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Nanohoop Rotaxane Design to Enhance the Selectivity of Reaction-Based Probes: A Proof-of-Principle Study

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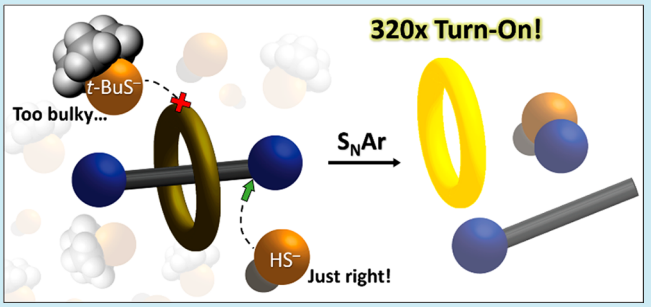
ABSTRACT: Mechanical interlocking of a nanohoop fluorophore and a reactive thread couples the benefits of a reaction-based probe with a sterically congested active site for enhanced selectivity. Advantageously, the thread design uses dual function stoppers that act as both a quencher and a trigger for sensing. In progress toward expanding this approach to biologically relevant analytes, this system is used to demonstrate steric differentiation and provide a selective turn-on fluorescent response with size selectivity for HS^- rather than larger thiolates.



The development of fluorescent sensors for biologically relevant analytes is a rapidly growing field of research, due in part to the utility, simplicity, and versatility of these systems.[1−5] These probes are used for detection and quantification of chemical species with documented roles in various disease states and also as tools to obtain a better understanding of biological processes.[1,4,6,7] In many cases, the effective concentration of a particular analyte can be linked with disease progression, and therefore the ability to study an analyte in a natural biological environment is critical.[5,7,8] This requirement, however, presents a formidable challenge because probes need to be highly selective due to the large number of reactive species present in complex biological systems. Simultaneously, heightened sensitivity is required due to the low physiological concentrations of these species, all while operating in a very competitive solvent (water).[6−11] Obtaining analyte selectivity has traditionally relied on the creation of highly specific binding sites; however, these "lock-and-key" systems come with challenges (Figure 1a).[12] Sensors based solely on supramolecular or coordination-driven interactions can be heavily influenced by solvation effects and changes in pH, issues that are amplified in aqueous media.[7] Alternatively, reaction-based probes can be designed to contain a "trigger" that reacts with an analyte of interest, and therefore, selectivity is a function of differences in reactivity (Figure 1b).[7,13−16] This mode of selectivity, however, can be difficult to achieve when considering a group of analytes with similar reactivity, such as reactive sulfur species (RSS). To our knowledge, a yet unexplored route to enhancing probe selectivity is the pairing of these two powerful methods of analyte sensing by constructing a sterically encumbered reactive probe via mechanical interlocking.

Mechanically interlocked molecules (MIMs) have recently garnered interest for a variety of biological applications. The mechanical bonds of MIMs often give rise to unique molecular recognition sites not accessible via traditional covalent

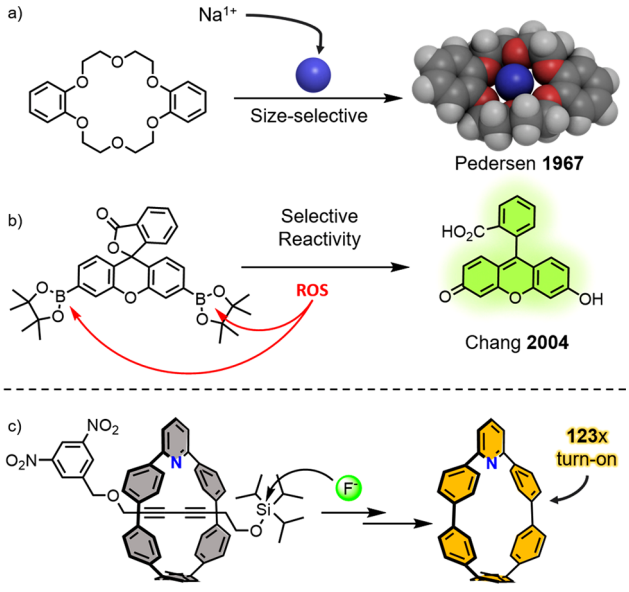


Figure 1. Classic examples of (a) size-selective[12] and (b) reaction-based sensing platforms.[16] (c) A previously published nanohoop[2]-rotaxane-based fluorescent fluoride sensor.[28]

