

Fluorescent Molecular Thermometers Based on Monomer/Exciplex Interconversion

Nirmala Chandrasekharan and Lisa Kelly
University of Maryland, Baltimore County

Introduction

Material-based sensors have attracted an enormous amount of recent interest. Biological and chemical sensors are being rapidly developed to offer sensitivity and specificity for the analyte of choice. Far less attention has been devoted to developing new materials as sensors of fundamental thermodynamic properties, such as temperature. In this article, we will: (i) provide an introduction to the kinds of chemical systems that have utility as fluorescent temperature sensors; (ii) discuss perspectives on applications of such materials and (iii) present some of our recent developments in this area.

In sensor applications, fluorescence is frequently the observable of choice. Very sensitive detectors in the visible spectral region are widely available.¹ Since the fluorescence intensity is measured against a dark background, it is substantially more sensitive than transmittance or color changes. The sensors can be used for remote temperature monitoring, and the intensity can be quantitatively related to the physical property. Broad-ranging applications are found in the medical and industrial arenas.² A temperature-sensitive material, coated on the tip of an optical fiber, would provide a flexible and rapid temperature probe for surgical applications. In addition, fluorescence-based temperature sensors have been used to monitor the processing of polymers.^{3,4}

The applications described above generally require the measurement of temperature at a single point. However, applications in aerodynamics and hydrodynamics require the measurement of global, two-dimensional maps of pressure and temperature distributions. Conventional methods use thermocouples, thermistors or resistance thermometers. In these sensors, measurement is accomplished by means of electrical signals that are generated and converted to temperature.⁵ In many applications, it is essential to obtain temperature data by non-electrical means. For example, when temperature distribution over large areas is to be measured, machining an array of thermocouple taps is impractical and expensive. Moreover, temperature-dependent electrical signals will be altered in environments where large electric or magnetic fields are present or where corrosion of thermocouple junctions will occur. In these cases, conventional approaches to temperature measurement require the sensor and electrical leads to be physically connected to the object being probed. As a result, it has become important to explore new approaches to the measurement of temperature. In this context, there has been a great deal of interest during the past decade in new strategies to measure temperature non-intrusively and remotely and map surface temperature distributions of objects.

Driven largely by the need for these new diagnostic measurements in wind tunnel testing, advances in digital imaging technology and new, luminescent materials have received considerable attention from scientists and engineers. In these applications, it is critical to map two-dimensional pressure and temperature distributions to investigate frictional heating and dynamics during fluid or gaseous flow. The object is coated, illuminated, and imaged to provide a real-time temperature map of the surface. The approach represents an extremely cost-effective alternative to mapping

Continued on page 3

From the Executive Director

D. C. Neckers, Executive Director, Center for Photochemical Sciences, Bowling Green State University

Southern Illinois University (SIU) is located in Carbondale about 60 miles north of the tip of the state at Cairo and about 25 miles east of the Mississippi River. The area is filled with abandoned coal mines and Tennessee Valley Authority lakes. Southern Illinois is quite poor and less touched by contemporary America than its more sophisticated counterparts on the West Coast and the East Coast. It is truly rural America. The nearest airport is in St. Louis nearly 2 1/2 hours to the northwest.

SIU chemistry celebrated my Uncle Jim Neckers' 100th birthday with a symposium in his honor on October 4, 2002. Jim Neckers earned a Ph.D. at the University of Illinois in inorganic chemistry in 1927 where he knew Wallace Caruthers, watched Red Grange, and learned chemistry. He was appointed as an assistant professor of chemistry at Southern Illinois Normal School the day after he received his Ph.D. degree. He moved to Carbondale where he still lives today.

Southern Illinois, when he arrived, had 1,500 undergraduate students and offered one four-year degree, a bachelor's degree in education. Jim Neckers was the second faculty member appointed who held a Ph.D. degree. In 1929 he was appointed chair of the department of chemistry, a position he held until 1965. When he retired from active teaching in 1968, SIU offered all of the degrees in chemistry including the Ph.D. degree. By this time SIU was a comprehensive university with about 25,000 students at two geographically separated campuses.

All of the symposium speakers and attendees except for me were alumni, chemistry majors with B.S., M.S., and Ph.D. degrees. They included corporation presidents, deans, distinguished professors, and former presidents of the American Chemical Society. All grew up in the region immediately near Carbondale, and all had the same story. They studied at SIU because it was the only place they could afford. They took advantage of various work-study programs to pay tuition. When they started school, most had never heard of chemistry, let alone advanced degrees in chemistry. Some of them had to be convinced that a graduate education was a good investment of their time. Jim Neckers and his three colleagues who comprised the chemistry department from 1930 to 1946 and later other members of the faculty encouraged these bright young people to continue their studies. SIU provided the opportunity; Jim Neckers and his colleagues provided the mentoring, the academic rigor, and the discipline. The result was that young people became all they could be, and more, because of the opportunities higher education provided.

As I sat at the banquet in my Uncle's honor (he gave a speech, incidentally, at 100.5 years of age), I thought about good teaching in chemistry, and the many, many other persons who, like Jim Neckers, provided opportunities to bright, hard-working young persons by opening doors. Good teachers are rigorous and demanding, but they also mentor, guide, and assist. A good teacher often has more confidence in a young person's ability than that young person has in his/her own. Every SIU alumni who spoke that day had a story, but in every case, the institution unlocked their own inner abilities. Education opened vistas of opportunity.

These SIU chemistry alumni were exceptional people. They loved science, loved learning, loved research, and worked hard. Good and motivated students plus dedicated professors make a combination hard to beat. I'm impressed with SIU and the exceptional contributions of my Uncle to help create what it is today.

Now it's up to another generation to keep it that way.

In This Issue

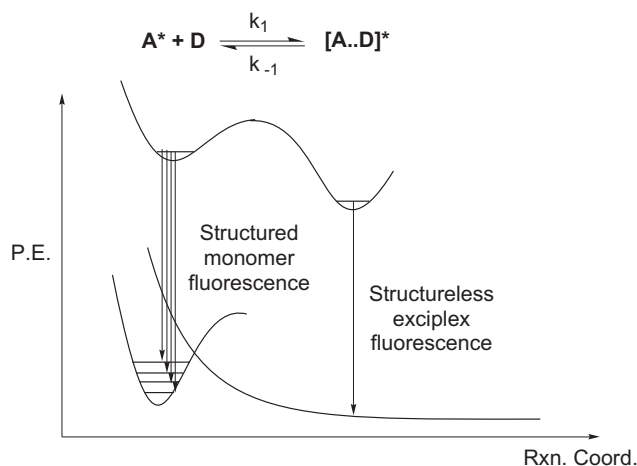
Fluorescent Molecular Thermometers Based on Monomer/Exciplex Interconversion	1
From the Executive Director	2
Photocyclization	8
Photochemistry of Some Heteroaromatic Compounds	15
Center for Photochemical Sciences Publications	23

Continued from page 1

these parameters with arrays of conventional temperature or pressure sensors. In addition, the spatial resolution is inherently limited by the camera used to obtain the image, not by how many sensors are machined into the surface.

In this context, we turn to fundamental photophysics. During the past decade, the mapping of pressure and temperature distributions has been accomplished by incorporating chromophores into an oxygen-permeable binder as reporters of pressure and temperature. For example, the luminescent metal-to-ligand charge transfer (MLCT) state of ruthenium (II) complexes has been widely employed.^{6,7} Since the lifetime of these excited states is quenched by oxygen in a Stern-Volmer fashion, the luminescence intensity is a direct reporter of oxygen partial pressure on the coated surface. In a similar way, the quantum yield for luminescence is well-known to be temperature dependent. Thus, at constant pressure, the intensity has utility to map temperature distribution on a surface.⁸ Likewise, porphyrin compounds possessing long-lived and luminescent excited states have been used in an equivalent way in temperature and pressure sensitive coatings.⁹ In short, these examples illustrate how elementary photophysics has great utility in developing new coating and sensor technology.

In considering luminescence as an experimental “reporter” of temperature, virtually any fluorescent system that we learn about in a first-semester photophysics course will work! Fluorescence quantum yield represents the competition between the radiative and non-radiative deactivation of an excited state, and thus is temperature dependent. Several classes of “two-component” systems involve a temperature-dependent equilibrium. For example, the temperature-dependent high-spin / low-spin interconversion of a nickel (II) macrocycle covalently attached to a fluorophore has been shown to have utility as a “molecular thermometer” in fluid solution.¹⁰ The endothermic high-spin \rightarrow low-spin equilibrium is shifted towards the low-spin form of the transition metal complex as the temperature is increased. The naphthalene “reports” the temperature increase as an enhancement in the luminescence quantum yield. In other words, the sensor “lights up” as it is heated.



Scheme I. Reaction coordinate for exciplex formation and decay.

As another textbook example, it is well-established that the excited state of aromatic hydrocarbons form excited state dimers (excimers) or excited state complexes (exciplexes) with their ground states or appropriate electron donors in solution. Under steady-state illumination, the amount of broad-structureless excimer or exciplex emission, relative to the vibronically structured “monomer” emission depends on temperature, since both the forward and reverse (k_1 , k_{-1}) reactions are activated processes (Scheme I). As a temperature sensor, this system has an important advantage: The fluorescence is two-color. As a consequence, the temperature may be measured as the ratio of the two emissions. The measurement will be independent of illumination intensity (e.g. calibrations for different sources will be unnecessary) and, more importantly, any real-time fluctuations or drift in illumination intensity will be normalized out. This eliminates a problematic source of noise in mapping the temperature distribution during the time course of a test.

Exciplex Formation in Polymeric Coatings

During the past year, we have been exploring the phenomenon of exciplex formation in polymeric coatings, for temperature mapping applications. The temperature dependence of the excited state dimer or complex formation, as well as the decay kinetics, is well understood in solution.¹¹ Thus, the concept was deemed to have utility in preparing temperature sensitive fluorescent coatings. In this report, we present some of our results that demonstrate how these coatings are synthesized and characterized, and discuss how the temperature sensitivity may be optimized and quantified.

To date, we have investigated the temperature dependence of a polymeric film in which perylene is encapsulated into a synthetic co-polymer of styrene and one of two polymerizable aniline derivatives (**An-I** and **An-II** shown in

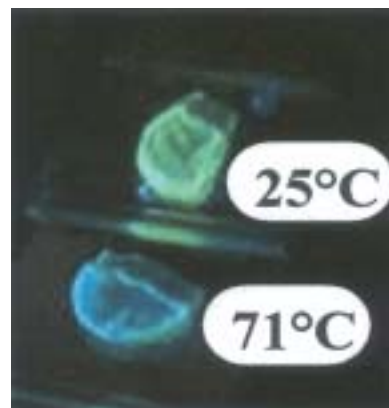
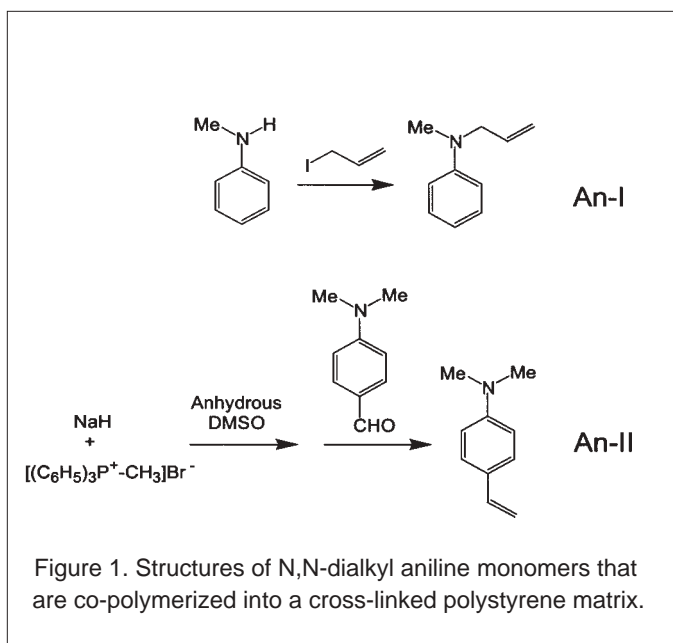
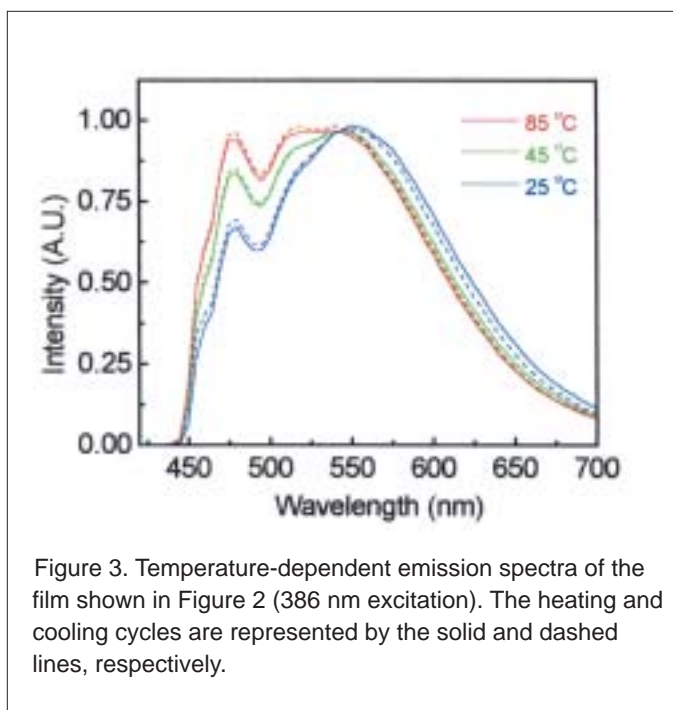


Figure 2. Fluorescence observed from a co-polymer film prepared from styrene and N-allyl-N-methylaniline (**An-I**) at indicated temperatures upon UV irradiation.

Figure 1). Upon UV excitation of the perylene, thermodynamics favors exciplex formation with the aniline derivative. The exciplex is stabilized by partial electron transfer from the lone electron pair on the aniline nitrogen to the partially vacant pi molecular orbital of the perylene excited state.

