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REVIEW OF DOCTORAL DISSERTATION
entitled 'HOST-GUEST COMPLEXES AND ASSEMBLIES BASED ON CALIX[N]ARENES:
STRUCTURAL DIVERSITY AND TRANSFORMATIONS

The doctoral dissertation submitted by Ms. Kateryna Kravets for the degree of Doctor of Philosophy was prepared at the Institute of Physical Chemistry, Polish Academy of Sciences, under the supervision of Dr hab. Oksana Danylyuk, prof. IPC PAS. The project was funded 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 research was conducted within the Warsaw PhD School in Natural and BioMedical Sciences (Warsaw-4-PhD Doctoral School) at the Institute of Physical Chemistry, Polish Academy of Sciences.

The doctoral dissertation examines the supramolecular synthesis of host-guest systems comprising *p*-sulfonatocalix[*n*]arenes (*n* = 4, 6, 8) as hosts and selected cationic guests, including amidine derivatives, alexidine, pillar[*n*]pyridinium (*n* = 4, 6), berberine, and iproniazid. The primary objective is to identify the factors governing their solid-state assembly, with particular emphasis on host size and conformational flexibility, guest functionalization, solvent composition, and crystallization pathways. Special attention is devoted to the formation of specific supramolecular synthons, detailed analysis of non-covalent interactions and conformational adaptation of both host and guest upon binding.

The research addresses an important and still insufficient explored area in crystal engineering, material chemistry and related fields, namely the relationship between structural features (host sizes, flexibility, counterions, and solvent) and the resulting solid-state architectures and properties. A key contribution of the work is the elucidation of the pronounced C6S and C8S structural adaptability, which generate diverse binding modes, including inclusion, exclusion, and multi-guest architectures through the formation of pseudo-cavities and flexible binding surfaces. The study further identifies the counterion as an active structure-directing component, particularly in sodium-containing systems where it mediates extended supramolecular connectivity. The dissertation also highlights the importance of both classical and non-classical supramolecular interactions, demonstrating that even systems lack conventional hydrogen-bond donors assemble through alternative interactions such as C-H $\cdots\pi$, anion $\cdots\pi$, and $\pi\cdots\pi$. Insights into time-dependent crystallization processes, metastable intermediate phases as well as unusual cases of structural robustness and single-crystal-to-single-crystal transformations upon dehydration are also provided.

The macrocycles of interest, *p*-sulfonatocalix[n]arenes (C_nS, n = 4, 6, 8), are water-soluble hosts which were first reported in 1984. The introduction of sulfonate groups at the para positions of the phenolic units generates polyanionic macrocycles with strong affinity for cationic and electron-deficient guests. Among this series, C4S is the most structurally well-characterized geometry, typically adopting a rigid cone conformation and forming a wide range of inclusion complexes and higher-order assemblies, including bilayers, channels, and vesicle-like structures. In contrast, the larger homologues C6S and C8S exhibit increasing conformational flexibility and higher charge density, leading to more complex and less predictable assembly behaviour and binding modes. These features make them valuable building blocks for crystal engineering, thereby justifying the scope and relevance of the research undertaken in this doctoral thesis.

In her research, the Candidate primarily employed single-crystal X-ray diffraction analysis supported by Cambridge Structural Database analysis and complementary techniques such as powder X-ray diffraction, TGA–DSC analysis and NMR spectroscopy. The dissertation includes data for 26 host–guest complexes (15 involving C4S, six C6S, and five C8S), including sodium-containing systems.

The dissertation reports a traditional structure and begins with the List of Scientific Publications and Scientific Presentations, both oral and poster, Abstracts in English and Polish, followed by Outline, Introduction, Literature Review, Experimental Part, Results and Discussion, Conclusions, References and Annex I.

The Introduction chapter is concise and provides essential background on the motivation for studying such complex systems, the research objectives and the techniques used for their characterization.

Chapter 2 of this Thesis, the Literature Review presents key concepts necessary for understanding the context of the findings discussed in the Results and Discussion section. The Candidate concisely describes intermolecular interactions underlying molecular recognition and addresses fundamental aspects of crystal engineering, including hydrogen-bonded homo- and heterosynthons. This is followed by a discussion of commonly studied macrocyclic compounds, highlighting their structural features relevant to supramolecular chemistry with particular emphasis on *p*-sulfonatocalix[n]arenes, which constitute the primary focus of the research. The chapter concludes with a description of the guest molecules used to construct the investigated supramolecular complexes. Although this section is well structured and provides the necessary background, in my opinion it would benefit from the inclusion of quantitative data defining sulfur–sulfur distances corresponding to ideal cone and pinched conformations. Such data would facilitate a clearer correlation between structural descriptions and measurable criteria.

