1 Supplementary Information

1.1 Schematic S1: Reaction template for the hydrolysis of a representative ester molecule

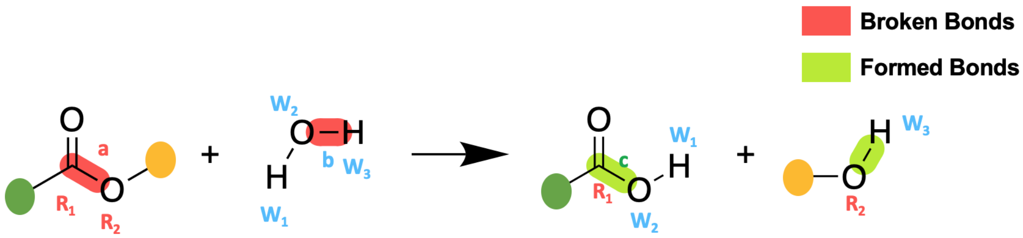


Figure S1: The set of bond cleavage and formations necessary to generate hydrolysis products for a representative ester molecule.

As a representative example, if an ester functional group was detected in a molecule, bond ‘a’ in the reactant and bond ‘b’ in the water molecule was deleted with the `RemoveBond` functionality available in `RDKit`. Then, `AddBond` was used to create bonds ‘c’ and ‘d’ between atoms R1-W2 and R2-W3 respectively, to yield a carboxylic acid and an alcohol as the respective products.

1.2 Schematic S2: Dataset Augmentation

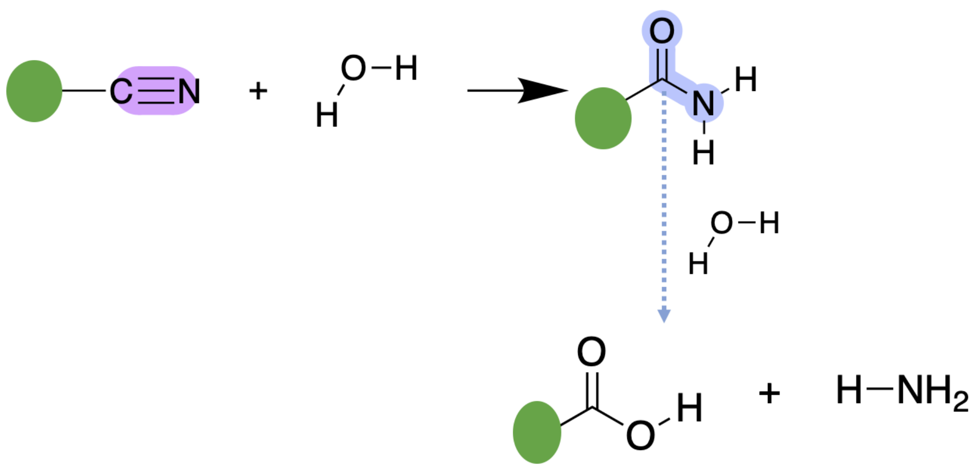


Figure S2: Amide reactions from the products of nitrile hydrolysis.

1.3 Schematic S3: Neutral pH vs. Acidic pH Hydrolysis

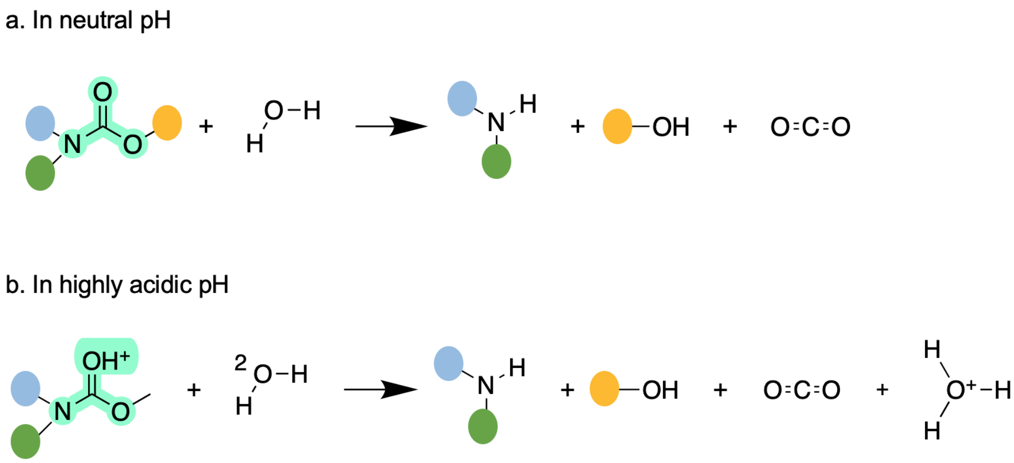


Figure S3: Hydrolysis reaction template for a representative carbamate molecule in (a.) Neutral pH and (b.) Highly acidic pH conditions.

