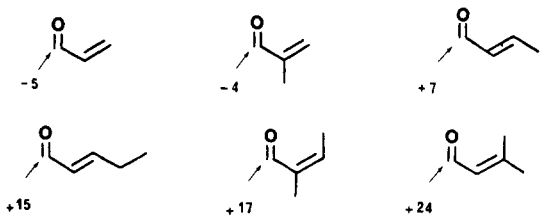
Chart II[a]



[a] $\Delta H_5°$ in kJ mol^{-1} (see text for the definition).

methyl group is significantly increased in the aldehyde series whereas it does not show up in either ketones or carboxylic acids.

The role of a hydroxyl group substitution in C(1) may be similarly discussed. The enthalpy variation associated with reaction 5 is equal to $\Delta H_5° = PA(M_H) - PA(M_{OH})$.

$$M_{OH} + (M_H + H)^+ \rightarrow M_H + (M_{OH} + H)^+ \quad (5)$$

Examination of the data contained in Chart II reveals a contrasting behavior.

In an intuitive picture, the π-donating effect of the hydroxyl group is expected to increase the basicity of the carbonyl oxygen. An increase in proton affinity is indeed observed when passing from aldehyde to acid for the first two couples **10**/**16** and **11**/**17** ($\Delta H_5° = -5$ and -4 kJ mol^{-1} respectively). However, in all other cases, the proton affinity of the acid is found to be lower than that of the corresponding aldehyde by an amount as large as 15–24 kJ mol^{-1}.

This lowering in PA upon going from an aldehyde to the analogous acid parallels the behavior of conjugated aromatic compounds as exemplified by the proton affinity values of benzaldehyde (838 kJ mol^{-1}) and benzoic acid (829 kJ mol^{-1}).[7]

Conclusion

A complete set of α,β-unsaturated carbonyl compounds has been examined, and the results allow the following conclusions: a good correlation of $\Delta H_f°(MH^+)$ with the logarithm of the number of atoms is observed, pointing to protonation on the oxygen of the carbonyl group; the effect of methyl substitution upon gas-phase basicities is to increase significantly the latter when situated on position C(1) or C(3); the gas-phase basicity of an α,β-unsaturated acid is generally lower than that of the corresponding aldehyde.

Competitive Singlet–Singlet Energy Transfer and Electron Transfer Activation of Aryl Azides: Application to Photo-Cross-Linking Experiments

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Direct irradiation of 4-[(dimethylamino)carbonyl]phenyl azide (DAA) in an inert solvent with UV light causes ring expansion to an intermediate dehydroazepine and eventual isolation of 4,4′-azobis[[(dimethylamino)-carbonyl]benzene] (AZB). The dehydroazepine can be trapped with nucleophilic reagents to give substituted 3*H*-azepines. The photochemistry of DAA takes a different course when it is sensitized by pyrene, 1-acetamidopyrene (**5**), or 9-acetamidoacridine (**2**). Under these conditions, single-electron transfer occurs in competition with energy transfer as evidenced by detection of radical ions in laser transient absorption spectroscopy and by formation of 4-[(dimethylamino)carbonyl]aniline (DAH) as a major product. Energy transfer and electron transfer compete also when the sensitizer and the aryl azide are linked together by a flexible chain of methylene groups. These results have particular significance for the application of such compounds to photolabeling experiments.

The photochemistry of aryl azides (ArN_3) plays an important role in biochemistry and biology. Irradiation of these reagents with UV light leads to loss of nitrogen and formation of highly reactive intermediates. The intermediates may form bonds rapidly at the site of their generation to give products that can be used to identify the targeted macromolecules. These transformations form the central part of several procedures generically identified as photolabeling experiments.[4] It was previously believed that the key reactive intermediates in these photolabeling experiments were arylnitrenes (ArN). However, recent work in our laboratories has confirmed earlier speculation that dehydroazepines, from ring expansion of singlet nitrenes or the excited azides themselves, are probably the intermediates involved in the bond-forming step.[5,6]

