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Oxatub[4]arene: a smart macrocyclic receptor with multiple interconvertible cavities

A naphthalene-based flexible macrocycle, namely oxatub[4]arene, has been presented. This "smart" macrocycle can adopt four deep-cavity conformations through the flipping of one or two naphthalene units. These conformers vary in size and shape, and show different binding affinity toward the same guest. Thus, one specific guest selects the best-fit conformer(s) to achieve the optimal binding. This unique macrocyclic host may further enrich the toolbox of supramolecular chemistry.

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Oxatub[4]arene: a smart macrocyclic receptor with multiple interconvertible cavities†

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There are a large number of synthetic macrocyclic receptors in the literature. No particular one is suitable for all guests or purposes. For a broader guest binding scope or multiple purposes, a macrocycle with multiple interconvertible cavities will be advantageous. Here, we report a naphthalene-based macrocyclic receptor with an adaptable cavity, namely oxatub[4]arene. It has four representative conformations resulting from the flipping of naphthalene rings, each with a deep and well-defined cavity. Different guests select one host conformer or a combination of conformers. All the four conformers have been detected and characterized based on 2D NMR spectra and X-ray single crystal structures. Thermodynamically, these conformers constitute a reservoir, that responds to the structural changes of guests, and thus maximizes the association free energies. This smart macrocycle may provide a new platform for the construction of molecular machines and devices or stimuli-responsive materials.

Introduction

Macrocyclic receptors[1] are the major workhorses in supramolecular chemistry. These compounds not only contribute to the basic understanding on molecular recognition,[2] but also find applications in molecular machines and devices,[3] supramolecular polymers,[4] stimuli-responsive materials,[5] and drug-delivery systems.[6] During the last decade, a number of new macrocyclic receptors with novel properties have been reported, including heterocalix[n]aromatics,[7] pillar[n]arene,[8] bambus[n]uril,[9] "Texas-sized" box,[10] cyanostar,[11] molecular triangles,[12] ExBox and ExCage,[13] calix[n]imidazole,[14] biphen[n]arene,[15] coron[n]arene,[16] and others.[17] These macrocycles show very different guest binding properties, and have certainly enriched the toolbox of supramolecular chemists.

For a given guest or purpose, one of these macrocycles will be the best. Minor structural change of guests or a different kind of guests may significantly affect the corresponding binding affinity. No one macrocycle is suitable for all guests or purposes.

Can we design a macrocyclic receptor at least for a broader guest binding scope or multiple purposes? One possibility is to connect several macrocycles covalently together. Thus, the resulting receptor will have all the abilities of these macrocycles. However, its synthesis is too tedious, and when binding a specific guest, only one of these macrocycles in the receptor is used and others are idle. A more ideal receptor should possess several interconvertible cavities and can choose an appropriate one for a given guest to obtain an optimal binding. Recently, we employed dynamic combinatorial chemistry[18] and constructed a pair of dynamic configurational macrocycles which can interconvert.[19] The two configurations have different cavity parameters and different guests can thermodynamically select different host isomers. Research on similar but covalent receptors confirms the two isomers have very different guest preferences and binding abilities.[20] This dynamic system is already close to the "ideal" macrocycle with multiple interconvertible cavities, but it is still a complex mixture.

How can we unify several interconvertible cavities into one kinetically inert macrocycle? Conformational change may be resorted to. Calix[n]arene[21] and related compounds are well known to possess several conformations, but not all the conformers have a well-defined cavity. Even though they can interconvert, not all of them show satisfactory guest binding properties. To the best of our knowledge, this kind of smart macrocycles have not been well demonstrated. In the present research, we report a naphthalene-based macrocyclic receptor with four interconvertible and deep cavities. This macrocycle can choose an appropriate cavity for a specific guest and achieve the optimal binding.

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Results and discussion

Design and synthesis of oxatub[4]arene

Naphthalene-based macrocycles are relatively rare in the supramolecular literature.[19a,20,22,23,24,25] The large π system is expected to create a macrocycle with a deep or wide cavity; however, most of known naphthalene-based macrocycles often suffer from complicated regioisomeric products with ill-defined and shallow cavities, and rarely show satisfactory guest binding performance.