1.4 Schematic S4: GNN Model Architecture

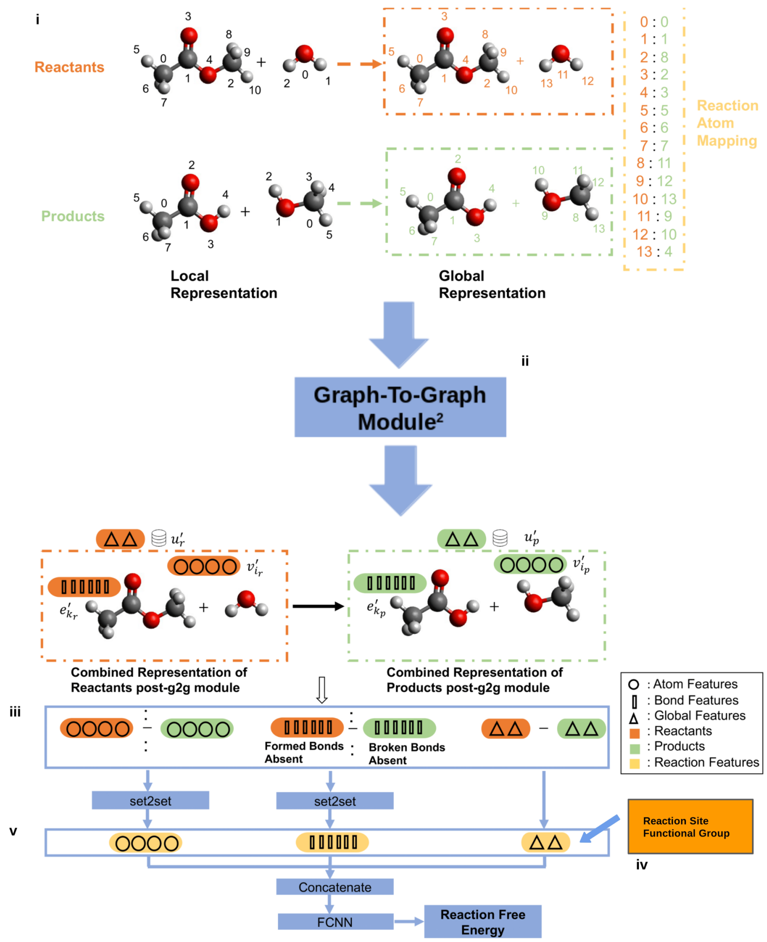


Figure S4: The user inputs atom-mapped sets of reactants and products (i) which undergo message-passing and update steps (ii). Using the user-specified mappings, these updated features are mapped to a global reaction graph (iii) where functional groups are the reaction site is added as a global feature (iv). Embeddings of bond and atom features plus global features directly serve as the fixed-size vector used in a conventional dense neural network for property prediction.

