

SELF-ASSEMBLY OF BORON CLUSTER COMPOUNDS  
AND THEIR COASSEMBLY WITH POLYMERS

A summary of dissertation presented

by

Vladimír Ďord'ovič

to

Department of Physical and Macromolecular Chemistry

in partial fulfillment of the requirements for the degree of  
Doctor of Philosophy in the subject of Physical Chemistry

CHARLES UNIVERSITY

Faculty of Science

Supervisor: RNDr. Pavel Matějček, Ph.D.

Advisor: Ing. Mariusz Uchman, PhD.

Prague 2017



## **Abstract**

This thesis focuses on the self-assembly of the boron cluster compounds and the coassembly of metallacaborane cobalt bis(dicarbollide), COSAN, with hydrophilic polymers. The research was motivated by the discovery of HIV inhibition by COSAN and its conjugates. Therefore, we decided to study in detail the behavior of boron cluster compounds in water. We demonstrated the amphiphilic character of several boranes and carboranes by the study of surface tension and self-assembly despite the absence of classical amphiphilic topology. The behavior of COSAN showed similarities with classical surfactants, such as SDS, whereas the behavior of smaller clusters with high charge density reminded hydrotropes or chaotropes. Furthermore, we searched for the most suitable carriers of COSAN for drug delivery. Based on the earlier findings that COSAN interacts with both poly(ethylene oxide), PEO, and poly(2-oxazoline), POX, we prepared nanoparticles by mixing COSAN with block copolymers of various types of POX. Comparing linear and star-like block copolymers, we showed that the polymer architecture has a crucial role in the morphology of nanoparticles. In addition, we proved different selectivity of alkaline cations towards PEO and POX, resulting in the different structures of nanoparticles depending on the present cations. Cation selectivity was also achieved by the synthesized COSAN conjugates, dumbbells, in which two COSAN anions were connected by an oligo(ethylene oxide) linker. Finally, we extended the studies of polymeric COSAN carriers by thermoresponsive block copolymer of POX. Its interaction with COSAN led to the nanoparticles which structure showed dependence on the temperature. The presented results have a potential for tailored nano-carriers in drug delivery and other applications. For the characterization of all the assemblies studied we used light and X-ray scattering,  $^1\text{H}$  and DOSY NMR spectroscopy, transmission electron microscopy, surface tension, calorimetry, and conductometry.

**Keywords:** self-assembly, borane, carborane, polymer, nanoparticle

# Contents

1	Introduction .....	1
2	Theoretical background .....	1
3	Materials and methods .....	2
3.1	Studied materials .....	2
3.2	Characterization methods .....	4
4	Research aims .....	5
5	Results .....	6
5.1	Paper I .....	6
5.2	Paper II .....	7
5.3	Paper III .....	8
5.4	Paper IV .....	9
5.5	Paper V .....	10
5.6	Paper VI .....	11
6	Conclusions and summary .....	12
7	References .....	16
	Curriculum vitae .....	17
	List of papers .....	19



# 1 Introduction

This dissertation consists of the studies on the self-assembly of boranes and carboranes, the interactions between metallacarborane and polymers, and the preparation of polymeric nanoparticles with COSAN. This research was conducted in the Boron cluster laboratory of my supervisor, Dr. Pavel Matějček, which is part of the Soft Matter group of prof. Karel Procházka, at the Department of Physical and Macromolecular Chemistry at Charles University in Prague, from September 2013 to April 2017. Thanks to MŠMT/DAAD funding (7AMB16D007/57220012), I could also spend three months in the group of prof. Michael Gradzielski at Technical University in Berlin and the group of Dr. Reinhard Miller at Max Planck Institute for Colloids and Interfaces in Gölml, where I mainly studied metallacarboranes behavior at water/air interface by different tensiometry techniques. The results of this thesis are presented as the collection of six, thematically ordered, publications. In these, where I am the first author, my contribution was in preparation of the nanoparticles, conducting most of the experiments and writing manuscripts. In two publications, where I am not the first author, my contribution was in measurements of dynamic light scattering, solubility determinations, Cryo-TEM micrograph analyzes and  $^1\text{H}$  NMR measurements. The support of the Grant Agency of Charles University (GAUK 512214) and the Czech Science Foundation (P205/14-14608S; P208/17-00648S) is gratefully acknowledged.

## 2 Theoretical background

Boranes are compounds of boron and hydrogen with the generic formula  $\text{B}_x\text{H}_y$ . This work focuses on closed clusters *closo*-boranes,  $[\text{B}_n\text{H}_n]^{2-}$ , and their subgroups carboranes and metallacarboranes (Figure 1). Carboranes are defined as carbon-boron clusters of four or more vertices in which non-classical (electron-delocalized multicenter) bonding plays a significant role.<sup>[1]</sup> Carboranes have the extraordinary ability to incorporate metal atoms, which led to the synthesis of metallacarboranes. The most studied metallacarborane is cobalt bis(dicarbollide),  $[3,3'\text{-Co}(\text{C}_2\text{B}_9\text{H}_{11})_2]^-$  anion, also known as the COSAN (Figure 1), which contains cobalt sandwiched by two dicarbollide *nido*-clusters.

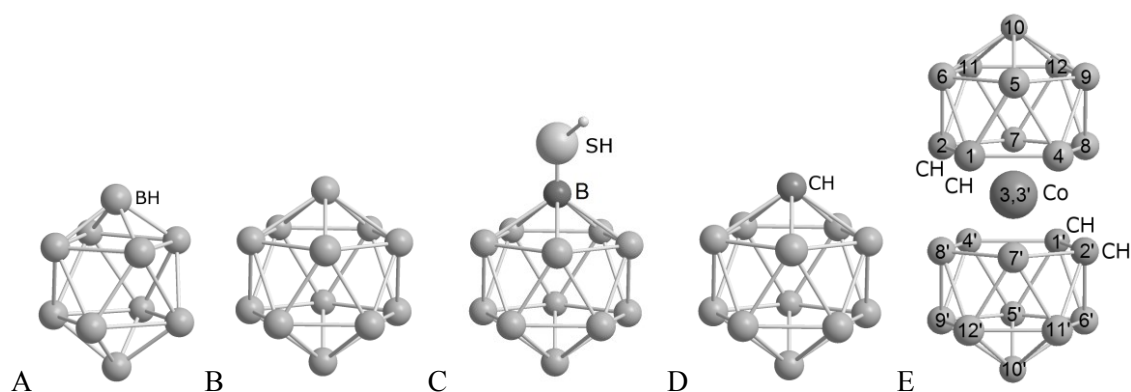
Boranes show many unique properties, such as multicenter “electron deficient” bonding (B–B–B or B–H–B) and cluster aromaticity. Partial negative charge on hydrogens of boranes can provide dihydrogen bonds with positively charged hydrogens.<sup>[2]</sup> These

hydrogens also influence hydration of boranes and causes their unusual solution behavior. The main structural unit of *closo*-boranes is the 12 vertices-icosahedron, B<sub>12</sub>, which is to boron what the hexagon is to carbon. All icosahedral compounds are exceptionally stable and [B<sub>12</sub>H<sub>12</sub>]<sup>2-</sup> is even claimed to be the most stable molecule known to chemistry, withstanding temperatures above 800°C. Other typical phenomenon of some anionic clusters is charge delocalization, which leads to their very low-coordinating character.

