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REVIEW OF THE DOCTORAL DISSERTATION

of Ms Anna Maria Mazurek, MSc Pharm.

entitled

"Analysis of isosymmetric phase transitions using molecular modelling methods"

This report presents my evaluation of the doctoral dissertation authored by Anna Maria Mazurek, MSc Pharm. The dissertation was completed within the Department of Organic and Physical Chemistry at the Faculty of Pharmacy, Medical University of Warsaw, under the primary supervision of Dr. hab. Łukasz Szeleszczuk, alongside co-supervisor Dr. Monika Franczak-Rogowska.

The dissertation presents a comprehensive investigation of isosymmetric phase transitions (IPTs), a challenging class of polymorphic transformations, focusing on the analysis of experimentally observed IPTs in selected molecular crystals using periodic density functional theory (DFT)-based molecular modelling. The computational approach comprises dispersion-corrected structural optimisation, pressure-dependent lattice energy calculations, vibrational and phonon analyses, Raman spectrum simulations, and molecular dynamics simulations. The aim of this integrated work is to understand the molecular mechanisms underlying IPTs, verify the effectiveness of the proposed computational method in identifying and interpreting them, and establish an effective methodological framework for potentially predicting IPTs.

The research presented in this dissertation tackles a complex subject of considerable scientific and industrial importance. Crystal phase transitions are a ubiquitous phenomenon across a wide spectrum of materials. Within the pharmaceutical industry in particular, active drug substances and excipients frequently exist in multiple solid forms, where specific polymorphs offer distinct advantages regarding clinical efficacy, manufacturability, and shelf-life stability. Yet, despite their widespread occurrence, our understanding of the underlying mechanisms and the driving factors that govern these transitions is still relatively rudimentary. Among these, IPTs represent a unique

and underexplored class that presents significant challenges to conventional classification schemes. Because their complexity hinders both experimental detection and computational prediction, the candidate's focus on methodological innovation is both timely and necessary.

A detailed review of the dissertation follows below. In summary, it is an exceptionally well-structured and logically developed work that stands as a highly valuable scientific achievement. The candidate has demonstrated a profound understanding of solid-state chemistry, polymorphism, molecular crystal thermodynamics, and periodic DFT calculations. Supported by a thorough and critical engagement with current literature, she consistently poses insightful questions and delivers answers backed by well-documented results. She has unequivocally proven her capacity to synthesise complex concepts and conduct rigorous, independent scientific research.

Crucially, the candidate's extensive knowledge allows her to critically evaluate the experimental data and identify the precise computational tools required for the task. By employing periodic DFT to optimise crystal structures, simulate pressure, analyse vibrations, and track molecular movement, she moves beyond standard modelling. Instead, she builds a rigorous, foundational procedure capable of explaining these subtle polymorphic phase transformations. By delivering an integrated computational framework to identify and predict IPTs, the candidate provides an original and highly innovative approach to a critical challenge in pharmaceutical systems.

Overall, **the dissertation receives an unequivocally positive assessment and fully satisfies all requirements for a doctoral degree. I rate the doctoral dissertation of Ms. Anna Maria Mazurek, MSc Pharm., very highly and recommend that she be awarded a Ph.D. with distinction.**

1. Dissertation assessment

1.1. Descriptive part

The dissertation is composed of a comprehensive descriptive part alongside four published articles, which form its core. In the introduction, the candidate clearly defines the research subject, extensively justifying its significance. Her thorough descriptions demonstrate a deep, detailed understanding of the field and its inherent challenges. It is evident that the topic has been rigorously researched, the methodology is sound, the aims are clearly defined, and the literature is adequately cited. Furthermore, the candidate lays a solid foundation for addressing the problem through an integrated experimental-computational approach. She specifically highlights the integration of periodic DFT calculations, bringing an innovative perspective to the study of IPTs. Finally, by emphasizing the study's relevance to the pharmaceutical sciences, she strongly establishes the rationale for her doctoral research.

A brief overview of the four publications resulting from this study follows. While Publication #1 serves as a general review of IPTs, the primary investigation - detailed in Publications #2, #3, and #4 - focuses on IPTs in molecular systems, which are of direct pharmaceutical interest.