In the present research, we designed and synthesized a naphthalene-based macrocycle (Fig. 1a) and gave it a trivial name – oxatub[4]arene in view of its tube-like cavities and the O atom in the linker (in analogy to oxacalix[3]arene[26]). Oxatub[4] arene has the following features in its structure: (a) a longer linker is used instead of the often-seen methylene linker. The short linker is believed to cause steric hindrance between neighboring naphthalenes, and the macrocycles may twist, resulting in ill-defined cavities. A longer linker may solve this problem, leading to a macrocycle with a deep cavity. (b) Specifically, the linker CH_2–O–CH_2, as used in oxacalix[3] arene,[26] is employed. Thus, macrocyclization might be readily achieved through Williamson ether synthesis. In addition, the linker may not be innocent and may get involved in binding when the ether oxygen atoms are inwardly-directed. (c) The use of 2,6-dihydroxynaphthalene as the repeating unit and the linking on its 1,5-positions minimize potential isomerism, and also avoid the self-occupation of the cavity as observed in zorb [4]arene,[24c] in favour of maintaining deep cavities and good host–guest binding. (d) More importantly, the flipping of naphthalene rings leads to multiple conformers with deep cavities.

The synthesis of oxatub[4]arene is straightforward (Fig. 1a). Both the precursors 1 and 2 can be obtained in three steps from commercial materials with or without simple column chromatography. The octabutyl oxatub[4]arene (**TA4**) was synthesized with a reasonable yield (21%) in a one-pot reaction under a high-dilution condition. The hexamer oxatub[6]arene was also detected by ESI-MS, but remains elusive to isolation.

Properties of oxatub[4]arene

TA4 is a flexible macrocycle and thus possesses numerous conformations. However, the flipping of naphthalene rings as the major activation barriers separates four representative conformations or conformational sets (Fig. 1b). Analogous to calix[4]arene, we name these four conformers as zigzag (**I**), disrupted zigzag (**II**), 1,2-alternate (**III**), and 1,3-alternate (**IV**), respectively. In order to show the cavity's size and dimension, the models of these conformers are presented in the most expanded form by forcing all the methylene protons in the linkers directed outwards and the oxygen atoms inwards. In contrast to calix[4]arenes, all four conformers possess well-defined cavities which may offer good guest binding properties. Moreover, the cavity of each conformer is different. The diameter and length of conformer **I** (D_{2d}) are 6.2 and 10 Å, respectively. This is similar to conformer **II** which, however, has the

lowest symmetry (C_2). Conformer **III** (C_{2h}) has a much deeper cavity than the other conformers, while conformer **IV** (D_4) has a much wider cavity. The differences in cavity sizes and lengths are expected to result in different guest binding preferences. According to their different symmetries, ^{1}H NMR can be used to distinguish them when the exchange of guests is slow on the NMR timescale.

The ^{1}H NMR spectrum of **TA4** is surprisingly simple and clean (Fig. 2a). It seems there is only one conformer (**I** or **IV** according to their symmetries). However, the methylene protons on CH_2–O–CH_2 appear as a singlet, which should be two doublets (diastereotopic protons) for either conformer **I** or **IV**. Only one explanation can account for this: the two protons on the same methylene group may exchange their positions very quickly and this can only occur through a rapid flipping of the naphthalene rings. In order to slow down the ring flipping, variable-temperature NMR experiments (Fig. S1†) were performed. At temperatures below −60 °C, all the peaks are significantly broadened and new peaks appear. One may argue this is caused by aggregation at low temperatures. However, NMR experiments at −60 °C but different concentrations (Fig. S2†) rules out this possibility. At −80 °C, a very complex NMR spectrum was obtained, suggesting the existence of several conformers of **TA4**. Consequently, there is a conformational ensemble of **TA4** in solution. These conformers undergo quick interconversion at room temperature.

