

Styrene–amine and stilbene–amine intramolecular addition reactions

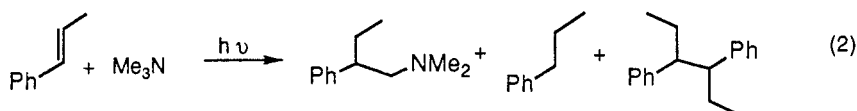
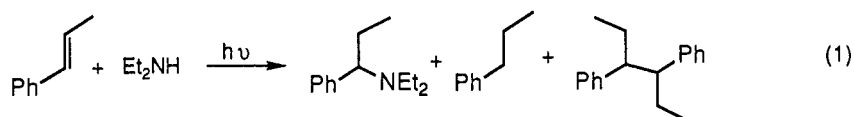
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Abstract: Two mechanisms have been reported for the intermolecular photochemical addition reactions of styrenes and stilbenes with amines. Direct irradiation results in electron-transfer quenching of the singlet styrene by the amine, followed by hydrogen transfer and radical pair coupling. Electron-transfer-sensitized irradiation results in the formation of the styrene or stilbene cation radical which undergoes nucleophilic attack by amines. The intramolecular analogues of these reactions have been investigated and are found to provide a versatile method for the synthesis of nitrogen heterocycles. The synthetic aspects of these reactions are discussed in the context of their reaction mechanisms.

INTRODUCTION

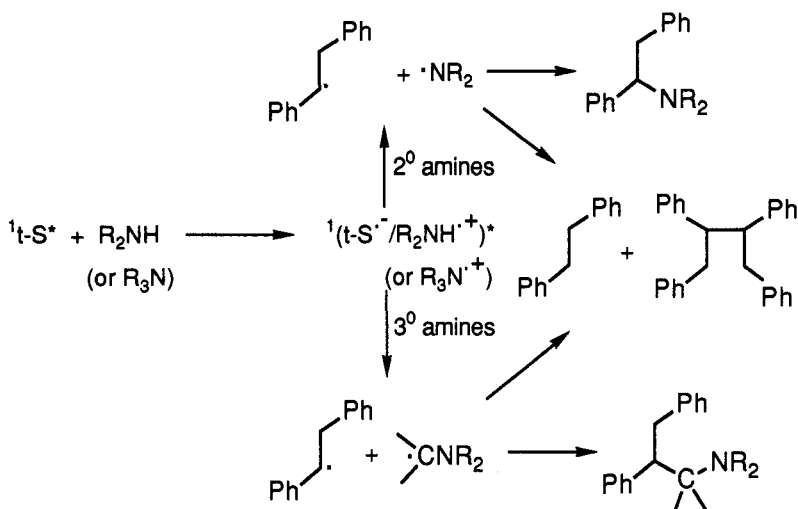
The intermolecular photochemical addition reactions of styrenes (ref. 1) and stilbenes (ref. 2) with aliphatic amines were initially reported over two decades ago. The addition of styrene and of its alpha and beta alkyl derivatives with secondary and tertiary amines occurs regioselectively to yield a single N-H adduct (eq. 1) and C-H adduct (eq. 2), respectively, along with styrene reduction products (refs. 1, 3, 4). Regioselective addition of some nonsymmetrically-substituted tertiary amines to stilbene has been observed (ref. 5). However, addition of secondary amines (ref. 6) and tertiary amines (ref. 7) to substituted stilbenes yields 1:1 mixtures of regioisomers. Such reactions proved to be of greater interest mechanistically than synthetically; their synthetic utility being limited by (a) the necessity of using high concentrations of amine to quench the short-lived aryl olefin singlet states, (b) the low preparative yields of aryl olefin-amine adducts, and (c) the competition of aryl olefin reduction with addition.



