INNOVATIONS IN GREEN CHEMISTRY: THE APPLICATION OF COMPUTATIONAL MODELING IN SUSTAINABLE PROCESSES

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ABSTRACT: Computational modeling has been a powerful tool for implementing sustainable practices in chemical processes. The first case study discusses the choice of green solvents based on computational simulations, highlighting the effectiveness of deep eutectic solvents (DESs) and their natural variants (NADESs) in improving CO_2 biocatalysis. The second study addresses the optimization of synthetic routes and crystallization in the pharmaceutical industry, using the CAMbD method to reduce environmental impacts and improve process efficiency. Finally, the third study exemplifies the application of computational modeling in predicting toxicological properties and exposure to chemicals, contributing to the creation of safer and more sustainable products. Computational modeling allows for a more rational and effective approach, aligned with the principles of Green Chemistry, such as the prevention of environmental impacts and the reduction of toxicological risks.

INTRODUCTION

Computational modeling has established itself as an essential tool for applying the principles of Green Chemistry,

promoting more sustainable and efficient chemical processes. In various areas, such as the pharmaceutical industry and the conservation of cultural assets, these approaches have been used to optimize processes, replace conventional reagents, and predict environmental and toxicological impacts. This paper presents three case studies that illustrate the application of computational modeling to promote greener and more sustainable practices in chemistry, focusing on the choice of solvents, optimization of synthetic routes, and prediction of toxicological properties, highlighting how these practices directly contribute to the Principles of Green Chemistry.

CASE STUDIES

Computational modeling has proven to be a strategic tool for implementing the principles of Green Chemistry in various contexts, from the pharmaceutical and chemical industry to the conservation of cultural assets. In this section, we present three case studies that illustrate the practical application of this approach in sustainable chemical processes.

Selection of Green Solvents Based on Computational Simulations

Replacing conventional solvents with green alternatives is one of the central strategies of Green Chemistry. In this context, deep eutectic solvents (DESs) and their natural variants (NADESs) have emerged as promising options, given their biodegradability, low toxicity, and ease of preparation. In the study conducted by Logarušić *et al.* (2024), the combination of experimental screening and computational modeling allowed the identification of a mixture of choline chloride and glycerol as the most effective system for the biocatalytic reduction of CO_2 to formate, catalyzed by formate dehydrogenase (FDH). The use of the selected DES resulted in a 15-fold increase in the half-life of the enzyme, as well as greater stability of the NADH cofactor and process productivity.

At the same time, molecular simulation studies and methods such as COSMO-RS have been used to predict the physicochemical and solubility properties of these solvents in different matrices. Tolmachev *et al.* (2022) highlight the role of simulations based on molecular dynamics and quantum mechanics in understanding the structure and behavior of DESs, allowing for more rational planning of solvent-substrate systems even before their synthesis. These approaches contribute directly to Principles 5 (use of safer solvents), 9 (catalysis), and 12 (risk minimization) of Green Chemistry by enabling the choice of less toxic and more efficient solvents.

Optimization of Synthetic Routes with Less Environmental Impact

The second case exemplifies the application of computational tools to optimize synthetic routes and crystallization processes in the pharmaceutical industry. Muhieddine et al. (2022) proposed an approach based on the CAMbD (Computer-Aided Mixture

Design) method, which integrates thermodynamic modeling with environmental and economic performance indicators, such as the E-factor and crystalline yield. In the study, the mefenamic acid production process was optimized based on computationally predicted parameters, resulting in the selection of solvents and anti-solvents with lower environmental impact and higher purification efficiency. This methodology promotes a holistic view of the process, integrating the synthesis and separation steps and avoiding additional solvent exchange operations. Alignment with Principles 1 (prevention), 3 (design of less hazardous products), and 6 (atomic efficiency) is evident, since modeling allows for the avoidance of unwanted by-products and reduces the use of inputs.

In Silico Prediction of Toxicological and Exposure Properties

In addition to predicting physicochemical properties and optimizing synthetic routes, computational modeling also plays a key role in the preliminary toxicological evaluation of compounds. Buckley *et al.* (2023), in research conducted by the US Environmental Protection Agency (EPA), demonstrate how QSAR models and machine learning techniques have been used to predict human exposure to thousands of chemicals, prioritizing them for regulatory risk assessments. The integration of these tools into platforms such as ToxCast and ExpoCast enables high-speed screening, anticipating potential adverse effects and promoting substitution with safer substances.

Complementarily, Macchia *et al.* (2025) applied Hansen solubility parameters, integrated toxicity index (ITI), and computational modeling to assess the applicability of green solvents in cultural heritage conservation treatments. The results indicated that it is possible to predict with a high degree of reliability the efficacy and safety of alternative solvents, such as cyclic ethers and FAMEs, without compromising the original materials. These studies exemplify the relevance of computational modeling for Principles 3 (designing less hazardous products), 10 (designing for degradation), and 12 (minimizing risks) by anticipating environmental and toxicological impacts without resorting to excessive experimentation.

