Dithiane and trithiane-based photolabile molecular linkers equipped with amino-functionality: synthesis and quantum yields of fragmentation

Alexei N. Kurchan, Oleg D. Mitkin, Andrei G. Kutateladze

Department of Chemistry and Biochemistry, University of Denver, 2190 E. Iliff Ave., Denver, CO 80208 2436, USA

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Abstract

Addition of lithiated di- and trithianes to the in situ generated N-silylated imines produces N-aminoalkyldi- and trithianes capable of photoinduced fragmentation, similar to the fragmentation of the previously described N-hydroxyalkyldithianes. The initially generated primary amino-functionality is readily derivatized with various electrophiles providing access to biologically relevant functional groups such as amides, ureas and aminopyridines. Quantum efficiency of the photoinduced C-C fragmentation in the amino-derivatives is comparable to that of the parent hydroxyalkyl-dithianes (i.e. the adducts of lithiodithiane and aldehydes, approximately 0.12) and in some cases even higher, up to 0.17. The accessibility of sulfur moiety to the approaching ET-sensitizer improves the quantum yield of cleavage, as evidenced by more efficient fragmentation in trithiane adducts compared to dithianes. The presence of either O or N is necessary for the fragmentation to occur with a useful efficiency, because its deprotonation in the initially formed cation-radical by a general base present in the solution or by the benzophenone amion-radical accelerates the reaction.

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1. Introduction

We are developing a general strategy for assembly and photoinduced disassembly of modular photolabile molecular objects, designed for applications in chemical biology. At the core of this approach is the recently discovered photofragmentation in dithiane- or trithiane-carbonyl adducts, which is initiated by photoinduced electron transfer followed by mesolytic C-C bond scission in the generated cation-radical, Scheme 1 [1].

We use such adducts as photolabile “latches” that can hold together various molecular blocks and at the same time are capable of releasing them upon sensitized photoradiation. This approach was used by us to link calixarenes [2a,c], crown ethers [2c,d], carbohydrates [2c], hydrophobic tails and hydrophilic head groups of photolabile amphiphiles [2e] and even to tether modules equipped with hydrogen bond-based elements of molecular recognition, for example ureas or aminopyridines [2b]. In view of our particular interest in biologically relevant molecular systems, we sought to outfit such photosensitive assemblies with specific elements of molecular recognition and probe their compatibility with the conditions of photoinduced fragmentation. Most commonly, biological elements of molecular recognition are based on nitrogen-containing functionalities, for example, NH (amide) moiety H-bonding to a carbonyl group or a nitrogen heterocycle. It was therefore imperative for us to develop a facile and yet efficient approach to photolabile elements containing the amino group, which can be further modified with various electrophiles into a number of bio-related N-H hydrogen bond-based elements of molecular recognition. In this pa-
per, we report on synthesis of a family of amino-derivatized photobleachable compounds and the quantum yield study of their photofragmentation [3].

2. Materials and methods

2.1. General information

Unless otherwise specified, solvents and reagents were purchased from commercial suppliers and used without further purification. THF was refluxed over and distilled from potassium benzophenone ketyl prior to use. 1H and 13C NMR spectra were recorded at 25°C on a Varian Mercury 400 MHz instrument. In CDCl3, TMS was used as an internal standard. For quantum yield determination a degassed solution of the target compound was used. A classic benzhydrol/benzophenone actinometer system was used as a standard [4]. A square arrangement of only four RPR-3500 A lamps (λmax = 350 nm) was used to ensure averaging over multiple revolutions of the carousel, and at the same time keeping the conversions to no more than 20–25% in the benzophenone-benzhydrol actinometer. Quantum yields were measured by irradiating the degassed samples in acetonitrile-d3 in Pyrex NMR tubes (cut off of 300 nm) and monitoring the decrease in intensities of the signals belonging to the adducts by NMR spectroscopy. The measurements were taken in triplicate and averaged for each compound.

