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Self-assembled capsules based on tetrafunctionalized calix[4]resorcinarene cavitands

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Calix[4]resorcinarene-based cavitands with a bowl-shaped aromatic cavity are widely used as scaffolds for covalently bound and self-assembled capsules. There are two main categories of calix[4]resorcinarene-based cavitands that are tetrafunctionalized at the upper (wider) rim: one category includes derivatives that have functionalized bridges between pairs of hydroxy groups of the calix[4]resorcinarene, and the second category includes derivatives with functional groups at the 2-position on the resorcinol ring and the methylene bridge between pairs of hydroxy groups. This review describes capsular self-assemblies of the latter type of methylene-bridge cavitands, which are formed through hydrogen bonds, metal–coordination bonds, and dynamic covalent bonds.

1. Introduction

Molecular capsules (containers, cages) provide an isolated nanometer-sized cavity: a nanospace. In their pioneering work, Cram and co-workers developed carcerand **1** in 1985 and hemicarcerand **1′** in 1990, in which two calix[4]resorcinarene-based cavitands are held together by four or three covalent linkages, respectively (Fig. 1).[1] These covalently bound cavitand capsules have attracted considerable attention because they have applications in areas such as the stabilization and detection of reactive intermediates (encapsulation of guest molecules as the precursors, and then generation of the labile chemical species inside the capsules by an external stimulus) and as microvesicles for drug delivery, whereby the guest molecules are confined inside the capsules away from the bulk phase. The greatest benefit of covalently bound cavitand capsules is their stability, compared with self-assembled capsules (vide infra). However, the low yield of capsule formation and the requirement for rather drastic conditions for the encapsulation and release of guests are often disadvantageous for covalently bound cavitand capsules.

Error correction through thermodynamic equilibration, minimization of synthetic effort by the use of modular subunits, and control of assembly processes through subunit design are characteristics of supramolecular approaches to self-assembly.[2] Based on this concept, the field of molecular capsules has advanced over the last two decades to a stage in which self-assembly through noncovalent interactions has become a reliable tool. In 1993, in a pioneering work, Rebek and co-workers developed a dimeric capsular assembly that formed through self-complementary hydrogen bonding of two bis-glycoluril-derived subunits with concave surfaces; the authors

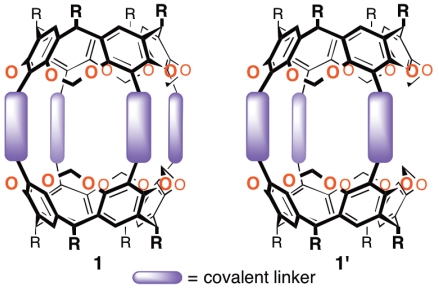

Fig. 1 Covalently bound cavitand capsules: carcerands **1** and hemicarcerands **1** or **1′**.

termed this assembly the tennis ball molecule.[3] In 1995, Fujita and co-workers developed a self-assembled capsule by using metal–ligand coordination; thus, six molecules of *cis*-coordinated square-planar Pd(II) complex were used as connectors and four molecules of a rigid tridentate pyridyl ligand were used as a paneling subunit.[4] Subsequently, various types of self-assembled capsules have been reported. The merits of self-assembled capsules include: (i) quantitative capsule formation under thermodynamic control if the molecular design is correct; (ii) encapsulation and release of guests on the NMR or human time scale under mild conditions; and (iii) in some cases, interconversion or alteration of the structure can be controlled by host–guest interactions (dynamic self-assembly).[5] Guest molecules confined within the self-assembled nanospace often show unique properties that are not observed in their free forms, such as stabilization of labile chemical species, acceleration of chemical reactions, and the emergence of novel stereoisomerisms.[5]

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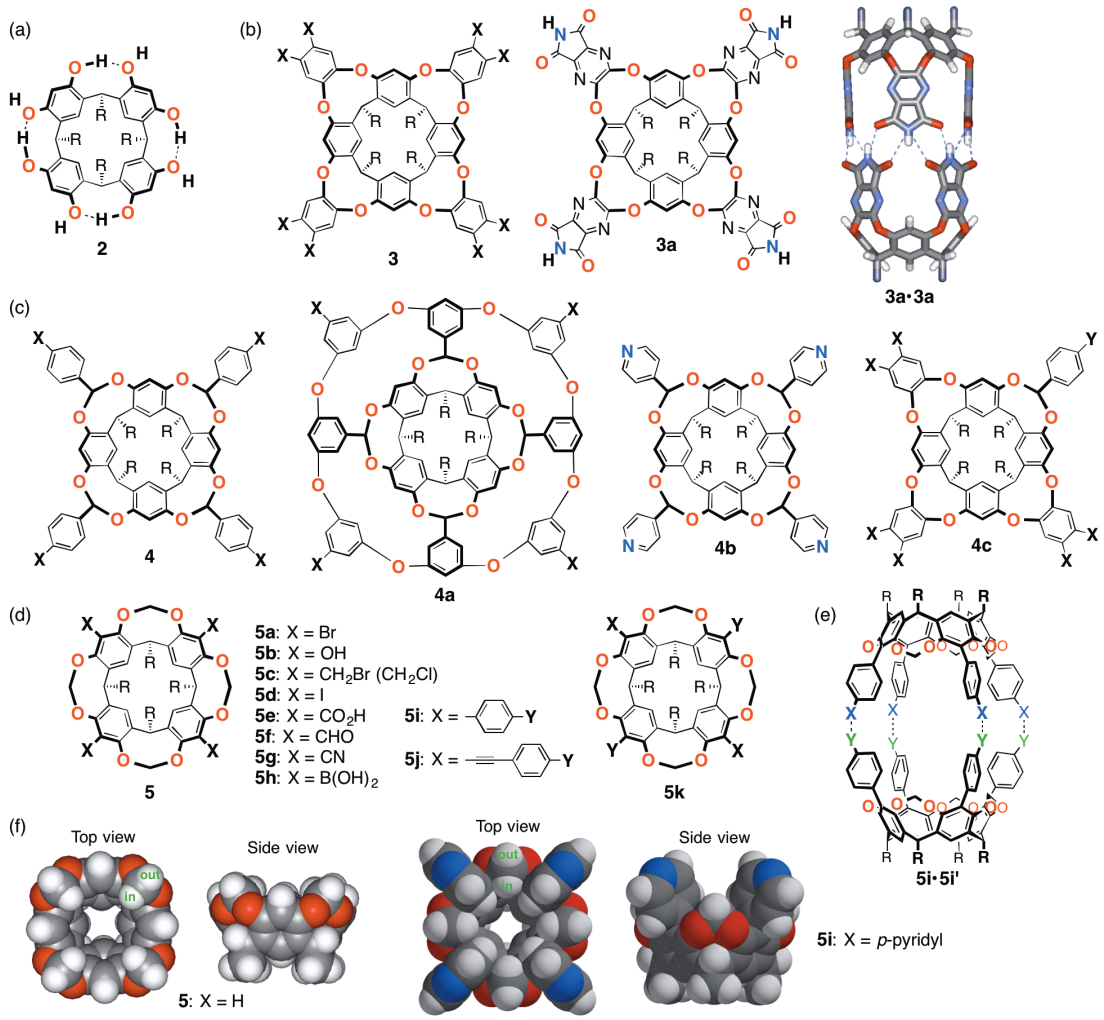

Fig. 2 (a) Structure of calix[4]resorcinarene **2**. Three types of tetrafunctionalized calix[4]resorcinarene-based cavitands at the upper rim: (b) aromatic ring-bridge cavitands **3** and Rebek's self-assembled capsule **3a•3a**, (c) benzal-bridge cavitands **4**, Gibb's **4a**, Dalcanale's **4b**, and Rebek's hybrid **4c**, (d) methylene-bridge cavitands **5**, and (e) schematic representation of a self-assembled capsule **5i•5i'**. (f) Molecular models of methylene-bridge cavitands with and without *p*-pyridyl group.

The correct design of subunits is key to the formation of self-assembled capsules. Self-assembly of preorganized subunits containing a concave cavity is one effective approach and, in this respect, the use of calix[4]resorcinarene-based cavitands is ideal. This class of molecule possesses a bowl-shaped aromatic cavity with a diameter of ca. 1 nm at the upper (wider) rim and, in the case of calix[4]resorcinarene **2** (Fig. 2a), the framework is rigidified by connecting a pair of hydroxy groups on adjacent benzene rings through bridging groups at four independent sites.[6] In this review, we describe self-assembled capsules based on calix[4]resorcinarene cavitands and discuss their properties. We focus on methylene-bridge cavitands, with functional groups at the 2-position on the resorcinol ring, which form capsular self-assemblies through hydrogen bonds, metal-coordination bonds, and dynamic covalent bonds.

2. Tetrafunctionalized calix[4]resorcinarene-based cavitands

The size, shape, and other properties of the capsular inner space can be tuned by adjusting the bridging and functional groups. There are two main categories of calix[4]resorcinarene-based cavitands that are tetrafunctionalized at the upper rim. One

category contains derivatives with functionalized bridges between a pair of hydroxy groups of calix[4]resorcinarene **2** (Fig. 2a); such derivatives include aromatic ring-bridge cavitands **3** (Fig. 2b)[6a,7-11] and benzal-bridge cavitands **4** (Fig. 2c).[12-14] A representative self-assembled capsule based on the aromatic ring-bridge cavitand **3** is Rebek's dimeric cylindrical capsule **3a•3a**, which forms through 16 self-complementary hydrogen bonds connecting two imide–pyrazine-bridge cavitands **3a** (Fig. 2b).[8] Representative self-assembled capsules based on benzal-bridge cavitands of type **4** are Gibb's dimeric capsule of water-soluble, deep-cavity cavitand **4a**, which forms as a result of hydrophobic interactions in the presence of an appropriate hydrophobic guest,[13] and Dalcanale's Pd–N coordination capsule, which is formed from two tetrakis(*p*-pyridylmethine)-bridge cavitands **4b** connected through four *cis*-coordinated square-planar Pd(II) complexes[14] (Fig. 2c). Recently, Rebek and co-workers reported a hybrid type of aromatic ring-bridge and benzal-bridge cavitand **4c**.[10b,c]

The second category of calix[4]resorcinarene-based cavitands contain functional groups at the 2-position on the resorcinol ring; the rings are linked by methylene bridges between pairs of adjacent hydroxy groups (Fig. 2d). The methylene-bridge cavitand **5** has been widely used as a scaffold for covalently bound and self-assembled capsules because this framework is more rigid (preorganized) than structures of type **3** and **4** (except for **4a**), and because a variety of functional groups can be introduced at the 2-position on the resorcinol ring. Tetrabromocavitand **5a**, which was developed by Cram,[6] can be converted into tetrahydroxycavitand **5b**,[15] tetra(bromomethyl)cavitand **5c**,[1a,6c,16] tetraiodocavitand **5d**,[17] tetracarboxycavitand **5e**,[6a,18,19] tetraformylcavitand **5f**,[20] tetracyanocavitand **5g**,[21] and tetrakis(dihydroxyboryl)cavitand **5h**.[22-24] Cavitands **5b** and **5c** are versatile synthetic intermediates that can be used to generate covalently bound capsules such as carcerands and hemicarcerands,[1,25] as well as to form capsular subunits with sites for hydrogen bonding, metal coordination, or ionic interaction connected to the cavitand core by flexible alkoxy or alkylamino linkers.[26,27] Cavitand **5d** is a key synthetic intermediate for the synthesis of tetraarylcavitands of type **5i** by Suzuki–Miyaura cross-coupling reactions and tetrakis(arylethynyl)cavitands **5j** by Sonogashira cross-coupling reactions, which serve as relatively rigid, capsular subunits (vide infra). Cavitands **5a–j** are C_{4v} symmetrical structures with each containing one type of functional group, whereas Sherburn and co-workers developed a methodology for the efficient synthesis of C_{2v} symmetrical cavitands **5k**, which contain two different functional groups (distal difunctionalization).[28]