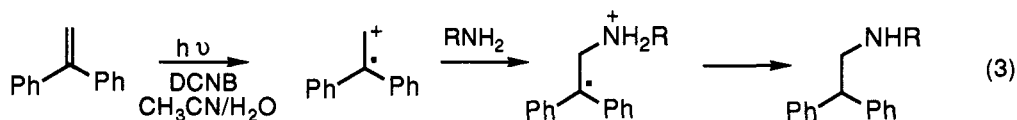
Investigations of intermolecular stilbene-amine addition reactions conducted in this laboratory led to the proposed mechanism for the addition of tertiary and secondary amines outlined in Scheme I (ref. 8). While addition of both tertiary and secondary amines was proposed to occur via a sequential electron-transfer, proton-transfer, radical pair coupling mechanism, significant differences were observed in the behavior of tertiary vs. secondary amines. First, quenching of stilbene singlets by tertiary amines results in the formation of a fluorescent stilbene-amine exciplex, whereas quenching by secondary amines does not. Evidence for exciplex formation in the case of secondary amines was indirect, based upon the increase in fluorescence quenching

rate constant with decreasing amine ionization potential and decreasing temperature. Second, tertiary amines form C-H adducts, the yields of which increase with increasing solvent polarity, whereas secondary amines form N-H adducts, the yields of which decrease with increasing solvent polarity. Collaborative investigations of the stilbene-tertiary amine reactions with Schneider and coworkers (ref. 9) established that hydrogen transfer in acetonitrile solution occurred in the initially formed contact radical ion pair and not after formation of a solvent separated ion pair or free radical ions. The increase in stilbene-tertiary amine addition efficiency with increasing solvent polarity was attributed to an increase in the charge-transfer character, and hence reactivity, of the singlet exciplex. Investigations of the addition reactions of secondary amines with singlet arenecarbonitriles led to the proposal that N-H addition was a reaction characteristic of relatively nonpolar exciplexes, while C-H transfer is characteristic of pure charge-transfer exciplexes (ref. 10). N-H hydrogen bonding between the arene and secondary amine in the nonpolar exciplex may provide a low-energy pathway for hydrogen transfer, thus accounting for the absence of exciplex fluorescence.

Scheme I



Photochemical addition of ammonia and primary amines to aryl olefins can also be effected by irradiation in the presence of an electron acceptor such as dicyanobenzene (DCNB) (ref. 11). In the sensitized addition reaction, electron transfer from the aryl olefin to the sensitizer (either of which may be excited) is followed by nucleophilic attack of the amine on the aryl olefin cation radical (eq. 3). While this reaction is mechanistically related to the electron-transfer sensitized hydration of aryl olefins (ref. 12), previous attempts to add weaker nucleophiles such as water or methanol to stilbene cation radicals proved unsuccessful. The sensitized addition of primary amines to 1,1-diphenylethylene and *para*-methoxy stilbene is regioselective, yielding the adducts with nitrogen bonded to the less substituted and unsubstituted benzylic positions, respectively (ref. 11).

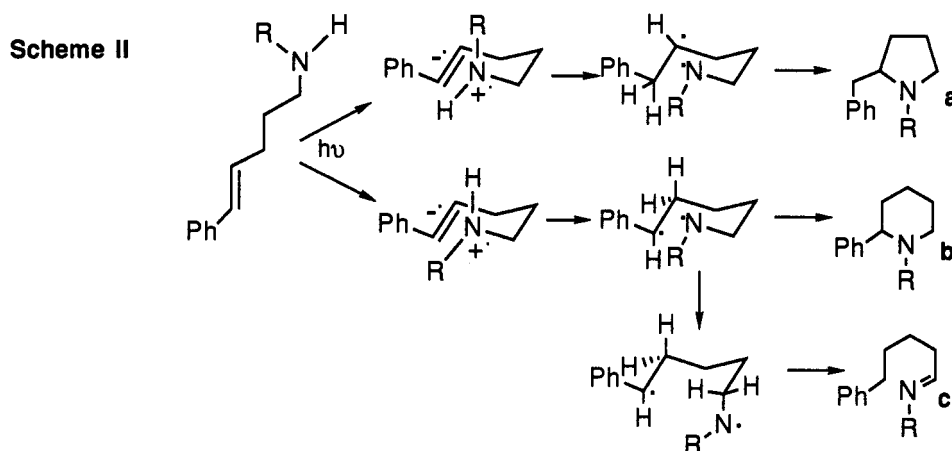


Several years ago, we embarked upon an investigation of the formation and behavior of intramolecular styrene-amine (ref. 4) and stilbene-amine exciplexes (ref. 13). The available literature at that time was, at best, modestly encouraging. Aoyama and co-workers (ref. 14) had reported that intramolecular addition of styrenes occurred for some styryl amides, ureas, and activated (benzyl) tertiary amines. Sugimoto, et al. (ref. 15) had reported that irradiation of secondary but not tertiary aminoalkylphenanthrenes resulted in intramolecular addition. There were no reports of electron-transfer-sensitized intramolecular arene- or aryl olefin-amine addition reactions.

