Account

The Synthetic Potential of SET Photochemistry of Silicon-Substituted Polydonor-Linked Phthalimides

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Our studies in the area of single electron transfer (SET) photochemistry have led to the discovery of efficient processes, in which regioselective formation of carbon-centered radicals takes place by nucleophile assisted desilylation of α-trialkylsilyl substituted ether, thioether, amine and amide centered cation radicals. The rates of bimolecular desilylation of the intermediate cation radicals exceed those of other cation radical α-fragmentation processes (*e.g.*, α-deprotonation). This sereves as the basis for the design of highly regioselective, SET-induced photomacrocyclization reactions of polyether, polythioether, polyamide, and polypeptide linked phthalimides. Photocyclization reactions of trimethylsilyl-terminated substrates in these families are unique in that they produce polyfunctionalized macrocyclic substances in a highly efficient and regioselective manner. In addition, our studies in this area have led to important information about the factors that govern chemical and quantum efficiencies that should be applicable to a wide variety of redox processes promoted by SET from substrates containing more than one electron donor site.

Key Words : SET-photochemistry, Silyl-substituted polydonor-phthalimide, Photomacrocyclization, Synthetic potential

Introduction

SET-Photochemistry. Owing to the large energetic driving force provided by the high energies of electronic excited states, single electron transfer (SET) is a key mechanistic event in a wide variety of photochemical processes.[1] Photoinduced SET between neutral donors and acceptors results in the generation of radical ions, highly reactive intermediates which participate in facile and selective reactions as part of mechanistic routes leading to product formation. Consequently, the unique feature of SET-photochemical processes is that reactivity is governed principally by the chemical properties of the radical cation and radical anion intermediates.

One of the most common reaction pathways open to radical ions is α-heterolytic fragmentation. In processes of this type, either an electrofugal or nucleofugal group is expelled from a position adjacent to a respective positively or negatively charged radical center. Both processes produce a stabilized neutral radical intermediate (Scheme 1). Owing to the pivotal role they play in SET photochemistry, α-heterolytic fragmentation reactions have been the subject of a wide variety of studies aimed at elucidating the rates of the processes and determining how the rates depend on the structure of the ion radicals and the reaction medium.[2]

SET-Photochemistry of Organosilanes. Silicon-containing organic compounds serve as key reagents in numerous, synthetically useful chemical reactions.[3] Perhaps the most common role played by these substances is as equivalents of allylic and enolate anions. For example, activation of allysilanes using potent silophiles, such as fluoride, leads to formation of silicon centered anions, which react with electrophilic reagents to yield products resulting from nucleophilic addition and substitution. In addition, when partnered with strong electrophiles, allylsilanes and enolsilanes undergo addition reactions proceeding *via* the intermediacy of α-silicon stabilized carbenium ions that

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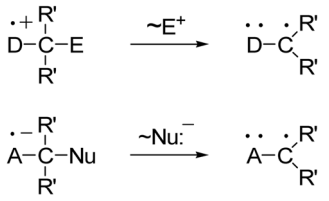
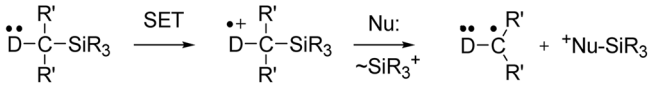


Scheme 1

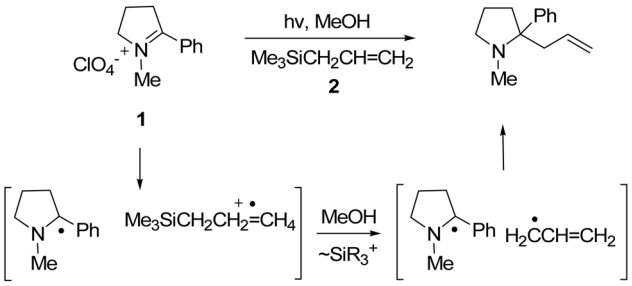


Scheme 2

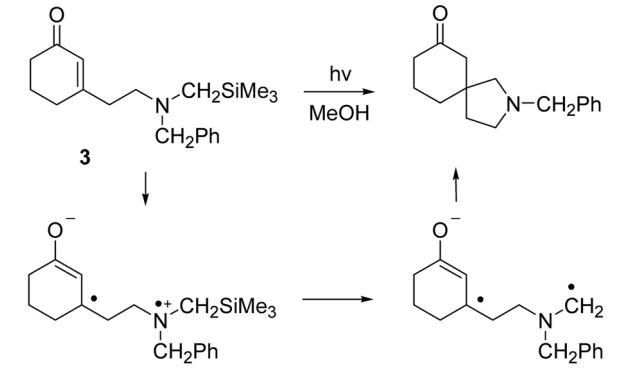
readily transfer their silyl groups to even weak silophiles.

A variety of photochemical and electrochemical investigations over the past two decades have uncovered another interesting feature of organosilanes. Substances in this family, in which silyl-substitution exists at sites adjacent to electron donor centers, undergo ready oxidation to generate silicon stabilized cation radicals (Scheme 2). Comprehensive theoretical and electrochemical studies by Yoshida and his co-workers[4] have shown that stabilization by trialkylsilyl groups in these reactive intermediates is a consequence of hyperconjugative interactions. Specifically, the effect results from overlap of the relatively (compared to C-C bonded analogues) high energy doubly occupied $\sigma_{C\text{-}Si}$ orbitals with half-filled heteroatom centered n-orbitals or alkene centered π-orbitals, which leads to stabilization of the cation radicals. Moreover, the odd electron and positive charge delocalization that results from these interactions, weakens the $\sigma_{C\text{-}Si}$ bond and makes the silicon center more electropositive. Consequently, these short-lived intermediates participate in fast silophile promoted desilylation reactions to produce neutral, carbon-centered free radical intermediates.

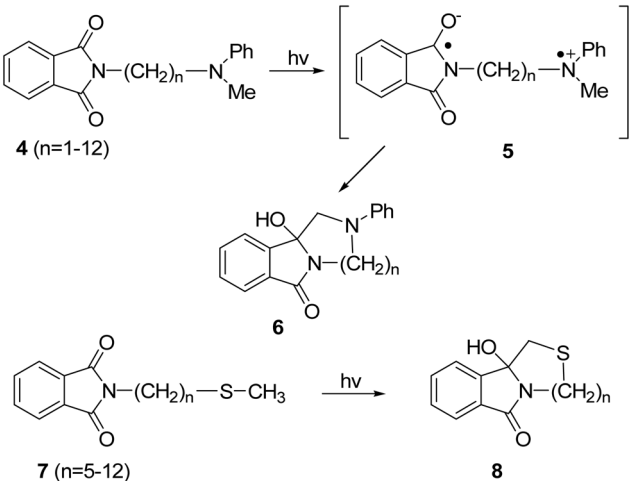
The redox properties and reactivity profiles of their cation radicals profoundly impact the nature and efficiencies of SET-promoted photochemical reactions of organosilanes. Owing to their low oxidation potentials, substances in this family serve as excellent electron donors to excited states of a variety of acceptors, including iminium salts, conjugated ketones, and cyanoarenes.[5] In addition, the large rates of desilylation of cation radicals, formed by these SET processes, often drive selective formation of carbon centered radicals that undergo C-C bond formation with either acceptor-derived radicals or neutral unsaturated substrates. Early examples of reactions which operate through this pathway are found in the direct irradiation-induced photoaddition of allyltrimethylsilane (**2**) to 1-methyl-2-phenylpyrrolinium perchlorate (**1**) (Scheme 3)[6] and the SET-sensitized photocyclization of the silylamino tethered cyclohexenone **3** (Scheme 4).[5,7] When viewed from the perspective SET photochemistry, α-silyl substituted electron donors are chemical equivalents of carbon-centered free radical intermediates. This conceptual connection that enables the design of new excited state reactions, in which C-C bond formation occurs by radical coupling and radical addition pathways.



Scheme 3



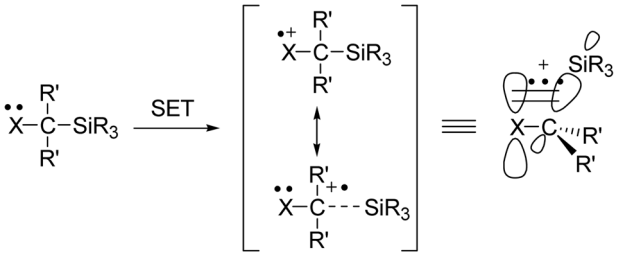
Scheme 4



Scheme 5

Phthalimide SET-Photochemistry. Extensive studies begun in the 1970s by Kanaoka[8] and his coworkers have demonstrated that phthalimides undergo a number of interesting photochemical reactions. Like their aromatic ketone counterparts, phthalimide excited states participate in intermolecular and intramolecular hydrogen atom abstraction and numerous examples of photochemical processes initiated in this manner have been uncovered.[9,10] Kanaoka's pioneering work with phthalimides led to the discovery of another interesting type of excited-state reaction. As illustrated by the photochemical reactions of the phthalimido-amines **4**[11,12] and phthalimido-thioethers **7**[13] (Scheme 5), the normal preference for γ-hydrogen atom abstraction is not seen in the excited states of phthalimides which contain good election

donors in their N-tethered side chains. As a consequence of their large excited state reduction potentials ($E^{S1}(-) = 2.1$ V, $E^{T1}(-) = 1.6$ V),[14] phthalimides participate in highly efficient photoinduced, intermolecular and intramolecular SET reactions. When phthalimide excited states interact with donors that have oxidation potentials less than *ca.* 2.1 V, the free energy for SET is negative and, consequently, SET occurs rapidly (*ca.* 1×10^{10} M^{-1} s^{-1}).[15] In substrates that contain N-linked thioether and amine electron donors, SET dominates over other pathways for excited-state decay, and it generates intermediate zwitterionic biradicals (*e.g.*, **5**) that serve as precursors of the heterocyclic products **6** and **8**.

