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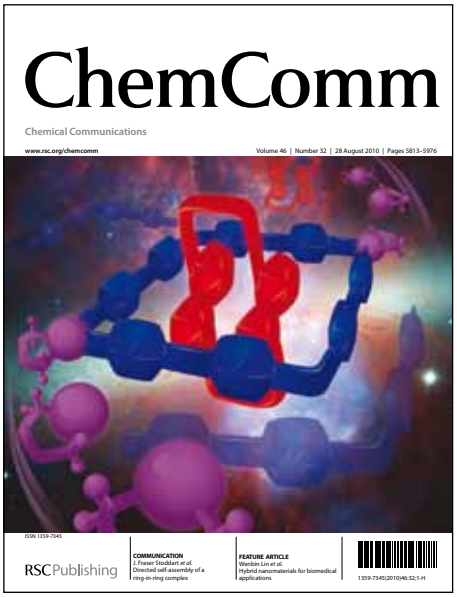

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Selective encapsulation of volatile and reactive methyl iodide†

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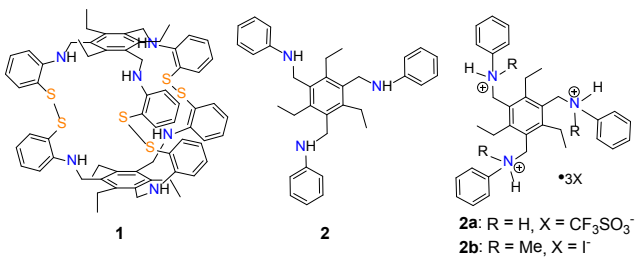
A simple organic molecular container can selectively encapsulate the volatile and highly reactive MeI through hydrogen-bonding interactions in solution. The remarkable encapsulation of MeI without self-methylation of the container appears to be determined by the complementary binding sites and the rigidity of the hydrogen-bonding array constrained by the molecular framework.

Molecular recognition is the fundamental property of a synthetic or biological host that aids the specific selection of guests and plays an important role in a wide variety of functions such as sensing, adsorption, complexation, drug delivery, catalysis, and membrane transportation.[1] In the past three decades, numerous host-guest complexes have been reported, and the key factors controlling host-guest binding interactions have been identified to be (i) preorganization of the receptors and (ii) complementary stereoelectronic arrangement of binding sites in the host and guest molecules.[2] For the encapsulation of unreactive small neutral molecules in solution,[3] many elegant containers with defined small internal volumes have been constructed from unimolecular containers of Cram[4] and Collet[5], to the more recent, self-assembling systems of Rebek.[6] Nevertheless, the recognition and encapsulation of small, highly reactive and hazardous species such as phosgene, PBr_3, H_2O_2, and methyl iodide (MeI) have not been achieved because these species tend to react with the specific functional groups (SFGs) of the synthetic molecular host and form irreversible adducts. One approach to overcome this challenge involves designing a host that does not have SFGs but allows for noncovalent bonding interactions within its complementary cavity. While there are a few examples[7] that demonstrate this principle, this approach is not practical because the host-guest interactions are dependent on the molecular packing arrangement and specific selectivity is poor. Employing host molecules with shape-persistent architectures and sterically constrained SFGs is an alternative solution, but there are no published reports in this regard. Despite their ability to react with suitable guests, the SFGs may become inert if structurally rigid, thereby facilitating encapsulation and significant stabilization of the guest molecule through effective interactions such as hydrogen bonding. In the present study, we employed this principle for the recognition and encapsulation of the highly reactive molecule MeI. MeI shows moderate-to-high acute toxicity for inhalation and ingestion;[8] further, it is an environmental pollutant[9] and is an important component of radioactive nuclear waste.[10] Molecular encapsulation is considered a desirable method for MeI removal since this method facilitates non-destructive removal and recovery of MeI, which can then be used in various organic syntheses.

