CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

Title: From photoinduced to dark cytotoxicity via an octahedral cluster hydrolysis

Authors: Ekaterina V. Svezhentseva, Yuri A. Vorotnikov, Anastasiya O. Solovieva, Tatiana N. Pozmogova, Ilia V. Eltsov, Anton A. Ivanov, Darya V. Evtushok, Svetlana M. Miroshnichenko, Vadim V. Yanshole, Charlotte J. Eling, Ali M. Adawi, Jean-Sebastien G. Bouillard, Natalia V. Kuratieva, Maria S. Fufaeva, Lidiya V. Shestopalova, Yuri V. Mironov, Olga Efremova, and Michael A. Shestopalov

To be cited as: *Chem. Eur. J.* 10.1002/chem.201804663

Link to VoR: http://dx.doi.org/10.1002/chem.201804663

Supported by
ACES

WILEY-VCH

10.1002/chem.201804663

WILEY-VCH

COMMUNICATION

From photoinduced to dark cytotoxicity *via* an octahedral cluster hydrolysis

Ekaterina V. Svezhentseva,[a,b] Yuri A. Vorotnikov,[a] Anastasiya O. Solovieva,[c,d] Tatiana N. Pozmogova,[b,c] Ilia V. Eltsov,[b] Anton A. Ivanov,[a,d] Darya V. Evtushok,[a] Svetlana M. Miroshnichenko,[c,d] Vadim V. Yanshole,[e] Charlotte J. Eling,[f] Ali M. Adawi,[f] Jean-Sebastien G. Bouillard,[f] Natalia V. Kuratieva,[a,b] Maria S. Fufaeva,[d] Lidiya V. Shestopalova,[b] Yuri V. Mironov,[a,b] Olga A. Efremova,*[f] Michael A. Shestopalov*[a,b,c,d]

Abstract: Octahedral molybdenum and tungsten clusters have the potential for biological applications such as photodynamic therapy and bioimaging. However, poor solubility and hydrolysis stability of these compounds hinder their application. The first water-soluble photoluminescent octahedral tungsten cluster $[\{W_6I_8\}(DMSO)_6](NO_3)_4$ was synthesised and demonstrated to be at least one order of magnitude more stable towards hydrolysis than its molybdenum analogue. Biological studies of the compound on larynx carcinoma cells suggest that it has a significant photoinduced toxicity, while the dark toxicity increases with the increase of the degree of hydrolysis. The increase of the dark toxicity is associated with the *in situ* generation of nanoparticles that clog up the cisternae of rough endoplasmic reticulum.

[a] E. V. Svezhentseva, Y. A. Vorotnikov, A. A. Ivanov, D. V. Evtushok, Dr. N. V. Kuratieva, Dr. Y. V. Mironov, Dr. M. A. Shestopalov
Nikolaev Institute of Inorganic Chemistry SB RAS
3 acad. Lavrentiev ave., 630090 Novosibirsk (Russia)
E-mail: shtopy@niic.nsc.ru

[b] E. V. Svezhentseva, T. N. Pozmogova, Dr. I. V. Eltsov, Dr. N. V. Kuratieva, Dr. Lidiya V. Shestopalova, Dr. Y. V. Mironov, Dr. M. A. Shestopalov
Novosibirsk State University
2 Pirogova st., 630090 Novosibirsk (Russia)

[c] Dr. A. O. Solovieva, T. N. Pozmogova, Dr. S. M. Miroshnichenko, Dr. M. A. Shestopalov
Research Institute of Clinical and Experimental Lymphology – Branch of the ICG SB RAS
2 Timakova st., 630060 Novosibirsk (Russia)

[d] Dr. A. O. Solovieva, A. A. Ivanov, Dr. S. M. Miroshnichenko, Dr. M. S. Fufaeva, Dr. M. A. Shestopalov
The Federal Research Center of Fundamental and Translational Medicine
2 Timakova st., 630117 Novosibirsk (Russia)

[e] Dr. V. V. Yanshole
International Tomography Centre SB RAS
3a Institutskaya st., 630090 Novosibirsk (Russia)

[f] C. J. Eling, Dr. Ali M. Adawi, Dr. J.-S. G. Bouillard, Dr. O.A. Efremova
School of Mathematics and Physical Sciences, G.W. Gray Centre for Advanced Materials University of Hull
Cottingham Road, HU6 7RX, Hull (United Kingdom)
E-mail: o.efremova@hull.ac.uk

Supporting information (including experimental details, IR, XRPD, NMR spectra, crystallography data, mass spectra, DLS and details of biological experiments) for this article is given via a link at the end of the document.

Octahedral molybdenum and tungsten clusters of the general formula $[\{M_6X_8\}L_6]^n$ (where M = Mo, W, X=Cl, Br or I and L are apical organic or inorganic ligands) have become a subject of extensive studies after several exceptionally good luminophores were discovered among these compounds, in particular those of molybdenum.[1] Thanks to intense emission in the red and near-infrared region of the spectrum and a concomitant ability to generate singlet oxygen, these compounds and the materials based on them were considered in a range of applications including bioimaging,[2] photodynamic therapy,[2b, 2c, 3] antibacterial,[4] antiviral,[5] light emitting materials,[6] catalysis[7] and many others.

