Starting Materials for the Synthesis of Biradicaloid Heterocycles as
Small Chromophores for Singlet Fission

by

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A thesis submitted to the
Faculty of the Graduate School of the
University of Colorado in partial fulfillment
of the requirement for the degree of
Master of Science
Department of Chemistry and Biochemistry
2016
This thesis entitled:
Starting Materials for the Synthesis of Biradicaloid Heterocycles as Small Chromophores for Singlet Fission
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The final copy of this thesis has been examined by the signatories, and we Find that both the content and the form meet acceptable presentation standards Of scholarly work in the above mentioned discipline.
The present work is directed toward the synthesis of small chromophores capable of exhibiting singlet fission which can be utilized for application in solar cells to increase efficiency. Singlet fission is a process by which an excited chromophore shares its excitation energy with a neighboring ground state chromophore and they both are converted into triplet excited states. The chromophores under investigation are based on the structure of 2,5-diketopiperazines and their derivatives. The synthesis of 3,6-dibromo-1,4-dimethyl-2,5-diketopiperazine, which is the precursor to the desired biradicaloid species, was achieved successfully. The final reduction to give the biradicaloid species and an alternate route to get to the biradicaloid involving pyrazine derivatives were also attempted. The synthesis of derivatives with tert-butyl groups on the ring were attempted. The synthesis of 3,6-di-tertbutyl-piperazine-2,5-dione, was achieved successfully and it was fully characterized. The subsequent methylation reaction was attempted.
Acknowledgments

First and foremost, I would like to express my gratitude to Prof. Josef Michl for not only giving me a very challenging project to work on but also for his constant support and guidance.

I would also like to express my gratitude to all the past and present members of the Michl group, both at CU Boulder and at IOCB Prague, for their help and support.

A very special thanks to Jennifer Winer, an undergraduate research assistant who worked with me, for all her help with the synthesis work.

Thanks to Steven Fatur for his help with the UV-vis data and thanks to Dr. Jeremy Balsbaugh for his help with the mass spectrometry data.

Thanks to my favorite band Deep Purple, for giving me all that great music and creating the soundtrack of my life without which I would never have got through those late nights in the laboratory.

Last but not least I would like to thank my parents, family, friends, my girlfriend Michelle and her parents for their unconditional support without which none of this would have been possible.
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GLOSSARY OF TERMS

DMF - Dimethylformamide

UV - Ultraviolet

NMR - Nuclear Magnetic Resonance

THF - Tetrahydrofuran

DDQ - 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

NCS - N-chlorosuccinimide

AIBN - 2,2'-Azobis(2-methylpropionitrile)

TLC - Thin Layer Chromatography

BOC - tert-butyloxycarbonyl protecting group

HATU - 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate

LDA - Lithium diisopropylamide

MS - Mass Spectrometry

NaH - Sodium hydride

Me₂SO₄ - Dimethyl sulfate

MeOH - Methanol
CH₂Cl₂ - Dichloromethane
Br₂ - Bromine
NaHCO₃ - Sodium bicarbonate
MgSO₄ - Magnesium sulfate
CCl₄ - Carbon tetrachloride
HClO₄ - Perchloric acid
HCl - Hydrochloric Acid
K₂CO₃ - Potassium carbonate
NaOH - Sodium hydroxide
Na₂SO₄ - Sodium sulfate
DIPEA - N,N-Diisopropylethylamine
CDCl₃ - Deuterated chloroform
THF-d₈ - Deuterated tetrahydrofuran
DMSO - Dimethyl sulfoxide
D₂O - Deuterium oxide
KBr - Potassium bromide
Chapter I. Introduction

Statement of the Project

The purpose of this project was to explore the synthesis of small molecules capable of exhibiting singlet fission. These molecules would be able to find application in solar cells in order to increase their efficiency. This in turn would help solar cells compete against cheaper, yet environmentally destructive, fossil fuels.\(^3\) The proposed molecule was one on which calculations had been done and it was shown that it might be a suitable candidate for exhibiting singlet fission.\(^4\) The proposed molecule is the captodatively stabilized biradicaloid 1.\(^{4,5}\)

![Fig. 1.1 Target Molecule 1](image)

The synthesis of this target molecule was attempted using known chemical reactions. Two different routes were explored.

A structural modification was made to the above target molecule in the hopes of stabilizing it. The second target molecule is the biradicaloid species shown in Fig. 1.2. The synthesis of this target molecule was also attempted using known chemical reactions.
Methodology

Calculations had been done on target molecule 1 by computational chemists and they showed that it was capable of exhibiting singlet fission and might produce good triplet yields. The synthesis of this molecule was then designed and two routes were attempted. One was the dibromide route, which involved a three step synthesis, and the second was the dimethoxypyrazine route, which involved a five step synthesis. The starting material for both routes was the cheap commercially available reagent 2,5-diketopipereazine marketed as glycine anhydride.

No calculations were done on the target molecule 2, but was believed that its photophysics would be similar to that of 1, but that the tert-butyl groups on the ring would stabilize the radical centers and the steric bulk would prevent the biradicaloid from polymerizing. The synthesis of this target molecule was not as straightforward since there was no commercially available starting material. The substituted 2,5-diketopiperazine was not known and had to be synthesized. The starting material for this synthesis was the commercially available amino acid L-tert-leucine.
Chapter II. Background Information

Singlet Fission

Singlet fission is a spin-allowed process where an organic chromophore excited to its first excited singlet shares its excitation energy with a neighboring chromophore in its ground state, and both are converted into their triplet states. The process can be extremely rapid and takes place usually in a matter of picoseconds. The two triplets are coupled into an overall singlet and this is why the process is spin allowed. The exact details of the mechanism are not fully understood. Singlet fission is observed in molecular crystals where the two chromophores are aligned in such a way that one excited molecule can share its energy with the neighboring molecule. The process of singlet fission was first observed in 1965 during an attempt to describe the photophysics of anthracene. Subsequent studies have been done on it over the years but it has not been until recently that it became popular since it was pointed out that the phenomenon can be utilized in solar cells to increase their efficiency.

