PHYSICAL CHEMISTRY 2016

13th International Conference on
Fundamental and Applied Aspects of
Physical Chemistry

Proceedings
Volume I

B E L G R A D E
September 26 - 30, 2016

ISBN 978-86-82475-34-7
Title: Physical Chemistry 2016 (Proceedings)
Editors: Željko Čupić and Slobodan Anić
Published by: Society of Physical Chemists of Serbia, Studentski trg 12-16, 11158, Belgrade, Serbia.
Publisher: Society of Physical Chemists if Serbia
For Publisher: S. Anić, President of Society of Physical Chemists of Serbia
Printed by: "Jovan", Printing and Publishing Company; 200 Copies.
Number of pages: 6+502; Format B5; printing finished in September 2016

Text and Layout: "Jovan"

200 - *Copy printing*

PHYSICAL CHEMISTRY 2016

13th International Conference on
Fundamental and Applied Aspects of
Physical Chemistry

Organized by

The Society of Physical Chemists of
Serbia

in co-operation with

Institute of Catalysis Bulgarian Academy of Sciences

and

Boreskov Institute of Catalysis Siberian Branch of
Russian Academy of Sciences

and

University of Belgrade, Serbia:

Faculty of Physical Chemistry
Institute of Chemistry, Technology and Metallurgy
Vinča Institute of Nuclear Sciences
Faculty of Pharmacy
Institute of General and Physical Chemistry, Belgrade, Serbia

International Organizing Committee

Chairman:	S. Anić (Serbia)
Vice-chairman:	M. Gabrovska (Bulgaria) A. A. Vedyagin (Russia) S. N. Blagojević (Serbia)
Members:	N. Cvjetićanin (Serbia), S. M. Blagojević (Serbia), M. Daković (Serbia), J. Dimitrić-Marković (Serbia), T. Grozdić (Serbia), Lj. Ignjatović (Serbia), D. Jovanović (Serbia), J. Jovanović (Serbia), M. Kuzmanović (Serbia), D. Marković (Serbia), B. Milosavljević (USA), M. Mojović (Serbia), N. Ostrovski (Serbia), N. Pejić (Serbia), M. Petković (Serbia), A. Popović-Bjelić (Serbia), B. Simonović (Serbia), D. Stanisavljev (Serbia), M. Stanković (Serbia), Z. Šaponjić (Serbia), B. Šljukić (Serbia) , G. Tasić (Serbia), N. Vukelić (Serbia), V. Vukojević (Sweden)

International Scientific Committee

Chairman:	Ž. Čupić (Serbia)
Vice-chairmans:	V. N. Parmon (Russia) S. Rakovsky (Bulgaria) B. Adnađević (Serbia)
Members:	S. Anić (Serbia), A. Antić-Jovanović (Serbia), G. Bačić (Serbia), R. Cervellati (Italy), G. Ćirić-Marjanović (Serbia), A. Cricenti (Italy), V. Dondur (Serbia), S. D. Furrow (USA), L. Gábor (Hungary), Vilmos Gáspár (Hungary), K. Hedrih (Serbia), M. Jeremić (Serbia), E. Kiš (Serbia), Lj. Kolar-Anić (Serbia), U. Kortz (Germany), T. Kowalska (Poland), V. Kuntić (Serbia), Z. Marković (Serbia), S. Mentus (Serbia), K. Novaković (UK), B. Novakovski (Poland), T. Parac Vogt (Belgium), M. Perić (Serbia), M. Plavšić (Serbia), G. Schmitz (Belgium), I. Schreiber (Czech Republic), P. Ševčik (Slovakia), N. Stepanov (Russia), M. Trtica (Serbia), V. Vasić (Serbia), D. Veselinović (Serbia), Á. Tóth (Hungary)

Local Executive Committee

Chairman:	S. N. Blagojević
Vice-chairmans:	A. Ivanović-Šašić A. Stoiljković
Members:	M. Ajduković, P. Banković, N. Bošnjaković, I. N. Bubanja, D. Dimić, A. Dobrota, J. Dostanić, A. Ignjatović, S. Jovanović, Z. Jovanović, A. Jović, N. Jović-Jovičić, D. Lončarević, M. Kragović, J. Krstić, S. Maćešić, J. Maksimović, V. Marković, D. Milenković, M. Milovanović, B. Nedić-Vasiljević, M. Pagnacco, A. Pavićević, N. Potkonjak, D. Ranković, M. Ristić, B. Stanković, A. Stanojević