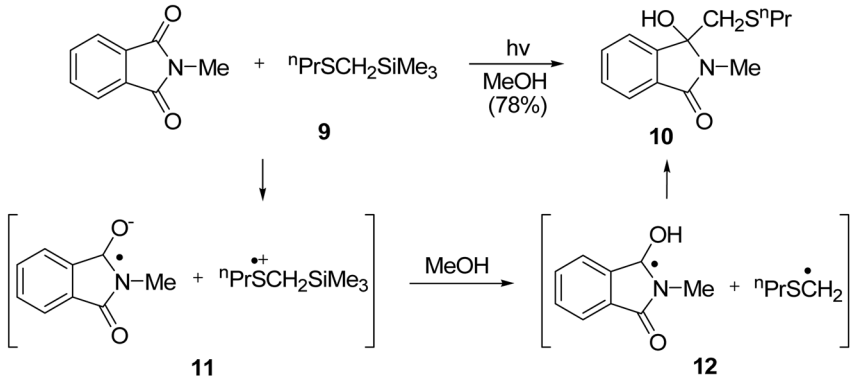


Scheme 6

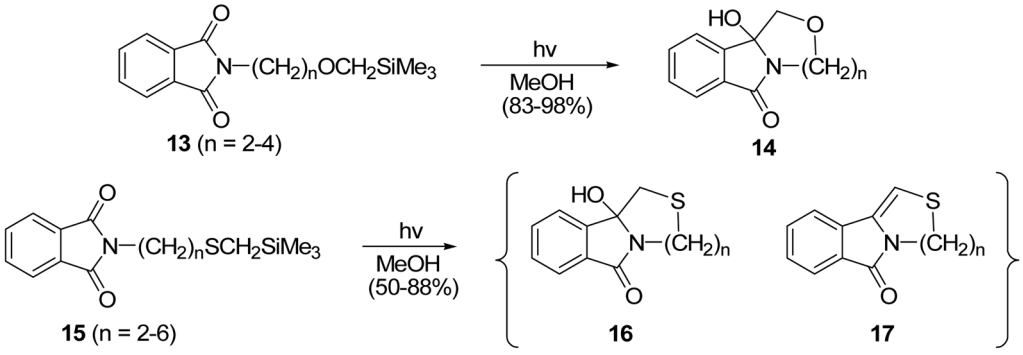
SET-Photochemistry of Silicon-Substituted Phthalimides

Photoaddition and Photocyclization Reactions of Phthalimides with α-Silyl Electron Donors. As mentioned above section, α-trialkylsilyl substitution in heteroatom-containing substances has a profound effect on their oxidation potentials.[4] Substitution of this type results in thermodynamic stabilization of the cation radicals that arise by one-electron oxidation of α-trialkylsilyl substrates. Overlap of the relatively high energy, doubly occupied $\sigma_{C\text{-}Si}$ orbital with the half-filled heteroatom orbital in the cation radical results in lowering of the energy of the charged radical (Scheme 6). From this view, the delocalized silicon-stabilized cation radical can be pictured as a species with positive charge and odd electron density distributed over the heteroatom, α-carbon, and silicon centers. The thermodynamic stabilization instills kinetic instability into these high-energy intermediates since the orbital interactions weaken the C-Si bond and make the silicon center even more electropositive than it is in neutral alkylsilanes. Consequently, silophile-induced α-heterolytic fragmentation of these intermediates is a facile process that results in production of heteroatom-stabilized, carbon-centered radicals.

Our studies of SET-induced excited-state reactions of phthalimides with α-trialkylsilyl-substituted ethers, thioethers, amines, and amides have shown that cation radical desilylation drives a host of interesting processes which proceed by pathways involving generation and carbon-carbon bond-forming coupling of radical intermediates. In an early study, we observed that simple α-silyl ethers, thioethers, and amines undergo modestly efficient photoaddition to phthalimide and its *N*-methyl derivative.[16] The highest yields in this series of closely related reactions were



Scheme 7

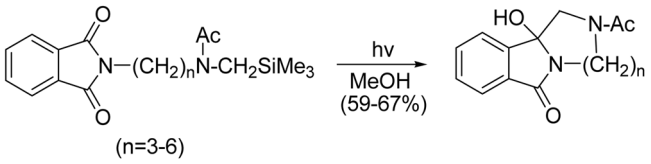


Scheme 8

obtained with the silylmethyl-propyl thioether **9**, which undergoes photoaddition with *N*-methylphthalimide to produce adduct **10** in a 78% yield (Scheme 7). The general mechanistic pathway, followed in this and related processes, involves thermodynamically and, thus, kinetically driven SET from **9** to the phthalimide excited state leading to formation of the ion radical pair **11**. Solvent (MeOH)-promoted desilylation of the cation radical and protonation of the anion radical then provides the radical pair **12** which serves as a direct precursor of adduct **10**.

Intramolecular photoreactions of phthalimides containing *N*-tethered α-silyl donors proceed with high chemical efficiencies to generate novel heterocyclic products. For example, irradiation of MeOH solutions of the phthalimido-ethers **13** leads to formation of the amidol-containing oxygen heterocycles **14** in excellent yields (Scheme 8).[17] Analogous photocyclization reactions are observed with the phthalimido-thioethers **15**.[18] Although dehydration of the primary photoproducts (**16** → **17**) occurs with varying ease in these systems, the overall yields of the reactions remain high, even when the size of the ring that is formed in the ultimate biradical cyclization steps is large.

A parallel investigation of the photochemistry of α-silylamine- and α-silylamide-linked phthalimides has provided a more in-depth understanding of the factors that govern both the chemical and quantum yields of SET-promoted photocyclization reactions.[19,20] Specifically, irradiation of a MeOH solution of the (silylamino)-phthalimide **18** leads to nonselective formation of a mixture of products, including the fused diazines **19** and **20** and amidol **21** (Scheme 9). In stark contrast to this, the tricyclic sulfonamide **23** is formed in high yield when the (silylamido)-phthalimide **22** is irradiated in MeOH (Scheme 9). These divergent results suggest that the preparative utility of photocyclization reactions, operating by sequential SET desilylation pathways, could be enhanced by using substrates that contain α-silylamide rather than α-silylamine donor sites. Support for this proposal is found in photoinduced cyclization of the acetamide derivatives shown in Scheme 10. Quantitative studies showed that the quantum yields of photocyclization reactions of the linked phthalimides **18** and **22** are also greatly dependent on the nitrogen substituent, with the amide substrate reacting with a greater efficiency (Φ = 0.12)

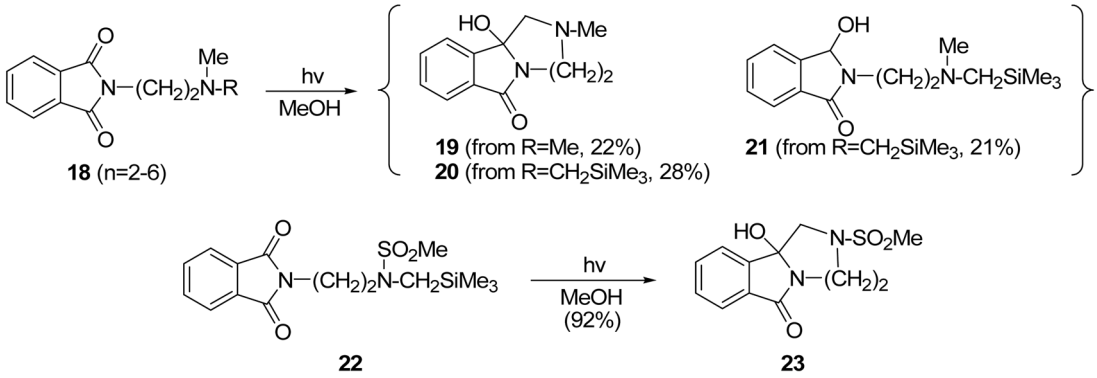


Scheme 10

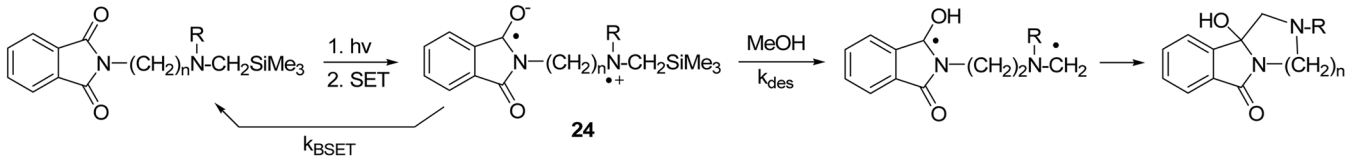
than the amine (Φ = 0.04).

When viewed in a perfunctory way, the results presented above appear counterintuitive in that they lead one to question why the SET-promoted photoreactions are more efficient when they involve poorer electron donors (oxidation potentials of amines are often *ca.* 0.5 V lower than those of the corresponding amides). The answer comes from an analysis of the key factors involved in determining the chemical and quantum efficiencies of excited-state reactions that proceed *via* pathways in which initial SET is followed by secondary reaction of charged radical intermediates. In the case at hand, SET from both α-silylamide and α-silylamine donors to the singlet excited state of the phthalimide chromophore should be highly exothermic. As a result, both intramolecular SET processes should occur at rates ($>1 \times 10^{10}$ s^{-1})[15] that are competitive with other pathways responsible for decay of the excited phthalimide. In this respect, Coyle and coworkers[21] have suggested that the n-π* singlet excited state of phthalimides is quenched by SET from pendant amino groups and that this quenching process is on the pathway for cyclization reaction of these substrates. The intermediate zwitterionic biradicals **24** (Scheme 11) formed by excited-state SET in (silylamino)- and (silylamido)-phthalimides can react by several different routes. For example, exothermic back-SET would generate the ground-state starting materials with rates which are essentially independent of the nitrogen substituent. Competing with back-SET are secondary fragmentation reactions such as methanol-induced α-desilylation.