Our initial materials were prepared by free-radical polymerization of the monomer **An-I** with styrene.¹² Since the polymer films were found to melt in the temperature range of interest, the materials were cross-linked with divinylbenzene to provide structural and thermal rigidity in the matrix. To prepare the material, a monomer solution containing 18.96 wt % of N-allyl-N-methyl-aniline (**An-I**), 55.94 wt % styrene, and 0.017 wt % perylene was co-polymerized with 5.63 wt % divinylbenzene (cross-linker), 19.27 wt % methylsalicylate (plasticizer) and 0.2 wt % AIBN as the initiator. The mixture was deaerated and heated in an oil bath at 80 °C for one hour. In these materials, there are, on average, 3.4 styrene units per aniline. As seen in Figure 2, the sample fluoresces green at room temperature when illuminated with a UV handlamp. When the sample is heated, the fluorescence becomes predominantly blue. When we first made this observation, the green to blue reversible fluorescence change that accompanied sample heating/cooling was found to be intense enough to be visually discernable.



When we first made this observation, the green to blue reversible fluorescence change that accompanied sample heating/cooling was found to be intense enough to be visually discernable.

To quantify and verify the response, we use steady-state fluorescence spectroscopy. The results on the first system we have studied are shown in Figure 3. On controlled heating of the film, the intensity of the bands at 463 nm and 475 nm increases. An isoemissive point at 543 nm is observed. A concomitant intensity decrease in the long-wavelength region of the spectrum is observed. The temperature response of the material, defined as the percent change in the ratio of blue/green intensity, was found to be 1% per °C. A temperature change of 2 °C could be detected with the spectrometer and scan rate used.

More recently, we have used a different aniline derivative anchored in our co-polymer: p-dimethylaminostyrene (**An-II**) was co-polymerized with styrene and cross-linker. Preparation of the aniline derivative was adapted from a published report¹³ using the Wittig reaction shown in Figure 1. This monomer is expected to have a reactivity ratio

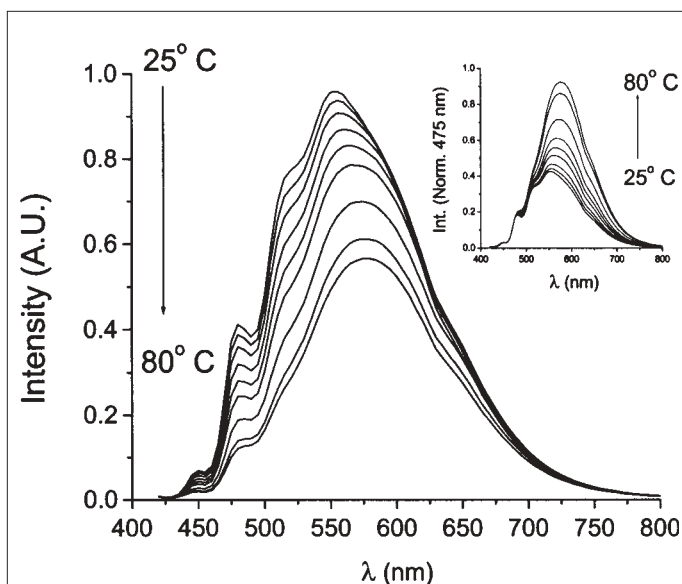


Figure 4. Temperature-dependent emission spectra of the material prepared from p-dimethylaminostyrene (**An-II**) and styrene (see composition in the text). Spectra normalized to 475 nm are shown in the inset. 410 nm excitation was used.

elasticity of the polymer, the materials are non-responsive to changes in temperature. We attribute this observation to the need for some diffusion or reorganization prior to exciplex formation.

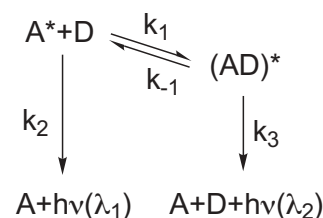
The temperature-dependent fluorescence spectra of this material are shown in Figure 4. In contrast to the first system we investigated, the temperature dependence of this material shows several distinct differences: (i) the emission maximum of the exciplex is significantly red-shifted compared to the spectra shown in Figure 3; (ii) the exciplex emission intensity, relative to the monomer fluorescence, increases with increasing temperature, and no isoemissive point is observed; (iii) the temperature sensitivity, defined as the change in ratiometric response vs. temperature, is substantially improved. The temperature response of the material, defined as the percent change in the ratio of green/blue intensity, was found to be 6%/°C, substantially larger than that described above. With this modification, a temperature change of 0.5 °C can be readily detected.

Interpreting the Temperature Response

From the results described above, we have characterized two closely related systems as prospective temperature-sensitive coatings. The current generation of these materials turns out to be very robust, in that they can be repeatedly exposed to heat/cool cycles and provide identical ratiometric response. In addition, the materials show no sign of degradation with time. To date, we have developed fluorescent materials that exhibit a monomer/exciplex ratiometric fluorescence of 6%/°C. Thus, these materials are ideal for quantifying small temperature variations across a 2D surface.

To understand our results, we turn to the simple kinetic scheme for exciplex formation and decay shown in Scheme II. There are two regimes in which a change in the excimer/monomer intensity ratio will exhibit a temperature dependence.

Case I. If the equilibrium shown in Scheme II is fast ($k_1, k_{-1} \gg k_2, k_3$), we expect the interconversion of A^* to $(AD)^*$ to be modeled simply by the thermal population of the upper state (A^*). In this model, the ratio of luminescences corresponding to each state will be fitted to the van't Hoff equation (eq 1).



Scheme II. Kinetic scheme for exciplex formation and decay.

that is more similar to styrene than **An-I** and be more readily incorporated into the polystyrene backbone. We anticipated that the temperature-dependent exciplex formation would exhibit behavior similar to that described above. However, the differences were quite pronounced.

As in the material described above, perylene was encapsulated in the co-polymer and the temperature response was investigated. We have investigated in detail the effect of polymer composition on the temperature response, but present results from the material that shows the highest magnitude temperature response. To prepare the material, a monomer solution containing 20.8 wt % of p-dimethylaminostyrene (**An-II**), 39.4 wt % styrene, and 0.039 wt % perylene was co-polymerized with 2.0 wt % divinylbenzene (cross-linker), 37.6 wt % dibutylphthalate (plasticizer) and 0.14 wt % AIBN as the initiator. The mixture was deaerated and heated in an oil bath at 72 °C for one hour, with continued heating at 60 °C for 24 hours to complete the polymerization. In this material, there are, on average, 2.2 styrene units per aniline. We have noted that, in the absence of a plasticizer to allow for some

$$\ln \left[\frac{\left(\frac{I_{(AD^*)}}{I_{A^*}} \right)_{T_2}}{\left(\frac{I_{(AD^*)}}{I_{A^*}} \right)_{T_1}} \right] = \frac{-\Delta H}{R} \left(\frac{1}{T_2} - \frac{1}{T_1} \right) \quad (1)$$

In eq (1), the intensities (I), represent the fluorescence quantum yield of monomer (A^*) and exciplex (AD^*) and are experimentally obtained from the steady-state spectra at T_1 and T_2 . Since exciplex formation is enthalpically downhill ($\Delta H < 0$), the equation predicts that the slope of eq (1) will be positive.

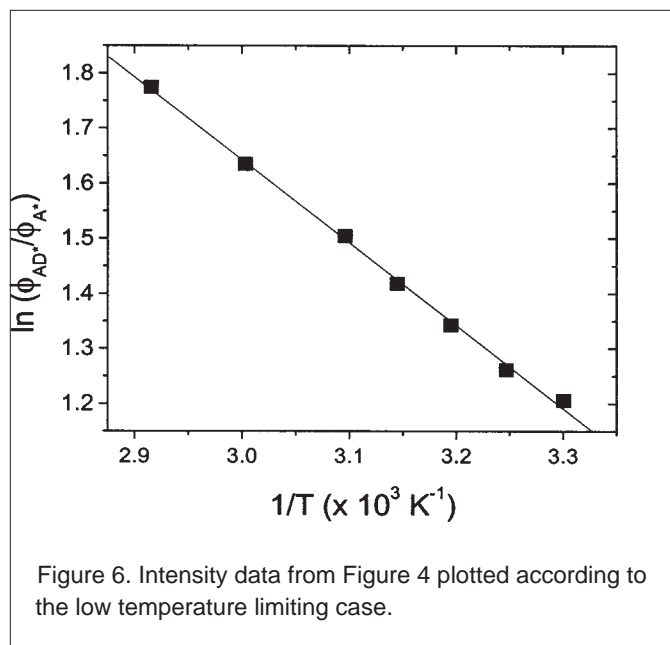
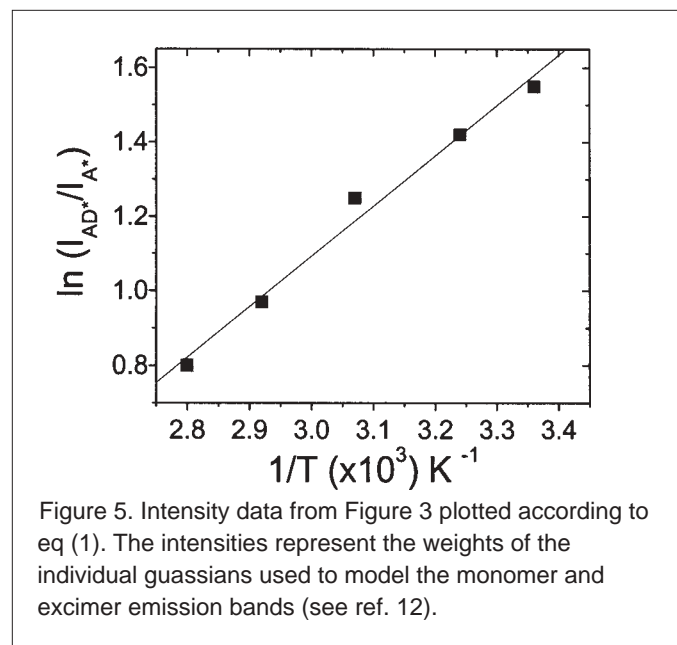
From the spectra shown in Figure 3, it is clear that the equilibrium depicted in Scheme 1 is shifted towards the monomer as the temperature is increased. The isoemissive point is evidence for the simple two-state model shown in Scheme 1. We attribute this to thermal population of A^* on the excited state potential energy surface. This represents the high temperature regime, where the monomer/exciplex equilibrium is rapidly established relative to deactivation of either species. The ratios of these intensities were plotted logarithmically as a function of reciprocal temperature, according to the van't Hoff equation (Figure 5). From the slope of the line, the enthalpy of exciplex (AD^*) formation was determined ($\Delta H = -2.6 \pm 0.2$ kcal/mole). No temperature dependence is observed in the fluorescence spectrum of a polystyrene film containing only perylene.

Case II. If repopulation of the monomer excited state (k_{-1} in Scheme II) is slow, we expect the interconversion of A^* to (AD^*) to be modeled as an activated process. In this case, the exciplex population (and thus intensity) is expected to increase with temperature. This is exactly what is observed in our materials that exhibit the most sensitive temperature response.

From the classic treatment of this model presented by Birks, it can be readily shown that the ratio of excimer to dimer fluorescence intensities is given by the Arrhenius model in eq (2).

$$\frac{I_{AD^*}}{I_{A^*}} \propto \exp\left(\frac{-E_A}{RT}\right) \quad (2)$$

In eq (2), the activation energy for exciplex formation from the perylene excited state (E_A) may be obtained. Shown in Figure 6 are the data extracted from the spectra shown in Figure 4. The data fit the model well, and an activation energy for exciplex formation of 3.0 kcal/mole is obtained.



The above treatments illustrate how the results of simple steady-state measurements can be interpreted to extract estimates of kinetic and thermodynamic parameters within fluorescent films. Time-resolved measurements, including anisotropy measurements, are currently underway to provide a more detailed understanding of diffusional vs. static excimer formation within the materials.

Prospects for Future Sensors

In conclusion, there continue to be endless opportunities to design sensors, both chemical and physical, using elementary principles of photophysics. Coupling these principles with material science opens new avenues for sensors of physical properties such as temperature. We must simply capitalize on what is well understood in solution, and couple it to material science. From our initial pursuits, it is clear that "what is well-understood in solution" does not hold true when the phenomena are studied in synthetic materials (e.g., Why do the two categories of materials discussed in this article exhibit strikingly different temperature dependences?). Clearly, there is a great deal of fundamental understanding that needs to be gained in studying these materials. At the same time, practical and functional materials can be developed for sensor applications.

References

1. Collins, S. F.; Baxter, G. W.; Wade, S. A.; Grattan, K. T. V.; Zhang, Z. Y.; Palmer, A. W. *J. Appl. Phys.* **1998**, *84*, 4649-4654.
2. Fernicola, V. C.; Zhang, Z. Y.; Grattan, K. T. V. *Rev. Sci. Instrum.* **1997**, *68*, 2418-2421.
3. Bur, A. J.; Vangel, M. G.; Roth, S. C. *Polym. Eng. Sci.* **2001**, *41*, 1380-1389.
4. Bur, A. J.; Roth, S. C. *Antec* **2001**, 3071-3075.
5. Childs, P. R. N.; Greenwood, J. R.; Long, C. A. *Rev. Sci. Instrum.* **2000**, *71*, 2959-2978.
6. Shen, Y.; Bedlek-Anslow, J. M.; Hubner, J. P.; Carroll, B. F.; Ifju, P. G.; Schanze, K. S. *Polym. Prepr.* **2002**, *43*, 69-70.
7. Hai-Feng, J.; Shen, Y.; Hubner, J. P.; Carroll, B. F.; Schmehl, R. H.; Simon, J. A.; Schanze, K. *Appl. Spectrosc.* **2000**, *54*, 856-863.
8. http://www.aero.ufl.edu/~bfc/html/psp_tsp.htm
9. Gouterman, M. *J. Chem. Educ.* **1997**, *74*, 697.
10. Engeser, M.; Fabbrizzi, L.; M. L.; Sacchi, D. *Chem. Commun.* **1999**, 1191-1192.
11. Birks, J. B.; Lumb, M. D.; Munro, I. H. *Proc. R. Soc. London, Ser. A* **1964**, *280*, 289-297.
12. Chandrasekharan, N.; Kelly, L. A. *J. Am. Chem. Soc.* **2001**, *124*, 1988-1999.
13. Iida, T.; Itaya, T. *Tetrahedron* **1993**, *49*, 10511-10530.