Host–guest properties and assignments of conformations

Computations indicated all the conformers are electron-rich in their cavities (Fig. S3†), suggesting organic cations would be good guests. The host–guest chemistry of **TA4** was initially tested with guest **D2D^{2+}**. The ^{1}H NMR spectrum (Fig. 2) shows that the signals of both host and guest undergo very large shifts, indicating a binding event. Control experiments (Fig. S4†) with excess guest or host support a slow exchange on the NMR timescale. Free guest or host is not detected, providing evidence for a very strong binding ($K_a > 10^4$ M^{-1}). The NMR integrals and mass spectrum (Fig. S6†) suggest a 1 : 1 binding stoichiometry. Meanwhile, the flipping of the naphthalene rings is slow, since the cavity is occupied and the guest exchange is slow. This was further supported by the splitting of proton signals a, b and c (diastereotopic protons). The aromatic protons of the hosts appear as two doublets. According to the conformers' symmetries, the host in this solution can be assigned to a single conformer: either **I** (D_{2d}) or **IV** (D_4). That is, only one conformer was selected from the conformational ensemble. The other three conformers are not detected at all, suggesting the binding constant of **D2D^{2+}** to the conformer present to be at least one order of magnitude larger than those to the other conformers.

Encouraged by the initial results, we systematically studied guests **D2D^{2+}**–**D12D^{2+}** (Fig. 3a and S5†). For guest **D3D^{2+}**, two new aromatic peaks appeared, indicating the existence of a new host conformer in addition to the conformer observed for **D2D^{2+}**. These two peaks become more prominent in the case of **D4D^{2+}**, and dominate for **D5D^{2+}**. The peaks are slightly broadened. In the case of **D6D^{2+}**, proton peaks a + b split into two
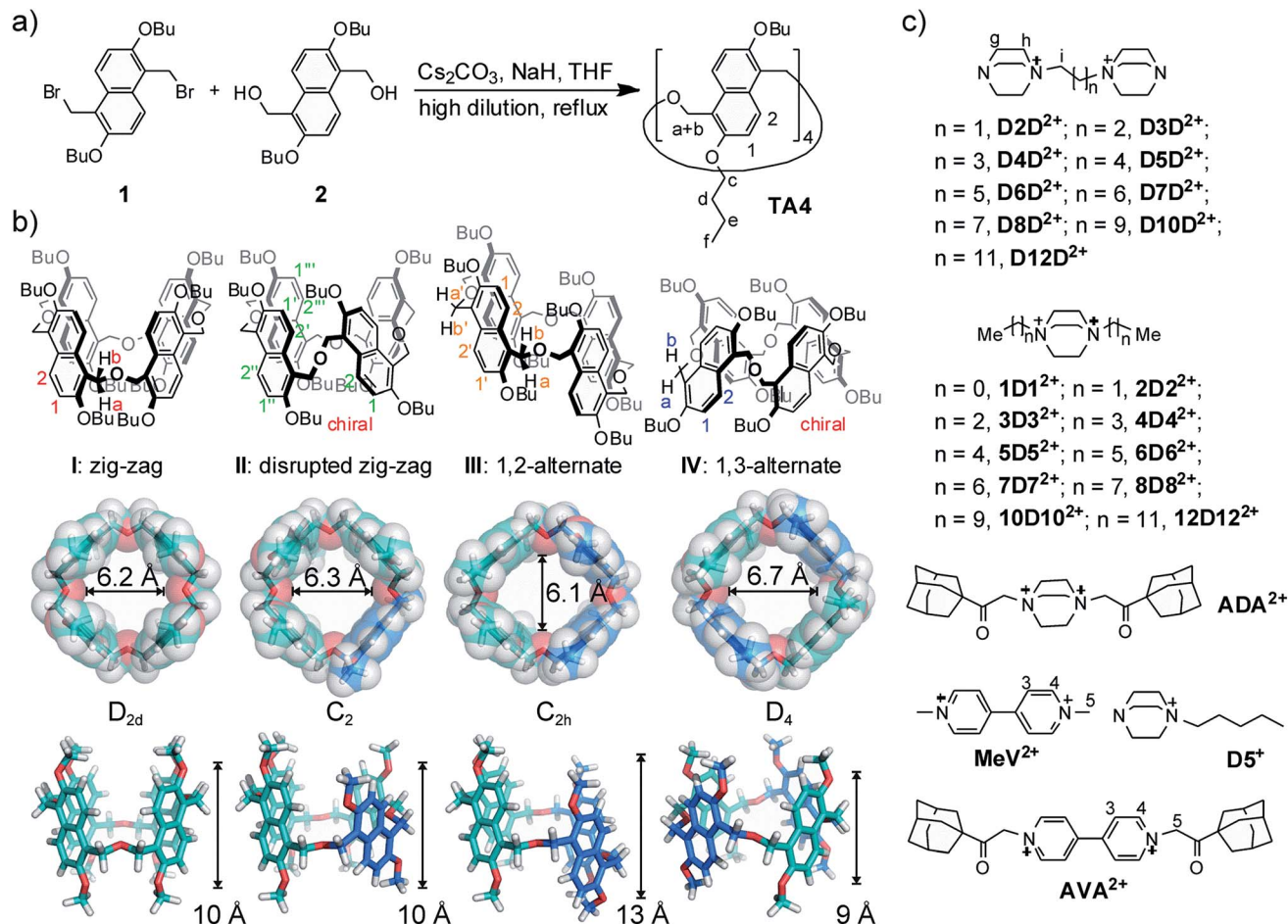
Fig. 1 (a) The synthetic procedure of octabutyl oxatub[4]arene (**TA4**); (b) chemical structures of four representative conformers of **TA4** resulting from naphthalene flipping, and the top and side views of their models. In order to show the cavity in the most expanded forms, the models were obtained by forcing all the methylene protons in the linkers directed straight outwards and the oxygen inwards. Numbering on the structures corresponds to the assignment of NMR signals. Conformers **II** and **IV** are chiral, but only one enantiomer is shown here. The lengths of the cavities are based on the distance between two oxygen atoms on the same naphthalene ring. The flipped naphthalene rings in conformations **II**, **III**, and **IV** relative to conformation **I** are colored in blue. Butyl groups in the models were abbreviated to methyl groups for viewing clarity; (c) chemical structures of all the guests involved in this research; the counterions are PF_6^-.

