index, taken as a measure for the synergism of the POMs with beta-lactam antibiotics. This is expected, as not all of the compounds investigated are stable in the bacterial growth medium, and the actual active species remains unknown in such cases. However, some trends are apparent. Decatungstates, Andersontype compounds and large polyoxotungstates have generally a higher FIC index, i.e. lower synergistic efficiency than Keggin-type

compounds. The lacunary Keggin species $[PW_{11}O_{39}]^{7-}$ seems to be more efficient than its parent saturated compound $[PW_{12}O_{40}]^{3-}$. This is surprising as the latter hydrolyzes rapidly at near neutral pH to yield the lacunary complex and tungstate. In the same way, $[SiW_{11}O_{39}]^{8-}$ is formed from $[SiW_{12}O_{40}]^{4-}$. The lacuna itself is not required for antibacterial activity, as a large number of substituted Keggin ions $[MSiW_{11}O_{39}]^{(8-n)-}$ where the lacuna is filled with another transition metal M^{n+}, are more active than $[SiW_{11}O_{39}]^{8-}$. (75) The author concluded that $[Co^{II}SiW_{11}O_{39}]^{6-}$ represents the best compromise between toxicity and sensitizing effect. He further confirmed its suppressive effect on PBP production. (76) In fact, $[Co^{II}SiW_{11}O_{39}]^{6-}$ not only markedly reduced the amount of PBP 2', but also that of ordinary PBP 1-4. He also confirmed that the sensitizing effect of $[SiW_{11}O_{39}]^{8-}$ is due to reduced expression of PBP 2'. (77) It is noteworthy that the presence of small and lipophilic cations increase the sensitizing effect of $[SiW_{11}O_{39}]^{8-}$.

Selected Keggin ions were also tested together with oxacillin against Methicillin Susceptible Staphylococcus Aureus (MSSA) strains. (73) The enhancement of the antibiotic activity of oxacillin against these bacteria is considerably lower than in the case of MRSA strains, suggesting that the synergistic effect of polyoxotungstates with oxacillin is selective for MRSA. The Keggin ion $[PTi_2W_{10}O_{40}]^{7-}$ inhibits the formation of PBP2' in the MRSA strains ATCC43300 (73) and MRS3941 (74), as it was found for Factor T, (71) and for $[Co^{II}SiW_{11}O_{39}]^{6-}$ (76) and this would explain the observed antibacterial selectivity. Furthermore, it was found that $[PTi_2W_{10}O_{40}]^{7-}$ depresses the production of beta-lactamases, which contributes also to the synergistic effect with beta-lactam antibiotics. No synergism was found with other antibiotics.

In the context of the effect of POMs on the production of beta-lactamases, a preliminary note by Davies should be considered. He reported the induction of beta-lactamases expression in Bacillus Licheniformis upon addition of vanadate, tungstate or molybdate to the growth medium. (78) The composition of the medium favors the formation of POMs. It would therefore be of interest to check the influence of POMs on the production of beta-lactamases in different cell lines.

Besides this synergistic effect of polyoxotungstates, Yamase reported also an antibacterial effect of polyoxovanadates against six strains of penicillin resistant Streptococcus pneumonia. (79) The vanadates have MICs in the range of 4-32 µg/mL. In comparison, a selection of 9 polyoxotungstates and polyoxomolybdates have MICs in the range of 500-8000 µg/mL. The effect of the vanadates seems to be limited to Streptococcus pneumonia, as the activity against other pathogenic bacteria such as MRSA, MSSA, coagulase-negative staphylococci, Enterococcus faecalis, Escherichia coli and Pseudomonas aeruginosa was negligible.

The polyoxometalates examined so far for their antibacterial activity were too toxic to envision their clinical use, although their MRSA inhibition is patented. (80) Nevertheless, their use as a tool in microbiology laboratories is a conceivable application. (81)

4.4. Diabetes

Diabetes mellitus is the name given to a multiple group of disorders in the carbohydrate, protein and fat metabolism, characterized by a high blood glucose level. (82, 83) It is associated with insulin deficiency (Type I, insulin-dependent-diabetes-mellitus) or insulin resistance (Type II, non-insulin-dependent-diabetes-mellitus). Insulin is a peptidic hormon synthesized by the pancreatic beta-cells. Because type II diabetes represent around 90% of all cases, and also because insulin can not be administered orally, the development of new, preferentially oral, treatments is an important goal in pharmaceutical research. In the 1980's, the insulin-mimetic effect of vanadium salts was recognized in cells and in animal models of diabetes. (84-86) A large number of vanadium (IV and V) compounds with different organic ligands have been tested, and the results have been reviewed extensively. (87, 95) Although it is established that orally administered vanadium complexes alleviate the symptoms of diabetes also in human beings, (96, 97) their mode of action is not fully understood. It is commonly admitted that vanadium does not replace insulin, but enhances its action through competitive inhibition of regulatory protein phosphatases in the insulin signaling system.