About the Authors

Nirmala Chandrasekharan completed her Ph.D. in 1994 at the Indian Institute of Science, Bangalore, India, in the area of magnetic materials. She is currently a Research Associate in the Department of Chemistry and Biochemistry at the University of Maryland, Baltimore County. The focus of her work is luminescent polymeric materials as molecular pressure transducers and thermosensors.

Lisa Kelly obtained a M.S. degree at the University of Rochester, then went on to complete her Ph.D. in the Center for Photochemical Sciences at Bowling Green University under the direction of Prof. Michael A. J. Rodgers. After completion of her Ph.D. in 1993, she obtained a Department of Energy Distinguished Post-Doctoral Fellowship to work at the National Synchrotron Light Source and Biology Department at Brookhaven National Laboratory. She started as a tenure-track faculty member at the University of Maryland, Baltimore County, in 1996 and was recently promoted to the rank of Associate Professor. Besides her research interests in the area of fluorescent sensors, she is interested in developing photoactivated synthetic systems to probe DNA and protein structure, combining the fields of synthetic chemistry, fast spectroscopy, and biophysical chemistry. Dr. Kelly's address is Department of Chemistry and Biochemistry, University of Maryland, Baltimore County, 1000 Hilltop Circle, Baltimore, MD 21250; e-mail: lkelly@umbc.edu.

Photocyclization

Steven A. Fleming and Susan C. Ward, Brigham Young University,
Can Mao, Boehringer Ingelheim, and Ephraim E. Parent, University of Illinois

Introduction

There are many examples of organic photochemical ring forming reactions in the literature. Most have been summarized in reviews or recent works that describe the synthetic utility of the methodology. These photocyclizations include: 2+2,¹ 3+2,² 4+2,³ 4+4,⁴ carbene insertions,⁵ nitrene insertions,⁶ meta-photocycloaddition,⁷ Paterno-Buchi photocycloaddition,⁸ di- π -methane reactions,⁹ electrocycloaddition,¹⁰ photo-Bergman cyclization,¹¹ enone rearrangement,¹² dienone rearrangement,¹³ excited pyrone trapping,¹⁴ excited pyridinium trapping,¹⁵ and ynone trapping.¹⁶ Photochemical radical pathways that have been employed for cyclizations include: Yang cyclization,¹⁷ Norrish Type I,¹⁸ enone hydrogen abstraction,¹⁹ alkene hydrogen abstraction, alkyl halogen homolytic cleavage,²⁰ pseudo-halogen homolytic bond cleavage,²¹ homolytic allylic²² or benzyl bond cleavage,²³ and radical cation-radical anion photochemistry.²⁴ Probably the most frequently employed approach for cyclization in synthetic methodology is the 2+2 reaction. The 2+2 photocycloaddition has been observed between alkenes and excited enones, excited aromatic rings, or excited alkenes.

Photocycloaddition between an alkene and an excited alkene is a difficult procedure. Usually the obstacle is a function of the photophysics of the alkene. Alkenes are: 1) typically poor chromophores and 2) short-lived excited states. Thus the excited state can be difficult to reach and would likely decay to ground-state before colliding with another alkene. Therefore, the classical 2+2 that one might expect from a Woodward-Hoffman perspective between two alkenes is not common. For example, there are few reports of the stereochemical outcome for singlet alkene + alkene photocycloaddition. Symmetry rules, of course, predict that this is a stereospecific reaction.

There are several techniques that can enhance the yield of alkene photocycloadditions. An obvious choice that leads to improvement is use of an aryl substituted alkene as the chromophore. The extended π system of a styrene or stilbene moiety allows for a more accessible photoexcited state. Alternatively, sensitization of the alkene can circumvent the difficulty of exciting an alkene. This also can result in formation of a longer lived triplet excited state, or one can improve the reliability of the cyclization by employing a tether between the reacting alkenes. Another approach is use of solid state photochemistry, particularly in crystal structures that are well defined. In this report we will describe our results from direct irradiation of tethered alkenes.

Tethered 2+2 Photocycloaddition

Stereocontrol of the 2+2 photocycloaddition has been an attractive goal for a number of reasons. First, the reaction offers an efficient pathway to small ring synthesis. The cyclobutane ring can be expanded, contracted, or opened. Control of this carbon-carbon bond forming process allows formation of four contiguous stereocenters in one reaction, not an easy process to duplicate with enolate chemistry or other typical carbon-carbon bond forming reactions.

Second, investigation of the regio- and stereochemical outcome of the cyclization process allows for a better understanding of the mechanistic pathway the reaction takes. The reaction is studied not only for synthetic exploitation, but for basic understanding of the photochemical process.

A third reason for our interest in the 2+2 is that it allows for a logical analysis of orbital symmetry arguments. Few photochemical reactions are as predictable as the thermal Diels-Alder reaction, but the 2+2 photocycloaddition is a good starting point for comparison.

Regio- and stereocontrol of the photochemical 2+2 has been demonstrated by tethering the chromophore to trapping reagents such as alkenes, dienes, or alkynes. This methodology allows for conformational control which can translate into regio- and stereocontrol of the cyclization. Tethering also circumvents the problem of a short-lived excited state. There is increased likelihood of collision between the excited alkene and the trapping alkene when they are tethered. There is literature support for π stacking between alkenes that are within 5 Å which could also improve

the chromophore. The pi systems may be able to stabilize the ground state by stacking and thereby lend rigidity to the tethered groups.

A related method for enhancing the regio- and stereocontrol of this photochemical process includes using substituent stabilization to affect the orientation of the appended groups and, as a result, the photoselectivity. As mentioned above, irradiation in the solid-state also lends control of cycloaddition. The types of photoreactions that have been investigated using these techniques are numerous.²⁵

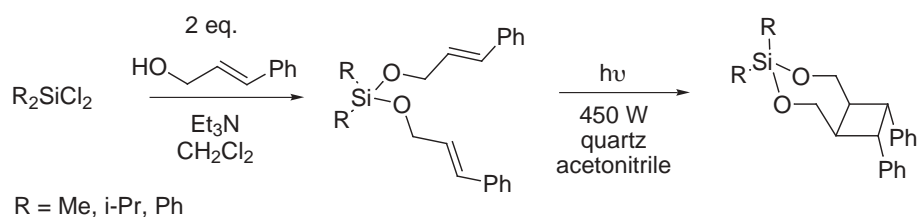
One drawback related to covalent tethering of reagents is that a robust tether can be difficult to remove. Tethers which have been employed in cycloaddition reactions include sugar alcohols such as D-mannitol and L-erythritol,²⁶ diazacrown ethers,²⁷ cyclophanes,²⁸ and silanes.²⁹ Cu(I),³⁰ and magnesium have been useful as non-covalent tethers although an organometallic process is undoubtedly involved in the examples that use copper. Of the covalent tethers, removal of the silane linked by oxygen has shown promise for synthetic utility.

In most studies, the tether preorganized alkenes yield head-to-head adducts. This propensity is best explained by ground state conformations and ring size geometry in most cases, although electronic control has not been ruled out. Dipole interactions, such as hydrogen bonding, have been effective in preorganizing adducts.

Our Work Using Tethered Alkenes

Our work with tethered alkene photochemistry began ten years ago. The first attempt was using titanium as a covalent linker for cinnamic acids. This approach was abandoned due to the difficulty associated with removing the metal linker. We also had evidence of excited-state quenching by the titanium. We turned to lithium coordination of

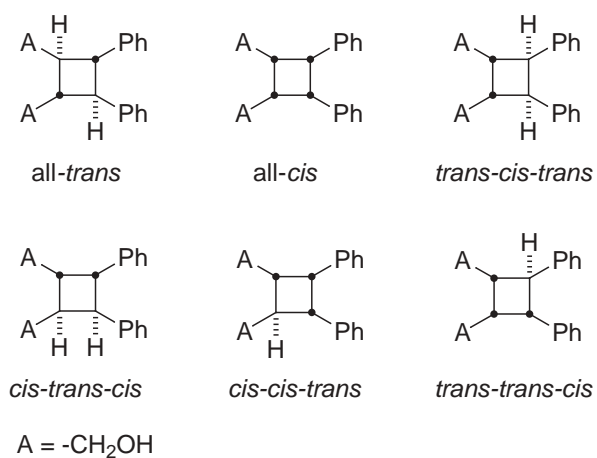
alcohol substituted alkenes, but struggled with the obvious solubility problems related to lithium alkoxides. Fortunately, we turned to silicon tethering next. The synthesis of dicinnamyloxydimethylsilane was straightforward and its irradiation gave a single cyclobutane diastereomer (see Scheme 1). Dicinnamyloxydiphenylsilane



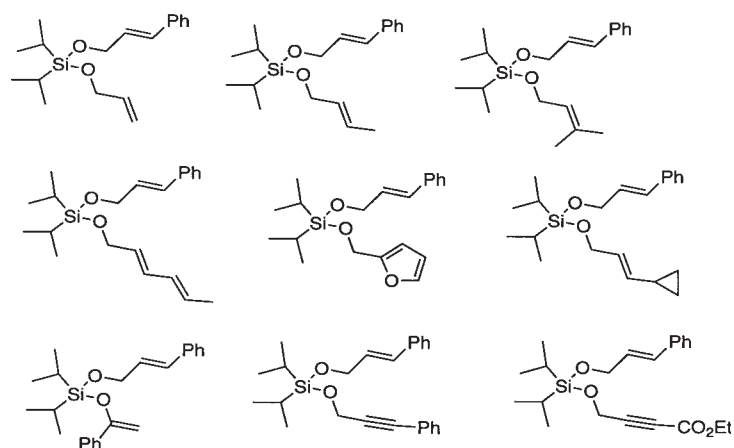
Scheme 1

(Scheme 1, R = Ph) and dicinnamyloxydiisopropylsilane (R = iPr) were also successful in their photocycloaddition. Each gave a high yield of a single diastereomeric photoadduct.

In our effort to identify the photoadduct, we were able to rule out head-to-tail dimers due to the proton coupling data. The potential head-to-head products for this photocycloaddition following removal of the silyl tether are shown in Scheme 2. The symmetry of the spectral data for the observed hydrolyzed product was consistent with the all-*trans*, the all-*cis*, the *cis-trans-cis*, and the *trans-cis-trans* isomeric diols. We felt that it was unlikely a *cis* relationship would preferentially form between the methylene group and the phenyl group since they were initially *trans*. In fact, we later found that the *cis*-cinnamyl group does not undergo efficient photocycloaddition. That left only the all-*trans* and the *trans-cis-trans* dimers. We initially assigned the all-*trans* structure based on the fact that it was the lowest energy species.³¹ Caldwell also reported a stereoselective [2+2] photocycloaddition where the major product was the most thermodynamically stable cyclobutane product with the two aryl groups *trans* to each other predominating, although not the exclusive product.³² But in our case, we were able to chemically relate the silyl tethered photo-product to the truxinic acid photodimer obtained from cinnamic acid which established the *trans-cis-trans* as the product.



Scheme 2

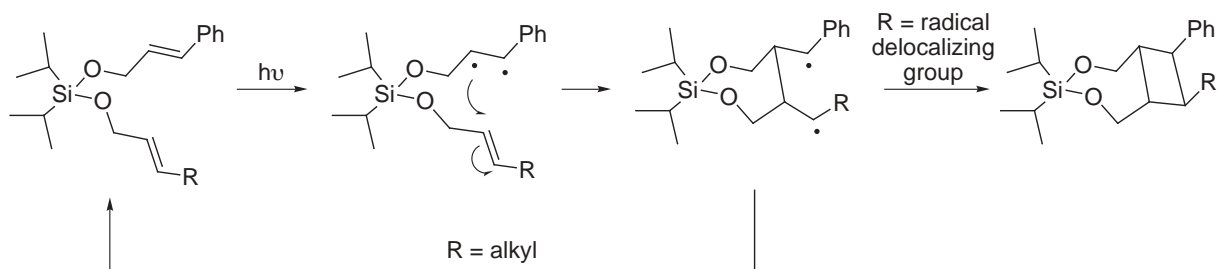


Scheme 3

substituted alkene resulted in *cis-trans* isomerization of the cinnamyl group or hydrogen-abstraction products (see Scheme 4) from the excited cinnamyl group. Although there may be some utility in this carbon-carbon bond forming process, it was not a result that we wanted to explore further at the time. We attempted sensitization and addition of copper I, but no 2+2 photocycloaddition was observed.

This places a limit on the utility of our silicon tethered alkene-alkene photocycloaddition process, however mechanistic inferences can be made based on the results. One possible conclusion is that the alkene-alkene 2+2 reaction is a stepwise process that proceeds forward only if the incipient radicals are both stabilized (see Scheme 5). This certainly is the case for triplet photochemistry where the diradical intermediate has a long lifetime, sufficient to allow for bond rotation and arrival at the more stable conformation prior to bond formation.

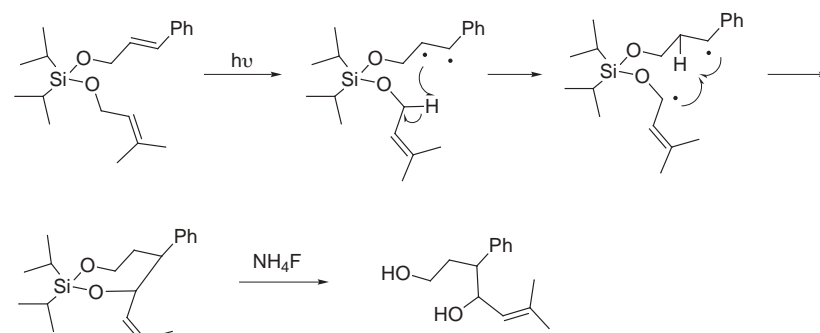
Another possibility is that the extended π system allows for conformational control in the ground or excited state. This would be a π stacking phenomenon. Interestingly, the radical stabilization reaction pathway (the stepwise process) would produce the more stable all-*trans* photoproduct. However, the observed cyclobutane products all resulted from intermediates whose conformations allow for the maximum possible π -overlap between the two ligands, thereby producing the *cis*-diphenyl ring systems. A similar effect is seen in the reaction of tethered alkenyl-substituted phenanthrenes reported by Nishimura.³³ These results support the idea that π -stacking plays an important role in the preorganization of the reactants.