![Fig. 2.1 Process of Absorption Followed by Singlet Fission](image)

Fig. 2.1 Process of Absorption Followed by Singlet Fission
Fig. 2.1 is a diagrammatic representation of the process of singlet fission. The chromophore on the left gets excited to the first singlet state. It then undergoes singlet fission and it shares its excitation energy with the ground state chromophore on the right and they both get converted into triplet states.6

**Application in Photovoltaic Cells**

The process of singlet fission can be applied to solar cells to increase the efficiency and most of the current research in this area is directed towards this objective.6 This was proved by a quantitative study9 which indicated that the Shockley-Queisser limit12, which is 1/3 for the efficiency of an ideal photovoltaic cell, could be increased to nearly 1/2 when the cell contains a sensitizer which is capable of exhibiting singlet fission. This will happen only if the two triplets that are formed after absorbing a photon of adequate energy and become independent of each other, thereby producing separate electron-hole pairs.6 Photons of lower energy are absorbed in a second layer of an ordinary sensitizer, in which the absorption of a single photon produces one electron-hole pair.6,13 This results in an overall increase in efficiency of the photovoltaic cell.

**Choosing Suitable Candidates**

The use of sensitizers capable of exhibiting singlet fission in solar cells is a promising prospect but the problem is finding suitable candidates to do the job. Much of the current research in the area of singlet fission is directed towards finding the right molecules that meet the required criteria.
A number of photochemical processes can compete with singlet fission and depopulate the first excited singlet state, reducing the triplet yield.\textsuperscript{5} The main challenge is to try and find molecules for which the process of singlet fission is fast enough such that it can outpace all other processes, thereby generating triplets with a quantum yield of nearly 200%.\textsuperscript{5} The triplets should have a relatively long lifetime and their mutual destruction should be slow so that they can be effectively used for charge separation.\textsuperscript{5} In other words molecules where the rate of singlet fission is high and the rate of all other processes is low would be the best candidates for application in photochemical cells.\textsuperscript{5}

Singlet fission is presumed to take place from the lowest excited singlet $S_1$ because the process of internal conversion usually depopulates the higher excited singlets.\textsuperscript{4} Thus singlet fission would now have to only compete with the process of fluorescence.\textsuperscript{4} Chromophores that have a high quantum yield of fluorescence would therefore be suitable candidates.\textsuperscript{4} The other factor that has to be kept in mind is that the two lower energy triplets can combine to produce a single triplet of higher energy.\textsuperscript{4,6} This has to be somehow prevented as well.

It is very clear from the factors discussed above that in order to find suitable candidates for singlet fission, there would have to be certain energy criteria that must be met by the chromophores. The first singlet excitation energy $S_1$ should be either greater than or equal to twice the excitation energy of the first triplet $T_1$.\textsuperscript{6,13} The second triplet excitation energy $T_2$ should be higher than the first singlet excitation energy $S_1$.\textsuperscript{6,13} This would prevent lower energy triplet recombination to give the higher energy triplet because the process will not be energetically favorable.\textsuperscript{6} This gives the overall energy criteria $E(T_2) > E(S_1) \geq 2E(T_1)$.\textsuperscript{13}
A number of different chromophores have been explored and by calculation they have shown energy level positions suitable for exhibiting singlet fission. Some of these chromophores are anthracene, pentacene, tetracene, diphenyltetracene, rubrene and 1,3-diphenylisobenzofuran. There have been two problems with the search for suitable candidates for singlet fission. Firstly, there are very few chromophores that actually meet the energy criteria for exhibiting singlet fission. Secondly, most of the molecules that have shown the suitable energy levels, are very big molecules and the calculations on these chromophores have proven to be very challenging and inaccurate. The answer to this would be to find small molecules that match the energy criteria and make the calculations much more feasible. The search for small molecules capable of exhibiting singlet fission is the main focus of this project.
Chapter III. Theoretical Part

Description of the Molecule

The molecule of interest is the biradicaloid heterocycle I shown previously in Fig. 1.1. This biradicaloid heterocycle is based on the structure of 2,5-diketopiperazine, a naturally occurring cyclic dipeptide, usually formed by the condensation of two amino acids. The synthesis and properties of 2,5-diketopiperazines have been extensively studied and they have been found to have application in pharmaceuticals and drug discovery. They are small, constrained heterocycles with the distinctive feature of being able to undergo changes in functional group in up to six positions.

The biradicaloid target molecule is a captodatively stabilized biradicaloid. A captodative radical is one in which the radical is stabilized by simultaneously present neighboring electron withdrawing and electron donating groups. The electron withdrawing groups are said to be the “captor” substituents and the electron donating groups are said to be the “dative” substituents. The captodative effect is a much studied area. It is believed that the radical stability is increased kinetically and thermodynamically. The presence of these electron withdrawing and electron donating substituents increases the steric bulk around the radical center and this prevents other molecules and radicals from reacting with this center. This is the kinetic stability. The radical is thermodynamically stabilized by the substituents because they increase the delocalization of the radical through resonance. This is indicated in Fig. 1.1 where one of the resonance structures for the biradicaloid is shown.

Why This Molecule?

As indicated earlier the search for a suitable candidate for singlet fission is always of interest
and much work is being done on this. How did the search lead to this molecule?

