Investigation of the Effect of the Acid-Base and Redox Properties on the CPET Reactivity of Base-Appended Phenols

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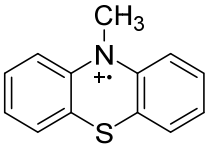
Introduction and Previous Work

Protons and electrons are involved in a wide variety of chemical contexts. They are important in photosynthesis, enzyme activity, antioxidant chemistry, and certain industrial reactions. Many reactions involve the transfer of both protons and electrons, and understanding how these reactions work is fundamentally important and aids in the development of new reactions. The transfer of protons and electrons may occur either separately or simultaneously. As an example, acid-base reactions are proton transfers while oxidation-reduction reactions are electron transfers. Protons and electrons may also be transferred simultaneously in a concerted reaction called a hydrogen atom transfer. Separate and simultaneous transfers are related; however, organic compounds undergo whichever process has the lowest energy barrier. This means that the type of transfer performed is based on the particular reagents and the reaction conditions.[1]

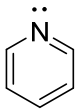
There are different types of hydrogen atom transfers which are based on the orbital systems involved in the transfer of the particles. Specifically, hydrogen atom transfer is the transfer of a proton and electron from a particular orbital system to that same orbital system. On the other hand, concerted proton-electron transfer (CPET) occurs when a proton and electron are transferred between different orbital systems in a single step. The process explored in this project is CPET.[1]

In previous work on the project, the organic oxidant 10-methylphenothiazinium was combined with the base pyridine resulting in a molecule called 10-(pyridin-2-yl)-10*H*-phenothiazinium (**py-PT**). Once **py-PT** was transformed into the radical cation **py-PT**$^{\bullet+}$, it was determined that the molecule was able to undergo CPET reactions.[2] The focus of the research for

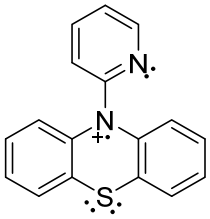
this thesis is to explore the effects of structurally modifying the acid-base and redox properties of **py-PT**$^{\bullet+}$on the CPET reactivity of the molecule.



10-methylphenothiazinium, 10-MePT$^{\bullet+}$



pyridine



py-PT$^{\bullet+}$

The method of structurally modifying the acid-base and redox properties of **py-PT**$^{\bullet+}$ is based on the idea of tuning bond strengths. The bond strength of the molecule is measured as the N–H bond dissociation free energy (BDFE) of the protonated compound, $^{+}$**Hpy-PT**. The BDFE of the compound can be measured by a thermochemical cycle as shown in **Figure 1** on the following page. The BDFE includes the pK_a of $^{+}$**Hpy-PT** and the reduction potential (E) for **py-PT**$^{\bullet+}$.