Scheme 5

The use of diisopropylsilyl ether as a tethering reagent was essential for this project because doing so allowed us to append dissimilar alcohols onto the silicon. A variety of dialkenyloxysilanes were prepared (see Scheme 3), where one of the alkenyloxy groups in each case was cinnamyl, which has a styrenyl group to serve as the chromophore. Irradiation of those compounds that had radical-stabilizing π systems resulted in cyclobutane formation in good to excellent yields with single diastereomers being formed in each case. Diastereomer assignments were based on comparison to the cinnamyl photodimer.

Irradiation of the styrenyl group appended to an unsubstituted or a simple alkyl

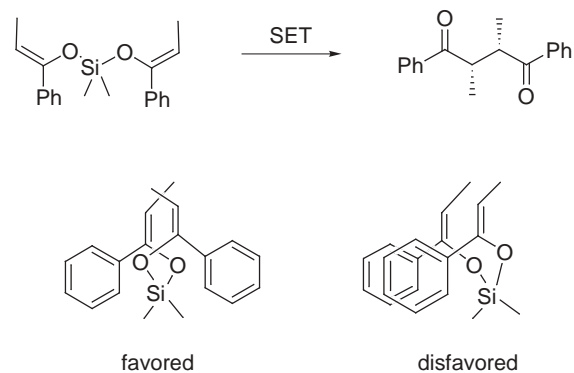


Scheme 4

A final explanation that should be considered is that the alkyl substituted alkenes are simply too sterically hindered to allow for cyclization. It was been suggested that with trisubstituted alkenes no cycloaddition occurs due to the crowding.³⁴ Perhaps the same problem occurs with our alkyl alkenes. This would not explain the lack of cycloaddition for the monosubstituted alkene.

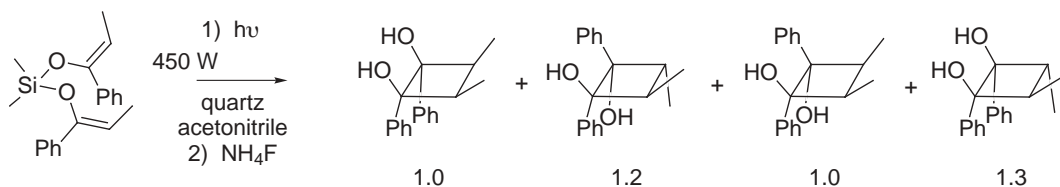
Our results compare well with cyclophane studies³⁵ and an interesting amine tethered study which have both been shown to undergo 2+2 cycloaddition with high stereoselectivity attributed to steric interactions in the triplet biradical intermediate.

A silicon tethered system was recently described which undergoes carbon-carbon bond formation when converted to a radical cation (see Scheme 6).³⁶ The authors justified the diastereoselectivity for the reaction by arguing that the "bulk of the phenyl groups repel each other" as the carbon-carbon bond is formed. We felt that stereochemical analysis of the cyclobutane(s) formed from the irradiation of this silyl tethered diene would answer our mechanistic questions. If the reaction is stepwise and the phenyl groups sterically repel each other, then the major 2+2 product should have the phenyl groups *trans* to each other on the ring. If there is π stacking in the excited state, then the 2+2 should form the *cis*-diphenylcyclobutane preferentially.

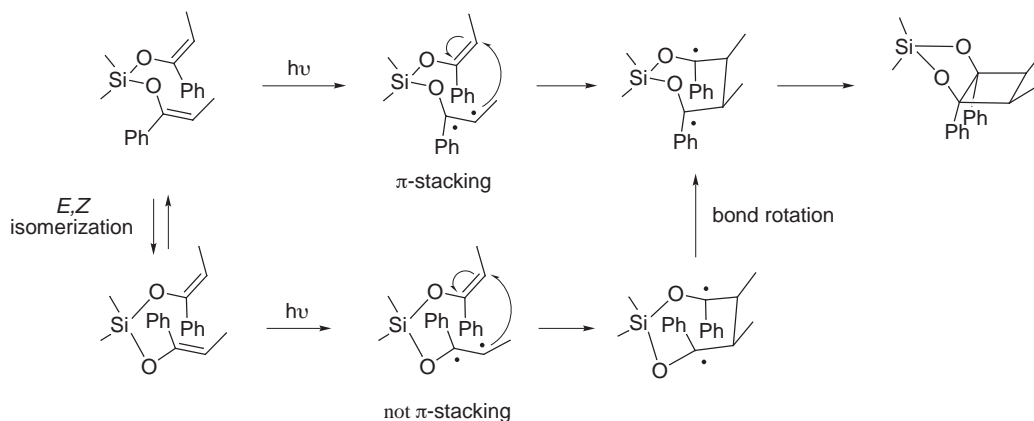


Scheme 6

Irradiation of the (*Z, Z*) bis-silyl enol ether resulted in formation of four cyclobutanyl products (see Scheme 7). Unfortunately, the ratio of products was nearly equal (1:1:1:1). We were puzzled by this result until we looked at the results from low conversion runs. Analysis of the recovered starting material established that the styrenyl group was undergoing *Z* to *E* isomerization. Therefore, the source of the cyclobutanes could not be determined with confidence. For example, the *trans-cis-trans* product might logically arise from π stacking of the original *Z, Z* isomer of the bis-silyl enol ether. However, it could also be a photoproduct of the *E, Z* isomer which follows the stepwise pathway of excited alkene addition to the ground-state alkene to give the most stable diradical intermediate which has time to rotate then close to form the more stable *cis*-[3.2.0] bicyclic ring system (see Scheme 8).



Scheme 7

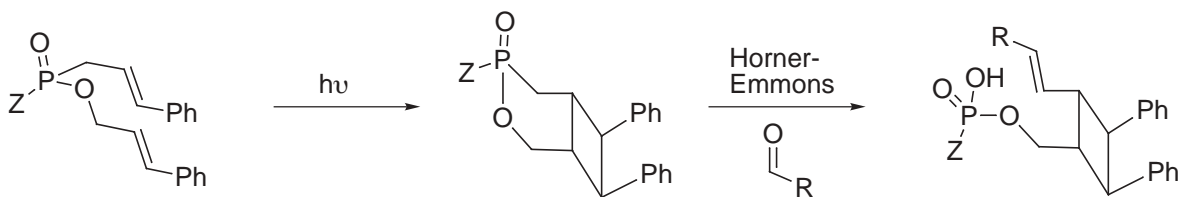


Scheme 8

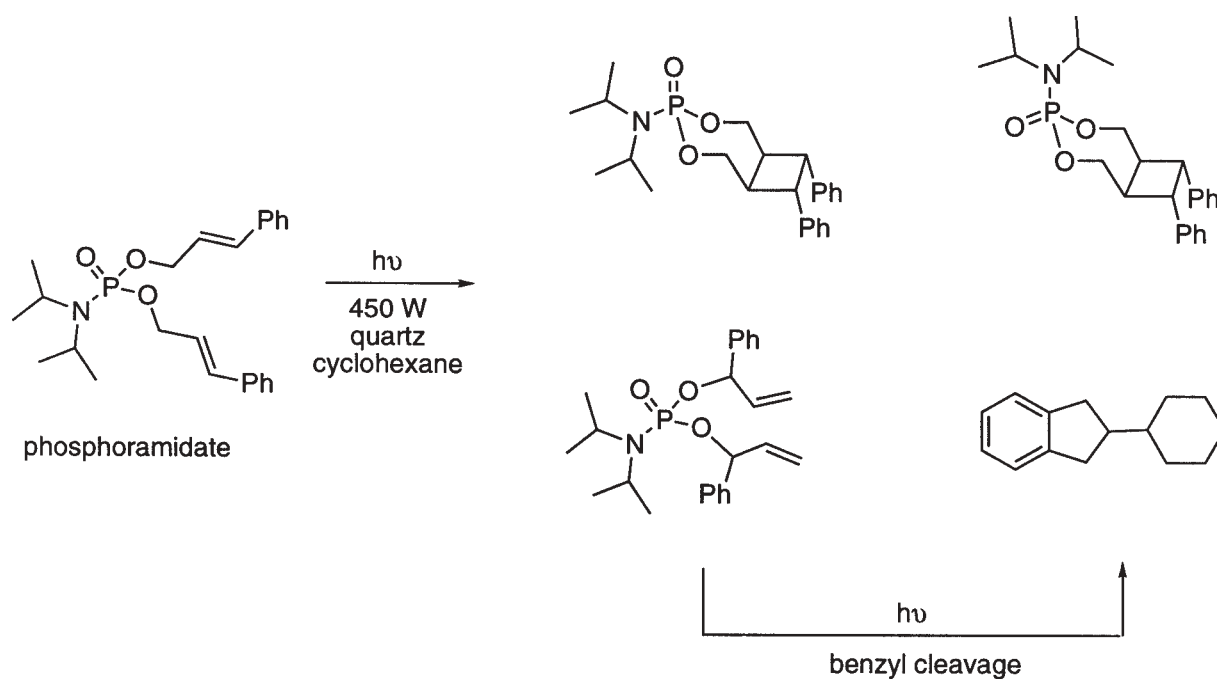
We are currently exploring other silyl tethered systems that have potential for clarifying the mechanistic pathway for 2+2 photocycloaddition between alkenes. In the meantime, we have studied the use of phosphorus as a tethering reagent for this potentially useful synthetic process.

Phosphorus has several advantages over the use of silicon as a tether. First, the phosphorus is more versatile in linking the alkenes. For example, a phosphorus-carbon bond is easier to form. Second, there are further synthetic options for a phosphorus system that are not available with the silicon. Specifically, we are interested in using the Wittig reaction of a phosphorus-carbon linked alkene. This would allow for a smooth entry into a vinylcyclobutane framework (see Scheme 9). A third reason for exploring the phosphorus tether is that the phosphorus stereocenter is much easier to work with than the corresponding silicon stereocenter. This is relevant since we ultimately want to use the tethers as enantioselective templates.

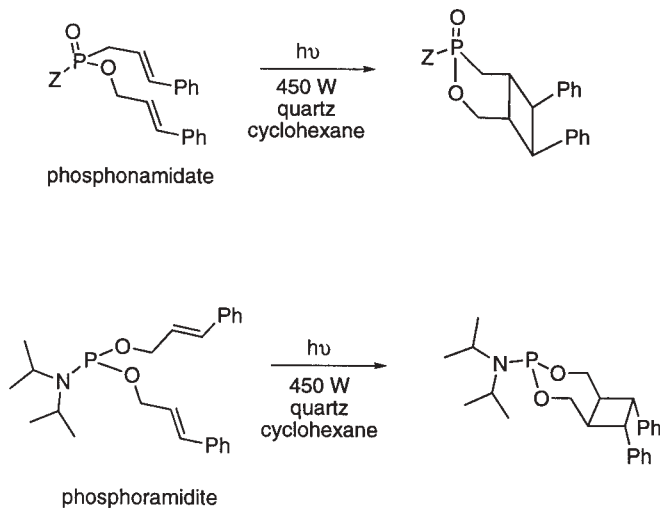
Synthesis and irradiation of the dicinnamyl diisopropylaminephosphoramidate shown in Scheme 10 led to at least two diastereomeric cycloadducts. In addition, we observed a 1,3-sigma-tropic shift at low conversions. Prolonged irradiation resulted in loss of this benzylic phosphoramidate. At the same time there was an increase in dicyclohexane and a non-polar compound that we have tentatively assigned as 2-cyclohexylindane. The radical nature of these products suggests that radical cleavage occurs, perhaps via secondary photochemistry of the benzyl phosphoramidate.



Scheme 9



Scheme 10



Scheme 11

We have investigated the photochemistry of cinnamyl cinnamyl diisopropylaminephosphonamidate and dicinnamyl diisopropylaminephosphoramidite (see Scheme 11). Both of these phosphorus tethered reagents undergo 2+2 photocycloaddition. The phosphonamidate provided the higher yield of cyclobutane. Although removal of the phosphorus tether has not yet been optimized, we anticipate a wide range of applications for this synthetic methodology.

Conclusion

The examples presented here indicate tethering alkenes helps to facilitate the 2+2 photocycloaddition reaction and allows control of the regiochemistry and the stereochemistry as well. We can also see that there is still much room for the study of the mechanism and stereoselectivity of cyclobutane formation.