Firstly, the molecule is small. This compact heterocycle and derivatives of it, are small enough for computational chemists to run accurate calculations and study the dynamics of singlet fission.\textsuperscript{4} This overcomes the problems they faced with bigger molecules like tetracene and 1,3-diphenylisobenzofuran.

Secondly, since studies have indicated that the previously mentioned captodative effect stabilizes monoradicals,\textsuperscript{28} the hope is that the same effect will stabilize the biradicaloid as well.\textsuperscript{4}

Thirdly, this molecule is structurally very different from the previously studied molecules. It does not represent just a small change in structure. Rather, it is inherently very different from other singlet fission candidates.\textsuperscript{4}

Lastly and most importantly, the energy levels for this molecule have been calculated and it is found that theoretically it is an excellent candidate for singlet fission.\textsuperscript{4,5}

It is an inherent property of biradicals that the $S_0$-$T_1$ gap is much smaller than the $S_0$-$S_1$ gap.\textsuperscript{29,30} This will not produce efficient singlet fission.\textsuperscript{4} The biradicals, however, can be subjected to a structural perturbation which causes the degeneracy of the two non-bonding orbitals to be removed.\textsuperscript{31,32} This converts the biradical to a biradicaloid and the $S_0$-$T_1$ gap is increased while the $T_1$-$S_1$ gap is not affected as much.\textsuperscript{4,5} When this perturbation is sufficiently strong, the important energy criteria $E(T_2) > E(S_1) \geq 2E(T_1)$, will be met.\textsuperscript{33}

The biradical is perturbed into the biradicaloid depicted in Fig. 1.1, where two captodatively stabilized radicals are joined together to make one conjugated system.\textsuperscript{4} Two radical centers were created and placed next to the electron withdrawing carbonyl group and the electron donating amine.\textsuperscript{4} The two radicals share the electron withdrawing and electron donating substituents resulting in a six
membered ring.\textsuperscript{4}

The energy levels for this molecule were calculated and it was proven that it would be a successful candidate for singlet fission theoretically.\textsuperscript{4,5} But what about practically? Many compounds with similar structures have been called betainic, named after the zwitterion betain.\textsuperscript{34-37} Various six-membered betainic rings have been found to be stable but not many organic chemists have been interested in taking on the synthesis of such molecules.\textsuperscript{4}
Chapter IV. Results

Biradicaloid Synthesis

Route 1 - The Dibromide Route

The synthesis of the biradicaloid species 1 was attempted via two routes. The first route was through the dibromide intermediate as shown in Fig. 4.1. The first step in this synthesis started with the commercially available compound known as glycine anhydride 3 and the methylation of the nitrogens was attempted using a previously published procedure, in which sodium hydride and dimethyl sulfate were used with DMF as the solvent. The reaction worked well and the pure product was obtained with a yield of 49%.

The second step in this synthesis proved to be difficult but the challenges were overcome. The bromination of compound 4 to give compound 5 was first attempted using a modification to a previously known procedure. This procedure involved heating compound 4 with bromine in o-dichlorobenzene at 150 °C for 18 hours. The resulting crude product was recrystallized with benzene but it still did not yield a pure product, but subsequent sublimation at 125 °C yielded a pure white powder. This reaction proved to be very unreliable. The reaction could not be reproduced on the same scale and under the same conditions over a period of time. The procedure was then followed exactly as published although in this procedure the compound was never isolated and it was used
directly in subsequent steps. The procedure involved adding bromine to compound 4 in o-dichlorobenzene at 150 °C under UV irradiation and stirring for 1 hour. The solution was then cooled to room temperature, flushed with argon and diluted with hexane to give a brown product. This product was purified by sublimation under the same conditions as stated previously. This reaction again worked for a while and then proved to be difficult to reproduce. The procedure was modified and instead of adding hexane, dry and distilled cyclohexane was added and the resulting precipitate was not exposed to air from then on. A filtration under argon was carried out, the product was dried under reduced pressure and then transferred to a flask in the glovebox. After purification by sublimation, the product was stored in a vial in the glovebox. This procedure proved to be very reliable, giving the pure product in a 58% yield.

A chemical reduction was subsequently attempted using a variety of reducing agents including sodium amalgam, zinc powder, magnesium powder, titanium trichloride, Rieke magnesium and Rieke zinc. These reactions were attempted in sealed NMR tubes with deuterated THF as the solvent and were monitored by NMR. There was no reaction with any of the reducing agents even at elevated temperatures, except for Rieke zinc. In the case of Rieke zinc the NMR indicated that a reaction took place. The product was subjected to analysis by 1D and 2D NMR and by mass spectrometry. The results indicated that the reaction yielded two major products and several minor products. When the reaction mixture was exposed to air, and analyzed, it showed a mixture of different products. Attempts were made to separate these mixtures using chromatography, recrystallization and gas chromatography with the hope of being able to characterize the compounds, but all attempts proved unsuccessful.

**Route 2 - The Dimethoxypyrazine Route**
The previously described dibromide route proved to be difficult and unsuccessful. The synthesis of the dibromide itself had its problems but it was the final reduction step that proved to be a failure in terms of the compound we were expecting to synthesize. An alternate route was attempted to get to the same biradicaloid species but not through the dibromide product. This route involved dimethoxypyrazine and the proposed synthesis is explained below in Fig. 4.2.

![Chemical Structure](image)

**Fig. 4.2 Dimethoxypyrazine Route to 1**

The starting material for this synthesis was compound 3 which is commercially available and marketed as glycine anhydride. 3 Was reacted with freshly prepared trimethyloxonium tetrafluoroborate in dichloromethane for 4 days at 40 °C according to a previously published procedure. The reaction yielded pure product 6 but the yield was only 30%.