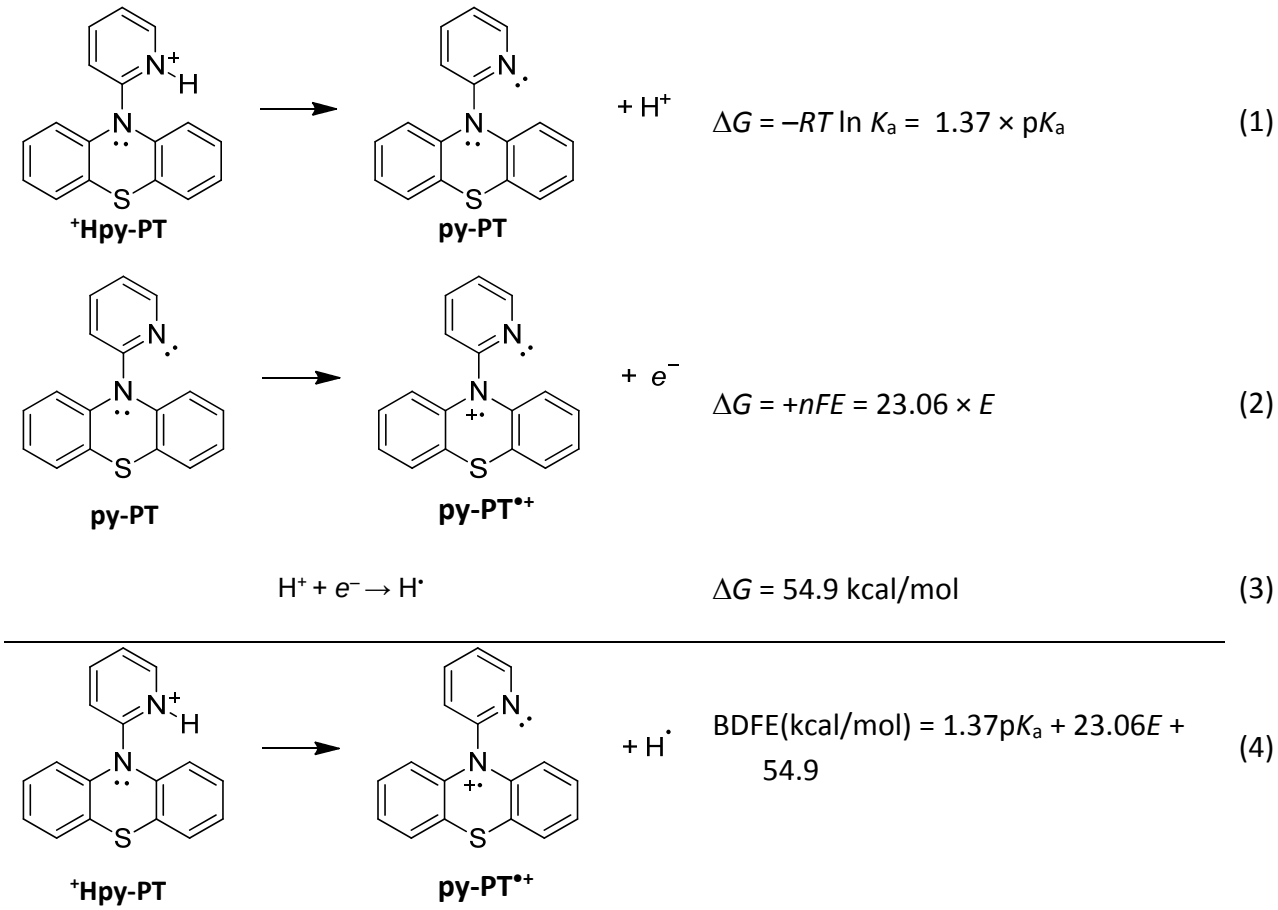


Figure 1. Thermodynamic cycle to determine the BDFE of **$^{+}$Hpy-PT.**

By changing the substituents on the generic **py-PT$^{\bullet+}$** it is possible to create a more strongly oxidizing radical cation and a more basic pyridine. These changes will favor a stronger N-H bond and as a result net hydrogen atom abstraction reactions that are energetically further downhill (Figure 2). According to Nocera,[3] "Model systems [for CPET] need to be developed that allow the proton and electron to be orthogonalized so that the proton and electron transfer distances and driving forces may be independently controlled." The substitution of different substituents explores the ability of independently controlling the proton and electron transfer.

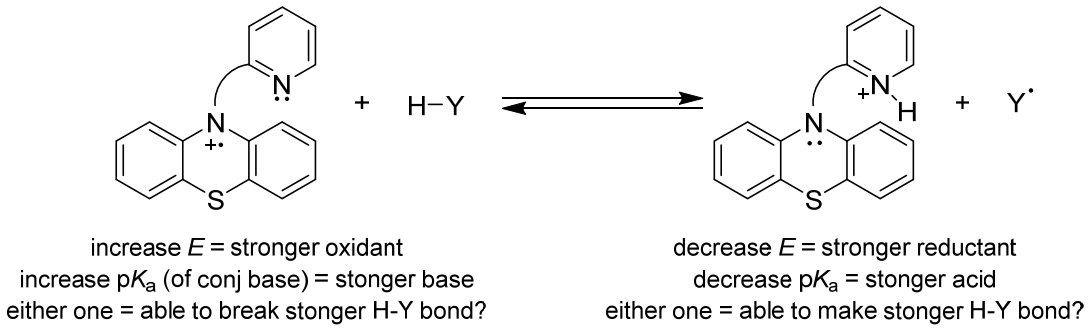


Figure 2. Hypothesized effects of reduction potential and pK_a values on substituted compounds

Project Overview

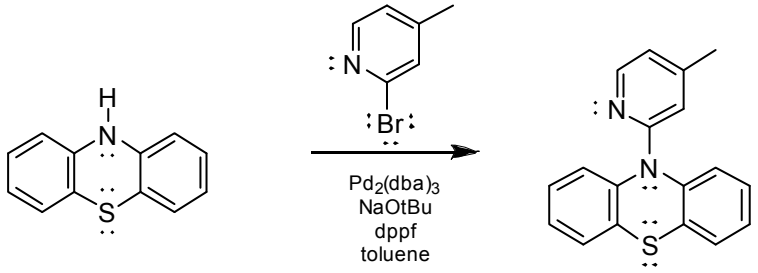
Two base-appended radical cations were synthesized to study the effects of modifying the substituents of the original compound **py-PT$^{\bullet+}$**. To generate a more basic compound, the pyridine ring was substituted with a methyl group opposite the nitrogen. The substituted compound is a structural isomer of that of a previous student, Evan Welker. Welker's compound placed the methyl group ortho to the nitrogen where in this study the methyl group is para to the nitrogen. In a previous study, in order to generate a more oxidizing compound, the phenothiazine ring was substituted with a trifluoromethyl group. In this study, the effects of combining the trifluoromethyl-substituted phenothiazine ring with the *para*-methylpyridine ring were studied.

More basic or oxidizing compounds will have higher driving forces for abstraction of a hydrogen atom, and overall more favorable reactions. The substituents are likely to affect the basicity and the oxidizing ability; however, the effects are competing: an electron withdrawing group makes a compound more oxidizing, and an electron donating group makes the compound more basic. Despite this, the rotation of the pyridine ring relative to the phenothiazine ring may reduce the interaction of these effects due to the inability of the π systems to overlap effectively.

In this case, it may be possible to combine the effects of both an electron withdrawing group and an electron donating group to increase the ability of a molecule to undergo CPET reactions.

