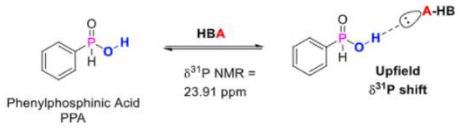
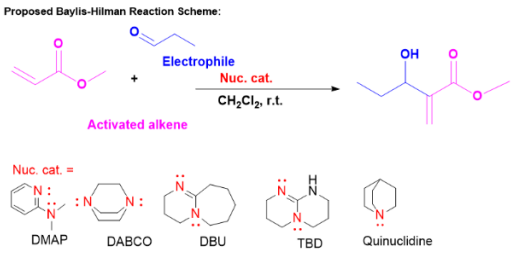
1. NMR Spectroscopy as a Tool to Quantify Hydrogen-Bond Accepting Ability

Hydrogen-bonding is a critical parameter in the preliminary stages of drug design. Finely-tuned hydrogen-bonding interactions between a drug molecule and receptor protein enhance and regulate the uptake and potency of the pharmaceutical agent.[1] In addition, hydrogen-bonding is an important mode of activation that can be used utilized to catalyze a variety of reactions for organic synthesis. Current methods to quantify hydrogen-bonding include estimates based on p*K*a/p*K*b scales, UV/vis spectroscopy, and computational studies; however, methods to quantify the hydrogen bond *donating* and *accepting* abilities of organic molecules are far from efficient. Reliable p*k*a/p*k*b scales are often difficult to obtain, whereas computational studies are highly complex, time-consuming, and often only possible with costly, specialized software not accessible to all researchers.

The Franz group has recently elucidated the power of triethylphosphine oxide (TEPO) as a probe using ^{31}P Nuclear Magnetic Resonance (NMR) to rapidly quantify hydrogen bond donating ability of a variety of organocatalysts, using a modified Guttmann-Becket method.[2,3] In literature, there have been efforts to quantify hydrogen-bond *accepting* abilities of organic molecules with ^{19}F NMR[4;] yet these methods were imprecise, and replicated results were highly inconsistent with original results. The goal of my research is to develop an accurate, simple, and accessible method to quantify HBA ability with ^{19}F and ^{31}P NMR spectroscopy.



In my proposed method (see left for ^{31}P NMR probe), I will be quantifying HBA ability by measuring the electron-donating effect exerted by an HBA compound in binding to a hydrogen-bond donating, fluorine or phosphorus containing "probe" compound, in solution with ^{19}F and ^{31}P NMR spectroscopy. The electron-donating effect is recorded as an NMR spectrum, which I will compare against the NMR spectrum of an external standard of the unbound hydrogen bond donor probe. The numerical differences, or Δδ values, between the highest peaks in each spectrum represent the extent HBA ability of the compound, where the greater the Δδ value, the stronger the HBA ability. To validate these results, NMR shift values will be plotted against established Hammett σ constants, and if strong correlations ($R^2 \geq 0.7$) are present, this would indicate that my method is truly an accurate measurement of HBA ability.[5] I additionally propose to perform kinetic studies to investigate the potential correlation between hydrogen-bond accepting ability and catalytic activity for Baylis-Hillman coupling reactions of methyl acrylate and propionaldehyde, catalyzed by a variety of commonly utilized HBA nucleophilic organocatalysts such as DABCO, DMAP, DBU, and TBD[6] (see right). Catalytic activity will be assessed by relative rate analysis with isolation and analysis of product yields; if not feasible, catalytic activity will instead be measured through direct reaction rate analysis using ^{19}F NMR.



The anticipated timeline of this project (see below) spans nine months, and I initiated the project in February 2019.

Task	Month(s)
Identify and investigate potential probe compounds, perform titration studies, select optimal probe(s) to use for study.	February-April
Perform binding studies with selected HBA functional groups/classes.	April—June
Perform kinetic studies.	July-August
Write manuscript, submit for review and publication.	August-November

Through this method, my goal is to create and publish a database of NMR shift values to elucidate how structure and secondary effects of medicinally relevant HBA compound classes, including sterically and electronically modified anilines, imidazoles, and coumarins, determine hydrogen-bond accepting ability, in addition to whether HBA ability may correlate to catalytic activity. This project will contribute to the understanding of hydrogen-bonding in the design of novel bioisosteres and organocatalysts for drug discovery and catalysis.