2.2. Synthetic procedures

2a-(1,3)Dithian-2-yl phenylamine (3): A solution of hexamethyldisilazane 4.56 g (28 mmol) in 100 mL of freshly distilled THF was cooled to 0°C and n-butyllithium (1.6 M solution in hexane, 30 mmol, 19.36 mL) was added with vigorous stirring under N2 atmosphere. The reaction mixture was stirred at this temperature for 1.5 h. A 2.97 g (28 mmol) of (1-(1,3-dithian-2-yl)-phenylmethyl)amine 4.56 g (28 mmol) in 100 mL of freshly distilled THF was cooled to −25°C under nitrogen. n-butyllithium (1.6 M solution in hexanes, 30 mmol, 19.36 mL) was added dropwise upon stirring; the mixture was stirred for 2 h at −25°C. This solution was added to the resulting yellow solution of N-silylated benzaldehyde and the reaction mixture was allowed to warm to room temperature under nitrogen with stirring continued overnight. The solution was washed with 100 mL saturated NaHCO3, and the solvent was removed under reduced pressure. The resulting yellow oil was dissolved in 200 mL of EtOAc and extracted 2 × 100 mL of 10% HCl. The acid extracts where combined and pH was adjusted to 12 with 20% aqueous NaOH. After that the aqueous layer was extracted with 3 × 100 mL of EtOAc. The organic extracts where combined and washed with water 3 × 100 mL, dried over MgSO4 (anhydrous) and the solvent was removed under reduced pressure to give a yellow oil 6.2 g (97%) that was used without further purification. 1H NMR (CDCl3, δ (ppm) 7.42–7.22 (5H, m), 4.23 (2H, dd, J1 = 7 Hz, J2 = 6.6 Hz), 2.92–2.73 (4H, m), 2.12–2.04 (1H, m), 1.82–1.92 (1H, m).

N-(1-(1,3)dithian-2-yl-phenylmethyl)-4-nitrobenzamide (16): This trithiane anion was generated with n-butyllithium and added to benzaldehyde by a procedure described above for dithiane. The product was purified by column chromatography (EtOAc:hexane, 1:4). Yield: 80%. 1H NMR (CDCl3, δ (ppm) 7.42–7.28 (5H, m), 4.48 (1H, d, J = 4.4 Hz), 4.32–4.21 (3H, m), 4.04–3.90 (2H, m). Calcd for C18H19NOS2, %: C 64.14, H 5.81. Found, %: C 64.28, H 5.98.

α-(1,3)Dithian-2-yl phenylamine (3): a solution of hexamethyldisilazane 4.56 g (28 mmol) in 100 mL of freshly distilled THF was cooled to 0°C and n-butyllithium (1.6 M solution in hexane, 30 mmol, 19.36 mL) was added with vigorous stirring under N2 atmosphere. The reaction mixture was stirred at this temperature for 1.5 h. A 2.97 g (28 mmol) of (1-(1,3-dithian-2-yl)-phenylmethyl)amine 4.56 g (28 mmol) in 100 mL of freshly distilled THF was injected with syringe and the resulting mixture was kept at 0°C for 1 h. The THF solution of 1,3-dithian-2-yl anion was prepared as follows: a solution of 1,3-dithiane (3.39 g, 28 mmol) in 100 mL of freshly distilled THF was cooled to −25°C under nitrogen. n-butyllithium (1.6 M solution in hexanes, 30 mmol, 19.36 mL) was added dropwise upon stirring; the mixture was stirred for 2 h at −25°C. This solution was added to the resulting yellow solution of N-silylated benzaldehyde and the reaction mixture was allowed to warm to room temperature under nitrogen with stirring continued overnight. The solution was washed with 100 mL saturated NaHCO3, and the solvent was removed under reduced pressure. The resulting yellow oil was dissolved in 200 mL of EtOAc and extracted 2 × 100 mL of 10% HCl. The acid extracts where combined and pH was adjusted to 12 with 20% aqueous NaOH. After that the aqueous layer was extracted with 3 × 100 mL of EtOAc. The organic extracts where combined and washed with water 3 × 100 mL, dried over MgSO4 (anhydrous) and the solvent was removed under reduced pressure to give a yellow oil 6.2 g (97%) that was used without further purification. 1H NMR (CDCl3), δ (ppm) 7.42–7.22 (5H, m), 4.23 (2H, dd, J1 = 7 Hz, J2 = 6.6 Hz), 2.92–2.73 (4H, m), 2.12–2.04 (1H, m), 1.82–1.92 (1H, m).

