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Internally Hydrogen-Bonded PRODAN Derivatives

Douglas William Cheek

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Internally Hydrogen-Bonded PRODAN Derivatives

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Bachelor of Science, College of William & Mary, 2014

A Thesis presented to the Graduate Faculty
of the College of William and Mary in Candidacy for the Degree of
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Master of Science

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ABSTRACT

Two 5-acyl-2-dimethylaminonaphthalene derivatives with varied chain length between the hydroxyl hydrogen and carbonyl oxygen of the acyl group are studied as sensors of hydrogen-bond-donating ability in protic solvents. Previous studies showed carbonyl-twisted PRODAN derivatives’ quenching order of magnitude to be linearly related to the hydrogen-bond-donating ability of the solvent as quantified by the solvent acidity (SA) scale and that quenching of the derivatives requires a doubly hydrogen-bonded carbonyl oxygen in the excited state. The effect of adding an internal hydrogen bond to the PRODAN derivatives is studied. The internal hydrogen bond interacts with the excited state via an in-plane mode; however, the molecules still require two external hydrogen bonds to induce quenching. The effect of the internal hydrogen bond was more pronounced in the shorter chain derivative, given that the longer chain derivative showed greater preference for the external hydrogen bonds.
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CHAPTER 1: INTRODUCTION

Molecular sensors are an integral part of chemistry, biology, and materials science. Exploration into the utility and nature of molecular sensors is an important area of research. Information about a molecule’s nanoscale environment can be determined using molecular sensors. Free moving chemosensors are useful to numerous areas of chemistry and biology in acquiring information about a solvent or surface.\(^1\)

In particular, fluorescent sensors are an important area of research. In different environments, the fluorescent probe will emit differently.\(^1\) The emission wavelength maximum, intensity, and lifetime can change with respect to the molecule’s environment and can be quantifiably measured. Fluorophores have been used extensively in studies of the properties of solvents, surfaces, proteins, membranes, cells, and more.\(^1\) For example, biologists have developed fluorescent probes that yield real-time images of cells. The probes have also been useful in monitoring the complex cellular processes such as small-molecule-messenger dynamics, enzyme activation and protein–protein interactions.

Fluorescent molecular sensors provide numerous benefits.\(^1\) High sensitivity of detection can be achieved with fluorescent probes, and in some cases down to a single molecule. The quenching of fluorescence in certain environments gives fluorescent probes an “on-off” capability. Similarly, fluorescent probes provide submicron visualization and sub-millisecond temporal resolution.\(^1\)
CHAPTER 2: BACKGROUND

PRODAN, or 6-propionyl-2-(dimethylamino)naphthalene was first synthesized by Weber and Farris in 1979 in order to study the binding pocket of bovine serum albumin. The molecule was developed in order to act as a fluorescent probe. Based on the fluorescence characteristics of PRODAN, i.e. the wavelength and intensity, the polarity of the immediate environment could be determined. As the solvent polarity increased, the fluorescent wavelength maximum increased as well. In cyclohexane, a highly nonpolar solvent, PRODAN emits at 401 nm; however in water, a highly polar solvent, PRODAN emits at 531 nm. The property described is known as solvatochromism and arises when the ground state dipole moment and excited state dipole moment of a fluorescent molecule are notably different. When the solvent is highly polar, the excited state is more stable, making the transition from the excited state to ground state involve less energy and, therefore, result in a longer wavelength emission.

Weber and Farris synthesized the solvatochromic molecule by placing a good electron donor and good electron acceptor on an aromatic ring system. PRODAN, as seen in Figure 1, contains a good electron donor, the tertiary amine, and a good electron acceptor, the carbonyl-containing acyl group. The strongest solvatochromic effects are observed when...
The substituents are placed as far apart as possible, which explains why the groups are on positions two and six of the naphthalene ring.

The solvatochromic molecule is known as a push-pull, charge-transfer chromophore, which results in a large change in the dipole moment upon photochemical excitation.¹,³ The dipole moment of the ground state is half of that of the excited charge-transfer state. The amino group donates electrons to the aromatic ring system, which then transfers electrons to the electron withdrawing acyl group, as seen in Figure 2. The charge-transfer state is formed from an initially excited state, known as the locally excited state (LE). In polar solutions, PRODAN transitions back to the ground state from the charge-transfer state in a process known as fluorescence. However, in nonpolar solutions, PRODAN emits from the locally excited state.

Weber and Farris first hypothesized the polarity difference between the two states to be roughly Δμ~20 D. Recent studies by Balter and Samanta have revised this estimate to be significantly smaller at ~5-10 D.¹,³

Debate has occurred on whether PRODAN emits through a twisted intramolecular charge transfer (TICT) excited state, or from a planar intramolecular charge transfer (PICT) excited state. Given that, twisting of the electron donating and electron withdrawing groups leads to a greater charge

Figure 2: PRODAN Excited States
separation, the twisted intramolecular charge transfer hypothesis was first developed. In support of the hypothesis, similar fluorophores, such as 5-dimethylaminonaphthalene-1-sulfonic acid and dimethylaminobenzonitrile, have been shown to proceed through a twisted excited state. However, studies done by Abelt et al. have shown that the molecule most likely proceeds through a planar excited state.

By synthesizing constrained PRODAN derivatives, Abelt was able to test the TICT hypothesis. Abelt synthesized a PRODAN derivative with a planar amino group and a derivative with a twisted amino group. The planar-amino derivative exhibited identical fluorescent behavior as the original PRODAN molecule; however, the twisted-amino derivative only emitted in nonpolar solvents. The twisted-amino derivative in polar solvents may have been stable enough for the electronic energy transition to couple with internal conversion, thereby quenching fluorescence. Interestingly, derivatives with twisted and planar carbonyl groups showed no differences in solvatochromic properties when compared to PRODAN. Given that the twisted-amino structure did not behave similarly to PRODAN and the planar-amino structure did, Abelt was able to demonstrate with a high degree of certainty that PRODAN proceeds through a PICT.