As a common feature, cavitands **3**–**5**, as capsular subunits, have a bowl-shaped aromatic cavity made up of four electron-rich dialkylaryldioxybenzene or dialkoxydialkylbenzene rings, which serve as a π-base that interacts favorably with guest molecules through CH···π (dispersion)[29] and halogen···π interactions.[12,30] Several characteristics of self-assembled capsule **5i•5i′**, based on methylene-bridge tetraarylcavitands **5i** (Fig. 2e), differ from those of cylindrical hydrogen-bonded capsule **3a•3a**,[8] based on the aromatic ring-bridge cavitand (Fig. 2b). Capsule **3a•3a** possesses four aromatic π-face walls and relatively narrow equatorial windows (portals). Thus, the encapsulated guest can interact with the aromatic π-face walls as well as with the bowl-shaped aromatic cavity ends (cavitand scaffold) through CH···π (dispersion) interactions. In contrast, capsule **5i•5i′** possesses four aromatic π-edge walls and relatively wide equatorial windows, because the aryl group is apparently oriented perpendicular to the resorcinol ring (Fig. 2e and 2f). Therefore, CH···π interactions between guest and the aromatic π-edge walls in capsule **5i•5i′** would be weaker than the CH···π interactions between guest and the aromatic π-face walls in capsule **3a•3a**. Thus, the ability of capsule **5i•5i′** to encapsulate a guest strongly depends on the interactions between the bowl-shaped aromatic cavity ends and the guest molecule. As a result, the fit between the length of the cavity in the capsule and the molecular length of the guest, as well as the type of functional groups present on the guest, are more critical for guest encapsulation in capsule **5i•5i′** than in capsule **3a•3a**. Thus, capsule **5i•5i′** would strictly discriminate between guests based on the length of the guest as well as on which functional groups are present. The merits of capsule **5i•5i′**, which is based on the methylene-bridge tetraarylcavitand **5i**, are as follows.

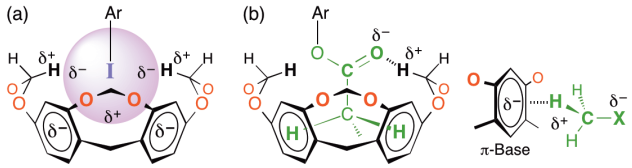

Fig. 3 Schematic representations for (a) halogen···π and CH···halogen interactions and (b) CH···π (dispersion) and CH···O=C interactions upon encapsulation in methylene-bridge cavitand capsule **5i•5i′**.

The first advantage stems from the characteristics of the methylene-bridge rim. The C–H bonds of the four methylene-bridge units (O–CH_2–O) of **5i** are polarized $\delta(+)$ and four of the eight C–H bonds are directed inward to the cavity (Fig. 2f). These inner protons of the four methylene-bridge units (O–$CH_{in}H_{out}$–O) of **5i** can interact with halogen atoms, especially iodine atoms of the guest (CH···halogen interaction),[12,31] and carbonyl oxygen atoms, in particular with acetoxy group of the guest (CH···O=C interaction),[32] as shown in Fig. 3. These interactions offer effective driving forces for the encapsulation of guests within **5i•5i′**-based capsules. It is known that I, Br, and Cl atoms bearing lone pairs of electrons are polarized $\delta(+)$ in the polar region and $\delta(-)$ in the equatorial region of the C–X bond (X = Cl < Br < I) as shown in Fig. 3a.[30b,31a,33] The second advantage of capsule **5i•5i′** is its relatively wide equatorial windows. The structural features of **5i•5i′**, including two polar bowl-shaped aromatic cavity ends and four large equatorial windows, make it possible to encapsulate the core of a guest molecule inside the capsule with the side arms of the guest protruding from the equatorial windows of the capsule.[34,35] Such a capsular design is expected to enrich the choice of suitable guest molecules available and expand the range of applications based on host–guest chemistry.

3. Self-assembled cavitand capsules based on hydrogen bonds

3-1. Homodimeric capsules via hydrogen bonds

A hydrogen bond is relatively weak (ca. 2−7 kcal mol^{-1}); however, multiple hydrogen bonds can form thermodynamically stable capsules. In pioneering work, Sherman and co-workers reported that a mixture of tetrahydroxycavitand **5b** and pyrazine as a guest self-assembles in the presence of base (DBU) into a guest encapsulated capsule pyrazine@(**5b**•**5b**)$^{4-}$ (Fig. 4).[36] Four charged hydrogen bonds between phenolic hydroxy and hydroxide groups are responsible for the attractive driving force acting on the capsular assembly.

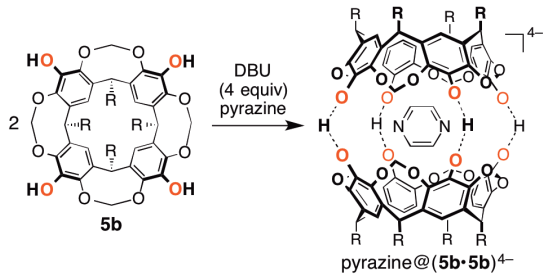

Fig. 4 Homodimeric capsule **5b**•**5b**$^{4-}$ via charged hydrogen bonds.

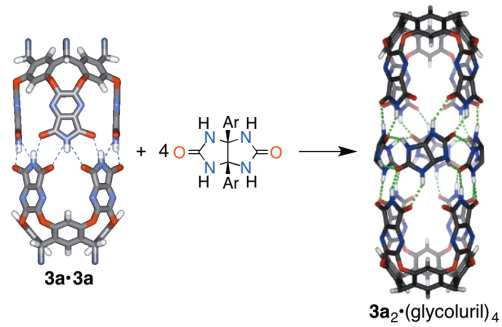

Fig. 5 Self-assembly of capsule **3a**•**3a** and glycoluril into expanded capsule **3a**$_2$•(glycoluril)$_4$.

As mentioned above, Rebek and co-workers developed a dimeric cylindrical capsule **3a**•**3a** through 16 self-complementary hydrogen bonds of imide–pyrazine-bridge vase-shaped-cavitand **3a** (Fig. 2b).[8] Various unique phenomena are associated with encapsulated guests that occupy the cylindrical cavity (ca. 425 Å^3) of the capsule **3a**•**3a**.[5d,h] For example, chemical reactions inside **3a**•**3a** show interesting characteristics, such as amplification, acceleration, and identification of labile molecules.[37] Restrictions of molecular motion in the cavity enable the detection of novel stereoisomerisms, i.e., social isomers and constellational isomers.[5d,38] Encapsulation of alkanes that are longer than the length of the cavity induces helical coiling.[5h] The cylindrical capsule can be expanded upon addition of four molecules of glycoluril to form **3a**$_2$•(glycoluril)$_4$ (Fig. 5).[5h,39] Analogous vase-shaped cavitands that contain cyclic ureas (imidazolones) or cyclic thioureas have also been reported by de Mendoza and Rebek, respectively.[9] Self-assembled dimeric capsules containing imidazolone-appended cavitands self-aggregate into linear supramolecular polymers or large reverse vesicles, depending on the side chains R at the lower rim.[9a]

Paek and co-workers reported benzoylhydrazide- and N-hydantoinylamide-substituted cavitands, which self-assemble into capsular molecules through self-complementary hydrogen bonds.[40] These capsules encapsulate anions as guests. Aakeröy and co-workers synthesized two or four 2-acetamidopyridyl-5-ethynyl substituted cavitands.[41] In the solid states, the bi-functionalized cavitand produces a polymeric assembly, whereas the tetra-functionalized cavitand yields a discrete capsular structure.

3-2. Multicomponent-assembled capsules via hydrogen bonds

The strategy for the construction of hydrogen-bonded self-assembled capsules has so far been mainly based on assembly of two identical and self-complementary subunits. In contrast, formation of a hydrogen-bonded capsule via multicomponent assemblies is rare,[5h,26c,39,42] although a hydrogen-bonded self-assembled capsule containing solvent molecules as one of the components is known,[5l,43] and coordination capsules are essentially multicomponent assemblies.[5c,f,g,j,n] Assembly of multicomponent capsules through hydrogen bonds is one of interesting topics in supramolecular chemistry, with a view to mimicking biological processes, as well as the construction of a variety of cavity libraries by increasing the tunable factors.

Our initial idea for multicomponent-assembled capsules came from the replacement of four covalent linkers in Cram's covalently bound cavitand capsule[1] by four hydrogen-bonding linkers. It is known that 2-aminopyrimidine (2-AP) is a divergent type of supramolecular synthon in the field of crystal engineering, wherein the combination of 2-AP with carboxylic acids forms a 1:2 hydrogen-bonded complex in the solid state.[44] Tetracarboxycavitand **5e** alone is scarcely soluble in $CDCl_3$ and completely insoluble in C_6D_6 because **5e** self-assembles into a 1D-type of hydrogen-bonded supramolecular polymer in the solid state, which further self-aggregates into a microporous packing structure.[19] A solubility test of **5e** indicated that addition of 2 equiv of 2-AP to **5e** is essential for the complete dissolution of **5e** in these solvents. We found that two molecules of **5e** as a hydrogen-bonding hemisphere and four molecules of 2-AP as a hydrogen-bonding linker assemble into capsule **5e**$_2$•(2-AP)$_4$ (**7**) via 16 hydrogen bonds (Fig. 6a).[45a] The six-component capsular assembly **7** was confirmed by the ^{1}H NMR titration and X-ray crystallographic analysis (Fig. 7a). Capsule **7** can encapsulate various aromatic guest molecules, such as 2,6-dimethoxynaphthalene and 2,6-dibromonaphthalene, via CH···π, halogen···π, and CH···halogen interactions.[45b] The combination of **5e** and a linker affords a tunable capsule space (Fig. 6a).[45b] Two molecules of **5e** and four molecules of tetrahydro-2-pyrimidinone (THP), as an alternative to 2-AP, also self-assemble into capsule **5e**$_2$•(THP)$_4$ (**8**). The long axis of the THP-based capsule **8** was estimated to be approximately 0.7 Å shorter than that of the 2-AP-based capsule **7**. As a result, **8**

