

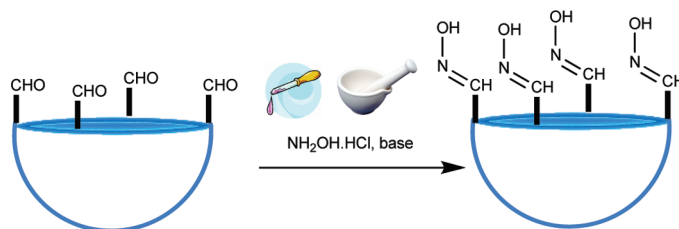
Oxime Decorated Cavitands Functionalized through Solvent-Assisted Grinding

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Received October 6, 2010

ABSTRACT



In order to assemble supramolecular capsules, there is a need for reliable and effective synthetic methods for decorating cavitand-based host structures with appropriate functional groups. The synthesis of four different cavitands of significantly different depth and interior volume functionalized with four aldoxime groups capable of forming homomeric or heteromeric capsules through hydrogen bonding is reported. The final step in each synthesis, the aldehyde to oxime transformation, has been achieved in excellent yields through 'solvent assisted grinding'.

Cavitands represent a class of rigid, bowl-shaped molecules, with an inner cavity large enough to accommodate a variety of guest molecules or ions.¹ One of the most important applications of such molecules is in the design and assembly of discrete molecular capsules that can subsequently be used, for example, for catalysis,² molecular sensing,³ and stabilization of reactive intermediates,⁴ and recently as photosensitizers and as a protection against undesired photochemical reactions.⁵ All these properties are a function of the assembled state and unique to and controlled by the precise metrics that define space, volume, and chemical characteristics of the internal volume of the capsule. The ability to decorate the rim of a cavitand with a variety of functional groups in any geometric configuration therefore continues

to be the focus of intensive research,⁶ since the presence of appropriate molecular recognition entities on these molecular container compounds can produce a range of capsules of different shapes and sizes. The presence of self-complementary functional groups (in the context of intermolecular interactions) can result in the formation of homomeric capsules,⁷ whereas if complementary entities are located on two different hosts, a heteromeric capsule can be assembled.^{8,9} In addition, two different cavitands can be brought together into a capsule using a linker with appropriate molecular recognition sites.¹⁰ To date, methylene bridged resorcinarene based cavitands have been functionalized with hydrogen-bonding functionalities such as a pyridyl,¹¹ carboxylic acid,¹⁰ hydroxyl group,⁹ to facilitate the reversible noncovalent synthesis of molecular capsules. However, only

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a small number of potentially suitable hydrogen-bonding moieties have been employed in this context, primarily due to synthetic challenges, and as a result, the potential of cavitands as a foundation for functional molecular capsules has yet to be fully realized.

Oximes are highly effective and versatile hydrogen-bonding groups capable of forming self-complementary hydrogen-bonded dimers and chains,¹² and they can also form strong and directional intermolecular interactions with a wide range of other hydrogen-bond acceptors, Figure 1.¹³

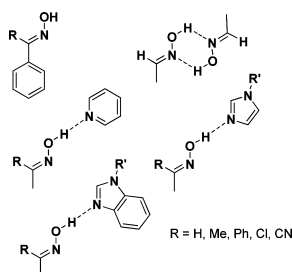


Figure 1. Tunable nature of the oxime group along with possible homomeric and heteromeric hydrogen-bond interactions.

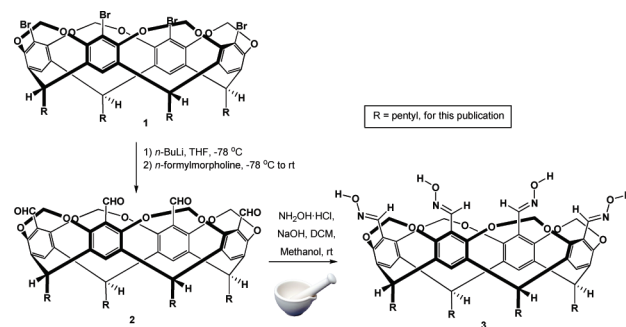
Oximes typically exhibit pK_a values in a range between that of carboxylic acids and amides and, consequently, are less pH sensitive than carboxylic acids. They are therefore unlikely to undergo proton transfer to many N-heterocycle acceptors thereby avoiding the formation of organic salts which could lead to unwanted solubilities, unpredictable chemical compositions, and intermolecular interactions.^{13,14} More significant, however, is the fact that oximes offer the possibility of greater tunability by facile variation of the substituent R (Figure 1), which is not present in carboxylic acids or primary amides. The choice of this substituent also permits the solubility of the oxime building block to be modified, facilitating supramolecular synthesis in a wider range of solvent systems. Despite these numerous potential advantages of oximes as reliable supramolecular synthetic vectors, there have been no reports of oxime functionalized cavitands to date.

Over the past two decades, a major problem in the field of organic synthetic chemistry has been a lack of more environmentally friendly processes using safer reagents, generating fewer side products, and requiring less use of

organic solvents.¹⁵ In response to such concerns, the use of ‘dry grinding’ or ‘solvent assisted grinding’ for the synthesis of new materials has gained considerable attention and importance in recent literature.¹⁶ In this publication, we report the preparation of four new cavitands, each bearing four aldoxime groups, synthesized using ‘solvent assisted grinding’. It is worth mentioning that so far no examples of cavitand functionalization by use of ‘solvent assisted grinding’ have been reported. These cavitands have the potential to provide homomeric and heteromeric nanosized molecular capsules held together by hydrogen bonding, and they also have the capability to form extended capsules with a linker molecule. In addition, oximes can also act as ligands for transition-metal ions,¹⁷ and it is therefore possible to envision metal ions as the glue for bringing together extended cavitand-based architectures. The interior of each host can also be altered by controlling the exact location of the supramolecular functional group on the cavitand. Herein, we have employed stepwise and modular approaches for the synthesis of four new tetraoxime functionalized cavitands **3**, **6**, **7**, and **10**.