MODULATION OF ACETYLCHOLINESTERASE ACTIVITY INDUCED BY POLYOXOTUNGSTATES

M. Čolović [1], A. Bondžić [1], U. Kortz [2], V. Vasić [1] and D. Krstić [3]

[1] *Department of Physical Chemistry, Vinča Institute of Nuclear Sciences, University of Belgrade, Serbia (colovicm@vin.bg.ac.rs)*
[2] *Department of Life Sciences and Chemistry, Jacobs University, Bremen, Germany*
[3] *Institute of Medical Chemistry, Faculty of Medicine, University of Belgrade, Serbia*

ABSTRACT

The *in vitro* influence of five polyoxotungstates containing various central atoms on acetylcholinesterase (AChE) activity was investigated. $K_6[PV_3W_9O_{40}] \times 3H_2O$, $K_6H_2[TiW_{11}CoO_{40}] \times 13H_2O$, $(NH_4)_{14}[NaP_5W_{30}O_{110}] \times 31H_2O$, $K_7[SiV_3W_9O_{40}] \times 10H_2O$, and $K_7[Ti_2PW_{10}O_{40}]$ induced the enzyme inhibition in a concentration-dependent manner. Inhibitory power of the investigated compounds was evaluated using IC_{50} values. $K_7[SiV_3W_9O_{40}] \times 10H_2O$ affected AChE activity with lowest potency ($IC_{50} = 4.80 \times 10^{-4}$ mol/L). $K_6H_2[TiW_{11}CoO_{40}] \times 13H_2O$ and $K_7[Ti_2PW_{10}O_{40}]$ exhibited high affinity toward the enzyme, inducing half-maximum inhibition at micromolar concentrations (1.14×10^{-6} and 1.04×10^{-6} mol/L, respectively), while the same effect was achieved in the presence of about fifty times higher concentration of $K_6[PV_3W_9O_{40}] \times 3H_2O$. Finally, $(NH_4)_{14}[NaP_5W_{30}O_{110}] \times 31H_2O$ was found as the most potent inhibitor of AChE activity ($IC_{50} = 6.36 \times 10^{-7}$ mol/L), and consequently the most promising candidate for the treatment of neurological diseases associated with acetylcholine leakage.

INTRODUCTION

Polyoxometalates (POMs) are negatively charged inorganic complexes containing transition metal ions surrounded by oxygen atoms [1]. These anionic clusters are relatively stable, some of them are even highly stable in aqueous solutions at physiological pH values [2]. POMs have been shown to exhibit biological activities *in vitro* as well as *in vivo*, including anticancer [3], antibacterial [4], antiviral [5], and antidiabetic [6] activities. Their biological mechanisms of action at the molecular level are not well understood. It has been speculated that POMs are likely to act extracellularly, inhibiting several different enzyme families such as

phosphatases, kinases, sulfotransferases, sialyltransferases, and ecto-nucleotidases, which are mostly located on the plasma membrane and display extracellular binding sites [7]. In a recent study, Iqbal et al. [8] demonstrated the inhibition of acetylcholinesterase (AChE) and butyrylcholinesterase activities induced by micromolar concentrations of a group of polyoxotungstates. AChE (EC.3.1.1.7) belongs to a group of membrane bound serine hydrolases, and is involved in the termination of impulse transmission by rapid hydrolysis of the neurotransmitter acetylcholine in numerous cholinergic pathways in the central and peripheral nervous systems [9]. Reversible inhibitors mostly have therapeutic applications, while toxic effects are associated with irreversible AChE activity modulators. The reversible inhibition of brain AChE is the major therapeutic target in the treatment of Alzheimer's disease associated with loss of cholinergic neurons in the brain and the decreased level of acetylcholine [10].

Considering the fact that AChE inhibition presents one of the strategies in the therapy of neurological diseases, and the literature data about high inhibitory potential of POMs, the aim of this study is to investigate the *in vitro* influence of five newly synthesized heteropolyoxotungstates on AChE activity, as potential anti-Alzheimer drugs.

EXPERIMENTAL

Polyoxotungstates were synthesized and characterized by prof. Ulrich Kortz at Jacobs University, Bremen. Commercially available AChE purified from electric eel (Sigma, Germany) was exposed to the various concentrations of the investigated compounds during 20 minutes at 37°C. Afterwards, AChE activity was determined by slightly modified Ellman´s method [11].