Subsequently, the dissertation clearly outlines its objectives and justifies the selection of the molecular crystals investigated in the latter three publications. The central aim is explicitly stated: the development of a methodological framework utilizing advanced computational methods to facilitate more accurate predictions of IPTs in molecular crystals. This framework is detailed in the ensuing sections. The logical progression of these stages, and their complementarity in revealing IPT mechanisms, justifies the establishment of this computational framework as a tool of significant importance for pharmaceutical systems.

Finally, the findings concerning the three examined molecular crystals are summarized concisely and comprehensively, providing fundamental insights into IPTs. By employing the periodic DFT framework to optimise structures, apply pressure, simulate Raman spectra, analyse vibrations, and track molecular movement, the candidate builds a robust methodological foundation for identifying and predicting IPTs in molecular crystals.

1.2 Publications

The core of the dissertation comprises four articles published between 2025 and 2026 in recognized, peer-reviewed international scientific journals (*Crystals* and *Applied Sciences,* both of which hold an impact factor of 2.9). These publications constitute a thematically coherent series focused on the study of IPTs; the first is a review article, while the subsequent three are original research papers.

Ms. Anna Maria Mazurek is the first author on all four publications. As confirmed by the attached co-author statements, her contributions encompass conceptualisation, formal analysis, investigation, data curation, original draft preparation, review and editing, and visualisation. This substantial involvement unequivocally demonstrates her capacity to conduct independent scholarly research, thereby fulfilling a core requirement for earning a doctoral degree.

1.2.1. Review article (#1)

The first published article is a comprehensive review of IPTs in crystalline systems. In this work, the authors provide a thorough overview of the experimental and computational methods used to detect and characterise IPTs. Furthermore, they present a broad selection of pressure- and temperature-induced IPTs from the literature, discussing the principal microscopic drivers of these transitions, their functional consequences, and associated kinetic effects. This publication demonstrates the candidate's extensive command of the relevant literature and her profound understanding of the field. Crucially, it highlights her significant ability to critically analyse existing findings and seamlessly integrate them into the objectives of her own research, as explored in the three subsequent original research papers.

1.2.2. Research articles (#2, #3 and #4)

To assess the efficacy of DFT calculations in studying IPTs, the candidate focused on three selected molecular crystals. By combining structural optimisation, lattice energy analysis, phonon calculations, and vibrational studies, the methodology effectively explains the underlying molecular mechanisms, reproduces observed transitions, predicts transition pressures, and elucidates the thermodynamic basis of phase stability. The selection of these specific model

systems is well-justified, with each highlighting a distinct driving force or challenge. Collectively, they provide a comprehensive set of case studies proving that standard computational models are simply not enough to understand these complex phenomena.

Publication #2 utilises the sulfamic acid crystal as a model for high-pressure (10 GPa) phase transitions. By demonstrating that the transition requires a cooperative reconfiguration of hydrogen-bonded chains rather than simple elastic compression, the authors prove that static structural optimisation alone is insufficient for predicting IPTs. Instead, these complex dynamic reconfigurations must be explicitly accounted for in the computational model.

In Publication #3, resorcinol serves as an excellent baseline model for isosymmetric polymorphism occurring under normal, ambient conditions. The study demonstrates that the two crystal forms (α and β) share the exact same space group, with structural differences arising entirely from subtle shifts in hydrogen bond topology and hydroxyl group orientations, rather than from actual molecular deformation. This finding establishes a clear baseline, illustrating how the subtle reconfiguration of intermolecular interactions alone can drive IPTs, even in the absence of extreme pressure.

Finally, in Publication #4, L-serine is investigated to highlight the thermodynamic complexities of IPTs, yielding the most significant thermodynamic conclusions of the dissertation. The candidate reveals that relying on purely static lattice energy calculations leads to incorrect predictions regarding phase stability. Instead, the research demonstrates that the ambient phase is actually stabilised by vibrational entropy, whereas the high-pressure phase is stabilised by enthalpy. This critical finding proves that such transitions can be entirely entropy-driven. Consequently, it demonstrates that researchers cannot rely on simple enthalpy comparisons; a comprehensive Gibbs free energy analysis is absolutely essential for accurate phase predictions.