The majority of synthesised molybdenum clusters described so far are only soluble in organic solvents, which significantly hinders the examination (let alone utilisation) of the native clusters in biomedical research. In this regard, the chemistry of octahedral tungsten halide clusters is even less developed, as no water-soluble/dispersible compounds or materials have been reported so far. Indeed, only two water-soluble cluster complexes, $Na_2[Mo_6I_8(N_3)_6]$ and $Na_2[Mo_6I_8(NCS)_6]$, were reported.[8] However, this work as well as several other works demonstrated that molybdenum cluster complexes tend to hydrolyse with partial or full substitution of the apical ligands L by H_2O or OH^-.[3b, 8-9] Here, we demonstrate the first photoluminescent water-soluble tungsten cluster $[\{W_6I_8\}(DMSO)_6](NO_3)_4$ as well as its molybdenum analogue and compare the kinetics of their hydrolysis. Specifically, we show that the tungsten compound is stable for long enough at physiological temperatures to allow us to undertake the first biological studies on any of the tungsten clusters and demonstrate not only noticeable photoinduced cytotoxicity of the complex but also its ability to generate nanoparticles that are taken by the cells and cause dark cytotoxicity in the longer term.

Compounds $[\{M_6I_8\}(DMSO)_6](NO_3)_4$, M = Mo (**1**) and W (**2**), were obtained directly by heating $(Bu_4N)_2[\{M_6I_8\}(NO_3)_6]$ in DMSO solution at 100 °C in a dry inert atmosphere. $(Bu_4N)_2[\{M_6I_8\}(NO_3)_6]$ (M=Mo, W) are indeed well-recognised precursors for new octahedral complexes and materials based on them, due to the high lability of nitrato ligands.[1a, 2b-e, 3b, 9-10] Unlike the starting compounds, both **1** and **2** were soluble in water. FTIR spectra of **1** and **2** featured a signal at ~1370 cm^{-1} that corresponds to ν(N-O) in uncoordinated NO_3^-. The signal at ~930-940 cm^{-1} corresponds to the S–O stretching frequency in DMSO, but it is noticeably red-shifted relative to free DMSO (1005 cm^{-1}), as it coordinates to the metal centres *via* the oxygen atom (ESI Fig.

10.1002/chem.201804663

S1).[11] Similar to other octahedral compounds, **1** and **2** demonstrate luminescence in red/orange region with photoluminescence quantum yields of 0.19 and 0.18 in solid state at ambient conditions, respectively (ESI Fig. S2-S5, Table S1).

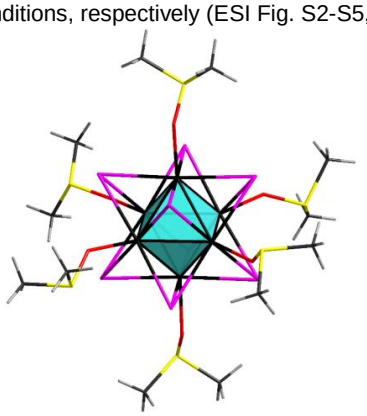


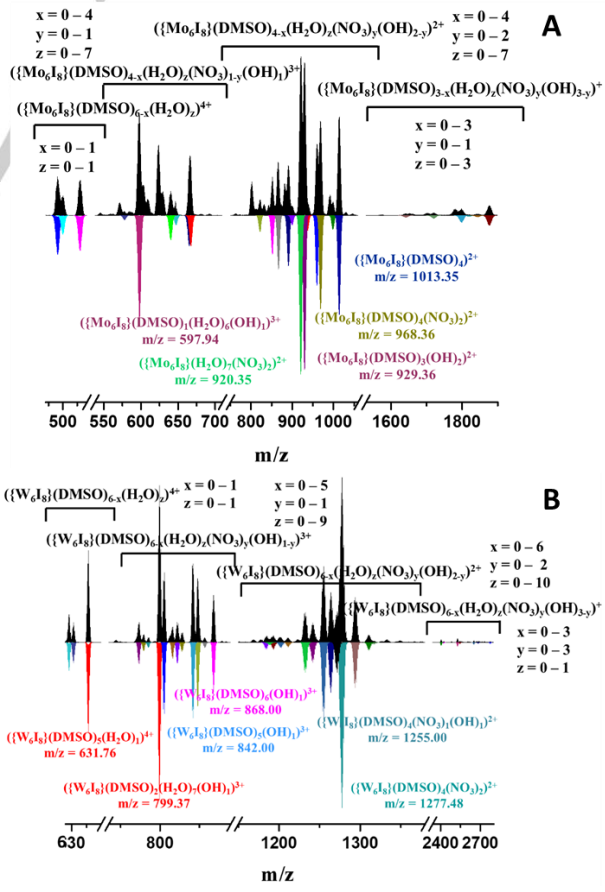
Figure 1. Structure of the cation $[\{Mo_6I_8\}(DMSO)_6]^{4+}$ observed in **1**·Me_2CO.