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Chart I

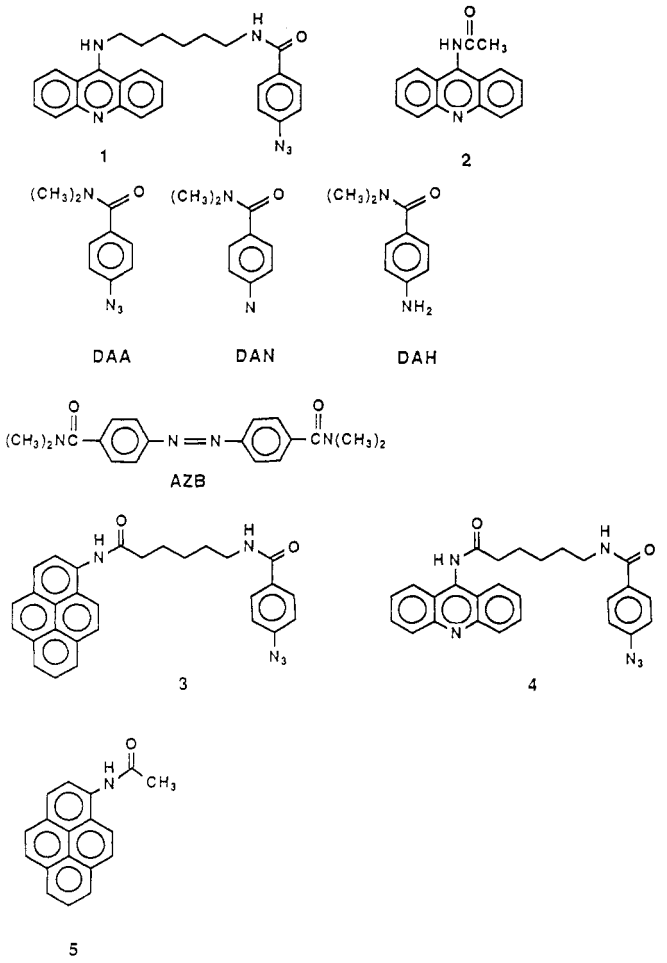

Photo-cross-linking and photoaffinity labeling are techniques useful for the study of macromolecular interactions in biochemical systems.[7] In such experiments, irradiation generates intermediates that join two macromolecules together or attach a label to a macromolecular target. For example, progress in understanding the interactions of proteins with nucleic acids in chromatin which is involved in the regulation of gene expression depends on elucidation of the structure and function of protein–nucleic acid complexes. Photo-cross-linking experiments offer the prospect of providing this information.[8] Their successful application in this area requires photoprobes that behave in a known and predictable fashion. Development of special reagents useful for this application has been under way in one of our laboratories for the past six years.[9]

The strategy for development of new cross-linking reagents for the study of DNA–protein interactions requires compounds where one ligand binds specifically to double-helixed DNA and another ligand, upon irradiation, bonds immediately and irreversibly to protein. Many substances known to intercalate into DNA can be adapted to carry a photoactivatable aryl azide. One of the successful approaches we have developed employs a 9-acridinylamino ligand connected by a flexible chain of methylene groups to an aryl azide (1, Chart I).

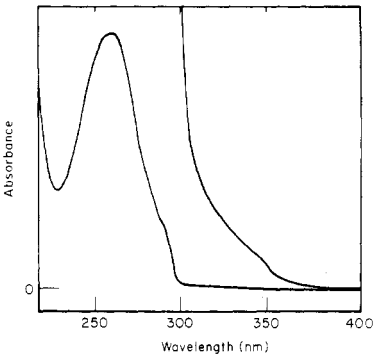

Figure 1. Optical absorption spectrum of DAA in acetonitrile solution, 5.0×10^{-5} M; expansion, 50 times more concentrated.

One of the intriguing questions surrounding the application of 1 and related substances to labeling experiments is the mechanism for energy transduction from the light absorber to the reactive unit of the linked azide systems. In particular, irradiation of 1 into the aminoacridine chromophore initiates chemical reactions of the aryl azide.[9b] Two general processes for remote activation of the azide may be considered: energy transfer and electron transfer. We report herein chemical and time-resolved spectroscopic experiments that clarify the mechanism for energy transduction and identify new strategies for remote control of chemical activity.

Results

A. Properties of 4-[(Dimethylamino)carbonyl]-phenyl Azide (DAA). The chemical and spectroscopic behavior of DAA was probed as a model for the properties of the more complicated linked activator–azide systems. DAA was prepared by a conventional route starting from 4-aminobenzoic acid and then purified extensively by recrystallization and chromatography. DAA is a very pale yellow crystalline solid (mp 41.4–42.6 °C) whose electronic absorption spectrum, shown in Figure 1, exhibits two components: a strong band (λ_{max} = 257 nm, ϵ = 20 400 M^{-1} cm^{-1}) and a weak long-wavelength band tailing at least to 400 nm. The absorption spectrum of DAA does not change measurably when it is repeatedly recrystallized (six times) or chromatographed on silica gel (three times).

It is a matter of importance to determine if the weak, long-wavelength component in the absorption of DAA is due to the azide itself or to a small amount of an inseparable, strongly absorbing impurity. Verification that the long-wavelength band is due to DAA comes from reversed-phase analytical HPLC. The retention volume of the azide determined by monitoring its strong absorption at 275 nm is precisely the same as the value obtained by monitoring the chromatography at 340 nm. No compounds other than DAA can be detected in the chromatogram. In particular, 4,4′-azobis[[(dimethylamino)carbonyl]benzene] (AZB), the most likely strongly absorbing colored impurity, was shown not to contaminate the azide.

No fluorescence can be detected from DAA at room temperature or at 77 K. This finding and the long asymmetric tail in the absorption spectrum suggest that electronic excitation of the azide leads to immediate fragmentation to [4-[(dimethylamino)carbonyl]phenyl]nitrene (DAN).[10] In this circumstance, a value for the energy of

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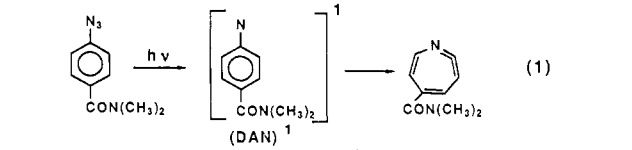
Table I. Direct Photolysis of DAA

solvent	trapping reagent	products, % AZB	3*H*-azepine	DAH
cyclohexane	–	72[a]	–	–
CH_3CN	–	70	–	–
CH_3CN	DEA (0.1 M)	–	91	–
CH_3CN	CH_3OH (20%)	26	31	–
CH_3CN	C_2H_5OH (20%)	51	15	4

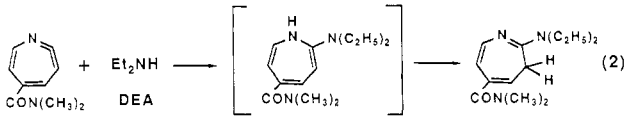
[a] Both the cis and trans isomers of the azo compound can be detected. The yield reported is the sum of both.

the excited singlet azide cannot be precisely defined. The transition from the ground state to the dissociative excited state merely becomes increasingly less probable as the energy of the photon (or singlet sensitizer) is lowered.