Although PRODAN was originally synthesized to be strictly a micropolarity sensor, studies have shown that the fluorescence of PRODAN is also dependent on other properties of the solvent environment. Two widely accepted definitions of solvent properties have been developed. The Kamlet-Taft definition classifies
solvents based on the polarity/polarizability (π*), hydrogen-bond donating ability (α), and the hydrogen-bond accepting ability (β). In addition to the Kamlet-Taft approach, Catalán has also defined solvents in a four-parameter approach. The solvent acidity (SA) and solvent basicity (SB) correspond to the hydrogen-bond donating ability (α) and accepting ability (β), respectively. However, the polarity term has been split into the dipolarity (SdP) and polarizability (SP) terms.

Studies have shown that the fluorescence wavelength and intensity are not only dependent on solvent polarity, but are also dependent on the hydrogen-bond donating ability of the solvent. When PRODAN is excited and transitions to an ICT excited state, hydrogen bonds between the solvent and the solute can quench the fluorescence and shift the wavelength maximum. Based on the Kamlet-Taft solvatochromic comparison method, the Stokes shift of PRODAN depends upon the hydrogen-bond donating ability of the solvent roughly half as much as it depends upon the polarity/polarizability of the solvent. Similar to the polarity dependence, as the hydrogen-bond donating ability of the solvent increases, the fluorescence wavelength maximum increases as well due to the excited state being more stable in more H-bond donating solvents. The dependence on the hydrogen-bond donating ability in addition to the polarity/polarizability of the solvent make analysis using PRODAN more complicated, and, therefore, requires more careful consideration when studying the micropolarity of a solvent.

In addition to shifting the fluorescence wavelength, strongly hydrogen-bond donating solvents, such as methanol, quench the fluorescence of PRODAN
by creating more favorable radiationless modes of deactivation. Studies done by Inoue and coworkers have focused on the influence of intermolecular hydrogen bonds on the electronic states of fluorescent molecules that undergo intramolecular charge transfer. When in the ICT excited states, the charges create a large dipole moment. The sudden change in dipole moment cause the solvent molecules to rearrange around the solvent quickly in order to minimize the total energy of the system. Hydrogen bonds formed between the negatively-charged oxygen of the ICT excited state can affect the way in which the molecule returns to the ground state. The hydrogen bond acts as the effective accepting mode of radiation-less transition through internal conversion because the high frequency of the hydrogen bond couples with the excited state and ground state of the solute very easily.

However, not all hydrogen bonds between PRODAN and protic solvents quench the solute’s fluorescence. Using kinetic analysis of fluorescence dynamic decay, Inoue determined at least two species of hydrogen-bonded fluorophores that undergo ICT excited states. The first is an emissive state in which the carbonyl oxygen of PRODAN is hydrogen bonded through an in-plane mode with the solvent, which is due to an interaction with the $2p_y$ orbital. The second is a non-emissive state in which the carbonyl oxygen is hydrogen bonded through an out-of-plane mode, which is due to an interaction with the $\pi^*(2p_z)$ orbital. Inoue also indicated a third species in which the solute is hydrogen bonded through two modes of deactivation being the in-plane and out-of-plane mode. All three species can be seen in Figure 3.
In addition to studying the solvatochromic properties of PRODAN, the molecule has been used in the study of preferential solvation. The study of solvatochromic properties becomes more complex when the solvatochromic molecule is solvated by more than one solvent. The concentration of solvents in the immediate environment around the solute molecule, called the solvation microsphere, may be different than the concentration of solvents in the bulk solvent. When the composition of solvents in the solvation microsphere is different than the composition of solvents in the bulk solvent, preferential solvation has occurred. In the case of PRODAN, preferential solvation results from hydrogen bonding interactions. In protic solvents, preferential solvation can be observed; however, in aprotic solvents, no preferential solvation occurs.
In general terms, solvent-solvent interactions and solute-solvent interactions are responsible for the occurrence of preferential solvation. Due to the low concentration of solute molecules within solution, solute-solute interactions are negligible.

The solvatochromic indicator, Dimroth-Reichardt betaine or 2, 6-diphenyl-4-(2,4,6-triphenyl-1-pyridinio)phenolate, has been widely used in preferential solvation studies. Similar to PRODAN, the Dimroth-Reichardt betaine molecule is sensitive to the polarity/polarizability of the solvent, $\pi^*$, as well as the hydrogen-bond donating ability, $\alpha$. The structure of the Dimroth-Reichardt betaine dye can be seen in Figure 4. The transition energy of the solute molecule is observed relative to the mole fraction of one solvent in the bulk solution. As the concentration changes, the transition energy changes as well. In a non-preferentially solvated solution, the transition energy of the solvatochromic indicator changes linearly with respect to the mole fraction of one of the solvents.

However, when preferential solvation occurs, the transition energy of the solute molecule changes with respect to the mole fraction of one of the solvents in a nonlinear fashion.

Rosés and Bosch have developed a popular model for preferential solvation. Connors and Skwierczynski have independently...
developed a similar model. These models explain the complex solute-solvent and solvent-solvent interactions that result in preferential solvation, specifically the one-step exchange model and the two-step exchange model.

The simplest model developed by Rosés, named the one-step exchange model, describes the interaction of the solute, I, with two solvents, S1 and S2.

\[ I(S1) + S2 \rightleftharpoons I(S2) + S1 \]  

(1)

Equilibrium between the two molecules, or the preference of the solvatochromic indicator to be solvated by solvent 2 relative to solvent 1 is calculated by \( f_{2/1} \), which is named the preferential solvation parameter or the complete exchange equilibrium constant. The mole fractions of the solvents in the bulk solvent are represented by \( x_2^0 \) and \( x_1^0 \), while the mole fractions of the solvents in the solvation microsphere are represented by \( x_2^s \) and \( x_1^s \). It is important to consider that for the one-step exchange model, \( x_1^0 + x_2^0 = x_1^s + x_2^s = 1 \).

\[ f_{2/1} = \frac{x_2^s / x_1^s}{x_2^0 / x_1^0} \]  

(2)