Compound 6 was then converted to compound 7. Initially, a previously published procedure, which involved the use of DDQ in toluene, was used to do the aromatization reaction as shown in Fig. 4.3.
This reaction worked but the product was lost while trying to evaporate the solvent since the product is volatile. This proved to be a difficulty because very little product was recovered so an alternate route was explored.

The aromatization reaction was then tried using NCS and AIBN in carbon tetrachloride solvent as shown in Fig. 4.2 according to a previously published result. This reaction worked well and the product was recovered but the yield was only 29%.

Conversion of compound 7 to compound 8 proved to be unsuccessful. The reaction was tried using the same methylating conditions used in step 1 in Fig. 4.1, but this time only half an equivalent of methylating agent was used in order to selectively methylate only one nitrogen. This reaction did not work. The methylating agent was changed from dimethyl sulfate to methyl iodide and this seemed to work. The solvent used was DMF and it proved very difficult to remove the solvent from the reaction mixture. The solvent was changed to acetonitrile but the methylation reaction did not work again. The final conditions used were compound 7 in DMF solvent with methyl iodide and the reaction mixture was heated to 80 °C overnight. The product was seen in the NMR but the purification of the compound proved to be challenging and unsuccessful. The compound was not visible on a TLC plate even after staining with various reagents. A sublimation was tried and a gradient sublimation was also tried but both were not successful. Since a pure sample of compound 8 could not be obtained, the rest of this synthesis could not be explored.
**Substituted Biradicaloid Synthesis**

The other target molecule that was explored was a substituted biradicaloid species. It was believed that putting tert-butyl groups on the ring might stabilize the radical centers and the substituted target compound might prove to be more stable. For the previous biradicaloid species the starting material in both routes was the commercially available glycine anhydride. The problem for the tert-butyl derivative was that the starting material with the tert-butyl groups on the ring was not commercially available. This had to be synthesized.

The synthesis of 2,5-diketopiperazine and its derivatives has been extensively studied. The method that seemed to be the most viable was starting with the corresponding protected amino acids and making the dipeptide which could then be subjected to a ring closure to yield the required compound as shown in Fig. 4.4.

![Proposed Synthesis of 3,6-tertbutylpiperazine-2,5-dione](image)

Fig. 4.4 Proposed Synthesis of 3,6-tertbutylpiperazine-2,5-dione
The first step in the synthesis was to start with the commercially available amino acid L-\textit{tert}-leucine 14 and protect the carboxylic acid end and the amino end. These protected amino acids were then converted to the corresponding dipeptide.

The amino end of the molecule was easily protected using a tert-butyloxy carbonyl (BOC) protecting group. This reaction was done using a previously published procedure\textsuperscript{42} reacting the amino acid with NaOH and di-tert-butyl dicarbonate as shown in Fig. 4.5. The reaction worked really well and gave the product 11 in 90% yield. This product was an extremely stable and robust compound.

![Fig. 4.5 BOC Protection of L-\textit{tert}-leucine](image)

The carboxylic acid protection proved to be a little more challenging. First, a reaction to protect the carboxylic acid as a methyl ester was tried. This reaction seemed to work well but the product was extremely unstable and the subsequent dipeptide reaction never worked. The carboxylic acid end was then protected as a tert-butyl ester as shown in Fig. 4.6, with the hope that the compound would be a little more stable.\textsuperscript{43} This reaction worked well and the product 10 was obtained in 71% yield after protection using tert-butyl acetate.

![Fig. 4.6 Carboxylic Acid Protection of L-\textit{tert}-leucine](image)
The dipeptide was then synthesized from these two protected amino acids as shown in Fig. 4.4, using 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU) as a coupling agent.

![Dipeptide Synthesis Diagram]

**Fig. 4.7 Dipeptide Synthesis**

A previously published procedure for making similar dipeptides was followed and the reaction gave the dipeptide but with a yield of 32%. This dipeptide still had the carboxylic acid end and amino end protected. It has not been previously synthesized and therefore I characterized it fully.

The dipeptide 12 was then subjected to a ring closing reaction to give the final product. The most common method for this ring closing reaction was subjecting the compound to high heat by refluxing it in a high boiling solvent like toluene or xylene. This supposedly deprotects the dipeptide and then closes the ring. This method was not successful and it was found that the ring was not being closed. This could possibly be due to the steric of the tert-butyl groups that prevent the ring from closing.

Another procedure that involved a microwave synthesis of these 2,5-diketopiperazines was explored. The dipeptide was subjected to a microwave synthesis in water at 190 °C, 300 W power and 250 psi pressure for 10 minutes, based on a previously published procedure for synthesizing these compounds. This method had been used to synthesize 2,5-diketopiperazines with various substituents from the protected dipeptides and this was a green chemistry initiative. The tert-butyl
derivative was never synthesized before.

When this reaction was done, it was observed that after 10 minutes, a pure dipeptide was obtained as a precipitate. The cyclization had not taken place but the pure dipeptide was obtained. This pure dipeptide was then subjected to a microwave synthesis for another 10 minutes but still there was no cyclization. It was then subjected to a microwave reaction for 20 minutes under the same conditions. There was no precipitate that was observed so the solvent was evaporated to yield a white powder. The NMR of this compound showed that the desired tert-butyl compound 13 was formed with a yield of 21%. The compound was fully characterized.

Once the tert-butyl derivative was obtained the biradicaloid species was to be synthesized via the dibromide, as shown in Fig. 4.7.