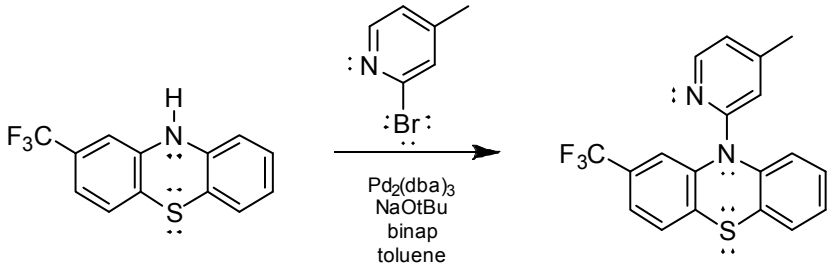
Experimental

Synthesis of 10-(5-methylpyrid-2-yl)-10H-phenothiazine (**Mepy-PT**).[4-7]



To 25 mL of dry toluene, phenothiazine (1.7947 g, 9.01 mmol); sodium *tert*-butoxide (1.3925 g), DPPF (1,1'-bis(diphenylphosphino)ferrocene, 33.0 mg), 2-bromo-4-methylpyridine (1.20 mL) and $Pd_2(dba)_3$ (40.3 mg; dba = dibenzylideneacetone) were added in that order. The reaction was refluxed overnight and extra $Pd_2(dba)_3$ (38 mg) and DPPF (32 mg) were added after 24 h; the mixture was refluxed overnight. The reaction was then filtered through Celite, which was washed with ethyl acetate, and the solvent was removed under reduced pressure. A crude compound was subjected to column chromatography (16/9/1 v/v/v hexanes/toluene/ethyl acetate) to produce an impure sticky yellow solid. The product was recrystallized once to form a colorless solid (0.514 g, m.p. 83-86.9°C) from hexanes before being used in cyclic voltammetry and equilibration studies.

Synthesis of 2-trifluoromethyl-10-(5-methylpyrid-2-yl)-phenothiazine (**Mepy-PTCF$_3$**).[4-7]



To 25 mL of dry toluene, 2-(trifluoromethyl)phenothiazine (2.400g, 8.99 mmol); sodium *tert*-butoxide (1.395 g), BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, 32.4mg), 2-bromo-4-methylpyridine (1.0 mL) and $Pd_2(dba)_3$ (40.5 mg; dba = dibenzylideneacetone) were added in that order. The reaction was refluxed overnight and extra $Pd_2(dba)_3$ (38.1 mg) and BINAP (30.2 mg) were added after 24 h; the mixture was refluxed overnight. The reaction was then filtered through Celite, which was washed with ethyl acetate, and the solvent was removed under reduced pressure. A crude compound was subjected to column chromatography (16/5/1 v/v/v hexanes/toluene/ethyl acetate) to produce an impure yellow/orange solid (0.197 g, m.p. 110-114 °C). Due to low yield, the impure product was used for preliminary cyclic voltammetry and equilibration studies rather than recrystallization.

***In Situ* Generation of Radical Cations.** The radical cation of **Mepy-PT** was synthesized by combining a solution of tris(*p*-bromophenyl)aminium hexafluorophosphate and a solution of excess radical cation precursor in acetonitrile.

Cyclic Voltammetry. Cyclic voltammetry was performed in 0.1 M Bu_4NPF_6 in acetonitrile with a glassy carbon working electrode, $Ag/AgNO_3$ (0.01 M) reference electrode and a platinum wire auxiliary electrode. Ferrocene was added as an internal standard.

Acid-Base Equilibrium for pK_a determination. The equilibrium constant for the radical cation precursors and thymol blue were determined by adding 50 μL aliquots of a 12.1 mM solution of the radical cation precursors to 3.0 mL of a 0.89 mM solution of thymol blue solution. The absorbance at 395 nm ($\varepsilon = 1.65 \times 10^4\ M^{-1}\ cm^{-1}$) corresponding to an absorption of the deprotonated thymol blue (TH^-)[8] was used to determine [TH^-] after correcting for volume. Equations 6, 7, and 8 were used to account for mass balance.

$$TH_2 + \text{Mepy-PT} \rightleftharpoons TH^- + \text{Mepy-PTH}^+$$

$$K_{eq} = \frac{[TH^-][\text{MePPTH}^+]}{[TH_2][\text{MePPT}]} \quad (5)$$

$$[TH_2] = [TH_2]_{initial} - [TH^-] \quad (6)$$

$$[\text{Mepy-PTH}^+] = [TH^-] \quad (7)$$

$$[\text{Mepy-PT}] = [\text{Mepy-PT}]_{initial} - [TH^-] \quad (8)$$

The slope of a plot of $[\text{Mepy-PTH}^+][TH^-]/[TH_2]$ vs. [Mepy-PT] provided the equilibrium constant. The procedure for the other compound was similar.

Results and Discussion

Synthesis of Radical Cation Precursors

10-(5-Methylpyrid-2-yl)-10*H*-phenothiazine (**Mepy-PT**) was the first precursor molecule of interest to be successfully synthesized. It was synthesized using a Buchwald-Hartwig amination reaction as described in the experimental section. **Mepy-PT** was characterized by ^{1}H NMR (Figure 4).