The similarities of molybdate $[MoO_4]^{2-}$ and tungstate $[WO_4]^{2-}$ with vanadate $[VO_4]^{3-}$ prompted a spanish group around Guinovart to study their effect on the glucose metabolism in isolated hepatocytes. (98) They found similar, although less strong effects for molybdate and tungstate. In a series of studies with animal models for type I and type II diabetes (Streptozotocin-induced diabetic, Neonatally Streptozotocin-induced, and Zucker Diabetic Fatty rats), they established the antidiabetic effect of tungstate *in vivo*. (99-101) These animal models have a more or less impaired hepatic glucose metabolism. Orally administered tungstate decreases the blood glucose level in these diabetic animals, but not in healthy animals. However, conclusions for the possible treatment of diabetes in human beings are premature, because the long-term effects depend largely on the animal model. In another animal model (Stroptozotocin-Nicotinamid induced) with a reduced pancreatic beta-cell mass, and with a normal hepatic glucose metabolism, no modification of the hyperglycemia was observed. Only a transient reduction of the glucose intolerance occurred. (102) These results suggest that tungstate is acting at the hepatic level, which is correlated with the inhibition of glucose-6-phosphatase (103) and with the glycogen synthesis activation (104) by tungstate. But as it is the case for vanadate, different mechanisms are most likely responsible for the normalization of glycaemia

Table 3. Trends in insulin-mimetic effects of polyoxotungstates (106)

Entry	Compound	Concentration (mM)	Blood glucose level relative to untreated group	Glucose lowering effect compared to $NaVO_3$	Body weight loss compared to $NaVO_3$ treated group
1	$Na_3[a\text{-}PW_{12}O_{40}]\cdot 8H_2O$	4.56	+	– –	– –
2	$K_6[alpha\text{-}P_2W_{18}O_{62}]\cdot 10H_2O$	3.03	–	+	–
3	$Na_2WO_4\cdot 2H_2O$	54.60	–	≈	– –
4	$K_4[alpha\text{-}PMo_{11}V^{V}O_{40}]\cdot 5H_2O$	3.31	+	– –	– –
5	$K_4[alpha\text{-}PW_{11}V^{V}O_{40}]\cdot 2H_2O$	3.27	≈	– –	–
6	$K_5[alpha\text{-}1,2\text{-}PW_{10}V_2{}^{V}O_{40}]\cdot 3H_2O$	1.64	–	–	–
7	$K_6[alpha\text{-}1,2,3\text{-}PW_9V_3{}^{V}O_{40}]\cdot 4H_2O$	1.11	≈	– –	≈
8	$K_8H[alpha\text{-}1,2,3\text{-}P_2W_{15}V_3{}^{V}O_{62}]\cdot 4H_2O$	1.10	–	–	≈
9	$K_6[alpha\text{-}1,4,9\text{-}PW_9V_3{}^{V}O_{40}]\cdot 4H_2O$	1.08	–	– –	≈
10	$K_8[alpha\text{-}1,2\text{-}P_2W_{16}V_2{}^{V}O_{62}]\cdot 9H_2O$	1.68	–	– –	–
11	$Na_6[V_{10}O_{28}]\cdot 14H_2O$	0.33	– –	–	–
12	$K_5[alpha\text{-}PW_{11}V^{IV}O_{40}]\cdot 12H_2O$	3.23	≈	– –	≈
13	$K_8[alpha\text{-}P_2W_{17}V^{IV}O_{62}]\cdot 14H_2O$	3.23	≈	– –	– –
14	$K_7[alpha\text{-}P_2W_{17}V^{V}O_{62}]\cdot 11H_2O$	3.19	– –	–	≈
15	$NaVO_3$	3.28			
			+ superior – inferior	+ stronger, – weaker effect	– more important loss

upon tungstate treatment. Very recently, the regeneration of pancratic beta-cell population in diabetic rats treated orally with sodium tungstate was reported. (105)

In comparison to mononuclear complexes, polyoxometalates have been far less studied in the context of diabetes. The most systematic work was done by Nomiya and his collegues, (106) who examined the insulin-mimetic effect of a series of forteen compounds, mostly polyoxotungstates and vanadium-substituted polyoxotungstates (Table 3). The data were obtained with groups comprising mostly 2-4 mice, who showed individual variability. The compounds were dissolved in the drinking solutions, to which the mice had free access. The consumption of the solutions differed strongly between the groups. On the forth day, the sample solutions were replaced with pure drinking water. The blood glucose level and the body weight were monitored over ten days. In several groups, the variations were rather irregular. In Table 3 are compiled some trends which can be seen: i) the variation in the blood glucose level compared to an untreated group, ii) the effect on the blood glucose level and iii) the effect on the body weight of each compound relative to that of $NaVO_3$. It should be noted that the authors started their work with the hypothesis that the active component in their compounds was vanadium. They therefore adjusted the concentrations of each complex such that the vanadium concentration was constant (except for homopolyoxotungstates). It can be seen from Table 3 that most polyoxometalates lower the blood glucose level, but only $K_6[alpha\text{-}P_2W_{18}O_{62}]$ (entry 2) seems to perform better than $NaVO_3$. One must notice that the positive effect of $K_6[alpha\text{-}P_2W_{18}O_{62}]$ was only occurring after three days. Before that, an increase in the blood glucose level was observed. Neither the structure nor the composition of the POMs seem to correlate with the lowering of glucose. This means that not the total vanadium content, but the intrinsic properties of each POM are responsible for the observed effect. Among the polyoxotungstates lowering noticeably the glucose level, those with a Dawson structure (entries 2, 8, 14) produce no or little body weight loss. The authors showed furthermore by ^{31}P NMR that $[alpha\text{-}P_2W_{18}O_{62}]^{6-}$ is stable at mM concentrations in water. Although these results need to be put on a larger basis, they show clearly that polyoxometalates have a potential in diabetes treatment.