B. Direct Irradiation of DAA. We recently reported[6] spectroscopic and chemical evidence showing that direct irradiation of DAA in an inert solvent such as cyclohexane or acetonitrile leads to loss of nitrogen and ring expansion to form the substituted dehydroazepine, eq 1. In the



(1)



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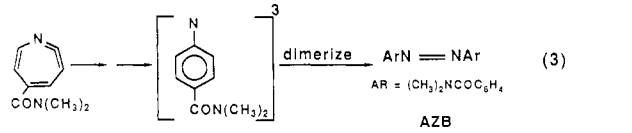


(3)

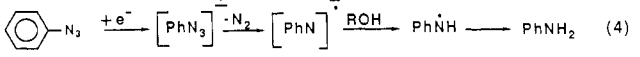
presence of a nucleophilic trapping reagent such as diethylamine (DEA) or an alcohol, the dehydroazepine is captured and a 3*H*-azepine is isolated in good yield, eq 2. If a nucleophilic trapping agent is not present in the photolysis solution, the dehydroazepine is slowly converted to the triplet nitrene, which ultimately dimerizes to give AZB, eq 3. It is important to note that 4-[(dimethylamino)carbonyl]aniline (DAH) is formed from the direct irradiation of DAA only when ethyl alcohol is present as a trapping agent and only in low yield (4%) under these conditions. These results are summarized in Table I.

C. Single-Electron Reduction of DAA. The electrochemistry of aryl azides in solution has not been studied extensively. Iversen reports that phenyl azide exhibits a pH-dependent, irreversible reduction wave at ca. –0.9 V vs SCE (aqueous solution, pH 2.5–6.2) and that aniline is isolated from its preparative electrolysis.[11] We examined the cyclic voltammetry of DAA in acetonitrile solution on a glassy carbon electrode. Under these conditions, DAA shows a two-electron reduction wave at –0.98 V and a one-electron reoxidation wave with peak current at –0.87 V. Thus, as expected, DAA is easily reduced, and its reduction product, the azide radical anion, is chemically reactive. This behavior in solution parallels findings from gas-phase studies. The phenyl azide radical anion is known to lose nitrogen and form the phenylnitrene radical anion in a flowing afterglow apparatus.[12] Under these conditions, the nitrene radical anion is a strong enough base to deprotonate alcohols and ketones and form the anilino radical, eq 4.

Table II. Sensitized Photolysis of DAA in CH_3CN

sensitizer	E_s[a] (eV)	trapping agent	products, % AZB[b]	3*H*-azepine	DAH
pyrene	3.34	none	101 ± 6	–	–
pyrene		CH_3OH[d]	39	16	11
pyrene		C_2H_5OH[d]	58	7	8
PyNHCOMe[c]	3.28	none	96 ± 6	–	–
PyNHCOMe		CH_3OH	25	11	10
PyNHCOMe		C_2H_5OH	65	8	12
acridine	3.17	none	82 ± 6	–	7
acridine		CH_3OH	<5	20	75
acridine		C_2H_5OH	<5	13	80

[a] Singlet energy of the sensitizer. [b] Both the cis and trans isomers of the azo compound can be detected. The yield reported is the sum of both. [c] 1-Acetamidopyrene. [d] The alcohols are present to the extent of 20% (v/v).



(4)

The fluorescence of pyrene in acetonitrile is quenched rapidly by DAA ($k_q\tau$ = 500 M^{-1}). Electronically excited states often function as one-electron reducing agents when the free energy for electron transfer to an acceptor (ΔG_{ET}) is favorable. In the present case, calculation of ΔG_{ET} with the Weller equation[13] shows that electron transfer from excited singlet pyrene (Py*) to DAA is exothermic by ca. 20 kcal/mol and thus is expected to occur at approximately the diffusion limited rate. Evidence in support of this hypothesis comes from the analysis of laser transient absorption spectra. Irradiation of an acetonitrile solution of pyrene containing 7 × 10^{-3} M DAA with the output of a nitrogen laser (337 nm, 13 ns, 7 mJ) gives a transient intermediate with absorption maximum at 450 nm assigned to the pyrene radical cation ($Py^{\bullet+}$), and an absorbance at 410 nm assigned to the triplet pyrene (Py^{*3}).[14] It is significant that Py^{*3} decays slowly (τ = ca. 1.5 μs) in this experiment. If the triplet energy of DAA were below that of pyrene, the lifetime of Py^{*3} under these conditions would be less than 10 ns.

Photosensitization of DAA with pyrene reveals the operation of a new reaction channel. Irradiation of an acetonitrile solution of DAA containing pyrene (Rayonet, 350 nm, pyrene absorbs the light) gives AZB as the only detected product. The azo compound may be formed from dimerization of the triplet nitrene or in a chain reaction of the azide initiated by the nitrene radical anion. Related chain reactions have recently been confirmed in the electrochemical reduction of diazo compounds.[15]

The pyrene-sensitized reaction of DAA takes a somewhat different course when conducted in acetonitrile containing methanol as a trapping agent. In this case three products are isolated: the methoxy-substituted 3*H*-azepine is found in 16% yield and the azo compound AZB in a yield of 39%, and significantly, the aniline DAH is formed in 11% yield, eq 5. The aniline is not detected in direct irradiation of DAA under these conditions. These results are summarized in Table II.

