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REVIEW

of the doctoral dissertation

entitled "*Analysis of isosymmetric phase transitions using molecular modelling methods*"

submitted by **Anna Maria Mazurek, MA of pharmacy** and prepared at the Department of Organic and Physical Chemistry, Faculty of Pharmacy, Medical University of Warsaw

under the supervision of **Łukasz Szeleszczuk, PhD** (Department of Organic and Physical Chemistry, Faculty of Pharmacy, Medical University of Warsaw)

and co-supervisor **Monika Franczak-Rogowska, PhD** (Department of Drug Chemistry, Pharmaceutical and Biomedical Analysis, Faculty of Pharmacy, Medical University of Warsaw)

Anna Maria Mazurek, MA submitted her doctoral dissertation titled "Analysis of isosymmetric phase transitions using molecular modeling methods" in the form of a thematically coherent series of four scientific publications, preceded by an extensive descriptive section, which complies with the statutory requirements regarding the form of doctoral dissertations (Article 187 §3 of the Act Law on Higher Education and Science).

The dissertation addresses the topic of high scientific relevance and application potential: the investigation of isosymmetric phase transitions (IPTs) in molecular crystals and the determination of the structural and thermodynamic factors governing their occurrence using molecular modeling methods. The research integrates both computational and experimental perspectives, enabling a comprehensive analysis of the mechanisms

underlying IPTs in selected model systems, including sulfamic acid, resorcinol, and L-serine. The pharmaceutical relevance of the topic is apparent, as evidenced by the direct impact of polymorphism and solid-state transformations on the physicochemical properties of active pharmaceutical ingredients (APIs). These transformations influence the bioavailability, stability, and manufacturability of APIs.

The research results presented in the dissertation were subsequently published in peer-reviewed international scientific journals. All papers were published between 2025 and 2026, with the Candidate serving as the first author in each case, thereby confirming her pivotal role in planning, execution, and analysis of the research. The cumulative impact factor of these publications stands at 9.7, and their total ministerial score, as reported in the dissertation, reaches 310 points. The following publications form the basis of the dissertation:

- Mazurek, A.M., Franczak-Rogowska, M., Szeleszczuk, Ł. (2025). Isosymmetric Phase Transitions in Crystals: From Subtle Rearrangements to Functional Properties. *Crystals*, 15(9), 807. https://doi.org/10.3390/cryst15090807 IF: 2.4; MNiSW = 70
- Mazurek, A.M., Franczak-Rogowska, M., Szeleszczuk, Ł. (2025). Predicting the Pressure-Induced Isosymmetric Phase Transition of Sulfamic Acid by Applying Periodic Density Functional Theory Calculations. *Applied Sciences*, 15(8), 4185. https://doi.org/10.3390/app15084185 IF: 2.5; MNiSW = 100
- Mazurek, A.M., Franczak-Rogowska, M., Szeleszczuk, Ł. (2026). Periodic DFT Investigation of Isosymmetric Alpha–Beta Phase Transition in Resorcinol Under Ambient and High Pressure. *Crystals*, 16(3), 215. https://doi.org/10.3390/cryst16030215 IF: 2.4; MNiSW = 70
- Mazurek, A.M., Franczak-Rogowska, M., Szeleszczuk, Ł. (2026). Entropy-Driven Isosymmetric Phase Transition in L-Serine under Pressure: A Periodic DFT Study. *Crystals*, 16(4), 266. https://doi.org/10.3390/cryst16040266 IF: 2.4; MNiSW = 70

The dissertation adheres to the conventional structure frequently employed in publications-based doctoral theses. It is composed of a 149-page monograph, which includes a list of abbreviations, abstracts in both Polish and English, an introduction and justification of the research topic, an overview of the four constituent publications, a statement of the aims of the thesis, a proposed methodological framework, a summary and conclusions,

a reference list, and reprints of the four publications with co-authors' statements. The organization of the text is coherent, logical, and reader-friendly.

The dissertation's introduction has been meticulously crafted, underpinned by a comprehensive and contemporary examination of the pertinent literature. The Author precisely delineates the fundamental concepts of molecular crystals, polymorphism, and isosymmetric phase transitions, emphasizing their significance within the realm of pharmaceutical sciences. The Author's capacity to critically assess the extant corpus of knowledge and to discern the research lacunae that underpin the selected topic is laudable.

The research objectives have been formulated in a clear and precise manner. These findings are consistent with the content of the dissertation and are realistic in the context of the selected methodology. The four objectives – identification and characterization of IPTs in model systems, elucidation of their molecular mechanisms, verification of the effectiveness of periodic density functional theory (DFT) methods, and development of a methodological framework – reflect a comprehensive, stepwise approach to the investigated problem.