Thanks to these properties, boron cluster compounds found their use in various fields. The most known medical application of boranes is BNCT (Boron Neutron Capture Therapy),<sup>[3]</sup> the treatment of cancer based on the nuclear reaction of <sup>10</sup>B producing high-energy ions that can selectively kill tumor cells. Metallocaboranes have been employed, for example, in radioactive ion extraction,<sup>[4]</sup> catalysis,<sup>[5]</sup> and also in biomedical research,<sup>[6,7]</sup> which results in the need of effective carrier of boron clusters. For this purpose, Matějčiek et al. prepared the first type of unique nanostructures based on the complexation of hydrophilic poly(ethylene oxide), PEO, with COSAN resulting in a nanocomposite.<sup>[8,9]</sup> This coassembly can be used for the preparation of nanoparticles with PEO block in combination with different stabilizing block.<sup>[8,10]</sup> The main driving force for COSAN complexation with polymers is dihydrogen bonding of the B–H vertices with the ethylene subunits of the PEO chain and with polymers consisting of a similar motif such as poly(2-alkyl-2-oxazolines).<sup>[10]</sup>

## 3 Materials and methods

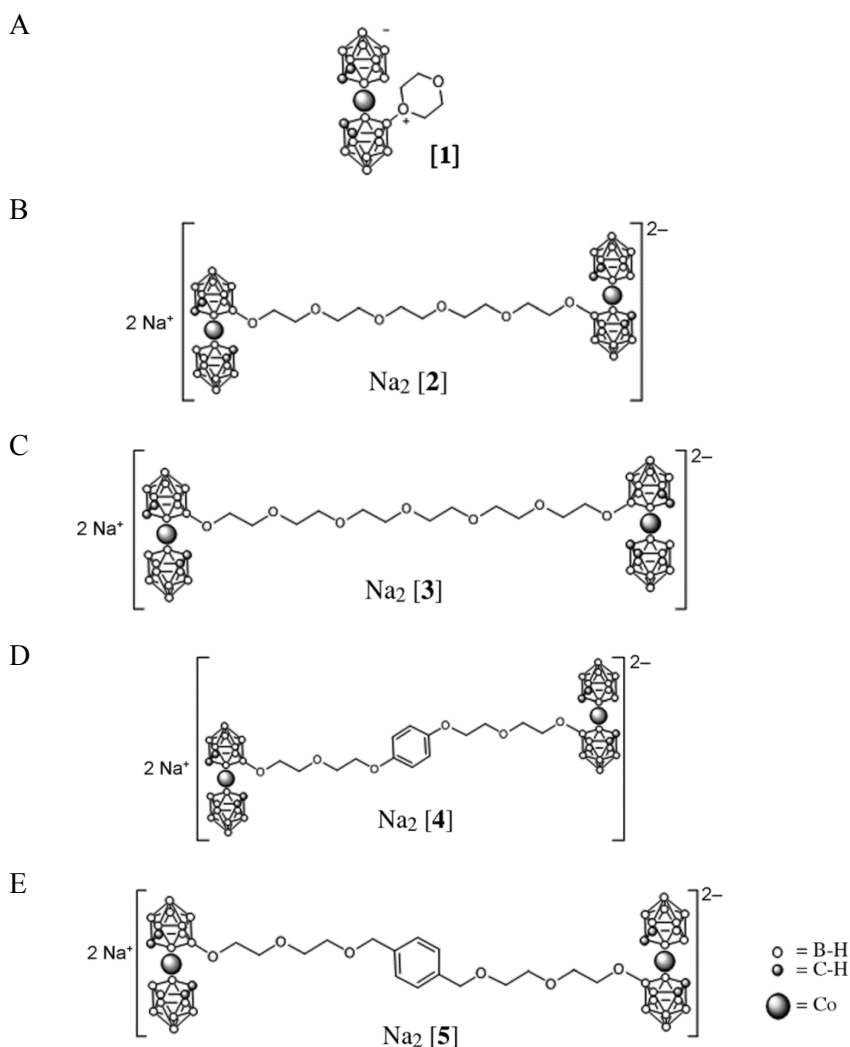
### 3.1 Studied materials



**Figure 1.** Structure of the studied boron cluster compounds: (A) [B<sub>10</sub>H<sub>10</sub>]<sup>2-</sup>, (B) [B<sub>12</sub>H<sub>12</sub>]<sup>2-</sup>, (C) [B<sub>12</sub>H<sub>11</sub>SH]<sup>2-</sup>, (D) [CB<sub>11</sub>H<sub>12</sub>]<sup>-</sup>, and (E) [3,3'-Co(C<sub>2</sub>B<sub>9</sub>H<sub>11</sub>)<sub>2</sub>]<sup>-</sup>.

In this thesis, following compounds were used:

- Boron cluster compounds (Figure 1): sodium decaborate,  $\text{Na}_2[\text{B}_{10}\text{H}_{10}]$ , sodium dodecaborate,  $\text{Na}_2[\text{B}_{12}\text{H}_{12}]$ , potassium 1-carba-dodecaborate,  $\text{K}[\text{CB}_{11}\text{H}_{12}]$ , sodium mercaptododecaborate,  $\text{Na}_2[\text{B}_{12}\text{H}_{11}\text{SH}]$  or  $\text{Na}_2[\text{BSH}]$ , and various salts of [3-cobalt(III) bis(1,2-dicarbollide)] ( $-1$ ), COSAN.
- Dumbbells (Figure 2)
- Polymers (Figure 3): [poly(ethylene oxide)-*block*-poly(2-methyl-2-oxazoline)]<sub>4</sub>, [PEO-PMeOx]<sub>4</sub>, poly(ethylene oxide)-*block*-poly(2-ethyl-2-oxazoline), PEO-PEtOx, poly(2-ethyl-2-oxazoline)-*block*-poly(ethylene oxide)-*block*-poly(2-ethyl-2-oxazoline), PEtOx-PEO-PEtOx and poly(2-methyl-2-oxazoline)-*block*-poly(2-*n*-propyl-2-oxazoline), PMeOx-PPrOx.



**Figure 2.** Structures of (A) cobaltabisdicarbollide dioxanate **[1]** and (B) dumbbells:  $\text{Na}_2$ **[2]**, (C)  $\text{Na}_2$ **[3]**, (D)  $\text{Na}_2$ **[4]**, (E)  $\text{Na}_2$ **[5]**.





