

# Pharmaceutical Formulation

Schrödinger's Materials Science software suite offers a range of computational solutions for advancing pharmaceutical formulation, from crystalline or amorphous form characterization, to selection of materials and excipients for processing, to formulations and delivery of active pharmaceutical ingredients (APIs).

Keywords: Crystal structure prediction (CSP), Solubility, Amorphous solid dispersions (ASD), Lipid nanoparticle (LNP), Machine learning, Spectroscopy, Catalysis, API degradation

## Background

Due to the accelerating pace of drug discovery, fast and efficient ways to both preformulate and formulate new drugs are critical elements of pharmaceutical development. The latest advancements in molecular modeling and AI/ML are enabling atomistic-level insights to improve drug formulations and the ability to evaluate large numbers of candidate materials and formulations prior to experiments.



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# Crystal Structure Prediction

Early assessment of crystal polymorphism and thermodynamic solubility remains a challenge in drug discovery, particularly for poorly soluble drug candidates. Schrödinger's crystal structure prediction (CSP) method integrates a novel crystal packing search algorithm with a hierarchical energy ranking protocol, complemented by a free energy perturbation (FEP+) approach for predicting aqueous solubility to enable selection of a stable solid form. In this case study, we report a CSP method with state-of-the-art accuracy and efficiency, validated on a large and diverse dataset consisting of 66 drug-like molecules with 137 experimentally known polymorphic forms. Our method not only reproduces all the experimentally known polymorphs, but also suggests new low energy polymorphs yet to be discovered by experiment that might pose potential risks to development of the currently known forms of these compounds.<sup>1-2</sup>