References

1. a) Fleming, S. A.; Bradford, C. L.; Gao, J. J. *Organic Photochemistry; Molecular and Supramolecular Photochemistry* **1997**, *1*, 187-244. b) Schuster, D. I.; Lem, G.; Kaprinidis, N. A. *Chem. Rev.* **1993**, *93*, 3-22.
2. Saito, I.; Shimozono, K.; Matsuura, T. *J. Org. Chem.* **1982**, *47*, 4356-4358.
3. Saltiel, J.; Dabestani, R.; Sears, Jr., D. R.; McGowan, W. M.; Hilinski, E. F. *J. Am. Chem. Soc.* **1995**, *117*, 9129-9138.
4. a) Sieburth, S. McN. In *Advances in Cycloaddition*; Harmata, M., Ed.; JAI Press, 1999; Vol. 5, pp 85-118. b) Tung, C.-H.; Wu, L.-Z.; Yuan, Z.-Y.; Su, N. *J. Am. Chem. Soc.* **1998**, *120*, 11594-11602.
5. *Advances in Carbene Chemistry* Vol. 2; Brinker, U., Ed.; JAI Press, 1998.
6. a) Murata, S.; Abe, S.; Tomioka, H. *J. Org. Chem.* **1997**, *62*, 3055-3061. b) Chanda, B. M.; Vyas, R.; Bedekar, A. V. *J. Org. Chem.* **2001**, *66*, 30-34.
7. Fleming, S. A.; Turner, T.; Bahu, S.; Nilsson, B. *J. Het. Chem.* **2001**, *38*, 1341-1344.
8. Griesbeck, A. G.; Buhr, S.; Fiege, M.; Schmickler, H.; Lex, J. *J. Org. Chem.* **1998**, *63*, 3847-3854.
9. a) Armesto, D.; Caballero, O.; Amador, U. *J. Am. Chem. Soc.* **1997**, *119*, 12659-12660. b) Singh, V.; Samanta, B. *Tetrahedron Lett.* **1999**, *40*, 383-386.
10. a) Lewis, F. D.; Kalgutkar, R. S.; Yang, J.-S. *J. Am. Chem. Soc.* **2001**, *123*, 3878-3884. b) Bois, F.; Gardette, D.; Gramain, J.-C. *Tetrahedron Lett.* **2000**, *41*, 8769-8772. c) Wakita, K.; Tokitoh, N.; Okazaki, R.; Takagi, N.; Nagase, S. *J. Am. Chem. Soc.* **2000**, *122*, 5648-5649.
11. Evenzahav, A.; Turro, N. J. *J. Am. Chem. Soc.* **1998**, *120*, 1835-1841.
12. Schuster, D. I.; Rao, J. M. *J. Org. Chem.* **1981**, *46*, 1515-1521.
13. a) Caine, D.; Kotian, P. L.; McGuinness, M. D. *J. Org. Chem.* **1991**, *56*, 6307-6313. b) Schultz, A. G.; Reilly, J. *J. Am. Chem. Soc.* **1992**, *114*, 5068-5073.
14. West, F. G.; Fisher, P. V.; Willoughby, C. A. *J. Org. Chem.* **1990**, *55*, 5936-5938.
15. a) Acar, E. A.; Glarner, F.; Burger, U. *Helv.* **1998**, *81*, 1095-1104. b) Ling, R.; Mariano, P. S. *J. Org. Chem.* **1998**, *63*, 6072-6076.
16. Wolff, S.; Agosta, W. C. *J. Am. Chem. Soc.* **1984**, *106*, 2363-2367.
17. a) Sauer, S.; Schumacher, A.; Barbosa, F.; Giese, B. *Tetrahedron Lett.* **1998**, *39*, 3685-3688. b) Mal, J.; Venkateswaran, R. V. *J. Org. Chem.* **1998**, *63*, 3855-3858.
18. Datta, I.; Das, T. K.; Ghosh, S. *Tetrahedron*, **1990**, *46*, 6821-6830.
19. a) Gudmundsdottir, A. D.; Scheffer, J. R. *Tetrahedron Lett.* **1989**, *30*, 419-422. b) Brown, D.; Drew, M. G. B.; Mann, J. *J. Chem. Soc., Perkin Trans I* **1997**, 3651-3655.
20. a) Cossy, J.; Ranaivosata, J.-L.; Bellosta, V. *Tetrahedron Lett.* **1994**, *35*, 8161-8162. b) Dolbier, Jr., W. R.; Rong, X. X. *Tetrahedron Lett.* **1996**, *37*, 5321-5324.

21. a) Harrowven, D. C.; Hannam, J. C.; Lucas, M. C.; Newman, N. A.; Howes, P. D. *Tetrahedron Lett.* **2000**, *41*, 9345-9349. b) Pasto, D. J.; Cottard, F. *Tetrahedron Lett.* **1994**, *35*, 4303-4306.
22. Manning, T. D. R.; Kropp, P. J. *J. Am. Chem. Soc.* **1981**, *103*, 889-897.
23. Cameron, J. F.; Willson, C. G.; Frechet, J. M. J. *J. Am. Chem. Soc.* **1996**, *118*, 12925-12937.
24. a) Breslin, D. T.; Fox, M. A. *J. Org. Chem.* **1994**, *59*, 7557-7561. b) Khim, S. K.; Mariano, P. *Tetrahedron Lett.* **1994**, *35*, 999-1002. c) Pandey, G.; Hajra, S.; Ghorai, M. K.; Kumar, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 8777-8787. d) Ishii, H.; Hirano, T.; Maki, S.; Niwa, H.; Ohashi, M. *Tetrahedron Lett.* **1998**, *39*, 2791-2792. e) Lewis, F. D.; Wagner-Brennan, J. M.; Denari, J. M. *J. Photochem. Photobiol. A Chem.* **1998**, *112*, 139-143.
25. a) Adam, W.; Peters, K.; Peters, E. M.; Stegmann, V. R. *J. Am. Chem. Soc.* **2000**, *122*, 2958-2959. b) Mori, K.; Murai, O.; Hashimoto, S.; Nakamura, Y. *Tetrahedron Lett.* **1996**, *37*, 8523-8526. c) Sieburth, S. McN.; Chen, J. L. *J. Am. Chem. Soc.* **1991**, *113*, 8163-8164. d) Tung, C.-H.; Wu, L.-Z.; Yuan, Z.-Y.; Su, N. *J. Am. Chem. Soc.* **1998**, *120*, 11594-11602. e) Ito, Y. *Organic Photochemistry; Molecular and Supramolecular Photochemistry* **1999**, *3*, 1-70.
26. Bernstein, J.; Green, B. S.; Rejt^o, M. *J. Am. Chem. Soc.* **1980**, *102*, 323-328.
27. Inokuma, S.; Takezawa, M.; Satoh, H.; Nakamura, Y.; Sasaki, T.; Nishimura, J. *J. Org. Chem.* **1998**, *63*, 5791-5796.
28. Greiving, H.; Hopf, H.; Jones, P. G.; Bubenitschek, P.; Desvergne, P.; Bouas-Laurent, H. *Liebigs Ann. Chem.* **1995**, 1949-1956. b) Nakamura, Y.; Fujii, T.; Nishimura, J. *Tetrahedron Lett.* **2000**, *41*, 1419-1423.
29. Ward, S. C.; Fleming, S. A. *J. Org. Chem.* **1994**, *59*, 6476-6479.
30. a) Chebolu, R.; Zhang, W.; Galoppini, E.; Gilardi, R. *Tetrahedron Lett.* **2000**, *41*, 2831-2834. b) Galoppini, E.; Chebolu, R.; Gilardi, R.; Zhang, W. *J. Org. Chem.* **2001**, *66*, 162-168.
31. Fleming, S. A.; Ward, S. C. *Tetrahedron Lett.* **1992**, *33*, 1013-1016.
32. Unett, D. J.; Caldwell, R. A.; Hrcir, D. C. *J. Am. Chem. Soc.* **1996**, *118*, 1682-1689.
33. Takeuchi, M.; Nishimura, J. *Tetrahedron Lett.* **1992**, *33*, 5563-5566.
34. Nishimura, J.; Takeuchi, M.; Takashashi, H.; Sato, M. *Tetrahedron Lett.* **1990**, *31*, 2911-2914.
35. a) Greiving, H.; Hopf, H.; Jones, P. G.; Bubenitschek, P.; Desvergne, P.; Bouas-Laurent, H. *J. Chem. Soc., Chem. Commun.* **1994**, 1075-1076. b) Decout, J.-L.; Lhomme, J. *Photochem. Photobiol.* **1988**, *48*, 597-605.
36. Schmittel, M.; Burghart, A.; Malisch, W. M.; Reising, J.; Sollner, R. *J. Org. Chem.* **1998**, *63*, 396-400.

About the Authors

Steven A. Fleming is a professor in the Department of Chemistry and Biochemistry at Brigham Young University. He received his B.S. degree from the University of Utah (undergraduate research with Gary Keck) and this Ph.D. from the University of Wisconsin (graduate research with Howard Zimmerman). He was an NIH fellow at Colorado State University where he worked with Al Meyers. He has been at Brigham Young University since 1986. Dr. Fleming's e-mail is steve_fleming@bgu.edu.

Can Mao is a senior research assistant in the Medicinal Chemistry Department at Boehringer Ingelheim. She received her B. S. degree from Peking University (working with Haike Yan) and her M.S. degree from Brigham Young University in 2001.

Ephraim E. Parent is a M.D./Ph.D. graduate student in the Department of Chemistry at the University of Illinois (working with John Katzenellenbogen). He received his Honors in Chemistry B.S. degree from Brigham Young University in 2000.

Susan C. Ward is an associate professor in the Department of Chemistry at Brigham Young University-Idaho. She received her B.S. degree in 1990 and her Ph.D. in 1995 from Brigham Young University.

Correction

Bilal Kaafarani, a current student in the Center for Photochemical Sciences, was listed incorrectly in the spring 2002 issue of *The Spectrum* as a finalist for the Research Assistant Award at Bowling Green State University. Bilal actually was the recipient of the award, one of highest honors a graduate student at Bowling Green can receive.

Photochemistry of Some Heteroaromatic Compounds

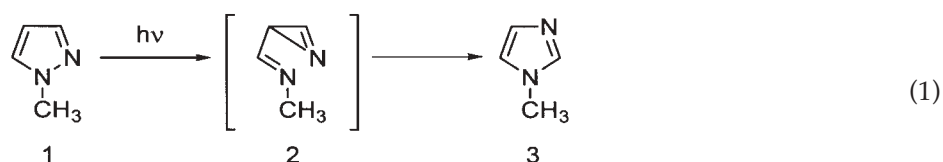
James W. Pavlik

Department of Chemistry and Biochemistry, Worcester Polytechnic Institute

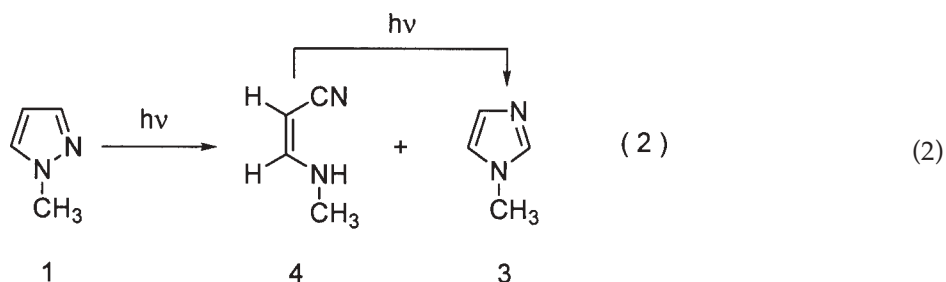
The report¹ in 1957 by Bryce-Smith and Blair that "irradiation of pure benzene under nitrogen at 50° produces a small portion of a yellow isomeric hydrocarbon, fulvene," initiated a fascinating period of research in the field of aromatic photochemistry. This led to the discovery of the valence isomers of aromatic compounds and to the various cycloaddition reactions of benzene including the synthetically important meta-cycloaddition reaction.

Our own interests in this area have been focused on the photochemistry of five- and six-membered heteroaromatic compounds. These compounds seem willing to provide an endless number of fascinating reactions. In particular, during the last decade, much of our time has been focused on the photochemistry of five-membered heteroaromatic compounds containing two heteroatoms.

Some years ago it was reported² that 1-methylpyrazole **1** undergoes phototransposition to 1-methylimidazole **3** (eq 1).



It was suggested that the reaction occurs by way of an initial photoring contraction to an undetected iminoazirine intermediate **2** and subsequent ring expansion to the observed product, 1-methylimidazole **3**. Later work in our laboratory³ showed that in addition to phototransposition to **3**, **1** also undergoes photocleavage to enaminonitrile **4** (eq 2).



Although **4** is readily isolable, it was observed to undergo photocyclization to 1-methylimidazole **3**. Thus the photocleavage-photocyclization route *via* an enaminonitrile represents one confirmed pathway for the pyrazole to imidazole phototransposition. The enaminonitrile to imidazole photocyclization reaction was observed to be a very inefficient reaction that could account for only a small portion of the imidazole formed. This indicated that other photopathways not involving enaminonitriles must also be available.

