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Review of the doctoral dissertation
of Kateryna Kravets, M.Sc.
entitled “Host–guest complexes and assemblies based on
calix[n]arenes: structural diversity and transformations”

Formal assessment The doctoral dissertation of Ms. Kateryna Kravets submitted for review was prepared within the Warsaw Doctoral School of Natural and Biomedical Sciences (Warsaw 4 PhD) at the Institute of Physical Chemistry of the Polish Academy of Sciences, under the supervision of Dr habil. Oksana Danylyuk, Prof. IPC PAS. The research presented in this dissertation was financed by the National Science Centre (NCN) under the PRELUDIUM BIS 1 grant no. 2019/35/O/ST4/01865 and by the Polish National Agency for Academic Exchange (NAWA) within the Programme for Foreign Doctoral Internships NAWA PRELUDIUM BIS 1.

The doctoral dissertation of Ms. Kravets follows a classical structure, comprises 263 pages, and is written in English. It contains 223 figures, 88 tables, and 197 literature references. The work opens with a presentation of the Doctoral Candidate’s scientific achievements, followed by abstracts in English and Polish. The Doctoral Candidate included a list of five scientific publications



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of which she is a co-author, as well as a list of oral (5) and poster (12) contributions presented at national and international conferences.

Chapter One of the dissertation consists of the introduction and the formulation of the objectives and concept of the work (3 pages). Chapter Two presents the literature review (29 pages), followed by chapters describing the research methodology (9 pages) and the results and discussion (150 pages). The dissertation concludes with final conclusions (3 pages) and the cited literature (12 pages). The work also includes an outline and an annex containing tabulated parameters of intermolecular interactions observed in the crystal structures of the *p*-sulfonatocalix[n]arenes ($n = 4, 6, 8$) complexes determined by the Doctoral Candidate.

Introduction and research objectives In the introduction, Ms. Kravets explains the motivation for undertaking this research in the context of supramolecular chemistry and crystal engineering achievements. She presents the objectives of her doctoral work, which were to determine how the final solid-state structures of supramolecular complexes and assemblies formed by *p*-sulfonatocalix[n]arenes ($n = 4, 6, 8$) are affected by the size and conformational flexibility of the host, the functionalisation of guest molecules, the solvent composition, and crystallisation pathways.

As guest molecules, the Doctoral Candidate selected various benzamidine and bisbenzamidine derivatives (e.g. pentamidine), enabling strong, charge assisted, highly directional amidinium–sulfonate hydrogen bonds, as well as molecules lacking classical hydrogen bond donors, such as pillar[n]pyridinium derivatives and berberine. Achieving these goals required obtaining crystals of appropriate quality of the designed complexes, analysing their morphology, and determining their crystal structures using single crystal X-ray diffraction. In several cases, the Doctoral Candidate complemented her analyses with powder X-ray diffraction measurements, DSC/TGA analysis, and solution NMR spectroscopy. The preparation of powder samples, diffraction experiments, and

diffraction pattern analysis were carried out by Ms. Kravets at the University of Bologna's Giacomo Ciamician Department of Chemistry during a doctoral internship supervised by Prof. Fabrizia Grepioni.

Substantive assessment The selection of a research topic related to supramolecular chemistry and crystal engineering is not surprising, as this is currently a very fashionable, dynamically developing, and extremely important area of scientific research. The subject fits well within the long standing and successful research lines pursued at the Institute. Ms. Kravets focused on the supramolecular chemistry of p-sulfonatocalix[n]arenes, which attract considerable scientific interest due to their relatively rigid cone conformation that favours inclusion binding of single guests and the formation of ordered layered structures. Owing to their binding selectivity, high water solubility, and low toxicity, p-sulfonatocalix[n]arenes are regarded to have promising applications in molecular recognition, sensors, separation processes, and supramolecular catalysis. Particular attention has also been paid to their biomedical potential, including the complexation of biologically active molecules, interactions with proteins, and the design of supramolecular drug delivery systems.