The one-step exchange model is capable of describing some binary solvents; however, the model is incapable of modeling synergistic systems and some other binary solvents. Synergism results from solvent-solvent interactions and generally occurs when binary solutions consist of one hydrogen-bond donating solvent and one hydrogen-bond accepting solvent. When a mixture of two solvents induces a larger transition energy than in either pure solvent, synergism has occurred.
In order to create a model that better fits binary solutions, Rosés and Connors developed the two-step exchange model.\textsuperscript{10-17} The model describes both solute-solvent interactions along with solvent-solvent interactions. Rosés developed a more general version of the two-step exchange model that takes into account multiple solvent molecules solvating the solute. The number of solvent molecules is represented by $m$, and a solvated species with an equal number of both solvent molecules is represented by $S_{12}$. Most systems can be modeled accurately by $m = 2$. In the two-step exchange model the two equilibria expressions model double and single solvent exchange.\textsuperscript{10-17}

$$I(S_1)_m + mS_2 = I(S_2)_m + mS_1$$

$$I(S_1)_m + \frac{m}{2} S_2 = I(S_{12})_m + \frac{m}{2} S_1$$

(3)

In addition to the complete exchange equilibrium constant, $f_{1/2}$, the two-step exchange model includes a half-exchange equilibrium constant, $f_{12/1}$.

$$f_{2:1} = \frac{x_1^i/x_1^i}{(x_2^0/x_1^0)^m}$$

(4)

$$f_{12:1} = \frac{x_1^i/x_1^i}{\sqrt{(x_{12}^0/x_1^0)^m}}$$

(5)

Abelt has recently developed a three-step exchange model to better model binary mixtures with carbonyl-twisted derivatives of PRODAN.\textsuperscript{19} The model is derived from the ternary preferential solvation model developed by Leitão and coworkers.\textsuperscript{20} The three-step exchange mode has three separate
equilibrium constants, $f_1$, $f_2$, and $f_3$.

\[
\begin{align*}
I(S1)_3 + S2 & \overset{f_1}{\leftrightarrow} I(S1,S1,S2) + S1 \\
I(S1)_3 + 2 S2 & \overset{f_2}{\leftrightarrow} I(S1,S2,S2) + 2 S1 \\
I(S1)_3 + 3 S2 & \overset{f_3}{\leftrightarrow} I(S2)_3 + 3 S1
\end{align*}
\]

(6)

Recent research of Abelt and coworkers has dealt with the synthesis and study of PRODAN derivatives. Specifically, Abelt et al. has synthesized PRODAN derivatives with two methyl groups adjacent to the carbonyl, which force the carbonyl to twist out of plane.\textsuperscript{21} Carbonyl-twisted PRODAN derivatives have been found to be highly responsive sensors of solvent acidity. Abelt found that the derivatives show strong fluorescence quenching in protic solvents. In fact, the quenching of PRODAN derivatives with twisted carbonyl groups is linearly related to the hydrogen bond donating ability of the solvent. Ideally, by measuring the magnitude of the fluorescence quenching, the solvent acidity can be determined.\textsuperscript{21}

Preferential solvation studies conducted by Abelt using the two-step exchange model have indicated that quenching of the carbonyl-twisted PRODAN derivatives occurs from a doubly-hydrogen bonded ICT excited state.\textsuperscript{22} However, the derivatives do not quench in a singly-hydrogen bonded ICT excited state. Given that quenching occurs through a doubly-hydrogen bonded state, Abelt has synthesized carbonyl-twisted PRODAN derivatives with nearby hydroxyl groups to form an intramolecular hydrogen bond with the carbonyl oxygen. The intramolecular hydrogen-bonded PRODAN derivatives are the subject of my thesis. The derivatives were synthesized in order to study the effect that one
intramolecular hydrogen bond has on the derivatives' quenching behavior. Abelt synthesized two different derivatives to study the effect of distance between the hydroxyl group and the carbonyl oxygen on the internal hydrogen bond. The derivatives' structures can be seen in Figure 5.

Figure 5: Compounds 1 and 2, respectively; Intramolecularly H-Bonded PRODAN Derivatives
3.1 SYNTHESIS

*Amidation of methyl 3-hydroxy-2,2-dimethylpropanoate*

To a three-stemmed round bottom flask under nitrogen containing 75 mL of THF, 30 mmol of methyl 3-hydroxy-2,2-dimethylpropanoate (3.96 g) and 45 mmol of N,O-methylhydroxylamine hydrochloride (4.40 g) were added. The flask was cooled to -20 °C, and 63.16 mL of 1.9 M iPrMgCl in THF (120 mmol) was added dropwise. The solution was allowed to warm to room temperature and stir for 1.5 hours.

A solution of 30 g NH₄Cl in 100 mL of H₂O was added to quench the reaction. The mixture was extracted with CH₂Cl₂ and dried with CaCl₂. The organic layer was then dried *in vacuo*. The product was then distilled under high vacuum, and 4.36 g (27.04 mmol) of 3-hydroxy-N-methoxy-N,2,2-trimethylpropanamide was recovered. The percent yield was determined to be 90.1%.

*Figure 6:*

![Diagram](image)

*Amidation of methyl 2-hydroxy-2-methylpropanoate*

To a three-stemmed round bottom flask under nitrogen containing 50 mL of THF, 15 mmol of methyl 3-hydroxy-2,2-methylpropanoate (1.77 g) and 22.5 mmol of N,O-methylhydroxylamine hydrochloride (2.20 g) were added. The flask
was cooled to -20 °C, and 31.5 mL of 1.9 M iPrMgCl in THF (60 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stir for 1.5 hours.

A solution of 15 g NH₄Cl in 50 mL of H₂O was added to the flask. The product was extracted with CH₂Cl₂ and dried with CaCl₂. The organic layer was then dried *in vacuo*. 9.51 mmol of 2-hydroxy-<i>N</i>-methoxy-<i>N</i>,2-diethylpropanamide was recovered, with a percent yield of 63.4%.