It is a matter of some importance to identify the route for formation of the aniline in the pyrene sensitization

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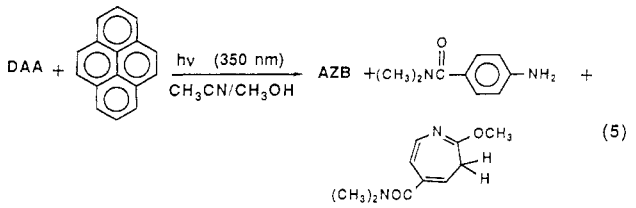

(5)

experiment. We considered two possible paths: electron transfer from excited pyrene singlet to form the azide radical anion, as indicated by the spectroscopic experiment, or energy transfer from Py^{*3}. If the second path is the operative mechanism, then any triplet sensitizer should initiate aniline formation. We chose 2-acetonaphthone as a model triplet sensitizer. Its triplet energy (61 kcal/mol) is above that of pyrene (48 kcal/mol). Irradiation of an acetonitrile solution of DAA containing methanol with 2-acetonaphthone as a sensitizer under precisely the same conditions used in the pyrene-sensitized experiment gives none of the aniline and hardly any reaction of the azide at all (the small amount of reaction that does occur is probably due to light unavoidably absorbed directly by the azide). This experiment supports the electron transfer path for pyrene sensitization. Additional evidence for this route comes from examination of other sensitizers.

The products obtained from photosensitization of DAA with excited electron donors depend on both the identity of the trapping agent and the properties of the sensitizer. We examined several of these reactions in detail. Irradiation of an acetonitrile solution of DAA containing methanol and aminoacridine acetamide **2** (Chart I) as sensitizer gives DAH in 78% yield, the 3*H*-azepine in 20% yield, and none of the azo compound AZB. This result is particularly meaningful in comparison with the direct irradiation under these conditions where none of the aniline is formed and AZB and the azepine are formed in a ca. 1:1 ratio. The triplet energy of aminoacridine (ca. 45 kcal/mol) is lower than that of 2-acetonaphthone, so activation of the azide by triplet energy transfer is not a possible option in this case. The results of this experiment and other related electron-donor-sensitized reactions, summarized in Table II, suggest operation of two routes for activation of DAA by these sensitizers: one gives dehydroazepine and azo compound, and the other leads to formation of the aniline. The second route dominates when the singlet energy of the sensitizer is low; the first becomes more important for sensitizers with high singlet energies.

D. Photochemistry of Linked Azide–Sensitizer Systems. We examined in detail two compounds containing aryl azides linked covalently to a sensitizer by a flexible chain of methylene groups. In the first of these (**3**, Chart I), aminopyrene is connected by an amide bond through five methylene groups to (aminocarbonyl)phenyl azide; the second (**4**) contains an aminoacridine similarly connected to the azide.

The fluorescent behavior of pyrene-linked azide **3** reveals a strong intramolecular interaction between the aminopyrene group and the azide. The fluorescence spectrum obtained by excitation of **3** at 370 nm is indistinguishable from that of acetamidopyrene **5**, selected as a model for the chromophore of **3**. However, the fluorescence intensity of **3** is reduced to only 20% that of **5** when the two compounds are compared under similar conditions. The reduction in intensity cannot be the result of intermolecular quenching since the concentration of **3** in these experiments is too low to permit collisional interactions within the 13-ns lifetime of the excited singlet state. The fluorescence lifetime of the linked azide **3**, as expected, is

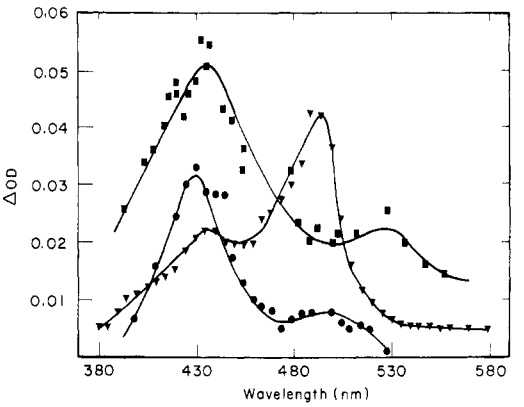

Figure 2. Triangles: transient absorption spectrum of acetamidopyrene **5** radical cation formed by its irradiation in acetonitrile solution containing *m*-dicyanobenzene as a quencher. Squares: transient absorption spectrum of acetamidopyrene **5** triplet formed by its irradiation in acetonitrile. Circles: Transient spectrum recorded after irradiation of linked azide **3** in acetonitrile solution with a nitrogen laser.

shortened in comparison with that of **5**. Time-correlated measurements reveal multiexponential behavior with a major component decaying in less than 2 ns for the linked compound.

Time-resolved absorption experiments, in principle, may distinguish intramolecular quenching in linked azide **3** operating by an energy-transfer mechanism from quenching by electron transfer. The radical cation of acetamidopyrene **5**, prepared independently by electron-transfer quenching with *m*-dicyanobenzene in acetonitrile solution, shows a strong, characteristic absorption band at 497 nm. The triplet–triplet absorption spectrum of **5** generated by laser flash photolysis in oxygen-free acetonitrile solution has an apparent maximum at 435 nm. Pulsed irradiation of linked azide **3** with a nanosecond laser at 337 or 355 nm (the light is absorbed primarily by the pyrene chromophore) generates a transient spectrum characteristic of the triplet pyrene. There is no evidence for formation of the amidopyrene radical cation in the nanosecond time-resolved photolysis experiments. These spectra are displayed in Figure 2. The intensity of the triplet–triplet absorption band in the linked azide is reduced considerably when compared with that for acetamidopyrene itself. This observation confirms the operation of a process that depletes the singlet excited pyrene in competition with its intersystem crossing to the triplet.