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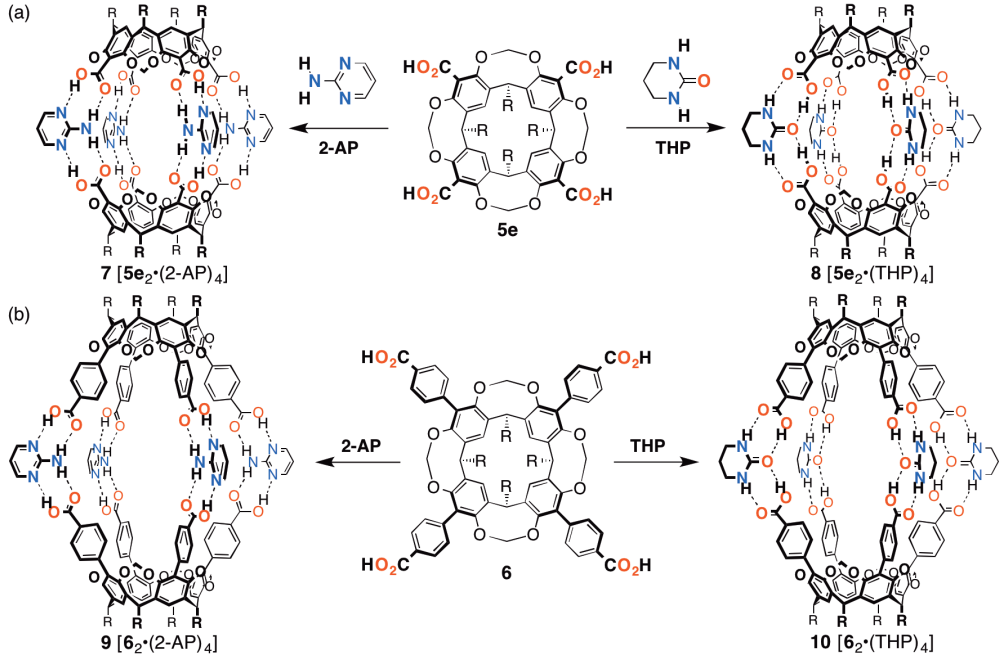

Fig. 6 (a) Self-assembly of tetracarboxycavitand **5e** and 2-AP or THP into capsules **7** and **8** and (b) self-assembly of expanded cavitand **6** and 2-AP or THP into capsules **9** and **10**.

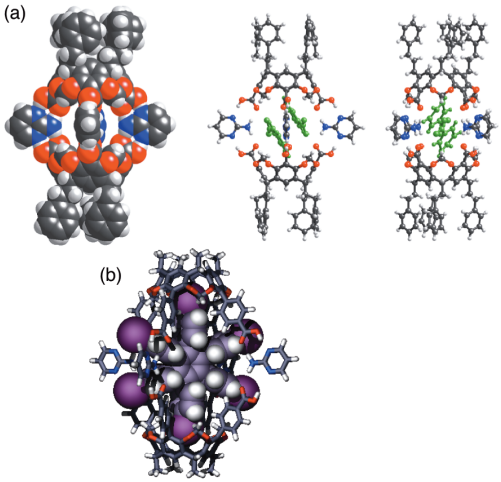

Fig. 7 (a) X-ray crystal structure of $(PhNO_2)_2$@**7** and (b) molecular model of hexakis(4-iodophenyl)benzene@**9**.

cannot encapsulate longer 2,6-dimethoxynaphthalene; however 2,6-dibromonaphthalene and other smaller guests suitable for the 2-AP-based capsule **7** are encapsulated in **8**.

The drastic expansion in cavity size is attained by the introduction of phenyl groups into **5e** (Fig. 6b).[45b] A 2:4 mixture of tetrakis(4-carboxyphenyl)-cavitand **6** and 2-AP self-assembles into an expanded capsule $\mathbf{6}_2$•$(2\text{-AP})_4$ (**9**) in the presence of appropriate guest molecules such as hexakis(4-methoxyphenyl)benzene[46] and hexakis(4-iodophenyl)benzene.[30c] It is noted that capsule **9** encapsulates the core moiety (*p*-terphenyl moiety) of these guests inside the capsule with the four aryl side arms of the guests protruding from two equatorial windows of the capsule (Fig. 7b). Expanded capsule $\mathbf{6}_2$•$(THP)_4$ (**10**), self-assembled by **6** and THP, can also encapsulate these guest molecules in the same manner (Fig. 6b). The hydrogen-bonding linkers 2-AP and THP cause different guest selectivity. In the presence of equimolar amounts of guest molecules hexakis(4-methoxyphenyl)benzene and hexakis(4-iodophenyl)benzene, the 2-AP-based **9** specifically encapsulates hexakis(4-iodophenyl)benzene. In marked contrast, under the same conditions, the THP-based **10** only encapsulates hexakis(4-methoxyphenyl)benzene.

3-3. Heterodimeric capsules via hydrogen bonds

Appropriate arrangement of hydrogen-bonding donors and acceptors in each cavitand forms a heterocapsule, which provides an unsymmetrical nanospace. Reinhoudt and co-workers synthesized carboxylmethyloxy- and pyridylmethyloxy-substituted cavitands from

tetrahydroxycavitand **5b**. A mixture of these cavitands forms a heterodimeric capsule in $CDCl_3$.[26b] Our strategy for cavitand-based heterodimeric capsules is as follows: the hydrogen-bonding donor and acceptor groups are directly connected to the cavitand core so as to minimize free rotation between the hydrogen-bonding sites and the cavitand core and to make the electronic nature of the hydrogen-bonding groups influence that of the cavitand core.

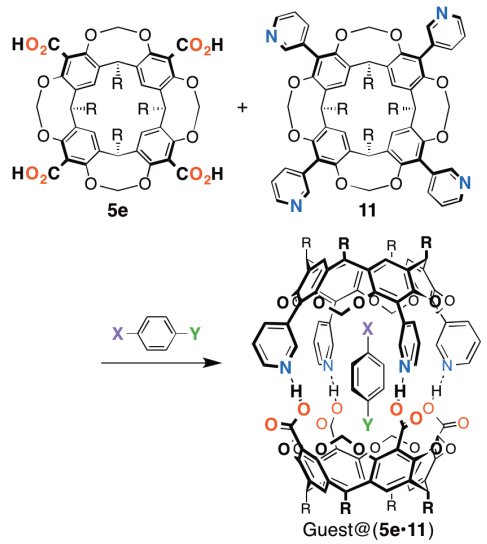

Fig. 8 Guest-induced assembly of tetracarboxycavitand **5e** and tetra(3-pyridyl)-cavitand **11** into heterodimeric capsule **5e•11** in the presence of 1,4-disubstituted-benzene guest to form guest@(**5e•11**).

We reported a guest-induced heterodimeric capsular assembly.[47] A 1:1 mixture of tetracarboxycavitand **5e** and tetra(3-pyridyl)-cavitand **11** in $CDCl_3$ is soluble, but gives a complex aggregated mixture, probably owing to random orientation of the N atom of the *m*-pyridyl group of **11**. The N atoms of four *m*-pyridyl groups have to be directed inward to the cavity of **11** for capsular assembly. However, in the presence of appropriate guests, **5e** and **11** self-assemble into a heterodimeric capsule **5e•11** even in $CDCl_3$ with guest encapsulation in a rim-to-rim fashion through four $CO_2H\cdots Py$ hydrogen bonds to form guest@(**5e•11**) (Fig. 8). In the absence of appropriate guests, the solvent effect is remarkable and the formation of **5e•11** increases in the order CD_2Cl_2, $CDCl_3$ << benzene-d_6 < toluene-d_8 < $CDCl_2CDCl_2 \leq$ *p*-xylene-d_{10} (Fig. 9). In *p*-xylene-d_{10}, **5e•11** is quantitatively formed, whereas a complex aggregated mixture is formed again in mesitylene-d_{12}. The solvent effect in the capsular assembly of **5e•11** could be explained by the concept of 55% solution rule proposed by Rebek and co-workers.[38a,48]

Heterodimeric capsule **5e•11** can encapsulate various 1,4-disubstituted-benzenes as guests. Tumbling of an encapsulated guest along the short axis of the capsule cannot occur on the NMR time scale. On account of this characteristic, encapsulations of unsymmetrical 1,4-disubstituted-benzenes inside the unsymmetrical nanospace produce a novel stereoisomerism, termed *orientational isomerism*.[49] The orientational isomeric selectivity of the unsymmetrical guests encapsulated in **5e•11** highly depends on the nature of guest substituents. For example, in 1-iodo-4-methoxybenzene@(**5e•11**), the iodo group was specifically oriented to the cavity of the **11**-unit (Fig. 10).[47a] On the other hand, in 1-ethyl-4-methoxybenzene@(**5e•11**), the methoxy group was specifically oriented to the cavity of the **11**-unit. Thus, the orientational preference of guest substituents to the cavity of the **11**-unit in **5e•11** increases in the order CH_2CH_3 < OCH_3 < I.[47b] Although the orientational isomeric selectivity of 1-chloro-4-iodobenzene@(**5e•11**) was I:Cl = 1.7:1 for the **11**-unit, the iodo and fluoro atoms of 1-chloro-3-fluoro-4-iodobenzene@(**5e•11**) were specifically oriented with respect to the cavity of the **11**-unit.[47b]

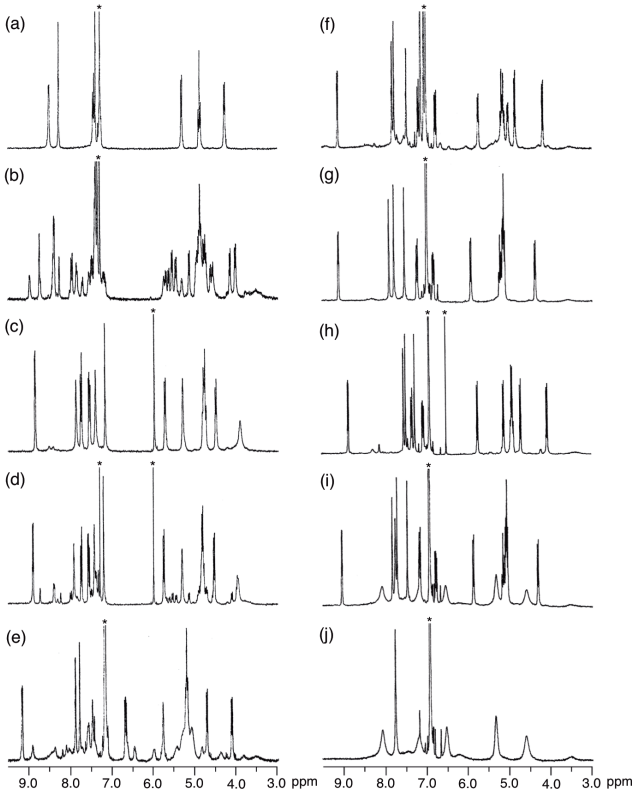

Fig. 9 ^{1}H NMR spectra: (a) **11** alone in $CDCl_3$; a 1:1 mixture of **5e** and **11** in (b) $CDCl_3$, (c) $CDCl_2CDCl_2$, (d) a 1:1 mixture of $CDCl_3$ and $CDCl_2CDCl_2$, (e) benzene-d_6, (f) toluene-d_8, (g) *p*-xylene-d_{10}, and (h) a 1:1 mixture of $CDCl_3$ and *p*-xylene-d_{10}; (i) a 1:2 mixture of **5e** and **11** in *p*-xylene-d_{10}; (j) **11** alone in *p*-xylene-d_{10}.