In our earlier laser flash photolysis studies,[2] we demonstrated convincingly that the rates of aminium radical fragmentation are highly dependent on the nitrogen substituent. Specifically, methanol-induced desilylation of silylamine carion radicals is 2 orders of magnitude slower than the analogous reaction of α-silylamide cation radicals. In more general terms, the rates of ion radical reactions are directly



Scheme 9



Scheme 11

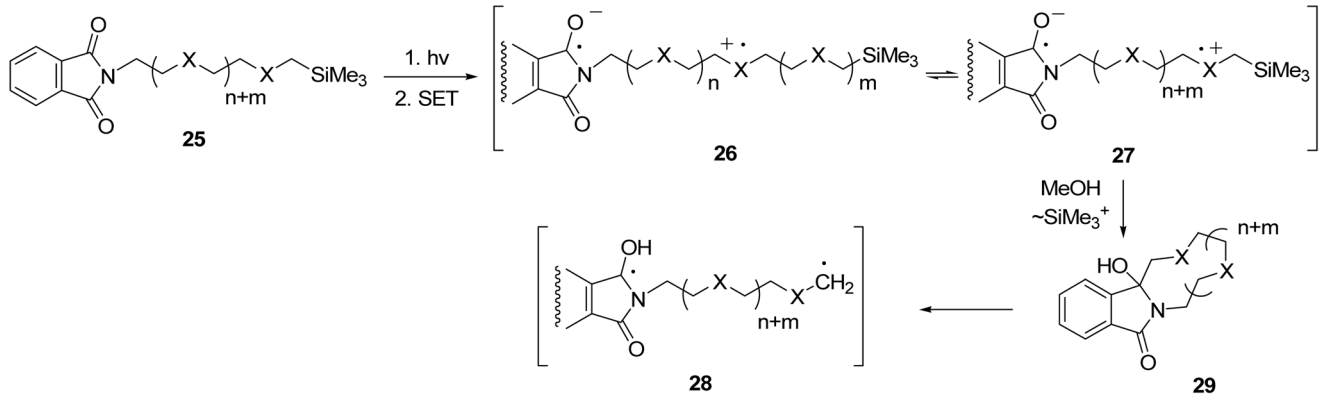
proportional to the stability of these short-lived intermediates, as judged from the redox potentials of neutral precursors. In summary, the large rate constants for desilylation of zwitterionic biradicals derived by photoinduced, intramolecular SET in α-(silylamido)-phthalimides translates into a larger rate constant ratio, $k_{des}/(k_{des} + k_{BSET})$. Consequently, larger quantum efficiencies are observed for biradical and, thus, product formation.

Photomacrocyclization Reactions of Silicon-Substituted Polydonor Linked Phthalimides. As a result of their high chemical yields, SET-promoted photocyclization reactions of linked phthalimide acceptors and α-silyl-substituted polyheteroatom containing donors can be incorporated into novel strategies for the preparation of interesting cyclic substances. This proposal is based on an analysis of the mechanistic pathways followed in the potentially competitive photoreactions of substrates in this family. As depicted in Scheme 12, irradiation of polydonor-linked phthalimides **25**, which possess trimethylsilyl groups at terminal donor sites, is expected to result in regioselective production of macrocyclic products **29**. The key excited state SET steps in these pathways should generate mixtures of possibly rapidly interconverting zwitterionic biradicals, **26** and **27**. The relative populations of these zwitterionic biradicals could be governed either by the rates of the intramolecular SET from each donor site or by the relative energies of the cation radicals, as judged by the oxidation potential at each heteroatom center. Importantly, the rates of secondary α-deprotonation and α-desilylation reactions that take place at centers adjacent to each of the cation radical sites would not depend on the relative populations of the zwitterionic biradicals. Rather, the relative rates of these processes which produce the 1,n-biradical precursors of cyclization products, should be determined by the rates of the competing fragmentation reactions. Since desilylation of the terminal cation radical **27** should be the most rapid process, regioselective generation of the diradical precursors **28** of the macrocyclic products **29** should be observed.

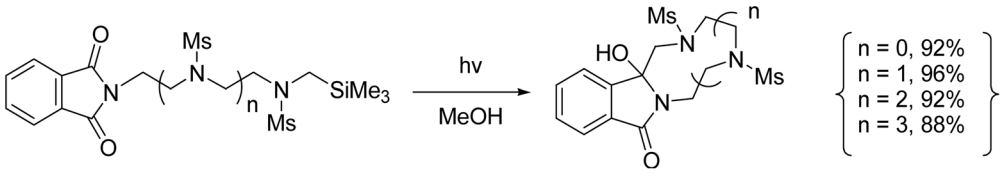
Photomacrocyclization Reactions of Polydonor Linked Phthalimides: A three-pronged approach has been used to (1) probe the scope and limitations of the SET-promoted photomacrocyclization processes, (2) gain information about the factors that govern chemical yields and quantum efficiencies, and (3) investigate applications to the preparation of potentially important materials.

Exploratory studies with a variety of phthalimides, containing trimethylsilyl-terminated polysulfonamide, polyether and polythioether chains, showed that these substances undergo modestly to highly efficient photocyclization reactions to produce the corresponding macrocyclic products. Examples of these processes are shown in Scheme 13 through Scheme 18.[22,23]

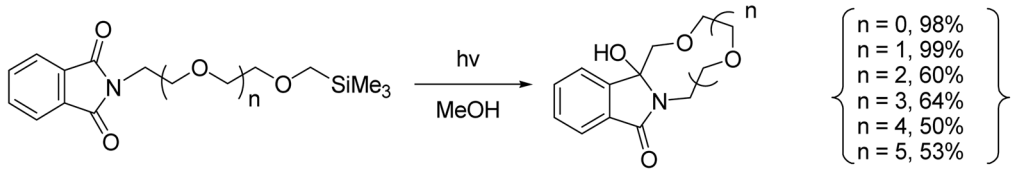
Factors Governing the Chemical and Quantum Yields of Photomacrocyclization Reactions of Polydonor Linked Phthalimides: As a consequence of their structural outcomes and high yields, the photomacrocyclization reactions shown above can serve as the foundation of practical synthetic routes for the preparation of polyfunctionalized macrocycles. However, before these methods can be practically implemented, a detailed understanding of the factors that govern chemical yields and quantum efficiencies of these photochemical reactions must be developed. As mentioned above, several factors can contribute in controlling the chemical and quantum yields in photoreactions of the polydonor-substituted phthalimides **30** (Scheme 19). For example, photoproduct distributions (yields) in these processes should to be governed by the relative rates of intramolecular SET from the respective donor sites to the excited phthalimide



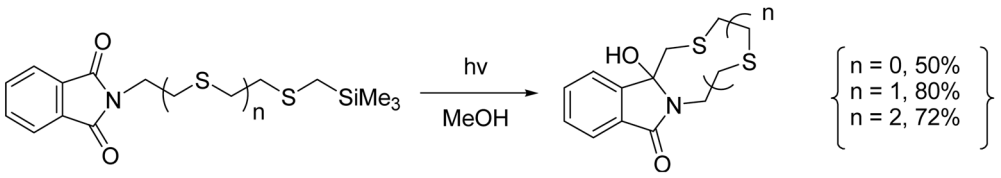
Scheme 12



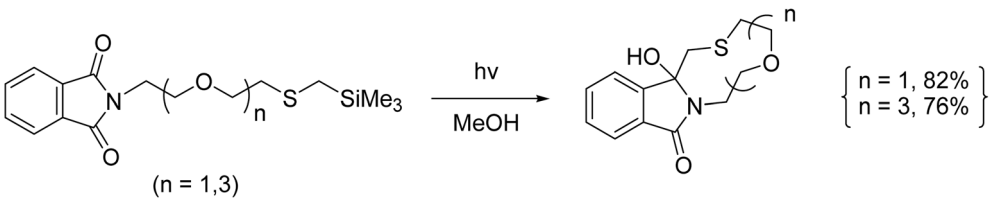
Scheme 13



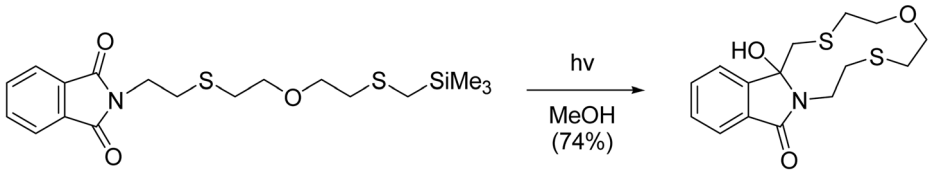
Scheme 14



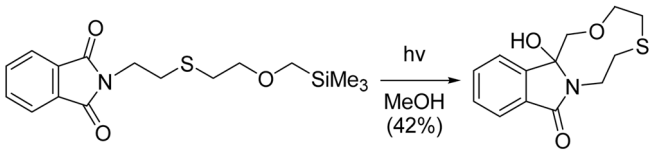
Scheme 15



Scheme 16



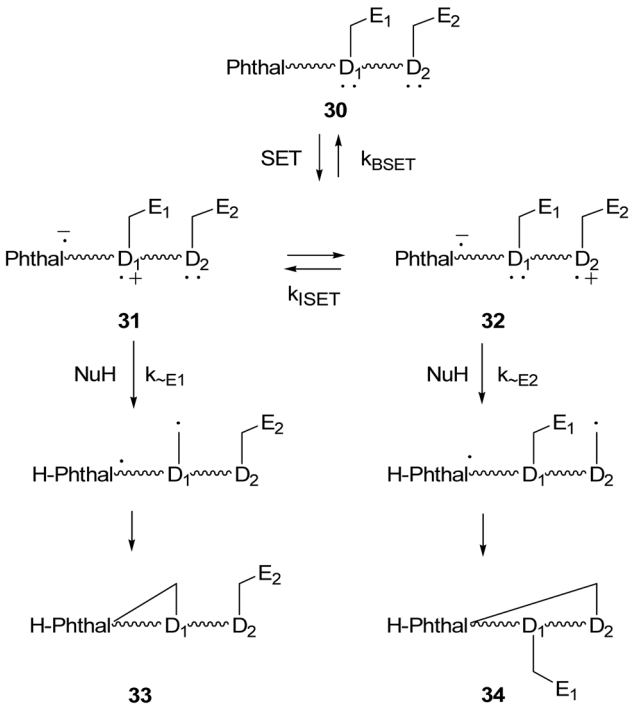
Scheme 17



Scheme 18

chromophore and the rates of cation radical fragmentation reactions of the intermediate zwitterionic biradicals **31** and **32**. This would be the case when interconversion of the initially formed zwitterionic biradicals is slower than the fragmentation reactions. In another limiting situation where zwitterionic biradical interconversion is faster than fragmentation, an equilibrium mixture of the zwitterionic biradicals will be generated in which the mole fraction of each is governed by the redox potential at each donor site. The chemical efficiencies for formation of products **33** and **34** in these cases will be dependent on the relative rates of the competing fragmentation reactions, if the energy barriers for fragmentation are higher than those for interconversion of the zwitterionic biradical. More complex situations exist in cases where the rates of zwitterionic biradical interconversion are either in the same range as or somewhat less than the rates of cation radical fragmentation.

