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Dithiane- and Trithiane-Based Photolabile Scaffolds for Molecular Recognition

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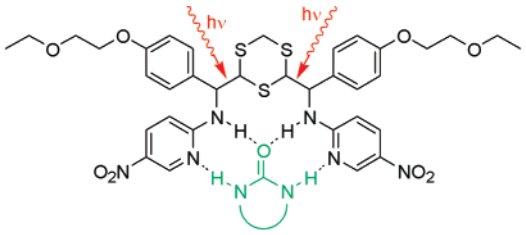
ABSTRACT



A modular synthetic approach to novel dithiane- and trithiane-based photolabile molecular hosts equipped with elements of molecular recognition is developed. The approach provides ready access to a family of amino-derivatized photocleavable molecular systems capable of hydrogen-bonding-based recognition of biologically relevant molecules, e.g., ureas, barbiturates etc. These systems undergo efficient photofragmentation in the presence of external (e.g., benzophenone) or internal (e.g., nitropyridine) electron-transfer sensitizers.

With so much effort directed over the past two decades toward improving our understanding of the underlying principles of molecular recognition, the elementary events involved in such processes are much better understood now than ever before.[1] Although predicting protein folding or docking patterns for relatively large polypeptides is still a task bordering on peering into a crystal ball, the behavior of much simpler systems is remarkably well understood. For example, hydrogen-bond-mediated self-association of various derivatives of urea and related heterocycles is becoming commonplace in supramolecular chemistry and is utilized widely for molecular templating etc.[2]

Our current interest is in developing molecular objects capable of photofragmentation, based on electron-transfer-induced C−C bond cleavage in hydroxyalkyl dithianes, which we previously reported.[3] In this context we developed a modular synthetic strategy utilizing spiro-bis-dithiane as a photolabile tether for assembling macromolecular photocleavable systems.[4] The next logical step was to equip such molecules with specific elements of molecular recognition and assess the compatibility of these elements with the photodisassembly step. For reasons mentioned above we focused on amino-derivatization—amides, ureas, and aminopyridines.

Although one can readily envision numerous potential applications of this methodology, at this time our strategic goal is in design and development of photoremovable inhibitors for biological systems.

(1) For recent reviews on various aspects of molecular recognition, see special issue of *Chem. Rev.* **1997**, *97*, issue 5, Gellman, S. H., Guest Editor.

(2) (a) Mertz, E.; Mattei, S.; Zimmerman, S. C. *Org. Lett.* **2000**, *2*, 2931. (b) Corbin, P. S.; Zimmerman, S. C. *J. Am. Chem. Soc.* **2000**, *122*, 3779. (c) Mak, T. C. W.; Xue, F. *J. Am. Chem. Soc.* **2000** *122*, 9860. (d) Suarez, M.; Lehn, J.-M.; Zimmerman, S. C.; Skoulios, A.; Heinrich, B. *J. Am. Chem. Soc.* **1998**, *120*, 9526. (e) Koyano, H.; Bissel, P.; Yoshihara, K.; Ariga, K.; Kunitake, T. *Langmuir* **1997**, *13*, 5426. (f) Sánchez-Quesada, J.; Seel, C.; Prados, P.; de Mendoza, J. *J. Am. Chem. Soc.* **1996**, *118*, 277 (g) Nowick, J. S.; Mahrus, S.; Smith, E. M.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 1066.

(3) McHale, W. A.; Kutateladze, A. G. *J. Org. Chem.* **1998**, *63*, 9924.

(4) (a) Wan, Y.; Mitkin, O.; Barnhurst, L.; Kurchan, A.; Kutateladze, A. *Org. Lett.* **2000**, *2*, 3817. (b) Mitkin, O. D.; Wan. Y.; Kurchan, A. N.; Kutateladze, A. G. *Synthesis* **2001**, in press.