References:

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5. Hansch, C.; Leo, A.; Taft, R. W. A Survey of Hammett Substituent Constants and Resonance and Field Parameters. *Chem. Reviews* **1991**, 91 (2), 165–195.
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Future Educational Goals

As an aspiring synthetic organic chemist, I believe the most crucial aspect of any research endeavor is its applicability, or greater impact. My intention is to create a rapid quantitative method that can be employed by a diverse population of researchers, not only for the early stages of drug design, but for the development of synthetic polymers and greener catalysts. This project offers me the remarkable opportunity to independently draw from literature precedents to develop my own novel method, that pushes me to think critically in selecting compounds to test, in preparing samples, operating the NMR spectrophotometer, and interpreting and analyzing data. Upon the completion of this project, I plan to submit a manuscript to a peer-reviewed journal, which in addition to helping me gain indispensable manuscript preparation experience, will facilitate graduate school admission. I eventually hope to pursue a PhD in organic chemistry, with an emphasis in asymmetric catalysis.

1. Budget Outline and Justification

	Quantity	Supplier	Total Cost	Justification
Lewis Base/HBA Compound Classes*				
Imidazoles (3)				Imidazole rings are present in pilocarpine alkaloids (natural products found in medications that treat pressure in eyes due to glaucoma, as well as dry mouth), in addition to showing promise as potential therapeutic agents for thrombosis, cancer, and inflammatory diseases.
2-Methylimidazole	1	Sigma Aldrich	$21.70 (100 g)	
2-Bromo-1*H*-imidazole	1	TCI Chemical	$13.00 (1 g)	
2-Mercaptoimidazole	1	Sigma Aldrich	$39.80 (1 g)	
Coumarins (4)				Coumarin and its derivatives, such as coumarin glycosides, possess potent biological activities, and are present in many antibiotic, antimitotic, antiviral, anticancer, anti-inflammatory, anticoagulant, antifungal, antioxidant, and cytotoxic agents.
3-Cyanocoumarin	1	Alfa-Aesar	$21.60 (1 g)	
3-Aminocoumarin	1	Alfa-Aesar	$24.30 (100 mg)	
3-Hydroxycoumarin	1	Chem-Impex Interntional	$20.70 (1 g)	
Coumarin-3-carboxylic acid	1	SynQuest Laboratories	$26.00 (5 g)	
Thiophenes (5)				Thiophene scaffolds are widely used as building blocks in the development of novel drugs and agrochemicals.
3-Bromothiophene	1	Sigma Aldrich	$24.00 (5 g)	
3-Thiophenecarbonitrile	1	Oakwood Chemical	$10.40 (1 g)	
Thiophene	1	Sigma Aldrich	$23.10 (5 g)	
3-Thiophenecarboxylic acid	1	Oakwood Chemical	$9.00 (1 g)	
3-Methylthiophene	1	Oakwood Chemical	$9.00 (1 g)	
NMR Usage Fee			$150	The usage time fee for the 400 mHz NMR spectrometer is $15/hour. I anticipate making ~10 samples/hour. overall, I estimate I will run ~100 samples total, so 100 samples total/10 samples/hour is ~10 hours of NMR time. NMR rates are $15/hour x 10 hours of NMR usage = $150.
Catalysts (1)				
Quinuclidine	1	TCI Chemicals	$34.00 (200 mg)	Quinuclidine has been reported to be a highly efficient Lewis-base catalyst for Baylis-Hillman reactions, and I would like to compare its HBA ability to its catalytic activity.
Compounds for Organocatalyst-				

catalyzed Baylis-Hillman Kinetic Studies (2)				
Methyl Acrylate	1	Acros Organics	$26.00 (500 mL)	Baylis-Hillman Reactions require an activated alkene, and I propose to use methyl acrylate (a commonly used activated alkene.).
Propionaldehyde	1	Acros Organics	$38.90 (100 mL)	In addition to activated alkenes, Baylis-Hillman reactions require carbon electrophiles (I will be using propionaldehyde).
NMR Supplies (2)				
NMR Tubes	2 packs	Fisher Scientific	2 x $52.50 (10 tubes total)	For running NMR samples.
d2-Dichloromethane (d2-DCM)	1	Acros Organics	$150 (10 x 0.75 mL ampoules, 7.5 mL total)	In order for the NMR instrument to "lock" on to compounds in a sample and produce spectra, costly, hygroscopic deuterated solvents ("deuterated" refers to the replacement of a hydrogen atom with a deuterium atom) are required. However, only 0.15 mL is needed per sample.
Additional Baylis-Hilman Reaction Supplies (1)				
TLC Plates	1 pack	Fisher Scientific	$99.00 (pack of 25)	TLC (thin-layer chromatography) is a laboratory technique for separating mixtures in chemical reactions, and for characterizing the compounds present in the mixture (TLC can show if one has their desired product present in the mixture or not).
Total: $845.00				

*All the compounds/supplies I have listed above are those <u>not</u> already in my laboratory's inventory. For specific classes (ie imidazoles), however, we may already some of the substituted versions in our inventory (ie we may already have *2-chloro*imidazole but not *2-mercapto*imidazole); these are not listed.