![Proposed Synthesis of Substituted Biradicaloid 2](image)

Fig. 4.8 Proposed Synthesis of Substituted Biradicaloid 2

The first step in this synthesis, methylating the nitrogens in compound 13, was not successful.
This methylation reaction proved to be very difficult compared with the previous methylation of the glycine anhydride, and it did not work. A number of methylating agents were used in order to accomplish this methylation including dimethyl sulfate, methyl iodide, methyl triflate and trimethyloxonium tetrafluoroborate. The base used in all these cases was sodium hydride. These reactions were tried in different solvents including DMF and acetonitrile and under different conditions including room temperature and at elevated temperatures. The reaction was also tried using LDA as a base to deprotonate the nitrogen. This was a failure because the LDA was deprotonating the nitrogen as well as the ring. This methylation reaction never worked and the subsequent bromination could not even be attempted.
Biradicaloid Synthesis

Route 1 - The Dibromide Route

This route proved to be very challenging and the results indicate that the target compound 1 is not stable under ambient conditions.

The first step in the synthesis shown in Fig. 4.1 worked well and it was a reliable reaction. Compound 4 has been synthesized before and the same procedure was followed. The synthesis of the dibromide compound 5 proved to be difficult and many modifications had to be made. Compound 5 has been synthesized before but it was immediately used for a subsequent reaction and therefore it was not fully characterized. It has now been synthesized and fully characterized. The protocol for the initial procedure, which was a modification of the one published, was developed by a postdoctoral scholar in our laboratory. This procedure worked initially but it could not be reproduced, especially in the summer. Various attempts were made to make it work, including distilling the bromine reagent, changing the reaction conditions, and using fresh dry solvent, but none of these measures helped. The procedure was then followed exactly as published and this was unreliable as well. Finally, reaction conditions were found that proved to be reliable and this is due to the fact that the entire synthesis, isolation and purification was done under anhydrous conditions.

The struggles with this synthesis could be attributed to the product itself which was difficult to work with. It was suspected that this product was sensitive to light so it was always stored away from light. More importantly, the product was sensitive to air or humidity. This was first observed when the reaction was done and after purification by sublimation, the product was recovered. The first attempt was with exposure to air and while trying to scrape the product off the cold finger with
a spatula, it was decomposing and turning into a red paste. This problem was overcome by recovering the compound in the glovebox and not exposing it to air or humidity. A teflon coated spatula was also used in place of the regular spatula to avoid contact with a metal surface. The synthesis as published\textsuperscript{39} used hexane to help in precipitating out the desired product. This proved to be unreliable, too, and only when hexane was substituted with dry and distilled cyclohexane, did this synthesis prove to be successful and reproducible. All this goes to show that dibromide product 5 is sensitive to air or humidity and it decomposes even with the smallest exposure to air. Hence it was always stored in the glovebox after purification.

The conversion of compound 5 to compound 1 has been attempted in multiple ways, but always failed. Samples of compound 5 were sent to an electrochemist Dr. Lubomir Pospíšil at the Czech Academy of Sciences in Prague to discover the specific reduction conditions required to convert compound 5 into the required biradicaloid species 1. Once these conditions were discovered, a large scale chemical reduction could be attempted. The electrochemical experiments proved unsuccessful in that the required product was not obtained, although another product was obtained. This was suspected to be a result of a replacement of both bromine atoms with hydroxyl groups, but it was not fully characterized and proven. A chemical reduction was anyway attempted by me, but it was not found to be successful.

The reduction with Rieke zinc seems to be the only one that showed product formation, but it is not clear what exactly is happening. The NMR data and the mass spectrometry data never matched. Mass spectrometric analysis indicates that the biradicaloid species might have been formed and then it immediately converted to dimers, trimers and higher oligomers. One of the possible structures indicated by the mass data could be the dimer shown in Fig. 5.1.
The NMR data do not indicate this product. They indicate two major products and some other minor components. The NMR and MS data could differ because of exposure to air. The product is presumed to be air sensitive. Therefore it could not be proven but it is a possibility. This might indicate that the biradicaloid target molecule 1 might be formed, but due to instability might be polymerizing.

**Route 2 - The Dimethoxypyrazine Route**

The dimethoxypyrazine route was explored as an alternative to the dibromide route since the latter resulted in minimal success and the dibromide compound 5 was not easy to handle. However, the dimethoxypyrazine route proved to be far less successful.

One of the problems faced with the synthetic steps in this route were the low yields encountered. The syntheses of both compounds 6 and 7 were difficult because of the low yields of 30% and 29%, respectively. Both these compounds have been previously synthesized. These low yields could be due to the fact that trimethyloxonium tetrafluoroborate is not very soluble in dichloromethane and it was found that triethyloxonium tetrafluoroborate works better. Compound 7 is not readily available commercially and it is expensive. The other problem with the reactions were that they never worked well when scaled up to even 0.1 mole. This proved to be a problem since they had to be synthesized in smaller amounts. This was a challenge that could be faced but
the main problem was the synthesis of compound 8.

The synthesis of compound 8 was partially successful in the sense that the reaction was working and the product was visible in the NMR but the purification of this compound was not successful. The purification was attempted on very small quantities since the yields of the previous reactions were low and this could be a reason why no success could be found in the purification of compound 8.

It is not known whether the subsequent step of methylating the second nitrogen would have worked. This seems improbable because there is a higher chance of the oxygen getting methylated and reverting back to compound 7. But this could not be explored because the synthesis and purification of compound 8 were not successful.

**Substituted Biradicaloid Synthesis**

The synthesis of this substituted biradicaloid species 2 was attempted and was partially successful. The synthetic route utilized L-tert-leucine as a starting compound in the synthesis of the substituted 2,5-diketopiperazine.