1.5 Section S5: Insights on the neutral hydrolysis database

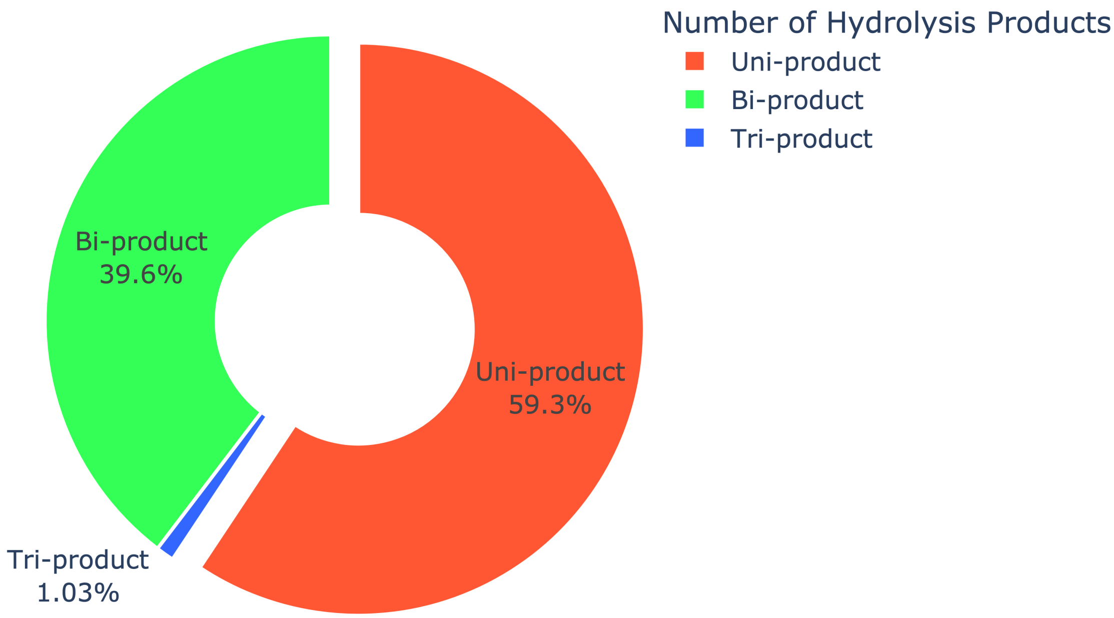


Figure S5(a): Distribution of hydrolysis reaction types based on the number of products generated.

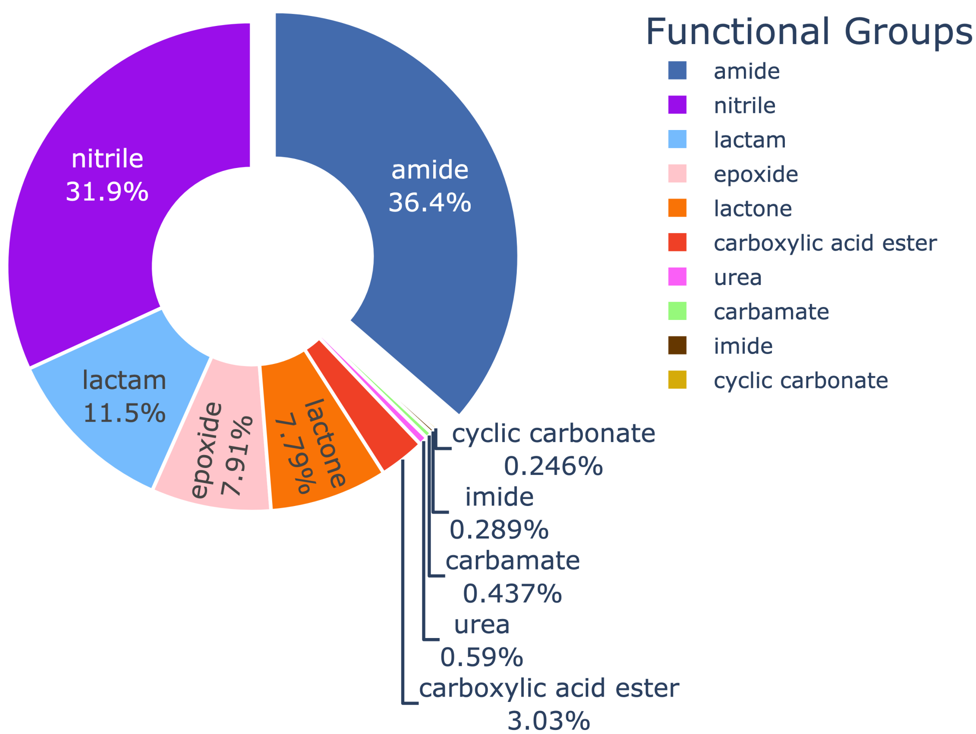


Figure S5(b): Distribution of hydrolysis reactions based on the hydrolyzing functional group.