Comments on the Literature Review section:

1. On page 33, the text refers to four basic conformations of calix[n]arenes. It is unclear whether these conformations apply generally to all calixarene sizes or only to calix[4]arenes, as Figure 10 illustrates only calix[4]arene conformations.



2. Starting from Figure 15, inconsistencies appear in the colour coding of molecular representations. The Author indicates that certain molecules are shown in a specific colour; however, in practice, only carbon atoms are coloured, while heteroatoms and hydrogen atoms retain standard colouring. Therefore, it would be more precise to state, for example "*carbon atoms of isoniazid are shown in pink*".
3. The section also contains several editorial issues, including incomplete sentences, (e.g. '*...crystal packing consists of layered stacks of C6S-cucurbit[8]uril units, with macrocycles oriented to maximize electrostatic and hydrogen-bonding interaction*' (p.44)), and pleonastic expressions such as "*more highly charged*" (p. 45), which should be reformulated for clarity and correctness.
4. The statement that C8S can accommodate a porphyrin molecule appears somewhat misleading, as only a fragment of the porphyrin is actually included within the macrocyclic cavity.
5. The caption of Figure 27 (p. 46), contains the phrase: '*The sclx8-Na complex*'. The abbreviation "sclx8" is not defined in the text and should be clarified.

The experimental section provides a general overview of the methods used for the complexes preparation in single crystal forms. At this point, I would like to commend the Candidate for her patience and determination in crystallization studies, including the application of non-standard crystallization techniques, which ultimately enabled the growth of diffraction-quality crystals. This aspect of the experimental work is crucial, as it directly determines the success of subsequent structural analysis. The section also includes a concise description of single-crystal X-ray methodology, along with structure solution and refinement procedures. I would appreciate clarification on the refinement strategy: specifically, why DFIX restraints were applied to the O-H bond distances rather than using an AFIX instruction to place and constrain the hydrogen atoms in idealized positions.

Since disorder was frequently encountered, the Author distinguishes between substitutional, and positional disorder (both static and dynamic), and solvent disorder treated as a separate category. However, according to the cited literature, disorder is generally classified into substitutional and positional types, with the latter already encompass both static and dynamic disorder. This raises the question of whether solvent disorder in the crystals investigated should indeed be treated as a distinct category, or rather as a case of positional disorder involving solvent molecules? The chapter concludes with brief description of complementary techniques, including thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), and NMR spectroscopy, which confirm complex formation.

Chapter 4 presents the Results and Discussion of extensive studies on C4S, C6S, and C8S inclusion complexes with sodium and various organic cations, organized into five thematic subsections. The results convincingly demonstrate how guest functionalization, host size, counterions, solvent,



and crystallization time influence supramolecular assembly. In the case of C4S complexes, the Candidate demonstrates that the presence of organic cations introduces subtle structural changes within the host skeleton, and the resulting crystalline forms are sensitive to crystallization history, including time-dependent dissolution and recrystallization processes. For C6S complexes, notable structural diversity is observed, including both the relatively rare up-up and the more common up-down conformations, along with the formation of stable, solvent-filled frameworks. Flexible multicationic drugs, such as pentamidine and alexidine, display clear solvent-dependent switching between inclusion and exclusion binding modes in C4S complexes, while involving pillar[n]pyridinium derivatives for C4S complex formation shows that electrostatically driven assembly predominates in the absence of classical hydrogen bonding. Finally, C8S-based systems exhibit dual behaviour, forming either sodium-coordination polymers or host-guest complexes with berberine, while also demonstrating reversible, hydration-driven transformations between open and collapsed structures.

Additional questions for the Candidate:

1. What is the overall depth of the C4S cavity in cone conformation and what is the maximum extent of guest penetration?
2. How was the water content determined with such high precision in some crystals (reported to the second decimal place)? Was the water content verified using techniques other than single-crystal X-ray diffraction?
3. Was complete dehydration of C6S_M-BNZ_dried attempted under vacuum and/or elevated temperature?
4. In the case of C6S_M-BNZ, what was the rationale for analysing structural void volumes separately for each component, given that they occupy similar regions within the crystal lattice? The observed disorder could indicate that the cavity is oversized relative to the guest molecule, allowing multiple orientations within the available volume?
5. Is it conceivable that the M-BNZ cation could be replaced by a slightly larger cation, for example via soaking C6S_M-BNZ in a solution containing an alternative guest?
6. Molecular conformation is typically defined by a set of torsion angles. In the case of the iproniazid molecule, what are the quantitative differences in torsion angles between the observed conformers?
7. Is the single-crystal-to-single-crystal dehydration process observed for C8S_IPR reversible upon exposure to water vapour or upon immersion in water?