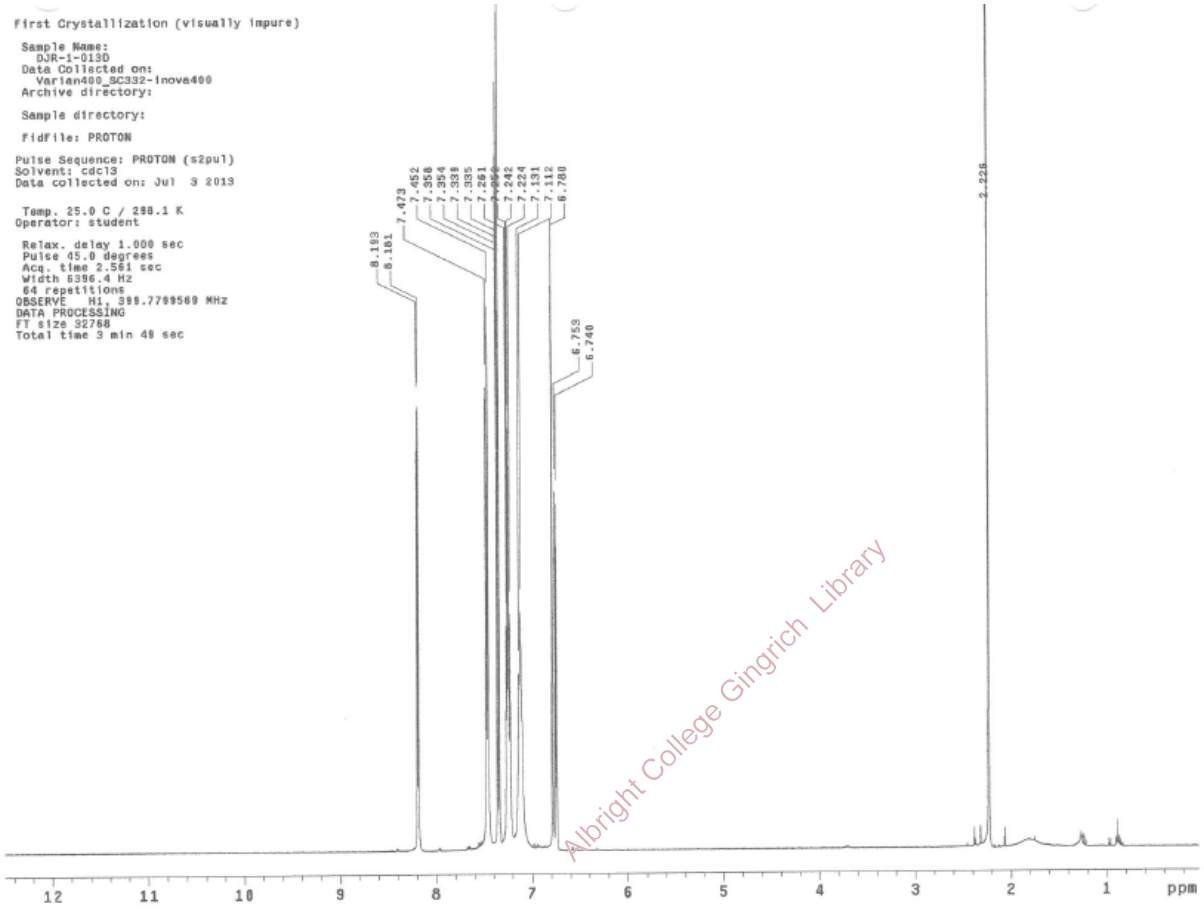


Figure 4. ^{1}H NMR of **Mepy-PT**.

The peak at ~8.2 ppm corresponds to the singular proton ortho to the pyridyl nitrogen. The series of peaks at approximately 7.46, 7.35, 7.25, and 7.12 ppm correspond to phenothiazine. The peak at 2.25 ppm corresponds to the methyl group on the pyridine ring. The combination of this information indicates that the desired product was isolated.

2-Trifluoromethyl-10-(5-methylpyrid-2-yl)-10*H*-phenothiazine (**Mepy-PTCF$_3$)** was also synthesized using the Buchwald-Hartwig amination; however, BINAP was used as the ligand rather than DPPF in hopes of reducing the amount of side products. The yield for this synthesis was very low, and it was decided to use the impure product for cyclic voltammetry and pK_a determination rather than risk losing more product during recrystallization. **Mepy-PTCF$_3$** was initially characterized by ^{1}H NMR (**Figure 5**).