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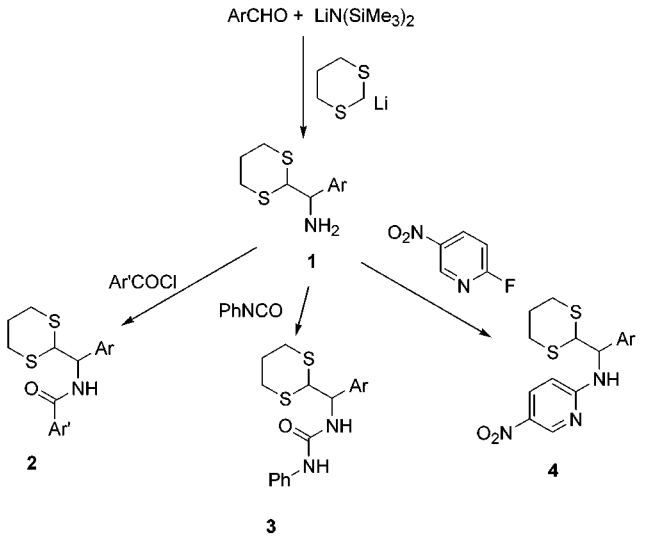
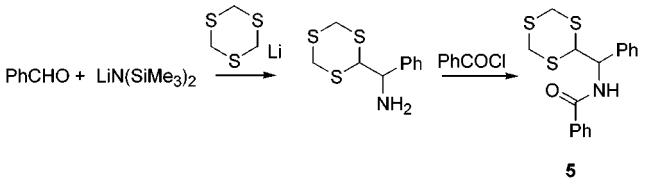
We first developed a straightforward synthetic approach to primary amines **1**[5] via addition of 2-lithio-1,3-dithiane to N-silylated benzaldimines, generated in situ[6] from aromatic aldehydes and lithium bis(trimethylsilyl)amide (LHMDS). Amines **1** were then treated with various electrophiles, including benzoyl chlorides, phenylisocyanate or 2-fluoro-5-nitropyridine to furnish a diverse set of photolabile molecules **2**−**4**.[7]

Scheme 1



We also found that *sym*-trithiane can be used in place of 1,3-dithiane in these synthetic sequences. For example, an analogous reaction with lithiated 1,3,5-trithiane afforded benzamide **5** (Scheme 2).

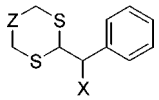
Scheme 2



Irradiation of adducts **2**, **3**, and **5** in acetonitrile in the presence of benzophenone as an external ET-sensitizer leads to a photofragmentation similar to what we described earlier for dithiane-carbonyl adducts,[3] with comparable quantum efficiencies (see Table 1). For a fair comparison we also measured the quantum yield for the photocleavage in trithiane-benzaldehyde adduct **6**.

The modular nature of our synthetic approach allows us to build hybrid molecular hosts by combining urea units with various other moieties, e.g., crown-ethers for enhanced complexation of alkali carboxylates (Figure 1). Host **3b**, for instance, was synthesized readily starting from 2-formyl-benzo-18-crown-6, LHMDS, and lithiodithiane, working up

Table 1. Quantum Efficiencies of Photoinduced Cleavage in Acetonitrile with Benzophenone as an External ET-Sensitizer



	quantum yield
Z = CH_2; X = OH	0.119
Z = CH_2; X = *p*-NO_2PhC(O)NH− (**2b**)	0.143
Z = CH_2; X = PhC(O)NH− (**2a**)	0.121
Z = CH_2; X = PhNHC(O)NH− (**3a**)	0.067
Z = S; X = PhC(O)NH− (**5**)	0.172
Z = S; X = OH (**6**)	0.068

the resulting amine with phenylisocyanate. Potassium acetate dissolves readily in the acetonitrile solution of **3b**, and the proton NMR spectrum of the resulting solution shows significant downfield changes in chemical shifts of the amide protons ($\Delta\delta$ > 2 ppm, Figure 1) indicating that the expected coordination of the acetate anion to the urea moiety does indeed occur.[8]