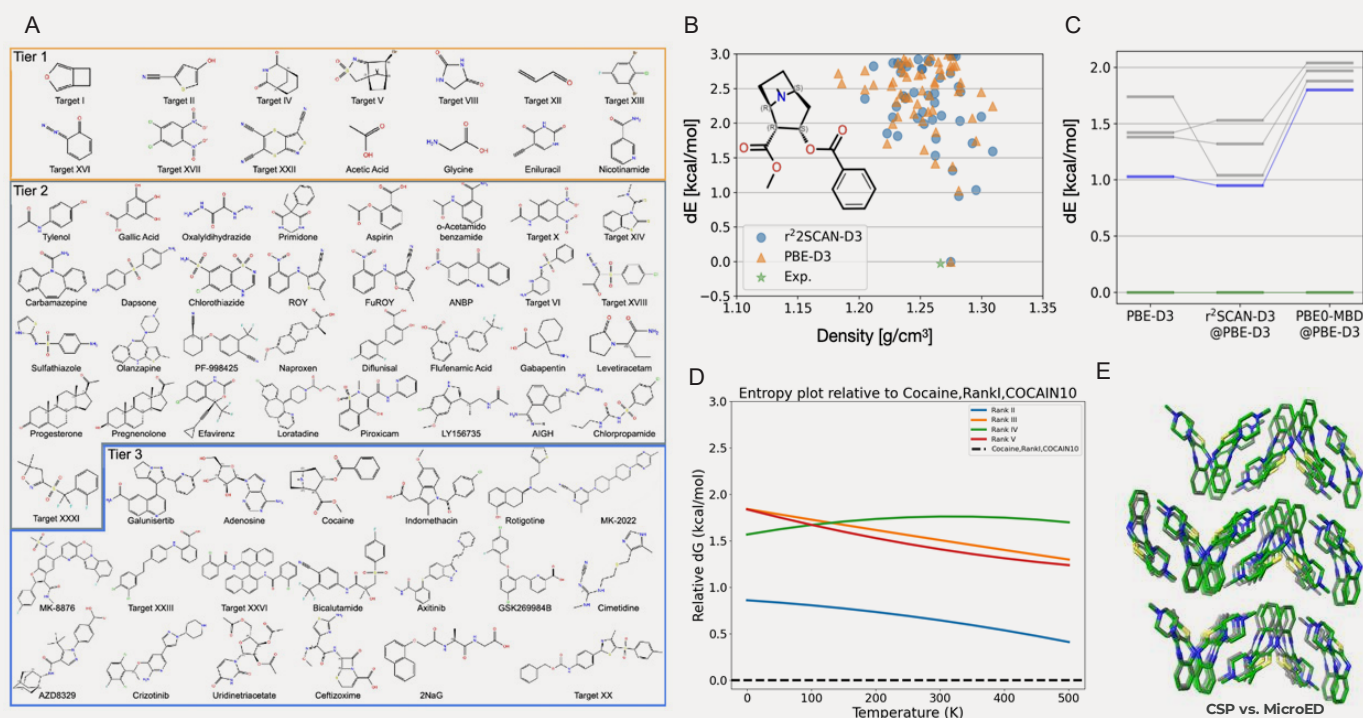


Figure 1: (A) 2D diagram and common names of 66 molecules for retrospective validation of CSP. A dataset of 66 molecules split into three tiers, orange for relatively rigid molecules, gray for small drug-like molecules with two to four rotatable bonds, and blue for larger drug-like molecules with five to ten rotatable bonds. (B) CSP landscape of cocaine with (C) DFT ranking of crystal polymorphs at 0K, and (D) Free energy corrections at RT. (E) Structural overlay comparison between Olanzapine form III, P21/c predicted crystal structure (Gray) and experimental form III (Green) single crystal structure resolved by MicroED experiments (RMSDn of 0.2<sub>33</sub> Å; RMSD of 0.2 Å for a cluster of 33 molecules).

1. Zhou D, et al. *Nat Comm*, 2025, 16, 2210.
2. Anyfanti G, et al. *IUCr*, 2024, 11, 843-848.

## APPLICATION

# Optimizing Drug Formulations with Machine Learning

Mixtures of chemical ingredients, such as formulations, are ubiquitous in materials science, but optimizing their properties remains challenging due to the vast design space. Experimentally fine-tuning formulations for desired properties is expensive because of the large design space of both ingredient structures and compositions. Machine learning (ML) approaches that can accurately map ingredient structure and composition to properties offer a promising solution to rapidly screen formulations for desired target properties. Using Schrödinger's automated Formulation ML workflow, we demonstrate that formulation-property models can accurately predict temperature-dependent drug solubilities for single or binary solvent systems. The parity plot shows that the Formulation ML workflow achieves a test set  $R^2$  of 0.96 (an ideal model would achieve  $R^2$  of 1.00), which highlights the accuracy of ML approaches. These tools enable rapid screening capabilities that transform the way we design drugs and take only seconds to generate a prediction, which is orders of magnitude faster than trial-and-error experimental exploration.<sup>1</sup>