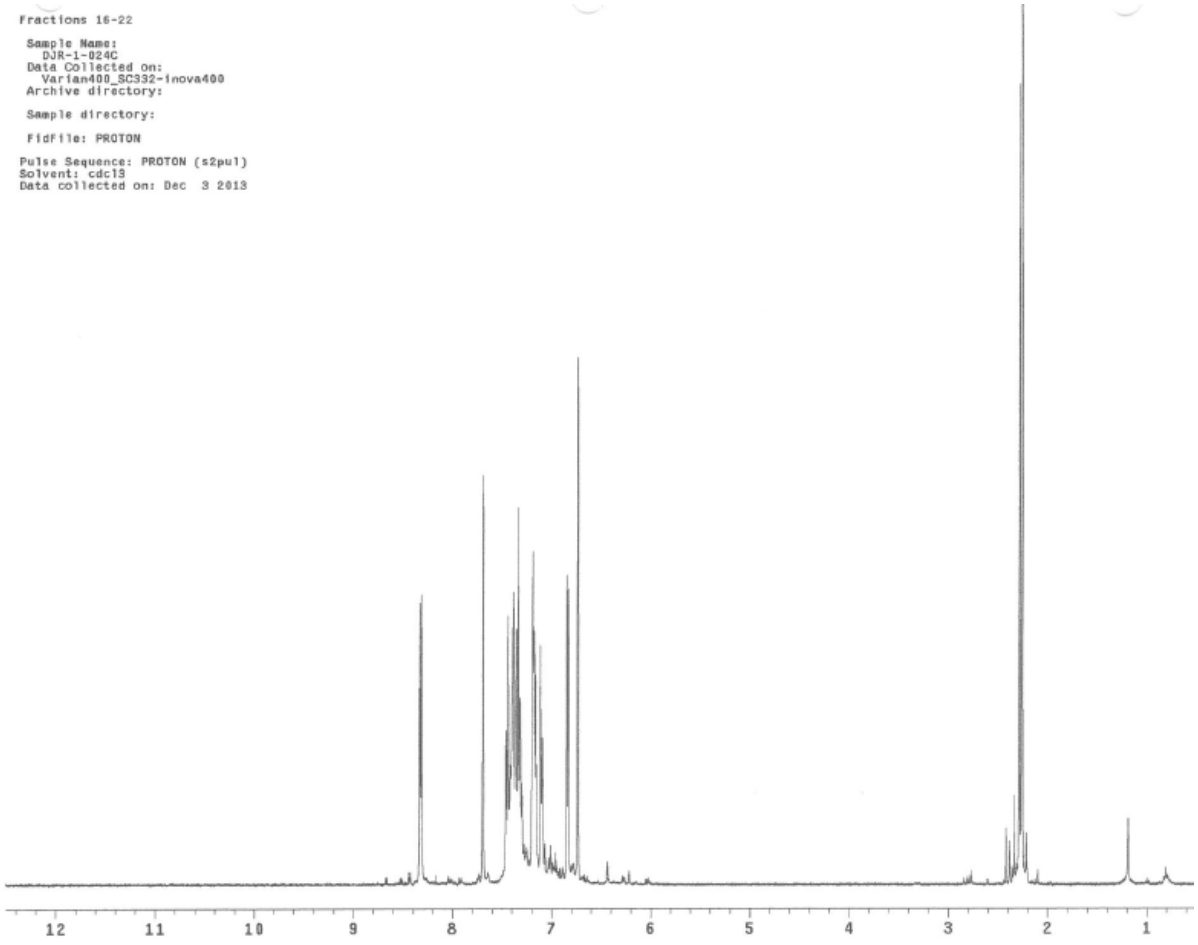


Figure 5. ^{1}H NMR of 2-trifluoromethyl-10-(5-methylpyrid-2-yl)-phenothiazine (**Mepy-PTCF$_3$)**.

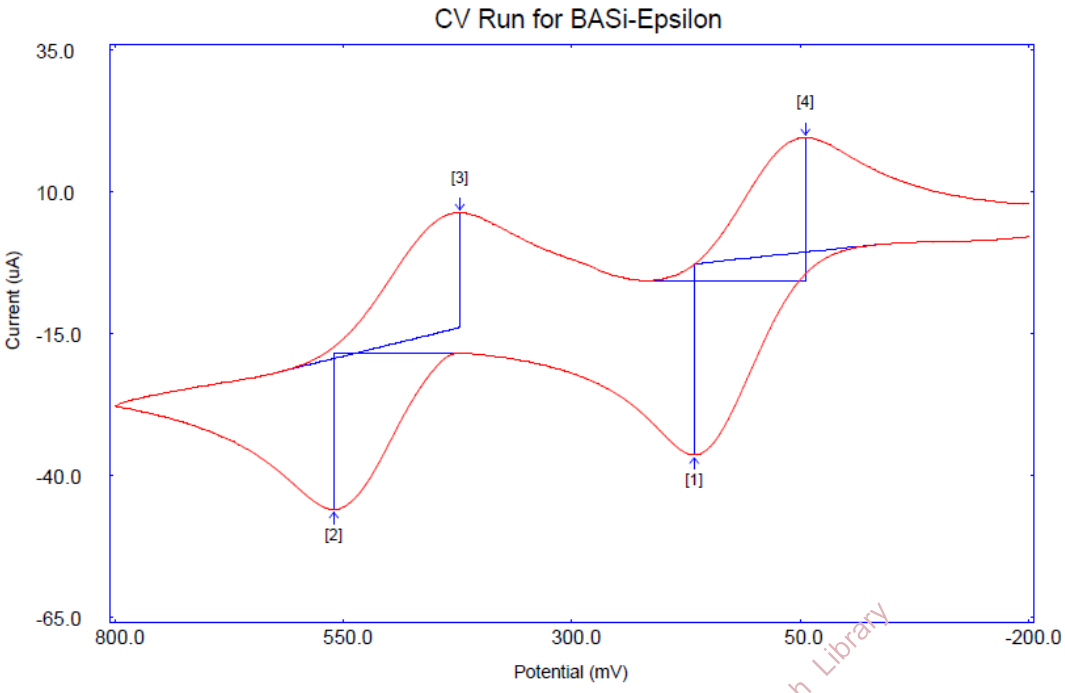
Although the spectrum is a bit messy due to impurities there is a well-defined peak at ~8.3 ppm corresponding to the singular proton ortho to the pyridyl nitrogen along with a series of aromatic peaks from the 2-(trifluoromethyl)phenothiazine ring. Additionally the peak at 2.25 ppm corresponds to the methyl group on the pyridine ring. This information indicates that the intended product was isolated.