1.6 Section S6: Effect of protonation on Hydrolysis ΔG_r

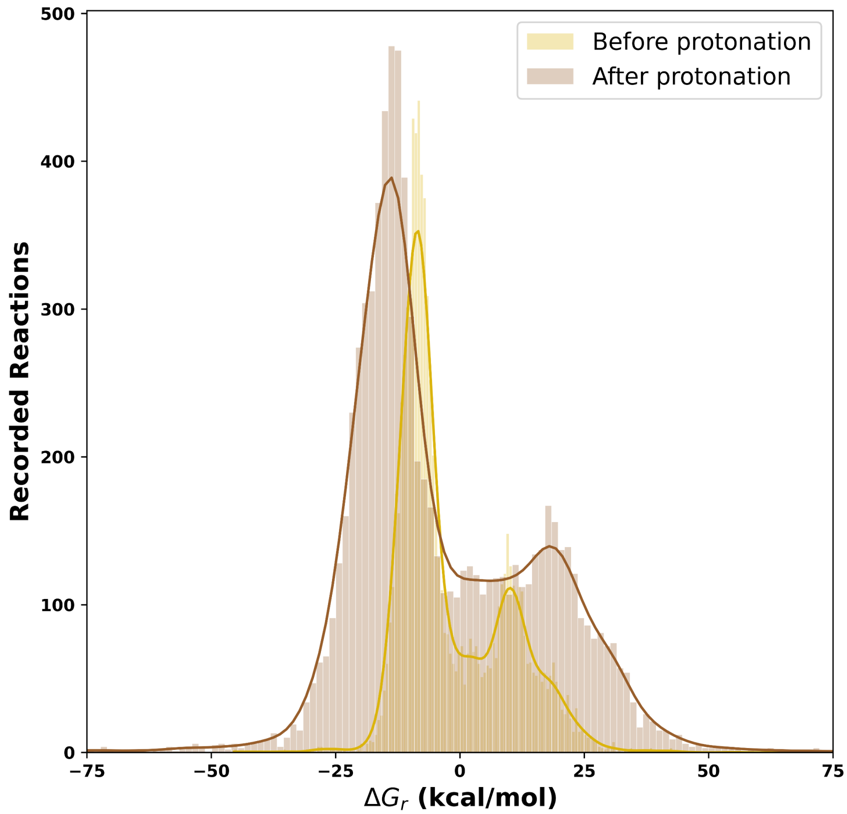
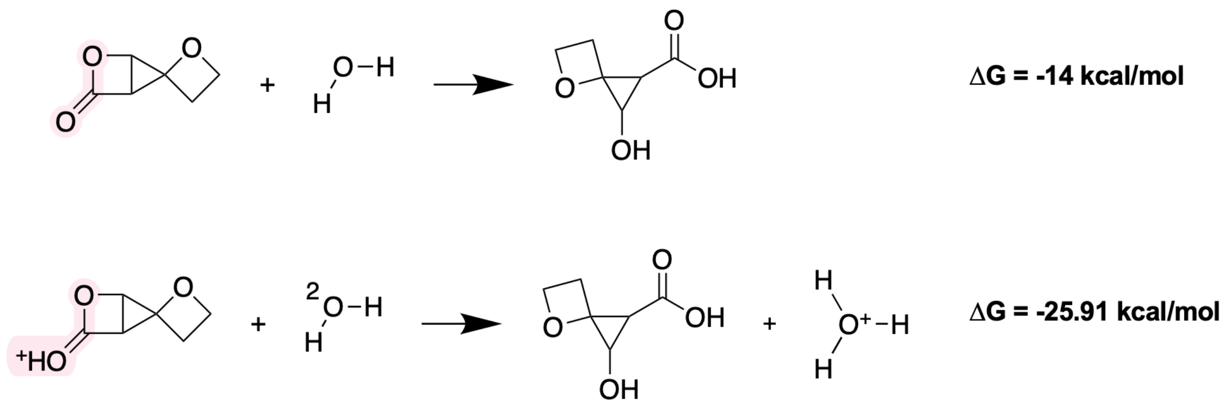
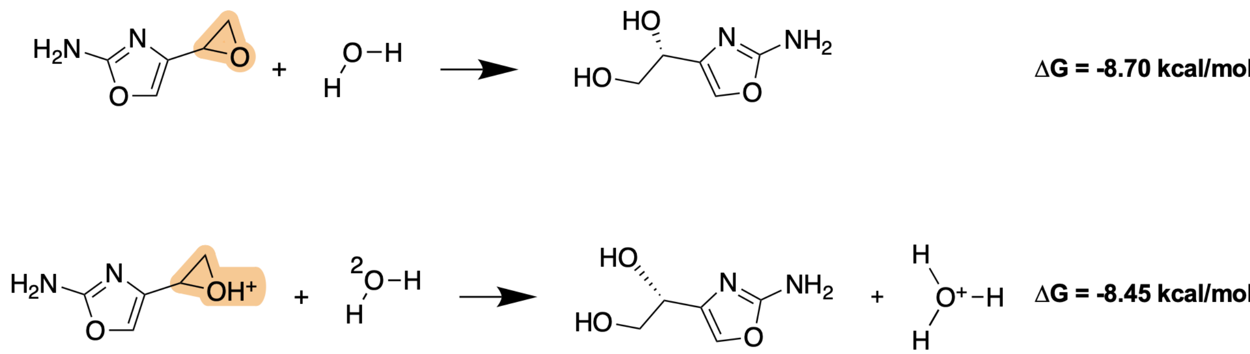


Figure S6: ΔG_r distribution before and after protonation.