The **literature review** prepared by the Doctoral Candidate is divided into eight subchapters. The first addresses host-guest supramolecular chemistry. Subsequent sections discuss intermolecular interactions in solids, macrocyclic hosts, calix[n]arenes, and p-sulfonatocalix[n]arenes ($n = 4, 6, 8$), as well as structural transformations in macrocycle-based complexes and guest molecules. Despite the concise structure of this chapter, the content has been appropriately selected to facilitate the reader's understanding of the objectives and detailed assumptions of the dissertation. The text is factually correct, clearly and engagingly presented, is supported by appropriate figures, and the cited literature is properly selected and organized. The Doctoral Candidate

demonstrated excellent familiarity with the subject matter and very good knowledge of the relevant literature.

In the **experimental section**, the Doctoral Candidate describes the preparation of the studied complexes in the form of single crystals, emphasizing the difficulty and labour-nature of this process. It should be noted that in supramolecular chemistry, crystallization of high-quality single crystals and the obtaining of structural data enabling the analysis of intermolecular interactions already constitute a significant achievement. Ms. Kravets demonstrated patience and creativity in optimizing new crystallization conditions to achieve her goals.

She employed several sophisticated crystallisation techniques, including slow cooling in hot glycerol using an isothermal apparatus, slow liquid–liquid diffusion in a U-shaped tube with agarose gel, slow liquid–liquid diffusion in an NMR tube, and vapour diffusion (gas phase diffusion). Undoubtedly, this experimental stage is one of the most important, as it determines the success of how mixtures of solvents used to obtain suitable crystal quality were selected; inclusion of such information would be a valuable aid for future researchers of similar crystalline systems.

This part of the dissertation then outlines the research workflow from crystal selection to diffractometric measurements. It also includes a concise description of the fundamentals of X-ray structural analysis and a detailed presentation of data related to structure solution and refinement. Given that the Doctoral Candidate frequently encountered disorder phenomena in the obtained crystals, this section also includes a brief characterization of substitutional, positional (static and dynamic), and solvent disorder. It should be added that the crystallographic experiments performed were difficult and time-consuming. Some of the crystals were unstable, often occurred as twins, and exhibited significant lattice defects, which the Doctoral Candidate handled exceptionally well and described in great detail in the **results and discussion**



section. It is worth noting that she determined 26 new structures characterized by a very high degree of diversity. Many of the obtained p-sulfonatokalix[n]arene complexes crystallize as various polymorphs, solvates, or hydrates. Particularly commendable is the systematic monitoring of crystal ageing processes and the interpretation of observed changes as dissolution–recrystallisation transformations. Such an approach is rarely documented with sufficient consistency and here constitutes an important element of the experimental narrative. The Doctoral Candidate demonstrates full competence in identifying and describing twinning (pseudo- and non-merohedral), recognising problems arising from metric symmetry, and selecting an appropriate data collection strategy consistent with crystal quality. The obtained R values (approximately 4–13%) should be regarded as acceptable and realistic for the systems studied and are properly discussed. Higher R factors are clearly linked to a high degree of disorder, the presence of numerous water molecules, and large unit cells.

The refinement section is one of the strongest parts of the dissertation. The Doctoral Candidate applies geometric and thermal restraints (SIMU, RIGU, DELU, SADI, SAME), disorder modelling (PART, S.O.F.), twin analysis and correction (BASF), and the SQUEEZE procedure freely and correctly, in accordance with best crystallographic practice. Importantly, SQUEEZE is not overused; its application is always substantively justified and clearly described. Decisions concerning hydrogen atoms (riding models, omission of H atoms for some water molecules) are reasonable and consistent with data quality. The quality of the obtained data is evidenced by publications in highly ranked crystallographic journals such as CrystEngComm (2 papers, both featured on the cover) and Crystal Growth & Design (1 paper), as well as chemical journals such as Chemistry – A European Journal (1 paper, featured on the cover) and Supramolecular Chemistry (1 paper). The total impact factor of these publications exceeds 16. It should be noted that, in all these papers, Ms. Kravets is the first author.