Cyclic Voltammetry

Cyclic voltammetry was performed on the synthesized radical cation precursors to determine a reduction potential for the radical cation-neutral couple. Ferrocene was used as an

internal standard as the ferrocenium/ferrocene couple. From the cyclic voltammogram of **Mepy-PT** (**Figure 6**), it was calculated that the reduction potential for **Mepy-PT**$^{\bullet+/0}$ is 0.38 V. This reduction potential indicates that the radical cation precursor is relatively oxidizing.

Figure 6. Cyclic voltammogram of **Mepy-PT** with added ferrocene.



Similarly, cyclic voltammograms (**Figure 7**) were acquired for **Mepy-PTCF$_3$**. The reduction potential of **Mepy-PTCF$_3$**$^{\bullet+/0}$ was calculated to be 0.531 V. This value is more oxidizing than a previous student, Evan Welker's, **py-CF$_3$PT**$^{\bullet+/0}$ reduction potential of 0.445 V. This data helps to support the idea that the effects of the trifluoromethyl group and the methyl group on the pyridine ring can be combined.

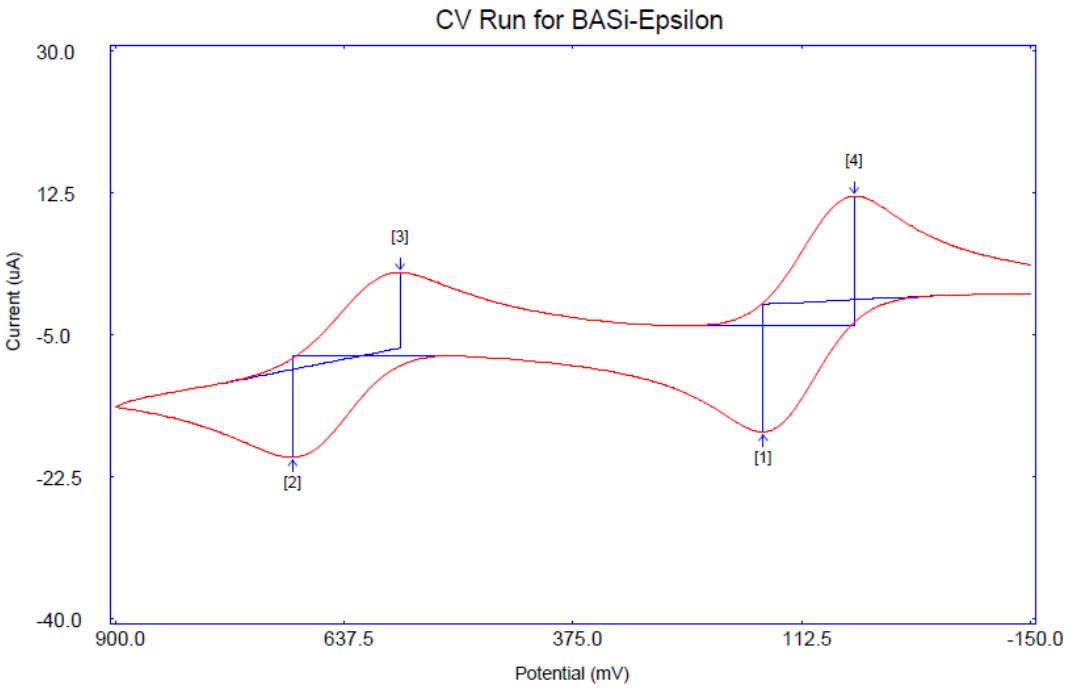


Figure 7. Cyclic voltammogram of **Mepy-PTCF$_3$** with added ferrocene.

pK_a Determination of the Radical Cation Precursors

pK_a values were determined for both **Mepy-PTH$^+$** and **Mepy-PTCF$_3$H$^+$** in order to determine the basicity of the compounds. The basicity of the compounds along with the reduction potentials from the cyclic voltammograms was used to determine their BDFE values. The pK_a values of **Mepy-PTH$^+$** and **Mepy-PTCF$_3$H$^+$** were measured by equilibrium titrations for which the neutral compounds were added to an indicator, thymol blue, with a known pK_a of 13.4. The absorbance of deprotonated indicator was monitored by UV-vis and concentrations were determined using Beer's law and mass balance. The concentration of the deprotonated indicator was plotted versus the concentration of the compound; Hess's law was then used to determine pK_a from the calculated equilibrium constant.

