Lipophilicity and Hydrolysis Rate of Fluorinated Aspirin

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Introduction

- First implemented into drug design in the 1950's, the small and extremely electronegative fluorine is often referred to as the "magic element" in drug development.
- In fact, in 2006 the two best selling drugs on the market were Lipitor and Advair. These two drugs had fluorine instead of hydrogen on the C-H and C-O bonds.
- Fluorine has quickly become the "second-favorite heteroatom" in drug design after nitrogen.

Rationale for a Fluorinated Derivative of Aspirin

- Fluorine is the most electronegative element meaning that it strongly pulls electron density within bonds towards itself.
- This results in highly polarized bonds with uneven sharing of electron density between the fluorine and the other atom of a bond.
- Fluorine has a small atomic radius size of 1.4 Å comparable to hydrogen at 1.20Å.
- Therefore, replacing hydrogen atoms of drugs with fluorine molecules does not change the size and shape of the molecules, but it does change the distribution of electron density.
- One of the most important benefits is the increased lipophilicity and membrane permeability.
- Fluorine can increase drug selectivity resulting in improved binding to target molecules.

Molecular Structure of Aspirin

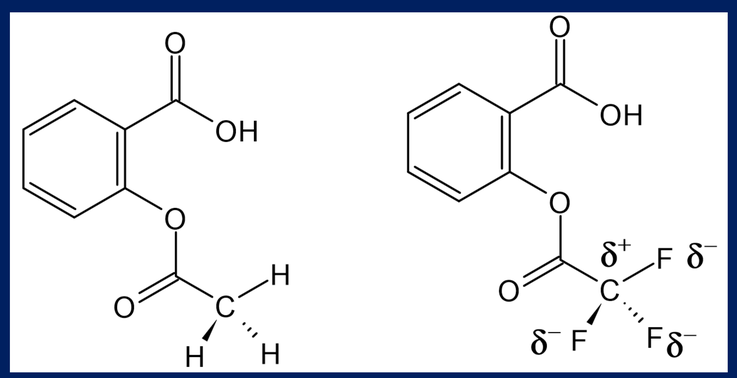
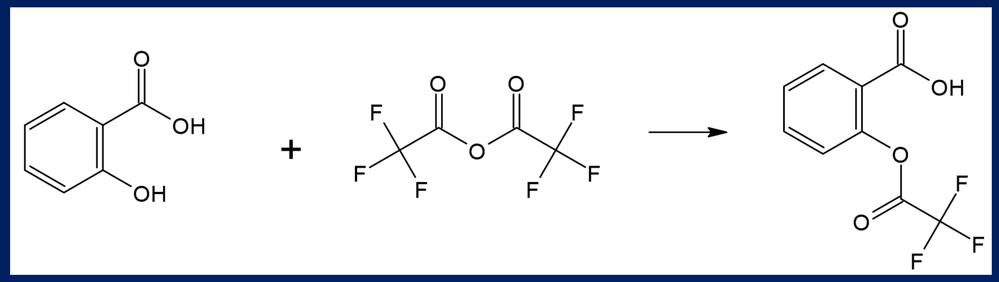