The “**Conclusions**” chapter provides a logical and concise summary of the research results presented in the dissertation. The Doctoral Candidate systematically refers to the research objectives formulated in the introduction and clearly demonstrates that they have been fully achieved. The structure of the chapter is transparent, and the conclusions are clearly formulated and easy to follow. They are fully consistent with the experimental results and directly stem from the conducted structural studies. The Doctoral Candidate avoids overinterpretation and excessively far-reaching generalizations, demonstrating appropriate scientific caution, which is particularly important for systems characterized by high conformational variability and a significant degree of structural disorder. Special emphasis should be placed on the clear highlighting of the Doctoral Candidate’s original contribution to the development of research on host–guest complexes. In particular, this includes an in-depth analysis of the influence of macrocycle size, guest type, and crystallization conditions on supramolecular architecture and crystal packing. The conclusions also clearly indicate the importance of solvation effects, alkali metal ions, and non-covalent interactions in stabilizing the studied structures. The Doctoral Candidate skillfully correlates structural observations with results from complementary techniques, giving the conclusions an interdisciplinary character and demonstrating a mature research approach. The summary goes beyond a simple listing of results and includes their critical evaluation and interpretation in the broader context of crystallography and supramolecular chemistry. An important element of the chapter is also the suggestion of potential future research directions that naturally arise from the obtained results.

Overall assessment The dissertation convincingly demonstrates that p-sulfonatocalix[n]arenes ($n = 4, 6, 8$) are not merely passive “containers” but dynamic structural units that can change conformation (cone, pinched cone, pleated loop, self closed), modify the depth and mode of guest inclusion, and reorganise hydrogen bonding networks and $\pi \cdots \pi$ interactions in response to subtle changes in the crystallization environment (solvent, co-solvent, metal



ion, degree of hydration). This constitutes a significant contribution to supramolecular crystallography, as the work is not limited to single structures but analyses entire comparative series. One of the key achievements is demonstrating that the presence of specific solvents (H₂O, EtOH, MeOH, IPA, acetone) as well as sodium ions or protonated water clusters (e.g. Zundel type) can entirely change the guest binding mechanism (inclusion vs. exclusion) and packing modes (layers, columns, bilayers, channels). Such a detailed crystallography-based analysis of solvation effects is rare and goes beyond standard descriptions of single crystal structures.

I have no comments regarding the substantive content of the dissertation, its discussion, or conclusions. The scientific value of the results has been previously confirmed and recognized during the peer review process of the publications. The language of the thesis is correct, though there are a few imprecise expressions, such as stating “release of approximately 2.16 molecules per formula unit” (page 108) without specifying which molecules were released. Fortunately, these minor errors and few typos do not affect the text’s readability or comprehensibility. Nevertheless, while reading the dissertation, several questions arose which I would be pleased to discuss with the Doctoral Candidate. I would like to emphasize that these questions are not criticisms but rather requests for clarification:

1. In the Doctoral Candidate’s opinion, could variable-temperature powder diffraction (VTPXRD) studies influence the assessment of the structural stability of the analyzed complexes or provide additional information not derived from single-crystal data? Furthermore, why were stability studies undertaken only in selected cases, and why was the decomposition temperature not determined for every obtained complex?

2. In terms of the potential applications of the obtained complexes, could you explain how the crystal structure might influence the kinetics and solubility of *p*-Sulfonatocalix[n]arene complexes in water and bodily fluids?

3. Which of the obtained *p*-Sulfonatocalix[n]arene complexes does the candidate consider to have the greatest application potential, and why? Furthermore, what further studies would be required to fully explore this potential?

Final recommendation In conclusion, the doctoral dissertation of Kateryna Kravets entitled “Host-guest complexes and assemblies based on calix[n]arenes: structural diversity and transformations” fulfils the requirements set out in Article 187 of the Act of 20 July 2018 – Law on Higher Education and Science (Journal of Laws 2018, item 1668, as amended). The Doctoral Candidate has demonstrated very good substantive preparation, very high quality of experimental work, and strong data analysis skills. She obtained results that make a significant contribution to the development of this scientific discipline, thereby proving her competence as an experienced researcher. Therefore, I submit a motion to the Scientific Council of the Institute of Physical Chemistry of the Polish Academy of Sciences to admit Kateryna Kravets to the subsequent stages of the doctoral proceedings.

Considering the very high scientific level of the dissertation, the originality of the obtained results, and the significant and well documented scientific output of the Doctoral Candidate – including five publications in prestigious scientific journals, seventeen conference presentations, participation in two crystallographic schools, implementation of the PRELUDIUM BIS 1 project, and a research internship at the University of Bologna – I further submit a motion to the Scientific Council of the Institute of Physical Chemistry of the Polish Academy of Sciences to **distinguish this doctoral dissertation**.

Edyta Pindelska