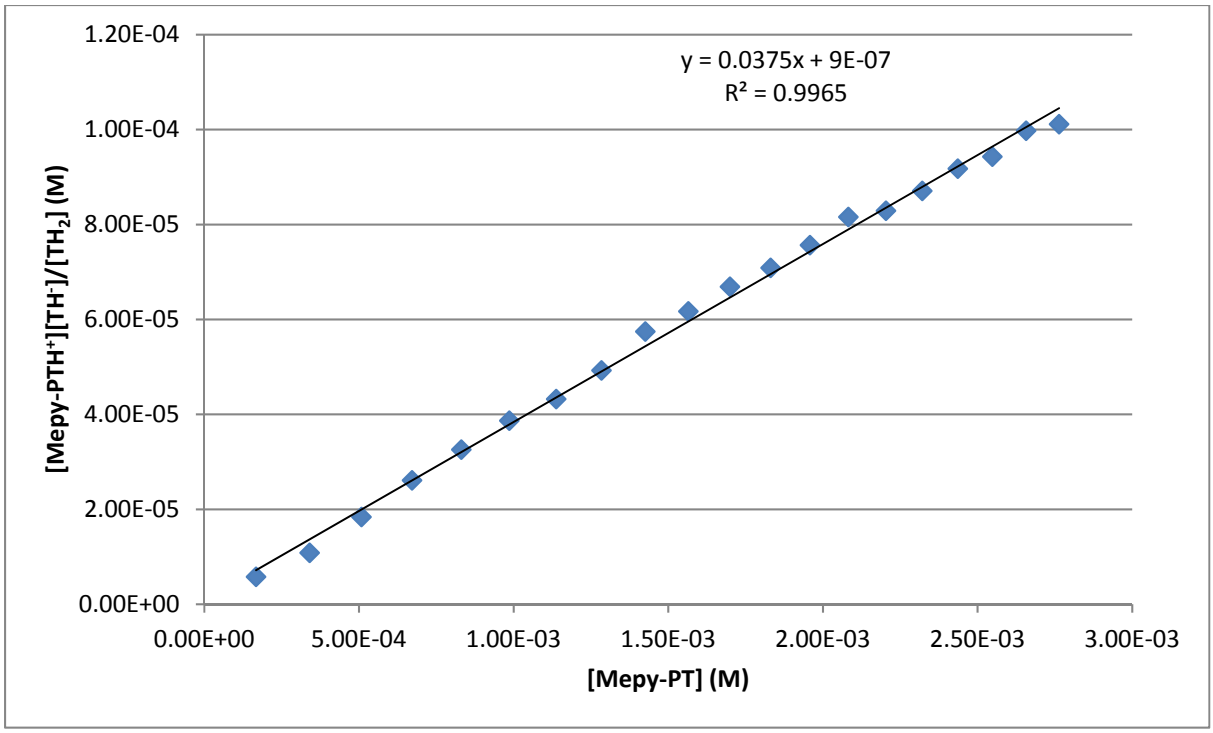


Figure 8. pK_a determination for **Mepy-PTH**$^+$.

The pK_a for **Mepy-PTH**$^+$ was calculated to be 11.97 from the calculated equilibrium constant (the slope of the line in Figure 8). This is a more basic pK_a than the previous structural isomer whose methyl group was placed ortho to the nitrogen rather than para. The pK_a for **Mepy-PTCF$_3$H**$^+$ was determined in a similar manner.

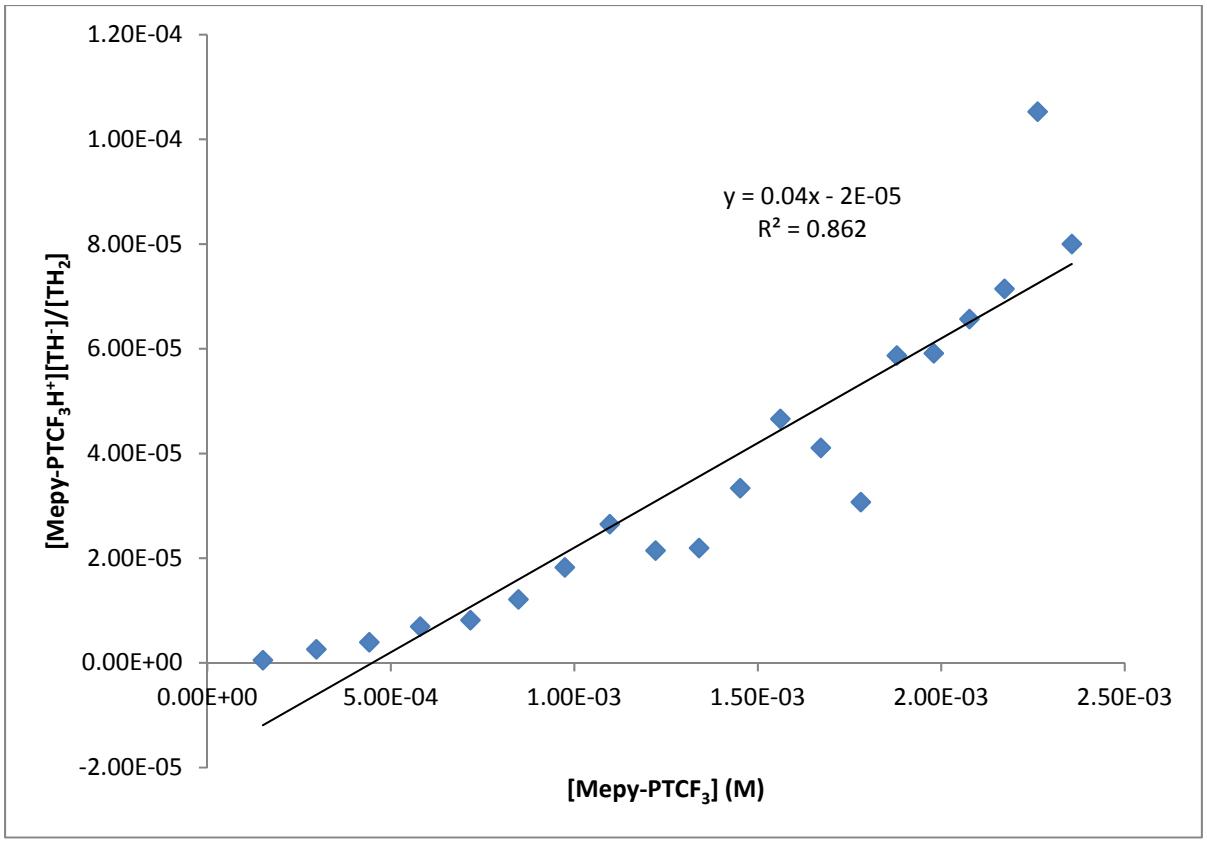


Figure 9. pK_a determination for **Mepy-PTCF$_3$H$^+$**.