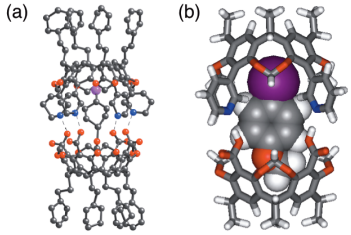

Fig. 10 (a) X-ray crystal structure and (b) molecular model of 1-iodo-4-methoxybenzene@(**5e•11**).

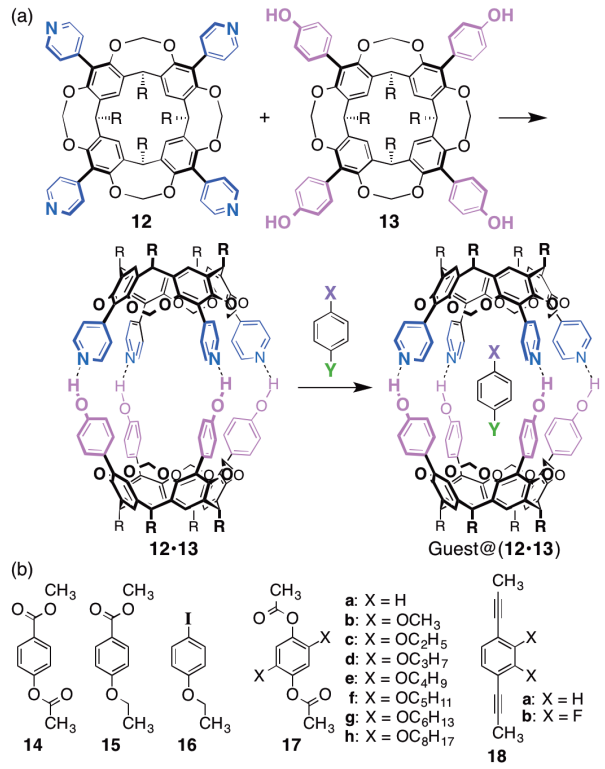

Fig. 11 (a) Self-assembly of tetra(4-pyridyl)-cavitand **12** and tetrakis(4-hydroxyphenyl)-cavitand **13** into heterodimeric capsule **12•13**, and (b) representative encapsulated guests **14**–**18**.

Tetra(4-pyridyl)-cavitand **12** and tetrakis(4-hydroxyphenyl)-cavitand **13** also self-assemble into a heterodimeric capsule **12•13** via four PhOH···Py hydrogen bonds (Fig. 11).[50] In contrast to **5e•11**, heterocapsule **12•13** is quantitatively formed even in the absence of an appropriate guest. Heterocapsule **12•13** also expresses the orientational isomerism of encapsulated unsymmetrical 1,4-disubstituted-benzene guests with high orientational isomeric selectivity because the electronic environment of the **12**-unit is different from that of the **13**-unit.[50a] The scope and limitation of guest encapsulation in **12•13**, including guest-binding selectivity and orientational isomeric selectivity, are described from the viewpoint of size complementarity as well as CH···π (dispersion), halogen···π, CH···halogen, and CH···O=C interactions between the unsymmetrical guests and the unsymmetrical cavity of **12•13**.[50b] The representative results for the orientational isomerism are shown in Figs. 12a and 12b.[50b,d] Ab initio molecular orbital calculations with the MP2 level electron-correlation correction led to the following four items.[50d] (i) The optimized structures (Fig. 12a) and charge distributions of the complexes suggest that the electrostatic interactions of oxygen atoms in guests **14**–**16** with the hydrogen atoms of aromatic rings and methylene-bridge rim in the heterocapsule **12•13** stabilize the complexes **14**–**16**@(**12•13**). The calculated relative energies of the two orientational isomers of the complexes well reproduce the experimentally observed orientational isomeric selectivity of **14**–**16**. (ii) The large electron correlation contributions to the attraction (–27.0 to –31.8 kcal mol^{-1}) show that the dispersion interactions are the major source of the attraction in **14**–**16**@(**12•13**), while the electrostatic interactions (–4.9 to –12.5 kcal mol^{-1}) are also an important source of the attraction. (iii) Although the electrostatic interactions are weaker than the dispersion interactions, the highly orientation dependent electrostatic interactions mainly determine the orientation of unsymmetrical **14**–**16** inside **12•13**. The electrostatic interactions in the major orientational isomer are 2.6–3.9 kcal mol^{-1} larger (more negative) than those in the minor orientational isomer, while the differences of other energy terms are small (less than 1.1 kcal mol^{-1}). (iv) The dipole moments of **12•13** and **14**–**16** always have antiparallel orientation in the major orientational isomers of the complexes (Fig. 13), which suggests that the electrostatic interactions mainly control the orientation of **14**–**16** encapsulated in **12•13**.

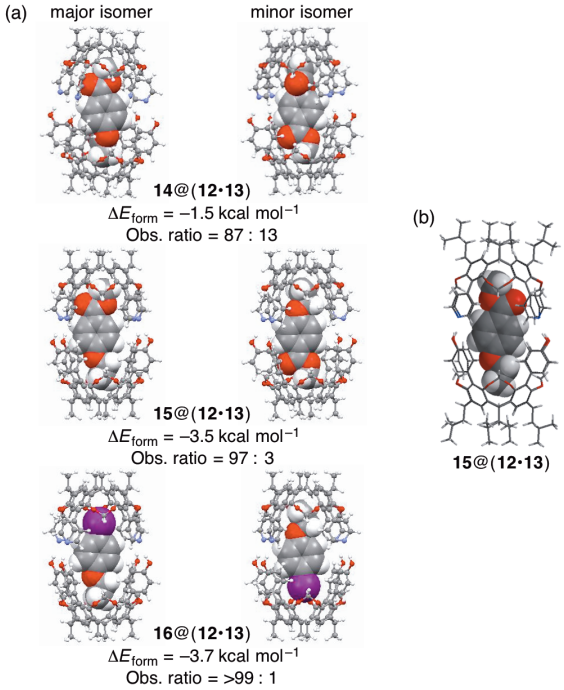

Fig. 12 (a) Geometries optimized for major and minor orientational isomers of three complexes **14**–**16**@(**12•13**). ΔE_{form} = difference of calculated stabilization energies by formation of major and minor orientational isomeric guest@(**12•13**). Obs. ratio = major and minor orientational isomeric ratios observed by ^{1}H NMR spectra. (b) X-ray crystal structure of **15**@(**12•13**).

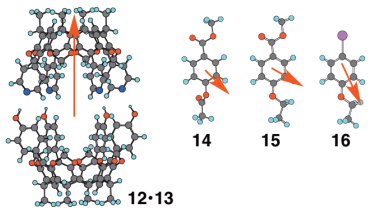

Fig. 13 Orientation of unsymmetrical guests **14**–**16** in major orientational isomers. Dipole moments of **12•13** and guests are shown by arrows.

Heterocapsule **12•13** also encapsulates 1,4-diacetoxy-2,5-dialkoxybenzenes **17a**–**h**, wherein the acetoxy groups at the

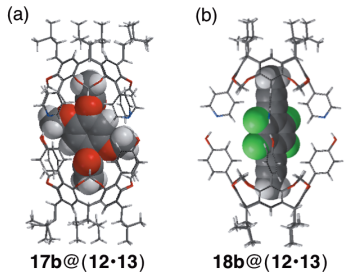

Fig. 14 X-ray crystal structures of (a) **17b**@(**12•13**) and (b) **18b**@(**12•13**). Occupancy factors of all F atoms = 0.5.

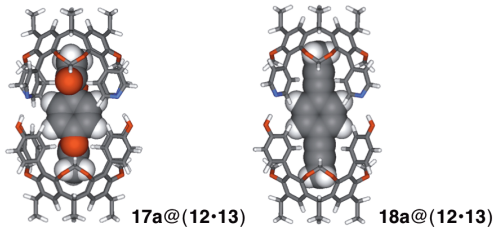

Fig. 15 Geometries optimized for **17a**@(**12•13**) and **18a**@(**12•13**) calculated at the HF/6-31G* level.

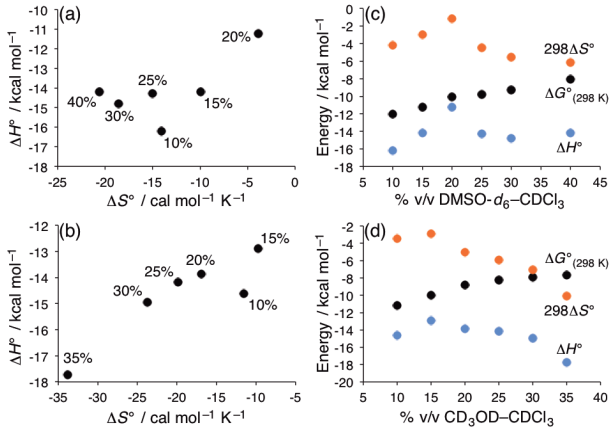

Fig. 16 Correlations between thermodynamic parameters for the formation of **18a**@(**12•13**): plots of $\Delta H°$ versus $\Delta S°$ in (a) 10–40% v/v DMSO-d_6/$CDCl_3$ and (b) 10–35% v/v $CD_3OD/CDCl_3$; plots of $\Delta H°$, $298\Delta S°$, and $\Delta G°_{(298K)}$ as a function of (c) DMSO-d_6 content and (d) CD_3OD content.

1,4-positions are oriented toward both aromatic cavity ends and the dialkoxy groups at the 2,5-positions are oriented toward equatorial windows of **12•13**. X-ray crystal structure of **17b**@(**12•13**) is shown in Fig. 14a.[50c] The encapsulated **17a**–**f** rotate along the long axis of **12•13**. Thus, the **12•13** (stator) with the encapsulation guest (rotator) behaves as a supramolecular gyroscope.[50c,51] A variable temperature (VT) ^{1}H NMR study in $CDCl_3$ showed that **17a** (X = H) within **12•13** rotates rapidly even at 218 K, whereas guest rotation is inhibited for **17g** (X = OC_6H_{13}) and **17h** (X = OC_8H_{17}) even at 323 K. For **17b** (X = OCH_3) ~ **17f** (X = OC_5H_{11}), the enthalpic ($\Delta H^‡$) and entropic ($\Delta S^‡$) contributions to the free energy of activation ($\Delta G^‡$) for the guest-rotational steric barriers within **12•13** were obtained, wherein the most sterically hindered **17f** showed the largest $\Delta H^‡$ = 29.0 kcal mol^{-1} and exceptionally large positive $\Delta S^‡$ = 38.9 cal mol^{-1} K^{-1}. The value of $\Delta G^‡$ at 298 K increased in the order **17b** (11.3 kcal mol^{-1}) < **17c** (13.2) < **17d** (14.5) < **17e** (15.3) < **17f** (17.4), as a result of enthalpy–entropy compensation. Thus, the elongation of the alkoxy chains at the 2,5-positions of **17** puts the brakes on guest rotation within **12•13**.