We based our strategy for decorating cavitands with oxime groups by appending aldehyde functionalities onto the cavitand backbone followed by transformations to the desired aldoxime. Our starting points for obtaining the desired precursors were tetrabromocavitand **1**¹⁸ and tetrabromomethylcavitand **8**,¹⁹ which were synthesized from their respective resorcinol derivatives in three steps as per reported literature procedures. To synthesize these aldoxime bearing cavitands we lithiated (*n*BuLi, THF) tetrabromocavitand **1**, Scheme 1, followed by addition of *n*-formylmorpholine as

Scheme 1. Synthesis of Tetraaldoxime Cavitand, **3**



the electrophile, which yielded tetraaldehyde cavitand **2** (60%).²⁰ When we tried to convert aldehyde **2** to oxime **3** using solution based synthesis it took 72 h for all aldehydes to react and substantial byproduct formation was unavoidable.

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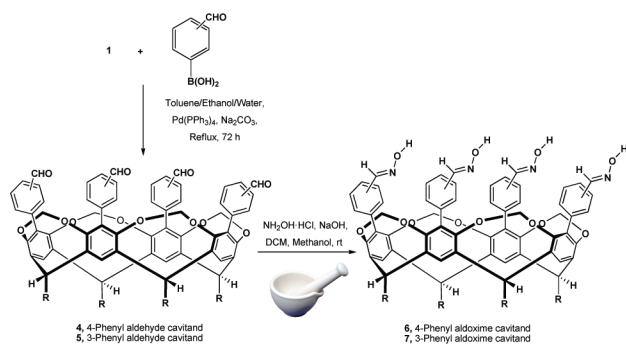
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In contrast, treatment of tetraldehyde cavitand **2** with 6 equiv of hydroxylamine hydrochloride in the presence of a strong base, NaOH, with a few drops of dichloromethane and methanol and grinding for 5 min yielded tetraaldoxime cavitand **3** (Scheme 1) without any byproduct formation. ‘Solvent assisted grinding’ has advantages such as (1) it saves reaction time as compared to conventional minimum solution-based synthesis, (2) it saves solvent for the reaction, and (3) no substantial byproducts were formed thereby avoiding tedious purification procedures.

To synthesize the deeper cavitands **6** and **7** with an aldoxime group at the 4- and 3-position respectively, we made use of Suzuki–Miyaura cross-coupling reactions to access the necessary parent aldehydes.²¹ Coupling tetrabromocavitand **1** with 4-formylphenylboronic acid yielded cavitand **4** in 95% yield after column chromatography. When **1** was coupled with 3-formylphenylboronic acid it gave **5** in 40% yield on purification. The ‘solvent assisted grinding’ protocol on cavitands **4** and **5** yielded aldoxime cavitands **6** and **7** respectively with no side reactions (Scheme 2).

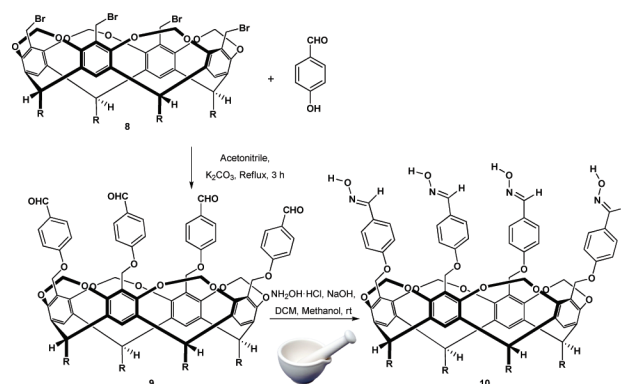
Scheme 2. Synthesis of Tetraphenyl Aldoxime Cavitands **6**, **7**



To obtain a somewhat deeper cavity with the potential for a more flexible interior space, we combined a tetrabromom-

ethyl cavitand **8** precursor and 4-hydroxybenzaldehyde. The substitution reaction of **8** with 4-hydroxybenzaldehyde with K_2CO_3 as a base yielded tetraaldehyde cavitand **9**²² which upon treatment with hydroxylamine hydrochloride under basic conditions afforded the flexible tetraaldoxime cavitand **10** (Scheme 3).

Scheme 3. Synthesis of Deep Tetraaldoxime Cavitand **10**



In summary, cavitand functionalization from tetraaldehyde to tetraoximes using ‘solvent assisted grinding’ was successfully achieved, irrespective of the position of the aldehyde. The presence of aldoxime functionalities with their well-established and reliable supramolecular capabilities on a cavitand scaffold opens up hitherto unexplored options for constructing homomeric and heteromeric capsules as well as metal-ion assembled architectures that may have unique structural features and function. We are currently exploring both solution- and solid-state assembly of discrete molecular capsules using noncovalent synthetic tools.

Acknowledgment. We are grateful for financial support from the NSF (CHE-0957607) and from the Terry C. Johnson Center of Basic Cancer Research.

Supporting Information Available: Detailed experimental procedures and characterization of compounds **3**, **4**, **5**, **6**, **7**, **10**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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