The protection of the amine end of this amino acid was successful and it resulted in compound 11. The protection of the carboxylic acid end to give compound 10 was also achieved successfully. The synthesis of both compounds 11 and 10 have been achieved previously. The coupling of these two compounds to give the dipeptide 12 was also achieved without much difficulty. Compound 12 is new and has not been previously synthesized. The problems were faced with the microwave synthesis of compound 13.

This synthesis proved to be challenging and many difficulties were faced even though the
desired compound was obtained. Compound 13 is new and has not been previously synthesized. The main problem was that the compound was not obtained in good yield. The yield was only about 21%, with the rest being decomposed starting material. This presented an obstacle when trying to use the compound for subsequent steps. This low yield could be attributed to the fact that the bulky t-butyl groups prevent effective cyclization. This is why the cyclization was not working with heat. The microwave synthesis was definitely cyclizing the dipeptide but it was still not effective enough. The other problem faced was the solubility of the compound. This compound was not very soluble in many solvents other than water. It was partially soluble in acetonitrile and a little more soluble in THF, but none of these solvents worked as well as water. Another problem with this synthesis was the inability to scale it up. It was found that only using about 0.145 g of the dipeptide in the microwave reaction, would work. The reaction never worked on a larger scale. This proved to be a very big difficulty.

The methylation reaction of compound 13 was also attempted using various conditions but the reaction was not successful. The reason for the failure of this reaction could be that the bulky tert-butyl groups were preventing the methylation of the nitrogen from taking place. It looked more probable that a smaller methylating agent like methyl iodide would work better, but this was not the case. This reaction was attempted a number of times and under many different conditions but it always gave negative results.
Chapter VI. Conclusions

This project on the synthesis of small molecules capable of exhibiting singlet fission was found to be very challenging. There were some parts of it which were successful and new compounds were synthesized and characterized but there were some parts of it which were not successful. The desired target compound proved to be very difficult to obtain but some of the precursors to the target compound were obtained.

The intended captodatively stabilized biradicaloid $1$ was approached via two different routes and both routes were only partially successful. In the dibromide route the precursor to the biradicaloid, which was the dibromide compound, was synthesized, isolated, and characterized. The subsequent reduction to give the biradicaloid was not successful. The dimethoxyopyrazine route was less successful and the synthesis of the biradicaloid was not achieved.

The synthesis of the biradicaloid with the tert-butyl groups $2$ was also attempted and was only partially successful. The tert-butyl derivative was synthesized and fully characterized but less success was seen with the methylation of this compound. Therefore the subsequent steps to give the final biradicaloid species could not be attempted.
Chapter VII. Experimental Part

Compounds 4, 6, 7, 10 and 11 are known and were synthesized using previously published procedures.\textsuperscript{38,40-43} Compound 5 has been previously synthesized but it was immediately utilized for a subsequent reaction and it was not fully characterized.\textsuperscript{39} It has been synthesized and fully characterized. Compounds 12 and 13 are new. They have been synthesized using previously published procedures that were employed for the synthesis of similar derivatives\textsuperscript{44,45} and have been fully characterized. Compounds 5, 12 and 13 could not be dried completely and still contain some solvent. The elemental analysis fits with the appropriate amount of solvent as indicated.

1,4-Dimethylpiperazine-2,5-dione (4). Compound 4 was synthesized according to a previously published procedure.\textsuperscript{38} A suspension of glycine anhydride 3 (2.502 g, 0.0219 mol) in DMF (40 mL), was cooled to 0 °C. NaH (60% suspension in mineral oil) (2.3 g, 0.0548 mol) was added in small portions and the reaction mixture was allowed to stir for 15 min. Then, MeSO\textsubscript{4} (4.2 mL, 0.046 mol) was added dropwise with stirring. The reaction was warmed to room temperature and stirred overnight. MeOH (10 mL) was added and the solvent was removed under reduced pressure. The precipitate was suspended in CH\textsubscript{2}Cl\textsubscript{2} (50 mL) and stirred vigorously overnight. The solid was filtered and washed with CH\textsubscript{2}Cl\textsubscript{2} (10 mL). The filtrate was collected and the solvent was removed under reduced pressure. Recrystallization from 1:1 mixture of CH\textsubscript{2}Cl\textsubscript{2}/ether yielded the product 4 as large colorless needles (1.54 g, 49%). \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): δ 2.99 (s, 6H, CH\textsubscript{3}), 3.99 (s, 4H, CH\textsubscript{2}). The NMR agrees with the published results.\textsuperscript{38}

3,6-Dibromo-1,4-dimethylpiperazine-2,5-dione (5).\textsuperscript{39} 1,4-Dimethylpiperazine-2,5-dione 4 (0.284 g, 0.002 mol) was taken in o-dichlorobenzene (2 mL) and heated to 150 °C. Br\textsubscript{2} (0.22 mL, 0.0022 mol) in o-dichlorobenzene (1 mL) was added dropwise under UV irradiation. The solution was
heated for 1 h and then cooled to room temperature. Ar gas was bubbled through for 10 min and the reaction mixture was diluted with dry and distilled cyclohexane (25 mL) to give a dark brown product. The crude product was filtered under argon and left to dry under vacuum overnight. The crude product was then purified by sublimation overnight at a temperature of 125 °C to give a white powder (5) which was stored in a vial under argon (0.35 g, 58%). Mp: 148.7-151.8 °C. 1H NMR (300 MHz, THF-<i>d</i>8): δ 3.01 (s, 6H, CH<sub>3</sub>), 6.45 (s, 2H, CH). 13C NMR (300 MHz, THF-<i>d</i>8): δ 33.12, 63.18, 162.44. IR (KBr): 2996, 1685, 1447, 1402, 1316, 1260, 1022, 735 cm<sup>-1</sup>. HRMS (ESI+) m/z: [M + Li]<sup>+</sup> Calcd for C<sub>4</sub>H<sub>6</sub>Br<sub>2</sub>N<sub>2</sub>O<sub>2</sub>Li, 303.9092; Found 303.9104. UV-vis (CH<sub>2</sub>Cl<sub>2</sub>) <i>λ</i><sub>max</sub> (ε): 37.3 × 10<sup>5</sup> cm<sup>-1</sup> (6.8 × 10<sup>3</sup> M<sup>-1</sup> cm<sup>-1</sup>). Anal. Calcd for C<sub>6</sub>H<sub>5</sub>Br<sub>2</sub>N<sub>2</sub>O<sub>2</sub> + 0.06 C<sub>6</sub>H<sub>12</sub>: C, 25.05; H, 2.88; N, 9.23. Found: C, 25.31; H, 3.07; N, 9.62.