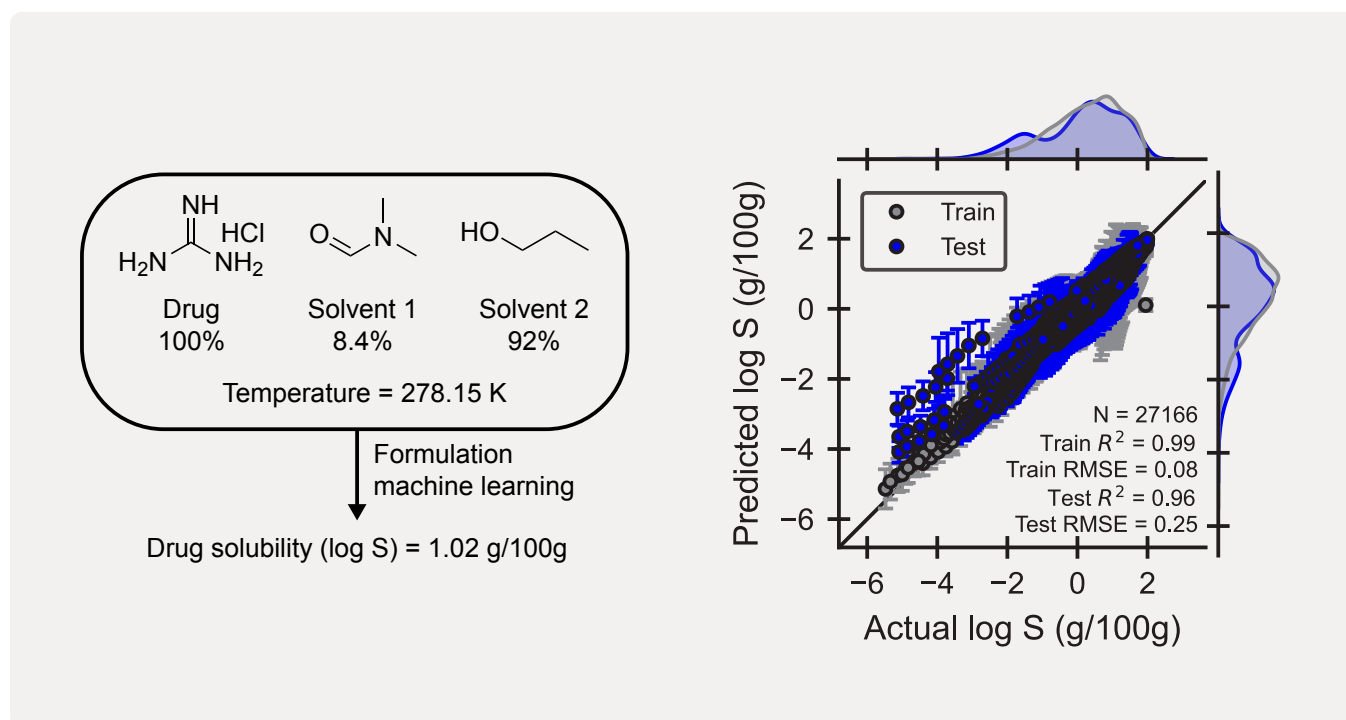


Figure 2: Example of a drug in single or binary solvent mixtures with compositions in mole percent and temperature that is passed into a formulation machine learning model to predict the drug solubility in grams drug / 100 grams solution using a dataset extracted from Bao, Z, et al. J Cheminform, 2024, 16, 117.

1. Chew AK, et al. *npj Comput Mater*, 2025, 11, 72.

## APPLICATION

# Accelerating Amorphous Solid Dispersion Development

Amorphous solid dispersions (ASDs) are widely used to formulate APIs into safe and effective media for human absorption. From screening for compatibility to understanding dissolution mechanisms, the Schrödinger Platform has tools for speeding ASD development.

Complex interactions between an API and key ASD components (e.g., polymers, surfactants, and stabilizers) during dissolution are easily viewed and analyzed with coarse-grained physics-based simulations such as dispersive particle dynamics (DPD) simulations. The underlying mechanisms governing the overall ASD dissolution process are then accessible, helping to solve practical challenges such as solvent-induced phase separation and the impact of drug load on ASD stability and miscibility. Beyond dissolution, other anhydrous dynamic processes are critical for ASD design. One key factor is the glass transition temperature ( $T_g$ ), as maintaining the ASD system below  $T_g$  prevents excessive polymer mobility that could lead to API recrystallization, ultimately reducing ASD efficiency and shelf-life. Schrödinger's molecular dynamics workflow provides a reliable method for estimating the  $T_g$  of the drug and ASD systems, allowing the targeted design of safe API ASD formulations.<sup>1-2</sup>