N-(1-(1,3)Dithian-2-yl-phenylmethyl)-4-nitrobenzamide (5b): 74% after recrystallization from methanol, m.p. 230–232°C. 1H NMR (CDCl3), δ (ppm) 8.31 (3H, d, J = 8.8 Hz), 8.00 (2H, d, J = 8.8 Hz), 7.45–7.29 (5H, m), 7.06 (1H, broad d, J = 7.2 Hz), 5.51 (1H, dd, J1 = 7.2 Hz, J2 = 5.6 Hz), 4.55 (1H, d, J = 5.6), 2.93–2.75 (4H, m), 1.86–1.92 (1H, m). Calcd for C13H12N2O2S2, %: C 56.72, H 5.98. Found, %: C 56.72, H 5.98.

N-(1-(1,3)Dithian-2-yl-phenylmethyl-4-nitrobenzamide (5a): 77% after recrystallization from methanol, m.p. 240–243°C. 1H NMR (CDCl3), δ (ppm) 7.84 (2H, d, J = 5.6 Hz), 7.56–7.23 (4H, m), 7.01 (1H, broad d, J = 7.5 Hz), 5.53 (1H, dd, J1 = 7.5 Hz, J2 = 7.3 Hz), 4.55 (1H, d, J = 7.3), 2.92–2.75 (4H, m), 1.25–2.04 (1H, m), 1.96–1.83 (1H, m). Calcd for C16H16N2O2S2, %: C 65.62, H 5.81. Found, %: C 65.53, H 6.03.

Phenylcarbamic acid [1,3]dithian-2-yl-phenylmethy ester (18): A solution of alcohol 14 (2.26 g, 10 mmol) in 15 mL of ether was added to the solution of phenylisocyanate (1.32 g,
11 mmol) in 50 mL of ether. The reaction mixture was stirred for 72 h at room temperature. The precipitated white powder was filtered and washed two times with ether, recrystallized from MeOH and dried under reduced pressure (3.1 g, 86%), m.p. 126–128 °C. 1H NMR (CDCl₃), δ (ppm) 7.42–7.28 (5H, m), 6.88 (1H, broad d, J = 7.0 Hz), 6.52 (1H, d, J = 5.4 Hz), 4.82 (1H, d, J = 5.4 Hz), 4.06–3.97 (2H, m), 2.79–2.69 (2H, m), 2.07–1.96 (1H, m), 1.23 (3H, t, J = 6.0 Hz). Calcd for C₁₉H₁₇NO₃S₂, %: C 61.10, H 5.13. Found, %: C 60.84, H 5.10.

3-Benzyl-N-[1,3,5]trithian-2-yl-phenylbenzamide (5d): benzoylbenzoic acid was refluxed in SOCl₂ for 2 h. The excess SOCl₂ was removed under reduced pressure. The resulting acyl chloride was reacted with amine 3 to give amide 5d; yield 75%, after recrystallization from chloroform. 1H NMR (CDCl₃), δ (ppm) 7.94 (2H, d, J = 8.1 Hz), 7.86 (2H, d, J = 8.1 Hz), 7.84–7.79 (2H, m), 7.65–7.58 (1H, m), 7.53–7.46 (2H, m), 7.33–7.28 (5H, m), 7.03 (1H, broad d, J = 7.4 Hz), 6.92 (2H, d, J = 8.6 Hz), 5.53 (1H, dd, J₁ = 7.4 Hz, J₂ = 5.6 Hz), 4.55 (1H, d, J = 5.6 Hz), 4.11 (2H, t, J = 5.0 Hz), 3.77 (2H, t, J = 5.0 Hz), 3.59 (2H, q, J = 6.6 Hz), 2.92–2.74 (4H, m), 2.18–2.02 (1H, m) 1.98–1.80 (1H, m), 1.23 (1H, t, J = 6.6 Hz). Calcd for C₂₉H₂₁NOS₂, %: C 66.77, H 5.99. Found, %: C 67.03, H 6.16.