RESULTS AND DISCUSSION

The effect of five newly synthesized polyoxotungstates: $K_6[PV_3W_9O_{40}] \times 3H_2O$, $K_6H_2[TiW_{11}CoO_{40}] \times 13H_2O$, $(NH_4)_{14}[NaP_5W_{30}O_{110}] \times 31H_2O$, $K_7[SiV_3W_9O_{40}] \times 10H_2O$ and $K_7[Ti_2PW_{10}O_{40}] \times 10H_2O$ on AChE activity was investigated by *in vitro* exposure of the enzyme to the polyoxotungstates in concentration range 1×10^{-10} - 2×10^{-3} mol/L. The dependence of the enzyme activity, expressed as a percentage of control value (the enzyme activity obtained without inhibitor), on the polyooxotungstate concentration fitted a sigmoidal function for all investigated compounds (Fig. 1a). IC_{50} values, the parameters of the inhibitory potential defined as the concentration which induces 50% inhibition of the enzyme activity, were determined by sigmoidal fitting the

experimental results as well as by Hill analysis (Fig. 1b) and are summarized in Table 1. The obtained results show that all five investigated polyoxotungstates inhibit AChE activity in concentration dependent manner, but with various potencies. $(NH_4)_{14}[NaP_5W_{30}O_{110}] \times 31H_2O$ is the most potent AChE inhibitor ($IC_{50} = 4.79 \times 10^{-7}$ mol/L), about a thousand times stronger than the inhibitory power of $K_7[SiV_3W_9O_{40}] \times 10H_2O$ ($IC_{50} = 4.80 \times 10^{-4}$ mol/L). The sensitivity of AChE toward $K_6H_2[TiW_{11}CoO_{40}] \times 13H_2O$ and $K_7[Ti_2PW_{10}O_{40}] \times 10H_2O$ was similar with IC_{50} values of 1.14×10^{-6} and 1.04×10^{-6} mol/L, respectively, but their inhibitory potentials were about two times weaker compared to $(NH_4)_{14}[NaP_5W_{30}O_{110}] \times 31H_2O$. The obtained diversity in the inhibitory power of the investigated compounds could result from their differences in size, shape and charge.

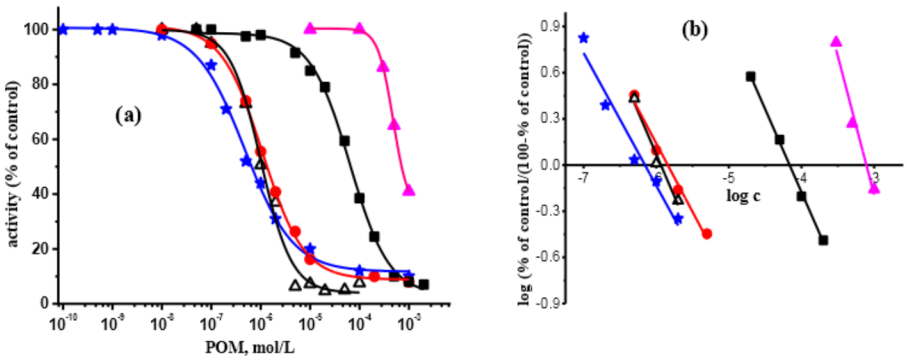

Figure 1. The concentration dependent (a) and Hill analysis (b) inhibition of AChE from electric eel induced by $K_6[PV_3W_9O_{40}] \times 3H_2O$ (square), $K_6H_2[TiW_{11}CoO_{40}] \times 13H_2O$ (circle), $(NH_4)_{14}[NaP_5W_{30}O_{110}] \times 31H_2O$ (asterisk), $K_7[SiV_3W_9O_{40}] \times 10H_2O$ (solid triangle), and $K_7[Ti_2PW_{10}O_{40}] \times 10H_2O$ (open triangle).

Table 1. IC_{50} values of AChE inhibition by five newly synthesized polyoxotungstates obtained by fitting the experimental points by sigmoidal function and Hill analysis.

