NICOLAUS COPERNICUS
UNIVERSITY
IN TORUŃ
Faculty of Pharmacy
Collegium Medicum in Bydgoszcz
Department of Toxicology and Bromatology

Bydgoszcz, 15th June 2026

Marcin Gackowski, PhD, DSc, NCU Professor

REVIEW OF THE DOCTORAL DISSERTATION

of Ms. Anna Maria Mazurek, MSc Pharm.

entitled

"Analysis of isosymmetric phase transitions using molecular modeling methods"

The doctoral dissertation of Ms Anna Maria Mazurek, MSc Pharm., submitted to me for assessment, was prepared at the Faculty of Pharmacy of the Medical University of Warsaw, in the Department of Organic and Physical Chemistry, under the supervision of Dr hab. Łukasz Szeleszczuk and co-supervised by Dr Monika Franczak-Rogowska. The dissertation concerns the analysis of isosymmetric phase transitions in molecular crystals using molecular modeling methods, primarily periodic DFT calculations supplemented by phonon analysis, simulated Raman spectra, and selected elements of molecular dynamics.

1. Formal assessment of the dissertation

The dissertation is presented as a thematically **coherent series of four scientific publications** preceded by an extensive descriptive part. In this introductory part, the Candidate explains the rationale for undertaking the topic, presents the theoretical background of polymorphism and phase transitions in molecular crystals, formulates the aims of the work, describes the proposed methodological framework, and provides a concise synthesis of the obtained results. English and Polish abstracts, a list of abbreviations, a bibliography, reprints of the publications, and co-author statements further supplement the dissertation. This **structure is clear and well-suited** to a doctoral dissertation based on a publication cycle.

The publication cycle forming the basis of the dissertation consists of one review article and three original research papers: a review devoted to isosymmetric phase transitions in crystals, a paper on a pressure-induced phase transition in sulfamic acid, a study of the isosymmetric relationship between the alpha and beta phases of resorcinol, and a paper analyzing the entropy-driven phase transition of L-serine under pressure. All papers were published in 2025-2026, and the Candidate is the first author of each. The total **impact factor** of these publications is **9.7**, while the total **ministerial score** indicated in the dissertation is **310 points**.

The co-author statements confirm the **substantial and direct contribution of Ms. Anna Maria Mazurek** to the works included in the dissertation. This contribution covered, among other elements, formal analysis, research, data processing, preparation of the original manuscript drafts, revision of the text, and visualization of the results. The presented publication cycle has a clear, common scientific core, and the **Candidate's contribution is sufficiently documented to serve as the basis for an independent scientific achievement in doctoral proceedings**.

From a formal and editorial standpoint, the dissertation has been prepared with care. The introductory part is written clearly, organizes the concepts necessary for understanding the subsequent research, and guides the reader logically from the

ul. dra Jurasza 2, 85-089 Bydgoszcz,
tel. +48 52 585 39 42, fax. +48 52 585 35 29
e-mail: marcin.gackowski@cm.umk.pl

general issue of polymorphism through the classification of phase transitions to the specificity of isosymmetric transitions and their relevance to the pharmaceutical sciences. The few minor stylistic or linguistic imperfections, typical of works prepared in English by non-native speakers, do not affect the substantive reception of the dissertation and do not diminish its scientific value.

2. Substantive assessment of the dissertation

The dissertation's **subject is well chosen and timely**. Isosymmetric phase transitions belong to a class of solid-state phenomena that can easily be overlooked when the analysis is limited to classical crystallographic criteria. Preserving the same space group may suggest structural continuity, whereas in reality, meaningful changes may occur in hydrogen-bond topology, functional-group orientation, molecular packing, and thermodynamic stability. For this reason, the work has **a distinct cognitive dimension, as well as a practical one**, since the correct recognition of subtle phase transformations is important for controlling the solid forms of active substances, maintaining the stability of crystalline materials, and predicting their physicochemical properties.