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chemistry, which can be useful for sensing, imaging, and drug delivery.[17−30] Furthermore, the steric encumbrance provided by the macrocyclic component of rotaxanes has been exploited to protect electron-deficient moieties from nucleophilic attack, modulate the reactivity of the thread component, and enhance the photophysical properties of dye-based axles.[18,30−33] Nanohoops are unique among macrocycles used for MIM synthesis,[34−36] due to their inherent fluorescence and highly rigid structure, particularly at small sizes.[37] As a consequence, minimal steric bulk is required to prevent dethreading via slippage, allowing for broad flexibility in thread design. Taking advantage of these properties, we recently illustrated the potential of nanohoop [2]rotaxanes as turn-on fluorescent sensors (Figure 1c).[35] Use of an electron-deficient 2,5-dinitrobenzylic alcohol as one of the stoppers quenches the fluorescence of the nanohoop in the interlocked state. A fluoride-triggered silyl deprotection of the triisopropylsilyl ether stopper results in dethreading of the macrocycle, dissociation of the quencher and fluorophore, and ultimately a 123-fold turn-on in fluorescence.

Building from this example, we sought to target a more challenging analyte to demonstrate the advantage of the congested reaction site of the interlocked sensor. As noted above, one group of analytes that has proved challenging to sense selectively is RSS. The smallest species in this family is hydrogen sulfide (H_2S), one of three currently recognized gasotransmitters.[38] H_2S is involved in a wide variety of regulatory processes, and the diverse roles in human physiology make it an important target of research.[39−42] Selective reaction-based probes that rely on H_2S/HS^- nucleophilicity are often challenging to design because other biologically relevant nucleophilic thiols are present in much greater concentrations (low nM for H_2S vs low mM concentrations for glutathione).[13,43−51] Herein, we report a novel turn-on fluorescent nanohoop [2]rotaxane[52] for selective sensing of HS^- in organic solution based on the well-documented S_NAr reaction of thiolates with 2,4-dinitrophenyl (DNP) ethers.[44−46] We provide a proof-of-principle demonstration that encapsulation of a DNP ether thread within a nanohoop via mechanical interlocking effectively couples the benefits of a reactive probe with a sterically tailored active site, enhancing the selectivity of the probe.

As previously mentioned, our group recently accessed a variety of nanohoop [2]rotaxanes, where "2" denotes the number of component molecules in the MIM. These structures can be prepared by incorporation of a 2,6-pyridine unit into the backbone of a carbon nanohoop that can then participate in active metal templating via a Cadiot−Chodkiewicz (CC) cross-coupling reaction.[35,36,53,54] With this methodology in mind, rotaxane sensor **4** was envisioned with **1** as the templating macrocycle, which again is notable for its small size, rigidity, and fluorescence (Figure 2a). The thread component was designed to have two multifunctional DNP units that serve as stoppers, reactive probes, as well as fluorescence quenchers. To this end, terminal alkyne coupling partner **2** was prepared via deprotonation of DNP alcohol with potassium carbonate and reaction with propargyl bromide. The requisite halo-alkyne coupling partner **3** was then easily obtained in good yield via treatment of **2** with silver nitrite and *N*-bromosuccinimide. Treatment of both thread components **2** and **3** with $[Cu(MeCN)_4][PF_6]$ in the presence of nanohoop **1** delivered the desired interlocked rotaxane **4** in 18% unoptimized yield. Notably, the isolated yellow solid was

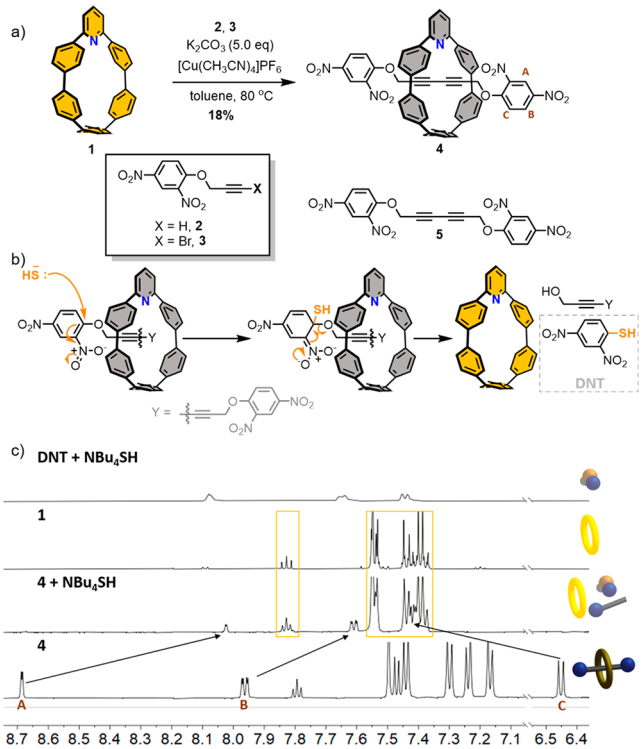

Figure 2. (a) Synthesis of rotaxane **4** and free thread **5**, (b) proposed mechanism of rotaxane dethreading in the presence of HS^-, and (c) ^1H NMR spectra (aromatic region) of rotaxane **4** in CD_3CN, before and after addition of 1 equiv of NBu_4SH, compared with free macrocycle **1** and DNT in the presence of NBu_4SH.