Despite the overall quality of the 'Results and Discussion' section, several editorial issues remain. Selected comments are provided below.

1. In my opinion the parts of the work related to the crystallization protocols and detailed refinement procedures would be more appropriately placed in the Experimental section.



- At present, these descriptions are repeated multiple times, often separated only by tables containing crystallographic data, which unnecessarily lengthens the dissertation.
2. On p.69, the statement '*...which is shorter than the standard distance between two water molecules (2.82 Å).*' requires a reference. The origin of this "standard" value should be clearly indicated.
 3. On p. 94, it is unclear which host is being discussed, C4S or C6S, as both are mentioned within the same description.
 4. On p. 100, benzamidine is referred to as the guest, whereas the correct compound appears to be 4-methylbenzamidine
 5. On p. 106, in the sentence '*Dehydration commonly leads to a loss of crystallinity and gradual or rapid decomposition of the crystals*' the term "*fragmentation*" would be more appropriate than "*decomposition*."
 6. As a technical remark, in MSROLL open channels can be handled by applying constraints at their termini; however, this procedure is generally more straightforward to perform using MERCURY.
 7. On p. 117, regarding the sentence '*The source of sodium cation in the complex C4S_A-BNZ_II might stem from the contamination of commercial p-sulfonatocalix[4]arene sulfonic acid used for the cocrystallization*' it is worth noting that, based on my experience, sodium ions may also originate from glassware (e.g., vials).
 8. On p. 118, an abbreviation ABZ is used without prior definition and should be properly introduced.
 9. On p. 126, within the description of C6S_H-BNZ the following sentence appears to be incorrectly inserted: '*The packing exhibits a layered arrangement of C4S with benzamidine guests included within the macrocyclic cavities, while additional benzamidine molecules are located between adjacent layers*'
 10. Some subchapters lack proper numbering. Additionally, the labelling (a, b and c) for NMR spectra in Figs. 167 and 176 is missing, which reduces clarity.
 11. On p. 148, the following sentence is unclear and requires reformulation '*The resulting capsule has a size of 15.7 Å, defined of the C4S cone is defined by the distance between the opposite sulfur atoms, resulting in values of 11.38 and 8.87 Å, 11.27 and 8.84 Å, 11.50 and 8.83 Å.*'
 12. On p. 186, the chemical structure of C8S_Na is missing and should be included for completeness.
 13. On p. 189 in the sentence '*As shown in Figures 197a,b, macrocycles are slightly offset by approximately 5°*' the term 'tilted' would be more appropriate than 'offset'.

The above remarks and comments do not affect the overall positive evaluation of the dissertation, as '*only those who do nothing make no mistakes*'. The Candidate has performed comprehensive and systematic analysis of intermolecular interactions and supramolecular motifs governing the assembly of complexes formed by *p*-sulfonatocalix[n]arenes (n = 4, 6, 8) with organic cations into



larger and more complex architectures. The presented results constitute a significant contribution to the field of supramolecular chemistry and may prove valuable for future applications in biomolecular recognition, drug delivery, and the development of porous molecular materials.

As a final remark, I would like to emphasize that the results presented in this dissertation have been published in five scientific articles in well-recognized specialist journals, including *Crystal Growth & Design* (IF = 3.4), *CrystEngComm* (IF = 2.6), *Chemistry – A European Journal* (IF = 3.7), and *Supramolecular Chemistry* (IF = 2.6). Notably, three of these publications were featured on journal covers. The Candidate has also presented her research findings at both national and international conferences, delivering five oral presentations and contributing twelve poster presentations. Furthermore, she has enhanced her scientific qualifications by participating in crystallography schools organized in Switzerland (in person) and Hungary (online).

In summary, the research goals set by Ms. Kateryna Kravets and the results presented in her doctoral dissertation entitled '*Host-guest complexes and assemblies based on calix[n]arenes: structural diversity and transformations*' meet the formal requirements for doctoral dissertations specified in Article 187 of the Act of 20 July 2018, the Law on Higher Education and Science, Republic of Poland (Journal of Laws of 2024, item 1571, as amended). Therefore, I recommend that the Scientific Council at the Institute of Physical Chemistry, Polish Academy of Sciences, allows Kateryna Kravets, M.Sc., to proceed to the next stages of the doctoral examination process in the field of natural sciences, in the discipline of chemical sciences.

Agnieszka Janiak