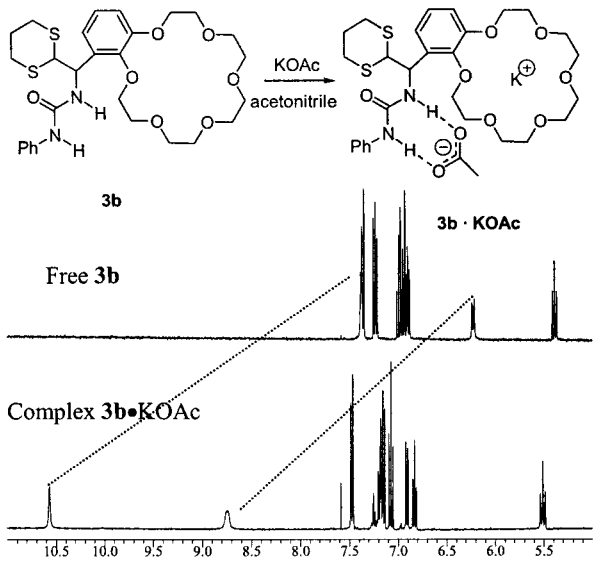
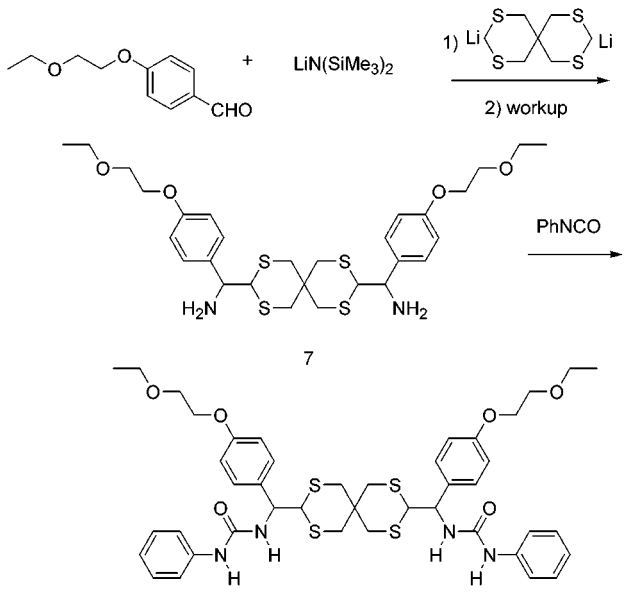


Figure 1. Binding of potassium acetate in acetonitrile.

Utilizing novel spiro-bis-dithiane as a photolabile tether we synthesized more elaborate bidentate molecular hosts, such as **8** (Scheme 3), suitable for dicarboxylate binding. Judging by signal broadening in proton NMR spectra, diastereomers **8** are heavily self-associated in nonpolar solvents, e.g., chloroform. Expectedly, such hydrogen-bond-based self-association is disrupted in methanol or acetonitrile.

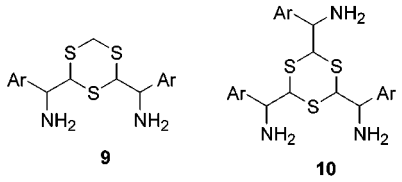
As it follows from Scheme 1 we also introduced the 5-nitro-2-aminopyridine moiety as yet another element of molecular recognition. The nitro group not only facilitates the aromatic nucleophilic substitution of fluorine but also shifts the UV absorption band of the product to λ_{max} = 335 nm, rendering **4** suitable for self-sensitization. Direct irradia-

Scheme 3



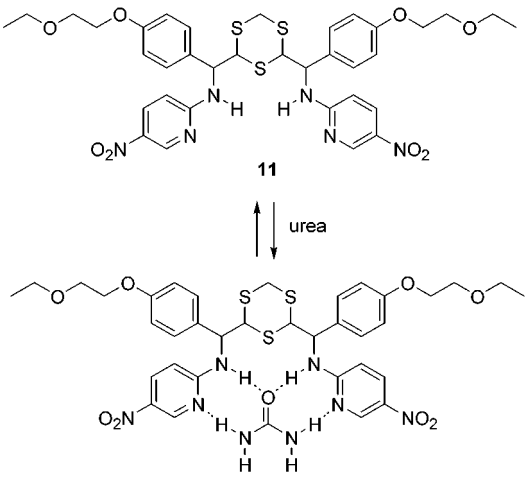
tion of **4** in acetonitrile using a medium-pressure mercury lamp and Pyrex filter resulted in an efficient photofragmentation reaction.[9] 2-Aminopyridines are known to serve as a molecular recognition moiety for carboxylic derivatives[10] or even to mimic nucleotides.[11] Aminopyridine **4** thus combines molecular recognition functionality with the ability to induce fragmentation upon direct irradiation.

Just as with bisurea **8**, bidentate compounds bearing *two aminopyridine* moieties can be synthesized from spiro-bis-dithiane-based diamine **7** and excess 2-fluoro-5-nitropyridine. An alternative general approach to bi- or tridentate molecular hosts is to utilize multiply lithiated trithiane. It has been reported in the literature that 1,3,5-trithiane can form di- and even trianions when treated with excess butyllithium.[12] We therefore were able to synthesize di- and trisubstituted trithianes **9** and **10** bearing amino groups, which can be readily modified.