**Figure 7:**

![Etherification of 3-hydroxy-<i>N</i>-methoxy-<i>N</i>,2,2-trimethylpropanamide](image)

*Etherification of 3-hydroxy-<i>N</i>-methoxy-<i>N</i>,2,2-trimethylpropanamide*

To a 100-mL round bottom flask under nitrogen containing 15 mL CH₂Cl₂ at room temperature, 7.94 mmol of 2-hydroxy-<i>N</i>-methoxy-<i>N</i>,2-diethylpropanamide (1.28 g) and 11.9 mmol of diisopropylamine (1.21 g) were added. After adding 15 mmol of MOMCl (1.20 g), the solution was allowed to stir. An additional 11.9 mmol of diisopropylamine (1.21 g) and 15 mmol of MOMCl (1.20 g) were then added and the reaction was stirred for 8 hrs. The solution was stirred for another 8 hrs.

The reaction was quenched with 150 mL of H₂O. The product was extracted twice with CH₂Cl₂, and the organic layer was dried with CaCl₂. The solvent was then removed *in vacuo*. The dried organic layer was distilled, and
4.58 mmol of \(N\)-methoxy-3-(methoxymethoxy)-\(N,2,2\)-trimethylpropanamide (0.94 g) was recovered with a percent yield of 57.7%.

**Figure 8:**

\[
\begin{align*}
\text{HO} & \quad \text{diisopropylamine} \\
\rightarrow & \quad \text{MOMCl} \\
\text{CH}_2\text{Cl}_2 & \quad \rightarrow \\
\text{O} & \quad \text{O}
\end{align*}
\]

**Etherification of 2-hydroxy-\(N\)-methoxy-\(N,2\)-dimethylpropanamide**

To a 100-mL round bottom flask under nitrogen containing 15 mL \(\text{CH}_2\text{Cl}_2\) at room temperature 9.24 mmol of 2-hydroxy-\(N\)-methoxy-\(N,2\)-dimethylpropanamide (1.36 g) and 13.8 mmol of diisopropylethylamine (1.79 g) were added. Next, 13.8 mmol of MOMCl (1.12 g), the solution was allowed to stir. An additional 13.8 mmol of diisopropylamine (1.79 g) and 13.8 mmol of MOMCl (1.12 g) were then added after allowing the solution to stir for 8 hours. The solution was then stirred for another 8 hours before working up the reaction.

The reaction was quenched with 150 mL of \(\text{H}_2\text{O}\). The product was extracted twice with \(\text{CH}_2\text{Cl}_2\), and the organic layer was dried with \(\text{CaCl}_2\). The solvent was then removed *in vacuo*, and the product was distilled under high vacuum. 6.38 mmol of \(N\)-methoxy-2-(methoxymethoxy)-\(N,2\)-dimethylpropanamide (1.22 g) was recovered, with a percent yield of 69%.

**Figure 9:**

\[
\begin{align*}
\text{HO} & \quad \text{diisopropylamine} \\
\rightarrow & \quad \text{MOMCl} \\
\text{CH}_2\text{Cl}_2 & \quad \rightarrow \\
\text{O} & \quad \text{O}
\end{align*}
\]
**Esterification of methyl 3-hydroxy-2,2-dimethylpropanoate**

To a 100 mL round bottom flask, 50 mL of dimethoxymethane, 12.90 mmol LiBr (1.12 g), 42.90 mmol methyl 3-hydroxy-2,2-dimethylpropanoate (5.67 g), and 5.78 mmol p-toluenesulfonic acid monohydrate (1.10 g) were added. The solution was left to stir for two days while under nitrogen with no heat.

After two days, the reaction was quenched with a solution of 50 mL DI water, 10.00 g NaCl, 1.05 g NaHCO₃, and 1.03 g Na₂CO₃. Two diethyl ether extractions of 50 mL were conducted. After drying the organic layer with MgSO₄, the solution was filtered by gravity filtration. The solvent was then removed *in vacuo*. The product was distilled under high vacuum. 29.11 mmol of methyl 3-(methoxymethoxy)-2,2-dimethylpropanoate (5.13 g) was recovered with a percent yield of 69%.

**Figure 10:**

![Diagram of molecular structure]

**Lithiation of N-methoxy-3-(methoxymethoxy)-N,2,2-trimethylpropanamide**

In a flame-dried three-neck flask, 7.28 mmol of 6-bromo-N,N-dimethylNaphthalen-2-amine (1.82 g, sublimed just before use) were added to 50 mL of dry THF under nitrogen. The solution was cooled to -78 °C, and 4.85 mL of 1.6 M n-BuLi (7.76 mmol) were added dropwise while stirring. The solution was then stirred for 30 minutes at -78 °C. A mixture of 7.66 mmol N-methoxy-2-(methoxymethoxy)-N,2-dimethylpropanamide (1.57 g) in 5 mL of THF was then
added drop wise. The reaction was then stirred for 1.5 hours and was warmed to room temperature.

The reaction was quenched with 100 mL of H₂O. The product was extracted three times with 75 mL CH₂Cl₂, and the organic layer was dried with CaCl₂. The solvent was then removed in vacuo.

Figure 11:

![Chemical structure](image)

**Lithiation of N-methoxy-2-(methoxymethoxy)-N,2-dimethylpropanamide**

To a flame-dried three-neck flask containing 7.56 mmol of 6-bromo-N,N-dimethylnaphthalen-2-amine (1.89 g, sublimed just before use), 50 mL of dry THF was added under nitrogen. The solution was cooled to -78 °C, and 5.0 mL of 1.6 M n-BuLi (8.12 mmol) was added dropwise while stirring. The solution was then stirred for 30 minutes at -78 °C. A mixture of 7.95 mmol N-methoxy-2-(methoxymethoxy)-N,2-dimethylpropanamide (1.51 g) in 5 mL of THF was then added drop wise. The reaction was then stirred for 1.5 hr and allowed to warm to room temperature.