In order to limit the number of mechanisms possible for a transposition, it was deemed necessary to determine where each ring atom in the product originated in the reactant. This provides specific knowledge about all bonds broken and formed during the reaction and limits the number of mechanisms possible. Barltrop and Day of the Oxford Photochemistry Group formalized this approach as permutation pattern analysis.⁴ They recognized that there are just 12 different ways to scramble the atoms in a five-membered ring resulting in the 12 permutation patterns labeled P_1 - P_{12} shown in Table 1. According to their symbolism, the outer pentagon represents the order in which the ring atoms are bonded in the reactant while the inner pattern represents the order in which the ring atoms are bonded in the transposed product. The permutation pattern can be experimentally determined by studying the

Table 1

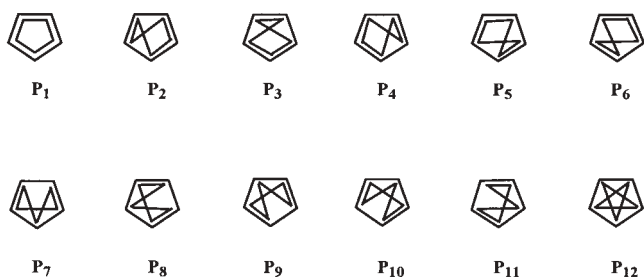


Table 2

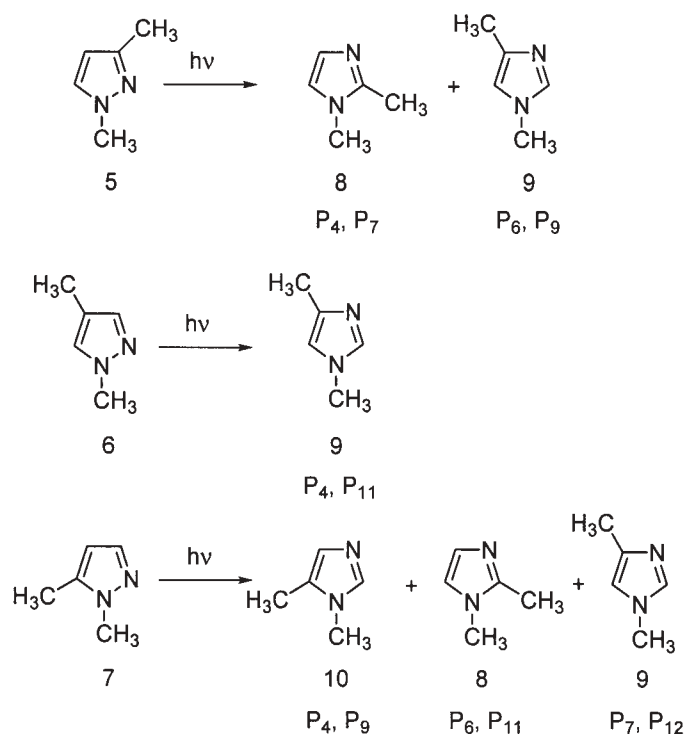
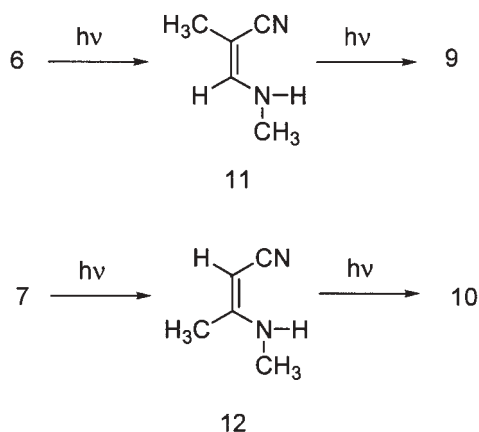


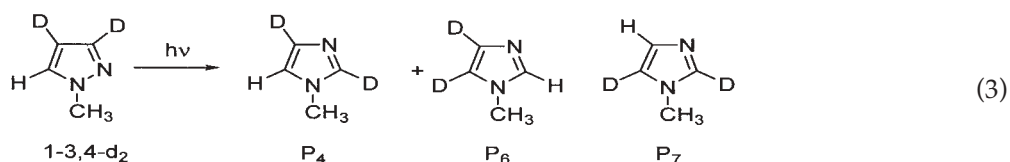
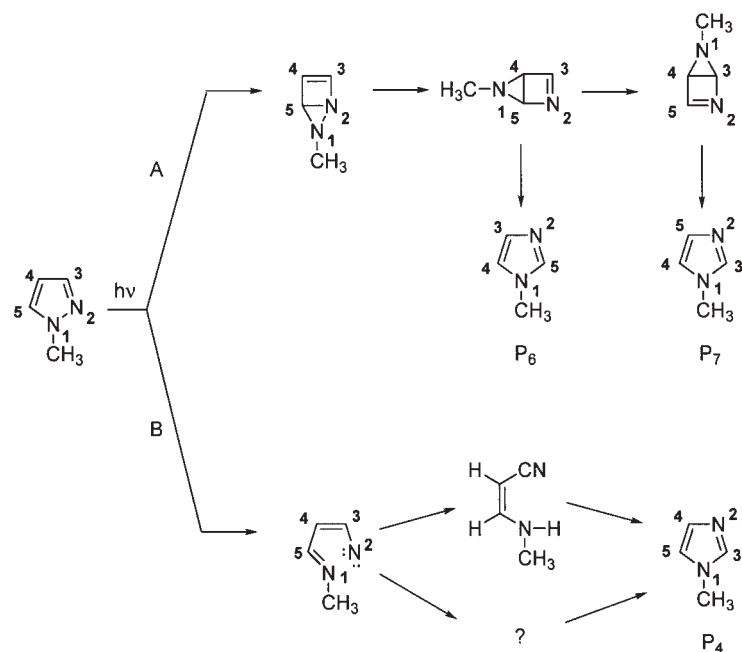
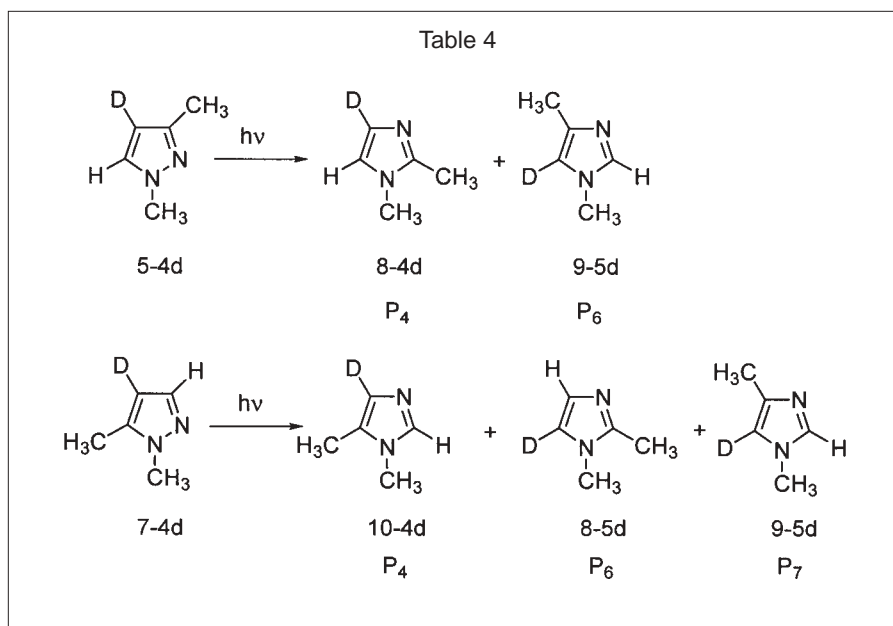
Table 3



phototransposition of a reactant in which each ring atom is uniquely substituted or by studying a series of reactions in which each ring atom is systematically labeled. In the case of a pyrazole to imidazole reaction this latter approach requires studying three reactions since there are three carbon atoms to follow.

Permutation pattern analysis was applied to the pyrazole to imidazole transposition by studying the photochemistry of the three 1-methylpyrazoles (5-7) that were each systematically substituted with a second methyl group.³ The transposition products and the possible permutation patterns are shown in Table 2. In addition to phototransposition, dimethylpyrazoles 6 and 7 also undergo photoring cleavage as shown in Table 3 to yield 2-methyl-3-(N-methylamino)propenenitrile 11 and 3-(N-methylamino)butenenitrile 12, respectively which undergo inefficient photocyclization to dimethylimidazoles 9 and 10, respectively.

Since each reactant in Table 2 has two ring carbon atoms that cannot be distinguished, each reaction could have occurred by two permutation patterns. Thus, products 8, 9, and 10 could have been formed from 5, 6, and 7 by either P₄ or P₇, P₄ or P₁₁, or P₄ or P₉ permutation patterns, respectively. It is important to distinguish between these possibilities since each pattern requires different bond breaking and bond forming requirements and would require different mechanistic pathways. The simplest inference is that these products are P₄ permutation pattern products since this pattern is common to all cases. Similar reasoning suggests that 9 and 8 are P₆ products from 5 and 7, respectively. Finally, it seems likely that 9 is formed from 7 *via* a P₇ permutation process since the alternative P₁₂ process would require a mechanism by which all bonds within the ring are broken. The products formed from deuterium labeled 5-4d and 7-4d shown in Table 4 resolve these ambiguities. It should be noted that in 5-4d and 7-4d all ring positions are uniquely labeled so that product identification allows unambiguous assignment of the permutation patterns. These results show that these dimethylpyrazoles undergo pyrazole to imidazole isomerizations by up to three different permutations and thus by up to three different mechanistic pathways.



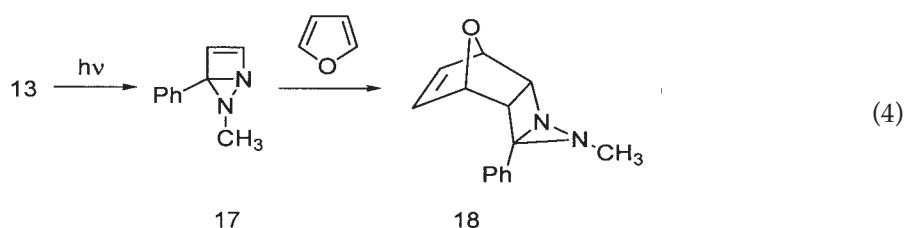
A mechanistic scheme which is consistent with these observations is shown in Scheme 1. According to this mechanism, the photochemistry of 1-methylpyrazoles involves competition between electrocyclic ring closure (Path A) and cleavage of the N1-N2 bond (Path B). Path A results in the formation of a 1,5-diazabicyclo[2.1.0]pentene species to yield 1-methylimidazoles in which the ring atoms have permuted according to patterns P_6 and P_7 . It is interesting to note that since only pyrazole to imidazole transpositions have been observed, the [1,3]sigmatropic shift of nitrogen must take place away from the azetine nitrogen to form a 2,5-diazabicyclic species but not in the opposite direction to yield an isomeric 1,5-diazabicyclic species and eventually a P_5 pyrazole to pyrazole transformation. Alternatively, Path B requires photocleavage of the N1-N2 bond leading to a species that can be viewed as a vinyl nitrene, which is the precursor of the P_4 imidazole. In order to study the phototransposition chemistry with minimum substituent perturbation, the phototransposition chemistry of 3,4-dideuterio-1-methyl-pyrazole **1-3,4d₂** was also studied. After less than 10% photoconversion of **1-3,4d₂**, ¹H-NMR analysis of the dideuterio-1-methylimidazole **2-d₂** revealed that the C5 proton of the reactant had transposed to ring positions 5,2 and 4 of the dideuterio-1-methylimidazole (eq 3) ring confirming that **1-3,4d₂** undergoes phototransposition *via* the P_4 , P_6 and P_7 pathways in a ratio of 4.8:6.5:1.0.

A key mechanistic step in the formation of the P_6 and P_7 imidazoles is the proposed electrocyclic ring closure leading to a transient 1,5-diazabicyclo[2.1.0]pentene. A study of the photochemistry of 1-methyl-5-phenylpyrazole **13**

Table 5

	13	14	15	16
%	-23.2	16.0	30.3	45.6
Φ	0.0410	0.0080	0.140	0.0220

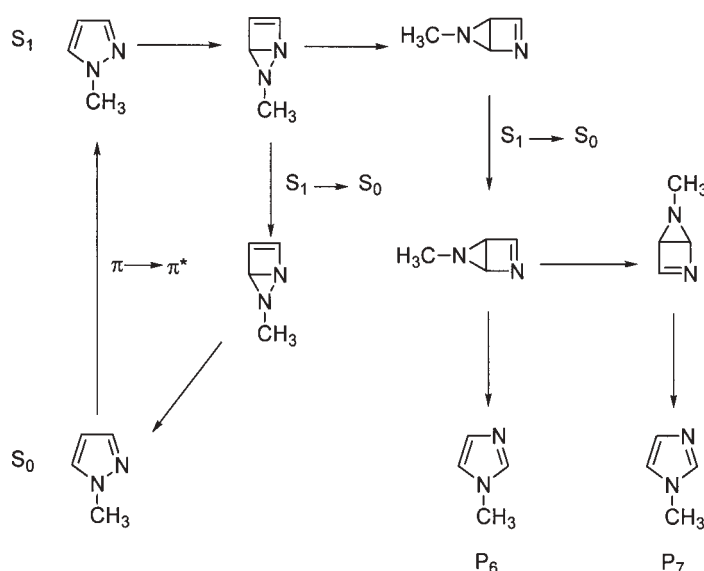
provided convincing evidence for the existence of this species. Thus, whereas irradiation of **13** in methanol solvent results in the formation of the anticipated P_4 , P_6 , and P_7 imidazoles **14**, **15**, and **16** in the chemical and quantum yields shown in Table 5, irradiation of **13** in neat furan led only to the pyrazole-furan [4+2] adduct **18** (eq 4). The formation of this product is consistent with trapping of the photochemically generated 1,5-diazabicyclopentene species **17**.



In addition to permutation pattern analysis and trapping experiments, MNDO calculations have provided insights into the electronic details of the structural changes occurring during the electrocyclic ring closure-heteroatom migration pathway in Scheme 1.⁶ According to these calculations, $\pi \rightarrow \pi^*$ excitation converts the planar ground-state 1-methylpyrazole to the Franck-Condon excited singlet shown in Scheme 2. As this planar excited singlet relaxes, calculations show that the ring begins to undergo disrotatory deformation, resulting in an energy minimized S_1 1-methylpyrazole in which the 1-methylnitrogen is $\sim 12^\circ$ out of the plane of the ring. From this point the molecule undergoes facile electrocyclic ring closure to yield the initial 1,5-diazabicyclic species.

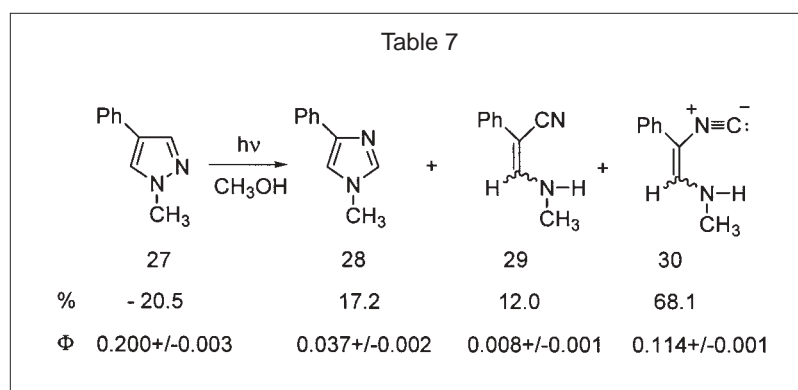
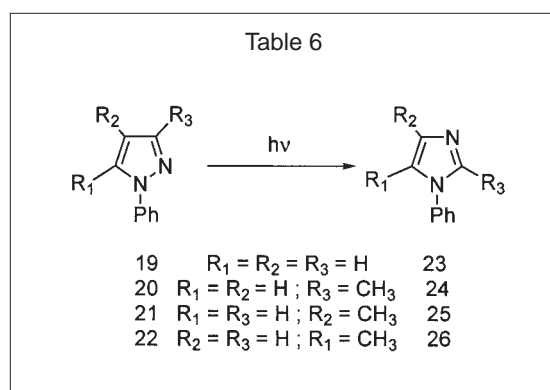
At this point the calculated energy gap between the S_1 and S_0 surfaces is relatively small. It was concluded, however, that nonradiative crossover to the S_0 surface would lead only to aromatization to the reactant pyrazole and would thus be an energy wasting process. The first [1,3]-sigmatropic shift of nitrogen was thus predicted to occur on

the S_1 surface to yield the 2,5-diazabicyclopentene excited singlet state. At this point on the reaction coordinate it was predicted that the molecule crosses over to the S_0 surface and that the ground state diazabicyclo species either aromatizes to the P_6 imidazole or undergoes a second nitrogen migration to an isomeric 2,5-diazabicyclopentene and ultimately the P_7 imidazole. This suggests that the ratio of the P_6 to the P_7 imidazole is determined by the activation barriers for rearomatization and the second sigmatropic shift of nitrogen.