The Candidate adopted as the main aim of the dissertation the identification and characterization of isosymmetric phase transitions in selected molecular crystals, together with the determination of the structural and thermodynamic factors responsible for their occurrence. The choice of the model systems - sulfamic acid, resorcinol, and L-serine - is appropriate, because each of them captures a different aspect of the problem studied. Sulfamic acid provides an example of pressure-induced reorganization of a hydrogen-bond network, and resorcinol enables analysis of the isosymmetric relationship between two crystalline forms belonging to the same space group. At the same time, L-serine clearly illustrates the importance of the entropic contribution and the limitations of an interpretation based solely on static lattice energy.

I particularly appreciate the methodological consistency of the entire cycle. The Candidate did not limit the work to a simple comparison of crystal structures, but combined periodic-geometry optimizations, analyses of energy and enthalpy as a function of pressure, phonon calculations, the quasi-harmonic approximation, simulated Raman spectra, and, where justified, elements of ab initio molecular dynamics. This selection of tools is appropriate for the nature of the phenomenon under investigation, because small energy differences and subtle, yet cooperative, changes within the network of intermolecular interactions usually govern isosymmetric phase transitions.

The first publication, which is a review article, plays an important organizing role in the dissertation. In this work, the Author presents isosymmetric phase transitions as phenomena that should not be reduced to insignificant distortions within a single crystal structure. The paper situates subsequent research in an appropriate literature context. It convincingly shows that the absence of a change in symmetry does not imply the absence of a genuine phase transition. The emphasis placed on the need to combine experimental data with computational modeling is also valuable and is subsequently developed in the three original research papers.

In the work on sulfamic acid, the Candidate demonstrated that a pressure-induced isosymmetric phase transition cannot be reliably explained by static structure optimization alone. Although the compression of the crystal lattice was reproduced correctly, direct optimization did not spontaneously yield the high-pressure structure, indicating the presence of a finite energy barrier. Of particular importance is the juxtaposition of computational results with Raman spectroscopy data, as well as the use of ab initio molecular dynamics, which allowed the transition to be related to the cooperative reorganization of hydrogen-bond chains and the coordinated motion of NH_3^+ and SO_3^- fragments. This is a very good example of a study

in which molecular modeling not only reproduces experimental observations but also helps explain the phenomenon's mechanism.

The analysis of resorcinol is another strong component of the dissertation. The Author showed that the alpha and beta forms, despite belonging to the same Pna21 space group, differ in the orientation of their hydroxyl groups and in the topology of their hydrogen-bond networks. Periodic calculations confirmed the agreement between the optimized structures and the crystallographic data and enabled tracking changes in the relative stability of the phases under pressure. In my view, the main value of this part lies in showing that isosymmetry is not merely a crystallographic curiosity, but a real interpretative problem in which phase stability is determined by a subtle balance between O-H...O hydrogen bonds, weaker intermolecular interactions, and packing efficiency.

The most convincing and, at the same time, the most mature part of the cycle appears to be the paper devoted to L-serine. In this case, the Candidate demonstrated that an analysis based solely on static lattice energy would lead to an incomplete or even misleading interpretation of phase stability. Only the inclusion of the phonon contribution and the quasi-harmonic approximation made it possible to show that the experimentally observed phase under ambient conditions is stabilized by vibrational entropy. In contrast, under pressure, the enthalpically more favorable high-pressure phase begins to dominate. This is an important result because it clearly shows the limits of simplified energetic analyses in molecular crystals and convincingly justifies the need to calculate Gibbs free energy rather than merely compare static energies.

One of the most important achievements of the dissertation is the **proposal of a practical methodological framework for identifying and predicting isosymmetric phase transitions**. The scheme comprising periodic optimizations as a function of pressure, analysis of relative energies and enthalpies, phonon calculations, entropic contributions, and molecular dynamics in cases where the transition is blocked by an energy barrier has clear practical value. It is not merely a summary of calculations already performed, but an attempt to generalize the results in a way that may be useful for further studies of molecular crystals, including potentially pharmaceutical substances.