Heterocapsule **12•13** also encapsulates 1,4-bis(1-propynyl)benzene **18a** and its derivative **18b**.[50e] It is noteworthy that heterocapsule **12•13** can finely tune the cavity dimensions, depending on the nature of guest, with keeping average hydrogen-bonding distances between **12** and **13** almost constant. This behavior was revealed by the comparison of the X-ray crystal structures of **15**@(**12•13**) (Fig. 12b),[50b] **17b**@(**12•13**) (Fig. 14a),[50c] and **18b**@(**12•13**) (Fig. 14b).[50e] The molecular length of **18b** is 1.23 Å and 1.14 Å longer than those of **17b** and **15**, respectively. The polar dimension in **18b**@(**12•13**) is 0.21 Å and 0.12 Å longer than in **17b**@(**12•13**) and **15**@(**12•13**), respectively, while the equatorial dimension of the **12** unit or the **13** unit in **18b**@(**12•13**) is 0.20 Å and 0.18 Å or 0.19 Å and 0.16 Å shorter than those of the **12** units or the **13** units in **17b**@(**12•13**) and **15**@(**12•13**), respectively. Thus, **12•13** can adjust the cavity dimensions, depending on the guest size, shape, and/or functional group. In all cases, it is also noted that the equatorial dimension of the **12** unit is 0.21–0.23 Å shorter than that of the **13** unit.

The encapsulation of 1,4-bis(1-propynyl)benzene **18a** remarkably enhances stability of hydrogen-bonded heterocapsule **12•13** (Fig. 15).[50e] The association constant of **18a** with **12•13** is $K_a = 1.14 \times 10^9$ M^{-1} in $CDCl_3$ and $K_{app} = 1.59 \times 10^8$ M^{-2} in 10% v/v $CD_3OD/CDCl_3$ at 298 K. In 10% v/v $CD_3OD/CDCl_3$, **12** and **13** exist as monomers instead of **12•13** in the absence of appropriate guests. The **18a**–**12•13** interactions support the hydrogen bonds between **12** and **13** in polar solvents. Although the formation of **18a**@(**12•13**) is enthalpically driven ($\Delta H° < 0$ and $\Delta S° < 0$), there is a unique inflection point in the correlation between $\Delta H°$ versus $\Delta S°$ as a function of polar solvent content (Fig. 16). The ab initio calculations revealed that favorable guest–capsule dispersion and electrostatic interactions between the *acetylenic parts (triple bonds)* of **18a** and the aromatic inner space of **12•13**, as well as less structural deformation of **12•13** upon encapsulation of **18a** and the perfect match of dimensions, play important roles in the remarkable stability of **18a**@(**12•13**). The guest@(**12•13**) offers the great advantage that its thermodynamic stability is controlled by guests **14**~**18** in the range $K_a = 1 \times 10^9$~1×10^4 M^{-1} in $CDCl_3$ at 298 K.[50] This implies that the unit of guest@(**12•13**) is a promising candidate as an affinity-variable supramolecular synthon for supramolecular architectures such as supramolecular capsule polymers.

Several groups have also reported cavitand-based heterocapsules based on hydrogen bonds. Naruta and co-workers reported the formation of a hemispherical capsule by self-assembly of **5e** and *meso*-tetra(2-pyridyl)porphyrin.[52] The small cavity enables the encapsulation of gas molecules, such

as methane, ethylene, and acetylene. Adenine- and thymine-appended cavitands were synthesized by Hong and co-workers.[27g] Tetra(adenyl)-cavitand and tetra(thymidyl)-cavitand form a heterodimeric capsular structure via Hoogsteen-type of hydrogen bonds.

4. Self-assembled cavitand capsules based on metal–ligand coordination bonds

4-1. Homocavitand Assemblies via coordination bonds

Metal−ligand coordination bonds are stronger than hydrogen bonds. Introduction of an appropriate functional group as a ligand at the upper rim of the cavitand allows capsular assembly in the presence of an appropriate metal ion. In pioneering work, Dalcanale and co-workers synthesized tetracyanocavitand **5g** as a hemispherical ligand (Fig. 17).[53a] Two molecules of **5g** and four molecules of *cis*-coordinated square-planar Pd(dppp)$(OTf)_2$ self-assemble into a capsule $\{\mathbf{5g}_2\bullet[Pd(dppp)]_4\}^{8+}\bullet(TfO^-)_8$ (**19a**).[53] Encapsulation of one of eight counteranions (triflates) was found in both the ^{19}F-NMR spectrum and single-crystal X-ray diffraction analysis. Two molecules of tetrakis(4-cyanophenyl)-cavitand **20** and Pt(dppp)$(OTf)_2$ also form an expanded-capsule **21b** (Fig. 17).[54] Moreover, a mixture of tris(4-cyanophenyl)-(4-pyridylethynyl)-cavitand, Pd(dppp)$(OTf)_2$, and Pt(dppp)$(OTf)_2$ in a 2:3:1 ratio gives a thermodynamically stable heteronuclear capsule.[17b]

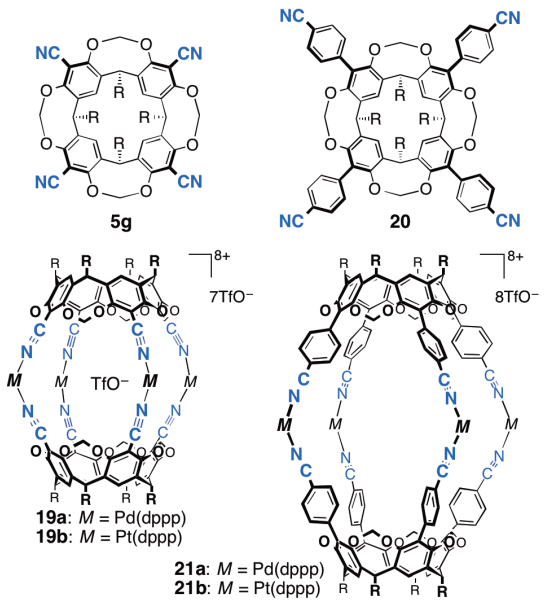

Fig. 17 Tetracyanocavitand **5e**, the metal-coordinated capsule **19**, tetrakis(4-cyanophenyl)-cavitand **20**, and the metal-coordinated capsule **21**. dppp = 1,3-bis(diphenylphosphino)propane; TfO^- = trifluoromethanesulfonate.

As mentioned above, Dalcanale and co-workers also designed and synthesized tetrakis(*p*-pyridylmethine)-bridge cavitand **4b** (Fig. 2c).[14] A mixture of **4b** and Pd(dppp)$(OTf)_2$ in a 2:4 ratio self-assembles into a capsule $\{\mathbf{4b}_2\bullet[Pd(dppp)]_4\}^{8+}\bullet(TfO^-)_8$,[14] in which one molecule of eight triflates as counteranions and two molecules of acetone as a crystallization solvent are accommodated in the cavity.[55] This capsule has enough space to encapsulate a fullerene derivative with K_a = 150 M^{-1} in CD_2Cl_2 at 298 K.[55] Tetrakis(*p*-pyridylphenylmethine)-bridge cavitand as an expanded-version of **4b** also self-assembles into capsular structures in the presence of two equiv of Pd(dppp)$(OTf)_2$ or Pt(dppp)$(OTf)_2$.[56a] In contrast to **5g**-based capsule and **4b**-based capsule, for this expanded capsule, the eight triflates are placed outside the cavity, near the metal centers. Modifications of alkyl groups at the lower rim of the expanded cavitand make it possible to detect a single capsule molecule on Au(111) or Si(100) surfaces.[56b,c]

Haino and co-workers reported the self-assembly of a tetrakis(4-(2,2′-bipyridyl)phenyl)-cavitand **22** and $AgBF_4$ in a 2:4 ratio to form a capsule **23** (Fig. 18).[57] The silver cation coordinates to two bipyridyl groups in a tetrahedral fashion. The capsule **23** encapsulates a variety of aromatic and non-aromatic guest molecules. It is noted that, depending on the molecular length, selective coencapsulation of carboxylic acids was achieved.

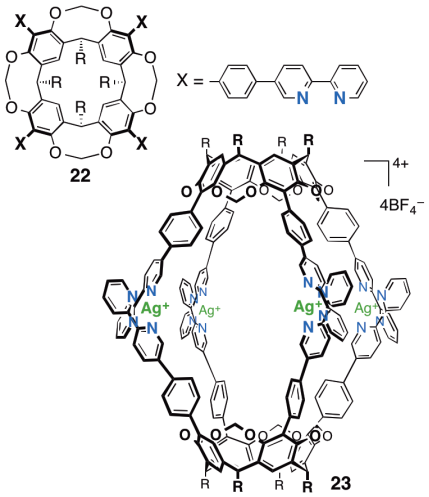

Fig. 18 Octadentate-cavitand **22** and the self-assembled capsule **23**.

Harrison and co-workers synthesized four iminodiacetate groups appended cavitand.[27a,c] Octa-anionic capsule molecules were constructed through self-assembly of the cavitand and cobalt(II) or iron(II) ions in water. The cobalt capsule can encapsulate a variety of guest molecules, such as hydrocarbons, halo-alkanes, aromatic compounds, alcohols, and ketones. Beer and co-workers reported the self-assemblies of dithiocarbamate-functionalized cavitand with late transition metals (Ni, Pd, Cu, Au, Zn, and Cd).[27b,f] Mixtures of the cavitand and nickel(II), palladium(II), copper(II), copper(III), or gold(III) ions form octanuclear capsular complexes. Hexanuclear molecular loop structures are obtained from mixtures of the cavitand with zinc(II) or cadmium(II) ions. These architectures have enough cavities to encapsulate fullerenes (C_{60} and C_{70}). Hong and co-worker reported the self-assembly of a tetrakis(pyridylmethyloxy)-cavitand and Pd(dppp)$(OTf)_2$ or Pt(dppp)$(OTf)_2$ in a 2:4 ratio.[58] This capsule