## 4 Research aims

The research of carboranes in the laboratory of my supervisor Dr. Matějčíček began more than ten years ago and the main stimulus was the discovery of the inhibition of HIV protease by cobalt bis(1,2-dicarbollide), COSAN, and its conjugates. Besides that, other potential applications have been known mostly related to medicine. However, the understanding of the behavior of COSAN and other boron cluster compounds in water and salt was unclear. Because the aggregation of boron drugs can influence the potential medical use, we focused on the amphiphilicity of cluster compounds. Furthermore, we searched for the most suitable drug delivery carriers of COSAN. In summary, the aims of this thesis were:

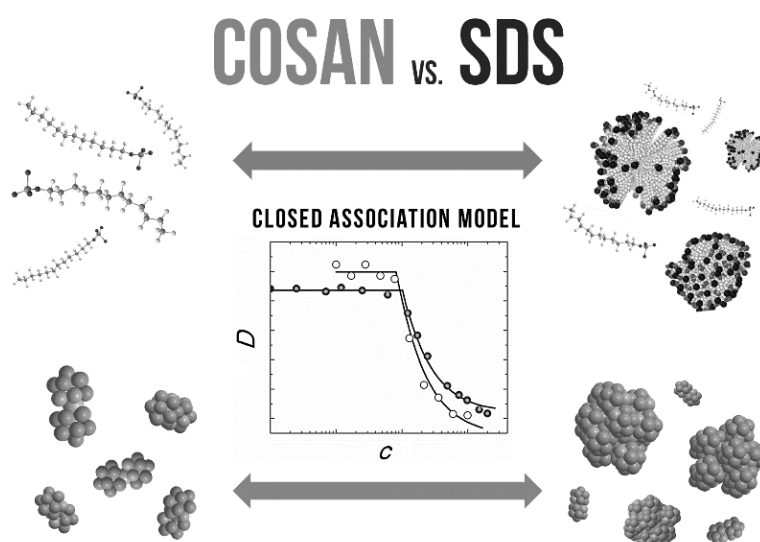
- The description of the self-assembly processes of various boron cluster compounds and their conjugates in water.
- The clarification of the hydrophobic or amphiphilic character of boron cluster compounds.
- The preparation of polymeric carriers of COSAN and the study of the interactions between COSAN and block copolymers. Additionally, the focus was on the stimuli, which can be possibly used for drug release.

## 5 Results

### 5.1 Paper I

#### Classical amphiphilic behavior of nonclassical amphiphiles: A comparison of metallacarborane self-assembly with SDS micellization\*

\* Published as: Uchman, M., Ďord'ovič, V., Tošner, Z., Matějček, P.: Classical Amphiphilic Behavior of Nonclassical Amphiphiles: A Comparison of Metallacarborane Self-Assembly with SDS Micellization, *Angewandte Chemie – International Edition* **2015**, *54*, 14113–14117.

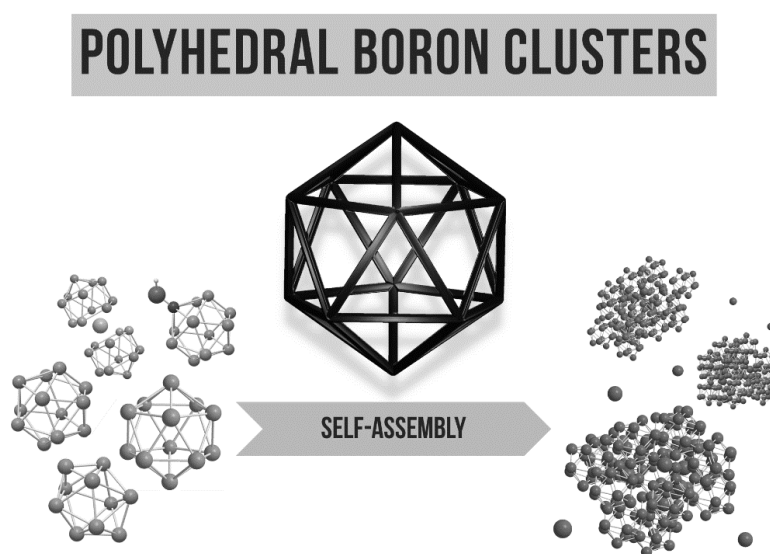


The self-assembly of metallacarboranes, a peculiar family of compounds showing surface activity and resembling molecular-scale Pickering stabilizers, has been investigated by comparison to the micellization of sodium dodecylsulfate (SDS). These studies have shown that molecules without classical amphiphilic topology but with an inherent amphiphilic nature can behave similarly to classical surfactants. As shown by NMR techniques, the self-assembly of both metallacarboranes and SDS obey a closed association model (see the concentration dependence of diffusion coefficients in graphical abstract). The aggregation of metallacarboranes is found to be enthalpy-driven, which is very unusual for classical surfactants. Possible explanations of this fact were outlined.

## 5.2 Paper II

### Stealth Amphiphiles: Self-Assembly of Polyhedral Boron Clusters\*

\* Published as: Ďord'ovič, V.; Tošner, Z.; Uchman, M.; Zhigunov, A.; Reza, M.; Ruokolainen, J.; Pramanik, G.; Cígler, P.; Kalíkova, K.; Gradzielski, M.; Matějček, P.: Stealth Amphiphiles: Self-Assembly of Polyhedral Boron Clusters. *Langmuir* **2016**, *32*, 6713–6722.

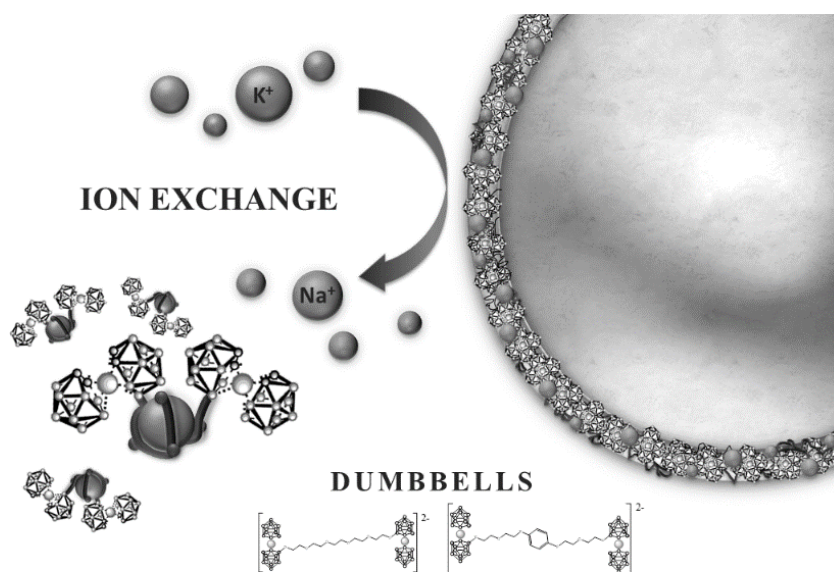


This is the first experimental evidence that both self-assembly and surface activity are common features of all water-soluble boron cluster compounds. The solution behavior of anionic polyhedral boranes (sodium decaborate, sodium dodecaborate, and sodium mercaptododeca-borate), carboranes (potassium 1-carba-dodecaborate), and metallacarboranes {sodium [cobalt bis(1,2-dicarbollide)]} was extensively studied, and it is evident that all the anionic boron clusters form multimolecular aggregates in water. However, the mechanism of aggregation is dependent on size and polarity. The series of studied clusters spans from a small hydrophilic decaborate-resembling hydrotrope to a bulky hydrophobic cobalt bis-(dicarbollide) behaving like a classical surfactant. Despite their pristine structure resembling Platonic solids, the nature of anionic boron cluster compounds is inherently amphiphilic – they are stealth amphiphiles.