The dissertation also has **clear relevance to pharmaceutical sciences**. The Author correctly points out that isosymmetric transitions may be difficult to detect in routine solid-form analysis because they do not produce signals as obvious as those of classical polymorphic transitions associated with a change in space group. Nevertheless, even small changes in molecular conformation, hydrogen-bond geometry, or packing may influence solubility, stability, behavior under pressure, susceptibility to transformations during storage, or material behavior during technological processing. In this sense, the dissertation fits well into the modern approach to solid-state studies of medicinal substances, in which experiment and computational modeling complement one another.

3. Detailed remarks and questions for discussion

I do not raise any major substantive objections to the dissertation. The work is coherent, well planned, and based on results published in peer-reviewed journals. The following comments are intended as points for discussion and do not affect my very high assessment of the dissertation.

First, it would be interesting to discuss more broadly to what extent the predicted transition pressures and the order of phase stability depend on the choice of the exchange-correlation functional and the dispersion-correction scheme. The Author rightly notes that the energy differences between competing structures are small; therefore, the sensitivity of the results to the computational protocol is particularly important for the further use of the proposed procedure.

Second, during the public defense, I would be interested to hear the Candidate's view on which elements of the proposed scheme are, in her opinion, necessary in a routine investigation of potential isosymmetric phase transitions, and which may be treated as deeper, follow-up stages applied only when static energy calculations and structural analysis yield ambiguous results.

Third, an interesting direction for further research would be to transfer the proposed approach from model systems to molecules of direct pharmaceutical relevance, especially those for which the technological process involves compression, milling, drying, or other conditions that may induce subtle reorganizations in the crystal lattice. I do not regard this as a limitation of the dissertation, but rather as a natural and valuable direction for continuation of the research presented.

4. Summary of the assessment

In summary, **I assess the doctoral dissertation of Ms. Anna Maria Mazurek, MSc Pharm., very highly**. The presented **publication cycle is a coherent, logically developed, and valuable scientific achievement** that addresses phenomena difficult to capture unambiguously, both experimentally and computationally. The Candidate has demonstrated a sound understanding of solid-state chemistry, polymorphism, thermodynamics of molecular crystals, and periodic modeling methods. Importantly, the work is not limited to the use of available computational tools, but leads to the formulation of a generalized procedure that may be applied in further research on subtle phase transformations.

The dissertation makes an original contribution to pharmaceutical sciences and solid-state chemistry by showing that isosymmetric phase transitions should be treated as genuine first-order phase transitions rather than minor deformations of a single crystal structure. It also demonstrates that a correct interpretation of such phenomena requires the combined analysis of structural, energetic, vibrational, entropic, and dynamic factors. Particularly valuable are the documentation of the role of vibrational entropy in stabilizing the L-serine phase and the demonstration of the limitations of static optimization alone in sulfamic acid.

The **dissertation fulfills the requirements set for doctoral dissertations**. In particular, it presents an original solution to a scientific problem, confirms the Candidate's general theoretical knowledge in the discipline of pharmaceutical sciences, and demonstrates her ability to conduct scientific work independently. The substantive level of the publication cycle, methodological consistency, topicality of the subject, and clearly demonstrated cognitive and practical value of the results justify an unequivocally positive assessment.

5. Final recommendation

I hereby state that the doctoral dissertation of Ms Anna Maria Mazurek, MSc Pharm., entitled "Analysis of isosymmetric phase transitions using molecular modeling methods", **fulfills 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.

At the same time, taking into account the coherence and topicality of the publication cycle, the Candidate's first-author contribution to all papers, the high methodological level of the research, the proposal of a useful framework for identifying and predicting isosymmetric phase transitions, and the value of the results obtained for solid-state chemistry and pharmaceutical sciences, **I recommend that the doctoral dissertation be distinguished**.

Respectfully submitted,

Marcin Gackowski, PhD, DSc, NCU Professor
Bydgoszcz, 15th June 2026