N-diphenyl-1,3,5-trithian-2-yl-methylbenzamide (7b): 65% after recrystallization from methanol. 1H NMR (CDCl₃), δ (ppm) 7.74 (2H, d, J = 5.0 Hz), 7.60–7.26 (13H, m), 7.09 (1H, broad s), 6.17 (1H, s), 4.56 (2H, d, J = 4.8 Hz), 3.89 (2H, d, J = 5.6 Hz). Calcd for C₂₉H₂₁NOS₂, %: C 65.21, H 5.00. Found, %: C 65.52, H 5.08.

N-[1,3,5]trithian-2-yl-diphenylbenzamide (6): 60% 1H NMR (CDCl₃), δ (ppm) 7.8 (2H, d, J = 6.0 Hz), 7.60–7.30 (13H, m), 7.23 (1H, broad s), 5.83 (1H, s), 3.10–2.96 (2H, m), 2.84–2.75 (2H, m), 2.10–1.96 (1H, m), 1.82–1.64 (1H, m). (1H)Dithian-2-yl-diphenylglycine-2-vinylamine (17): 71% 1H NMR (CD₃CN), δ (ppm) 7.84 (1H, m), 7.60–7.50 (4H, m), 7.35–7.17 (7H, m), 6.49–6.44 (1H, m), 6.33–6.28 (1H, m), 6.14 (1H, broad s), 5.94 (1H, s), 3.06–2.96 (2H, m), 2.79–2.69 (2H, m), 2.07–1.96 (1H, m + solvent peak), 1.62–1.44 (1H, m).

3-[3-(11)-Dithian-2-yl-hydroxy-methyl(phenoxy)propene-1-sulfonic acid, lithium salt (19): to a solution of 1.6 g (6.61 mmol) of 3-[3-(11)-dithian-2-yl-hydroxy-methyl)phenol in 50 mL of THF at 0 °C 3.5 mL of BuLi (1.6 M solution on hexanes, 5.56 mmol) was added under nitrogen and reaction mixture was allowed to warm to room temperature. To this solution 0.52 g (4.26 mmol) of propane sulfone in 10 mL of THF was added dropwise and the reaction mixture was stirred overnight. Aqueous work up included addition of 50 mL of diethyl ether and 100 mL of water followed by vigorous shaking in the separatory funnel. The aqueous layer was separated and water was removed by air stream. Resulting soapy solid was
dried under reduced pressure (1 mm Hg) and used without further purification. 1.24 g, 80%. 1H NMR (D2O), δ (ppm): 7.21 (1H, t, J = 7.8 Hz), 7.93–6.81 (3H, m), 4.73 (1H, d, J = 7.0 Hz), 4.30 (1H, d, J = 7.0 Hz), 4.03 (2H, t, J = 6.2 Hz), 2.96–2.88 (2H, m), 2.82–2.64 (4H, m), 2.10–2.00 (2H, m), 1.98–1.88 (1H, m), 1.68–1.54 (1H, m).