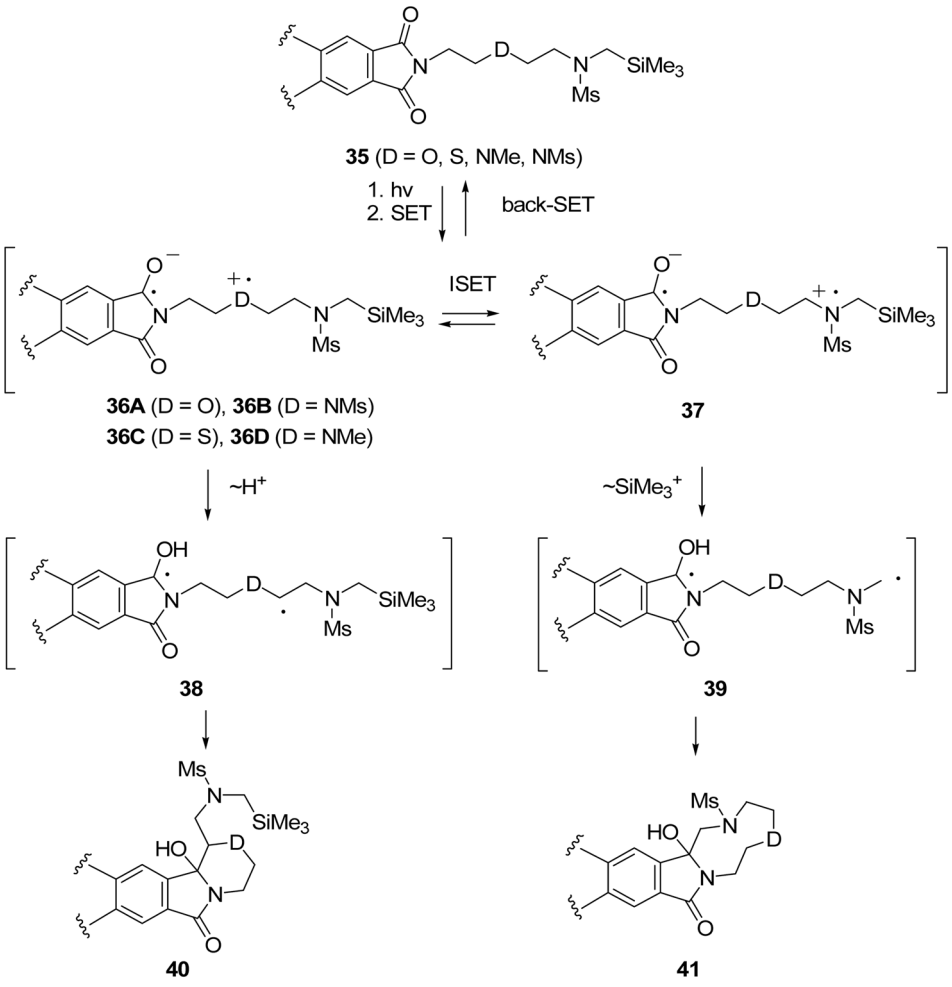
This mechanistic analysis demonstrates that the chemical efficiencies of SET-promoted reactions of polydonor-linked phthalimides could depend on the number, types, location and reactivity of ion radical centers formed by either initial excited state SET or intrasite-SET. Clearly, knowledge about how these factors govern product yields, regiochemical selectivities and quantum efficiencies is crucial to the design of synthetically useful photochemical reactions of these substrates. Recent studies[24] with substrates **35** (Scheme 20) containing light absorbing phthalimide and naphthalimide



Scheme 19

acceptor moieties and a variety of N-linked bis-donor sites have provided information about these issues. A standard donor group ($NMsCH_2SiMe_3$) with known oxidation potential and rate of methanol induced cation radical fragmentation was incorporated at the terminal position in each of these substances. Finally, the oxidation potentials and fragmentation rates at the other donor sites in these substances were varied by using different heteroatoms and/or substituents.

Fluorescence spectroscopic studies with donor-linked 2,3-naphthalimides have shown that the rates of intramolecular SET from donors to the naphthalimide singlet excited state vary over three orders of magnitude range and are directly dependent on the electron donating ability of the donor. For example, first-order rate constants for SET from tertiary amine centers in naphthalimides **35** (D = NMe) is 4×10^9 s^{-1}. In contrast, SET from the α-silylsulfonamide donor site in **35** (D = NMs) is much slower (1×10^8 s^{-1}). Thus, the rates of intramolecular SET from the donor sites in the linked naphthalimides parallel those predicted by using simple free energy calculations. Accordingly, SET from the tertiary amine centers ($E_{1/2}(+)$ = *ca.* 0.6 V) to the singlet excited 2,3-naphthalimide chromophore ($E_1^{S1}{}_{(-)}$ = *ca.* 1.8 V)[25] is highly exothermic in contrast to SET from more weakly donating sulfonamide ($E_{1/2}(+)$ = *ca.* 2 V)[20,26] and ether ($E_{1/2}(+)$ = *ca.* 2



Scheme 20

V)[27] donors. As a consequence, the relative populations of zwitterionic biradicals **36** and **37** (Scheme 20), formed initially by intramolecular excited state electron transfer, should be biased in favor of those that contain lower energy cation radical sites.

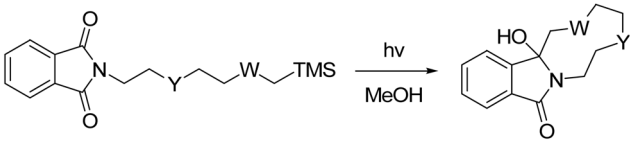
Several interesting trends can be seen in the results of preparative photochemical reactions with these substrates. Firstly, α-silylsulfonamido-phthalimide and α-silylsulfonamido-naphthalimide that contain other heteroatom donor sites (*e.g.*, O, NMs) with higher or nearly equal oxidation potentials as compared to the terminal sulfonamide undergo chemically efficient and highly regioselective photocyclization reactions *via* sequential SET-desilylation pathways. Examples are found in photocyclization reactions of phthalimides **42-45** (Scheme 21) and naphthalimides **46-49** (Scheme 22). Secondly, α-silylsulfonamide substrates that possess an internal, strongly electron donating tertiary amine site undergo low yielding unselective photoreactions.

In these cases, exemplified by the amino-sulfonamides **50** and **51** (Scheme 23), the major pathway involves α-proton transfer from the internal tertiary aminium radical centers followed by biradical cyclization or disproportionation. Finally, the thioether containing phthalimide-sulfonamide **52** (Scheme 24) represents an intermediary case where highly efficient photocyclization takes place *via* a sequential SET-desilylation route despite the presence of a sulfur donor site that has a significantly lower oxidation potential than the terminal α-silylsulfonamide.

These observations suggest that at least two factors contribute in governing the chemical efficiencies/regioselectivities of photocyclization reactions of the bis-donor linked, α-silylsulfonamide terminated phthalimides and naphthalimides. The first contribution comes from the relative intrinsic rates of the α-heterolytic fragmentation processes (~H^+, ~$SiMe_3^+$) which can occur at each cation radical site. A second factor is the relative energies of the zwitterionic biradicals which not only control the initial and final populations but also govern the energy barriers for the competing α-heterolytic fragmentation processes. Thus, fast α-desilylations at α-silylsulfonamide sites of zwitterionic biradicals **37** (Scheme 20) are the dominant reaction pathways followed when the competitively formed, zwitterionic biradicals **36**, which can only undergo slow α-deprotonation, are of near equal or higher energy than **37**. However, when the internal zwitterionic biradicals **36** have significantly lower energies than their terminal counterparts **37**, pathways involving α-deprotonation at the internal cation radical site can predominate.

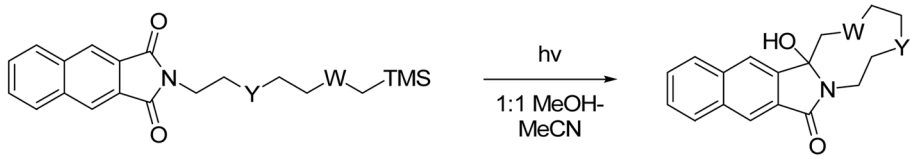
Important information about how the energies and fragmentation rates of zwitterionic biradical intermediates govern the nature and efficiencies of SET-promoted photoreaction of acceptor-polydonor substrates, has been gained from reaction quantum yield measurements. Based on the mechanistic sequence shown in Scheme 20, it is expected that the quantum efficiencies for reactions of the bis-donor substrates will depend on the relative rates of the fragmentation reactions which compete with back-SET for deactivation of the zwitterionic biradical intermediates. Specifically, the fraction of the biradical intermediates, which react to form products, is dependent on the combined rates of α-deprotonation and α-desilylation as compared to that for back-SET. Also, depending on whether interconversion of the zwitterionic biradicals is faster or slower than their decay, the equilibrium constants for interconversion of these intermediates will also contribute in governing reaction quantum yields.

Data accumulated earlier in studies of photocyclization reactions of mono-donor substituted aminoethyl-phthalimide derivatives provide a framework for the development of a plausible interpretation of the quantum yields for reactions

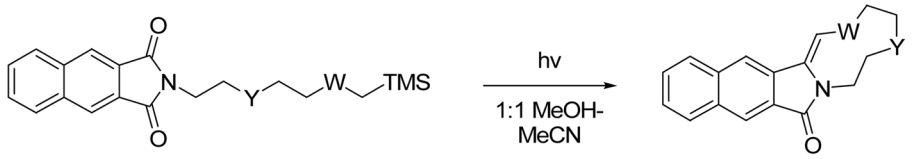


42 (Y = W = NMs) (96%)
43 (Y = O, W = NMs) (91%)
44 (Y = O, W = NAc) (93%)
45 (Y = OCH_2CH_2O, W = NMs) (89%)