2,5-Dihydro-3,6-dimethoxypyrazine (6). Compound 6 was synthesized according to a previously published procedure. A dry schlenck tube was charged with glycine anhydride 3 (1.141 g, 0.010 mol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL). Trimethyloxonium tetrafluoroborate (4.44 g, 0.030 mol) was added in a glovebox. The reaction mixture was stirred at 40 °C for 4 days. The reaction mixture was cooled to room temperature and a saturated NaHCO<sub>3</sub> solution (100 mL) was added carefully. The organic layer was separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 x 50 mL). The organic layers were combined and dried over MgSO<sub>4</sub>, filtered and the solvent was removed under reduced pressure (20 °C/15 torr) to give a pure light brown product 6 (0.426 g, 30%). 1H NMR (300 MHz, CDCl<sub>3</sub>): δ 3.71 (s, 6H, OCH<sub>3</sub>), 4.06 (s, 4H, 2- and 5-H). The NMR agrees with the published results.

2,5-Dimethoxypyrazine (7). Compound 7 was synthesized according to a previously published procedure. Dihydrodimethoxypyrazine 6 (0.71 g, 0.005 mol), NCS (0.73 g, 0.0055 mol) and AIBN
(0.01 g, 0.061 mol) were taken in CCl₄ (25 mL) and slowly refluxed at 80 °C for 12 h. The reaction mixture was cooled to room temperature and the solid succinamide was filtered off and washed with CCl₄ (5 mL). The filtrates were collected and the solvent was removed under reduced pressure keeping the water bath cold and pressure low, to yield pure yellowish crystals 7 (0.20 g, 29%). ¹H NMR (300 MHz, CDCl₃): δ 3.92 (s, 6H, OCH₃), 7.78 (s, 2H, Ar-H). The NMR agrees with the published results.⁴¹

**L-tert-Leucine tert-butyl ester (10).** Compound 10 was synthesized according to a previously published procedure.⁴³ L-tert-leucine 14 (1.5 g, 0.01 mol) was dissolved in tert-butyl acetate (30 mL) at 0 °C. HClO₄ (1.51 g, 1.0 ml, 0.015 mol) was added dropwise with constant stirring. The reaction mixture was warmed up to room temperature and stirred for 48 h. The organic phase was washed with water (50 mL) and 1M HCl (30 mL). The aqueous phases were combined and K₂CO₃ solution was added to it till it reached a pH of 9. The aqueous phase was extracted with CH₂Cl₂ (3 x 40 mL), and combined with the previous organic phase. The solvent was removed under reduced pressure keeping the water bath at room temperature to yield a yellow oil. The product was purified by flash column chromatography using ethyl acetate:heptanes (1:1) as the eluent to give a colorless liquid 10 (1.33 g, 71%). ¹H NMR (300 MHz, CDCl₃): δ 0.97 (s, 9H, CH₃), 1.47 (s, 9H, CH₃), 1.92 (d, J = 5.2 Hz, 2H, NH₂), 3.03 (s, 1H, CH). The NMR agrees with the published results.⁴³

**L-tert-Butoxycarbonyl-tert-leucine (11).** Compound 11 was synthesized according to a previously published procedure.⁴² L-tert-leucine 14 (2 g, 0.015 mol) and 1 M NaOH solution (15 mL), were taken in MeOH (15 mL) at 0 °C. Di-tert-butyl dicarbonate (4 g, 0.018 mol) was added under constant stirring. The reaction mixture was warmed to room temperature and stirred for 18 h. Most of the methanol was evaporated and the solution was acidified to pH 2 with 1 M HCl and extracted with
ethyl acetate (3 x 40 mL). The organic layer was washed with brine (2 x 10 mL) and dried over Na₂SO₄. The organic layer was filtered and the solvent evaporated to give a sticky oil. The product was left overnight to form a solid. The solid was dried completely and crushed with a mortar and pestle to give 11 as a white powder (3.12 g, 90%). ¹H NMR (300 MHz, DMSO): δ 0.93 (s, 9H, CH₃), 1.38 (s, 9H, CH₃), 3.75 (d, J = 9.0 Hz, 1H, NH), 6.81 (d, J = 9.0 Hz, 1H, CH), 12.42 (s, 1H, COOH). The NMR agrees with the published results.⁴²