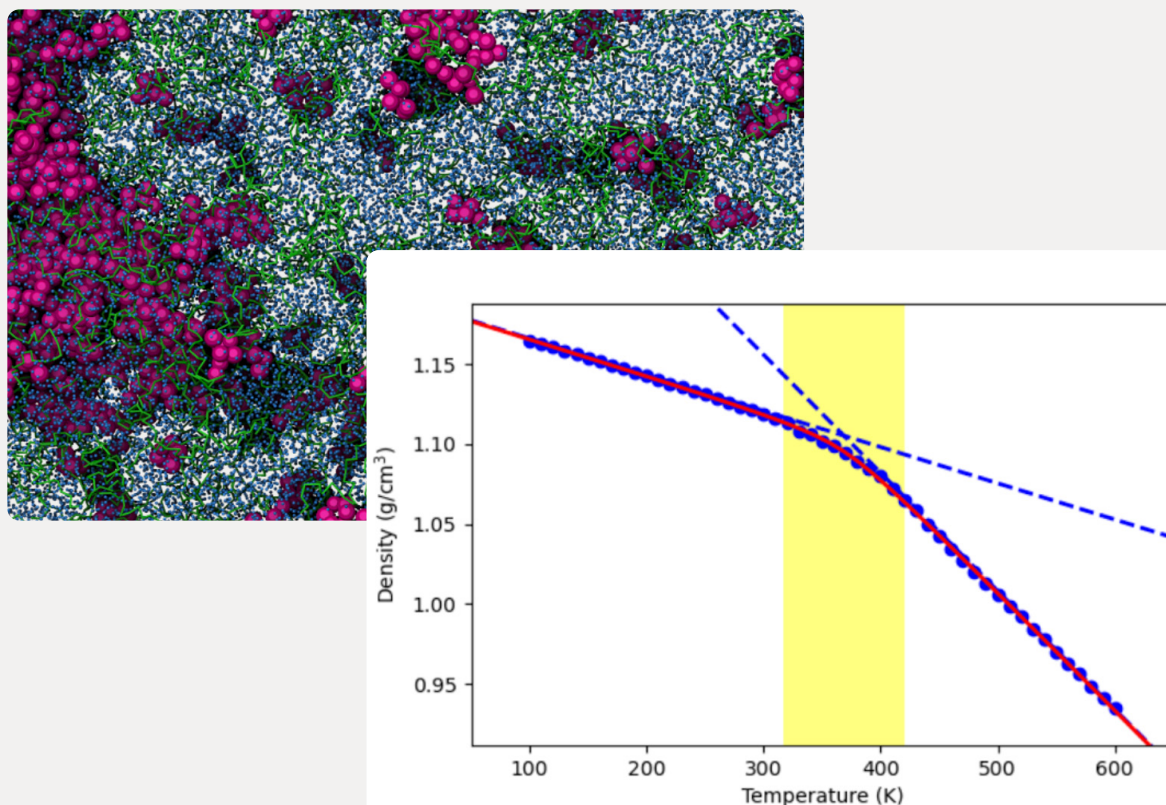


Figure 3: Molecular simulation applications for amorphous solid dispersions. Top: DPD simulations reveal polymer-surrounding API aggregates in a ritonavir (purple balls) - copovidone (green tubes) ASD. Bottom: Schrödinger's molecular dynamics workflow estimates the glass transition temperature ( $T_g$ ) of bucindolol with a 3.6% error relative to the experimental value.

1. Afzal M, et al. [Mol Pharmaceutics](#), 2021, 18, 11, 3999-4014.
2. Walter S, et al. [Pharmaceutics](#), 2024, 16, 10, 1292.

# Modeling Lipid Nanoparticle Formulation

Lipid nanoparticle (LNP)-based drugs are being created to treat many health issues including infectious diseases, cancer, genetic disorders, neurological disorders, and heart failure. A detailed understanding of LNP structures and their behaviors will aid in implementing and optimizing many therapeutics. However, many aspects of LNP creation and behavior are poorly understood at the molecular and supramolecular level. Schrödinger is expanding into this area with the goal of advancing lipid selection, improving encapsulation efficiency and stability, enhancing endosomal release, and enabling targeted delivery to tissues beyond the liver and spleen. Leveraging atomistic and coarse-grained modeling, scientists can predict the apparent pKa values of ionizable lipids, as well as LNP formation and response to changing environments.<sup>1-2</sup>