Crystals of **1** suitable for single crystal XRD analysis were obtained by slow diffusion of acetone vapour into a DMSO solution of the complex. According to single crystal XRD, **1** crystallises as a solvate **1**·Me_2CO in the trigonal crystal system (space group $P\bar{3}1c$, ESI Table S2). The structure of the cluster cation $[\{Mo_6I_8\}(DMSO)_6]^{4+}$ is presented in Figure 1, while the unit cell packing in Fig S6. The structure of the cluster core $\{Mo_6I_8\}^{4+}$ is similar to that found in the starting material and in the related compounds,[1a, 1b, 9, 10b, 12] and consists of Mo_6 octahedron with Mo–Mo distances being equal to 2.6430(5)–2.6591(5) Å with triangle faces capped by iodine atoms with Mo–I distances of 2.7736(4)–2.7836(4) Å. In accordance with FTIR, each Mo atom is coordinated via O atoms in DMSO (Mo–O = 2.120(3) Å). Unfortunately, we were not successful in growing good quality crystals of **2** for single crystal XRD. However, since all known Mo_6 and W_6-cluster complexes generally show very similar molecular structures[13] and chemical behavior it is reasonable to expect that composition of tungsten cluster complex **2** will be the same as the molybdenum analogue**.** Indeed, the nearly identical powder XRD patterns of **1** and **2**, and good agreement in elemental analysis and NMR data clearly confirm that both compounds not only have similar molecular structure but also crystallise in the same crystal structure. (ESI Fig. S7).

Although, **1** and **2** were readily soluble in water, some precipitation occurred after keeping the aqueous solution thereof for several days. These X-ray amorphous precipitates had poor luminescence (ESI Fig. S8) and were not soluble in any solvents or in water even under heating at different values of pH. The W:S ratio of 6:0.23 determined by EDX as well as FTIR (ESI Fig. S9) suggested that the replacement of DMSO ligand took place, likely due to hydrolysis. Indeed, the formation of poorly soluble aqua-hydroxo complexes $[\{M_6I_8\}(H_2O)_2(OH)_4]\cdot xH_2O$ upon hydrolysis is well documented.[10a, 13a, 14]

Mass spectroscopy (ESI-MS) experiments of **1** and **2** in fresh aqueous solution, in fresh 1% DMSO solution and in aqueous solution aged for four days (Fig. 2, ESI Fig. S10-S13) detected the whole family of chemical forms and associates with general formula $[\{M_6I_8\}(DMSO)_{6-x}(H_2O)_z(OH)_y(NO_3)_{k-y}]^{4-k}$ (M = Mo, W, x = 0-6, z = 0-10, y = 0-3, k = 0-3). The composition of the chemical forms in the solutions depended on the age of the solution, i.e. the degree of hydrolysis increased after 4 days. The hydrolysis was, however, noticeably slower for the tungsten compound, as unlike **1**, there was still a significant amount of the chemical forms containing up to 5 DMSO ligands in the aqueous solution of **2** after 4 days (ESI Fig. S13). Notably, in both cases the presence of 1% DMSO in the fresh aqueous solution significantly increased the amount of DMSO-containing forms (ESI Fig. S10 and 12), which suggests that the hydrolysis is to some extent reversible. Such a significant discrepancy in the reaction kinetics on Mo and W metal centres in complexes was mentioned in literature.[15]

The detailed kinetic studies of hydrolysis of **1** and **2** were undertaken in pseudo-first order conditions in saturated D_2O solution using ^1H NMR (ESI Fig. S14-S19) at temperatures of 300, 320 and 340 K. The pre-exponential kinetic factor (k_0) and activation energy (E_a) as well as entropy ($\Delta S^{\neq}$) and the enthalpy ($\Delta H^{\neq}$) of transition states, were determined according to Arrhenius and Eyring equations, respectively (ESI Fig. S20-S21, Table S9). Our data demonstrate that the hydrolysis of **1** at each temperature point is approximately one order of magnitude faster than **2**, which agrees well with ESI-MS data. The activation energy, as well as the transition state enthalpy for hydrolysis of **2** is higher than that of **1** by about 27 kJ/mol. This difference may signify Mo-DMSO bond being somewhat weaker than W-DMSO, which explains the higher stability of **2**. The estimated value of transition state entropy of **1**, –44 ± 3 kJ mol^{-1}, suggests that it hydrolyses *via* the associative mechanism. In regards to **2**, the proximity of the entropy value to 0 suggests that both associative and dissociative mechanisms take place, probably, at the different stages of hydrolysis.



10.1002/chem.201804663

Figure 2. ESI-MS spectra (black) of the fresh aqueous solution of **1** (A) or **2** (B) and a simulation of some cluster forms (coloured)