The calculated equilibrium constant in Figure 9 was used to calculate a pK_a of 12.00. There is significant scatter in the plot and a retesting with the thymol blue indicator will be needed to determine a better value for the pK_a of **Mepy-PTCF$_3$H$^+$**.

Calculated Bond Dissociation Free Energy Values (BDFE)

Using the pK_a values and the reduction potentials, the bond dissociation free energies (BDFEs) can be determined using the thermodynamic cycle in Figure 1. The BDFE value of **Mepy-PT$^{\bullet+}$** was calculated to be 80.2 kcal/mol and the BDFE value of **Mepy-PTCF$_3^{\bullet+}$** was calculated to be 83.6 kcal/mol. As hoped the value for **Mepy-PTCF$_3^{\bullet+}$** was larger than either

Mepy-PT$^{\bullet+}$'s value of 80.2 kcal/mol or one of Evan Welker's compound's **py-CF$_3$PT**$^{\bullet+}$ value of 82.5 kcal/mol. These data provide evidence that adding both a trifluoromethyl group as well as a methyl group opposite the nitrogen on the pyridine ring helps to increase the molecule's BDFE.

Generation of the Radical Cations

One-electron oxidation reactions between tris(4-bromophenyl)aminium and the compounds to produce the radical cations that were analyzed by UV-vis spectroscopy. One-electron oxidation of **Mepy-PT** produces a pale orange colored liquid that was analyzed by UV-vis spectroscopy. Due to the suspicion that the tris(4-bromophenyl)aminium is no longer viable, the spectrum is not included in this report. The UV-vis spectrum was obtained to determine that the spectrum of **Mepy-PT** is consistent with a phenothiazinium radical cation.[9] The radical cation of **Mepy-PTCF$_3$** has not yet been generated.

Preliminary Kinetics Trials

Unfortunately due to the rapid reaction of **Mepy-PT**$^{\bullet+}$ with a donor atom the standard UV-Vis spectrophotometer is not able to measure the kinetics of the reaction accurately. Additionally the rapid mix/rapid scan UV-Vis spectrophotometer is not mixing as quickly as intended and therefore kinetics trials of either compound have not yet been able to be performed.

Conclusion

The table below shows a summary of the cyclic voltammetry, pK_a titrations, and BDFE calculations for both compounds. The results indicate that a methyl group opposite the nitrogen on the pyridine ring (**Mepy-PT**, pK_a: 11.97) significantly increases the basicity of the compound when compared to both the unsubstituted (**py-PT**, pK_a: 10.9) and the structural isomer previously synthesized by Evan Welker (pK_a: 11.2). The reduction potential appears to be relatively unchanged compared to Welker's reduction potential of 0.39V. The reduction potential of **Mepy-PTCF$_3$** (0.531 V) is significantly higher than any other compounds previously studied in this project.[10] Its pK_a, however, will definitely need to be redetermined due to scatter in the data. As a whole, it appears that combining the basic effects of a methyl group opposite the nitrogen on the pyridine ring with the electron withdrawing effects of the trifluoromethyl group on the phenothiazine ring system significantly increases the BDFE of the molecule.

Table 1. Summary of results

compound	E (V)[a]	pK_a[b]	BDFE (kcal/mol)[c]
Mepy-PT	0.385 V	11.97	80.2
Mepy-PTCF$_3$	0.531 V	12.00	83.6

[a] E(**Xpy-PTY**$^{\bullet+/0}$) vs. $Cp_2Fe^{+/0}$ in 0.1 M Bu_4NPF_6 in MeCN. [b] **Xpy-PTYH**$^+$ → **Xpy-PTY** + H^+ in MeCN [c] Calculated from 1.37pK_a + 23.06E + 54.9.

Works Cited

(1) Warren, J. J.; Tronic, T. A.; Mayer, J. M. *Chem. Rev.* **2010,** *110,* 6961-7001.

(2) Welker, E. A.; Rhile, I. J. Unpublished results.

(3) Reece, S. Y.; Nocera, D. G. "Proton-Coupled Electron Transfer in Biology: Results from Synergistic Studies in Natural and Model Systems." *Annu. Rev. Biochem.* **2009,** *78,* 673-99.

(4) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.*, **1996,** *118,* 7217-7218.

(5) Franz, A. W.; Popa, L. N.; Thomas, J. J. M. *Org. Biomol. Chem.* **2009**, *7*, 469-475.

(6) Jovanovic, Misa. V.; Biehl, Edward R. *J. Heterocyclic Chem.* **1983,** *20,* 1667-80.

(7) Gilman, H.; Ranck, R. O. *J. Org. Chem.* **1958**, *23*, 1903-1906.

(8) Kolthoff, I. M.; Chantooni, M. K., Jr.; Bhowmik, S. *Anal. Chem.* **1967**, *39*, 315-320.

(9) Rosokha, S. V.; Kochi, J. K. *J. Am. Chem. Soc.* **2007,** *129,* 3683-3697.

(10) Simpson, F. M. C.; Welker, E. A.; Reigel, A. D.; Rhile, I. J. Unpublished results.