Although fluorescent sensors for the detection of MeI through methylation in solution have recently been developed,[11] synthetic receptors for the recognition and encapsulation of intact molecular MeI have not been designed. Hydrogen bonding mediated by amino or amido groups (hydrogen-bond donors) in the host is, by far, the most common noncovalent interaction for recognition processes in supramolecular and biological host-guest chemistry.[12] Such interactions are also effective in mediating binding with I_2[13] or I^- guests[14] in artificial receptors. However, special methods must be adopted to design a receptor with NH functionalities for the specific selection of MeI, so that methylation of the hydrogen-bonding donor atoms is prevented. We demonstrate for the first time that the highly reactive MeI can be trapped selectively and intact by a simple molecular container in solution through NH···I interactions, under ambient conditions. Methylation of the secondary amine is prevented by delocalization of the lone pair of electrons on the nitrogen atom and the rigidity of the molecular container. In addition, the ability of the container to prevent the evaporation of MeI is demonstrated.



Scheme 1 Chemical structures of the compounds discussed here.

In our research, we focused on the self-assembly and encapsulation performance of cage-type molecules with dynamic covalent bonds.[15] We report a cylindrical organic container **1**,[16] which is a dimer of tripodal trisulfide precursors linked by three disulfide bonds, as shown in Scheme 1. The container, which is insoluble in most organic solvents but shows high solubility in benzene or toluene, can encapsulate I_2 in solution or in amorphous solid state through NH···I interactions.[13a] On the basis of the crystal structure of the I_2⊂**1** adduct and the architectural stability of the container, we state that the internal microenvironment of **1** with the rigidified hydrogen-bonding array is ideal for trapping a single molecule of MeI.

Before performing experiments on MeI encapsulation, the stability of the container toward protonation was investigated, since protons are smaller entities that are more susceptible to nucleophilic attack than is MeI. The chemical nature of **1** remained unaffected even after treatment for 3 days with excess CF_3SO_3H (strong organic acid) in toluene or with H_2SO_4 (strong inorganic acid) in a toluene/CH_3CN mixture, indicating that this molecular container is resistant to protonation and can encapsulate MeI without undergoing self-methylation.

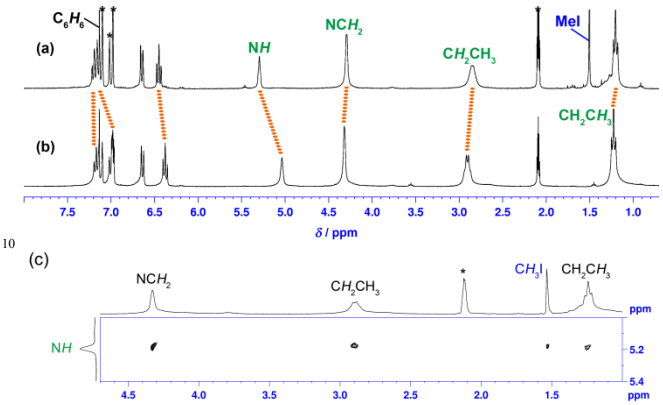


Fig. 1 ^{1}H NMR spectra (300 MHz, 298 K, toluene-d_8 (*)) of MeI⊂**1** (a) purified **1** (b). (c) partial ^{1}H-^{1}H NOESY spectrum of MeI⊂**1**.