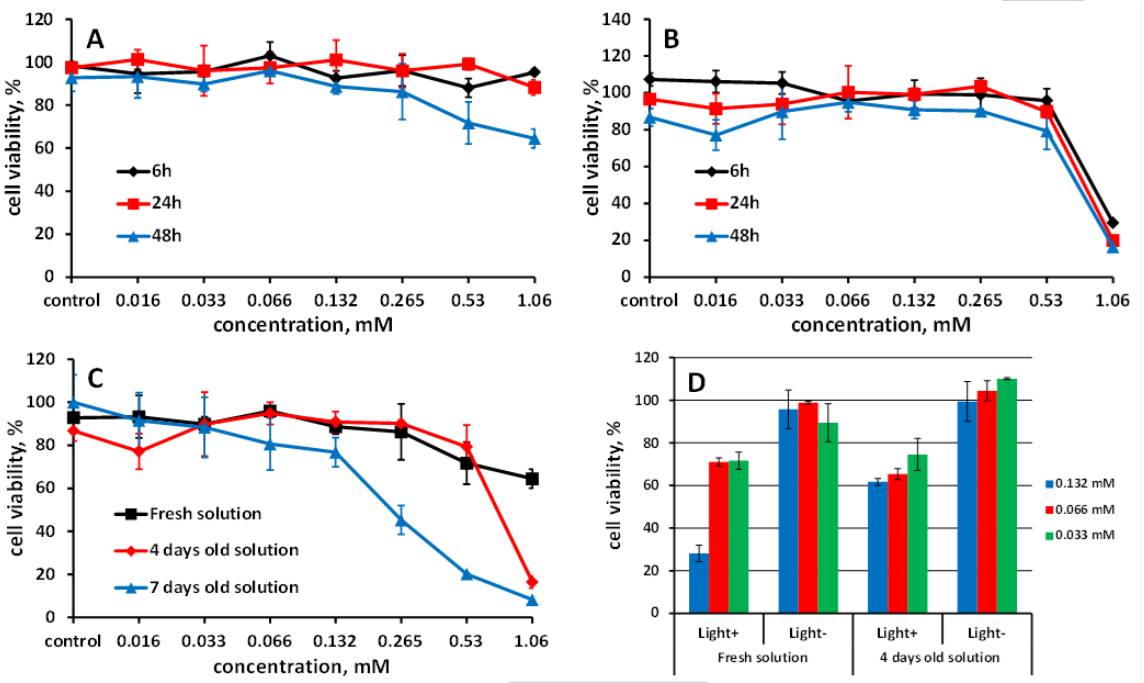


Figure 3. Dark and photoinduced cytotoxicity of **2** for Hep-2 cells. A) Cytotoxicity of fresh aqueous solutions against incubation time; B) Cytotoxicity of 4-days old aqueous solutions versus incubation time; C) Cytotoxicity of fresh, 4- and 7-days old solutions after incubation for 48 hours, D) Photoinduced toxicity of fresh and aged solutions after light irradiation (a total light dose 20 J/cm^2). Error bars represent the standard error of the mean cell viability for at least 3 replicate measurements.

Although for many applications of metal complexes, hydrolysis is detrimental, it should be noted that for antitumor activity of a majority of transition metal-based drugs, such as cisplatin, RAPTA and alike, hydrolysis is an important step in the mode of their actions. Moreover, it is often important that hydrolysis is not too fast to allow the drug molecules to internalise into cells efficiently and bind to DNA but not so slow that the hydrolysis happens before the drug elimination.[16] From the kinetic data we estimated the half-life time in aqueous solutions under physiological temperature (37 °C) of **1** is equal to only 52 min, which is too short for biological applications, while it is 34 h for **2**, i.e. longer than the typical cellular uptake times. Therefore, we were interested to evaluate whether hydrolysis has any effect on both dark and light-induced cytotoxicity of this compound.

All cytotoxicity studies were undertaken on human larynx carcinoma cells (Hep-2) using MTT assay. For the dark cytotoxicity studies, the cells were incubated for 6, 24 or 48 h with either freshly prepared solution of **2** or the solutions aged at room temperature for several days (Fig. 3A-C). The assays on the fresh solution of **2** showed that its cytotoxicity gradually increased with the increase of time of incubation. However, the half-maximal inhibitory concentration (IC_{50}) value was still not achieved within the studied concentration range (*i.e.* IC_{50}>1.06 mM). Notably, aged solutions had a significantly higher cytotoxic effect with IC_{50} values of 0.85±0.07 mM (for 4-day old solution) and 0.24±0.01 mM (for 7-day old solution) after 48 h of incubation. These data demonstrate that hydrolysed forms have higher dark cellular toxicity in comparison with the starting DMSO complexes. For comparison, IC_{50} values for the only known water-soluble molybdenum clusters, namely $Na_2[\{Mo_6I_8\}(NCS)_6]$ and $Na_2[\{Mo_6I_8\}(N_3)_6]$, studied *in vitro* HeLa and HEK 293T cells, were about one order of magnitude smaller. Notably, the toxicity of $Na_2[\{Mo_6I_8\}(NCS)_6]$ demonstrated a similar pattern as **2**, i.e. the toxicity of the solution increased with the incubation time: IC_{50} for HeLa was 33 to 48 and 18 μM cells after 24, 48 and 72 h, respectively. The higher long-term toxicity of $Na_2[\{Mo_6I_8\}(NCS)_6]$ might also be associated with the increased toxicity of the partially hydrolysed species $[\{Mo_6I_8\}(NCS)_5(OH)]^{2-}$, which the article authors have detected.[8]

Earlier, we demonstrated that silica nanoparticles doped by octahedral molybdenum cluster complexes exhibit significant photoinduced toxicity.[2b] Moreover, the vast range of theoretical and experimental studies convincingly demonstrate that molybdenum clusters are capable of singlet oxygen generation.[1b, 2b, 2c, 3b, 4, 8, 10a, 12a, 17] Tungsten cluster complexes are far less studied in this regard. Hence we also undertook photoinduced toxicity studies. The viability test was performed after 4 h incubation of the cells with either freshly prepared or aged for 4 days solutions of **2** within the safe concentration range followed by an irradiation of the cells with the light (λ ≥ 400 nm) for 30 min. Our data demonstrate that at the highest tested concentration (132 μM), the fresh solution of **2** is more phototoxic than that of

10.1002/chem.201804663

the aged solution: 28±4 % of cells survived with the fresh solution vs. 62±2% with the aged solution (Fig. 3D). This demonstrates the higher photodynamic activity of **2** in comparison with its hydrolysed forms.