### 5.3 Paper III

#### Aqueous self-assembly and cation selectivity of cobaltabisdicarbollide dianionic dumbbells\*

\* Published as: Tarrés, M.; Viñas, C.; González-Cardoso, P.; Hanninen, M.; Sillanpää, R.; Ďord'ovič, V.; Uchman, M.; Teixidor, F.; Matějček, P.: Aqueous Self-Assembly and Cation Selectivity of Cobaltabisdicarbollide Dianionic Dumbbells, *Chemistry – A European Journal* **2014**, *20*, 6786–6794.

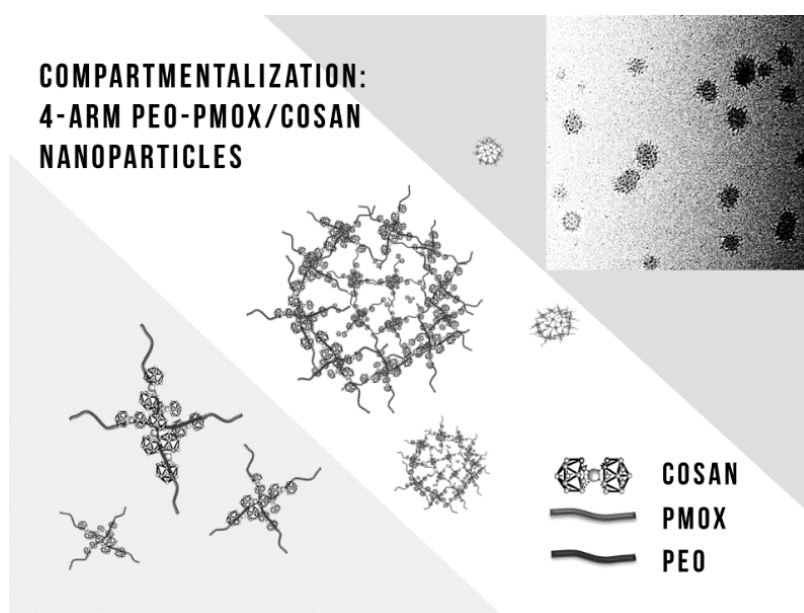


It was known that the COSAN anion produces aggregates in water solution. In this work, we demonstrate that it is possible to generate aggregates even after the incorporation of additional functional groups to the COSAN units. The approach has been to join two COSAN anions by a linker (compounds called dumbbells, Figure 2) that can adapt itself to perform as a crown ether. The linker has been chosen to have six oxygen atoms that is the ideal number for  $K^+$  selectivity in crown ethers. It is demonstrated that the linker binds the alkaline metal ions with different affinities. The highest affinity is shown towards  $K^+$  from a mix containing  $Li^+$ ,  $Na^+$ ,  $K^+$ ,  $Rb^+$  and  $Cs^+$ . The distinct affinity towards alkaline metal ions was corroborated by solubility studies and ITC thermograms. Further, cryo-TEM micrographs, along with light scattering results, reveal the existence of small self-assemblies and compact nanostructures. The studies reported here have shown that these dumbbells can be in water or lipophilic phases with different appearances, either molecules or aggregates, offering a distinct model as drug carriers.

## 5.4 Paper IV

### Compartmentalization in hybrid metallacarboranes nanoparticles formed by block copolymers with star-like architecture\*

\* Published as: Ďordovič, V.; Uchman, M.; Zhigunov, A.; Nykanen, A.; Ruokolainen, J.; Matějček, P.: Compartmentalization in Hybrid Metallacarborane Nanoparticles Formed by Block Copolymers with Star-Like Architecture, *ACS Macro Letters* **2014**, *3*, 1151–1155.

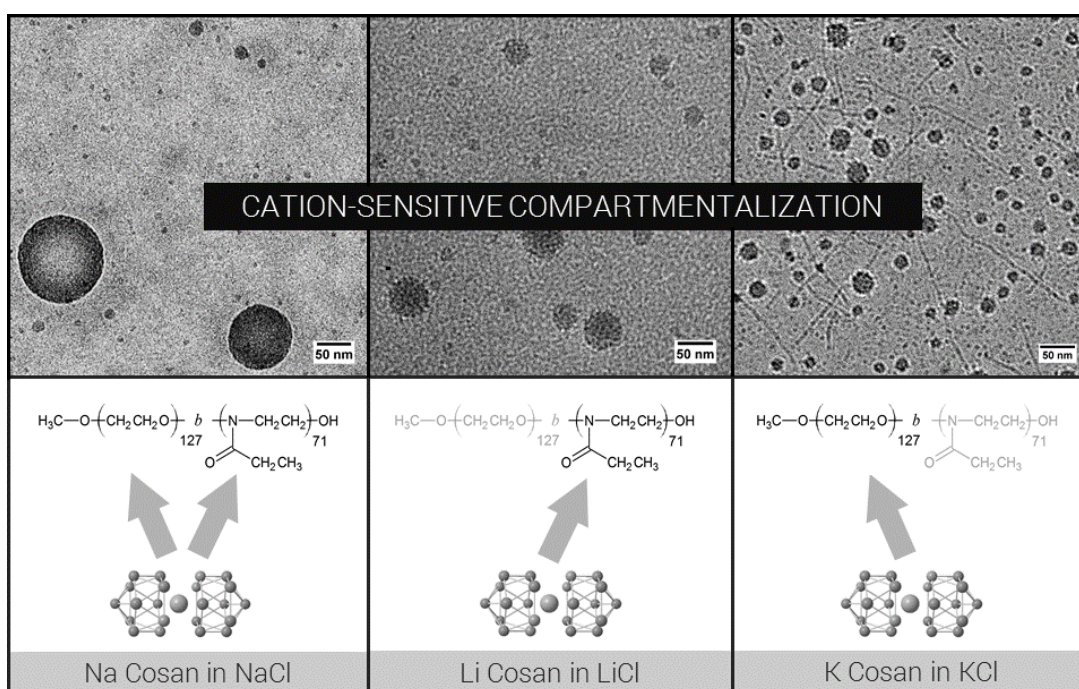


One strategy to control the morphology of hybrid polymeric nanostructures is the proper selection of macromolecule architecture. We prepared metallacarborane-rich nanoparticles by interaction of doublehydrophilic block copolymers consisting of both poly(2-alkyl-2-oxazolines) and poly(ethylene oxide), PEO, blocks with cobaltabisdicarbollide anion in physiological saline. The inner structure of the hybrid nanoparticles was studied by cryo-TEM, light scattering, SAXS, NMR, and ITC. Although the thermodynamics of diblock and star-like systems are almost identical, the macromolecular architecture has a great impact on the size and inner morphology of the nanoparticles. While hybrid nanoparticles formed by linear diblock copolymers are homogeneous, resembling gel-like nanospheres, the star-like shape of 4-arm block copolymers with PEO blocks in central parts of macromolecules leads to distinct compartmentalization.