Addition of 1 mol equiv of MeI to a stirred toluene solution of **1** at ambient temperature resulted in the formation of a large amount of light-yellow precipitate within 2 min, confirming that **1** is capable of encapsulating MeI in solution. The ^{1}H NMR spectrum of the precipitate in toluene-d_8 was recorded at room temperature, although the precipitate was only sparingly soluble in this solvent. The spectrum showed significant shift of the host signals, especially the amino and aromatic proton signals (Fig. 1a and b). The C_3 symmetry of the container remained unchanged, indicating that none of the nitrogen atoms was uniquely methylated. Besides, NOESY spectrum (Fig. 1c) showed a cross peak between the MeI and N-H resonances of **1**, revealing the weak spatial correlation between the protons of MeI and the amino protons oriented toward the cavity. These observations along with DOSY NMR experiments (ESI†) indicated that the MeI molecules were well accommodated in the cavity of **1** in solution. The packing coefficient (PC)[17] of 0.57 for MeI (ESI†) is in good agreement with the optimal packing in solution postulated by Rebek. No chemical shift was observed in the spectrum of **1** when iodides with larger molecular volume such as EtI (ESI†) or *i*PrI were used, consistent with their larger PCs (>75%). However, CH_2Cl_2 with similar volume to MeI showed no evidence of encaptulation.[13a] Thus, more specific interactions other than just molecular packing should be involved for the encaptulation of MeI in solution, as compared to other similar C_3 symmetric hosts.[18] The solid-state IR spectrum of the precipitate showed N-H stretching bands with equal intensities at 3370 and 3390 cm^{-1}, which were identical to the stretching vibrations for I_2⊂**1**and **1**, respectively, indicating that only three of the six NH groups of **1** were involved in hydrogen bonding with MeI in the solid state (Fig. 2a, b, and c).

MeI⊂**1** crystals suitable for X-ray crystallographic analysis were prepared by slow diffusion of neat MeI into a toluene solution of **1** at -20°C. Comparison of the structures of different **1**-adducts (i.e., **1** having various encapsulated guests) revealed no notable change in the structural parameters of the container (ESI†), thereby confirming the architectural rigidity of the container. As shown in Fig. 3, a single molecule of MeI is accommodated in the cavity of **1** through weak three-point NH···I hydrogen-bonding interactions (van der Waals radii: H, 1.20 Å; I, 1.98 Å).[19] The C-I bond distance in the trapped MeI was comparable with that in crystalline MeI at high pressures.[20] Besides, a nonbonding (lone pair) I···Ph (aromatic base) interaction[21] was observed (van der Waals radii: C, 1.70 Å; I, 1.98 Å) in the crystal structure.

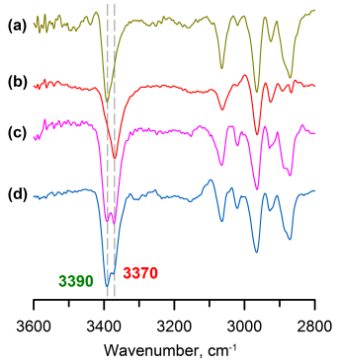


Fig. 2 Partial solid-state IR spectra of **1** as synthesized (a), crystalline I_2⊂**1** (b), crystalline MeI⊂**1** (c), and soild MeI⊂**1** after exposure to the atmosphere for over 24 h under ambient conditions (d). The dashed gray lines represent the N-H stretching frequencies at 3370 and 3390 cm^{-1}.

Upon encapsulation in **1**, MeI became less volatile, and the amount of MeI⊂**1** solid immersed in toluene remained unchanged even after exposure to the atmosphere for over 4 months under ambient conditions. This behavior was contradictory to that of the naked MeI in toluene under the same concentration conditions: in this case, MeI vaporized completely within 7 days. As the temperature of the mixture increased to 80°C, the precipitates dissolved within 2 h and the trapped MeI was released from the cavity, with the concurrent regeneration of **1**, as revealed by ^{1}H NMR analyses. In the IR spectrum of the solid MeI⊂**1** exposed to the atmosphere at ambient temperature for 24 h, the intensity of the NH stretching band at 3370 cm^{-1} decreased by about 10%, indicating that **1** efficiently retarded the evaporation of MeI even under non-solvated conditions (Fig. 2d).