To establish whether the photoinduced toxicity is caused by reactive oxygen species (ROS) (including singlet oxygen), we determined the level of intracellular ROS within Hep-2 cells by using cell-permeable fluorescent probe 5,6-carboxy-2′,7′-dichlorofluoresceindiacetate (DCFH-DA). Specifically, the cells were first incubated with **2** followed by incubation with DCFH-DA and then the fluorescence level of the cells (indicative of ROS concentration) was measured using IN Cell Analyzer. The cells incubated with either a cluster-free media or with H_2O_2 (i.e. irradiation-independent ROS source) were used as a negative and a positive control, respectively. Our data (Fig S22-F23) demonstrate that the levels of ROS in the positive and in the negative control experiments were invariant to irradiation, whereas the level of ROS in the presence of both fresh and 4-day old solutions of **2** was significantly higher after photoirradiation. Notably, the level of ROS in the cells treated by **2** without photoirradiation was the same as for the negative control meaning that intracellular ROS were generated by **2** solely upon photoirradiation. Moreover, the level of ROS in the cells incubated with the fresh solution of **2** was about 50% higher than that for the aged solution, which follows the same trend as the photoinduced toxicity data above. Although, the DCFH-DA probe does not differentiate between singlet oxygen and other ROS, similarity in the optical properties of molybdenum and tungsten clusters [17b, 18] suggests that the photoinduced toxicity of **2** is likely to be due to the singlet oxygen generation. Although detailed spectroscopic studies are still required to establish details of photosensitisation mechanism of **2**.

To understand, why hydrolysis of the cluster increases its dark cellular toxicity, we have studied internalisation of **2** in Hep-2 cells in more detail. Flow cytometry (FACS) analysis of the cells after 15 min and 4 h of incubation with the freshly prepared and aged for 4 days solutions at non-toxic concentration demonstrate that the cluster from the aged solution is taken up by the cells better than from the fresh solution (Fig. 4A and S24). Indeed, despite the fact that hydrolysis of **2** leads to significant decrease of luminescence intensity of metal cluster[13a], the cells incubated with the aged solution were noticeably more emissive already after 15 minutes than those incubated with the freshly prepared solutions.

Confocal laser scanning microscope (CLSM) imaging of the cells incubated with the 4-day-aged solution of **2** (0.132 mM) for 24 h demonstrated bright red emission localised in the perinuclear space (Fig. 4B-D). TEM imaging provided even more detailed information about localisation and the chemical form of the clusters within the cells. Namely, it demonstrated that the clusters within a cell were in the form of nanoparticles of various sizes < 40 nm (Fig. 5). For comparison, the size of one cluster with the ligands is no more than 1 nm. The dynamic light scattering of the studied solution, indeed, confirmed the presence of nanoparticles with the average size of 20 nm (ESI Fig. S25), which are likely agglomerates of fully and/or partially hydrolysed species held together by strong intermolecular hydrogen bonding. Indeed, the emission profile of the nanoparticles separated from solution (Fig. S4) is similar to the literature data for $[\{W_6I_8\}(H_2O)_2(OH)_4]\cdot 6H_2O$. According to the FACS data (Fig. 4A) the presence of the nanoparticles in the cells with concomitant higher intensity of luminescence from the cells suggests that the particles are taken up more easily than the non-hydrolysed complex **2**, possibly due to the difference in the mechanism of uptake between nanoparticles and molecular complexes. Moreover, Fig. 5 also shows that the nanoparticles are located within single membrane vesicles as well as in the cisternae of endoplasmic reticulum (ER).

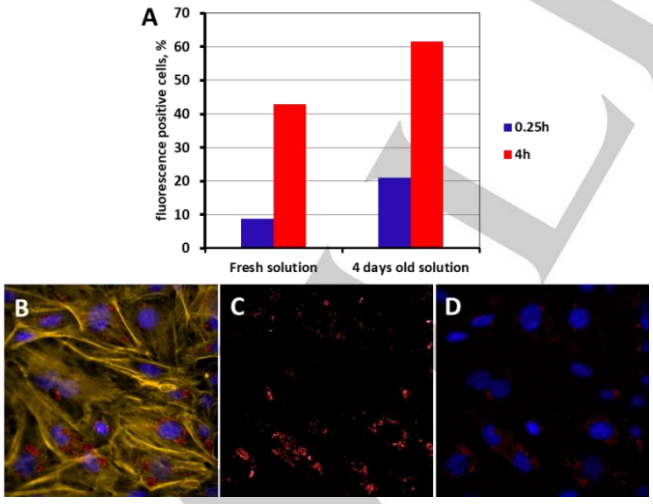


Figure 4. Percentage of fluorescence positive cells after incubation with fresh solution and 4-days old solution of **2** for 0.25 and 4 hours (A). Fluorescent microscopic images (B, C and D) of Hep-2 cells incubated with **2**, where yellow is cytoskeleton stained by Phalloidin, blue is nucleus stained by Hoechst33342 and red is emission from **2**.