Collectively, these peer-reviewed articles demonstrate a coherent, strategic approach to developing a comprehensive methodology for identifying and predicting IPTs. Notably, the candidate's work demonstrates a clear progression, growing increasingly mature and robust with each successive publication. This evolution, combined with the exceptional overall quality of the studies, underscores the immense potential of her approach to predict subtle polymorphic phase transformations, such as IPTs, which is of great scientific and industrial importance in the pharmaceutical sciences and beyond.

Questions for discussion

This work is highly commendable. It is a meticulously designed, coherent study, that offers both significant theoretical value and practical promise for the pharmaceutical sciences. As the core content has already been validated through peer review and published in recognised scientific journals, I have no major substantive objections and hold the work in high regard. The following comments and questions are therefore intended primarily to stimulate discussion during the doctoral defence.

1) The first original research article presented in this dissertation - which serves as the starting point for the proposed methodological development - builds upon a previous publication by Dr. Łukasz Szeleszczuk and his research team [*Szeleszczuk, Ł., et al., Int. J. Mol. Sci. 2021, 22, 10100*]. While both studies share the objective of computationally predicting and describing pressure-induced isosymmetric phase transitions (IPTs) using periodic density functional theory (DFT), their methodological frameworks diverge significantly regarding functional benchmarking, optimisation strategies, and the analytical tools used to verify the transitions.

In light of these methodological shifts, I would ask the candidate to describe the specific reasons that led her to adopt this new strategy. Specifically, why was a much more extensive benchmarking process of DFT functionals and dispersion corrections, alongside discrete pressure sampling, chosen over the narrower benchmarking and continuous pressure sampling approach utilised previously?

2) One of the significant conclusions of this study is that 'the predictive power of periodic DFT for isosymmetric transitions remains system-dependent and requires careful benchmarking.' Given this, the candidate is asked to explain why the PBE-TS functional was selected over PBESOL-TS for the calculations subsequent to the static lattice energy and geometry optimisation steps in Publications #2 and #4. Interestingly, in the phonon-derived thermodynamic calculations of Publication #3, PBESOL-TS provided the most consistent agreement with experimental data. Does she believe that in the cases of sulfamic acid and L-serine, where the systems were examined at high pressures of 20.1 GPa and 8.8 GPa, respectively, employing PBESOL-TS instead of PBE-TS would yield no significant difference due to the overwhelming magnitude of the mechanical work ($P\Delta V$) within the enthalpy term?

3) Finally, I would like to ask the candidate to consider the following scenario: imagine a molecular crystal of pharmaceutical interest for which structural and spectroscopic data (SCXRD, Raman, and FT-IR) are available exclusively at ambient conditions. My questions are:

(i) What procedural steps would she take to attempt to predict a pressure-induced phase transition?

(ii) Secondly, what does she perceive as the primary bottlenecks hindering the translation of this integrated methodology to application-driven challenges within chemical and pharmaceutical workflows where the ultimate goals are to inform fewer and better experiments, facilitating more effective products made efficiently, and time reduction to market?

(iii) Lastly, how would she approach the further optimisation and development of the framework presented in this dissertation?

Final recommendation

I hereby state that the doctoral dissertation of Ms Anna Maria Mazurek, MSc Pharm., entitled "Analysis of isosymmetric phase transitions using molecular modelling methods", fulfils the requirements specified in Article 187 of the Act of 20 July 2018 - Law on Higher Education and

Science. Accordingly, I respectfully request that the Council of the Discipline of Pharmaceutical Sciences at the Medical University of Warsaw admit Ms Anna Maria Mazurek, MSc Pharm., to the subsequent stages of the proceedings for the award of the degree of Doctor of Medical and Health Sciences in the discipline of Pharmaceutical Sciences.

Furthermore, taking into account the exceptional quality of the research and its significance for both solid-state chemistry and the pharmaceutical sciences, alongside the candidate's significant role as the first author on all publications, I recommend that this doctoral dissertation be awarded with distinction.

reviewer's signature

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