3-(4-Benzoyl-phenoxy)-propane-1-sulfonic acid (20): 5.5 mL of t-BuLi (1.7 M in pentane, 9.35 mmol) was added to a solution of the 2.2 g (11.1 mmol) of 4-hydroxybenzophenone in 50 mL THF at 0 °C under nitrogen and the reaction mixture allowed to warm to room temperature. A solution of 0.97 g (7.9 mmol) of propansulfone in 20 mL THF was added and reaction mixture was refluxed overnight. The reaction mixture cooled to room temperature; 50 mL of ether and 100 mL of water were added and extracted in separatory funnel. The water layer was separated and concentrated with air stream forming white precipitate, which was collected and dried in vacuum (1 mm Hg), yielding 1.6 g of 20 (63%). 1H NMR (D2O), δ (ppm): 7.52–7.44 (3H, m), 7.41 (2H, d, J = 7.2 Hz), 7.36–7.28 (2H, m), 6.78 (2H, d, J = 7.2 Hz), 3.97 (2H, t, J = 6.4 Hz), 2.89 (2H, t, J = 8.0 Hz), 2.10–2.00 (2H, m).

2,4-Bis-[amino-(4-fluorophenyl)-methyl]-[1,3,5]trithiane (23) and 2,4,6-Tris-[amino-(4-fluorophenyl)-methyl]-[1,3,5]trithiane (25): bis-lithiated trithiane was prepared by adding 19 mL of 1.7 M solution of t-butylithium (30 mmol) to a suspension of 2 g (14.6 mmol) of finely milled 1,3,5-trithiane in 100 mL of freshly distilled THF at −35 to −40 °C and stirring at this temperature for 4 h. N-Silylated benzaldimine in THF, prepared as described above, was added dropwise to the trithiane dianion solution under stirring which continued overnight at −20 °C. The solvent was removed in vacuum. The residue was shaken in a separatory funnel with the mixture of 100 mL of CH3Cl and 100 mL of water. The organic layer was separated, extracted with 2 × 30 mL of 2% HCl, and 30 mL of water. Acetic extracts were combined, made basic with saturated sodium carbonate, and extracted with 3 × 30 mL of CH3Cl. Organic extracts were combined and dried over Na2SO4. For separation, the free amines were derivatized with tert-Boc: 9.4 g (43.4 mmol) of di-tert-butyl dicarbonate was added to the CH3Cl solution of the amines followed by overnight stirring at room temperature; the solvent was removed in vacuum; the residue was separated by column chromatography (chloroform/acetoneitrile, 49:1). The mixture of diastereomers Boc-23 was recrystallized from acetonitrile to yield 818 mg of pure meso-isomer, and 967 mg of mixture containing enriched dl-isomer was recovered from the mother liquor. The second chromatographic fraction contained mainly diastereomers of Boc-25. Recrystallization of this fraction from acetonitrile gave 60 mg of the C3-symmetric diastereomer. The Boc protection was removed as follows: 60 mg of Boc-25 was dissolved in 10 mL of EtOH, 1 mL of concentrated HCl.

was added, and resulting mixture was refluxed for 30 min. The solution was allowed to cool, 20 mL of NaHCO₃ was added, and the water phase was extracted with 2 × 10 mL of CH₂Cl₂. Organic layer was dried with Na₂SO₄; the solvent was removed in vacuum to give 43.2 mg of pure 25 (C₃-symm). ¹H NMR (CDCl₃) δ (ppm): 7.28–7.38 (m, 6H), 7.08–6.96 (m, 6H), 4.35 (d, J = 4.5 Hz, 3H), 4.32 (d, J = 4.5 Hz, 3H).