## 5.5 Paper V

### Cation-sensitive compartmentalization in metallacarborane containing polymer nanoparticles\*

\* Published as: Ďord'ovič, V.; Uchman, M.; Reza, M.; Ruokolainen, J.; Zhigunov, A.; Ivankov, O.; Matějček, P.: Cation-Sensitive Compartmentalization in Metallacarborane Containing Polymer Nanoparticles. *RSC Advances* **2016**, *6*, 9884–9892.

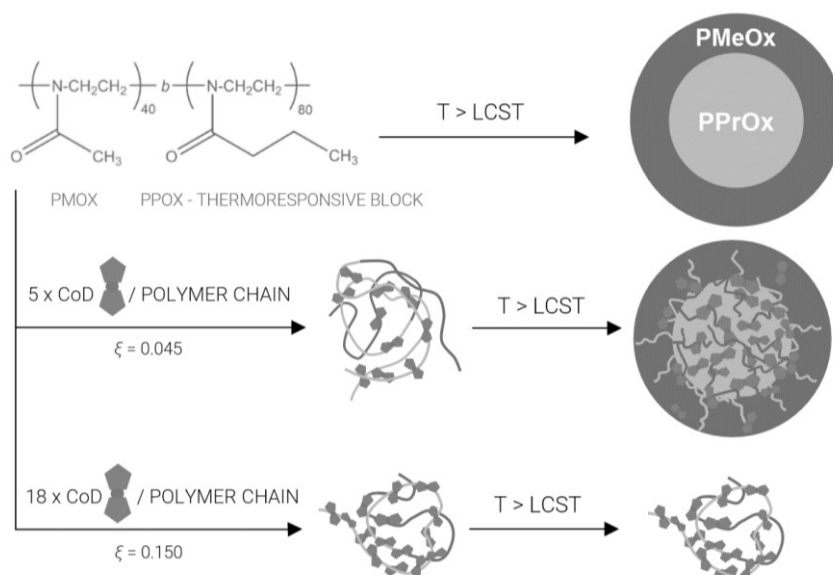


Alkaline cations ( $\text{Li}^+$ ,  $\text{Na}^+$  and  $\text{K}^+$ ) are introduced as agents suitable to control compartmentalization in metallacarborane-rich nanoparticles of double-hydrophilic block copolymer poly(ethylene oxide)-*block*-poly(2-alkyl-2-oxazoline), PEO–PEtOx. Interaction of COSAN with PEO–PEtOx is based mainly on dihydrogen bonding between metallacarborane boron clusters and the polymer backbone resulting in compact nanoparticles. However, the cations are a crucial factor as to whether interaction with PEO or POX segments is preferred. Changes in the bulk concentration of alkaline cations can thus provoke changes in the inner structure of polymeric nanoparticles, which is accompanied by exchange of boron clusters and alkaline cations like  $\text{Li}^+$ . Because of the biomedical importance of metallacarboranes, their conjugates and also lithium salts, the hybrid nanoparticles can act as stimuli-responsive systems for drug delivery.

## 5.6 Paper VI

### Tuning of thermoresponsivity of poly(2-alkyl-2-oxazoline) block copolymer by interaction with surface active and chaotropic metallacarborane anion\*

\* Manuskript: Ďordovič, V.; Verbraeken, B.; Hogenboom, R.; Kereiche, S.; Matějček, S.; Uchman, M. Tuning of thermoresponsivity of poly(2-alkyl-2-oxazoline) block copolymer by interaction with surface active and chaotropic metallacarborane anion.

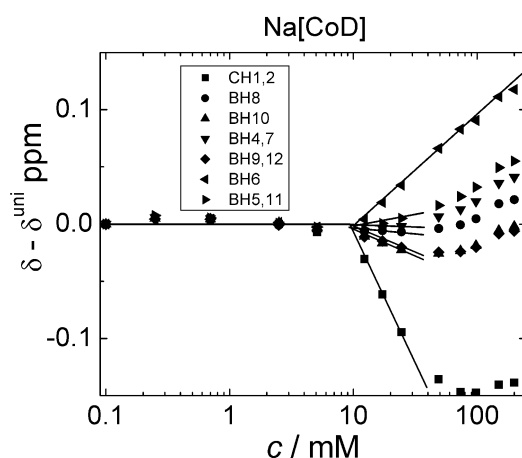


We prepared thermoresponsive nanoparticles based on interaction of metallacarboranes, bulky chaotropic and surface active anions, with poly(2-alkyl-2-oxazoline) block copolymers. Recently, metallacarboranes gained a great potential in biomedicine and many delivery nanosystems have been proposed. However, none of them have thermoresponsive character. Therefore, we synthesized a thermoresponsive block copolymer poly(2-methyl-2-oxazoline)-*block*-poly(2-*n*-propyl-2-oxazoline), PMeOx-PPrOx. Light scattering, NMR spectroscopy, ITC and cryo-TEM were used to characterize all the solutions of the formed nanoparticles. The cloud point temperature of the block copolymer was observed at 30°C and above this temperature polymeric micelles were formed. Metallacarborane COSAN, was found to interact with both polymeric segments. Depending on COSAN concentration, this affinity influenced the phase transition of thermoresponsive PPrOx block. LCST was shifted to lower values at mild COSAN content. At elevated concentrations of COSAN, the hybrid nanoparticles are fragmented into relatively small species and the increase in temperature leads to higher polymer mobility and COSAN release.

## 6 Conclusions and summary

Among the studied boron cluster compounds were sodium COSAN,  $\text{Na}[\text{Co}(\text{C}_2\text{B}_9\text{H}_{11})_2]$ , sodium decaborate,  $\text{Na}_2[\text{B}_{10}\text{H}_{10}]$ , sodium dodecaborate,  $\text{Na}_2[\text{B}_{12}\text{H}_{12}]$ , potassium 1-carbadodecaborate,  $\text{K}[\text{CB}_{11}\text{H}_{12}]$ , and sodium mercaptododecaborate,  $\text{Na}_2[\text{B}_{12}\text{H}_{11}\text{SH}]$ . We described their behavior in water and all the studied compounds were found to behave as amphiphiles, which was demonstrated by their surface activity and aggregation.