Undetectable amidopyrene radical cation on a nanosecond time scale does not necessarily rule out the operation of an electron-transfer mechanism for activation of linked azide **3**. It is reasonable that intramolecular electron transfer to form the pyrene radical cation and azide radical anion, loss of nitrogen from the azide radical anion, and back electron transfer to leave the neutral nitrene and ground-state amidopyrene could all occur so fast that the radical cation would be completely consumed within a few nanoseconds.[16] Picosecond-time-scale experiments unfortunately give ambiguous results. Irradiation of acetamidopyrene **5** with a 20-ps pulse at 355 nm gives a strong, broad absorption band with λ_{max} at 500 nm assigned to singlet–singlet (S^1–S^n) transitions of the pyrene.[17] The

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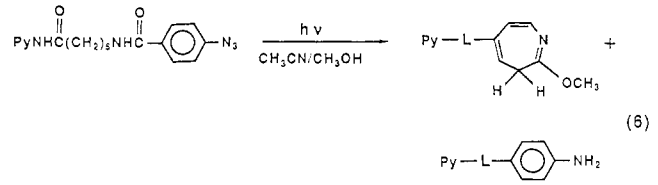
singlet–singlet absorption decays over a period of several nanoseconds, but its presence completely obscures the spectral region that could reveal the amidopyrene radical cation at times immediately after the laser pulse.

Less ambiguous evidence for the mechanism of activation of linked azide **3** comes from analysis of reaction products. Irradiation of **3** at 350 nm in acetonitrile containng methanol gives both the ring-expanded 3*H*-azepine (60%) and the aniline (13%), eq 6. Recall that the aniline



(6)

is only formed from irradiation of DAA under electron-transfer conditions. If the pyrene in the linked azide of **3** were acting merely as a singlet energy donor, aniline formation should not have occurred. This trend is even more clearly revealed in the photochemistry of the aminoacridine-linked azide **4**. In this case, irradiation in acetonitrile solution containing methanol gives the aniline in 61% yield.

Discussion

It is clear from the results described above that electronic excitation initially localized on the absorbing chromophore of the linked compounds **3** and **4** is capable of initiating reactions of the remotely bound aryl azide. Two intramolecular mechanisms for energy migration appear to play important roles in these compounds: singlet energy transfer and electron transfer.

On first examination, singlet–singlet energy transfer from an amidopyrene or an amidoacridine (ΔE_{00} = 76 and 72 kcal/mol, respectively) chromophore to DAA seems impossible on energetic grounds. However, close examination of the electronic spectrum of the azide shows a weak, long-wavelength absorption feature that signals the possible existence of an unbound excited singlet state. Similar features are present in the absorption spectra of organic peroxides.[18] Singlet and triplet energy transfer to peroxides has been examined in detail.[19] The rate constant for sensitization drops off rapidly as the energy of the sensitizer declines, but even low-energy sensitizers are capable of initiating reactions of the peroxides. These findings were explained by assuming that energy transfer can occur to peroxide molecules at nonequilibrium geometries. We propose operation of a related mechanism in the singlet sensitization of DAA. Energy transfer from the aminopyrene or the aminoacridine to vibrationally excited azide occurs at a slow rate, but leads to formation of the excited singlet azide, which than initiates chemical reactions typical of arylnitrenes.

Singlet energy transfer cannot be the only excitation mechanism operating. If it were, sensitization should give precisely the same outcome as direct irradiation. This is not the case. Both inter- and intramolecular sensitization reactions in the presence of alcohols give aniline products that are unobserved in direct irradiations. In all cases, electron transfer is energetically permitted, and for the intermolecular examples, this path is supported by spectroscopic evidence. Single-electron reduction of the azide to form its dissociative radical anion readily accounts for the formation of aniline in these experiments.

Singlet energy transfer and electron transfer can both occur either by short-range collisional or long-range mechanisms. In the present case, long-range, singlet–singlet energy transfer seems improbable because of the small oscillator strength of the relevant absorption of the azide.[20] Long-range electron transfer through saturated bonds has recently been documented in several systems.[16] We suggest that the mechanism for energy transduction in the linked azides depends on the conformation of the molecule when it is excited. If stretched in a "linear" fashion, electron transfer may be the predominant process. If the linked azide is in a "U shape" that brings the chromophore and azide into near-contact distances, energy transfer may predominate. We are presently undertaking the preparation of rigidly linked systems to explore this question further.

The mechanism for energy transduction in the linked-azide systems has obvious implications for the use of these compounds in photolabeling experiments. The nature of the key reactive intermediate and its location relative to the absorbing chromophore will depend critically on the active mechanism. Generation of a nitrene radical anion by electron transfer that ultimately gives an aniline will not form a cross-link. Generation of the singlet excited azide only when it is in contact with the sensitizing chromophore is a problem if the chromophore is bound as an intercalator.

Thus these results imply that irradiation with light that is absorbed by the acridine chromophore, even though resulting in the desired photolabeling in model systems,[9b] may not result in efficient labeling in a more complex biological system, in situ. The results obtained with compounds **3** and **4** could have even wider implications for photolabeling experiments in biological systems using aryl azides in general. Often the aryl azide is not the chromophore in the system absorbing at the longest wavelengths, and irradiations are furthermore usually performed with light (λ of approximately 300 nm) which is also absorbed by the biological system, e.g., by tyrosine and tryptophan residues in proteins, with which the aryl azide can be in close contact. Perhaps energy-transfer mechanisms analogous to the ones described in this paper could be operating not only within the photolabeling reagent itself but also between the reagent and its biological macromolecular target.

Experimental Section

Materials. Acetonitrile (Aldrich Gold Label) was distilled from calcium hydride under nitrogen. Absolute methanol (J. T. Baker) was distilled from magnesium. Ethanol (U.S.I.) was distilled from sodium, and diethylamine (Aldrich) was distilled under nitrogen. The synthetic precursors 1-aminopyrene, 6-aminohexanoic acid, and 4-aminobenzoic acid were used as received (Aldrich).