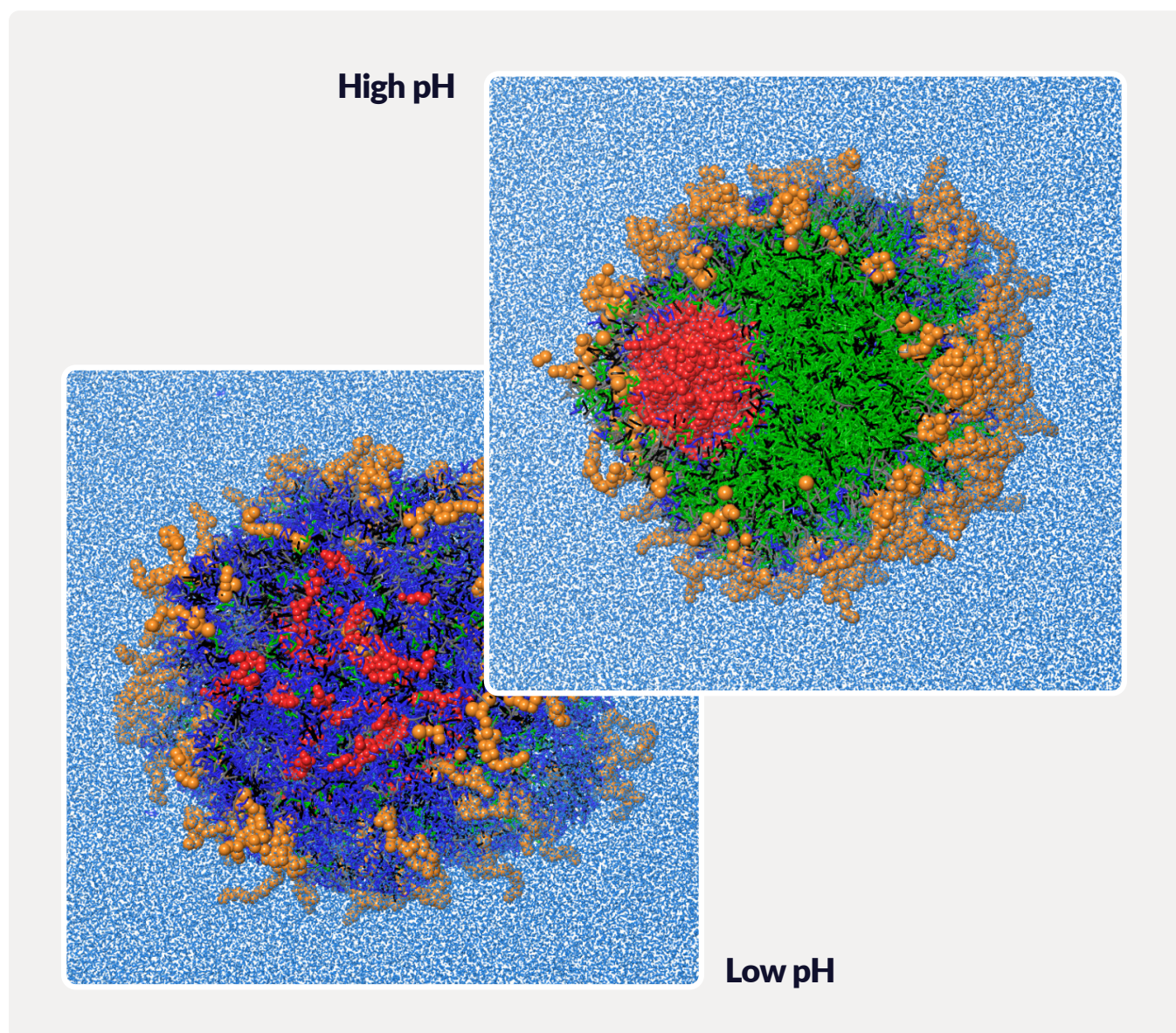


Figure 4: Bleb formation is an active area of LNP research that is believed to affect mRNA expression levels. Schrödinger can simulate the transition from mRNA dispersed within the LNP at low pH (left) to its localization in a bleb at high pH (right). Light blue: Water; Dark blue: Positively charged ionizable lipid; Green: Neutral ionizable lipid; Orange: Pegylated lipid; Light grey: cholesterol or DSPC; Red: mRNA.