β -(ω -AMINOALKYL)STYRENES

The results of our investigations of this system have been published (ref. 4) and thus only selected features will be reviewed. Evidence for the occurrence of intramolecular electron-transfer quenching of singlet styrene by primary, N-methyl, and N,N-dimethyl amines was provided by a decrease in the singlet lifetime in comparison to that of 1-phenylpropene and by the observation of exciplex emission from the dimethyl aminoethyl and aminopropylstyrenes. The calculated rate constants for intramolecular quenching by both secondary and tertiary aminoalkyl substituents are larger for propyl vs. ethylamines and then decrease as the length of the polymethylene chain separating the styrene and amine is increased. Similar behavior has previously been reported for several arene-amine systems (ref. 16).

Aminopropylstyrenes. Irradiation of the primary and secondary, but not tertiary aminopropylstyrenes results in the formation of intramolecular styrene-amine adducts. In this respect, our results are similar to those previously reported by Sugimoto, et al. (ref. 15) for secondary and tertiary aminoalkylphenanthrenes. Triplet sensitization results in *trans*, *cis* isomerization, but not intramolecular addition, establishing that the latter is a singlet state process. The photochemical behavior of the aminopropylstyrenes (Scheme II) serves to illustrate the dependence of product formation upon N-alkylation, reaction temperature and solvent polarity. The primary and N-methyl amines yield piperidine (**b**) and pyrrolidine (**a**) products in a ratio of $b/a = 1.4:1$ and $2.4:1$, respectively, in acetonitrile solution. The N-*iso*-propylamine yields a 5:1 mixture of piperidine (**b**) and imine (**c**), while the *tert*-butylamine yields only the imine (**c**).

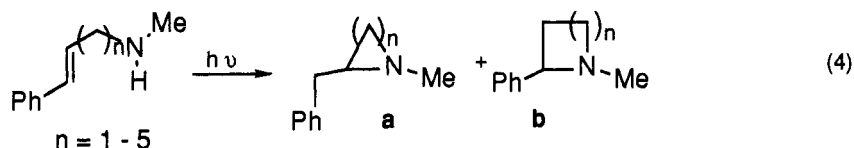


We have rationalized the above results using the mechanism outlined in Scheme II. Intramolecular electron-transfer quenching of singlet styrene by amine is proposed to result in folding of the trimethylene chain into a chair-like conformation in which an N-substituent is either equatorial or axial. Migration of the equatorial and axial hydrogens via least-motion pathways yields the 1,5- and 1,6-biradical intermediates, respectively. Increasing the bulk of the N-substituent should raise the energy of the transition state leading to the 1,5-biradical, thus explaining the decrease in yield of the pyrrolidine product with the bulk of the substituent. The bulk of the N-substituent also determines the behavior of the 1,6-biradical intermediate, cyclization to the piperidine being favored when $R = H$ or methyl and imine being favored when $R = \textit{tert}$ -butyl. Deuterium labeling established that imine formation occurs via the 1,6- rather than the 1,5-biradical. Further evidence for the formation of products via short-lived singlet biradical intermediates is provided by stereochemical analysis of the piperidine product formed from the *trans*- and *cis*-N-deutero-N-methylamine. The *trans* isomer forms only the *syn* addition product, while the *cis* isomer forms a mixture of the *syn* and *anti* addition products, indicative of partial conformational equilibrium in the biradical derived from the *cis* isomer, but not the *trans* isomer.

Both the quantum yields for adduct formation and the ratio of regioisomeric adducts are dependent upon solvent polarity and reaction temperature. For N-methyl aminopropyl-styrene, changing the solvent from acetonitrile to cyclohexane results in a 50% increase in total adduct quantum yield and a change in the ratio of regioisomers **b/a** from 2.4:1 to 0.9:1. Decreasing the temperature results increased regioselectivity (**b/a** = 6.2:1 at -40 °C in acetonitrile solution) and a decrease in the relative quantum yield for addition vs. styrene isomerization. The temperature dependence can be explained in terms of a slightly higher enthalpy of activation for formation of the 1,5- vs. 1,6-biradical (Scheme II). Interpretation of the solvent dependence is more complicated, as increasing solvent polarity should increase the charge-transfer character of the exciplex, increase the equilibrium donor-acceptor separation, and possibly disrupt intramolecular hydrogen bonding.