The reaction was quenched with 100 mL of H₂O. The product was extracted three times with 75 mL CH₂Cl₂, and the organic layer was dried with CaCl₂. The solvent was then removed in vacuo.
Lithiation of methyl 3-(methoxymethoxy)-2,2-dimethylpropanoate

To a three-neck flask under nitrogen, 6-bromo-N,N-dimethyl-naphthalen-2-amine (0.81 g, 3.24 mmol) was dissolved in 15 mL of THF. The solution was cooled to -80°C, and n-BuLi (2.6 mL) was added dropwise. The solution was stirred at constant temperature for 12 min. Next, 5.79 mmol methyl 3-(methoxymethoxy)-2,2-dimethylpropanoate (1.02 g), was added dropwise. The flask was immediately warmed to room temperature and was allowed to stir overnight.

The reaction was quenched with 100 mL DI water. Three 75 mL extractions of CH₂Cl₂ were conducted, and the solution was dried with CaCl₂ before being filtered by gravity filtration. The solvent was then removed in vacuo.

Deprotection of 1-(6-(dimethylamino)naphthalen-2-yl)-3-(methoxymethoxy)-2,2-dimethylpropan-1-one

To a 100-mL round bottom under nitrogen, 5.00 mmol of 1-(6-(dimethylamino)naphthalen-2-yl)-3-(methoxymethoxy)-2,2-dimethylpropan-1-one
(1.58 g) and 15 mL of ethanol were added. Next, 5 mL of 6 N HCl was added, and the solution was warmed to 60-65 °C.

After 2 hours, the reaction was cooled and 100 mL of water was added. The product was extracted three times with 75 mL CH₂Cl₂, and the solvent was removed in vacuo. The product was separated using column chromatography with solutions of ethyl acetate and hexanes. The fractions containing the product were dried in vacuo, and were distilled. 0.10 g of 1-(6-(dimethylamino)naphthalen-2-yl)-3-hydroxy-2,2-dimethylpropan-1-one (0.44 mmol) was recovered with a percent yield of 6.04%.

**Figure 14:**

![Deprotection reaction](image)

*Deprotection of 1-(6-(dimethylamino)naphthalen-2-yl)-2-(methoxymethoxy)-2-methylpropan-1-one*

To a 100-mL round bottom under nitrogen, 5.00 mmol of 1-(6-(dimethylamino)naphthalen-2-yl)-2-(methoxymethoxy)-2-methylpropan-1-one (1.51 g) and 15 mL of ethanol were added. Next, 5 mL of 6 N HCl was added, and the solution was warmed to 60-65 °C.

After 2 hours, the reaction was cooled and 100 mL of water were added. The product was extracted three times with 75 mL CH₂Cl₂, and the solvent was removed in vacuo. The product was separated using column chromatography with solutions of ethyl acetate and hexanes. The fractions containing the product
were dried in vacuo, and were distilled. 0.25 g of 1-(6-
(dimethylamino)naphthalen-2-yl)-2-hydroxy-2-methylpropan-1-one (1.17 mmol)
was recovered with a percent yield of 15.4%. \( ^1 \)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.46
(d, \( J=1.8 \), 1H), 7.98 (dd, \( J=8.8, 2.0 \) Hz, 1H), 7.80 (d, \( J=9.2 \) Hz, 1H) 7.64 (d,
\( J=8.8 \), 1H), 7.18 (dd, \( J=9.2, 2.6 \) Hz, 1H), 6.86 (d, \( J=2.6 \) Hz, 1H), 3.12 (s, 6H),
1.73 (s, 6H). \( ^{13} \)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 29.19, 40.61, 105.21, 116.50,
124.94, 126.17, 126.19, 126.37, 131.19, 132.31, 137.77, 150.71, 203.65. HRMS
(ESI): calcd. for C\(_{16}\)H\(_{13}\)NO\(_2\)Na\(^+\) [M+Na]\(^+\) 280.13080; found 280.13089.

Figure 15:

![Chemical structure diagram]

3.2 GENERAL

After completion of the synthesis, compounds 1 and 2, 1-(6-
(dimethylamino)naphthalen-2-yl)-3-hydroxy-2,2-dimethylpropan-1-one and 1-(6-
(dimethylamino)naphthalen-2-yl)-2-hydroxy-2-methylpropan-1-one, respectively,
were sublimed under vacuum before use in absorption and fluorescence studies.
All solvents, except acetonitrile, were spectrophotometric grade. Acetonitrile was
distilled before each use. Fluorescence emission data were collected using a
fiber optic system with a 366 nm LED light source and an Ocean Optics Maya
CCD detector. Samples were thermostated at 23°C. Absorption spectra were
acquired from the same system with a miniature deuterium/tungsten light source.
Adding 5 mg of each to 10 mL of toluene made stock solutions of compounds 1 and 2, which were used in both the absorption and fluorescence studies.

3.3 ABSORPTION

Absorption data for the toluene/methanol and acetonitrile/methanol combinations were acquired using the method of standard additions. Five 5 µL aliquots of compound 1 or 2 stock solution were added to each 2.0 mL cell. The absorbance was recorded for the blank and after each addition. The dark signal was subtracted from the transmission signals to give the net intensity. The value of log(\(\frac{I_0}{I}\)) at 366 nm was determined for each dilution. The slope of the line of the plot of log(\(\frac{I_0}{I}\)) vs. \(x=1-5\) gives the absorbance of the solution with one aliquot. The absorbance values for a set of evenly spaced binary mixtures, in 10% increments from pure toluene/acetonitrile to pure methanol, were determined. The relative molar absorptivities for the solutions used in the fluorescent studies were determined using the best-fit third-order polynomial to the plot of normalized absorption vs. mole fraction. The solution compositions are shown below for the toluene/methanol solutions and the acetonitrile/methanol solutions in Figures 11 and 12, respectively.
Table 1: Toluene/Methanol Absorption

<table>
<thead>
<tr>
<th>Sample #</th>
<th>Volume Toluene (in ul)</th>
<th>Volume Methanol (in ul)</th>
<th>Mole Fraction Toluene</th>
<th>Mole Fraction Methanol</th>
</tr>
</thead>
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<td>1</td>
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<tr>
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Table 2: Acetonitrile/Methanol Absorption