	Hill analysis	**Sigmoidal function**
POM	**IC_{50}, mol/L**	**IC_{50} , mol/L**
$K_6[PV_3W_9O_{40}] \times 3H_2O$	6.56×10^{-5}	6.36×10^{-5}
$K_6H_2[TiW_{11}CoO_{40}] \times 13H_2O$	1.23×10^{-6}	1.14×10^{-6}
$(NH_4)_{14}[NaP_5W_{30}O_{110}] \times 31H_2O$	6.00×10^{-7}	4.79×10^{-7}
$K_7[SiV_3W_9O_{40}] \times 10H_2O$	5.82×10^{-4}	4.80×10^{-4}
$K_7[Ti_2PW_{10}O_{40}] \times 10H_2O$	1.15×10^{-6}	1.04×10^{-6}

CONCLUSION

In the present study, the potencies of five newly synthesized polyoxotungstates to decrease AChE activity were investigated for the purpose of their potential application in the therapy of neurological diseases associated with acetylcholine deficiency. The obtained results showed that three of five investigated compounds - $(NH_4)_{14}[NaP_5W_{30}O_{110}] \times 31H_2O$, $K_6H_2[TiW_{11}CoO_{40}] \times 13H_2O$, and $K_7[Ti_2PW_{10}O_{40}] \times 10H_2O$ remarkably affected the enzyme activity at micromolar concentrations. Consequently, these polyoxotungstates could be considered promising therapeutics in the treatment of Alzheimer's disease, and require further preclinical studies.

Acknowledgement

This study was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia (Project No. 172023).

REFERENCES

[1] B. Hasenknopf, Front. Biosci., 2005, **10**, 275–287.
[2] G. Geisberger, S. Paulus, M. Carraro, M. Bonchio, G.R. Patzke, Chem. Eur. J., 2011, **17**, 4619–4625.
[3] X. Wang, J. Liu, J. Li, Y. Yang, J. Liu, B. Li, et al. J. Inorg. Biochem., 2003, **94**, 279–284.
[4] A. Seko, T. Yamase, K. Yamashita, J. Inorg. Biochem., 2009, **103**, 1061–1066.
[5] Y. Qi, Y. Xiang, J. Wang, Y. Qi, J. Li, J. Niu, et al. Antiviral Res., 2013, **100**, 392–398.
[6] K. Nomiya, H. Torii, T. Hasegawa, Y. Nemoto, K. Nomura, K. Hashino, et al. J. Inorg. Biochem., 2001, **86**, 657–667.
[7] S-Y. Lee, A. Fiene, W. Li, T. Hanck, K. Brylev, V. Fedorov, et al. Biochem. Pharmacol., 2015, **93**, 171–181.
[8] J. Iqbal, M. Barsukova-Stuckart, M. Ibrahim, S. Ali, A. Khan, U. Kortz, Medicinal Chem. Res., 2013, **22**, 1224–1228.
[9] J. Bajgar, Adv. Clin. Chem., 2004, **38**, 151–216.
[10] M. Čolović, D. Krstić, T. Lazarević-Pašti, A. Bondžić, V. Vasić, Curr. Neuropharmacolog., 2013, **11**, 315 335.
[11] G.L. Ellman, K.D. Courtney, V. Andreas, R.M. Featherstone, Biochem. Pharmacol., 1961, **7**, 88–90.

CIP - Каталогизација у публикацији - Народна библиотека Србије, Београд

544(082)
66.017/.018(082)
502/504(082)
663/664:658.56(082)
615.31:547(082)

INTERNATIONAL Conference on Fundamental and Applied Aspects of Physical Chemistry (13 ; 2016 ; Beograd)
Physical Chemistry 2016 : proceedings. Vol. 2 / 13th International Conference on Fundamental and Applied Aspects of Physical Chemistry, Belgrade, 26-30 September 2016 ; [editors Željko Čupić and Slobodan Anić]. - Belgrade : Society of Physical Chemists of Serbia, 2016 (Belgrade : Jovan). - IV, 507-930 str. : ilustr. ; 24 cm

Tiraž 200. - Bibliografija uz svaki rad.

ISBN 978-86-82475-33-0

1. Society of Physical Chemists of Serbia (Beograd)
a) Физичка хемија - Зборници b) Наука о материјалима - Зборници c) Животна средина - Заштита - Зборници d) Животне намирнице - Контрола квалитета - Зборници e) Фармацеутска хемија - Зборници
COBISS.SR-ID 225802508

08. 09. 2016