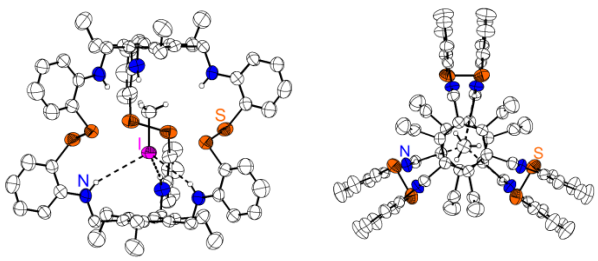


Fig. 3 Molecular structure of MeI⊂**1**: side view (left) and top view (right). The thermal ellipsoids are drawn at a 35% probability level. The MeI molecule is statically disordered with the two positions for carbon and iodide atoms interchangeable. Hydrogen atoms bound to carbon atoms in **1** are omitted for clarity. The dashed lines represent NH···I hydrogen bonding interactions. Selected distances [Å] and angles [°]: C-I 2.100, NH···I 3.238, I···X 3.462 (X = centroid of the aromatic base); N-H-I 156.7, C-I-X 180.0.

To assess whether MeI encapsulation occurred without the self-methylation of **1**, we synthesized a modified receptor **2**, which does not have disulfide linkages, and investigated its electronic and structural features after protonation and methylation. The (Ph)C–N bond distances in **2** (ESI†) were similar to those in the **1**-adducts and the trimethylated product obtained from the trisulfide precursor of **1** (ESI†) and were typical of aniline-type C–N bonds with partial double-bond character. The reaction of **2** with 3 equiv CF_3SO_3H in CH_2Cl_2 readily afforded the triprotonated salt in quantitative yield within 3 h. However, treatment of **2** with 6 equiv MeI in toluene under ambient conditions afforded the methylated products in very low yield (15%) after 12 h, presumably because delocalization of the lone-pair of electrons weakened the nucleophilicity of the nitrogen atoms toward MeI. Crystal structure analysis of the protonation and methylation products of **2** (**2a** and **2b**, respectively) revealed that the aminophenyl rings, which were perpendicular to the plane of the triethylbenzene base, were significantly tilted because of the sp^3-hybridized nitrogen atoms and the steric hindrance caused by the attached methyl groups (for **2b**, Fig. 4; for **2a**, ESI†). Such a structural adaptation was not possible in **1** because all the six phenyl rings were almost orthogonal to the benzene bases and held together tightly by disulfide linkages. Thus, the difficultly involved in the protonation or methylation of the secondary amines in **1** could be explained by their electronic and steric features.

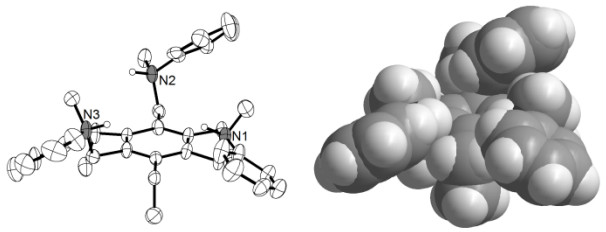


Fig. 4 The molecular structure (left) and space-filled model (right) of the cation part of compound **2b** with the same orientation. The thermal ellipsoids are drawn at a 35% probability level. Hydrogen atoms bound to carbon atoms, and the iodide anions were omitted for clarity. The detailed NH···I hydrogen bonding interactions were shown in the ESI†.

A promising strategy for the selective encapsulation of volatile and reactive species on the basis of the steric hindrance of a reactive functionality constrained by a simple, structurally rigid organic capsule with a complementary cavity is proposed. This method allows for the selective recognition and encapsulation of the environmentally relevant and highly reactive MeI in solution. The structurally rigidified reactive functional groups within the host's skeleton provide a stabilizing effect that aids the selective recognition and encapsulation of reactive substances. Our approach can be extended to other reactive and hazardous species through appropriate design of the functional cavity and molecular framework. Preparation of larger water-soluble analogs of **1** that act as hosts for highly complicated reactive guest species and have greater biological relevance is currently underway.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimetal details and single-crystal data. CCDC 883531 (MeI⊂**1**), 883532 (**2**), 883533 (**2a**), and 883534 (**2b**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b000000x/

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