Scheme 21

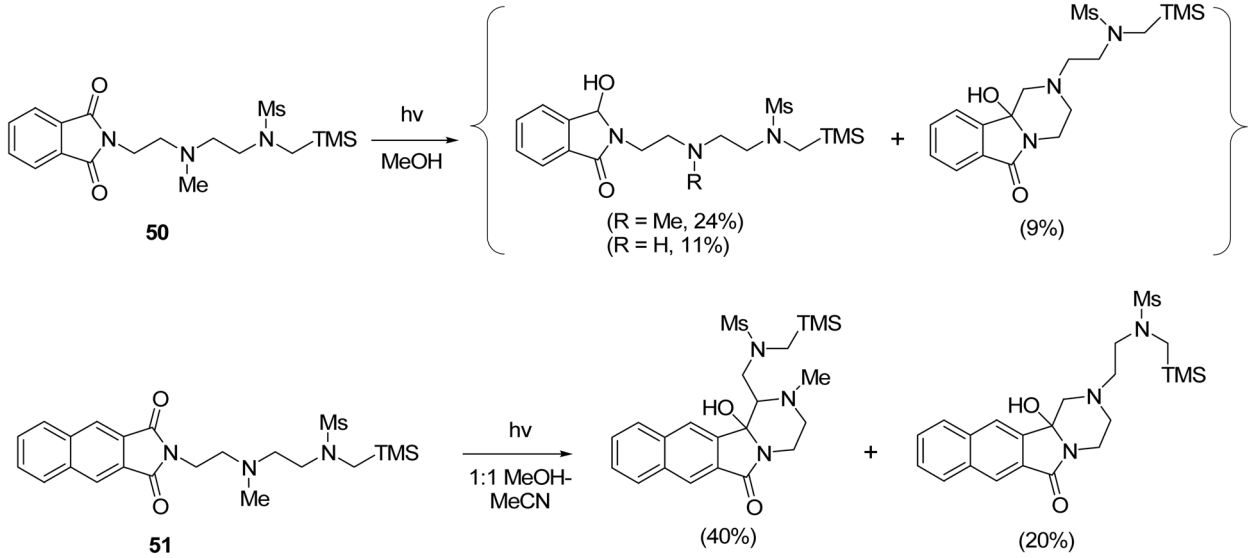


46 (Y = W = NMs) (100%)
47 (Y = O, W = NMs) (88%)

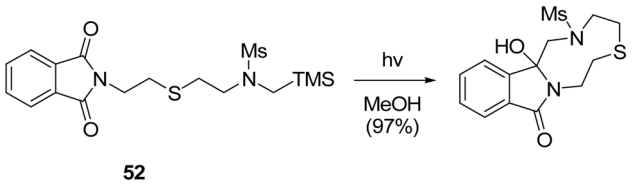


48 (Y = OCH_2CH_2O, W = NMs) (70%)
49 (Y = O, W = NAc) (80%)

Scheme 22



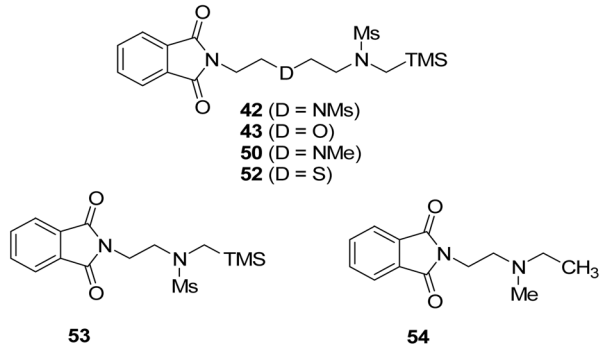
Scheme 23



Scheme 24

of the bis-donor substituted phthalimides (Table 1). Earlier, we observed that the quantum efficiencies for photocyclization reactions of substituted aminoethyl-phthalimides vary in a regular manner with the nature of the α-electrofugal group (E=H, TMS) and nitrogen substituent (R=Me, Ac, or Ms).[2b,20] Accordingly, the quantum yields for photocyclization reactions of the α-silylsulfonamido terminated bis-donor-

Table 1. Quantum yields for reactions of the α-silylsulfonamido-terminated phthalimides



Compounds	Quantum Yield (ϕ)[a]
42	0.12
43	0.14
50	0.04
52	0.02
53	0.12
54	0.003

[a]measured in CH_3OH

phthalimides should be in the range of those for the mono-silylsulfonamido-phthalimide **53** (Φ = 0.12, Table 1) if the radical cation sites in zwitterionic biradicals derived from the former substances reside exclusively at the terminal sulfonamide moieties. Interestingly, this is the case for photoreaction of the bis-sulfonamide **42** (Φ = 0.12) and ether-sulfonamide **43** (Φ = 0.14), which have photoreaction quantum yields that a nearly equal to that of the mono-α-silylsulfonamidoethyl-phthalimide **53** (Φ = 0.12). In contrast, photoreaction of the tertiary amine containing α-silyl-sulfonamide **50** (Φ = 0.04) has a quantum efficiency that matches those of tertiary aminoethyl-phthalimides that undergo photoreactions *via* a sequential SET-proton transfer pathway (*e.g.*, **54**, Φ = 0.003). Moreover, although proceeding with a high chemical yield, photoreaction of the thioether-silyl-sulfonamide **52** has a much lower quantum efficiency (Φ = 0.02) than those of the model mono-silyl-sulfonamide (*e.g.*, **53**, Φ = 0.12).

The combined results of this effort provide a view of the factors that control the chemical and quantum efficiencies of photochemical reactions of polydonor-substituted phthlimides. This is best seen by using the energy profiles shown in Figure 1. Assignments of the relative energies of the zwitterionic biradicals, **36A-D** and **37** (Scheme 20), which serve as intermediates in photoreactions of the bis-donor linked phthalimides probed in this effort, are made on the basis of the known oxidation potentials of model ethers (*ca.* +2.5 V),[27] methanesulfonamides (*ca.* +2.5 V),[26] α-silyl-methanesulfonamides (*ca.* +2.0 V),[20] thioethers (*ca.* +1.4 V),[28] and tertiary amines (*ca.* +0.6 V).[29] In addition, the relative heights of the intrinsic energy barriers for competing α-heterolytic fragmentation reactions (~H^+, ~$SiMe_3^+$) of the zwitterionic biradicals are estimated by using kinetic data obtained from studies of α-deprotonation and α-desilylation reactions of tertiary amine and amide derived cation radi-cals.[2] Accordingly, the intrinsic barriers for MeOH induced desilylation are lower than those for deprotonation of amine,

thioether, ether and sulfonamide cation radicals. The kinetic and thermodynamic estimates presented in Figure 1 lead to the experimentally verified conclusion that reactions of the (potentially) rapidly interconverting mixture of zwitterionic biradicals, **36A** (D = O)-**37** and **36B** (D = NMs)-**37**, formed from by SET in the corresponding ether-sulfonamides **35** (D = O) and bis-sulfonamide **35** (D = NMs), will be dominated by α-desilylation. Moreover, in cases where the lowest energy zwitterionic biradicals **37** (D = O or NMs) which have α-silyl substituents are also the most reactive, the energy barriers (thus rates) for desilylation ($\Delta E_{37\sim E}$) will be nearly the same as that for desilylation of the zwitterionic biradicals derived from the mono-silylsulfonamide **53**. This prediction is consistent with the observation that the quantum yields for photocyclization reactions of ether-sulfonamide **43** (Φ = 0.14) and bis-sulfonamide **42** (Φ = 0.12) are in the same range as that for photocyclization of the corresponding mono-donor model **53**.

The situation is different in the case of the zwitterionic biradicals **36C** (D = S)–**37** arising from the thioether-sulfonamide substituted phthalimide **52**. The observation that **52** undergoes chemically efficient photocyclization by a sequential SET-desilylation pathway suggests that the energy of the transition state for desilylation ($\neq_{\sim E}$) of **37** (D = S) is lower than the transition state for α-deprotonation ($\neq_{\sim H}$) at the internal thioether cation radical center in **36C** (D = S). The unique/distinguishing feature of photoreaction of thioether-sulfonamide **52** is that the energy of the apparently reactive zwitterionic biradical **37** (D = S) is significantly higher (*ca.* 14 kcal/mol) than that of its apparently unreactive partner **36C** (D = S). Although this difference does not influence the chemical yield/regioselectivity of the process, it has a profound effect on the quantum efficiency. Specifically, the energy barrier for desilylation of the zwitterionic biradicals **36C** (D = S)–**37** ($\Delta E_{36C\sim E}$) is now much greater than that ($\Delta E_{37\sim E}$) for desilylation of either **36A** or **36B** (D = O or NMs)-**37** and, as a result, desilylation is less competitive with back-SET.

Photoreaction of the tertiary amine containing α-silyl-sulfonamide **50** represents the third scenario for photoreactions of polydonor-substituted phthalimides, which proceed *via* the intermediacy of two or more potentially interconverting zwitterionic biradicals. In this case, the energy of the tertiary aminium radical containing zwitterionic biradical **36D** (D = NMe) is much lower (*ca.* 44 kcal/mol) than that of its α-silylsulfonamide cation radical partner **37** (D = NMe). As a result, the energy barrier for desilylation of **36D** (D = NMe)-**37** is insurmountably high. Consequently, photoreaction of this substrate takes place by the lower energy pathway involving slow deprotonation of **36D** (D = NMe). Also, this process has the same low quantum efficiency (Φ = 0.04) as do photoreactions of tertiary-aminoethyl-phthalimides which take place by sequential SET-deprotonation routes.

This investigation has provided some general guidelines for predicting the chemical yields/regioselectivities and quantum efficiencies of SET-promoted photochemical reactions of acceptor-polydonor systems. For example, when the lowest energy zwitterionic biradical, derived by intramolecular and/or intrasite SET in a substrate of this type, also contains the most reactive cation radical site, a highly chemically efficient/regioselective photoreaction will ensue. Also, the quantum efficiency of the process will be in the range of that for photoreaction of a simple acceptor-monodonor model. On the other hand, photoreactions of substrates in which the lowest energy zwitterionic biradical is also the least reactive will have low quantum efficiencies. In addition, these processes will have either high or low chemical yields/regioselectivities, depending on whether the relative energies of the transition states for competing cation radical fragmentation processes are large or small.