2,4,6-Tris-[((2-aminoacetylamino)-(4-fluorophenyl)-methyl]-[1,3,5]trithiane (27): 43.2 mg of triamine 25, 73.5 mg of N-(t-Boc)glycine, 86.7 mg of dicyclohexylcarbodiimide, 48.3 mg of N-hydroxysuccinimide and 62.2 mg of 4-pyrrolidinopyridine were dissolved in 10 mL of DMF and stirred overnight at room temperature. Twenty milliliter of CH₂Cl₂ was added to the reaction mixture, the reaction mixture washed with 2 × 10 mL of saturated sodium carbonate, 10 mL of brine, and solvents removed in vacuum furnishing 66.6 mg of t-Boc 27. ¹H NMR (methanol-d₄) δ (ppm) 7.36–7.24 (m, 6H), 7.24–6.94 (m, 6H), 5.35 (d, J = 5.5 Hz, 3H), 4.84 (s, 6H), 4.75 (d, J = 6.2 Hz, 3H), 1.41 (s, 27H). A 66.6 mg of t-Boc protected 27 was then dissolved in 10 mL of trifluoroacetic acid, and stirred at room temperature for 2h. Trifluoroacetic acid was removed in vacuum to yield 67.3 mg of tris-trifluoroacetate 27. ¹H NMR (methanol-d₄) δ (ppm) 7.38–7.30 (m, 6H), 7.08–6.90 (m, 6H), 5.33 (d, J = 7.1 Hz, 3H), 4.88 (s, 6H), 4.86 (d, J = 7.1 Hz, 3H). HRMS (m/z) free triamine-Na⁺: calcd for C₃₀H₃₃F₃N₆O₃S₃Na: 701.16205, found: 701.16138 (<1 ppm).

3. Results and discussion

Addition of lithiated dithianes and trithianes to aldehydes and ketones produces secondary or tertiary alcohols containing the respective sulfur heterocycle. We reasoned that similar addition to imines should furnish the desired amines containing a photocleavable bond to dithiane. In a recent study, Welch and co-workers have demonstrated that N-silylated imines (2) of non-enolizable aldehydes and ketones can be prepared in situ by stirring an appropriate carbonyl compound with lithium bis(trimethylsilyl)amide (LHMDS) in THF at 0°C [5]. We found that the imines generated this way react with lithiated dithianes and trithianes producing primary amines 3, 4 in moderate to good yields after aqueous work-up.

3.1. Synthesis of derivatized α-aminalkyl dithianes and trithianes

The 16 derivatives thus prepared represent a diverse set of model compounds that address various electronic and steric aspects of the photofragmentation in dithiane and trithiane adducts with aldehydes and ketones. Table 1 lists the quantum yields of the cleavage that are obtained using benzophenone-benzyldrol actinometer system [4] in the carousel Rayonet reactor. A square arrangement of only four RPR-3500 A lamps (λₘₐₓ = 350 nm) was used to ensure averaging over multiple revolutions of the carousel and, at the same time keeping the conversions to no more
Quantum yields were measured by irradiating the degassed samples in acetonitrile-d$_3$ in pyrex NMR tubes and monitoring the decrease in intensities of signals belonging to the adducts by NMR spectroscopy. The measurements were taken in triplicate and averaged for each compound, the average values with standard deviations are shown in Table 1.

It follows from the table that for the most part the amino-counterparts of the Corey–Seebach adducts cleave with quantum efficiencies similar to that of the parent hydroxy-compounds, except for several special cases. Entries 15 and 16 (adducts 8 and 18) indicate that either O$_2$H- or N$_2$H is necessary for the fragmentation to occur with a useful efficiency.

It has been previously shown that deprotonation of the β-OH in the initially formed cation-radical by a general base present than 20–25% in the benzophenone-benzhydrol actinometer.

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than 20–25% in the benzophenone-benzhydrol actinometer.
in the solution or by the benzophenone anion-radical accelerated reaction fragmentation cf. [11a]. The phthalimide derivative 8 and the urethane 16 are both missing such proton and cleave with poor efficiency.