For example, treating diamine **9** (Ar = *p*-ethoxyethoxyphenyl) with 2 molar equiv of 2-fluoro-5-nitropyridine furnished compound **11**.[13]

Scheme 4



Photolabile host **11** is capable of binding urea, as evidenced by signal shifts in proton NMR. Although the

(5) **Typical Experimental Procedure.** A solution of 4.56 g (28 mmol) of 1,1,1,3,3,3-hexamethyldisilazane in 100 mL of freshly distilled THF was cooled to 0 °C, and 19.4 mL of *n*-butyllithium (1.6 M solution in hexanes, 30 mmol) was added with stirring under N_2 atmosphere. The reaction mixture was stirred at this temperature for 1.5 h. Next, 3 g (28 mmol) of benzaldehyde was slowly added, and the resulting mixture was stirred at 0 °C for 1 h. Lithiated dithiane was prepared by adding 19.4 mL of 1.6 M *n*-butyllithium (30 mmol) to a solution of 3.39 g (28 mmol) of 1,3-dithiane in 100 mL of freshly distilled THF at −20 to −25 °C and stirring at this temperature for 2 h. The solution of lithiodithiane was added slowly to the solution of silylated benzaldimine, the cooling bath was removed, and the reaction mixture was stirred overnight at room temperature. The resulting red solution was washed with 100 mL of saturated NH_4Cl, and THF was removed in a vacuum, producing a yellow oil, which was dissolved in 200 mL of EtOAc and extracted with 2 × 100 mL of 10% HCl. The acid extracts were combined, pH was adjusted to 12 with 20% NaOH, and the water layer was extracted with 3 × 100 mL of EtOAc. Organic extracts were combined and washed with water 3 × 100 mL. The organic layer was dried over anhydrous $MgSO_4$, and the solvent was removed in a vacuum, furnishing **1a** (Ar = Ph, 6.2 g, 97%) as a yellow oil, which was used without further purification. ^{1}H NMR ($CDCl_3$) δ (ppm) 7.42−7.22 (5H, m), 4.25 (1H, d, J = 6.6 Hz), 4.22 (1H, d, J = 6.6 Hz), 2.92−2.73 (4H, m), 2.12−2.04 (1H, m), 1.82−1.92 (1H, m).

(6) Gyenes, F.; Bergmann, K. E.; Welch, J. T. *J. Org. Chem.* **1998**, *63*, 2824.

(7) More experimental details can be found in the Supporting Information.

(8) Downfield shift of N−H protons is indicative of H-bonding; see, for example: (a) Ösapay, K.; Case, D. A. *J. Am. Chem. Soc.* **1991**, *113*, 9436. (b) Wishart, D. S.; Sykes, B. D.; Richards, F. M. *J. Mol. Biol.* **1991**, *222*, 311. (c) Williamson, M. P.; Asakura, T. *J. Magn. Res.* **1993**, *B 101*, 63.

(9) (a) Photophysical details for this cleavage and a more complete quantum yield study for a variety of substituted **2**−**5** will be reported in the full paper. (b) Although the C−C bond cleavage in the self-sensitized reaction of **4** was expected by analogy with the previously observed photofragmentations, we carried out the product study and investigated the mass balance for the reaction of **4b** (the adduct of a DHP-protected *p*-hydroxybenzaldehyde, Ar′ = *p*-DHP−O−C_6H_4). Direct irradiation of **4b** in acetonitrile produced only the corresponding imine and products of its hydrolysis. After chromatographic separation, 17% of the imine, Ar′CH=N−Py, was isolated along with 35% of the aldehyde, Ar′CHO, 39% of 2-amino-5-nitropyridine and 21% of unreacted **4b**, accounting for at least 71% in C−C bond cleavage.

(10) (a) Karle, I. L.; Ranganathan, D.; Haridas, V. *J. Am. Chem. Soc.* **1996**, *118*, 7128. (b) Garcia-Tellado, F.; Geib, S. J.; Goswami, S.; Hamilton, A. D. *J. Am. Chem. Soc.* **1991**, *113*, 9265.

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(12) Schumaker, R. R.; Rajeswari, S.; Joshi, M. V.; Cava, M. P.; Takassi, M. A.; Metzger, R. M. *J. Am. Chem. Soc.* **1989**, *111*, 308.