The most hydrophobic and the largest among the studied compound is COSAN. Its behavior showed evident similarities with the classical surfactant, such as SDS, despite the absence of amphiphilic head-tail topology (paper I). The aggregation obeyed closed association model resulting in the CAC (Figure 4) and the formation of aggregates, which size did not depend on concentration. These aggregates could not grow beyond a certain limit because of electrostatic restrictions, as almost all the counterions were not condensed in the aggregates. Furthermore, both COSAN and SDS formed complexes with cationic polyelectrolytes and also with electroneutral poly(ethylene oxide). However, thermodynamics of SDS micellization was driven by entropy, whereas the self-assembly of COSAN is enthalpy-driven.

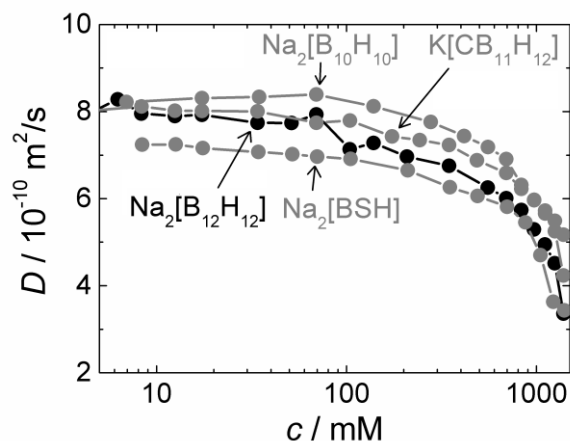


**Figure 4.** Changes in the relative chemical shifts for signals in the  $^1\text{H}\{^{11}\text{B}\}$  NMR spectra of  $\text{Na}[\text{COSAN}]$  (see Figure 1 for numbering scheme).

On the other hand, anions  $[\text{B}_{10}\text{H}_{10}]^{2-}$ ,  $[\text{B}_{12}\text{H}_{12}]^{2-}$ ,  $[\text{CB}_{11}\text{H}_{12}]^-$  and  $[\text{B}_{12}\text{H}_{11}\text{SH}]^{2-}$  are less hydrophobic, their size is smaller and the charge density is higher comparing to COSAN (paper II). Their aggregates grew with an increasing concentration without a limit with the aggregation number higher than that of COSAN, and without an electrostatic restriction because of the effective counterion condensation. Their behavior resembled



hydrotropes or chaotropes. Interestingly, the presence of the exoskeletal substitution (–SH group) or the C–H unit within the cluster did not influence the aggregation process. Thus, the most probable reason of this “stealth” amphiphilicity is nonclassical hydrophobic effect related to the unusual hydration.



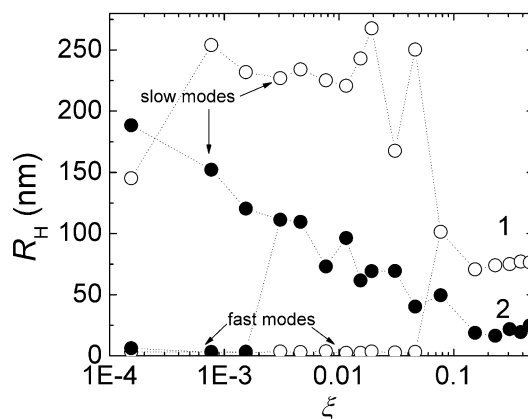
**Figure 5.** Diffusion coefficients as function of concentration obtained from  $^1\text{H}$   $\{^{11}\text{B}\}$  DOSY NMR of  $\text{Na}_2[\text{B}_{10}\text{H}_{10}]$ ,  $\text{Na}_2[\text{B}_{12}\text{H}_{12}]$ ,  $\text{K}[\text{CB}_{11}\text{H}_{12}]$ , and  $\text{Na}_2[\text{B}_{12}\text{H}_{12}\text{SH}]$ .

In the study of COSAN conjugates (paper III), two COSAN anions were connected by a linker to achieve a function of cations complexation. The four synthesized conjugates, dumbbells, differed in length and nature of the oligo(ethylene oxide) linker. All the dumbbells aggregated in water and the aggregate morphology could be tuned by salt concentration from spheres to vesicles and small self-assemblies consisting of only several molecules. The linker was found to bound to the alkaline metal ions with different affinities, resembling crown ether effect. From a mixture containing  $\text{Li}^+$ ,  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Rb}^+$  and  $\text{Cs}^+$ , the highest affinity was shown towards  $\text{K}^+$ . ITC study of  $\text{K}^+$  complexation provided evidence for three binding sites on the dumbbell molecules. Apparently, the ring around cation was closed by two COSAN anions at the two ends of the linker.

Further research focused on coassembly of COSAN with block copolymers and was based on the earlier findings that COSAN interacts with poly(ethylene oxide), PEO, and poly(2-ethyl-2-oxazoline), PEtOx, via dihydrogen bonding between B–H vertices and C–H groups of the polymeric backbone.

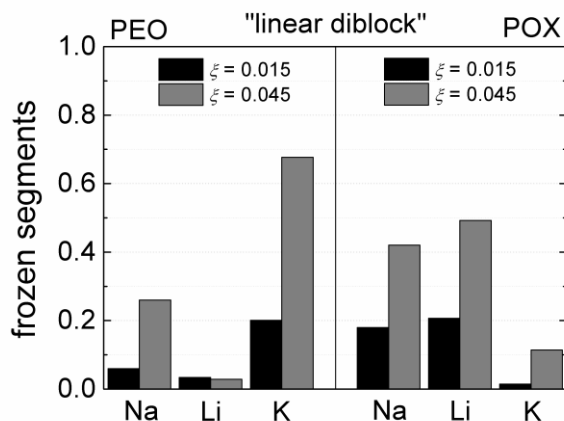
In the first study of polymeric nanoparticles in the thesis (paper IV), we prepared COSAN multicompartament nanoparticles by the mixing of COSAN with star-like double-hydrophilic polymer, [poly(ethylene oxide)-*block*-poly(2-methyl-2-oxazoline)]<sub>4</sub>, [PEO–

PMeOx]<sub>4</sub> in physiological saline (see light scattering results in Figure 6). The nanoparticles consisted of approximately 30 compartments that were formed by one [PEO–PMeOx]<sub>4</sub> molecule with COSAN clusters densely packed within the central parts of the compartment in which PEO segments are located. Comparing to the previously studied linear block copolymer, PEO–PEtOx, we demonstrated that the polymer architecture has a crucial role in the morphology of nanoparticles.



**Figure 6.** Dependence of hydrodynamic radius,  $R_H$ , on the addition of Na[COSAN] to PEO–PEtOx (hollow circles, curves 1) and [PEO–PMeOx]<sub>4</sub> (black circles, curves 2) solutions (2 g/L) in 0.154 M NaCl.