1. Hamilton NB, et al. *Mol Pharmaceutics*, 2025, 22, 588-593.
2. Grzetic DJ, et al. *Mol Pharmaceutics*, 2024, 21, 4747-4753.

# Automated Spectroscopic Modeling for Drug-Like Molecules

Structural characterization of drug-like molecules and their precursors can be achieved by comparing the molecule's experimental and simulated spectra. In particular, vibrational circular dichroism (VCD) spectroscopy enables assignment of chirality to one or more stereo-centers, whereas the widely used nuclear magnetic resonance (NMR) spectroscopy can provide a broad range of structural information: 2D connectivity, tautomeric stability, 3D conformational orientation, non-covalent interactions, and more. The Jaguar Spectroscopy workflow offers automated computation of several types of spectra, including VCD and NMR, with a built-in conformational search. VCD calculations are bundled with automated alignment between experimental and theoretical spectra, and are also automated for prediction of VCD spectra of atropisomers. While empirical NMR predictors can provide accurate chemical shifts for well-known types of molecules with uncomplicated interactions, only DFT-based predictors, such as Jaguar Spectroscopy, can be used for modeling subtle effects driven by 3D interactions.

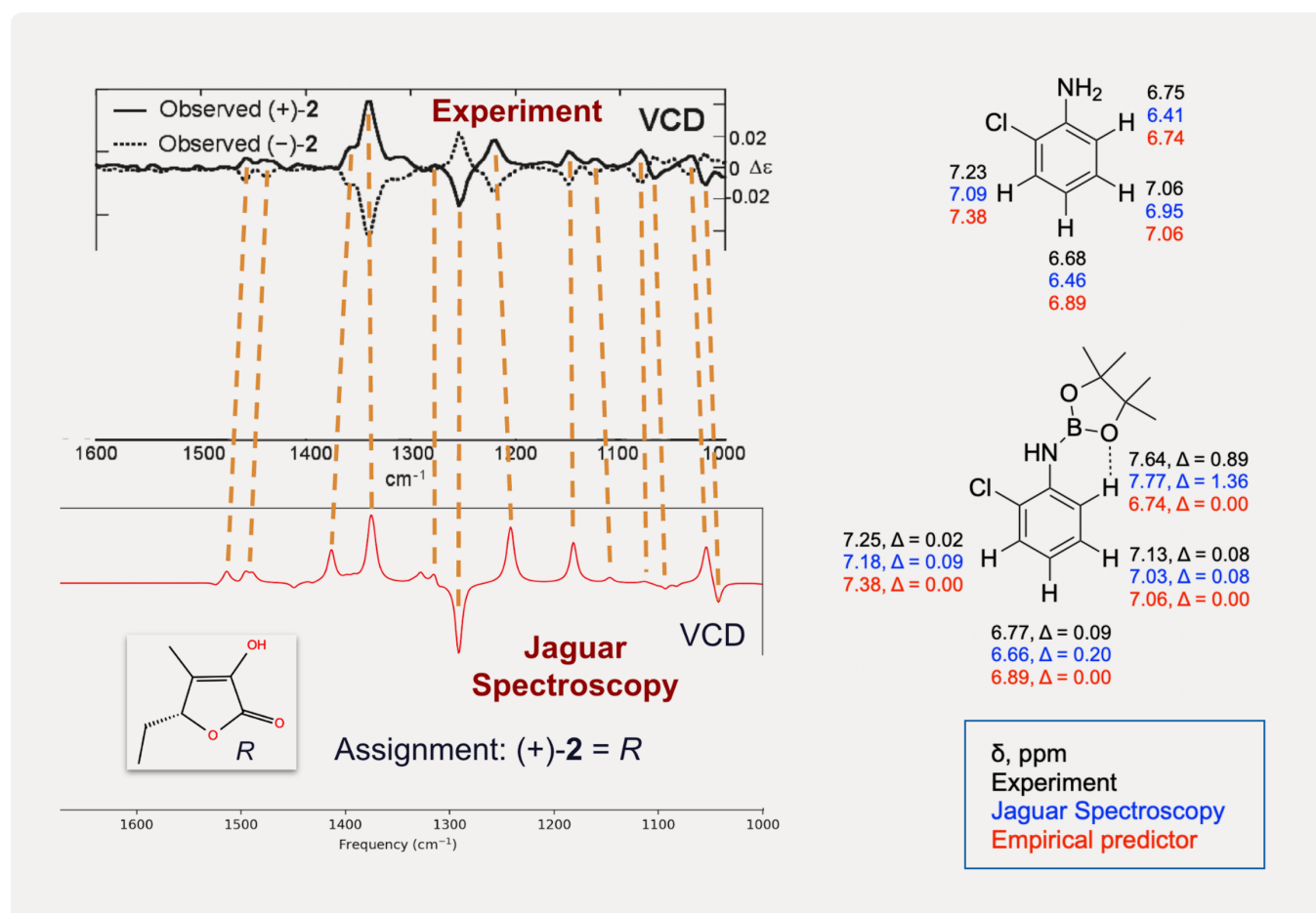