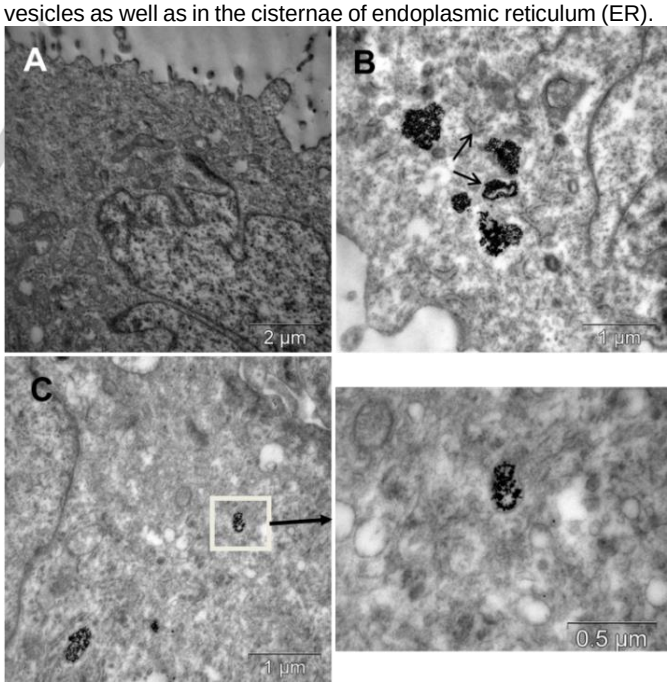


Figure 5. TEM images of ultrathin sections of Hep-2 cells: (A) control cells; (B-C) are the cells incubated with **2**. Selected region of cytoplasm with single-membrane vesicles containing nanoparticles generated from **2** is shown at greater scale in panel. Arrows on (B) point to the ER's cisterns.

The overload of ER (the organelle responsible for the accumulation of exogenous and endogenous molecules and ions among other functions) with the nanoparticles might lead to the expansion of ER followed by the cell death. Indeed, it is generally agreed that exposure of cells to nanoparticles can induce cellular toxicity via ER stress (i.e. accumulation of the misfolded proteins in the ER),[19] upon which the size of the ER can expand to increase protein folding capacity.[20] Moreover, in several studies it was also shown that cancerous cells may be particularly prone to apoptosis mediated by ER stress.[21] On the other hand the close proximity of the cluster to the cellular nucleus facilitates the photodynamic toxicity demonstrated above.

There are several major conclusions that can be drawn from this work. Firstly, using $[\{W_6I_8\}(DMSO)_6](NO_3)_4$ as an example, it is demonstrated that photoluminescent cluster complexes may have an advantage over similar molybdenum compounds for biomedical applications due to significantly increased stability of the latter towards hydrolysis. Secondly, upon hydrolysis octahedral clusters initially assemble into nanoparticles that retain some photoluminescent properties. This unexpected feature will require further investigation into how the properties and sizes of the particles can be controlled and whether they can be functionalised. This is particularly important in the context of the third conclusion – the cellular uptake of the metal cluster-based nanoparticles was more efficient than that of the molecular complex, probably due to the differences in the uptake mechanisms between complexes and nanoparticles. Finally, although IC_{50} values for **2** were about an order of magnitude higher than the state-of-the-art anti-cancerous drugs, the concept of a drug that initially is luminescent (and thus can be employed as an imaging and/or PDT agent), but consequently is capable to convert into a cytostatic moiety could be an interesting and novel approach to the development of theranostic and/or multimodal therapeutic agents. In this respect octahedral cluster complexes may be of particular interest due to their photoluminescence combined with the ability to hydrolyse and to bind strongly to a range of donor groups.[16b-d]

Acknowledgements

We are grateful for the financial support the Russian Science Foundation (No. 15-15-10006). In addition, M.A. Shestopalov thanks the Grant of the President of Russian Federation [grant no. MK-180.2017.3], Y.A. Vorotnikov thanks the Russian Foundation for Basic Research [grant no. 18-33-00209] and O.A. Efremova is grateful to EPSRC (EP/R006393/1) and Royal society (grant RSG\R1\180123). C.J Eling thanks the University of Hull for funding her PhD study. The authors would like to thank Dr I. A. Pyshnaya from the core facility of ICBFM SB RAS for DLS spectra. We are grateful to the multi-access centre – "Spectrometric measurements" (Institute of Biochemistry, Novosibirsk, Russia) for granting access to the equipment.

Conflict of interest

The authors declare no conflict of interest.

Keywords: cluster compounds, molybdenum, tungsten, hydrolysis, cytotoxicity

[1] a) Efremova, O. A., Shestopalov, M. A., Chirtsova, N. A., Smolentsev, A. I., Mironov, Y. V., Kitamura, N., Brylev, K. A. and Sutherland, A. J., *Dalton Trans.*, 2014, **43**, 6021-6025; b) Efremova, O. A., Vorotnikov, Y. A., Brylev, K. A., Vorotnikova, N. A., Novozhilov, I. N., Kuratieva, N. V., Edeleva, M. V., Benoit, D. M., Kitamura, N., Mironov, Y. V., Shestopalov, M. A. and Sutherland, A. J., *Dalton Trans.*, 2016, **45**, 15427-15435; c) Kirakci, K., Kubát, P., Langmaier, J., Polívka, T., Fuciman, M., Fejfarová, K. and Lang, K., *Dalton Trans.*, 2013, **42**, 7224-7232; d) Sokolov, M. N., Mihailov, M. A., Peresypkina, E. V., Brylev, K. A., Kitamura, N. and Fedin, V. P., *Dalton Trans.*, 2011, **40**, 6375-6377.