nonfluorescent in the solid and solution state as predicted. Free thread **5** was prepared as a control compound using similar methods. All compounds were characterized by ^1H and $^{13}C\{^1H\}$ NMR spectroscopy, mass spectrometry, and IR spectroscopy (see SI for full details).

DNP reacts with HS^- via an S_NAr mechanism.[44,45] Based on this, we expected HS^- to react with rotaxane **4** to first generate a Meisenheimer complex (Figure 2b). Collapse of this intermediate would release 2,4-dinitrothiophenol (DNT), an equivalent of diyne, with subsequent dethreading of the nanohoop and a concomitant turn-on in fluorescence (Figure 2b). We first investigated this process via ^1H NMR spectroscopy. For these studies, we used the organic soluble tetrabutylammonium hydrosulfide (NBu_4SH) because HS^- is the most prevalent protonation state of H_2S under physiological conditions and is the active species responsible for cleavage of DNP groups. Figure 2c illustrates the immediate response upon treatment of 4.5 mM rotaxane **4** with 1 equiv of NBu_4SH in acetonitrile-d_3 at 25 °C. Consistent with the mechanism in Figure 2b, we see the return of free macrocycle **1** (resonances outlined in yellow) as well as the appearance of resonances that suggest the formation of S_NAr byproduct DNT. Moreover, at the conclusion of the experiment, the sample showed bright yellow fluorescence under UV irradiation, also consistent with dissociation of the thread from macrocycle **1**.

Next, we investigated the kinetics of the dethreading events using time-course fluorescence and UV−vis experiments. We added 10, 50, or 100 equiv of NBu_4SH to a solution of rotaxane sensor **4** in degassed MeCN and monitored changes in the fluorescence and absorbance spectra over time (see SI

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for further details.) Dethreading is complete within 30 min (based on lack of further change in fluorescence or UV−vis spectra) when either 50 or 100 equiv of NBu_4SH is introduced. With just 10 equiv of NBu_4SH, we see a 320-fold turn-on in nanohoop fluorescence, with the signal plateauing around 120 min (Figure 3). It should be noted that the immediate reaction

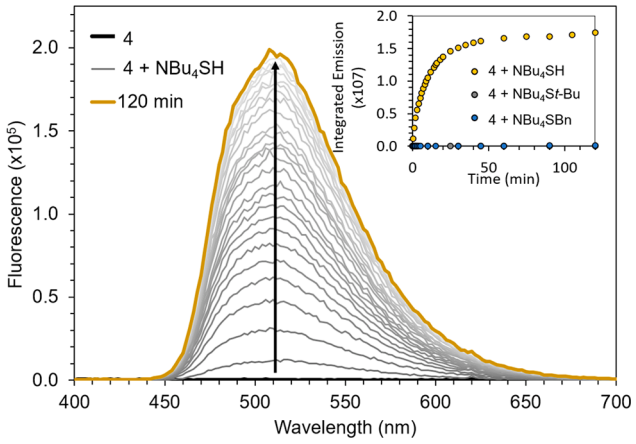

Figure 3. Time-course fluorescence (excitation 310 nm) of **4** (25 μM in acetonitrile) before and after addition of 10 equiv of NBu_4SH over 120 min. Inlay: integrated fluorescence of **4** over 120 min in the presence of 10 equiv of NBu_4SH, NBu_4St-Bu, or NBu_4SBn.