<table>
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<th>Volume Acetonitrile (in µl)</th>
<th>Volume Methanol (in µl)</th>
<th>Mole Fraction Acetonitrile</th>
<th>Mole Fraction Methanol</th>
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</tr>
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</table>

3.4 FLUORESCENCE

For the toluene/methanol studies, two solutions of identical concentrations of 1 or 2 in toluene and methanol were made by diluting 20 µL of a stock solution of 1 or 2 to 10 mL. Two solutions of identical concentrations of 1 or 2 in acetonitrile and methanol were made using the same procedure. Two sets of
emission data were acquired for each toluene/methanol combination and acetonitrile/methanol combination. First, 2.0 mL of the toluene or acetonitrile solution was sequentially spiked with 19 aliquots of the methanol solution, and then 2.0 mL of the methanol solution was spiked with 7 aliquots of the toluene or acetonitrile solution. Before each emission was recorded, the solution was allowed to stir for 30 seconds. The abscissa scale of the intensity vs. wavelength data was converted to wavenumbers before subsequent mathematical treatment. The electronic noise was subtracted from the raw emission intensity. The net intensity at each point was divided by the spectral response of the Hamamatsu S10420 CCD and multiplied by $\lambda^2/\lambda_{\text{max}}^2$ to account for the effect of the abscissa-scale conversion. The compositions of the toluene/methanol solutions and the acetonitrile/methanol solutions are shown below in Figures 13 and 14, respectively.
### Table 3: Toluene/Methanol Fluorescence

<table>
<thead>
<tr>
<th>Sample #</th>
<th>Volume Toluene (in µl)</th>
<th>Volume Methanol (in µl)</th>
<th>Mole Fraction Toluene</th>
<th>Mole Fraction Methanol</th>
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</thead>
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Table 4: Acetonitrile/Methanol Fluorescence

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<th>Volume Methanol (in µl)</th>
<th>Mole Fraction Acetonitrile</th>
<th>Mole Fraction Methanol</th>
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CHAPTER 4: RESULTS AND DISCUSSION

4.1 SOLVATOCHROMISM

Fluorescence emission center-of-mass as a function of solvent ET (30) parameter (generalized solvent polarity parameter), which was developed by Roses using the Dimroth-Reichard Betaine dye. The PRODAN derivatives were examined in solvents of increasing polarity to compare the derivatives’ degree of solvatochromic behavior.

Figure 16: Compound 1 solvatochromism

The fluorescence maximum shifted to lower energy as the solvent polarity increased. There was a slight concave upward curvature in the plot at high solvent polarity.
Similar to compound 1, the fluorescence maximum shifted to lower energy as the solvent polarity increased. There was a slight concave upward curvature in the plot at high solvent polarity.
4.2 FLUORESCENCE

The two spectral values, relative quantum yield and the emission center-of-mass, were determined by applying the mathematical model to the fluorescence spectra. The preferential solvation of the individual species hydrogen bonded to a varied number of methanol molecules could be determined using the spectral values. The effect of the intramolecular hydrogen bond on compounds 1 and 2 could be elucidated using the preferential solvation data.

The fluorescence readings were taken after successive titrations with methanol of the acetonitrile or toluene solutions containing compounds 1 or 2 by the method of standard addition.

Figure 18: Compound 1 fluorescence spectra of acetonitrile/methanol mixtures
As the concentration of methanol was increased, the fluorescence of compound 1 was steadily quenched. In addition to being quenched, the emission continuously shifted to lower energy as the concentration of methanol increased.

**Figure 19:** Compound 1 fluorescence spectra of toluene/methanol mixtures

Initially, the fluorescence of compound 1 in the toluene/methanol mixtures did not quench as the concentration of methanol was increased. However, at a mole fraction of 2% methanol, the fluorescence began to quench with increasing methanol concentration. In addition, the fluorescence wavelength maximum steadily shifted to lower energy as the methanol concentration increased.
For the acetonitrile/methanol study, the fluorescence of compound 2 steadily quenched as the methanol concentration increased. In addition, the fluorescence wavelength maximum continuously shifted to lower energy as the methanol increased.
Figure 21: Compound 2 fluorescence spectra of toluene/methanol mixtures

At very low concentrations of methanol, increasing the concentration of methanol in the toluene/methanol mixtures did not induce quenching of compound 2’s fluorescence. At a mole fraction of roughly 2% methanol, the fluorescence began to quench steadily with increasing methanol concentration. The wavelength maximum decreased in energy as the concentration of methanol increased.
4.3 ABSORBANCE

Absorbance spectra of compounds 1 and 2 were taken to account for differences in absorption at 366 nm as a function of solvent composition to accurately calculate the relative quantum yield. The absorbance readings were determined after successive titrations with methanol of the acetonitrile or toluene solutions containing compound 1 or 2 by the method of standard additions.

Figure 22: Compound 1 UV-Vis spectra of acetonitrile/methanol mixtures

As the concentration of methanol was increased, the absorbance spectrum of compound 1 in acetonitrile/methanol changed a negligible amount.
As the concentration of methanol was increased, the absorbance spectrum of compound 1 in toluene/methanol changed a negligible amount.
As the concentration of methanol was increased, the absorbance spectrum of compound 2 in acetonitrile/methanol changed a negligible amount.
As the concentration of methanol was increased, the absorbance spectrum of compound 2 in toluene/methanol changed a negligible amount.
4.4 Γ PLOTS

The absorption and fluorescence data were used to effectively calculate the two spectral values, the emission center-of-mass and the relative quantum yield. The spectral values, $Y$, are related to the preferential solvation equilibrium constants. $Γ$ represents the fractional change in the spectral values with respect to the less polar solvent.

Figure 26: Plots of $Γ_{CM,Q}$ (◇), $Γ_Q$ (□), and $Γ_{CM,Q} - Γ_Q$ (Δ) vs. mole fraction methanol for 4 μM solutions of 1 in toluene/methanol mixtures.