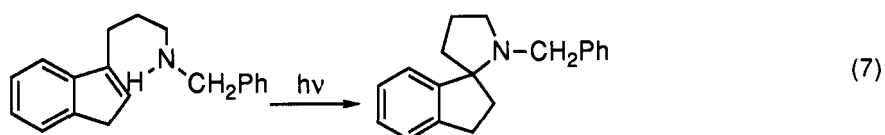
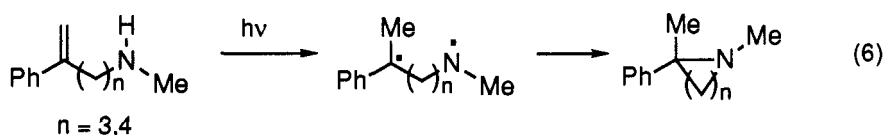
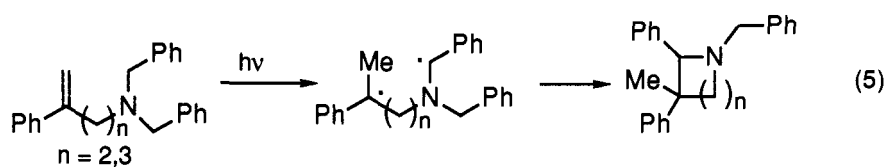
As a consequence of the more rapid intramolecular electron-transfer quenching by secondary vs. primary amines, intramolecular addition is more efficient than styrene isomerization for N-methyl aminopropylstyrene at room temperature; whereas the converse is true for the corresponding primary amine. A significant increase in the rate and optimum yield (>90% vs. 40%) of intramolecular adduct formation from the primary amine can be achieved by electron-transfer-sensitized irradiation (DCNB in 9:1 aceto-nitrile-water solvent). However, the ratio of pyrrolidine/piperidine intramolecular adducts is essentially the same in the direct and sensitized irradiations.

Chain length dependence. Intramolecular adduct formation has been observed for N-methyl aminoalkylstyrenes with one to five methylenes separating the styrene and amine (eq. 4, $n = 1 - 5$). The preparative yield, quantum yield, and ratio of regioisomeric adducts are dependent upon the length of the polymethylene chain. The product of addition of nitrogen to the benzylic carbon (**b**) is the major product for $n = 3$ and the predominant product for $n = 1, 2$, or 5 (**b/a** > 10:1 in acetonitrile solution), as is the case for the inter-molecular addition reaction (eq. 1). However, the product of addition to the non-benzylic carbon predominates when $n = 4$ (**a:b** = 7:1 in acetonitrile solution). When $n = 1$ or 2 the chain length may be too short to allow hydrogen transfer to the distal end of the C=C bond. When the chain is sufficiently long, the intramolecular exciplex would be expected to display chemical behavior similar to that of the intermolecular exciplex. For intermediate chain lengths ($n = 3$ or 4) the geometry of the exciplex, as determined by chain folding energetics, may determine the regioselectivity of hydrogen transfer. From a preparative point of view, the isolated yield of adducts is larger for $n = 2 - 4$ (60 - 80%) than for $n = 1$ (15%) or $n = 5$ ($n = 30\%$). The low yield for $n = 1$ may be related to the very rapid nonradiative decay commonly observed for aminomethylarenes (ref. 17), while the low yield for $n = 5$ can be attributed to the inability of intramolecular electron-transfer quenching to compete with radiative and nonradiative decay of the styrene singlet. It would be interesting to determine if the rate of quenching and efficiency of adduct formation increase for longer chain lengths (ref. 16).

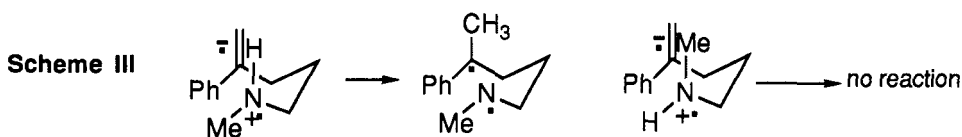


α -(ω -AMINOALKYL)STYRENES

Aoyama, et al. (ref. 14) have reported the observation of intramolecular styrene-amine exciplex fluorescence and C-H addition for alpha-linked N,N-dibenzyl aminoethyl and aminopropylstyrenes (eq. 5). In both cases, a single regioisomer is obtained as a mixture of cis and trans stereoisomers. We have initiated studies of the photochemical behavior of the alpha-linked secondary amines. Both the aminopropyl and aminobutyl styrene form a single adduct in which nitrogen is bonded to the benzylic carbon in excellent preparative yield (eq. 6). Similar regioselectivity is observed in the intramolecular addition of N-benzyl 1-(3-aminopropyl)indene (eq. 7).