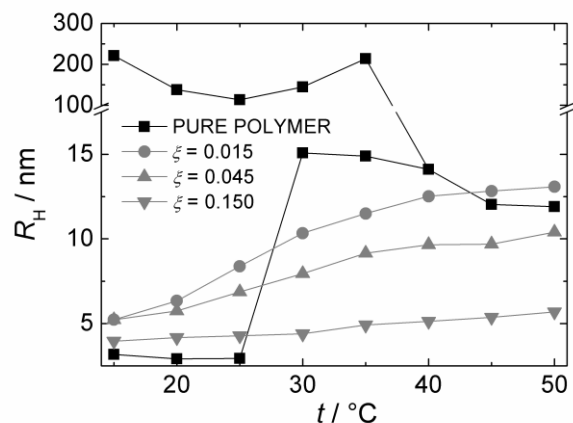
The further study (paper VI) deals with the selectivity of alkaline cations towards PEO and POX segments. Nanoparticles formed by the interaction of COSAN with POX were studied in three media: NaCl, KCl and LiCl. In the Na-medium, there was no preference and homogeneous nanospheres with COSAN bound to both types of segments were formed. In the Li-medium, interaction of both Li<sup>+</sup> and COSAN with POX segments was preferred resulting in distinct compartmentalization of POX segments within the hybrid nanoparticles. In the K-medium, the situation is just the opposite and PEO-compartments are formed instead. We also demonstrated an exchange of cations of different affinity, when even a small amount of K<sup>+</sup> and Na<sup>+</sup> ions to Li-medium changed the inner structure of the nanoparticles accompanied by the flux of COSAN clusters and alkaline cations.



**Figure 7.** Fraction of frozen polymeric segments in PEO–PEtOx/M[COSAN] in MCl (M = Na, Li, and K) differing in M[COSAN] content in 0.154 M MCl calculated from a decrease of corresponding  $^1\text{H}$  NMR signals related to pure block copolymer and *t*-BuOH (internal standard).

In the last study (paper VI), we prepared the first thermoresponsive metallacarborane nanoparticles by the interaction between COSAN and the block copolymer poly(2-methyl-2-oxazoline)-*block*-poly(2-*n*-propyl-2-oxazoline), PMeOx–PPrOx, which aqueous solution showed a cloud point at 30°C. Since both blocks formed complex with COSAN, we assumed the combined effect of thermoresponsivity of PPrOx and affinity of COSAN. The structure and size of the formed hybrid nanoparticles depended on COSAN concentration and temperature (Figure 8). We demonstrated that COSAN affinity influenced the phase transition of thermoresponsive PPrOx block and we observed the shift of LCST to lower values at mild COSAN content. At elevated COSAN concentrations, the hybrid nanoparticles are fragmented into relatively small species. The increase in temperature led to the higher polymer mobility and release of COSAN.

The COSAN/POX systems presented herein show excellent combination of three parameters, by which we can tune the nanoparticles formation: side alkyl groups of POX, type of present salt and COSAN counterion, and temperature. With respect to bio-activity of metallacarborane clusters, these findings can be utilized for stimuli-responsive drug delivery, as well as for the design of new materials for nanotechnology.



**Figure 8.** Temperature dependence of hydrodynamic radius,  $R_H$ , of PMeOx–PPrOx nanoparticles with different amount of COSAN (indicated as the COSAN-to-polymer segment ratio,  $\xi$ ).

## 7 References

- [1] Grimes, R. N. *Carboranes, Second Edition*. Academic Press: London, 2011; p.18.
- [2] Sedlak, R.; Fanfrlík, J.; Pecina, A.; Hnyk, D.; Hobza, P.; Lepšík, M. Noncovalent Interactions of Heteroboranes. In *Boron – The Fifth Element*; Hnyk, D.; McKee, M. L., Ed.; Springer International Publishing: Switzerland, 2015; p. 219.
- [3] Bregadze, V. I.; Sivaev, I. B. Polyhedral Boron Compounds for BNCT. In *Boron Science: New Technologies and Applications*; Hosmane, N. S., Ed.; CRC Press: New York, 2012; p. 181.
- [4] Plešek, J. *Chem. Rev.* **1992**, *92*, 269.
- [5] Volkis, V.; Mei, H.; Shoemaker, R. K.; Michl, J. *J. Am. Chem. Soc.* **2009**, *131*, 3132.
- [6] Lesnikowski, Z. *J. Med. Chem.* **2016**, *59*, 7738.
- [7] Cígler, P.; Kožíšek, M.; Řezáčová, P.; Brynda, J.; Otwinowski, Z.; Pokorná, J.; Plešek, J.; Grüner, J.; Dolečková-Marešová, L.; Máša, M.; Sedláček, J.; Bodem, J.; Kräusslich, H. G.; Král, V.; Konvalinka, J. *Proc. Natl. Acad. Sci.* **2005**, *102*, 15394.
- [8] Matějčíček, P.; Zedník, J.; Ušelová, K.; Pleštil, J.; Fanfrlík, J.; Nykänen, A.; Ruokolainen, J.; Hobza, P.; Procházka, K. *Macromolecules* **2009**, *42*, 4829.
- [9] Matějčíček, P.; Brus, J.; Zhigunov, A.; Pleštil, J.; Uchman, M.; Procházka, K.; Gradzielski, M. *Macromolecules* **2011**, *44*, 3847-3855.
- [10] Ďord'ovič, V.; Uchman, M.; Procházka, K.; Zhigunov, A.; Pleštil, J.; Nykanen, A.; Ruokolainen, J.; Matějčíček, P. *Macromolecules* **2013**, *46*, 6881.

# Curriculum vitae

**Name:** Vladimír Ďord'ovič

**Address:** Balbínova 550/10; Praha 2; 12 000

**Date and place of birth:** 27. 1. 1990, Vranov nad Topľou, Slovakia

## Education

- 2013–2017      Ph.D.: Faculty of Science, Charles University  
Field of study: Physical Chemistry
- 2011–2013      Master degree: Faculty of Science, Charles University  
Field of study: Physical Chemistry
- 2008–2011      Bachelor degree: Faculty of Science, Charles University  
Field of study: Chemistry

## Certificates

First Certificate in English, 2015 (level B2)

## Grant activities

- 2014–2016      Principal researcher of the project supported by Grant Agency of Charles University (GAUK 512214)  
Project title: Preparation and characterization of hybrid polymeric nanoparticles suitable for delivery of metallacarboranes
- 2014–2016      Researcher of the project of the project supported by Czech science foundation (GAČR P205/14-14608S)  
Project title: Preparation and characterization of new polymeric nanocomposites based on carboranes
- 2017              Researcher of the project supported by Czech science foundation (GAČR P208/17-00648S)  
Project title: Chaotrope, hydrotrope or surfactant? Anionic boron cluster compounds in water and in complexes of polymers

## Teaching experience

- 2014–2017      Faculty of Science, Charles University  
Courses:  
General chemistry (MC260P54)  
Practical Course in Physical Chemistry (MC260C45N)

## Internships

1. 11/2014 Institut de Ciència de Materials de Barcelona in Bellaterra (2 weeks): The group of prof. Teixidor (synthesis of carboranes, counterions exchange methods)
2. 7/2016 Technical University in Berlin (1 month): The group of prof. Gradzielsky (study of surface tension of metallacarboranes)