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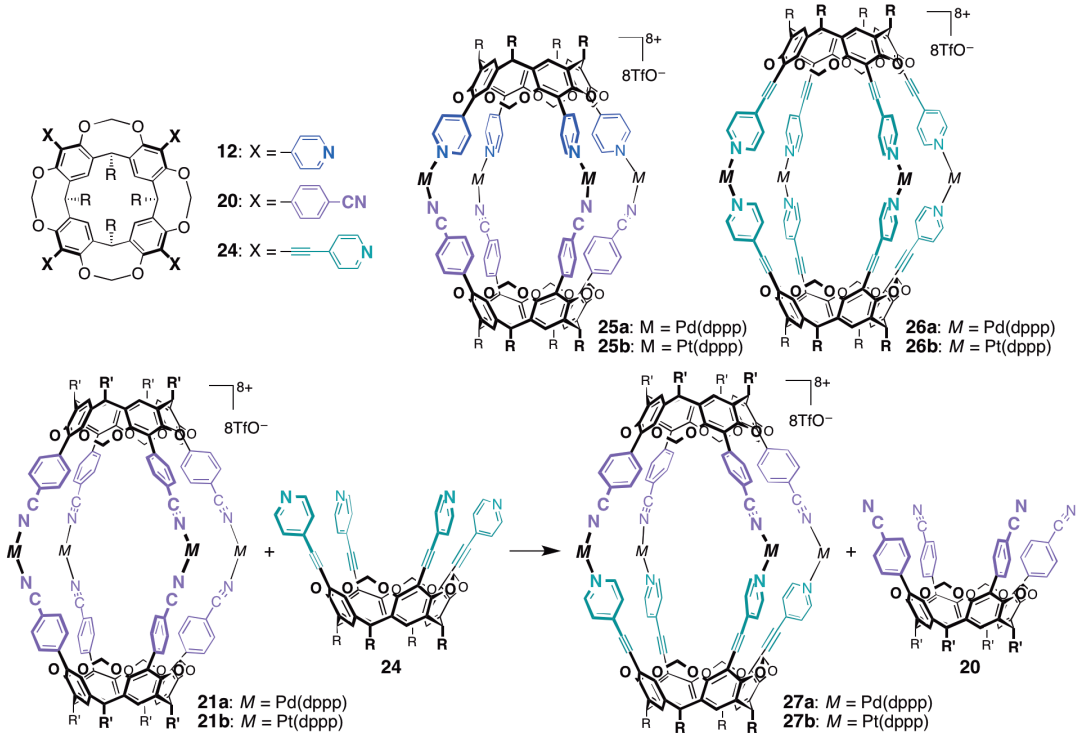

Fig. 19 Cavitand ligands **12**, **20**, and **24**, hetero-cavitand capsule **25**, homo-cavitand capsule **26**, and kinetic controlled formation of hetero-cavitand capsule **27**.

encapsulates a positively charged guest, such as methylviologen. A dynamic equilibrium between the capsule and intraclipped bowl structures was observed, specifically in nitromethane. A cavitand-based hexameric capsular structure via metal-coordination was reported by Mattay and co-workers.[59] A tetrakis(4-(terpyridyl)phenyl)-cavitand and a zinc(II) complex in a 6:12 ratio self-assemble into a huge capsule molecule with the diameter of the spherical cavity of ca. 3.0 nm.

4-2. Heterocavitand Assemblies via coordination bonds

In heteroassembly through metal-coordination, it is difficult to control the simultaneous coordination of two or more kinds of ligands with different coordination ability as donors on a metal as an acceptor. Therefore, hetero-cavitand capsules are rarely reported. We reported the formation of hetero-cavitand capsules through metal-coordination based on thermodynamic and kinetic control.[60] Three kinds of cavitand ligands, tetra(4-pyridyl)-cavitand **12**, tetrakis(4-cyanophenyl)-cavitand **20**, and tetrakis(4-pyridylethynyl)-cavitand **24** were synthesized by the Suzuki−Miyaura or Sonogashira cross-coupling reactions (Fig. 19). A 2:4 mixture of **12** and Pd(dppp)$(OTf)_2$ does not converge to a capsular assembly and affords various species of aggregates.[60a] On the other hand, a 2:4 mixture of **20** and Pd(dppp)$(OTf)_2$ forms a homo-cavitand capsule $\{\mathbf{20a}_2\bullet[Pd(dppp)]_4\}^{8+}\bullet(TfO^-)_8$ (**21a**).[54] Hetero-cavitand capsule $\{\mathbf{12}\bullet\mathbf{20a}\bullet[Pd(dppp)]_4\}^{8+}\bullet(TfO^-)_8$ (**25a**) is formed exclusively from a 1:1:4 mixture of **12**, **20**, and Pd(dppp)$(OTf)_2$, as shown in Fig. 19.[60a] The structure of **25a** was confirmed by ^1H and ^{31}P NMR spectroscopies and CSI-MS. This specific self-assembly arises from a combination of factors, such as the coordination ability and steric demand of the cavitand ligands. The pyridyl group of **12** is more sterically hindered than the cyanophenyl group of **20** toward the dppp group on the Pd complex, whereas the inherent coordination ability of the pyridyl group is greater than that of the cyanophenyl group. The rotation of pyridyl and cyanophenyl groups on the cavitand scaffold is highly restricted because the ligand moiety is placed between the two oxygen atoms on the cavitand scaffold. Thus, simultaneous *cis*-coordination of the pyridyl group of two molecules of **12** to Pd(dppp) gives complicated aggregates but does not form a homo-cavitand capsule. Upon addition of 1 equiv of **20**, aggregates are converted to the hetero-cavitand capsule **25a**. For these reasons, **25a** is specifically formed as the most thermodynamically stable species. A 1:1:4 mixture of **12**, **20**,

and Pt(dppp)$(OTf)_2$ self-assembles into a hetero-cavitand capsule **25b** after heating at 50 °C in $CDCl_3$. The pyridyl group of **24** is free from the steric hindrance that arises from the restricted rotation of the pyridine ring in **12** because the pyridyl group of **24** and the cavitand scaffold are connected by the triple bond. Consequently, 2:4 mixtures of **24** and Pd(dppp)$(OTf)_2$ or Pt(dppp)$(OTf)_2$ self-assemble into homo-cavitand capsules **26**.

A 1:1:4 mixture of **20**, **24**, and Pd(dppp)$(OTf)_2$ in $CDCl_3$ instantaneously produces two homo-cavitand capsules **21a** and **26a** in a 1:1 ratio. New signals from the hetero-cavitand capsule **27a** appear in the ^{1}H NMR spectrum after heating a solution of a 1:1 mixture of **21a** and **26a** at 50 °C. The molecular ion peaks of **27** in the CSI-MS spectrum of the mixture were independent of those of **21** and **26** when the side chain R of **20** is different from that of **24**. Hetero-cavitand capsule **27** is selectively formed by controlling the order of addition and stoichiometry of the cavitand ligands (Fig. 19).[60b] Partial ligand exchange between cavitand **24** and the most labile homo-cavitand capsules **21** proceeds based on kinetic control to form a mixture enriched in **27** prior to exchange toward **26**. Upon slow addition of 1 equiv of **24** to a solution of **21a**, the ratio of **27a**/**21a** increases to 3.0 at the initial stage. The mixture gradually reaches a thermodynamic equilibrium state in a few days at ambient temperature. The same strategy is also applicable to the formation of Pt-based hetero-cavitand capsule **27b**. Selective formation of **27b** is attained by adding 1 equiv of **24** to the solution of homo-cavitand capsule **21b**, and the ratio of **27b**/**21b** increases to 8.7 at the initial state and remains above 5.6 at room temperature even after a half year because of the kinetic stability of the Pt–pyridyl bond.

5. Self-assembled hybrid cavitand capsules based on hydrogen bonds and metal–ligand coordination bonds

A hybrid capsule constructed from several types of bonds with different strengths has advantages for controlled encapsulation because the encapsulation kinetics can be governed by association and dissociation of weaker bonds while maintaining a capsular structure through the stronger bonds. We designed and synthesized the C_{2v}-symmetrical cavitand **28** that has two 3-octylureidephenyl parts as hydrogen-bonding sites and two 4-pyridylethynyl parts as ligands for coordination bonds (Fig. 20).[61] A 1:1 mixture of **28** and Pt(dppp)$(OTf)_2$ in $CDCl_3$ affords hydrogen-bonded and metal–ligand coordinated hybrid capsule **29**. Encapsulation of triflate ions and self-penetration of alkyl chains of the ureide groups stabilize the hybrid-capsule; consequently, guest encapsulation does not occur by only adding a neutral guest molecule with a suitable size for the cavity. Encapsulation of 4,4′-diiodobiphenyl is achieved by the assistance of an externally added anion.[61a] The kinetics of guest exchange are controllable by the amounts and/or types of anions or other influences, such as the polarity of the solvent.[61b] For instance, the rate constant for guest release increases by approximately fourfold upon addition of DMSO because of

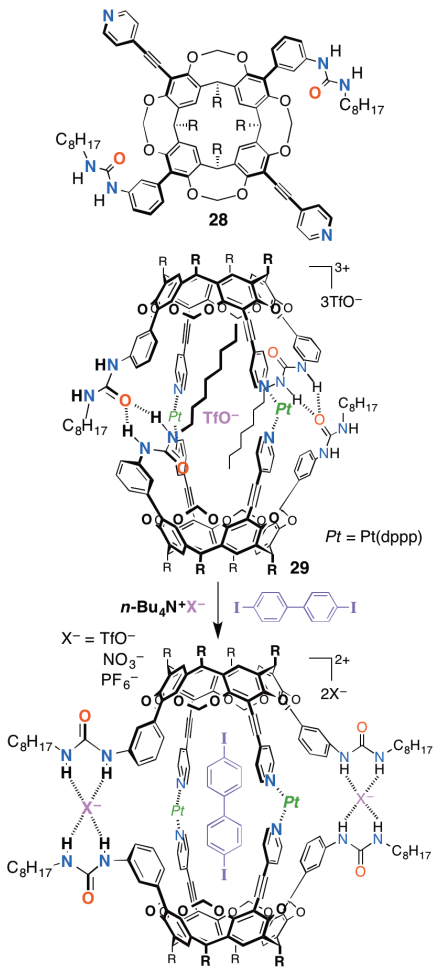

Fig. 20 C_{2v}-symmetrical cavitand **28**, hydrogen-bond and coordination hybrid cavitand capsule **29**, and the encapsulation complex assisted by anions.

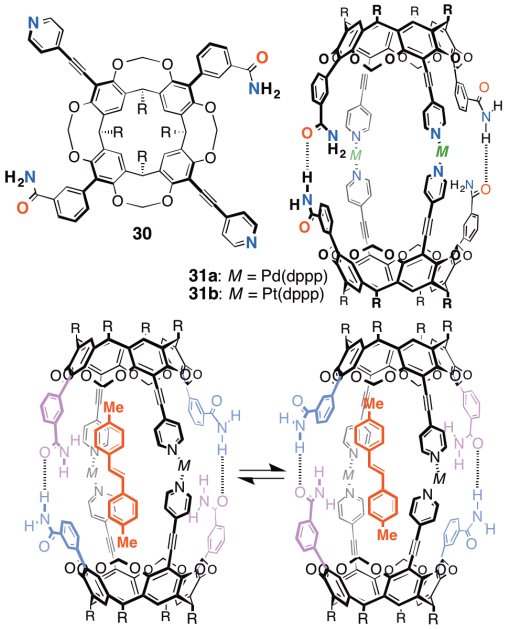

Fig. 21 C_{2v}-symmetrical cavitand **30**, hydrogen-bond and coordination hybrid cavitand capsule **31**, and C_{2h}-symmetrical guest encapsulated capsule.

