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Shedding Light on Diradical Forming Cyclizations and Cycloaromatizations
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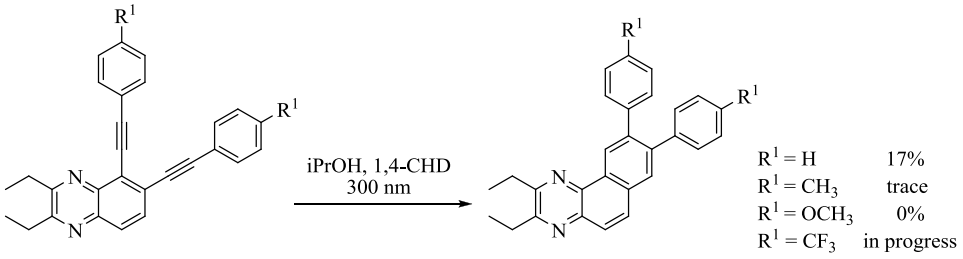
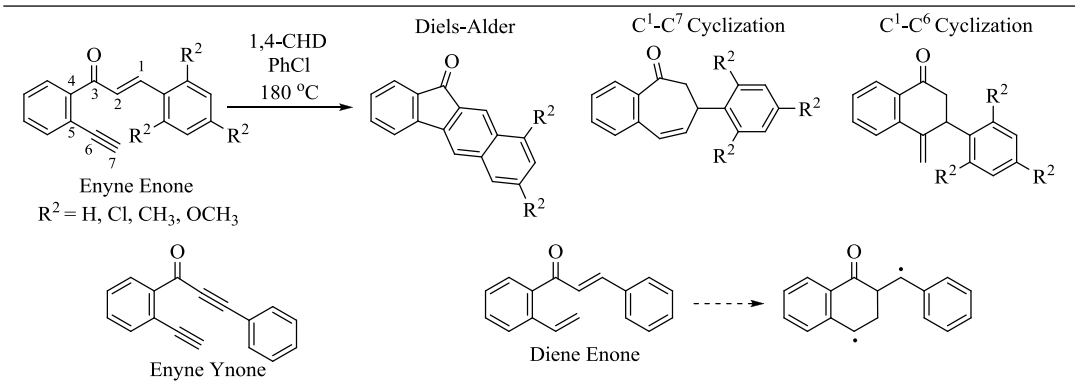
Goals:
Thermal and photochemical Bergman and related cyclizations of (Z)-hexa-3-ene-1,5-diynes, or enediynes, have a wide range of applications from DNA cleaving agents to materials chemistry while related radical producing cyclizations are known to occur under fuel rich combustion and have been used as a synthetic tool to prepare a diverse array of polycyclic aromatic hydrocarbons. Our group is currently exploring two areas of Bergman and related diradical cyclizations in effort to better understand factors that control these reactions. In the first project we have developed synthetic methodology to prepare isomeric quinoxalenediynes to examine the effect of linear versus angular extended benzannelation on enediyne reactivity. In a second project we are exploring the potential for new diradical cyclizations from polyunsaturated systems related to enediynes and enyne-allenes. During the term of this grant, we have developed multiple synthetic routes to prepare highly conjugated enediyne and related chromophores to examine their thermal and/or photochemical reactivity.

Research Progress:
In the third year of this grant we have explored substituent effects on the photo-Bergman cyclization of our quinoxalenediyne model system (Scheme 1). We previously reported the successful photo-Bergman cyclization of 2,3-diethyl-5,6-bis(phenylethynyl)quinoxaline to 2,3-diethyl-8,9-diphenylbenzo[*f*]quinoxaline in 17% yield. This represents a modest improvement in yield compared to the parent 1,2-bis(phenylethynyl)benzene which we attributed to the increased gain of aromatic stabilization energy as a new aromatic sextet is produced. In effort to further optimize photo-Bergman cyclization we have examined the effect of phenylethynyl substituents on photocyclization yields of the angular quinoxalenediyne derivative. Curiously, electron donating groups were found to hinder photo-Bergman cyclization as *p*-methylphenyl substituents show only trace product formation by NMR/GCMS while *p*-methoxyphenyl groups led to no observable product formation. The exact nature of how these electron donating groups hinder photo-Bergman cyclization of the quinoxalenediyne is currently under investigation experimentally as well as computationally. These studies include preparation of the related *p*-trifluoromethylphenyl derivative to examine the effect of electron withdrawing substituents on the phenylethynyl group. In addition, we have prepared the related mono-phenylethynyl derivative (2,3-diethyl-6-ethynyl-5-phenylethynylquinoxaline) and found it to also undergo successful photo-Bergman cyclization upon irradiation at 300 nm. Optimization of the mono-substituted derivative cyclization yield, synthetic preparation of the isomeric 2,3-diethyl-5-ethynyl-6-phenylethynylquinoxaline, and the effect of phenylethynyl substituents on these mono-substituted derivatives are currently in progress. Finally, to probe the role of the nitrogen atom on the photocyclization yields we have also prepared and examined the related 1,2-bis(phenylethynyl)naphthalene and the 1,2-bis(4-methoxyphenylethynyl)naphthalene derivatives. Upon irradiation at 300 nm, however, neither of the naphthyl derivatives produced photocyclization products. Studies are ongoing to examine what role the nitrogen atoms of the quinoxaline core play in facilitating photo-Bergman cyclization, including the potential for photoelectron transfer from the nitrogen atom to the enediyne pi-system. Overall, while these studies indicate extended angular benzannelation can lead to improved photo-Bergman cyclization yields supporting our computational data, other factors that influence photocyclization including alkyne substituent effects and the role of the nitrogen atom in quinoxalenediynes have arisen that are currently under investigation in our laboratory.