Methods. Cyclic voltammetric measurements of redox potentials were made in acetonitrile solution (10^{-4} M) with a 25-μm-diameter glassy carbon electrode, tetrabutylammonium tetrafluoroborate as a supporting electrolyte, and a silver/silver chloride reference electrode. Fluorescence quenching data were obtained in N_2-purged solutions on a Farrand Mark I spectrofluorometer. High-performance liquid chromatography was performed on an IBM Instruments Inc. LC/9560 ternary gradient liquid chromatograph with a Perkin-Elmer LC-75 absorbance detector. Fluorescence lifetimes were determined by the phase/modulation method at the Laboratory for Fluorescence Dynamics at the University of Illinois.

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Laser Flash Photolysis. Transient absorption measurements on a nanosecond time scale with 337.1-nm and 354.7-nm excitation were obtained on N_2 and Nd:YAG laser spectrometers respectively. Concentrations of the samples in solution were adjusted so that a significant fraction of the excitation beam was absorbed (OD = 2.0–4.0). The samples were placed in 10-mm quartz cuvettes and purged with a stream of dry N_2 to remove O_2. Laser excitation was done perpendicular to the probing beam. Picosecond time scale transient absorption experiments were done on the mode-locked Nd:YAG system (354.7-nm excitation). In the present work it was found necessary to generate continuum probing pulses from H_2O/D_2O because the continuum from CCl_4 was weak in intensity compared to the fluorescent background from the samples.

Analysis of Photoproducts. Solutions of DAA ($2–8 \times 10^{-3}$ M) in CH_3CN, with the appropriate trapping agent (methyl or ethyl alcohol, 1:4 v/v; solutions for sensitized irradiation also contained $1–9 \times 10^{-3}$ M sensitizer) were prepared and divided into two identical portions. Unless otherwise indicated, all solutions were purged for 10–15 min with dry N_2 prior to irradiation to remove O_2. In all cases the conversion of starting materials was less than 85%. While the first solution was irradiated (254 nm for direct irradiation of DAA, 350 nm broadband for others), the second, a control solution, was kept in the dark. After irradiation, the solvent was removed from both portions at 0.1 Torr and the nonvolatile residues were dissolved in 0.5 mL of $CDCl_3$ containing 6.20 μmol of hexamethyldisiloxane as a quantitative internal standard. The samples were analyzed by ^1H NMR (300 MHz, FT) spectroscopy.

4-[(Dimethylamino)carbonyl]phenyl Azide (DAA). 4-Azidobenzoic acid was prepared from 4-aminobenzoic acid by diazotization with sodium nitrite followed by reaction of the diazonium salt with sodium azide (79% yield): mp 183–185 °C (lit.[22] mp 185 °C). 4-Azidobenzoyl chloride was prepared from the acid and thionyl chloride. DAA was prepared by reaction of the acid chloride with dimethylamine (40% aqueous) in 38% yield. The resulting yellow oil was subjected to radial chromatography (silica gel, 40:60 EtOAc/hexane). This was repeated three times. Recrystallization of the resulting yellow solid (six times) from 50:50 ether/petroleum ether yielded DAA as pale yellow needles (mp 44–45 °C): ^1H NMR ($CDCl_3$) δ 7.05–7.45 (2 d, 4 H), 2.95–3.15 (d, 6 H). Further analysis of DAA by reversed-phase HPLC (25-cm C-18 column, 35% CH_3CN in H_2O, ramped to 70%) monitoring absorptions at 275 and 340 nm showed no absorbing impurities. Under these conditions, the DAA has a retention time of 7.15 min and is completely resolved from the corresponding azo compound, AZB (8.20 min). Elemental anal. Calcd for $C_9H_{10}N_4O$: C, 56.53; H, 5.29; N, 29.46. Found: C, 56.87; H, 5.39; N, 29.31.

4,4′-Azobis[[(dimethylamino)carbonyl]benzene] (AZB). 4-Nitrobenzoic acid was reductively coupled according to the method of Tomlinson[23] to form 4,4′-azobis(benzoic acid). This diacid was converted to the diacid chloride by reaction with thionyl chloride. 4,4′-Azobis(benzoyl chloride) was purified by recrystallization from methylene chloride/petroleum ether [mp 164 °C (lit.[23] mp 164 °C)] and subsequently converted to AZB by reaction with aqueous dimethylamine. Recrystallization from methylene chloride/petroleum ether gave orange plates (60%): mp 96 °C; ^1H NMR ($CDCl_3$) δ 7.55–7.95 (2 d, 8 H), 3.0–3.2 (2 s, 12 H); IR (Nujol) 1630 cm^{-1}. Elemental anal. Calcd for $C_{18}H_{20}N_4O_2$: C, 66.65; H, 6.62; N, 17.27. Found: C, 66.49; H, 6.18; N, 17.25.

4-[(Dimethylamino)carbonyl]aniline (DAH). The aniline was prepared by reduction of the nitro compound according to the method of Kuhn:[24] off-white needles, mp 151–154 °C; ^1H NMR (DMSO-d_6) δ 7.22 (d, 2 H), 6.51 (d, 2 H), 5.48 (s, 2 H), 2.95 (s, 6 H); IR (Nujol) 3450, 3350, 3250, 1650, 1600, and 1590 cm^{-1}. Elemental anal. Calcd for $C_9H_{12}N_2O$: C, 65.83; H, 7.4; N, 17.1. Found: C, 65.39; H, 7.30; N, 16.8.