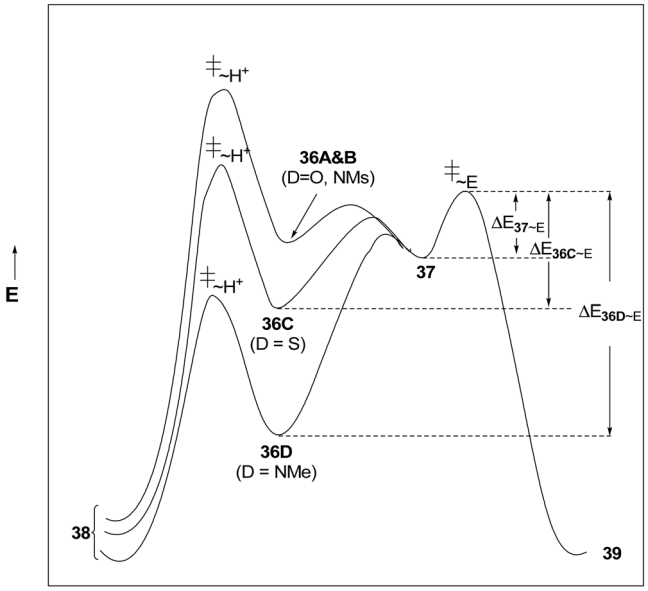
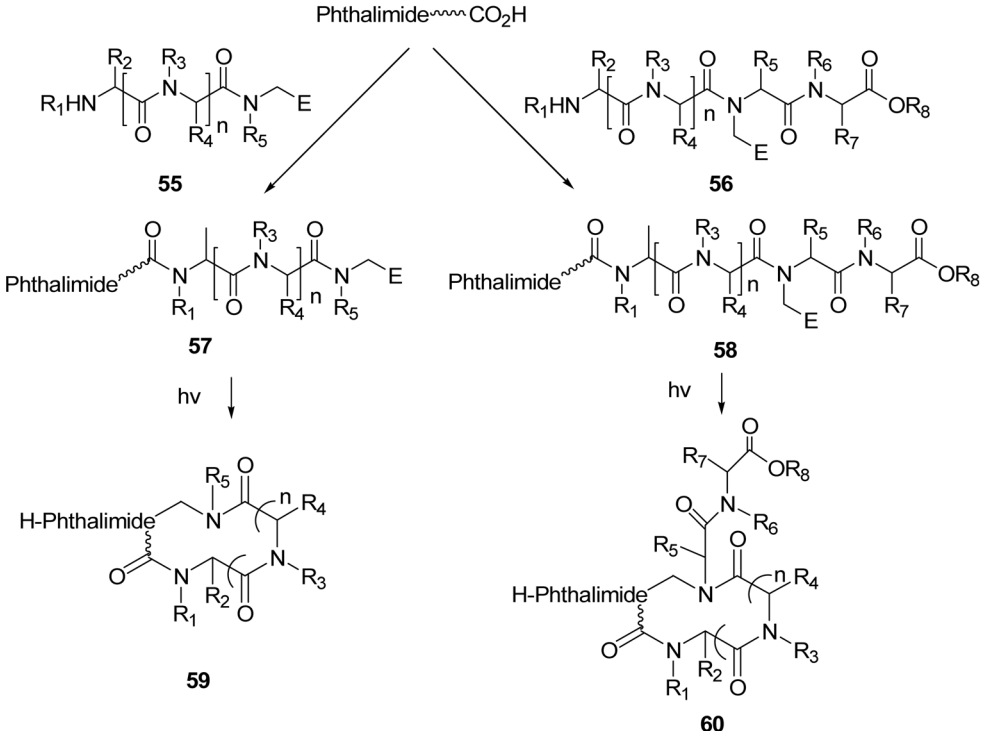
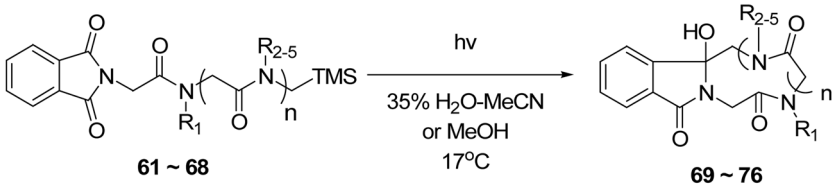


Figure 1. Energy profiles for competing α-deprotonation and α-desilylation reactions of zwitterionic biradicals **36** and **37** serving as intermediates in SET-promoted photochemical reactions of bis-donor substituted phtalimides. See Scheme 20 for the structures of the zwitterionic biradicals **36A-D** and **37** and biradicals **38-39**.

Application of SET-Promoted Photocyclization Reaction of Phthalimides to the Preparation of Cyclic Peptide Mimetics: As stated above, the unique features of SET-promoted photocyclization reactions of polydonor-linked phthalimides make these processes compatible with strategies for the efficient construction of highly functionalized macrocyclic targets. An example of this is found in a plan for synthesis of cyclic peptide mimics. The substrates for the key photomacrocyclization processes (**57** or **58**, Scheme 25) in the approach would be prepared by linking a carboxylic acid containing phthalimide to the *N*-terminal amino group of an intact peptide (**55** or **56**). The strategy used for preparation of the phthalimide-linked polypeptides would be guided by the structural requirements of the target cyclic peptides. Specifically, a precursor to a selectively reactive α-trimethylsilylamide cation radical site would be incorporated at a preselected location within or at the end of the peptide chain. Irradiation of the substrate is then expected to initiate a reaction cascade involving near neighbor SET, intra-chain SET, and desilylation at the reactive amide cation radical



Scheme 25



Substrate	Product	n	R_1	R_2	R_3	R_4	R_5	Yield
61	**69**	0	H	-	-	-	-	18%
62	**70**	0	Bn	-	-	-	-	60%
63	**71**	1	Bn	Bn	-	-	-	40%
64	**72**	1	Me	Bn	-	-	-	40%
65	**73**	2	Bn	Bn	Bn	-	-	55%
66	**74**	2	Me	Me	Bn	-	-	15%
67	**75**	3	Bn	Bn	Bn	Bn	-	70%
68	**76**	4	Bn	Bn	Bn	Bn	Bn	61%

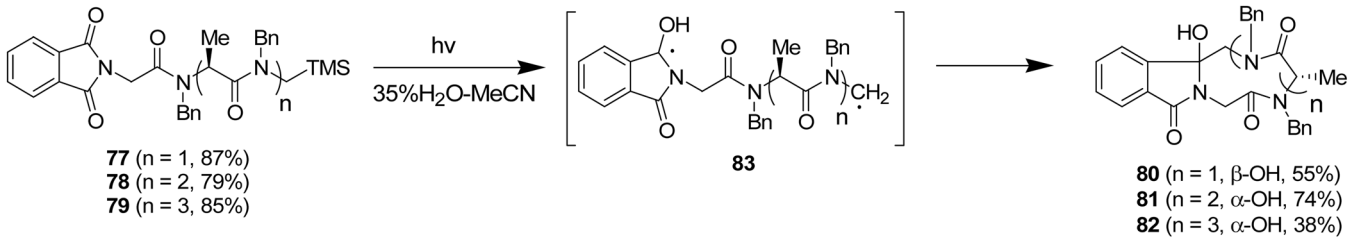
Scheme 26

position. Cyclization of the biradical, formed in this fashion, then produces the target cyclopeptide mimic, **59** or **60**.

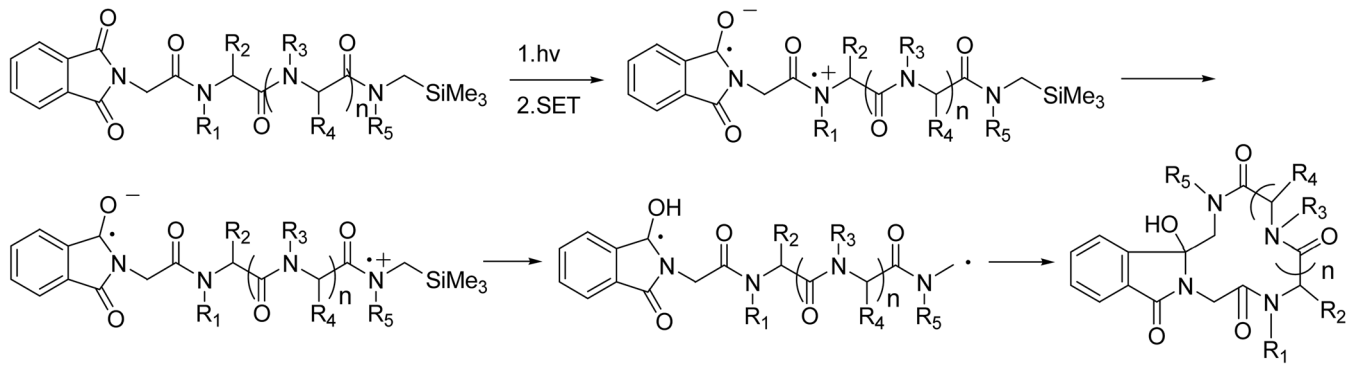
Studies with a series of TMS-terminated phthalimido-amides and phthalimido-peptides **61-68** were carried out in order to test the scope and potential limitations of this methodology for the preparation of cyclopeptide mimetics.[30] As seen by viewing the results summarized in Scheme 26, irradiation of the TMS-terminated phthalimidopeptides leads to modestly efficient production of the cyclopeptide analogs **69-76**.

In addition, photocyclization reactions of the TMS-terminated glycine-((S)-alanine)$_n$ peptides **77-79** were studied to show that the SET-photocyclization based methodology can be used to synthesize stereoregular cyclic peptide analogs (Scheme 27). An important feature of photoreactions of these substrates resides in the fact that a new chiral center is created at the bicyclic amidol carbon in the products **80-82**. Earlier studies with a wide variety of related phthalimide derived photoproducts have demonstrated that configurational inversion at amidol centers of this type, *via* either reversible *N*-acyliminium ion or amido-ketone forming pathways, is slow under neutral conditions.[31] As a consequence, stereochemical preferences in photocyclization reactions of alaninyl peptides **77-79** would need to be the result of kinetic factors governing the rates of cyclization of the ultimate biradical intermediates **83**. In light of these considerations, it is interesting that irradiation of the peptides **77-79** in 35% H_2O-MeCN leads to modestly efficient formation of the cyclic peptides **80-82**, each as a single diastereomer.