Scheme 2

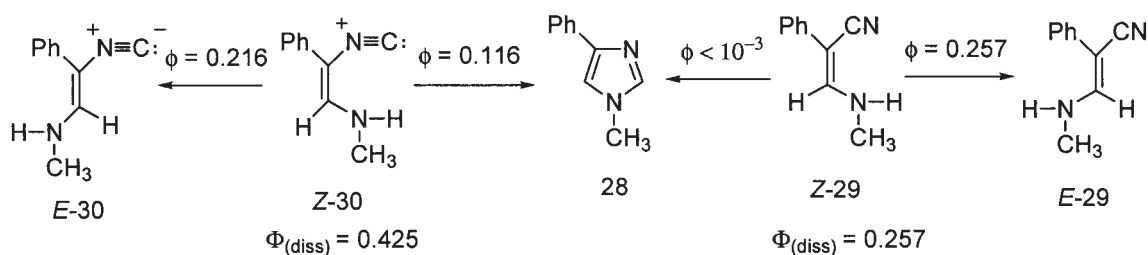
In the case of 1,5-dimethylpyrazole **7** (Table 2), the calculated activation barriers for these two pathways were found to favor formation of the P_6 imidazole by ~ 8 kcal mol⁻¹. Variable temperature studies of the phototransposition chemistry of **7** were consistent with this conclusion. Thus, although the total amount of **8** and **9** remained reasonably constant over the temperature range studied, the P_6 to P_7 ratio changed from 1.6 at 30 °C to 23 at -30 °C.⁷



Although the P_4 pathway, (Path B in Scheme 1), involves the interchange of fewer ring atoms (N2-C3 interchange), it has been found to be mechanistically complex. 1,4-Dimethylpyrazole **6** (Table 1), 1-phenylpyrazole **19**, and methyl substituted 1-phenylpyrazoles **20–22** shown in Table 6, were found to all undergo regiospecific P_4 phototransposition to 1,4-dimethylimidazole **9** or to 1-phenylimidazoles **22–26** via the excited singlet states of the heterocycles.⁸ Interestingly, unlike 1-methylpyrazole **1**, which is nonplanar in the first excited singlet state, computational studies revealed that the pyrazole ring in 1-phenylpyrazole **19** remains planar upon excitation. This is consistent with its lack of reactivity via the electrocyclic ring closure pathway. These calculations did reveal that excitation is accompanied by an increase in the N1-N2 bond length from 1.35 Å in S_0 to 1.78 Å in S_1 . This corresponds to a change in the N1-N2 bond order from 1.23 in S_0 to 0.38 in S_1 and indicates that by the time the molecule reaches the energy minimized S_1 state, the N1-N2 bond is essentially broken and the molecule is well along the P_4 reaction coordinate.

Extensive mechanistic studies have identified two photo-ring cleavage-photocyclization pathways that both lead to the P_4 imidazole. Thus, 1-methyl-4-phenylpyrazole **27** undergoes regiospecific phototransposition to the P_4 product, 1-methyl-4-phenylimidazole **28**, and to the two photocleavage products (*E, Z*)-3-(*N*-methylamino)-2-phenylpropenenitrile **29** and (*E, Z*)-2-(*N*-methylamino)-1-phenylethenylisocyanide **30** in the chemical and quantum yields shown in Table 7.^{5,9}

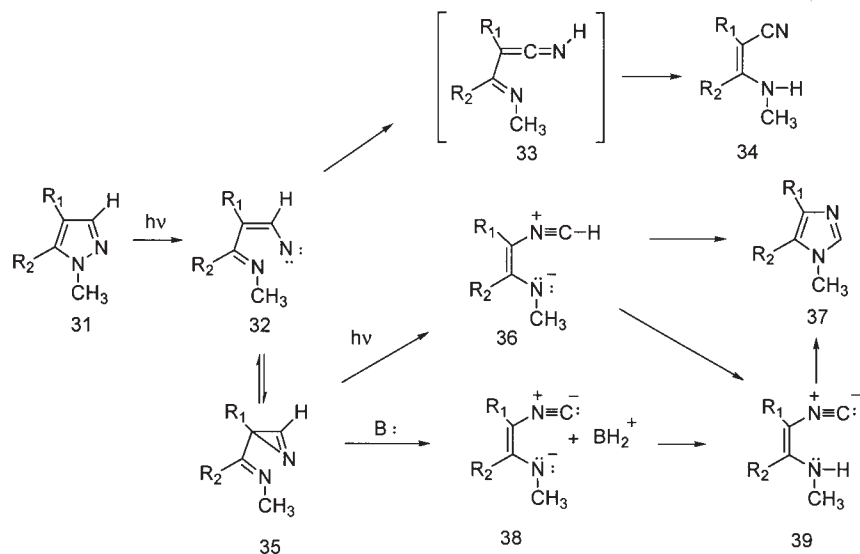
Direct irradiation of *Z*-enaminonitrile **Z-29** and *Z*-enaminoisocyanide **Z-30** shows (Scheme 3) that both undergo *Z* → *E* isomerization and photocyclization to 1-methyl-4-phenylimidazole **28**, the P_4 transposition product. Although the quantum yields shown in Scheme 3 confirm that the photocyclization of enaminonitrile **29** to **28** is very inefficient, chemical and quantum yields show that the photocleavage-photocyclization pathway via isocyanide **30** is a major route for the P_4 phototransposition. Furthermore, this pathway is general to the phototranspositions of a variety of pyrazoles that bear a hydrogen at the C3 ring position.⁵



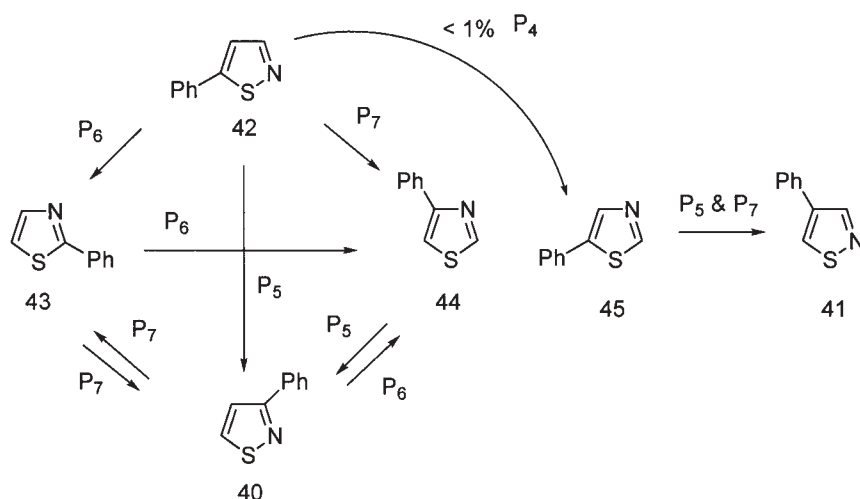
Scheme 3

The P_4 transposition can be viewed in terms of the mechanism shown in Scheme 4. Thus, photocleavage of the N1-N2 bond in **31** leads to β -iminovinyl nitrene **32**. Considering the known chemistry of vinyl nitrenes, **32** is a plausible precursor of enaminonitrile **34**, via **33**, and iminoazirine **35**.^{10,11} This species can be envisioned to undergo photo-ring expansion via nitrile ylide **36** to the P_4 imidazole **37**,¹² or base promoted isomerization to enaminoisocyanide **39**, a known precursor of the P_4 imidazole **37**. In this case either the pyrazole or imidazole could function as the base.

The photochemistry of substituted isothiazoles and thiazoles has also been extensively studied in our laboratory. Based on the photochemical products observed upon irradiation in benzene solution and the results of deuterium



Scheme 4



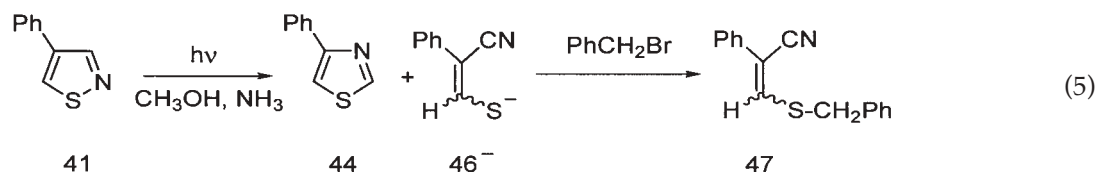
Scheme 5

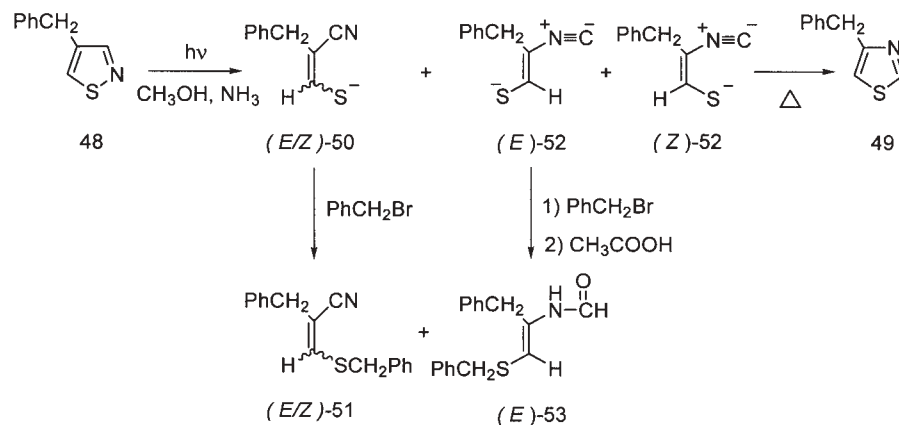
labeling studies, the six isomeric phenylisothiazoles **40-42** and phenylthiazoles **43-45** can be organized (Scheme 5) into a tetrad of four compounds interconverting by way of P_5 , P_6 , and P_7 transpositions and a dyad in which 5-phenylthiazole **45** transposes to 4-phenylisothiazole **41**, the only isomer which did not yield a transposition product upon irradiation in benzene solution.¹³ In addition to transposing to members of the tetrad, the transposition of 5-phenylisothiazole **42** to 5-phenylthiazole **45**, the first member of the dyad, in less than 1% yield, was the only observed conversion between the tetrad and the dyad. This conversion was assumed to occur *via* the P_4 transposition pathway.

The photoisomerizations within the tetrad are consistent with the electrocyclic ring closure-heteroatom migration pathway shown as Path A in Scheme 1 with one interesting difference. Although in pyrazole chemistry nitrogen migrates only away from the azetine nitrogen to give P_6 and P_7 transpositions, in the case of isothiazoles and thiazoles, sulfur migrates in both directions resulting in P_6 and P_7 isothiazole to thiazole conversions and to P_5 isothiazole to isothiazole isomerizations. Deuterium labeling studies revealed that

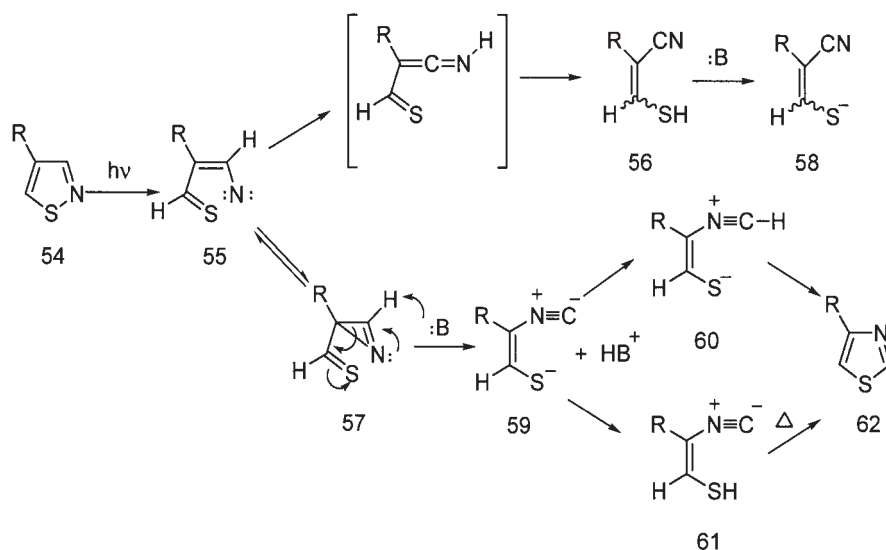
45 isomerizes to **41** by P_5 and P_7 pathways and also undergoes a P_6 transposition leading to itself.¹³ These results can also be explained by the electrocyclic ring closure-heteroatom migration mechanism.

Although 4-phenylisothiazole **41** did not yield a phototransposition product upon irradiation in pure benzene, when the photolysis was carried out in benzene or methanol containing a small quantity of base such as NH_3 , the P_4 phototransposition product, 4-phenylthiazole **44** was formed in 90% yield along with a small amount of the deprotonated cyanothiol photocleavage product **46**, which was trapped by reaction with benzyl bromide to yield the (*E/Z*)-benzylthioether **47**¹⁴ (eq 5).