3. 2/2017 Technical University in Berlin and Max Planck Institute of Colloids and Interfaces (50 days): The group of prof. Gradzielski the group of Dr. Reinhard Miller (study of dynamic surface tension and viscoelasticity of metallacarboranes solutions)

**List of the conference contributions (the presenting author is underlined):**

1. Uchman, M.; **Dordovic, V.**; Prochazka, K.; Spirkova, M.; Matejcek, P.: Polymeric Nanoparticles Formed by Self-assembly of Double Hydrophilic Block Copolymers with Metallacarboranes: Morphology Tuned by Salt Addition. Poster contribution at EUPOC 2010, Hierarchically Structured Polymers, Gargnano, Italy, May 30<sup>th</sup> – June 4<sup>th</sup> 2010.
2. Matejcek, P.; **Dordovic, V.**; Uchman, M.; Prochazka, K.; Gruner, B.; Nykanen, A.; Ruokolainen, J.; Gradzielski, M.: Double hydrophilic copolymer poly(ethylene oxide)-*block*-poly(2-ethyl oxazoline) as a carrier of cobalt bis(dicarbollide) conjugates designed as HIV protease inhibitors. Oral contribution at European Polymer Congress 2011, Granada, Spain, June 26<sup>th</sup> – July 1<sup>st</sup> 2011.
3. Matejcek, P.; Uchman, M.; **Dordovic, V.**; Tosner, Z.; Prochazka, K.; Brus, J.; Zhigunov, A.; Plestil, J.; Cigler, P.; Lepsik, M.: Poly(ethylene oxide) containing systems for drug delivery of boron cluster compounds. Poster contribution at Polymers in medicine, Prague, July 1–5<sup>th</sup> 2012.
4. **Dordovic, V.**; Uchman, M.; Plestil, J.; Zhigunov, A.; Matejcek, P.: Hydrophilic copolymers based on poly(2-alkyl oxazoline) as a carriers of cobalt bis(dicarbollide) conjugates designed as HIV protease inhibitors. Poster contribution at Polymers in medicine, Prague, July 1–5<sup>th</sup> 2012.
5. **Dordovic, V.**; Matejcek, P.: Solution behavior of cobalt bis(dicarbollides) conjugates with short PEG chains and their interaction with polymers in solution of various cations. Poster and flash presentation contribution at Euroboron6, Radziejowice, Poland, September 8–13<sup>th</sup> 2013.
6. Prochazka, K.; Matejcek, P.; **Dordovic, V.**; Uchman, M.; Stepanek, M.; Angelov, B.; Zhigunov, A.; Prevost, S.; Gradzielski, M.: Co-assembly of copolymers with amphiphilic molecules. Oral contribution at ICFPAM, International Conference on Frontiers of Polymers and Advanced Materials, Auckland, New Zealand, December 8–13<sup>th</sup> 2013.
7. Matejcek, P.; **Dordovic, V.**; Uchman, M.; Tosner, Z.; Brus, J.; Zhigunov, A.: Metallacarboranes as a New Class of Surfactants: Aggregation in Water and Interaction with Polymers. Oral contribution at UK Colloids 2014, London, England, 6–9<sup>th</sup> June 2014.
8. **Dordovic, V.**; Matejcek, P.; Uchman, M.: Interaction of cobalt bis(dicarbollide) anion with star-like copolymers. Poster contribution at ECIS 2014, Limassol, Cyprus, September 8–12<sup>th</sup> 2014.
9. **Dordovic, V.**; Matejcek, P.; Vrbata, D.; Zhigunov, A.; Ruokolainen, J.: Interaction of cobalt bis(dicarbollide) anion with PEG and glucose-PEG derivatives. Poster contribution

at ECIS 2015, Bordeaux, France, September 7–11<sup>th</sup> 2015.

10. Matejicek, P.; **Dordovic, V.**; Uchman, M.: Boron-Containing Polymeric Nanostructures Suitable for Drug Delivery. EMN Kaohsiung Meeting 2016 – Energy Materials Nanotechnology, Kaohsiung, Taiwan, March 14–18<sup>th</sup> 2016.
11. **Dordovic, V.**; Uchman, M.; Matejicek, P.; Hogenboom, R.: Thermoresponsive nanoparticles of polyoxazolines with cobalt bis(dicarbollide) anion. Poster contribution at ECIS 2016, Rome, Italy, September 5–9<sup>th</sup> 2016.

## List of papers

- Dordovic, V.**; Uchman, M.; Prochazka, K.; Zhigunov, A.; Plestil, J.; Nykanen, A.; Ruokolainen, J.; Matejicek, P.: Hybrid nanospheres formed by intermixed double-hydrophilic block copolymer poly(ethylene oxide)-*block*-poly(2-ethylloxazoline) with high content of metallacarboranes. *Macromolecules* **2013**, *46*, 6881–6890.
- [I] Tarres, M.; Gonzales-Cardoso, P.; Vinas, C.; Teixidor, F.; Hannine, M. M.; Sillanpaa, R.; **Dordovic, V.**; Matejicek, P.: Ion-Selectivity and Solution Behavior of Dianionic Dumbbells; *Chem. Eur. J.* **2014**, *20*, 6786–6794.
- [II] **Dordovic, V.**; Uchman, M.; Zhigunov, A.; Nykanen, A.; Ruokolainen, J.; Matejicek, P.: Compartmentalization in Hybrid Metallacarborane Nanoparticles Formed by Block Copolymer with Star-Like Architecture. *ACS Macro Lett.* **2014**, *3*, 1151–1155.
- [III] Uchman, M.; **Dordovic, V.**; Tosner, Z.; Matejicek, P. Classical Amphiphilic Behavior of Nonclassical Amphiphiles: A Comparison of Metallacarborane Self-Assembly with SDS Micellization. *Angew. Chem. Int. Ed.* **2015**, *54*, 14113–14117.
- [IV] **Dordovic, V.**; Uchman, M.; Reza, M.; Ruokolainen, J.; Zhigunov, A.; Ivankov, O.; Matejicek, P. Cation-Sensitive Compartmentalization in Metallacarborane Containing Polymer Nanoparticles. *RSC Advances* **2016**, *6*, 9884–9892.
- [V] **Dordovic, V.**; Tosner, Z.; Uchman, M.; Zhigunov, A.; Reza, M.; Ruokolainen, J.; Pramanik, G.; Cigler, P.; Kalikova, K.; Gradzielski, M.; Matejicek, P. Stealth Amphiphiles: Self-Assembly of Polyhedral Boron Clusters. *Langmuir* **2016**, *32*, 6713–6722.
- [VI] **Dordovic, V.**; Verbraeken, B.; Hogenboom, R.; Kereiche, S.; Matejicek, P.; Uchman, M.: Tuning of thermoresponsivity of poly(2-alkyl-2-oxazoline) block copolymer by interaction with surface active and chaotropic metallacarborane anion. (submitted **2017**)