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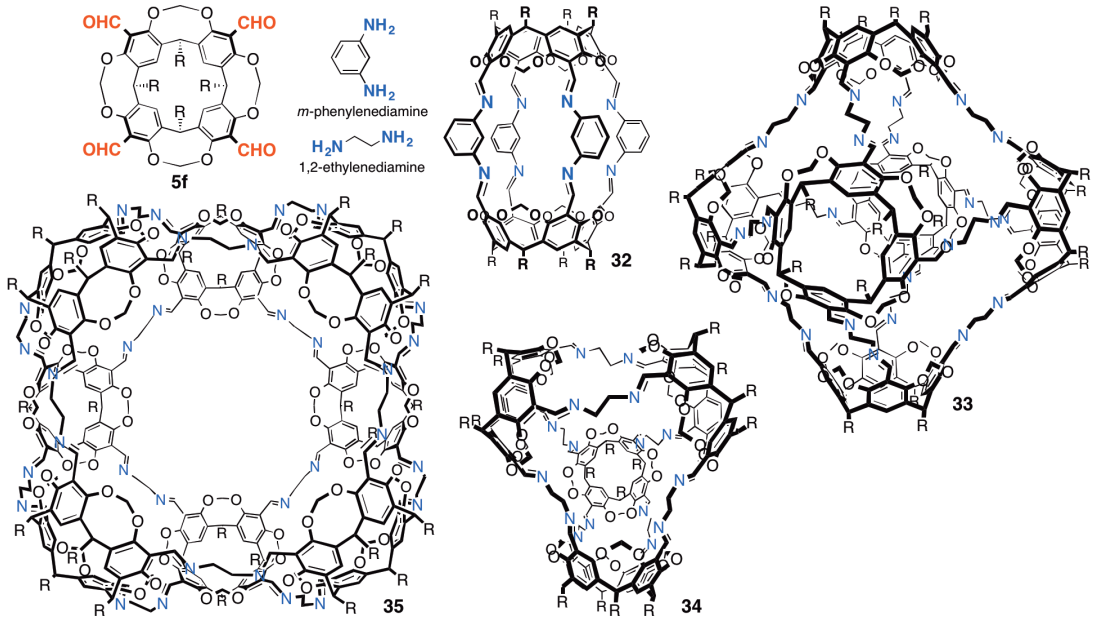

Fig. 22 Tetraformylcavitand **5f**, and hemicarcerand **32**, octahedral capsule **33**, tetrahedral capsule **34**, and square antiprism assembly **35** based on dynamic imine-bond formations between **5f** and *m*-phenylenediamine or 1,2-ethylenediamine as diamine-linkers.

weakened hydrogen bonds.

Heterofunctionalized C_{2v}-symmetrical cavitand **30** with 4-pyridylethynyl and 3-carbamoylphenyl groups in an alternating arrangement also self-assembles into hybrid capsule **31** in the presence of appropriate amounts of $Pd(dppp)(OTf)_2$ or $Pt(dppp)(OTf)_2$ through metal−ligand coordination and hydrogen bonds in $CDCl_3$ (Fig. 21).[62] The hybrid capsules **31** encapsulate guest molecules, such as *trans*-4,4′-dimethylstilbene. The ^{1}H NMR spectra of these encapsulation complexes were split into two sets of signals at low temperature. C_{2h}-symmetrical structures for the encapsulation complexes were identified because of the rotational regulation of the aromatic rings of 3-carbamoylphenyl groups. Structural alteration of hybrid capsule **31** is induced by guest encapsulation through weak van der Waals interactions.

6. Self-assembled cavitand capsules based on dynamic covalent bonds

6-1. Self-assembled cavitand capsules via dynamic imine or disulfide bonds

Dynamic covalent chemistry offers great advantages in supramolecular syntheses because dynamic covalent bonds contain reversible covalent bond-forming and bond-breaking processes under thermodynamic control; that is, they combine both the strength of covalent bonds and the reversibility of noncovalent interactions.[63] In pioneering work, the reversibility of the imine bond-forming reaction in the presence of a catalytic amount of CF_3CO_2H has been applied to cavitand-based capsule synthesis.[64] Originally, Cram and co-worker reported an octaimine-hemicarcerand **32** made by the condensation reaction of two molecules of tetraformylcavitand **5f** and four molecules of *m*-phenylenediamine in dry pyridine (Fig. 22).[20] Stoddart and co-workers found the near-quantitative formation of **32** in $CDCl_3$ in the presence of a catalytic amount of CF_3CO_2H and investigated the dynamics of **32** through imine exchange and guest release in the presence of CF_3CO_2H.[64]

Warmuth and co-workers developed cavitand-based capsular assemblies based on dynamic imine-bond formations between cavitand **5f** and various diamine-linkers in the presence of a catalytic amount of CF_3CO_2H (Fig. 22).[5k,65] The condensation reaction of **5f** and 1,2-ethylenediamine in $CHCl_3$ in the presence of a catalytic amount of CF_3CO_2H gives octahedral capsule molecule **33**, which is composed of six molecules of **5f** and 12 molecules of the diamine-linker through 24 newly formed imine bonds, in up to 82% yield.[65a] The capsule has a cavity volume of ca. 1700 Å^3. Dramatic solvent effects are found in the condensation reaction.[65b] A tetrahedral capsule **34** is formed by the reaction of four molecules of **5f** and eight molecules of 1,2-ethylenediamine in THF. In contrast, the

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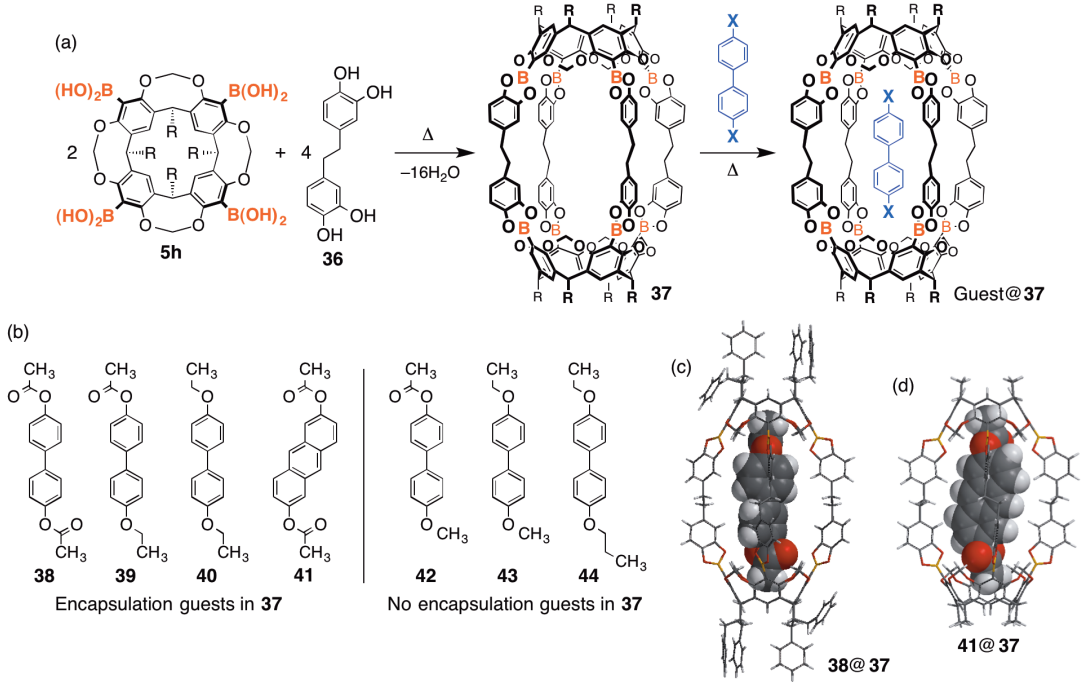

Fig. 23 (a) Formation of self-assembled boronic ester cavitand capsule **37** from cavitand tetraboronic acid **5h** and bis(catechol)-linker **36**, and guest encapsulation, (b) representative encapsulation guests **38**–**41** and no encapsulation guests **42**–**44**, (c) X-ray crystal structure of **38**@**37**, and (d) molecular model of **41**@**37**.

reaction between eight molecules of **5f** and 16 molecules of 1,2-ethylenediamine yields the square antiprism assembly **35** in CH_2Cl_2. A rhombicuboctahedral capsule composed of six molecules of **5f** and eight molecules of 1,3,5-tris(*p*-aminophenyl)benzene is formed in good yield.[65c] The capsule has a solvodynamic diameter of 3.9 nm and a cavity volume of ca. 4700 Å^3. The expanded tetraformylcavitand with phenyl spacers is effective for forming large capsules through dynamic imine bonds with di- or triamine-linkers.[65d] The largest cavity volume of the rhombicuboctahedral capsule reaches ca. 13000 Å^3. Recently, Rebek and co-workers reported a cylindrical type of dynamic imine-bonded capsules self-assembled by two molecules of a deep-cavity tetraacetal-cavitand and four molecules of *p*-aromatic diamine-linkers, such as 1,4-diaminobenzene and 4,4′-diaminobiphenyl, in the presence of a catalytic amount of CF_3CO_2H.[66]

Warmuth and co-workers also reported acylhydrazone bonds as useful dynamic covalent bonds for constructing cavitand-based capsular assemblies.[67] Various types of capsules are formed by condensations of **5f** and isophthalic dihydrazide, terephthalic dihydrazide, or trigonal planar trihydrazides in the presence of CF_3CO_2H.

Disulfide bonds are also widely used as dynamic covalent bonds for the construction of supramolecular architectures.[63,68] Sherman and co-workers reported that the use of a redox buffer allows a disulfide-linked cavitand capsule to form under reversible conditions.[69] The redox buffer facilitates guest exchange via disulfide bond rupture and reformation.

6-2. Self-assembled cavitand capsules via dynamic boronic ester bonds

Boronic ester bonds are also another reliable synthon for dynamic covalent chemistry to construct supramolecular architectures.[70,71] The merit of boronic ester bond is no requirement for the addition of external chemicals, such as acid or base, to promote the bond formation. The H_2O molecule that is produced by the condensation of arylboronic acid with catechol leads to the reversibility of boronic ester bond under thermodynamic control.

We demonstrated that two molecules of cavitand tetraboronic acid **5h** and four molecules of 1,2-bis(3,4-dihyroxyphenyl)ethane **36** as a bis(catechol)-linker quantitatively self-assemble into a capsule **37** through the formation of eight boronic ester bonds in $CHCl_3$ or C_6H_6 after heating at 50 °C for 3 h (Fig. 23a).[72] Capsule **37** is isolated and

purified just by evaporation of solvents and then reprecipitation from benzene–hexane. Unlike static covalently bound cavitand capsules,[1] self-assembled cavitand capsule **37**, based on the dynamic boronic ester bond, has two advantages. The first advantage is the achievement of quantitative guest encapsulation upon the addition of an equimolar amount of a guest if the guest size fits the capsule size and the guest interacts well with the capsule interior, because of a thermodynamically controlled encapsulation process (capsule partial opening, encapsulation of guest by attractive interactions, and capsule closing) that proceeds through the dynamic formation of boronic ester bonds.[72b] The second advantage is the on/off control of the capsule formation with guest encapsulation by the removal/addition of MeOH (Fig. 24).[72a] Addition of 5% CD_3OD (1000 equiv) to a solution of guest-encapsulating capsule **38@37** in C_6D_6 causes immediate dissociation of the boronic ester bonds of capsule **37** to release guest **38** and to produce cavitand **5h**–(methanol)$_n$ adducts and bis(catechol)-linker **36**. This mixture is completely restored to the original **38@37** by vacuum drying at room temperature and then heating in C_6D_6 at 50 °C for 3 h.