Scheme 6



Scheme 7

In addition to the cyanothiol photocleavage product, convincing evidence has also been observed for the involvement of isocyanothiol photocleavage products in isothiazole photochemistry. Thus irradiation of 4-benzylisothiazole **48** in methanol-NH₃ led to the formation (Scheme 6) of 4-benzylthiazole **49**, the P₄ transposition product, and to the nitrile photocleavage product **50**, which was trapped as the benzylthioether **51**, and to the formation of the (*E*)-isocyanide photocleavage product (*E*)-**52**, which was trapped by reaction with benzylbromide followed by hydrolysis to yield (*E*)-formamide (*E*)-**53**, and the (*Z*)-isocyanide photocleavage product (*Z*)-**52** which was thermally converted to the observed photo-transposition product **49**.¹⁴

The P₄ transposition pathway for 4-substituted isothiazoles is very similar to the P₄ reaction pathway in pyrazole photochemistry. Thus, as shown in Scheme 7, β-thioformylvinyl nitrene **55**, formed by photocleavage of the S-N bond in isothiazole **54**, is suggested to partition between cyanothiol **56** formation and cyclization to azirine **57**. Since isothiazoles and thiazoles are not sufficiently basic to deprotonate azirine **57**, in the absence of an added base, β-

thioformylvinyl nitrene **55** is converted totally to cyanothiol **56**. In the presence of NH₃, the base converts cyanothiol **56** to cyanosulfide **58** and, more importantly, deprotonates azirine **57** resulting in its conversion to either isocyanide **59** and formation of 4-substituted thiazole **62** either *via* **60** or **61**. Although 4-substituted isothiazoles react exclusively by this pathway, 3- and 5-substituted isothiazoles also transpose *via* the electrocyclic ring closure-heteroatom migration mechanism.¹⁵

These studies show that the photochemistry of these five-membered heteroaromatic compounds can be understood in terms of one general mechanistic scheme.

References

- Blair, J. M.; Bryce-Smith, D. *Proc. Chem. Soc.* **1957**, 287.
- Tiefenthaler, H.; Dorschelen, W.; Goth, H.; Schmid, H. *Helv. Chim. Acta* **1967**, *50*, 2244.
- Pavlik, J. W.; Kurzweil, E. M. *J. Org. Chem.* **1991**, *56*, 6313.
- Bartrop, J. A.; Day, A. C.; Irving, E. *J. Chem. Soc., Chem. Commun.* **1979**, 881.
- Pavlik, J. W.; Kebede, N. *J. Org. Chem.* **1997**, *62*, 8325.
- Connors, R. E.; Pavlik, J. W.; Burns, D. S.; Kurzweil, E. M. *J. Org. Chem.* **1991**, *56*, 6321.

7. Connors, R. E.; Burns, D. S.; Kurzweil, E. M.; Pavlik, J. W. *J. Org. Chem.* **1992**, *57*, 1937.
8. Pavlik, J. W.; Connors, R. E.; Burns, D. S.; Kurzweil, E. M. *J. Am. Chem. Soc.* **1993**, *115*, 7654.
9. Pavlik, J. W.; Kebede, N.; Bird, N. P.; Day, A. C.; Barltrop, J. A. *J. Org. Chem.* **1995**, *60*, 8138.
10. Hassner, A. In *Azides and Nitrenes. Reactivity and Utility*; Scriven, E. F. V., Ed.; Academic Press, 1984; pp 35.
11. Hassner, A.; Wiegand, N. H.; Gottlieb, H. E. *J. Org. Chem.* **1986**, *51*, 3176.
12. Padwa, A. *Acc. Chem. Res.* **1976**, *9*, 371.
13. Pavlik, J. W.; Tongcharoensirikul, P.; Bird, N. P.; Day, A. C.; Barltrop, J. A. *J. Am. Chem. Soc.* **1994**, *116*, 2292.
14. Pavlik, J. W.; Tongcharoensirikul, P.; French, K. M. *J. Org. Chem.* **1998**, *63*, 5592.
15. Pavlik, J. W.; Tongcharoensirikul, P. *J. Org. Chem.* **2000**, *65*, 3626.

About the Author

James W. Pavlik received his Ph.D. in organic chemistry from George Washington University in 1970. He held faculty positions at Haile Selassie I University (now Addis Ababa University) and the University of Wisconsin-River Falls. He has been on the faculty of Worcester Polytechnic Institute since 1974 and has served as Head of the Chemistry Department from 1980-1995 and as Professor of Chemistry from 1980 until the present time. Prof. Pavlik's address is Department of Chemistry and Biochemistry, Worcester Polytechnic Institute, 100 Institute Road, Worcester, MA 01609-2280; e-mail: jwpavlik@wpi.edu.

Copyright 2002 by the Center for Photochemical Sciences
The Spectrum is a quarterly publication of the Center for
Photochemical Sciences, Bowling Green State University,
Bowling Green, OH 43403.
Phone 419-372-2033 Fax 419-372-0366
Email photochemical@listproc.bgsu.edu
WWW <http://www.bgsu.edu/departments/photochem/>

Executive Director: D. C. Neckers
Principal Faculty: P. Anzenbacher, G. S. Bullerjahn,
J. R. Cable, F. N. Castellano,
M. E. Geusz, D. C. Neckers,
M. Y. Ogawa, V. V. Popik,
M. A. J. Rodgers, D. L. Snavely,
B. R. Ullrich
The Spectrum Editor: Pat Green
Production Editor: Alita Frater

COPYRIGHT PERMISSION

A person may make a single copy of any or all articles in this issue for personal use. Copying beyond that permitted by the U.S. Copyright law is allowed provided that the appropriate per copy fee is paid through the Copyright Clearance Center, Inc., 27 Congress St., Salem, MA 01970. For reprint permission, please write to the Center for Photochemical Sciences.

EDITORIAL POLICY

The Spectrum reserves the right to review and edit all submissions. The Spectrum is not responsible for contents of articles.

Articles submitted to The Spectrum will appear at the discretion of the editorial staff as space is available.

Center for Photochemical Sciences Publications

434. **Ullrich, B.**; Schroeder, R.; Graupnerb, W.; Sakaid, H. The influence of self absorption on the photoluminescence of thin film CdS demonstrated by two-photon absorption. *Optics Express* **2001**, *9*, 116.
435. Carney, J. R.; Fedorov, A. V.; **Cable, J. R.**; Zwiier, T. S. Infrared spectroscopy of H-bonded bridges stretched across the cis-amide group: I. Water bridges. *J. Phys. Chem. A* **2001**, *105* (14), 3487-3497.
436. **Cable, J. R.**; Carney, J. R.; Zwiier, T. S. Infrared spectroscopy of H-bonded bridges stretched across the cis-amide group: II. Ammonia and mixed ammonia/water bridges. *J. Phys. Chem. A* **2001**, *105* (35), 8162-8175.
437. Ren, K.; Malpert, J. H.; Li, H.; Gu, H.; **Neckers, D. C.** Studies of weakly coordinating anions paired with iodonium cations. *Macromolecules* **2002**, *35*, 1632-1637.
438. Kaafarani, B. R.; Pinkerton, A. A.; **Neckers, D. C.** High order stacking of a perfluoro 'Y-enyne'. *Tetrahedron Lett.* **2001**, *42*, 8137-8139.
439. Li, H.; Ren, K.; **Neckers, D. C.** Substituted cyclopropenium salts as photoinitiators for cationic polymerization of glycidyl phenyl ether. *Macromolecules* **2001**, *34*, 8637-8640.
440. Wang, F.; Wu, X.; Pinkerton, A. A.; Kumaradhas, P.; **Neckers, D. C.** Photoreaction of platinum(II) β -diketonate complexes with olefins. *Inorg. Chem.* **2001**, *40* (23), 6000-6003.
441. Li, H.; Ren, K.; **Neckers, D. C.** Substituted cyclopropenium salts - photochemical, thermal reactions and mechanistic investigations. Presented at RadTech Conference, Basel, Switzerland, 2001.
442. Ren, K.; Malpert, J. H.; Gu, H.; Li, H.; **Neckers, D. C.** Synthesis, properties and photolysis of new iodonium tetrakis(pentafluorophenyl)gallate photoinitiators and comparison with their indate and aluminate analogs. *Tetrahedron* **2002**, *58*, 5267-5273.
443. Tyson, D. S.; Luman, C. R.; Zhou, X.; **Castellano, F. N.** New Ru(II) chromophores with extended excited-state lifetimes. *Inorg. Chem.* **2001**, *40*, 4063-4071.
444. Wang, F.; **Neckers, D. C.** Photopolymerization of epoxides with platinum(II) bis(acetylacetonato)/silane catalysts. *Macromolecules* **2001**, *34*, 6202-6205.
445. Ren, K.; Serguievski, P.; Gu, H.; Grinevich, O.; Malpert, J. H.; **Neckers, D. C.** Relative photoactivities of iodonium tetrakis(pentafluorophenyl)gallates measured by fluorescence probe techniques. *Macromolecules* **2002**, *35*, 898-904.
446. Strehmel, V.; Stiller, B.; Strehmel, B.; Sarker, A. M.; **Neckers, D. C.** Photoinduced crosslinking of distyrylbenzene containing blockcopolymers for manufacture of new photoalignment layers. *Polym. Prepr.* **2001**, *42* (2), 749.
447. Tyson, D. S.; Henbest, K. B.; Bialecki, J.; **Castellano, F. N.** Excited state processes in ruthenium(II)/pyrenyl complexes displaying extended lifetimes. *J. Phys. Chem. A* **2001**, *105*, 8154-8161.
448. Sarker, A. A.; Kaneko, Y.; **Neckers, D. C.** Synthesis of tetraorganylborate salts. Photogeneration of tertiary amines. *Chem. Mater.* **2001**, *13* (11), 3949-3953.
449. **Ullrich, B.**; Schroeder, R. Green emission and bandgap narrowing due to two-photon excitation in thin film CdS formed by spray pyrolysis. *Semicond. Sci. Technol.* **2001**, *16*, L37.

450. Schroeder, R.; Ullrich, B.; Graupner, W.; Scherf, U. Excitation density and photoluminescence studies of polyfluorene excited by two-photon absorption. *J. Phys.: Condens. Matter* **2001**, *13*, L313.
451. Navarro, J. A.; Myshkin, E.; De la Rosa, M. A.; Bullerjahn, G. S.; Hervas, M. The unique proline of the *Prochlorothrix hollandica* plastocyanin hydrophobic patch impairs electron transfer to photosystem I. *J. Biol. Chem.* **2001**, *276*, 37501-37505.
452. Durham, K. A.; Porta, D.; Twiss, M.; McKay, R. M. L.; Bullerjahn, G. S. Construction and characterization of an iron-dependent *Synechococcus* sp. PCC7942 bioreporter. *FEMS Microbiol. Lett.* **2002**, *209*, 215-221.
453. Hervas, M.; Myshkin, E.; Navarro, J. A.; De la Rosa, M. A.; Bullerjahn, G. S. Proline 14 is impairing the electron transfer from plastocyanin to photosystem I in the prochlorophyte *Prochlorothrix hollandica*. In *Proceedings of the XIIth International Congress on Photosynthesis*; CSIRO Press: Sydney, 2001; pp S11-005.
454. Kornilova, A. Y.; Wishart, J. F.; Ogawa, M. Y. Effect of surface charges on the rates of intermolecular electron-transfer between *de novo* designed metalloproteins. *Biochemistry* **2001**, *40*, 12186-12192.
455. Li, H.; Ren, K.; Neckers, D. C. Photochemical reactions of substituted cyclopropenium salts. *J. Org. Chem.* **2001**, *66*, 8556-8562.
456. Kaafarani, B.; Gu, H.; Pinkerton, A.; Neckers, D. C. The crystal and molecular structures of 1-naphthylphenyliodonium tetrafluoroborate and 1-naphthylphenyliodonium tetrakis(pentafluorophenyl) gallate. *J. Chem. Soc., Dalton Trans.* **2002**, 2318.
457. Fedorova, A.; Ogawa, M. Y. Site-specific modification of *de novo* designed coiled-coil polypeptides with inorganic redox complexes. *Bioconjugate Chem.* **2002**, *13*, 150-154.
458. Schroeder, R.; Graupner, W.; Scherf, U.; Ullrich, B. Intrachain exciton quenching analysis in conjugated polymers by two-photon spectroscopy. *J. Chem. Phys.* **2002**, *116*, 3449-3454.
459. Myshkin, E.; Leontis, N. B.; Bullerjahn, G. S. Computational simulation of the docking of *Prochlorothrix* plastocyanin to Photosystem I: modeling the electron transfer complex. *Biophys. J.* **2002**, *82*, 3305-3313.
460. Komarova, E.; Ren, K.; Neckers, D. C. Influence of microencapsulation on stability and reactivity of 2,4,6-triphenylpyrylium tetrakis(pentafluorophenyl)gallate as a cationic photoinitiator. *Langmuir* **2002**, *18*, 4195.
461. Anzenbacher, P., Jr.; Marquez, M.; Aldakov, D. Toward anion sensing by conductive polymers. *Polym. Mater. Sci. Eng.* **2002**, *86*, 23-24.
462. Tyson, D. S.; Bignozzi, C. A.; Castellano, F. N. Metal-organic approach to binary optical memory. *J. Am. Chem. Soc.* **2002**, *124*, 4562-4563.
463. Anzenbacher, P., Jr.; Tyson, D. S.; Jursikova, K.; Castellano, F. N. Luminescence lifetime-based sensor for cyanide and related anions. *J. Am. Chem. Soc.* **2002**, *124*, 6232-6233.
464. Hoostal, M.; Bullerjahn, G. S.; McKay, R. M. L. Molecular assessment of the potential for *in situ* bioremediation of PCBs from aquatic sediments. *Hydrobiologia* **2002**, *469*, 59-65.

For reprints of any of these publications, please write or e-mail the Center for Photochemical Sciences and refer to the reprint by number.