The highest quantum yield in this series is 17% for 7a, which is a trithiane adduct. Comparison of quantum efficiencies of fragmentation in less hindered aldimine adducts of dithiane versus trithiane shows a slight preference for trithiane adducts. This trend, however, is much more pronounced in the case of sterically hindered benzophenone imine adducts 6 and 7b (0.01 and 0.045) with the trithiane adduct cleaving 4+ fold more efficiently. We interpret this as an indication that the approach of the ET-sensitizer (e.g. triplet benzophenone) is sensitive to steric. Trithiane, with one “terminal” sulfur atom being always exposed, offers an advantage over dithiane, where both sulfurs are buried closer to the core of the dithiane-benzophenone imine moiety. It is known that upon formation of the cation radical, all three sulfur atoms in trithiane participate in the delocalization of spin-density, leading to a more stable intermediate. We, therefore, rationalize that: (i) it is somewhat easier to initiate the fragmentation in sterically more accessible trithianes and (ii) due to the increased driving force for the forward electron transfer, there is less back electron transfer, which is detrimental for high quantum efficiency.

Finally, comparison of the dithiane derivatives 14 and 15 (adducts of benzaldehyde and benzophenone, respectively) illustrates that the effect of steric hindrance on QY can be seen in the parent hydroxy-adducts as well. Despite the fact that benzophenone offers a better stabilization of the transition state at the fragmentation step, the overall quantum efficiency is higher for less hindered benzaldehyde adduct 14. It is interesting to note that formation of the cleavage in these cases parallels the initial rates of electron transfer quenching of the triplet benzophenone determined in our earlier laser flash photolysis studies of the parent hydroxy-adducts [1b] Fig. 1 shows the Force Field geometries of adducts 14, 15, 6, and 7b. It helps to visualize the point expressed above: in the first two compounds, the arrows show less obstructed access to sulfurs in benzaldehyde adduct 14, as opposed to more sterically congested benzophenone adduct 15. The second two adducts demonstrate that for the sterically congested derivatives of benzophenone imine 6 and 7b, trithiane has an advantage over dithiane, because its exo sulfur atom is noticeably more exposed to the approaching ET-sensitizer.

Two water soluble sulfonates, the adduct 19 and benzophenone 20, were synthesized to test the fragmentation in water. At neutral pH, the quantum yield was rather low, approximately 2%. Judging by the previously observed acceleration of the initial electron transfer oxidation by triplet benzophenone upon increased content of water in acetonitrile, one has to conclude that the back electron transfer is facilitated as well, with the net result of lowering the overall quantum efficiency in water. One complicating issue is that in order to outfit the reacting blocks with sulfonate groups, we used p-hydroxybenzophenone as a precursor to the water-soluble sensitizer and m-hydroxybenzaldehyde as a precursor to the water-soluble adduct. In the course of related studies we have found that p-alkoxybenzenophenones are generally not as efficient ET-sensitizers of the cleavage in hydroxyalkylthianes as unsubstituted benzophenone, so at least partially the decrease of the cleavage efficiency in basic aqueous solution may be attributed to the less efficient sensitizer. Expectedly the efficiency was found to be higher in basic solution, for example, at pH 9.5 the quantum yield reached 4.6%.

Incorporation of the nitro-group into 2-aminopyridine derivatives 11a and b rendered them self-sensitized. Although the C-C bond cleavage in the self-sensitized reaction of pyridines 11 was expected by analogy with the previously observed photofragmentations, we carried out the product study and investigated the mass balance for the direct cleavage of 11b (the adduct of a DHP-protected p-hydroxybenzaldehyde) to prove that it is still the C-C bond scission which is a primary mode of fragmentation. Direct irradiation of 11b in acetonitrile produced only the corresponding imine and the product of its hydrolysis. After chromatographic separation, 17% of the corresponding imine, ArCHO:NaPy, was isolated along with 35% of the starting aldehyde, ArCHO, 39% of 2-amino-5-nitropyridine and 21% of unreacted 11b, accounting for at least 73% in C-C bond cleavage. Adduct 5d, containing the benzophenone moiety, was synthesized as another example of a self-cleaving photolabile latch. While it was clearly fragmenting, its poor solubility has prevented us from accurately measuring the quantum yields of cleavage. Outfitting this model compound with an ethoxyethoxy-tail (compound 5e) only partially improved the solubility, however, aggregation and precipitation of the photolytic products again interfered with quantum yield determination.