***N*-(1-Pyrenyl)acetamide (5).** 1-Aminopyrene (700 mg, 3.2 mmol) was heated at reflux for 1 h in a mixture of toluene (20 mL), acetic acid (25 mL), and acetic anhydride (1 g). The precipitate that formed was isolated by filtration and dissolved in methylene chloride, and the solution was dried (magnesium sulfate). The solvent was removed, and the solid residue was recrystallized from acetone to yield 600 mg (72%) of pale, fluffy needles: mp 264–265 °C (lit.[24] mp 260–261 °C); ^1H NMR (DMSO-d_6) δ 2.28 (s, 3 H), 8.0–8.4 (mult, 9 H), 10.35 (s, 1 H).

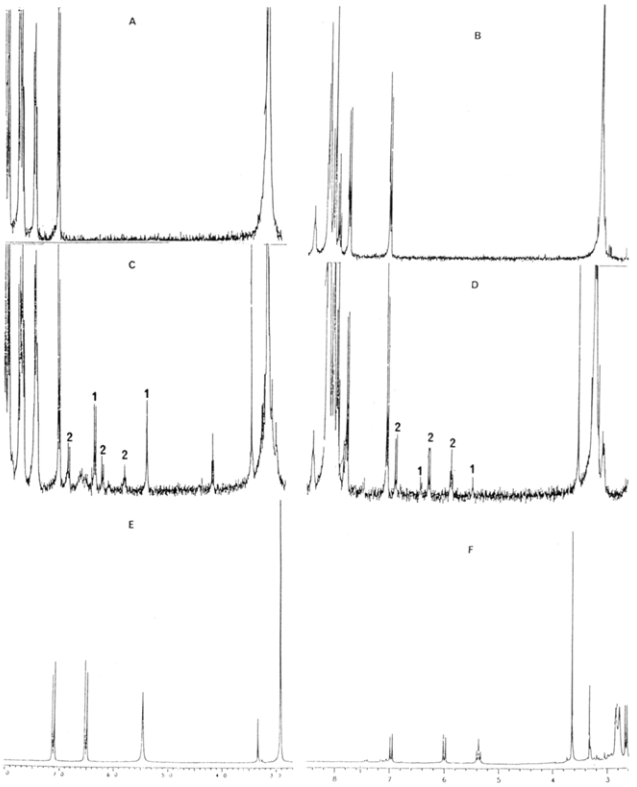

Figure 3. The ^1H NMR spectra of the following: (A) acridine linked azide **4**; (B) pyrene linked azide **3**; (C) the photoproducts formed by irradiation of acridine linked azide **4** in methanol/acetonitrile—peaks labeled with a 1 are assigned to the aniline product, and peaks labeled with a 2 are assigned to the dehydroazepine product; (D) the photoproducts formed by irradiation of pyrene linked azide **3** in methanol/acetonitrile—peaks labeled with a 1 are the aniline product, and peaks labeled with a 2 are assigned to the azepine product; (E) 4-[(dimethylamino)-carbonyl]aniline (DAH); (F) 2-methoxy-5-[(dimethylamino)-carbonyl]-3*H*-azepine. All spectra were recorded in DMSO-d_6 at 200 MHz.

***N*-(9-Acridinyl)acetamide (2).** A solution of 9-aminoacridine (500 mg, 2.6 mmol) was stirred at 60 °C for 1 h in a mixture of 10 mL of DMF and 1 g of acetic anhydride. The reaction mixture was then added to ice/water, and the precipitate that formed was recrystallized from acetone to yield 400 mg (66%) of fluffy yellow needles of **2**: mp 277–279 °C (lit.[26] 268–269 °C).

***N*-[5-[(1-Pyrenylamino)carbonyl]pentyl]-4-azidobenzamide (3).** Solid 4-azidobenzoyl chloride (4.9 g, 27 mmol) was added in small portions to a solution of 6-aminohexanoic acid (3.2 g, 24 mmol) in aqueous NaOH (2 g, 25 mL). The reaction mixture was maintained at 0 °C during the addition and for an additional 20 h and then acidified. The precipitated 6-[(4-azidobenzoyl)-amino]hexanoic acid was collected by filtration, washed with water, and recrystallized from ethyl acetate to yield 5.5 g (74%) of off-white needles: mp 136–139 °C (lit.[8d] mp 138–139 °C). A solution of the hexanoic acid (500 mg, 1.8 mmol) and 0.5 mL of triethylamine in dichloromethane (20 mL) was added to a cold (0 °C) solution of ethyl chloroformate (100 mg, 1.8 mmol) in methylene chloride (20 mL). The reaction mixture was stirred for 4 h at 0 °C, and subsequently a solution of 1-aminopyrene (700 mg, 3.2 mmol) in methylene chloride (10 mL) was added

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slowly. The mixture was stirred overnight, and the precipitate that formed was collected by filtration and recrystallized from methanol to yield the pyrene linked azide **3** as fluffy needles: ^{1}H NMR (DMSO-d_6) δ 10.25 (s, 1 H), 8.5 (t, 1 H), 8.35–8 (mult, 9 H), 7.9–7.15 (2 d, 4 H), 2.58 (t, 2 H), 1.9–1.4 (m, 8 H). Elemental anal. Calcd for $C_{29}H_{25}N_5O_2$: C, 73.24; H, 5.30; N, 14.73. Found: C, 72.88; H, 5.33; N, 14.52.

2-Methoxy-5-[(dimethylamino)carbonyl]-3*H*-azepine. An acetonitrile/methanol (4:1 v/v, 10 mL) solution of DAA (10 mg) was purged with N_2 and irradiated at 254 nm (Rayonet) for 7 min. The solvent was removed under vacuum, and the crude reaction mixture was analyzed by NMR spectroscopy. The results are reported in Table I. The 3*H*-azepine was isolated by chromatography on silica gel (31% based upon the amount of DAA consumed): ^{1}H NMR (DMSO-d_6) δ 6.9 (d, 1 H), 6.00 (d, 1 H), 5.38 (t, 1 H), 3.65 (s, 3 H); high-resolution mass spectrum calcd for $C_{10}H_{14}N_2O_2$ 194.1055, found 194.1042.