Figure 5: (Left): Comparison of experimental and computed VCD spectra leads to an assignment of the absolute configuration of a maple furanone compound. (Right): Experimental measurements reveal an unusual O-H interaction resulting in a large change of a  $^1\text{H}$  NMR chemical shift in  $\text{CDCl}_3$ : DFT-based Jaguar Spectroscopy (B3LYP-D3/6-31++G\*\*) reproduces the strong effect whereas the empirical NMR predictor is totally insensitive to it.<sup>1-2</sup>

1. Nakahashi A, et al. *J Nat Prod*, 2011, 74, 707-711.
2. Montero Bastidas JR, et al. *ACS Catal*, 2022, 12, 2694-2705.

## APPLICATION

# Predicting API Degradation

API degradation in a drug product is a critical concern in pharmaceutical development and manufacturing. Degradation can impact the drug's efficacy, safety, and shelf life, leading to reduced potency and the formation of harmful degradation products. Understanding degradation pathways is essential for ensuring drug stability and compliance with regulatory guidelines. Schrödinger provides automated methods for identifying degradation reaction pathways and predicting degradation products using quantum mechanics and/or surrogate methods (e.g. machine learning potentials), eliminating the need for predefined rules, templates, or prior chemical intuition. Our current offerings include two Nanoreactor-based molecular dynamics approaches for degradation analysis as well as an approach based on bond dissociation energy.

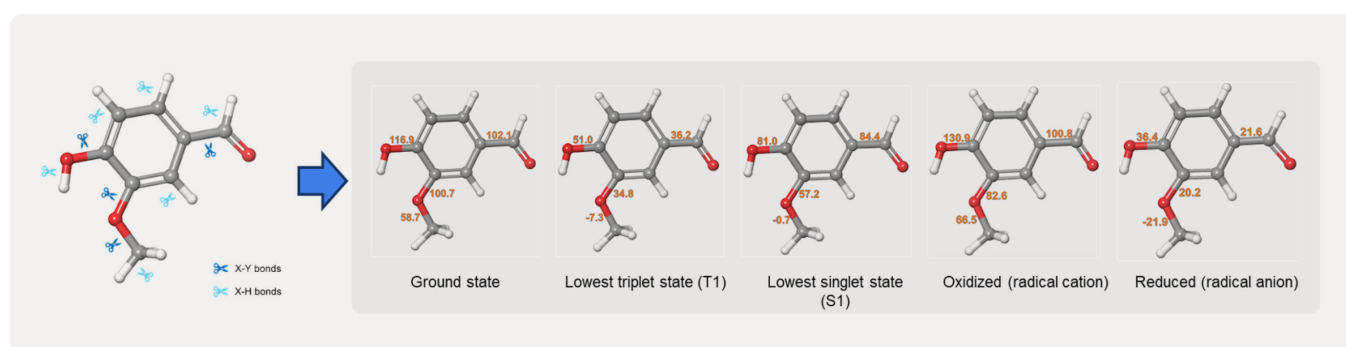


Figure 6: Bond dissociation energies (kcal mol<sup>-1</sup>) of vanillin under different conditions at the B3LYP/LACV3P\*\* level of theory.