The overview of the four publications comprises of the fundamental scientific contribution of the dissertation. The initial publication (a review article in Crystals, 2025) has organized the existing knowledge on IPTs across various classes of materials and has established the conceptual and methodological foundation for subsequent original studies. The second publication (Applied Sciences, 2025) focuses on sulfamic acid and demonstrates that pressure-induced IPTs involve cooperative molecular dynamics-specifically, collective rearrangement of hydrogen-bonded chains. These dynamics cannot be reproduced by static geometry optimization alone, thus providing compelling evidence of first-order transition behavior. The third publication (Crystals, 2026) concerns the classical case of resorcinol, in which the α and β polymorphs share the same space group ($Pna2_1$) despite substantial differences in hydroxyl-group orientation and hydrogen-bond topology. The Author demonstrates, through pressure-dependent lattice energy calculations, that the α–β relationship constitutes a genuine isosymmetric transition. The fourth publication (Crystals, 2026) focuses on L-serine and makes a significant thermodynamic contribution. Specifically, it reveals that the ambient-pressure phase is stabilized not by static lattice enthalpy but by vibrational entropy, as determined through phonon calculations within the quasi-harmonic approximation (QHA). This outcome underscores the notion that

the observed transformation is entropy-driven, thereby precluding interpretation based solely on static energy comparisons. The Author has demonstrated an exemplary mastery of the applied computational methods, including dispersion-corrected periodic DFT, phonon calculations, Raman spectrum simulations, and ab initio molecular dynamics (aiMD).

The proposed methodological framework for the identification and prediction of isosymmetric phase transitions represents a significant practical contribution of the dissertation. The protocol integrates pressure-dependent structural optimization, vibrational analysis with phonon calculations under the QHA, and aiMD simulations. It provides a coherent, validated protocol that may be directly applied to pharmaceutical systems in which unexpected IPTs could compromise the stability or performance of APIs.

The summary and conclusions are logically formulated, concise, and well-aligned with the stated research objectives. These findings accurately reflect the primary achievements of the dissertation and indicating potential areas for further exploration and advancement within the research field.

The reference list comprises of 43 positions for the monograph proper, supplemented by the full reference lists within each reprint. The references are meticulously selected and cited with precision throughout the text.

The dissertation of Anna Maria Mazurek's contributions to the field of isosymmetric phase transitions in molecular crystals are substantial. Her contributions have notably advanced the development of computational methodologies for predicting these transitions. The scientific value of the work is high, and the level of execution meets the requirements set for doctoral dissertations in the fields of medical and health sciences. Nevertheless, as a reviewer, it is my duty to note a few points that could be considered in future revisions or publications. In the overview of Publication No. 2 (sulfamic acid), the Author states that direct geometry optimization did not spontaneously reproduce the high-pressure phase. A more explicit discussion of why this observation constitutes evidence for a first-order transition character – rather than a limitation of the method – would strengthen the scientific narrative. The proposed methodological framework (Chapter 7) is presented primarily in a descriptive manner. The addition of a schematic diagram or flowchart that would illustrate the sequential steps would substantially improve its readability and practical usability for readers unfamiliar with periodic DFT methods. Throughout the monograph, the Author consistently employs dispersion-corrected functionals. However, the rationale for selecting

a specific correction scheme (Grimme's methods vs. the Tkatchenko–Scheffler scheme *vs.* many-body dispersion models) for each system is not always made explicit. It would be beneficial to provide a brief justification of these choices in the introduction or in the overview of publications. Finally, while the abstract and summary correctly identify the key conclusions for each model system, a more direct cross-system comparison – explicitly contrasting the enthalpically driven (resorcinol) and entropy-driven (L-serine) transitions with the dynamically governed case (sulfamic acid) – would render the overall conclusions more impactful.

These remarks are supplementary and editorial in nature and do not affect the overall assessment of the scientific value of the dissertation.

Summary and final conclusions

The doctoral dissertation of Anna Maria Mazurek's work is characterized by its exceptional scientific rigor, signifying a noteworthy contribution to the realm of research concerning isosymmetric phase transitions in molecular crystals and their significance in the context of pharmaceutical solid-state science. The Author has demonstrated scientific maturity, research independence, and an excellent command of advanced computational methods.

The observations presented in this evaluation do not detract from the scientific rigor of the dissertation, which I evaluate as being of the highest quality.

In conclusion, I affirm that the doctoral dissertation of Anna Maria Mazurek, MA of pharmacy, entitled "Analysis of isosymmetric phase transitions using molecular modelling methods", meets the requirements set for doctoral dissertations in accordance with Article 187 of the Act of 20 July 2018 Law on Higher Education and Science, and I hereby submit to the Council of the Discipline of Pharmaceutical Sciences of the Medical University of Warsaw a motion to admit Anna Maria Mazurek, MA of pharmacy, to the further stages of the procedure for the award of the degree of Doctor in the field of medical and health sciences, in the discipline of pharmaceutical sciences.

In consideration of the coherence and timelines of the publication cycle, the Candidate's primary authorship of all papers, the high methodological rigor of the research, the formulation of a practically applicable framework for identifying and

predicting isosymmetric phase transitions, and the substantial implications of the results for solid-state chemistry and pharmaceutical sciences, I strongly recommend that the doctoral dissertation be distinguished.

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reviewer's signature