Scheme 1. Photo-Bergman cyclization of 5,6-bis(phenylethynyl)quinoxalines

In a second major goal of the grant we explored the potential of new polyunsaturated substrates to undergo diradical forming cyclizations. We previously reported the cyclization of a phenyl substituted enyne-enone that undergoes an intramolecular dehydro Diels-Alder cyclization/dehydrogenation sequence along with two diradical cyclization reactions to produce the C^1-C^7 and C^1-C^6 products (R = H, Scheme 2). In an effort to hinder the competing Diels-Alder cyclization product we prepared a series of substituted enyne-enone derivatives to examine thermal reactivity. While introduction of a single *para*-substituent (OCH_3, Cl, NO_2) had little effect on the product distribution, incorporation of 2,4,6-trisubstituted aryl substituents was successful in preventing the competing Diels-Alder cyclization; however, no C^1-C^7 or C^1-C^6 products were observed for these substrates. While the original proposal also included a plan to investigate the related enyne-ynone derivative, as an alternative substrate we have prepared the related diene-enone derivative illustrated in Scheme 2 and are currently investigating thermal reactivity this fall. While the diene-enone may also undergo a competing Diels-Alder cyclization, an alternative C^2-C^7 cyclization in the presence of 1,4-cyclohexadiene can lead to a diradical intermediate in which each radical center is stabilized by resonance with an adjacent aromatic ring. We are currently examining this reactivity, along with substituent effects and computational analysis of the various reaction pathways.



Scheme 2. Thermal cyclization of phenyl substituted enyne-enone and related enyne-ynone and diene-enone

Impact on Undergraduates: Through the term of this grant 17 undergraduate chemistry majors have been involved in this research program, with an additional 5 undergraduate students conducting computational studies of these compounds in the Gherman research group, with each student working an average of 3 semesters/summers. From these 22 undergraduate students, a total of 28 off campus research presentations have been given (including 9 at National ACS meetings) with 5 students listed as co-authors on peer reviewed publications and an additional 5 student co-authors listed on manuscripts currently in preparation. From this group of students, 2 are currently in PhD chemistry programs, 1 is currently in an MS chemistry program, 1 is currently applying to chemistry graduate programs, 4 are employed in local chemistry related industry, 7 are currently in or are applying to medical/nursing/pharmacy/dental programs and 4 students are currently continuing with undergraduate research. For these students, participation in research provides a valuable learning experience that cannot be matched in the classroom, which has made them more attractive candidates for employment, graduate and professional schools, and participation in summer research would not be possible without support from this grant. In particular, the two students currently in PhD chemistry programs (UT Austin and UC Davis) had no intention of applying to or attending graduate school in chemistry prior to participating in research.

Impact on PI's Career: Funds from this grant have helped the PI maintain a strong tradition of undergraduate research where involving students in research is a primary mission of the department and college. During the term of the grant, the PI has received a number of small campus grants to supplement funding that has provided academic year release time, additional funding for supplies, and additional summer salary for students. In addition, the PI received a department teaching award in which working with undergraduate students in the research laboratory was a major component. Having the only active ACS-PRF grant in the department has benefited the PI and made him more competitive for these internal awards. In addition, the current grant has strengthened the collaboration with Prof. Ben Gherman (physical chemist in department) who has conducted computational studies on our models. We currently plan to submit an NIH R15 joint proposal based on the results from this grant in the near future. Finally, the PI was listed as a key collaborator on a funded NSF-MRI grant that brought an HPLC-MS research instrument to the department.