In the case of the nitropyridines 11, the additional “bonus” was that due to the charge transfer band (amine→nitro) in the UV spectrum of 5-nitro-2-aminopyridines 11, these compounds are slightly yellow (λ<sub>max</sub> of 11b is 358 nm, with ab-
sorption band trailing well above 400 nm) allowing utilization of longer wavelengths to initiate the fragmentation, which is advantageous for biological systems.

The wavelength of irradiation in the sensitized reactions is, of course, depends on the choice of the ET-sensitizer. In these quantum yield studies we used primarily benzophenone, which has a $n\rightarrow\pi^*$ band in the vicinity of 350 nm. However, many other sensitizers can be used to generate cation-radicals of dithianes or trithianes. The reduction potential of triplet benzophenone is $-1.68$ V versus SCE in acetonitrile [6], whereas various substituted dithianes oxidize in the range of $+0.73$ to $+1.18$ V in the same solvent [7]. This implies some surplus driving force for the electron transfer in the benzophenone case, permitting the use of sensitizers with lower triplet energy and the reduction potential. A representative example is anthraquinone, which has a low-lying triplet state and also a longer wavelength absorption maximum (>400 nm). Yet, it is capable of sensitizing the C–C cleavage in bis-calixarenic spiro-bis-dithiane adduct, described by us earlier [2a] with a higher efficiency than that of the benzophenone-sensitized photofragmentation. Conceivably it is the sensitizer’s propensity to pre-association with a particular dithiane substrate that modulates the overall efficiency of the fragmentation.

3.3. Photolabile tripods and bipods

The study of quantum efficiencies was conducted in order to justify subsequent synthetic effort, i.e., the development of more elaborate modular photolabile systems. Quantum efficiencies in the range of 0.1–0.17 are practical for the photoinduced disassembly of molecular hosts, as long as these systems do not undergo interfering side reactions. From our experience, we do not see any evidence of this happening, and therefore suggest that the amino derivatives, such as 21, 23 or 25, can be used as building blocks for modular photolabile host molecules equipped with biologically relevant elements of molecular recognition.

From the synthetic point of view, the amino-counterparts of Corey–Seebach adducts offer a straightforward approach to the core “photolabile buckles and latches”. The primary amino groups can be easily modified by a variety of electrophiles in a fashion compatible with generation of combinatorial libraries. Using either the trithiane or spiro-bis-dithiane core we can synthesize more elaborate bis- and even tridentate photolabile molecular hosts equipped with hydrogen bond-based elements of molecular recognition or even short peptides. Examples of these compounds are shown in Scheme 3.
Bis-urea 22 is synthesized by quenching dilithiated spiro-bis-dithiane with an \(N\)-silylated aldimine followed by aqueous work-up and subsequent reaction with phenylisocyanate. Trithiane is used as the core element for the bis- and tridentate photolabile systems 24 and 26. It is known that trithiane can be doubly or triply deprotonated with butyl lithium [8]. We isolated and purified the \(meso\)-diastereomer of amine 23 and synthesized the bis-aminopyridine (\(meso\))-24, which is a host for urea derivatives, including barbiturates. The \(C_3\)-symmetric diastereomer of triamine 25, purified by column chromatography and recrystallization, was found to be slightly sterically congested for DCC coupling with carboxylates. Its “arms” were then extended with \(t\)-Boc protected glycine to make it more suitable for direct coupling with the C-terminus of short peptides or for iterative peptide synthesis.

In conclusion, we have developed a straightforward modular approach to photolabile molecular hosts outfitted with hydrogen bond-based elements of molecular recognition and have demonstrated that they undergo photosensitized fragmentation, which is expected to dramatically modulate their complexation properties. No significant secondary photoprocesses were observed upon extended irradiation. The quantum efficiencies of fragmentation in the amino-derivatives of dithianes and trithianes determined in this study (up to .17) are comparable to that of the parent hydroxy adducts (approximately .12) and are adequate for potential applications in photobiology.

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