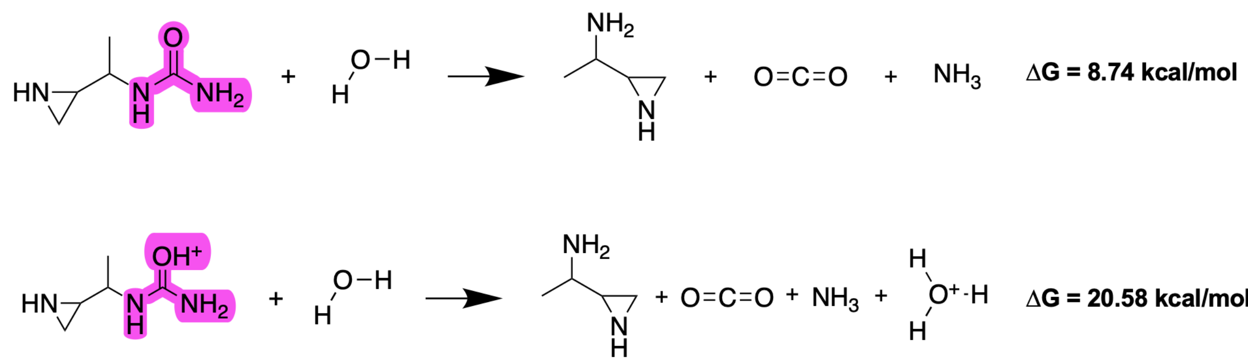
In the majority of these reactions (~64%), the introduction of acidic pH conditions shifts the ΔG_r values toward a more exergonic regime. The central peak shifts to more negative values and broadens as a greater number of hydrolysis reactions become thermodynamically favorable in the protonated state. Three representative examples from the protonated dataset are shown below which illustrates how protonation can impact the ΔG_r values.