2-Ethoxy-5-[(dimethylamino)carbonyl]-3*H*-azepine was prepared similarly by photolysis of DAA in acetonitrile containing ethanol: ^{1}H NMR ($CDCl_3$) δ 7.02 (d, 1 H), 6.1 (d, 1 H), 5.42 (t, 1 H), 4.15 (q, 2 H), 2.95–2.8 (d, 6 H), 2.7 (d, 1 H), 1.28 (t, 3 H); high-resolution mass spectrum calcd for $C_{11}H_{16}N_2O_2$ 202.1202, found 202.1212.

Photolysis of Linked Azide 3. Photolysis and quantitative analysis were performed analogously to the method outlined above. Because of their insolubility and the necessity to keep the photolysis to low conversion, the structural assignments for the photoproducts from **3** were based on comparison of ^{1}H NMR spectra with those of the analogous, fully characterized products from photolysis of DAA. The spectra are displayed in Figure 3. There is a clear correspondence of the proton resonances between the authentic product Figures 3E and 3F and that from irradiation of **3**, Figure 3D. Irradiation in a methanol/CH_3CN (1:4 v/v) solution gives linked aniline derivative (13%) on the basis of the NMR spectrum [(DMSO-d_6, 200 MHz) δ 6.5 (q, 2 H), 5.55 (s, 1 H)] and linked methoxyazepine derivative (60%) on the basis of the NMR spectrum [δ 7.0 (d, 1 H), 6.4 (d, 1 H), 6.0 (t, 1 H), 3.6 (s, 3 H)]. Irradiation in ethanol/CH_3CN (1:4 v/v) gives linked aniline derivative (19%) and ethoxy-substituted azepine derivative (58%) on the basis of the NMR spectrum [(DMSO-d_6) δ 7.0 (d, 1 H), 6.4 (d, 1 H), 5.95 (t, 1 H), 4.05 (q, 2 H)].

Acridine Linked Azide (4). The ethyl chloroformate mixed anhydride from 6-[(4-azidobenzoyl)amino]hexanoic acid (0.50 g, 1.8 mmol) was prepared as for **3**. 9-Aminoacridine (0.40 g, 2.01 mmol) in *N*,*N*-dimethylformamide (10 mL) and methylene chloride (10 mL) was added slowly at 0 °C to the mixed anhydride solution. The mixture was stirred for 12 h, and the precipitate was collected by filtration and washed with water. Recrystallization from methanol yielded 100 mg (12%) of azide **4** as yellow needles: ^{1}H NMR (200 MHz) δ 10.6 (s, 1 H), 8.5 (s, 1 H), 8.2–7.5 (m, 10 H), 7.15 (d, 2 H), 2.7 (t, 2 H), 1.9–1.4 (m, 8 H). Elemental anal. Calcd for $C_{26}H_{24}N_6O_2 \cdot {}^1/_2H_2O$: C, 67.66; H, 5.46; N, 18.21. Found: C, 67.61; H, 5.20; N, 18.09.

Photolysis of Azide 4. This compound was irradiated and analyzed in the same was as described above for pyrene linked azide **3**; the relevant ^{1}H NMR spectrum is shown in Figure 3C. The products formed by irradiation in methanol/acetonitrile (1:5 v/v) solution were the corresponding aniline (61% yield), on the basis of integration of the characteristic peaks in the NMR spectrum [δ 6.5 (q, 2 H), 5.5 (s, 2 H)], and the corresponding methoxyazepine (50% yield), on the basis of the integration of its characteristic peaks in the NMR spectrum [δ 6.95 (d, 2 H), 6.3 (d, 1 H), 5.9 (t, 1 H), 3.6 (s, 3 H)]. Similarly, the products from photolysis in ethanol/acetonitrile (1:5 v/v) solution were identified as the aniline (73%) and the corresponding ethoxyazepine (26%) on the basis of integration of the characteristic peaks in its ^{1}H NMR spectrum [δ 7.1 (d, 1 H), 6.3 (d, 1 H), 5.95 (d, 1 H), 4.1 (q, 2 H)].

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Reaction of Allylic Tin Reagents with Nitrogen Heteroaromatics Activated by Alkyl Chloroformates: Regioselective Synthesis of α-Allylated 1,2-Dihydropyridines and Change of the Regioselectivity Depending on Methyl Substituents at the Allylic Moiety

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Allyltin reagents readily react with pyridine and some substituted pyridines activated by alkyl chloroformates to give α-allylated 1,2-dihydropyridines regioselectively. Functional substituents such as halogeno, acetoxy, and formyl groups can be tolerated, demonstrating high chemoselectivity of the reactions. The regiochemistry of the attack on pyridine nuclei changes from α-addition to α- and γ-addition (nonregioselective) to γ-addition, depending on methyl substituents at the allylic moiety (from allyl to methallyl and crotyl to prenyl groups). It is also found that the reactions occur at the γ-position of allylic tin reagents, indicating the S_N2' character of the reactions. The present effective allylation method can be extended to isoquinoline and quinoline systems.

Regioselective addition of organometallic reagents to *N*-acylpyridinium salts has been increasingly important in the preparation of 2- and 4-substituted 1,2- and 1,4-dihydropyridines, which have proven to be valuable as synthetic intermediates for a variety of alkaloids as well as NADH models.[1-5] We have recently reported that a variety of alkynyl and alkenyl Grignard reagents add to *N*-(methoxycarbonyl)pyridinium chlorides (**1a**) in a highly

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