_L-tert-Leucine, N-[(1,1-dimethylethoxy)carbonyl]-L-tert-leucyltertbutyl ester (12).⁴⁴_ L-tert-Leucine tert-butyl ester 10 (0.44 g, 0.002 mol), L-tert-Butoxycarbonyl-tert-leucine 11 (0.54 g, 0.002 mol) and N,N-Diisopropylethylamine (DIPEA) (0.62 g, 0.84 mL, 0.005 mol) were taken in DMF (12 mL) at 0 ºC. 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU) (0.89 g, 0.002 mol) was added under constant stirring. The reaction mixture was brought to room temperature and stirred for 3 h. Ethyl acetate (36 mL) was added and the organic layer was washed with 0.5 N HCl (18 mL), saturated sodium bicarbonate solution (18 mL), water (18 mL) and brine (18 mL). The combined organic layers were dried over MgSO₄ and the solvent was filtered and removed under reduced pressure to yield a yellow product. The product was suspended in water (10 mL) in a microwave reactor and heated at 190 ºC under 150 psi pressure and 300 W power for 10 min, to give 12 as a pure light yellow product (0.26 g, 32%). Mp: 150.2-153.7 ºC. ¹H NMR (300 MHz, CDCl₃): δ 0.97 (d, J = 5.3 Hz, 18H, CH₃), 1.43 (d, J = 9.7 Hz, 18H, CH₃), 3.84 (d, J = 9.4 Hz, 1H, NH), 4.28 (d, J = 9.2 Hz, 1H, NH), 5.25 (d, J = 9.3 Hz, 1H, CH), 6.20 (d, J = 9.0 Hz, 1H, CH). ¹³C NMR (300 MHz, CDCl₃): δ 26.68, 26.73, 28.14, 28.42, 34.65, 34.95, 60.74, 62.84, 79.84, 82.15, 156.01, 170.30, 170.88. IR (KBr): 3365, 3327, 2966, 1733, 1711, 1711, 1651, 1521, 1242, 1152 cm⁻¹. HRMS (ESI+) m/z: [M + H]⁺ Calcd for C₂₁H₄₀N₂O₄H 401.3015; Found
3,6-Di-tert-butylpiperazine-2,5-dione (13). L-tert-Leucine, N-[(1,1-dimethylethoxy)carbonyl]-L-tert-leucyl-tert-butyl ester 12 (0.145 g, 0.0004 mol) was suspended in water (10 mL) in a microwave reactor and subjected to microwaves at 190 °C under 150 psi pressure and 300 W power for 20 min. The solvent was removed under reduced pressure to give 13 as a pure very light yellow solid (0.017 g, 21%). Mp: 134.9-137.8 °C. $^1$H NMR (300 MHz, D$_2$O): $\delta$ 1.01 (d, $J$ = 28.3 Hz, 18H, CH$_3$), 3.97 (d, $J$ = 65.1 Hz, 2H, CH). $^{13}$C NMR (300 MHz, D$_2$O): $\delta$ 25.57, 26.18, 33.21, 61.58, 167.69. IR (KBr): 3283, 2962, 1651, 1514, 1480, 1372, 1234 cm$^{-1}$. HRMS (ESI$^+$) m/z: [M + H]$^+$ Calcd for C$_{21}$H$_{40}$N$_2$O$_5$H 227.1759; Found 227.1758. UV-vis (H$_2$O) $\nu_{\text{max}}$ ($\varepsilon$): 46.7 × 10$^3$ cm$^{-1}$ (2.8 × 10$^3$ M$^{-1}$ cm$^{-1}$). Anal. Calcd for C$_{12}$H$_{22}$N$_2$O$_2$ + 1.2H$_2$O: C, 58.13; H, 9.92; N, 11.30. Found: C, 57.84; H, 9.81; N, 11.33.
Chapter VIII. Further Considerations

Although this project provided mixed results, there are some positive aspects to consider and these results can help in the modification of the target molecules going forward.

Firstly, the reduction step in the dibromide route to get to the captodatively stabilized biradicaloid can be explored further. The reduction with Rieke zinc appeared to be yielding some results that may have indicated that the biradicaloid was being formed but it was oligomerizing. If a method can be developed to capture the biradicaloid, then this might prove to be the way out. Other reducing agents can also be explored.

Secondly, the dimethoxypyrazine route to the biradicaloid maybe modified to give better results. Diethoxypyrazine could be used instead of dimethoxypyrazine. It has been noted that the synthesis of dihydrodiethoxypyrazine which is the precursor to diethoxypyrazine, is a better reaction with a yield of nearly four times more.\textsuperscript{41} This is due to the fact that the methylating agent, triethyloxonium tetrafluoroborate, is much more soluble in dichloromethane and therefore the yield is better.\textsuperscript{41} It is not known if subsequent steps will work but this is an avenue worth pursuing.

Lastly, the substituted biradicaloid synthesis can also be modified. The use of isopropyl and maybe even phenyl groups on the ring, might help in the methylation of the substituted 2,5-diketopiperazine. The isopropyl groups being smaller than the tert-butyl groups, might not hinder the methylation reaction as much. This is another area that might be worth exploring in the future.
Bibliography


Appendix

Compound 5 - $^1$H NMR / THF-$d_8$
Compound 5 - $^{13}$C NMR / THF-$d_8$

- $-162.44$
- $-67.57$ Tetrahydrofuran-$d_8$
- $-63.18$
- $-33.12$
Compound 5 - HRMS (ESI+)
Compound 5 - IR / KBr
Compound 12 - $^1$H NMR / CDCl$_3$
Compound 12 - ¹³C NMR / CDCl₃
Compound 12 - HRMS (ESI+)
Compound 12 - IR / KBr

Transmittance

Wavenumber (cm⁻¹)

4000
3500
3000
2500
2000
1800
1500
1000
500

50 60 70 80 90 100
Compound 13 - $^1$H NMR / D$_2$O

- 4.08
- 3.86
- 1.06
- 0.97

$\sim$ 4.79 Deuterium Oxide
Compound 13 - $^{13}$C NMR / D$_2$O

Chemical shifts:

-167.69
-61.58
33.22
33.19
26.18
25.57
Compound 13 - HRMS (ESI+)
Compound 13 - IR / KBr