The results of the investigation described above demonstrate



Scheme 27



Scheme 28

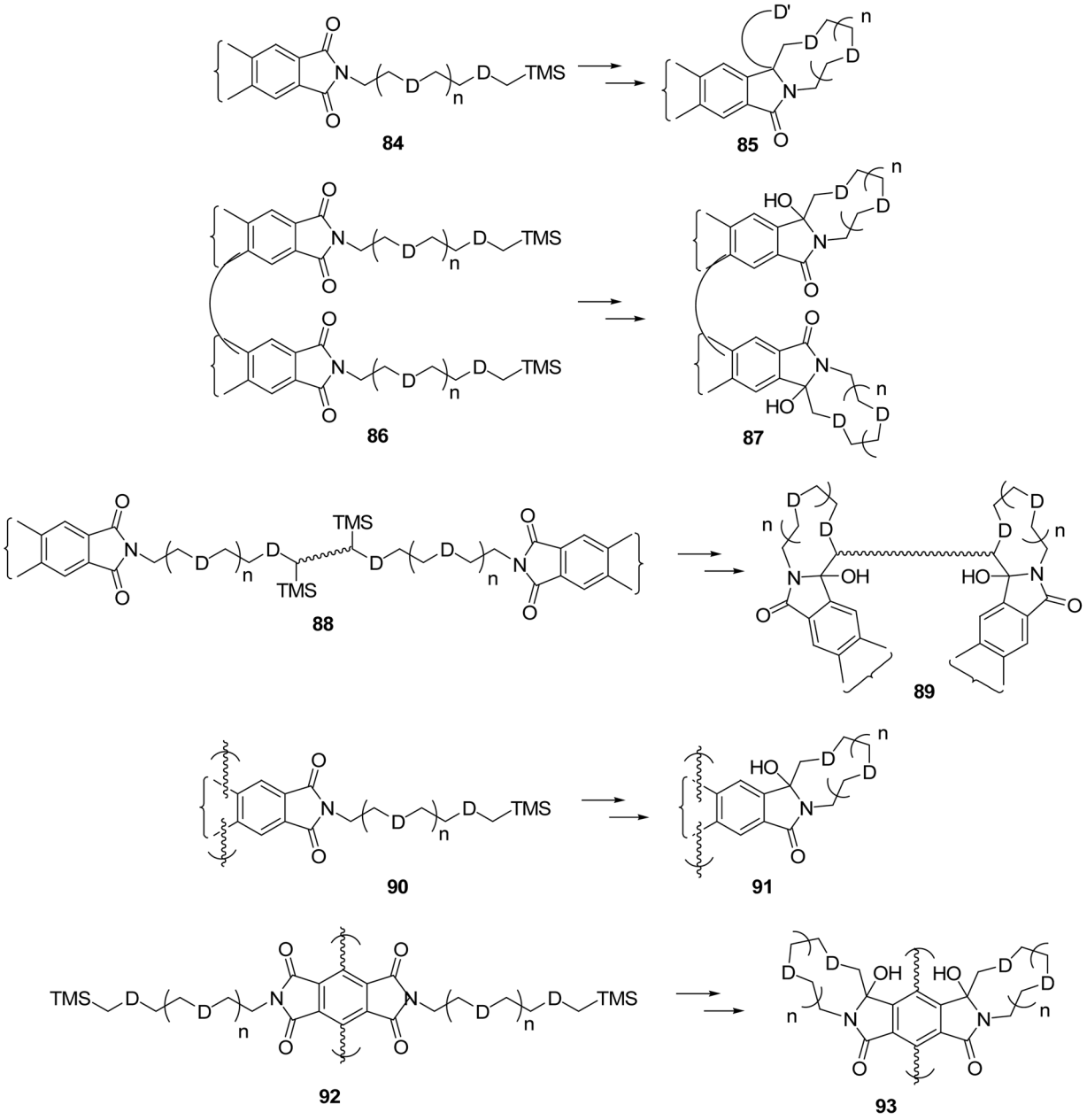
the feasibility of the photochemical based strategy for preparation of cyclic peptide analogs. The key step in routes based on this design involves SET-photoinduced cyclization of *N*-acceptor linked-peptides that contain C-terminal α-amido-trimethylsilyl groups. Photomacrocyclization reactions of the phthalimide linked-peptides take place by a sequence of events (Scheme 28) involving (1) intramolecular SET from near neighbor amide donor sites to the excited phthalimide chromophore, (2) amide cation radical migration to the α-amido-silane centers, (3) desilylation to form 1,n-biradical intermediates, and (4) biradical cyclization.

The modestly high yields observed for photocyclization reactions of substrates, which have a phthalimide acceptor group suggest that SET from amide donor sites in the peptide chains to the excited phthalimide chromophore occurs more rapidly than other typical excited state reaction modes (*e.g.*, H-atom abstraction).[9] In addition, the efficiencies of these processes are not significantly affected by the length of the polypeptide chain separating the centers at which bonding occurs. This result indicates that, following the initial SET event, migration of the radical cation center (hole migration) to the position in the peptide chain where the reactive trimethylsilyl electrofugal group is located takes place at a rate which is competitive with both back electron transfer, leading to the ground state reactant, and proton loss from benzylic sites in intervening cation radicals.[32-35] Furthermore, the apparent chain length independence of the efficiencies of these processes suggests that the rates of the biradical cyclization reactions that serve as ultimate mechanistic steps in the reaction sequences are not significantly influenced by entropy.[9,36,37]

Application of SET-Promoted Photocyclization Reaction of Phthalimide to the Preparation of Novel Crown Ethers: Another potentially interesting application of SET-promoted photocyclization reactions of TMS-terminated, polydonor-linked phthalimides is found in the synthesis of novel metal cation complexing agents related to the well-known crown ethers. For example, by using this process it should be possible to construct lariat-type crown ethers **85**, bis-crowns **87** and **89**, and polymeric crowns **91** and bis-crowns **93** from the corresponding phthalimide derivatives (Scheme 29).

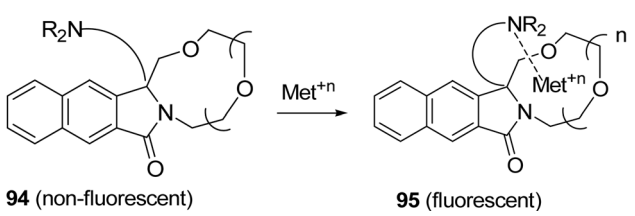
Although only at preliminary stages, studies in the authors' laboratories have already demonstrated that photocyclization reactions of polydonor-linked phthalimides can be used to generate a number of different crown ethers and their aza- and thia-analogs. An example of this is found in the route used for preparation of the possibly metal cation selective, fluorescence sensing, lariat-type crown ethers **95** shown in Scheme 30 which signal guest binding by blocking SET-quenching of excited states of fluorophores[38] appended to the host. This effort[39] has shown that irradiation of the polyether-linked naphthalimides **96-98** results in highly efficient photocyclization reactions that produce the polyether ring containing cyclic amidols **99-101** (Scheme 31). Introduction of an (*N,N*-dimethylamino)ethoxypropyl side chain into these substances is initiated by Lewis acid catalyzed allylation with allyltrimethylsilane. This is followed by hydroboration-oxidation to form the hydroxypropyl intermediates **102-104**, which are then smoothly converted to the target aza-lariat crown ether analogs **105-107**.

The tertiary aminoethoxy group in these substances was designed to serve as an SET-donor in order to quench the fluorescence of the naphthalene chromophore when a metal cation is absent. The pendant side chain oxygen (and perhaps nitrogen) would assist metal binding to the substances **105-107**

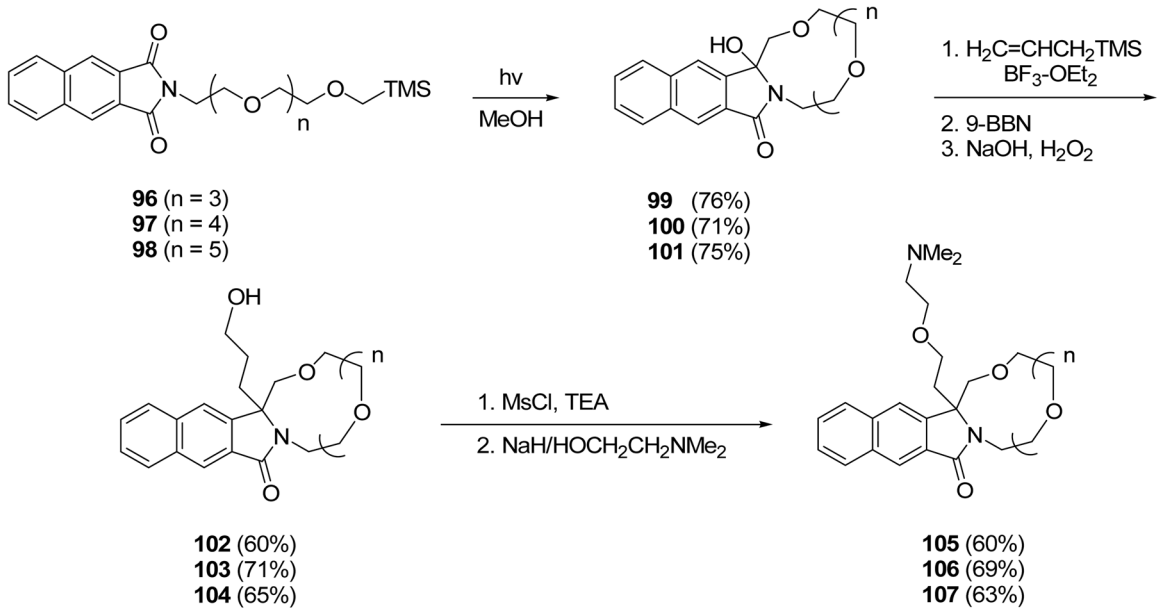


Scheme 29

which would be accompanied by dislocation of the side tertiary amine moiety with a concomitant reduction in intramolecular quenching of the naphthalene fluorescence. Owing to efficient SET quenching of the singlet excited naphthalene chromophore by the conformationally mobile tertiary amine groups, **105-107** have much reduced fluorescence quantum efficiencies (*ca.* 25-35%) as compared to those of the corresponding allyl derivatives. As expected, the studies of the effects of acid on the emission intensities revealed that the fluorescence intensities of **106-107** (1.4×10^{-5} and 8.6×10^{-6} M in MeCN) increase in a regular manner as the concentrations of added perchloric acid increased. Interestingly the fluorescence intensity reached a maximum when *ca.* 1 mole-equivalent of the acid present. Interestingly, no changes in the emission intensities of the crown ethers **106-107** take place when exceptionally high concentrations (*ca.* 10^{-3} M) of alkali metal (Na, K, Rb, Cs) perchlorates are present. In contrast, magnesium perchlorate pronouncedly enhances the fluorescence efficiency of the side chain amine tethered naphthalimide crown ethers **105** and **106** and the fluorescence intensities reach a maximum when *ca.* 1 mole-equi-



Scheme 30



96 (n = 3)
97 (n = 4)
98 (n = 5)

99 (76%)
100 (71%)
101 (75%)

102 (60%)
103 (71%)
104 (65%)