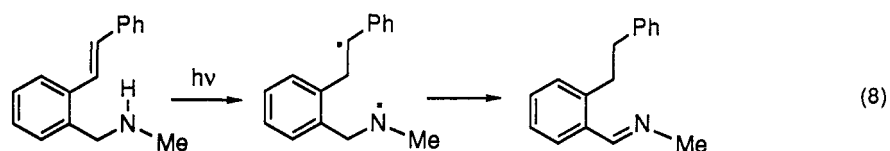
These results stand in marked contrast to our observations for beta-linked aminoalkyl styrenes, for which exciplex fluorescence, but no intramolecular addition, is observed for the tertiary amines and nonregioselective addition is observed for the secondary amines. Inspection of molecular models for the alpha-linked aminopropyl styrene suggests that N-H transfer to the terminal carbon can occur via a low energy folded conformation of the exciplex, but that N-H transfer to the benzylic carbon cannot (Scheme III). Alternatively, the more regioselective addition of the alpha- vs. beta-linked secondary amines may reflect a difference in the electronic distribution within the singlet exciplex. Further comparative studies of the alpha- and beta-linked aminoalkyl styrenes under both direct and electron-transfer-sensitized irradiation conditions are in progress.



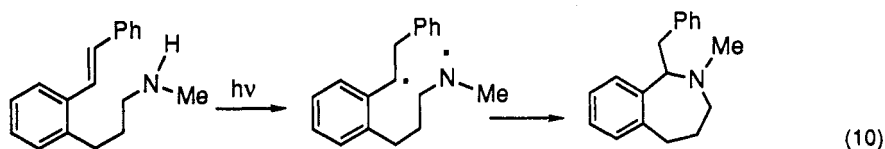
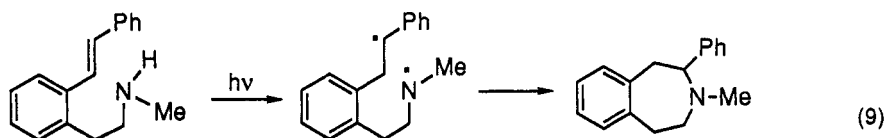
ortho-(ω -AMINOALKYLSTILBENES)

The photophysical and photochemical behavior of the *N,N*-dimethyl aminoalkylstilbenes is similar to that of the analogous beta-linked aminoalkylstyrenes in that irradiation results in *trans,cis* isomerization but not intramolecular addition. Efficient quenching of stilbene fluorescence is observed for the aminomethyl, ethyl, and propyl stilbenes and exciplex fluorescence is observed for the aminoethyl and propyl stilbenes. For the secondary *N*-methyl aminoalkylstilbenes, efficient quenching of stilbene fluorescence is observed for the aminomethylstilbene and partial quenching for the aminoethylstilbene. The absence of significant intramolecular quenching by the secondary aminopropyl substituents or any of the primary aminoalkyl substituents may reflect the short singlet lifetime of *trans*-stilbene (0.1 ns) when compared to that for *trans*-1-penylpropene (11.9 ns).

Direct irradiation. Whereas irradiation of either the tertiary or primary aminoalkylstilbenes results exclusively in *trans,cis* isomerization, irradiation of the secondary amines results in the formation of products derived from intramolecular N-H transfer. In the case of the aminomethylstilbene, the imine product is presumed to be formed via the disproportionation of the initially formed 1,6-biradical intermediate (eq. 8). Formation of tetrahydro-2- and 3-benz-