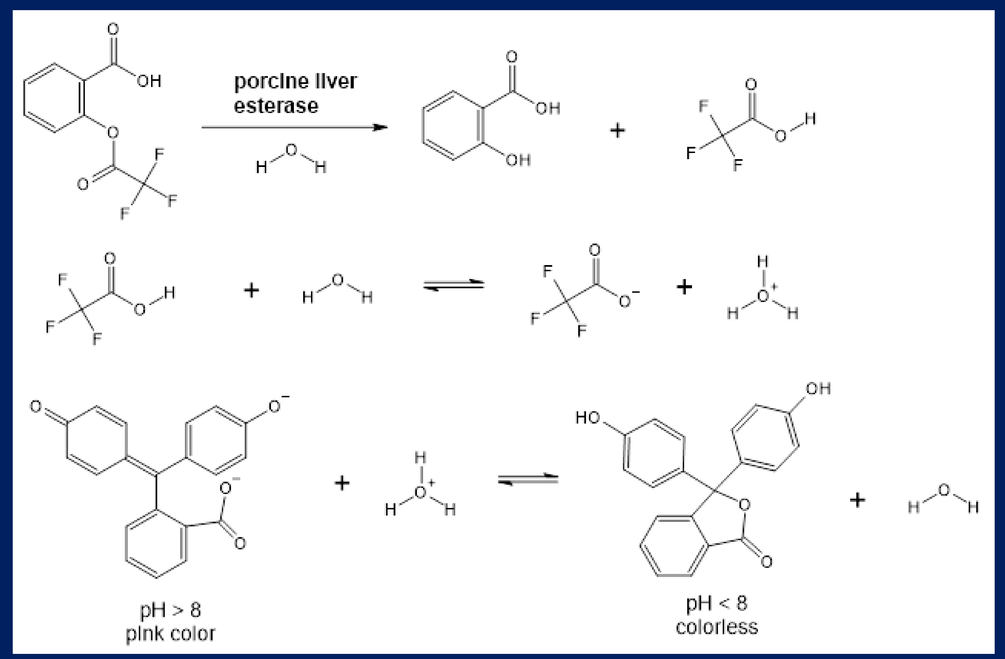
Figure 1. Structure of aspirin and the fluorinated derivative of aspirin.

Synthesis of Fluorinated Aspirin Derivative



Scheme 1. Synthesis of fluorinated aspirin from salicylic acid and trifluoroacetic anhydride.

Enzymatic Hydrolysis Rate



Scheme 2. Porcine liver esterase assay for the determining the enzymatic hydrolysis rate of aspirin and fluorinated aspirin derivative.

- Most of the biological effects of aspirin are due to the metabolite salicylic acid that results from the hydrolysis of the ester of aspirin by ubiquitous esterases.
- Therefore, it would be of interest if the replacing the hydrogen atoms of the methyl ester with fluorine atoms changed the rate of enzymatic hydrolysis.
- Porcine liver esterase is the enzyme that will be used for comparing the rate of enzymatic hydrolysis of aspirin with the fluorinated aspirin derivative.
- The rate of hydrolysis will be determined by observing the amount of time required to generate enough acid to lower the pH of the solution to below 8 converting phenolphthalein from its colored formed to its colorless form.

Determining Lipophilicity

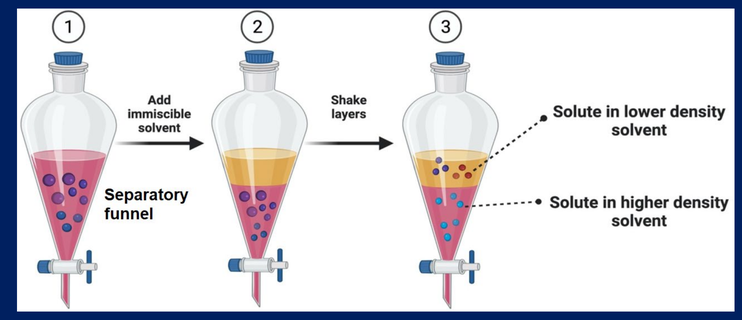


Figure 2. Comparison of lipophilicity by determining octanol/water partition coefficient.

- To evaluate lipophilicity of the fluorinated aspirin an octanol/water partition coefficient will be determined.
- Octanol/water partition is a simple model for the phospholipid bilayer of cells.
- Octanol has a polar hydroxyl group with a long nonpolar hydrocarbon (8 carbons), which is similar to the polar head groups and long hydrocarbon tails of phospholipids of cellular membranes.
- Molecules will be added to the octanol/water bilayer and will be allowed to partition between the two immiscible solvents.
- The concentration of the molecule in the octanol layer relative to the concentration of the molecule in the water layer will be determined.
- This partition coefficient experiment will be performed with both the synthesized fluorinated aspirin and a commercial aspirin sample to compare the lipophilicity of the two molecules.

Potential Impact

- The proposed research has the potential to develop an aspirin derivative with improved physicochemical properties.

Acknowledgments

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