5. CELL PENETRATION

POMs are large (in the nanometer size range) and highly negatively charged species. These two factors certainly don't facilitate their penetration into cells. One might therefore conclude that the observed activities result from the interaction of the POMs with the cell surface. Some studies however indicate that under certain circumstances, POMs can cross the barrier and penetrate inside a cell. Cibert and Jasmin have incubated C3HBi fibroblasts with $(NH_4)_{17}Na[NaW_{21}Sb_9]$ (HPA-23) at $3\cdot 10^{-6}$ M. (107) They found a cytoplasmic precipitate which they analyzed by Raman Laser microscopy. POMs have intense IR and Raman bands for the W-O-W and W=O stretching vibrations. In the present case, a Raman band at 947 cm^{-1} of the cytoplasmic precipitate can be attributed to the intact $[NaW_{21}Sb_9]^{18-}$ ion (937 cm^{-1} in $(NH_4)_{17}Na[NaW_{21}Sb_9]$). X-fluorescence microscopy was used to locate the polyoxotungstate in the treated cells. The authors concluded that HPA-23 enters the cells, but is not localized at any particular organelle.

Boudinot and his coworkers studied the uptake of $K_{12}H_2[P_2W_{12}O_{48}]$, $K_{10}[Zn_4(H_2O)_2(PW_9O_{34})_2]$, $[(CH_3)_3NH]_8[Si_2W_{18}Nb_6O_{77}]$ and $(NH_4)_{17}Na[NaW_{21}Sb_9]$ in the macrophage cell line J774. (108) This type of white blood cell is responsible for the removal of a range of polyanionic substances including modified albumin and acetylated low density lipoprotein (LDL). The presence of 15 μg/mL of

any of the above polyoxotungstates reduced the endocytosis of acetylated LDL by approximately 50%. This indicates that LDL and polyoxotungstates are competing for the macrophage receptors. Also, more vacuoles were observed under fluorescence microscopy in the cells after incubation with polyoxotungstates. A Transmission-Electron-Microscopy analysis of $[(CH_3)_3NH]_8[Si_2W_{18}Nb_6O_{77}]$ treated cells revealed the presence of highly dense granules inside these vacuoles. This suggests the endocytosis of $[(CH_3)_3NH]_8[Si_2W_{18}Nb_6O_{77}]$ by J774 macrophages, although the combination with energy dispersive X-ray microanalysis could not establish the composition of these granules.

Yamase and his coworkers analyzed the metal content in dried bacteria cells incubated with polyoxometalates (see above 4.3). (74) They found a significant amount of tungsten, and less molybdenum and vanadium. For two compounds, $K_7[PTi_2W_{10}O_{40}]$ and $K_6[P_2W_{18}O_{62}]$, they established their distribution between the cell wall, the cytoplasm and the membrane fraction of the cell lysate. Both compounds are associated with the membrane fraction, but this technique does not allow to conclude if the polyoxotungstates were inside the cell.

6. CONCLUSIONS

The diversity of polyoxometalates is reflected in the diversity of their biomedical applications, but the largest efforts have been so far devoted to the study of their antiviral, antitumoral and antibiotic properties. No polyoxometalate has been developed to the stage of a drug in clinical use. Their toxicity is certainly a major drawback. Several authors documented toxic side effects of polyoxometalates. (109, 110) However, several *in vivo* studies (vide supra) show that the administration of polyoxometalates is possible without acute toxic effects. The gap between a useful drug and a toxic substance is very narrow, and every chemist knows that small derivatizations can change the properties of compounds dramatically. Therefore further research on polyoxometalates in medicine is necessary.

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Footnotes: [1] ILS = 100(t-c)/c, where t is the mean survival time of the treated group and c is the mean survival time of the control group. [2] IC50 (50% inhibitory concentration) is the concentration that suppresses tumor cells by 50%. [3] The fractional inhibitory concentration (FIC) is an interaction coefficient indicating whether the combined inhibitory/bacteriostatic effet of drugs is synergistic, additive or antagonistic. FIC = A + B where A = (MIC of combination X + Y)/(MIC of drug X alone) B = (MIC of combination X + Y)/(MIC of drug Y alone) MIC (minimal inhibitory concentration) is the lowest concentration of an antibiotic that inhibits growth of >99% of the bacteria present. Interpretation: Synergistic: FIC smaller than or equal 0.5 Additive: FIC = 1 Antagonistic: FIC greater than or equal 4

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