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 amino-pyridines.

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

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 (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, 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-formylbenzo-18-crown-6, LHMDS, and lithiodithiane, working up 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 (Δδ > 2 ppm, Figure 1) indicating that the expected coordination of the acetate anion to the urea moiety does indeed occur.

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-

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

<table>
<thead>
<tr>
<th>Adduct</th>
<th>Quantum Yield</th>
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<tbody>
<tr>
<td>Z = CH₂; X = OH</td>
<td>0.119</td>
</tr>
<tr>
<td>Z = CH₂; X = p-NO₂PhC(O)NH⁻ (2b)</td>
<td>0.143</td>
</tr>
<tr>
<td>Z = CH₂; X = PhC(O)NH⁻ (2a)</td>
<td>0.121</td>
</tr>
<tr>
<td>Z = CH₂; X = PhNHC(O)NH⁻ (3a)</td>
<td>0.172</td>
</tr>
<tr>
<td>Z = S; X = PhC(O)NH⁻ (5)</td>
<td>0.067</td>
</tr>
<tr>
<td>Z = S; X = OH (6)</td>
<td>0.068</td>
</tr>
</tbody>
</table>

Figure 1. Binding of potassium acetate in acetonitrile.
tion of 4 in acetonitrile using a medium-pressure mercury lamp and Pyrex filter resulted in an efficient photofragmentation reaction. 2-Aminopyridines are known to serve as a molecular recognition moiety for carboxylic derivatives or even to mimic nucleotides. Aminopyridine 4 thus combines molecular recognition functionality with the ability to induce fragmentation upon direct irradiation.

Just as with bisurea, 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. 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.

Photolabile host 11 is capable of binding urea, as evidenced by signal shifts in proton NMR. Although the...
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 $C_3$-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).

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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