## APPLICATION

# Catalytic and Non-Catalytic Reaction and Reactivity Optimization

Virtual high-throughput screening (vHTS) is a computational approach designed to rapidly evaluate a large number of molecular candidates to identify optimal ones for a given application. Schrödinger offers automated solutions for homogeneous catalyst design, non-catalytic reaction, and reactivity optimization through vHTS.

In homogeneous catalysis, vHTS aims to:

- **Identify efficient catalysts:** Screen catalyst candidates for high activity (rate constant, turnover frequency) and/or selectivity
- **Minimize unwanted reactions:** By maximizing the energy difference between TOF-determining transition states, one can design more selective catalysts
- **Reduce experimental costs:** Minimize the need for trial-and-error synthesis and testing

For non-catalytic reactions, vHTS is used to:

- **Screen reaction conditions:** Identify favorable solvents, reagents, or additives for desired transformations
- **Identify the most reactive substrates:** Screen molecular candidates for desired reactivity profiles

## APPLICATION

# Predicting Active Pharmaceutical Ingredient Solubility

Solubility of an active pharmaceutical ingredient (API) in both aqueous and non-aqueous solvents plays a critical role in selecting the final form and process for generating a drug product at scale. During early stages of development, especially when an API is available in only small quantities, ML paired with physics-based simulation provides guidance for an efficient experimental design. Schrödinger's FEP+ Solubility workflow has been shown to predict and differentiate aqueous solubility across a set of chemically diverse, drug-like compounds. To synthesize crystalline forms, selecting an appropriate solvent and a miscible anti-solvent enables control over the crystallization process. This ensures a manufacturing process that can be used to reliably produce a safe drug product with predictable bioavailability. FEP+ Solubility explicitly models the chemical environment experienced by an API, enabling the method to predict relative solubility of an API in cosolvents of arbitrary complexity, including mixtures and polymers.<sup>1</sup>

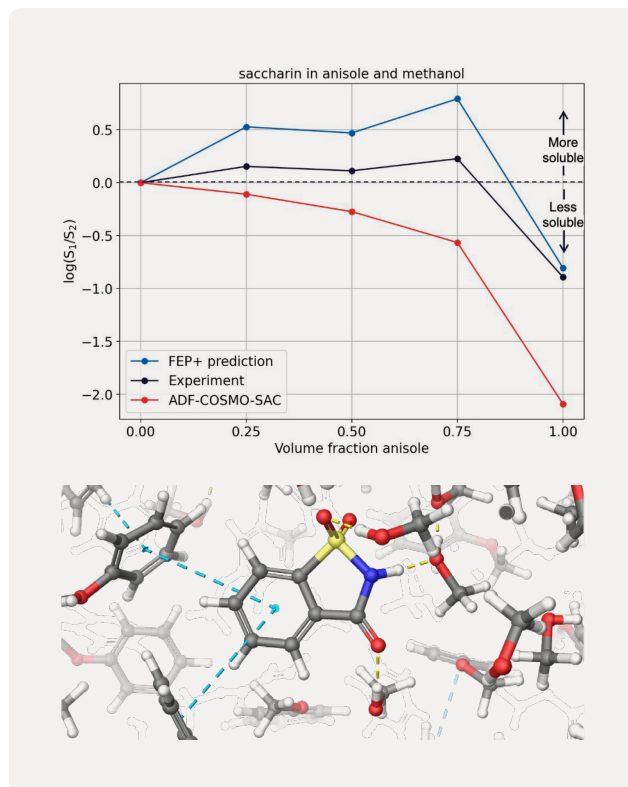


Figure 7: FEP+ Solubility identifies the ratio of anisole and methanol that maximizes saccharin solubility. Physics-based simulations capture the synergistic  $\pi$ - $\pi$  stacking and hydrogen bonding interactions which stabilize saccharin in this system.

1. Hong RS, et al. *J Med Chem*, 2023, 66, 15883-15893.

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