[2] a) Neaime, C., Amela-Cortes, M., Grasset, F., Molard, Y., Cordier, S., Dierre, B., Mortier, M., Takei, T., Takahashi, K., Haneda, H., Verelst, M. and Lechevallier, S., *Phys. Chem. Chem. Phys.*, 2016, **18**, 30166-30173; b) Solovieva, A. O., Vorotnikov, Y. A., Trifonova, K. E., Efremova, O. A., Krasilnikova, A. A., Brylev, K. A., Vorontsova, E. V., Avrorov, P. A., Shestopalova, L. V., Poveshchenko, A. F., Mironov, Y. V. and Shestopalov, M. A., *J. Mater. Chem. B*, 2016, **4**, 4839-4846; c) Svezhentseva, E. V., Solovieva, A. O., Vorotnikov, Y. A., Kurskaya, O. G., Brylev, K. A., Tsygankova, A. R., Edeleva, M. V., Gyrylova, S. N., Kitamura, N., Efremova, O. A., Shestopalov, M. A., Mironov, Y. V. and Shestopalov, A. M., *New J. Chem.*, 2017, **41**, 1670-1676; d) Vorotnikova, N. A., Edeleva, M. V., Kurskaya, O. G., Brylev, K. A., Shestopalov, A. M., Mironov, Y. V., Sutherland, A. J., Efremova, O. A. and Shestopalov, M. A., *Polym. Int.*, 2017, **66**, 1906-1912; e) Vorotnikova, N. A., Efremova, O. A., Tsygankova, A. R., Brylev, K. A., Edeleva, M. V., Kurskaya, O. G., Sutherland, A. J., Shestopalov, A. M., Mironov, Y. V. and Shestopalov, M. A., *Polym. Adv. Technol.*, 2016, **27**, 922-928.

[3] a) Brandhonneur, N., Hatahet, T., Amela-Cortes, M., Molard, Y., Cordier, S. and Dollo, G., *Eur. J. Pharm. Biopharm.*, 2018, **125**, 95-105; b) Cheplakova, A. M., Solovieva, A. O., Pozmogova, T. N., Vorotnikov, Y. A., Brylev, K. A., Vorotnikova, N. A., Vorontsova, E. V., Mironov, Y. V., Poveshchenko, A. F., Kovalenko, K. A. and Shestopalov, M. A., *J. Inorg. Biochem.*, 2017, **166**, 100-107.

[4] a) Beltrán, A., Mikhailov, M., Sokolov, M. N., Pérez-Laguna, V., Rezusta, A., José Revillo, M. and Galindo, F., *J. Mater. Chem. B*, 2016, **4**, 5975-5979; b) Felip-León, C., Arnau del Valle, C., Pérez-Laguna, V., Millán-Lou, M. I., Miravet, J. F., Mikhailov, M., Sokolov, M. N., Rezusta-López, A. and Galindo, F., *J. Mater. Chem. B*, 2017, **5**, 6058-6064.

[5] Rojas-Mancilla, E., Oyarce, A., Verdugo, V., Morales-Verdejo, C., Echeverria, C., Velásquez, F., Chnaiderman, J., Valiente-Echeverría, F. and Ramirez-Tagle, R., *Molecules*, 2018, **22**, 1108.

[6] a) Amela-Cortes, M., Molard, Y., Paofai, S., Desert, A., Duvail, J. L., Naumov, N. G. and Cordier, S., *Dalton Trans.*, 2016, **45**, 237-245; b) Amela-Cortes, M., Paofai, S., Cordier, S., Folliot, H. and Molard, Y., *Chem Commun*, 2015, **51**, 8177-8180; c) Efremova, O. A., Brylev, K. A., Kozlova, O., White, M. S., Shestopalov, M. A., Kitamura, N., Mironov, Y. V., Bauer, S. and Sutherland, A. J., *J. Mater. Chem. C*, 2014, **2**, 8630-8638; d) Nguyen, T. K. N., Grasset, F., Dierre, B., Matsunaga, C., Cordier, S., Lemoine, P., Ohashi, N. and Uchikoshi, T., *ECS J. Solid State Sci. Technol.*, 2016, **5**, R178-R186.

[7] a) Barras, A., Das, M. R., Devarapalli, R. R., Shelke, M. V., Cordier, S., Szunerits, S. and Boukherroub, R., *Appl. Catal., B*, 2013, **130-131**, 270–276; b) Feliz, M., Puche, M., Atienzar, P., Concepción, P., Cordier, S. and Molard, Y., *ChemSusChem*, 2016, **9**, 1963-1971; c) Kumar, P., Mungse, H. P., Cordier, S., Boukherroub, R., Khatri, O. P. and Jain, S. L., *Carbon*, 2015, **94**, 91-100.

[8] Kirakci, K., Kubát, P., Kučeráková, M., Šícha, V., Gbelcová, H., Lovecká, P., Grznárová, P., Ruml, T. and Lang, K., *Inorg. Chim. Acta*, 2016, **441**, 42-49.

[9] Vorotnikov, Y. A., Efremova, O. A., Novozhilov, I. N., Yanshole, V. V., Kuratieva, N. V., Brylev, K. A., Kitamura, N., Mironov, Y. V. and Shestopalov, M. A., *J. Mol. Struct.*, 2017, **1134**, 237-243.

[10] a) Vorotnikov, Y. A., Efremova, O. A., Vorotnikova, N. A., Brylev, K. A., Edeleva, M. V., Tsygankova, A. R., Smolentsev, A. I., Kitamura, N., Mironov, Y. V. and Shestopalov, M. A., *RSC Adv.*, 2016, **6**, 43367-43375; b) Vorotnikova, N. A., Vorotnikov, Y. A., Novozhilov, I. N., Syrokvashin, M. M., Nadolinny, V. A., Kuratieva, N. V., Benoit, D. M., Mironov, Y. V., Walton, R. I., Clarkson, G., J., Kitamura, N., Sutherland, A. J., Shestopalov, M. A. and Efremova, O. A., *Inorg. Chem.*, 2018, **57**, 811–820.