ENVIRONMENTAL AND ECONOMIC IMPACTS

Green Chemistry, as proposed by Anastas and Warner (1998), aims to integrate synthetic efficiency, chemical safety, and environmental sustainability. Computational modeling, as a tool for prediction and rational planning, has contributed to the consolidation of these principles by enabling cleaner and more economically viable chemical processes. In this context, its impacts can be analyzed along four main axes: optimization of resource use, replacement of animal experimentation, virtual life cycle analysis, and rationalization of industrial costs.

Computer simulation allows the chemical behavior of molecules and reactions to be predicted under different conditions, optimizing synthetic routes even before their experimental application. This anticipation results in the minimization of reagent use, the elimination of unnecessary steps, and, consequently, less waste generation. According to Mammino (2023), prior analysis by molecular modeling has the potential to guide synthetic planning, avoiding failed experimental attempts and promoting better rationalization of the use of energy, time, and laboratory resources.

Reduction in the Use of Reagents and Energy

According to Anastas and Kirchhoff (2002), the efficiency of chemical processes depends not only on the desired conversion, but also on the minimization of inputs (reagents) and unwanted by-products. Computational modeling acts in this context by allowing the simulation of reaction mechanisms, energy parameters, and thermodynamic feasibility of routes even before their experimental execution. This significantly reduces the number of experiments required, promoting savings in reagents and energy. In addition, as highlighted by Cavasotto and Orrico (2007), computational analysis of molecular interactions and electronic properties allows for the identification of more selective reaction pathways, which translates into energy savings and less waste generation. Thus, it operates as a mechanism for prevention and atomic efficiency, two pillars of Green Chemistry.

Replacement of *In Vivo* and *In Vitro* Tests with *In Silico* Tests

The replacement of experimental methods with computational tools is advocated by Hartung (2009), who proposes a toxicogenomic approach based on databases, algorithms, and artificial intelligence to reduce dependence on animal testing. QSAR (Quantitative Structure-Activity Relationship) models, for example, are recognized by the OECD as valid tools for chemical risk screening (OECD, 2014). In this sense, computational modeling contributes to the application of Principle 4 of Green Chemistry by enabling the design of substances with lower toxicity and risk. According to Todeschini and Consonni (2009), QSAR models offer robust predictions based on molecular descriptors, significantly reducing the need for synthesis and preliminary testing. Tools such as ToxinPred, based on neural networks trained with experimental data, have proven effective in predicting peptide toxicity (Gupta *et al.,* 2013), reinforcing the viability of using CM as an ethical, economical, and sustainable alternative.

Virtual Life Cycle Assessment of Compounds

Life cycle assessment (LCA) is considered a systemic approach to estimating the environmental impacts of a product, from cradle to grave. Heijungs and Guinée (2001)

emphasize that computer simulation applied to LCA allows impacts to be anticipated even before the prototyping stage, which significantly reduces the environmental and financial risks of new compounds. Methods such as CAMbD (Computer-Aided Mixture Design), discussed by Gani (2004), integrate thermodynamic simulations and sustainability parameters to guide the choice of solvents, anti-solvents, and reaction conditions with the least environmental impact. This computational integration of technical and ecological criteria exemplifies how CM can act as a catalyst for green innovation. In addition, parameters such as the integrated toxicity index (ITI) and Hansen parameters are widely used in simulating the environmental performance of solvents and materials, as demonstrated by Macchia *et al.* (2025), expanding the applicability of CM in diverse fields such as pharmacology and heritage conservation.

Economic Gains and Industrial Optimization

The adoption of computational tools in the industrial sector is aligned with the principles of Sustainable Chemistry, as advocated by Sheldon (2007), who highlights the importance of process efficiency (E-factor) as a metric for assessing the environmental and economic impact of chemical production. ML allows the anticipation of variables that influence this factor, reducing the number of steps, the consumption of inputs, and disposal costs. Krebs and McKeague (2020) emphasize that the use of *machine learning* in molecular modeling promotes significant advances in synthetic efficiency and property prediction, reducing the development time of new products. This translates into industrial scale optimization, minimization of experimental failures, and, above all, greater economic predictability in the development of sustainable chemical technologies.

The very conceptual foundation of Green Chemistry already highlighted the importance of breaking with classic paradigms of chemical experimentation. As Anastas and Warner (1998, p. 30) state

> Green Chemistry is not about limiting or reducing damage after it occurs, but rather about transforming the way chemicals are designed, developed, and used. It is about preventing the problem before it happens, replacing materials and processes with safer, more efficient, and sustainable alternatives.

This perspective is directly related to the use of computational modeling, as it allows for the selection of cleaner synthetic routes before practical implementation. The ability to simulate reaction mechanisms, predict thermal stability, and identify more selective molecular interactions reduces the number of synthetic steps and directly contributes to the principles of prevention (Principle 1) and atomic efficiency (Principle 2) proposed in Green Chemistry.

CONCLUSION

The case studies presented demonstrate the significant impact of computational modeling on the implementation of Green Chemistry principles. By enabling the most efficient choice of solvents, the optimization of synthetic routes, and the assessment of toxicological risks, these approaches contribute to cleaner, more economical, and safer chemical processes. The use of these tools not only minimizes the use of reagents and the generation of waste, but also anticipates possible risks, promoting more sustainable and ethical chemical production. Thus, computational modeling establishes itself as an essential ally for innovation in Green Chemistry, enabling industrial processes that meet both efficiency and environmental sustainability demands.

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