As the mole fraction of methanol increased, the relative quantum yield and product of the emission center-of-mass and relative quantum yield spectral values of compound 1 increased in an almost linear fashion for the
toluene/methanol mixtures. The spectral values increased at a faster rate at lower concentrations of methanol than at higher concentrations.

**Figure 27**: Plots of $\Gamma_{CM-Q}$ ($\bigcirc$), $\Gamma_Q$ ($\square$), and $\Gamma_{CM-Q} - \Gamma_Q$ ($\Delta$) vs. mole fraction methanol for 4 µM solutions of 1 in acetonitrile/methanol mixtures.

As the mole fraction of methanol increased, the relative quantum yield and product of the emission center-of-mass and relative quantum yield spectral values of compound 1 increased for the acetonitrile/methanol mixtures. The spectral values increased at a much faster rate at lower concentrations of methanol than at higher concentrations.
Figure 28: Plots of $\Gamma_{\text{CM},Q}$ (◇), $\Gamma_Q$ (□), and $\Gamma_{\text{CM},Q} - \Gamma_Q$ (Δ) vs. mole fraction methanol for 4 µM solutions of 2 in toluene/methanol mixtures.

As the mole fraction of methanol increased, the emission center-of-mass and product of the emission center-of-mass and relative quantum yield spectral values of compound 2 increased in a relatively linear fashion for the toluene/methanol mixtures.
As the mole fraction of methanol increased, the emission center-of-mass and product of the emission center-of-mass and relative quantum yield spectral values of compound 2 increased for the acetonitrile/methanol mixtures. The spectral values increased at a much faster rate at lower concentrations of methanol than at higher concentrations.
4.4 PREFERENTIAL SOLVATION TABLE

For the toluene and methanol experiments, the $Y_1$ spectral values are obtained in pure toluene, and the $Y_3$ spectral values are obtained in pure methanol. In the acetonitrile and methanol experiments, the $Y_1$ spectral values are obtained in pure acetonitrile, and the $Y_2$ spectral values are obtained in pure methanol. Both the $r$ and the $f$ values are obtained by fitting the two-step and three-step exchange models to the $\Gamma$ plots. The $r$ value represents the ratio $(Y_1 - Y_{12})/(Y_1 - Y_2)$ where $Y_{12}$ is the spectral value of the solvatochromic molecule solvated solely by $S_{12}$. The relative quantum yield and the product of the emission center-of mass and the relative quantum yield for $Y_{12}$ and $Y_{23}$ can be determined using equation 9 in the appendix. From the spectral values determined with equation 9, the emission center-of-mass for $Y_{12}$ and $Y_{23}$ can then be calculated.

For the three-step model, $r_1$ is the ratio of $(Y_1 - Y_{12})/(Y_1 - Y_3)$ and $r_2$ is the ration $(Y_1 - Y_{23})/(Y_1 - Y_3)$ where $Y_{12}$ represents $l(S_1,S_1,S_2)$ and $Y_{23}$ represents $l(S_1,S_2,S_2)$. The $\Gamma$ values for the three-step are defined in equation 1.

$$\Gamma = \frac{Y_1 - Y_{12}}{Y_1 - Y_3} = \frac{r_1 f_1 x (1-x)^2 + r_2 f_2 x^2 (1-x)}{(1-x)^2 + f_1 x (1-x)^2 + f_2 x^2 (1-x)}$$

(1)

The difference between the two spectral values, being the emission center-of-mass times the relative quantum yield and the relative quantum yield, is defined in equation 2. The $\Delta m$-terms are the changes in the limiting slopes at the beginning ($\Delta m_1, x \to 0$) and end ($\Delta m_2, x \to 1$) of the $\Gamma$ plots.

$$\Gamma_{CMO} - \Gamma_0 = \Delta m_1 x (1-x)^2 - \Delta m_2 x^2 (1-x)$$

(2)
In the toluene/methanol fluorescence studies, the first intermolecular hydrogen bond added by methanol increased the relative quantum yield, $Q_{rel}$, more for compound 2 than for compound 1 based on the $Y_{12}$ values. Given the large energy gap between the excited and ground states of the PRODAN
derivatives in toluene, the addition of a single intermolecular hydrogen bond does not lower the energy gap enough to couple to a quenched state. Additionally, the emission center-of-mass, $\bar{\nu}_{\text{CM}}$, for compound 2 shifted to lower energy more so than for compound 1 upon the addition of one intermolecular hydrogen bond. The addition of a second intermolecular hydrogen bond with methanol leads to significant quenching for both compound 1 and 2. The emission center-of-mass for compound 1 shifts to lower energy; however, there is no shift of $\bar{\nu}_{\text{CM}}$ for compound 2 upon addition of a second intermolecular hydrogen bond. The results indicate that the intra-molecular hydrogen bond provided by the hydroxyl group in both compounds is more important to compound 2 than to compound 1.

In the acetonitrile/methanol studies, the first addition of an intermolecular hydrogen bond quenches compound 2 more so than compound 1. The polar acetonitrile, lowers the energy gap of the excited and ground states enough so that the first intermolecular hydrogen bond can couple with the transition to induce quenching. Additionally, the addition of the second intermolecular hydrogen bond quenches the compounds with relatively equal magnitudes. Similarly, the results indicate that the intra-molecular hydrogen bond is more important for compound 2 than for compound 1.
CHAPTER 5: CONCLUSIONS

Upon review of the fluorescence and absorbance data, it is clear that the intra-molecular hydrogen bond supplied by the internal hydroxyl group is more important for compound 2 than for compound 1. Given that the preferential solvation parameters are much larger for compound 1 than for compound 2, the external hydrogen bonds donated by the methanol are much more preferred by compound 1 than for compound 2 because compound 2 has a more prominent internal hydrogen bond already. The internal hydrogen bond of compound 2, which forms a five-membered ring, is more entropically favored than the internal hydrogen bond of compound 1, which forms a six-membered ring.