[11] Diao, T., White, P., Guzei, I. and Stahl, S. S., *Inorg. Chem.*, 2012, **51**, 11898-11909.

[12] a) Kirakci, K., Kubát, P., Fejfarová, K., Martinčík, J., Nikl, M. and Lang, K., *Inorg. Chem.*, 2016, **55**, 803-809; b) Mikhailov, M. A., Brylev, K. A., Abramov, P. A., Sakuda, E., Akagi, S., Ito, A., Kitamura, N. and Sokolov, M. N., *Inorg. Chem.*, 2016, **55**, 8437-8445.

[13] a) Evtushok, D. V., Melnikov, A. R., Vorotnikova, N. A., Vorotnikov, Y. A., Ryadun, A. A., Kuratieva, N. V., Kozyr, K. V., Obedinskaya, N. R., Kretov, E. I., Novozhilov, I. N., Mironov, Y. V., Stass, D. V., Efremova, O. A. and Shestopalov, M. A., *Dalton Trans.*, 2017, **46**, 11738-11747; b) Evtushok, D. V., Vorotnikova, N. A., Logvinenko, V. A., Smolentsev, A. I., Brylev, K. A., Plyusnin, P. E., Pishchur, D. P., Kitamura, N., Mironov, Y. V., Solovieva, A. O., Efremova, O. A. and Shestopalov, M. A., *New J. Chem.*, 2017, **41**, 14855-14861.

[14] Mikhaylov, M. A., Abramov, P. A., Komarov, V. Y. and Sokolov, M. N., *Polyhedron*, 2017, **122**, 241-246.

[15] a) Li, J., Andrejić, M., Mata, R. A. and Ryde, U., *Eur. J. Inorg. Chem.*, 2015, **2015**, 3580-3589; b) Mikhailov, M. A., Gushchin, A. L., Gallyamov, M. R., Virovets, A. V., Sokolov, M. N., Sheven', D. G. and Pervukhin, V. V., *Russ. J. Coord. Chem.*, 2017, **43**, 172-180; c) Sung, K.-M., Holm, R. H., *J. Am. Chem. Soc.*, 2001, **123**, 1931-1943; d) Wang, J.-J., Kryatova, O. P., Rybak-Akimova, E. V. and Holm, R. H., *Inorg. Chem.*, 2004, **43**, 8092-8101; e) Pivovarov, A. P., *Russ. Chem. Bull.*, 2008, **57**, 289-291.

[16] a) Johnstone, T. C., Suntharalingam, K. and Lippard, S. J., *Chem. Rev.*, 2016, **116**, 3436‐3486; b) Egger, A., Cebrián‐Losantos, B., Stepanenko, I. N., Krokhin, A. A., Eichinger, R., Jakupec, M. A., Arion, V. B. and Keppler, B. K., *Chem. Biodivers.*, 2008, **5**, 1588-1593; c) Levina, A., Mitra, A. and Lay, P. A., *Metallomics*, 2009, **1**, 458-470 ; d) Narváez-Pita, X., Ortega-Zuniga, C., Acevedo-Morantes, C. Y., Pastrana, B., Olivero-Verbel, J., Maldonado-Rojas, W., Ramírez-Vick, J. E. and Meléndez, E., *J. Inorg. Biochem*, 2014, **132**, 77-91.

[17] a) Jackson, J. A., Newsham, M. D., Worsham, C. and Nocera, D. G., *Chem. Mater.*, 1996, **8**, 558-564; b) Jackson, J. A., Turro, C., Newsham, M. D. and Nocera, D. G., *J. Phys. Chem.*, 1990, **94**, 4500-4507; c) Kirakci, K., Fejfarová, K., Kučeráková, M. and Lang, K., *Eur. J. Inorg. Chem.*, 2014, **2014**, 2331-2336; d) Kirakci, K., Šícha, V., Holub, J., Kubát, P. and Lang, K., *Inorg. Chem.*, 2014, **53**, 13012-13018; e) Kirakci, K., Zelenka, J., Rumlová, M., Martinčík, J., Nikl, M., Ruml, T. and Lang, K., *J. Mater. Chem. B*, 2018, **6**, 4301-4307.

[18] Maverick, A. W., Najdzionek, J. S., Mackenzie, D., Nocera, D. G. and Gray, H. B., *J. Am. Chem. Soc.*, 1983, **105**, 1878-1882.

[19] Cao, Y., Long, J., Liu, L., He, T., Jiang, L., Zhao, C. and Li, Z., *Life Sci.*, 2017, **186**, 33-42.

[20] Huo, L., Chen, R., Zhao, L., Shi, X., Bai, R., Long, D., Chen, F., Zhao, Y., Chang, Y.-Z. and Chen, C., *Biomaterials*, 2015, **61**, 307-315.

[21] a) Tsai, Y.-Y., Huang, Y.-H., Chao, Y.-L., Hu, K.-Y., Chin, L.-T., Chou, S.-H., Hour, A.-L., Yao, Y.-D., Tu, C.-S., Liang, Y.-J., Tsai, C.-Y., Wu, H.-Y., Tan, S.-W. and Chen, H.-M., *ACS Nano*, 2011, **5**, 9354–9369; b) Wang, J., Fang, X. and Liang, W., *ACS Nano*, 2012, **6**, 5018-5030; c) Wang, L., Meng, J., Cao, W., Li, Q., Qiu, Y., Sun, B. and Li, L. M., *Methods*, 2014, **67**, 394-406.