Example reaction where protonation makes hydrolysis more exergonic



Example reaction where protonation has minimal effect on hydrolysis energy



Example reaction where protonation makes hydrolysis more exergonic

1.7 Section S7: Parity plots for benchmark models

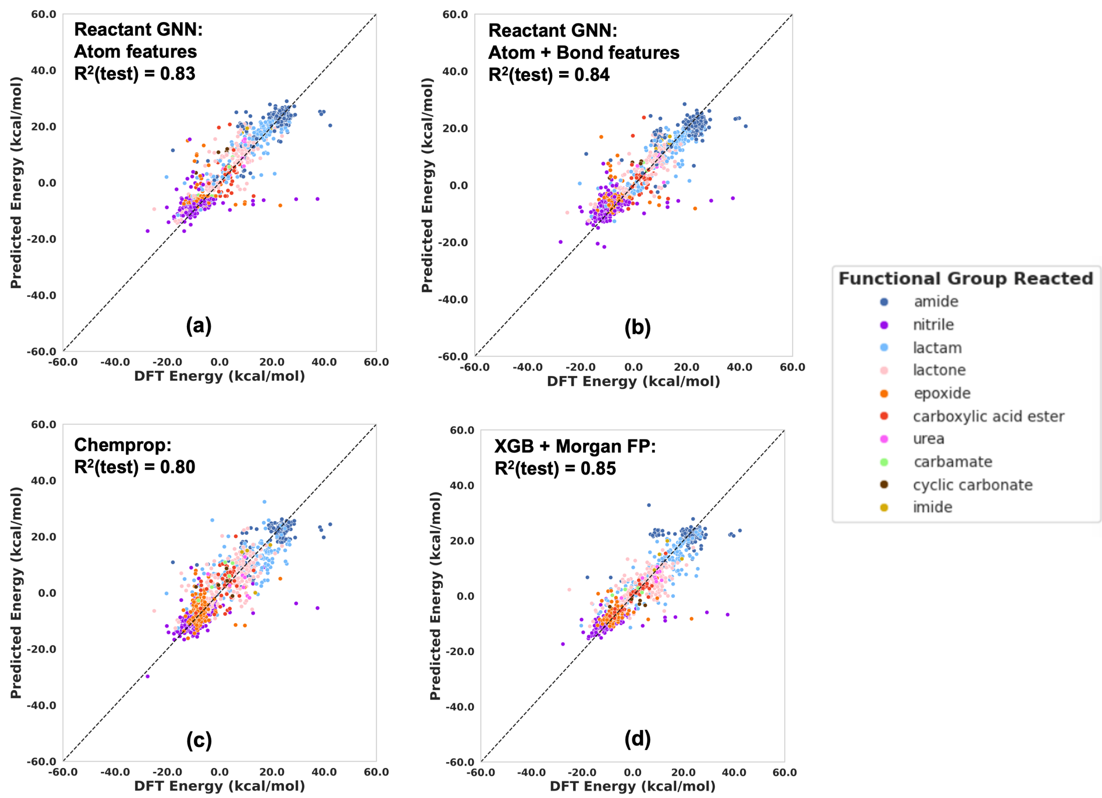


Figure S7: Parity plots for the different benchmark models. (a) Reactant GNN - atom features, (b) Reactant GNN - atom + bond features, (c) Chemprop, (d) XGBoost + Morgan Fingerprint

1.8 Section S8: UMAP embeddings for lactams and lactones

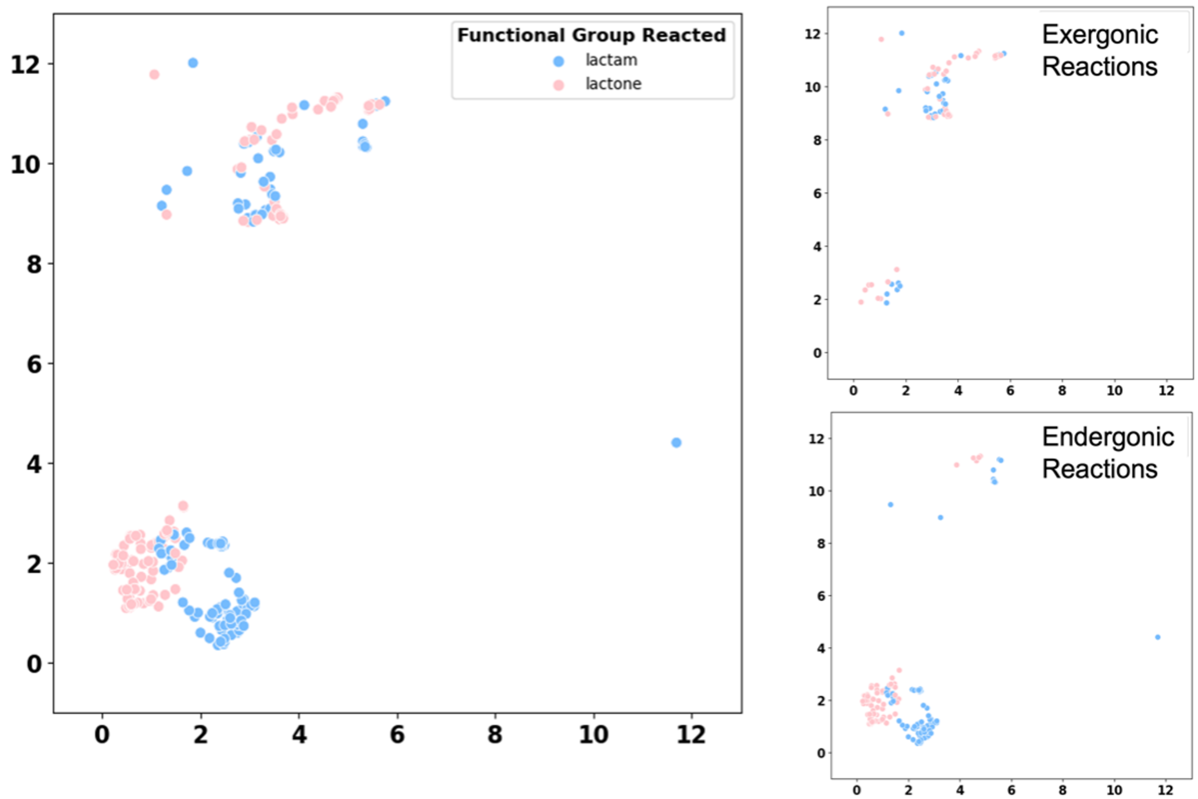


Figure S8: 2D reaction embedding for the lactone and lactam hydrolysis reactions and the separation of the exergonic and endergonic reaction space.