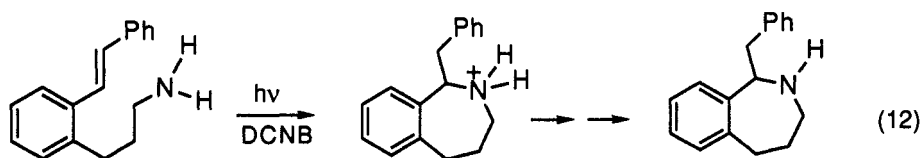
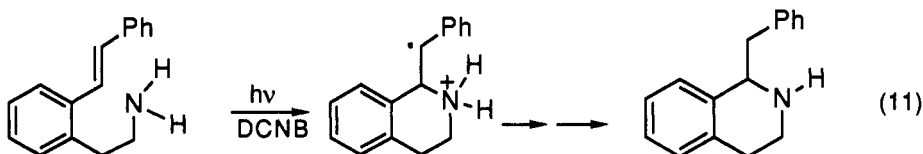


azepines from the aminoethyl and aminopropylstilbenes, respectively, is presumed to occur via 1,7-biradical intermediates (eqs. 9,10).



Since no regioselectivity is observed for intermolecular stilbene-amine addition reactions (ref. 6, 7), we assume that the regioselectivity observed in the intramolecular addition reactions is a consequence of the geometrical constraints placed upon the intermediate exciplexes by the alkyl chain connecting the stilbene and amine. Hydrogen transfer is restricted to the proximal end of the double bond when the alkyl chain is too short to allow transfer to the distal end of the double bond (eq. 8, 9). In the case of the aminopropylstilbene, the chain length is sufficiently long to allow transfer to either end of the double bond. The occurrence of 1,8-hydrogen transfer in preference to 1,7-hydrogen transfer suggests that the geometry of the exciplex is controlling the regioselectivity of hydrogen transfer, as is the case for the beta-linked aminopropyl and aminobutylstyrenes. The behavior of the biradical intermediate is also dependent upon the chain length, the aminomethyl biradical undergoing disproportionation and the aminoethyl and aminopropyl biradicals combination. This may be the consequence of either more favorable disproportionation for the aminomethyl biradical (6- vs. 7-membered transition state) or less favorable cyclization (poor overlap of the radical orbitals in a boat-like transition state).

Sensitized irradiation. Irradiation of the primary aminoethyl and aminopropylstilbenes in acetonitrile-water solution in the presence of DCNB results in the formation of isoquinoline and benzazepine products in good preparative yield (eq. 11, 12). The corresponding secondary amines also undergo sensitized intramolecular addition; however, the products are unstable under the reaction conditions and are converted to complex product mixtures.



Since the stilbene oxidation potential is lower than that of either primary or secondary amines, sensitized irradiation should initially yield the stilbene cation radical of both the primary and secondary aminoalkyl stilbenes. By analogy to the mechanism proposed for the intermolecular electron-transfer-sensitized addition of amines to arenes and aryl olefins (eq. 3, ref. 11), we assume that the regioselectivity of C-N bonding is determined by nucleophilic attack of nitrogen on the stilbene cation radical. The selective formation of the more stable regioisomer from the aminoethyl and aminopropylstilbenes and the failure of the aminomethylstilbene to undergo electron-transfer-sensitized intramolecular addition suggest that C-N bond formation is dependent upon the formation of a relatively strain-free cyclization product. Intramolecular addition results in the conversion of primary amines to secondary amines and of secondary amines to tertiary amines. The latter are more easily oxidized than is stilbene and are unstable under the reaction conditions.

CONCLUDING REMARKS

The direct and sensitized irradiation of the aminoalkylstyrenes and stilbenes offers a versatile method for the synthesis of nitrogen heterocycles with a variety of ring sizes. The two methods are complementary, offering a choice of nitrogen alkylation and control over the regioselectivity of C-N bond formation. We are currently planning the application of these reactions to the synthesis of macrocyclic amines and of more complex naturally-occurring alkaloids.

While this account has focused upon the synthetic aspects of our investigations, we have found the photophysical behavior of the aminoalkylstyrenes and stilbenes to be every bit as fascinating as their photochemical behavior. The fact that the chemically reactive excited states are fluorescent has allowed us to investigate the dynamics of intramolecular exciplex formation, and, in the case of some of the tertiary amines, to directly observe the exciplex intermediates. In the process of comparing the behavior of inter- vs. intramolecular exciplexes, we have also become aware of some fascinating differences in their photophysical and photochemical behavior, such as the occurrence of the inter- but not intramolecular addition of tertiary amines to several styrenes and stilbenes.

Acknowledgements

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