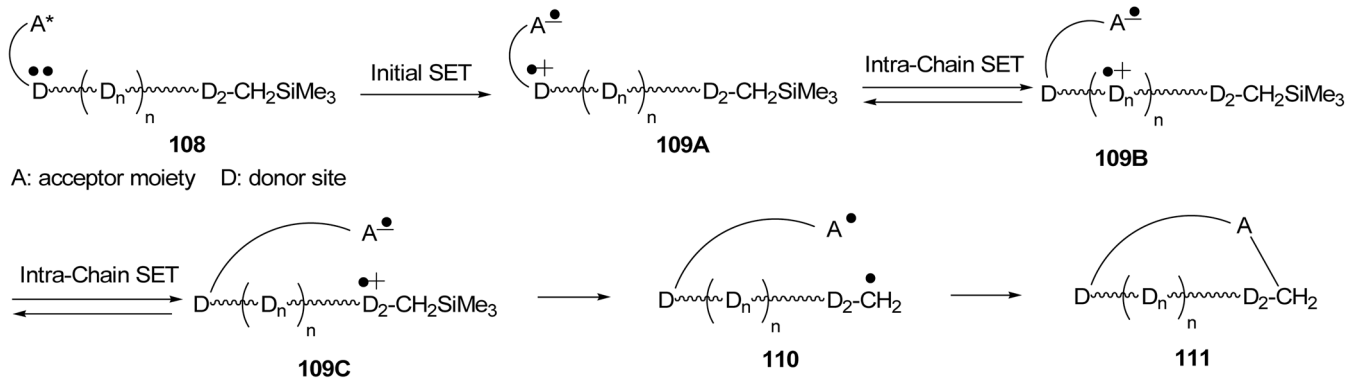
105 (60%)
106 (69%)
107 (63%)

Scheme 31

valent of magnesium perchlorate is present. Similar effects are observed when silver perchlorate and copper(II) triflate are added to MeCN solution of **105**. Although only at an early stages, the studies show that the SET-promoted photocyclization process serves as the cornerstone of a concise method for the preparation of novel lariat-type crown ethers. In addition, the crown ethers formed in this manner serve as effective fluorescence sensors for divalent Mg and Cu and monovalent Ag ions.

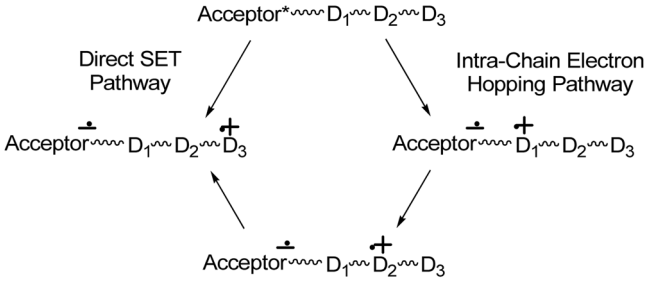
Factors Possibly Contributing to High Chemical Efficiencies of SET-Promoted Photocyclization Reactions of Phthalimide Acceptor-Polydonor Systems: The extremely high chemical efficiencies that accompany SET-promoted photocyclization reactions of polydonor-linked phthalimides are remarkable. It is interesting to speculate what factors may be responsible for this. The steady state concentrations of the biradical intermediates (*e.g.* **28**, **39**, and **83**) formed in these processes are controlled by the flux of the light used to promote reaction. As a consequence, the steady state concentrations of these intermediates are low so that competitive intermolecular radical coupling reactions, leading to dimerization or polymerization, are effectively prevented. Consequently, a high dilution methodology is not needed which contrasts with the situation of polar macrocyclization reactions involving bond formation between nucleophiles and electrophiles. Further the high chemical efficiencies observed in SET-promoted biradical photocyclization reactions of polydonor linked phthalimides might be due to other factors, including (1) in-chain donor promoted long-distance SET from remote terminal donor to excited phthalimde acceptors, and (2) charge promoted conformational biasing in the intermediate zwitterionic biradicals as seen in Scheme 32.

Initial intramolecular SET in the excited state of acceptor-polydonor systems **108** most likely occurs from near neighbor donor sites to the excited acceptor A*. This generates intermediate zwitterionic biradicals **109A** in which intrachain SET takes place to produce mixtures of interconverting zwitterionic biradical intermediates **109**. Interconversion of the zwitterionic biradical intermediates will be rapid when the polydonor radical cations have nearly the same energies. Among the interconverting zwitterionic biradiacal intermedi-



108
A: acceptor moiety D: donor site
109A
109B
109C
110
111

Scheme 32

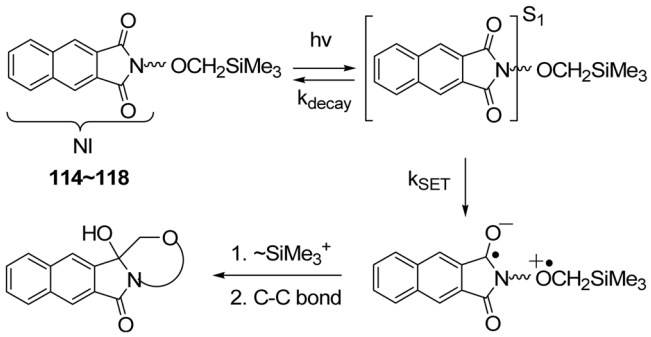


Scheme 33

ates, the most reactive α-silyl substituted zwitterionic biradicals **109C** undergo fast desilylation to generate biradical precursors **110** of the macrocyclic products **111**. It is expected that zwitterionic biradical interconversion will be accompanied by conformational changes caused by attractive electrostatic interactions between acceptor anion radical and donor cation radicals. These changes might help overcome the unfavorable entropic barriers typically associated with macrocyclization processes.

In order to probe whether SET in linked acceptor-polydonor systems takes place by direct SET from the reactive α-silyl substituted terminal donor site to the excited acceptor or by intra-chain electron hopping pathway (Scheme 33), pulsed laser spectroscopic studies of 1,8-naphthalimide-phenothiazine dyads **112** and **113** with different linkers, undecamethylene and trioxaundecyl have been recently initiated in collaboration with Majima and his coworkers.[40] Nanosecond and picosecond transient absorption measurements following 355-nm pulsed laser excitation of 1,8-naphthalimide-phenothiazine dyads (NI-L-PTZ) in acetonitrile. Excitation produces the naphthalimide anion radical ($NI^{\bullet -}$) and phenothiazine radical cation ($PTZ^{\bullet +}$) which have absorption bands around 420 and 520 nm, respectively.

Intramolecular SET from PTZ takes place in the singlet excited state (NI(S1)) as well as in the triplet excited state (NI(T1)) (Scheme 34). This study has shown that rates of SET largely depend on electronic coupling through polyether linker which suggest the operation of intra-chain electron hopping pathway. Specifically, the intramolecular SET rate from NI(S1) is increased by 3.5 times when the



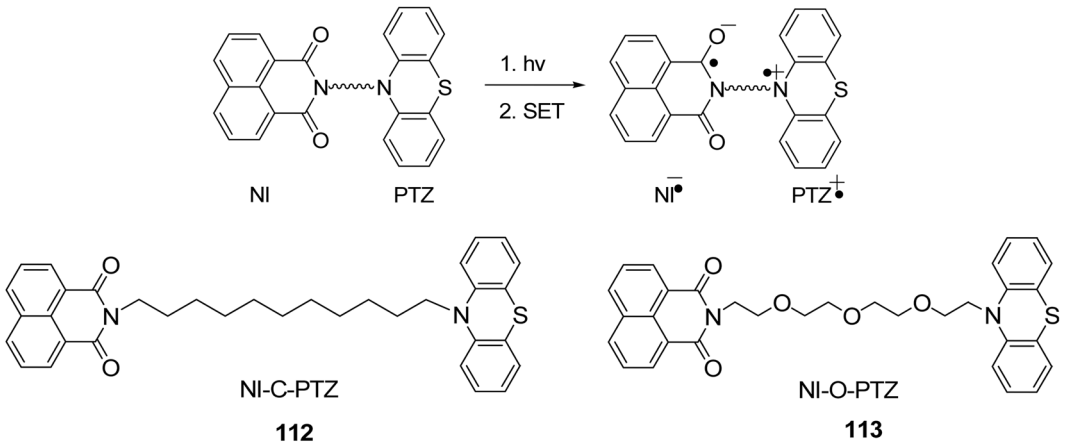
Scheme 35

Table 2.

Substrate	Chemical Yield	Relative Quantum Yield
NI-(CH2)3-O-SiMe3 **114**	40%	1.4
NI-(CH2)4-O-SiMe3 **115**	49%	1
NI-(CH2CH2O)3-O-SiMe3 **116**	76%	10
NI-(CH2CH2O)4-O-SiMe3 **117**	71%	7
NI-(CH2CH2O)5-O-SiMe3 **118**	75%	3

polyether trioxaundecyl linker ($k_{SET} = 3.5 \times 10^9\ s^{-1}$) is present as compared to the undecamethylene ($k_{SET} = 1.0 \times 10^9\ s^{-1}$) linker. In addition, the rate also increases about 4 times from NI(T1) when a polyether linker ($k_{SET} = 1.0 \times 10^9\ s^{-1}$) compared with the polymethylene linker ($k_{SET} = 2.6 \times 10^8\ s^{-1}$) is used.

Photocyclization quantum efficiency measurements of 2,3-naphthalimides[41] containing tethers differing in number of heteroatom, oxygen and total length also support the proposed intra-chain electron hopping pathway in the processes of SET in linked acceptor-polydonor systems. The results obtained from our preliminary photocyclization quantum efficiency measurements show two trends. First, an



Scheme 34

increase in the distance between acceptor 2,3-napthalimde and α-silyl ether donor leads to decrease of photocyclization quantum efficiency as seen in pairs of naphthalimide substances **114** and **115**, as well as the substances **116-117** where the quantum efficiency decreases in a regular manner (Table 2). Second, incorporation of oxygens into the tethers leads to about seven-fold increase in photocyclization quantum efficiencies, as seen in the comparisons of **114** with **116**, and **115** with **117**. Importantly, the quantum efficiencies for photocyclization reactions in these systems should be directly proportional to the rates of intra-chain SET (Scheme 35). Thus, the results obtained from the quantum efficiency measurements support the proposal that electronic coupling takes place through polyether linkage and by an intra-chain electron hopping pathway.

Summary

The studies described above, carried out in the authors' laboratories over the past decade, have contributed to an understanding of the factors that govern the nature and efficiencies of SET-promoted photochemical reactions. In these efforts, phthalimides have been used as excited state acceptors. The well-characterized photophysical properties of phthalimides guided this choice. However, the conclusions drawn from this work about the factors that govern chemical and quantum efficiencies should be generally applicable to a wide variety of photochemical processes promoted by SET from donors to excited states of acceptors. In addition, the synthetic strategies that have been developed for preparation of new phthalimide based materials should be generally applicable to a host of different targets.

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