(13) (a) *p*-Ethoxyethoxybenzaldehyde was used for improved solubility in organic solvents. (b) We did not separate individual diastereomers of **11** (2:1 ratio by NMR). 2,4-Disubstituted trithianes, formed by electrophilic quenching of lithiated trithianes, are believed to have *cis* geometry (see Fukunaga, M.; Sugawara, T.; Oki, M. *Chem. Lett.* **1972**, *1*, 55), and we therefore assume that the observed diastereomers are the *meso* and *d,l* pair as a result of the two chiral benzylic centers generated as a result of the anion addition to imine, not the *cis*−*trans* isomers.

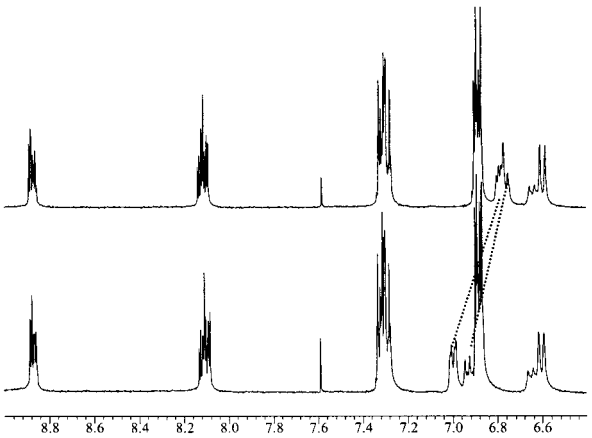

Figure 2. Free **11** (top) in acetonitrile and changes in NMR due to its complexation with urea (bottom).

changes in chemical shifts are not as pronounced as in the case of ionic acetate binding to **3b**, addition of urea to an acetonitrile-d_3 solution of **11** causes the signal of its N−H proton to shift downfield by about 0.3 ppm. (Figure 2).

We also optimized the geometry of the complex of *meso*-**11** with urea by utilizing a DFT level of theory and constraining the urea-aminopyridines fragment to planarity. Although there were no other constraints to impose a vertical plane of symmetry, the optimized structure is very close to

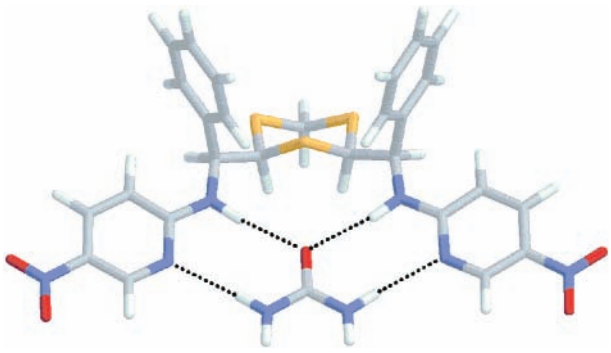

Figure 3. B3LYP/6-31G* geometry of *meso*-**11**·urea.

C_S-symmetric and has the urea molecule positioned equidistantly from the two aminopyridine fragments (Figure 3). The structure is practically free from steric strain, with two benzylamine fragments being in a nearly staggered conformation with respect to the trithiane's sulfurs.

To quantitatively evaluate the complexation ability of **11** in chloroform we carried out a NMR titration experiment with a $CDCl_3$-soluble urea derivative, imidazolidone. Upon addition of the guest, NMR spectra showed a similar downfield shift of the N−H protons in **11**, with calculated dissociation constant K_D= 32.2 mM (Figure 4).

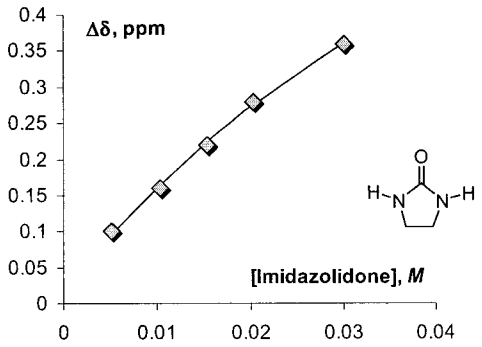

Figure 4. Changes in the chemical shift of N−H protons of **11** in $CDCl_3$ as a function of imidazolidone concentration (solid line is a calculated fit for K_D = 32.2 mM).

We are currently investigating the complexation properties for compounds of type **8** and **11**, which will be reported in the full paper. To summarize, we have developed a general modular approach for assembly of photolabile molecules, outfitted with hydrogen-bond-capable elements of molecular recognition.

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Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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