Although the hydroxyl group successfully introduces an internal hydrogen bond into the PRODAN structure, the requirement for two intermolecular hydrogen bonds to observe quenching is still observed. The internal hydrogen of the hydroxyl group forms an in-plane hydrogen bond with the carbonyl oxygen. The external hydrogen bonds donated by methanol are therefore in the out-of-plane modes. The effect may be due to an increase the rigidity caused by the internal hydrogen bond, making fluorescence a more likely pathway from the excited state to the ground state.
APPENDIX

In order to determine the concentration of species in the solvation microsphere in comparison to the bulk solvent, two spectral values were calculated: the relative quantum yield, \( Q_{\text{rel}} \), and the product of the emission center-of-mass and the relative quantum yield, \( \tilde{\nu}_{CM} \cdot Q_{\text{rel}} \). Using equation 1, the relative quantum yield was calculated using the integrated emission intensities, \( I_{\text{int}} \), the relative molar absorptivities, \( \varepsilon \), and the refractive indices, \( \eta \). Literature values of the refractive indices were used for the toluene/methanol and acetonitrile/methanol mixtures. The emission center-of-mass, \( \tilde{\nu}_{CM} \), was calculated using equation 2. Using equation 3, fractional changes in the spectral values, \( I \), were calculated. The two-step exchange model and three-step exchange model are represented by \( n = 2 \) and \( n = 3 \), respectively.

\[
Q_{\text{rel}} = \frac{I_{\text{adj}}}{(I_{\text{adj}})_{\text{max}}} \quad \text{where} \quad I_{\text{adj}} = I_{\text{int}} \cdot \frac{\varepsilon_{\text{max}} \cdot \eta^2}{\eta_{\text{min}}} \quad (1)
\]

\[
\tilde{\nu}_{CM} = \frac{\int I(\tilde{\nu}) \cdot \tilde{\nu} \, d\tilde{\nu}}{\int I(\tilde{\nu}) \, d\tilde{\nu}} = \frac{\int I(\tilde{\nu}) \cdot \tilde{\nu} \, d\tilde{\nu}}{I_{\text{int}}} \quad (2)
\]

\[
\Gamma = \frac{Y_1 - Y}{Y_1 - Y_n} \quad \text{where} \quad n = 2 \text{ or } 3 \quad (3)
\]

\[
\Gamma = \frac{Y_1 - Y}{Y_1 - Y_2} = \frac{f_{2,1} x^2 + f_{12,1} r x (1 - x)}{(1 - x)^2 + f_{2,1} x^2 + f_{12,1} x (1 - x)} \quad (4)
\]

The two-step exchange model is explained using the equilibrium constants in equation 4. The \( x \)-variable is the mole fraction of the more polar component, being methanol. The \( r \)-parameter is the ratio \( (Y_1 - Y_{12})/(Y_1 - Y_2) \) where \( Y_{12} \) is the
spectral value of the solvatochromic molecule solvated solely by S12. The $Y_1$ and $Y_2$ values represent the spectral values of the pure $I(S1)$ and $I(S2)$ species, respectively. The equilibrium constants, $f_{2/1}$ and $f_{12/1}$, are the same for spectral values, $\Gamma_{CMQ}$ and $\Gamma_Q$. Taking the difference of the two values is shown in equation 5.\textsuperscript{23}

$$\Gamma_{CMQ} - \Gamma_Q = \frac{f_{2/1} \Delta r x(1-x)}{(1-x)^2 + f_{2/1}x^2 + f_{12/1}x(1-x)}$$

where $\Delta r = r_{CMQ} - r_Q$.

The derivative with respect to the mole fraction gives a quadratic term in the numerator.\textsuperscript{23}

$$\frac{d(\Gamma_{CMQ} - \Gamma_Q)}{dx} = \frac{[x^2(1-f_{2/1})-2x+1](f_{2/1} \Delta r)}{[(1-x)^2 + f_{2/1}x^2 + f_{12/1}x(1-x)]^2}$$

(6)

Using the derivative in equation 6, the maximum value of the difference function, $\Gamma_Q - \Gamma_{CMQ}$, can be determined when the quadratic term equals zero.\textsuperscript{23}

$$x^2(1-f_{2/1})-2x+1 = 0$$

(7)

The maximum is determined by fitting six points around the maximum to a third-order polynomial, taking the derivative, setting it to zero, and solving for the mole fraction. Using the value of $x$ and rearranging the quadratic term in equation 7 determines the value of $f_{2/1}$.\textsuperscript{23}

$$f_{2/1} = \frac{1}{x^2} - \frac{2}{x} + 1$$

(8)

Using least-squares fitting for both spectral values, $\Gamma_{CMQ}$ and $\Gamma_Q$, the parameters, $f_{12/1}$ and $r$, can be determined. The relative quantum yield of the $I(S1)$ fluorophore is obtained using $r_Q$.\textsuperscript{23}
\[ Q_{12} = Q_1 (1 - r_Q) + Q_2 r_Q \]  

(9)

The emission center-of-mass for the \( l(S1) \) fluorophore is determined from \((v_{CM\star Q})_{12}\) and \(Q_{12}\).\(^{23}\)

\[ \tilde{v}_{CM(12)} = (\tilde{v}_{CM\star Q})_{12} / Q_{12} \]  

(10)
Figure 30: 3-hydroxy-N-methoxy-N,2,2-trimethylpropanamide
Figure 31: 2-hydroxy-N-methoxy-N,2-dimethylpropanamide
Figure 32: N-methoxy-3-(methoxymethoxy)-N,2,2-trimethylpropanamide
Figure 33: N-methoxy-2-(methoxymethoxy)-N,2-dimethylpropanamide
Figure 34: 1-(6-[(dimethylamino)naphthalen-2-yl]-3-hydroxy-2,2-dimethylpropan-1-one
Figure 35: 1-(6-(dimethylamino)naphthalen-2-yl)-3-hydroxy-2,2-dimethylpropan-1-one
Figure 36: 1-(6-(dimethylamino)naphthalen-2-yl)-2-hydroxy-2-methylpropan-1-one
Figure 37: 1-(6-(dimethylamino)naphthalen-2-yl)-2-hydroxy-2-methylpropan-1-one
BIBLIOGRAPHY