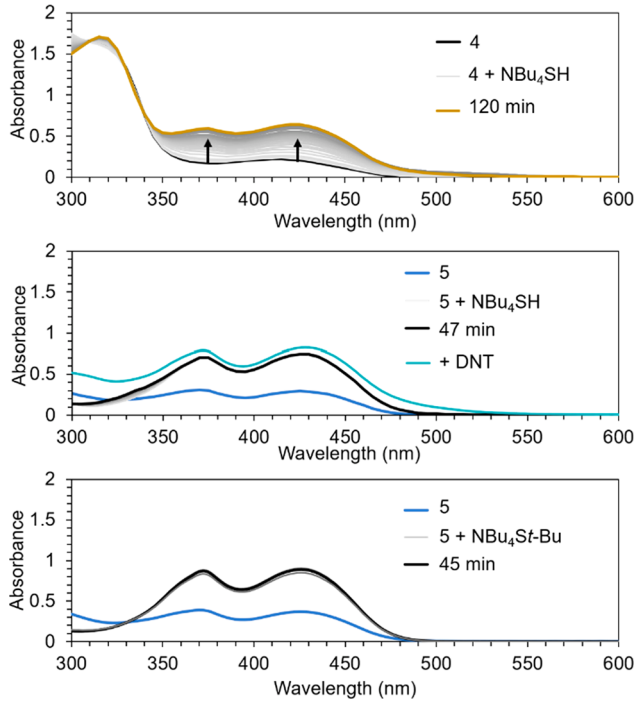

Figure 4. Time-course UV−vis spectra of **4** with 10 equiv of NBu_4SH (top) and of **5** with 10 equiv of NBu_4SH followed by addition of DNT (middle) and **5** with 10 equiv of NBu_4St-Bu (bottom). All probe concentrations are 25 μM each in acetonitrile.

seen by NMR is a consequence of the higher concentration regime utilized for NMR (4.45 mM **4**) versus photophysical (25 μM **4**) studies. The corresponding absorbance spectra show steady consumption of NBu_4SH at 270 nm (SI Figures S7, S9, and S11) along with a steady increase in absorbance around 375 and 425 nm, attributed to formation of DNT (Figure 4, top). In contrast, the absorbance of the nanohoop (320 nm) remains relatively constant over the course of the experiment, as expected, since **1** and **4** have similar absorption profiles.

Curiously, at the end of experiments using 50 or 100 equiv of the nucleophile, a slightly decreased maximum fluorescence emission is observed. Consistent with this observation, a separate control experiment (SI Figure S32) demonstrated a slight decrease in fluorescence when the free nanohoop **1** was treated with 10 equiv of NBu_4SH in the absence of the thread, which may explain the lower overall fluorescence observed with high NBu_4SH concentrations. The same decrease in fluorescence of **1** is not observed when in the presence of up to 100 equiv of NBu_4Cl (SI Figure S33), suggesting that high concentrations of HS^- can slightly modulate the fluorescence of the nanohoop. A Stern−Volmer analysis of this system (SI Figure S34) suggests this is likely due to dynamic/collisional quenching. These concentrations of NBu_4SH, however, are significantly higher than would be found in biological systems.

At the outset of this work, we hypothesized that the steric hindrance created by interlocking the reactive thread within the compact nanohoop should enhance selectivity for small nucleophiles such as H_2S/HS^-. To investigate this size-based selectivity, we next repeated these experiments with both NBu_4St-Bu and NBu_4SBn, more sterically demanding thiolates. After 120 min in the presence of the larger nucleophiles, we observed virtually no turn-on fluorescence response, which is consistent with a significant steric selectivity for HS^- (Figure 3, inlay). To further confirm the effect of interlocking the reactive unit, free thread **5** was also subjected to reaction with NBu_4SH, NBu_4St-Bu, and NBu_4SBn. In contrast to **4**, free thread **5** shows an immediate growth of peaks at 375 and 425 (DNT) without change over time (Figure 4, middle/bottom), suggesting that the free thread reacts nearly instantaneously regardless of nucleophile identity. Finally, in a competition experiment, both **4** and **5** were combined (25 μM each) with NBu_4St-Bu or NBu_4SBn (125 μM) and observed over time. While there is no change seen in the fluorescence spectrum over 30 min, addition of either thiolate results in the immediate appearance of S_NAr byproduct peaks in the UV−vis spectra, consistent with the breakdown of free thread **5** only. Taken together, these results confirm the successful enhancement of selectivity for this particular reactive probe via mechanical interlocking. We hypothesize that this concept will be broadly applicable to enhancing the selectivity of reaction probes for smaller analytes.

In summary, we have designed a turn-on fluorescent probe for HS^- that shows excellent selectivity over *t*-BuS^- and BnS^-. This study suggests the utility of such rotaxane-based probes to tune the size selectivity of reactive sensors due to the unique steric environment imparted by the mechanical bond. In conjunction with recent work in our laboratory toward creating biocompatible nanohoops for biological imaging/sensing, the development of these rotaxane sensor systems that can operate in aqueous media is an important and feasible next step.[55] We also note that the sensor reported here contains a symmetric thread where either end can function as a trigger. Future work investigating unsymmetric thread units that impart these nanohoop rotaxane sensors with enhanced function (e.g., payload release) is ongoing and will be reported in due course.

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■ ASSOCIATED CONTENT

Supporting Information

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Detailed synthetic procedures and characterization data; NMR spectra; and detailed photophysical experimental procedures and data (PDF)

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Notes

The authors declare no competing financial interest.

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