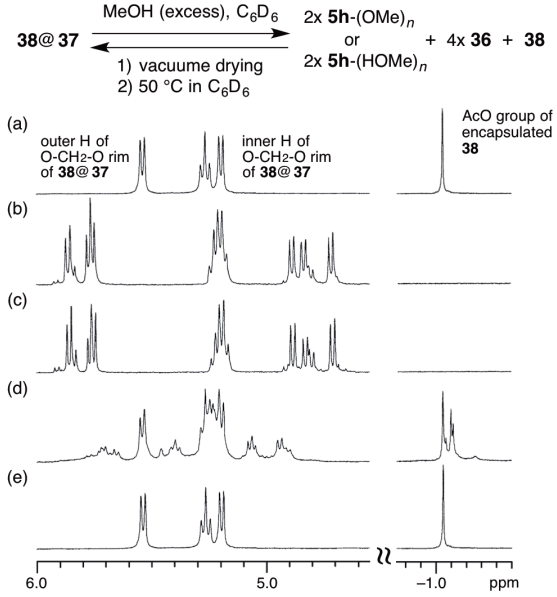

Fig. 24 On/off control of capsule formation with guest encapsulation by removal and addition of MeOH. ^{1}H NMR spectra: (a) **38@37** in C_6D_6, (b) after 3 min of **38@37** in 5% v/v CD_3OD–C_6D_6 (1000 equiv of CD_3OD), (c) **5h** in 5% v/v CD_3OD–C_6D_6, (d) vacuum-dried sample-b in C_6D_6 (heterogeneous), and (e) after heating sample-d in C_6D_6 at 50 °C for 3 h.

Capsule **37** encapsulates one guest molecule such as 4,4′-disubstituted-biphenyl or 2,6-disubstituted-anthracene derivatives in a highly selective recognition event. A catalytic amount of water that is inevitably present in $CDCl_3$ and C_6D_6 leads to the reversibility of boronic ester bond, capsule partial opening, and guest encapsulation in **37**. The association constants (K_a) of **37** with guests to form guest@**37** in C_6D_6 are much greater than those in $CDCl_3$ (450−48000-fold).[72b] The encapsulation of guests within **37** in C_6D_6 is enthalpically driven, whereas the encapsulation of guests within **37** in $CDCl_3$ tends to be both enthalpically and entropically driven. Thermodynamic studies suggest that the small K_a value with a considerable entropic contribution to guest@**37** in $CDCl_3$ arises from the character of $CDCl_3$ as a competitive guest for **37**. Kinetic studies of guest@**37** by 2D-EXSY measurements indicate partial dissociation of bis(catechol)-linkers as the mechanism for guest uptake and release. The 2D-EXSY studies also suggest that guest uptake in **37** follows second-order kinetics, and guest release out of **37** follows first-order kinetics. All guests encapsulated in **37** are oriented with the guest long axis aligned along the long axis of capsule **37**. Capsule **37** strictly discriminates between functional groups of a guest (Fig. 23b). In a series of 4,4′-disubstituted-biphenyl derivatives with a similar molecular length, the value of K_a of guest@**37** in C_6D_6 at 313 K increases in the order **40** (4,4′-OCH_2CH_3, $K_a = 1.30 \times 10^4$ M^{-1}) < **39** (4-OC(=O)CH_3-4′-OCH_2CH_3, $K_a = 1.24 \times 10^5$ M^{-1}) < **38** (4,4′-OC(=O)CH_3, $K_a = 1.26 \times 10^6$ M^{-1}). This selectivity arises from a combination of CH···π and CH···O=C interactions, which were found in the X-ray crystal structure of **38@37** (Fig. 23c).[72b] Capsule **37** also strictly discriminates a one-carbon atom difference in guest size. In contrast to **39** and **40** encapsulated in **37**, guests **42** and **43**–**44** were not encapsulated, respectively.

Unique optical properties of 2,6-diacetoxyanthracene **41** encapsulated in capsule **37** in C_6H_6 ($K_a = 1.83 \times 10^6$ M^{-1}) were discovered (Fig. 23d).[72c] Upon excitation at 285 nm, the encapsulated **41** shows strong fluorescence emission as a result of the energy transfer from the excited **37** to the encapsulated **41**, while **41** alone in C_6H_6 exhibits very weak emission. Upon photoirradiation at 365 nm, the encapsulated **41** also shows strong fluorescence emission and remains almost intact, whereas **41** alone in C_6H_6 gradually undergoes photodimerization and photooxidation. Thus, capsule **37** serves as a photosensitizer for the encapsulated **41** as well as a guard nanocontainer to protect against the photochemical reactions of **41**. Complex **41@37** possesses four equatorial windows, through which singlet oxygen, as the source of a 9,10-endoperoxide of **41**, can come into contact with the encapsulated **41**. However, **41** tightly encapsulated in **37** will not reach a transition state to the 9,10-endoperoxide with a bent molecular shape, because of the sp^3 carbon atoms at the 9,10-positions. Therefore, encapsulation by capsule **37** protects against the photooxidation of guest **41**.

9,10-Bis(phenylethynyl)anthracene (BPEA) and its derivatives are highly fluorescent dyes that possess superior luminescence properties and have applications in organic light-emitting diodes (OLEDs) and two-photon absorption (TPA) materials. However, it is known that photoirradiation gradually leads to the photodegradation (photobleaching) of BPEA and its derivatives, which is disadvantageous for the purpose of uses related to photonic applications. The encapsulation strategy is considered to be effective in solving this problem,[73] but it cannot be adapted in a straightforward manner to these types of molecules, owing to the cruciform shape of BPEA. We demonstrated that the self-assembled boronic ester cavitand capsule **37** quantitatively and tightly encapsulates BPEA

derivatives **45a–c** as highly fluorescent cruciform guests (Fig. 25).[72d] The structural features of **37**, which possesses two polar bowl-shaped aromatic cavity ends and four large equatorial windows connected by dynamic boronic ester bonds, made it possible to encapsulate cruciform **45** with protection of the reactive anthracene core inside **37** and with the two arylethynyl groups as π-conjugated arms protruding through the two equatorial windows of **37**. The encapsulation of guests **45** inside capsule **37** greatly influenced their photostability and photophysical properties. Thus, **45a–b@37** and **45c@(37)**$_2$ are more resistant towards photochemical reactions in solution (2~7 times) and fluorescence quenching in the powder state (3~6 times) than free **45**. This encapsulation also restricted free rotation of the arylethynyl groups of **45**, thereby leading to an enforced coplanar conformation between the arylethynyl groups and the anthracene core of **45**, which gave rise to a red-shift of absorption maxima (ca. 25 nm), as well as to enhancement of the peak TPA cross-sections of **45a–b@37** and **45c@(37)**$_2$ (ca. 2 times) compared with free **4**. Thus, capsule **37** serves as a guard nanocontainer for cruciform BPEA derivatives **45**, and **45a–b@37** and **45c@(37)**$_2$ serve as photostable luminescent and TPA materials. The formation of **45c@(37)**$_2$ also implies that capsule **37** is useful for the protection of a BPEA-polymer derivative.

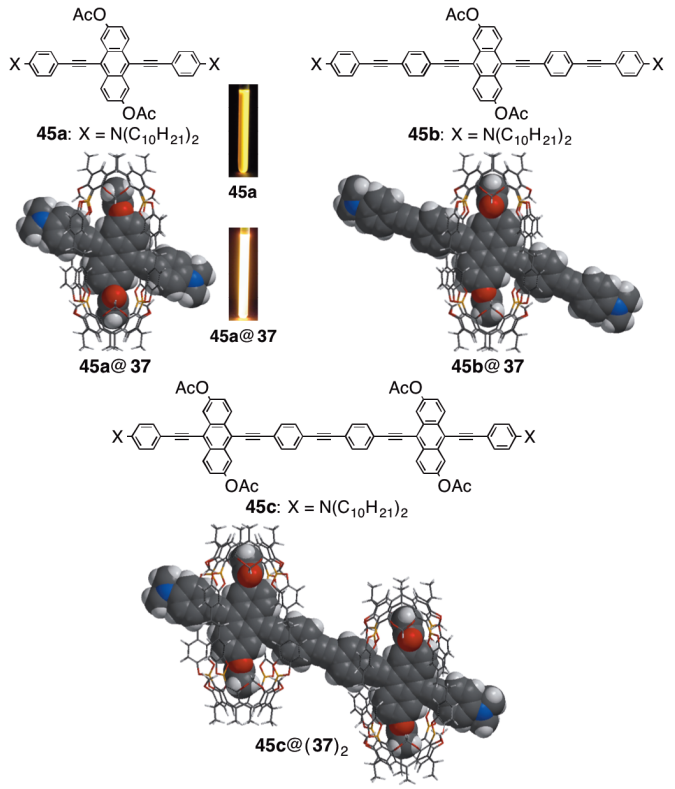

Fig. 25 BPEA derivatives **45a–c** and molecular models of **45a@37**, **45b@37**, and **45c@(37)**$_2$; photographs of solutions of **45a@37** and free **45a** upon excitation at 365 nm after room-light irradiation for 200 h in air.

Conclusion and outlook

We have reviewed self-assembled capsules based on tetrafunctionalized calix[4]resorcinarene cavitands, especially, methylene-bridge cavitands with functional groups at the 2-position on the resorcinol ring. The hemispherical structures of these cavitands are suitable for forming capsular assemblies through various interactions such as hydrogen bonds, metal–coordination bonds, as well as through dynamic covalent bonds under thermodynamic control. In addition to CH···π (dispersion) interaction arising from the size complementarity between guest and the cavity of capsule, CH···halogen interaction and CH···O=C interaction between the inner protons of the four methylene-bridge units (O–CH_{in}H$_{out}$–O) at the upper rim of the cavitand and the functional group of guest offer effective driving forces for the encapsulation of guests within the methylene-bridge-based cavitand capsules. Guest molecules encapsulated in these self-assembled isolated nanospaces have unique chemical and physical properties that are difficult to emerge in the bulk phase. It is expected that further research including a new molecular design in the field of self-assembled capsules will reveal additional interesting phenomena in physical organic chemistry and materials science as well as in host–guest chemistry, and that practical applications of self-assembled capsules and encapsulation complexes will appear in the near future, such as supramolecular capsule polymers, photoswitchable capsules directed to drug delivery, and capsular devices.

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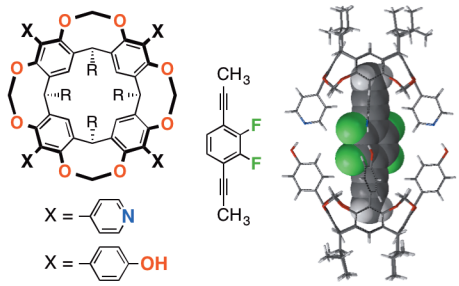

The hemispherical structures of calix[4]resorcinarene cavitands are suitable for forming capsular assemblies with guest encapsulations through various intermolecular interactions.