signals, suggesting the ring flipping and guest exchange is still slow at the NMR timescale. This conclusion is supported by use of the similar but monotopic guest **D5$^+$**. Accordingly, the new conformer can be assigned to either conformer **I** or **IV**. That is, both conformers **I** and **IV** coexist in the cases of **D3D^{2+}** and **D4D^{2+}**.

In contrast, **TA4** shows similar binding behaviors to guest series **1D1^{2+}**–**12D12^{2+}** (Fig. 3b and S22†). For **1D1^{2+}**, all the peaks of **TA4** appear to be broadened. A slow exchange is supported by the split of proton signals a + b of the NMR spectrum at room temperature and −20 °C (Fig. S33†). Aromatic protons appear as two peaks, again suggesting the existence of either conformer **I** or **IV**. With **2D2^{2+}**, the **TA4** appears as two sets of signals and one set is sharper than the other. For the guests with longer alkyl groups, the sharper signals become predominant. The peak patterns again suggest the existence of conformer **I** and/or **IV**. We compared the NMR spectra of these two guest series (Fig. S34†), and found that all the sharp peaks appear at almost the same chemical shifts and all the broadened peaks do too.

These results strongly support conformers **I** and **IV** are mainly involved in the binding of these two guest series.

In order to distinguish between conformers **I** and **IV**, we resorted to 2D NMR spectroscopy. As shown in Fig. 4, the models of conformers **I** and **IV** require that: in conformer **I**, proton 2 is in close proximity to proton b but farther away from proton a; while in conformer **IV**, proton 2 is close to both protons a and b in space. Thus, ROESY NMR experiments were performed on **D2D^{2+}@TA4** and **1D1^{2+}@TA4** since both of them have separate signals for protons a and b. A Nuclear Overhauser Effect (NOE) was detected between protons 2 and b for **D2D^{2+}@TA4**, but not between protons 2 and a, suggesting **TA4** exists as conformer **I**. The ROESY NMR spectra of **6D6^{2+}@TA4** and **ADA^{2+}@TA4** (Fig. S41†) were similar to that of **D2D^{2+}@TA4**. While for **1D1^{2+}@TA4**, proton 2 had a NOE effect with both protons a and b, indicating the predominance of conformer **IV**. These assignments are in line with the ROESY NMR spectrum of **D5$^+$@TA4** in which both conformers **I** and **IV** are observed. It is also supported by the peak line-shapes in the NMR spectra: the NMR
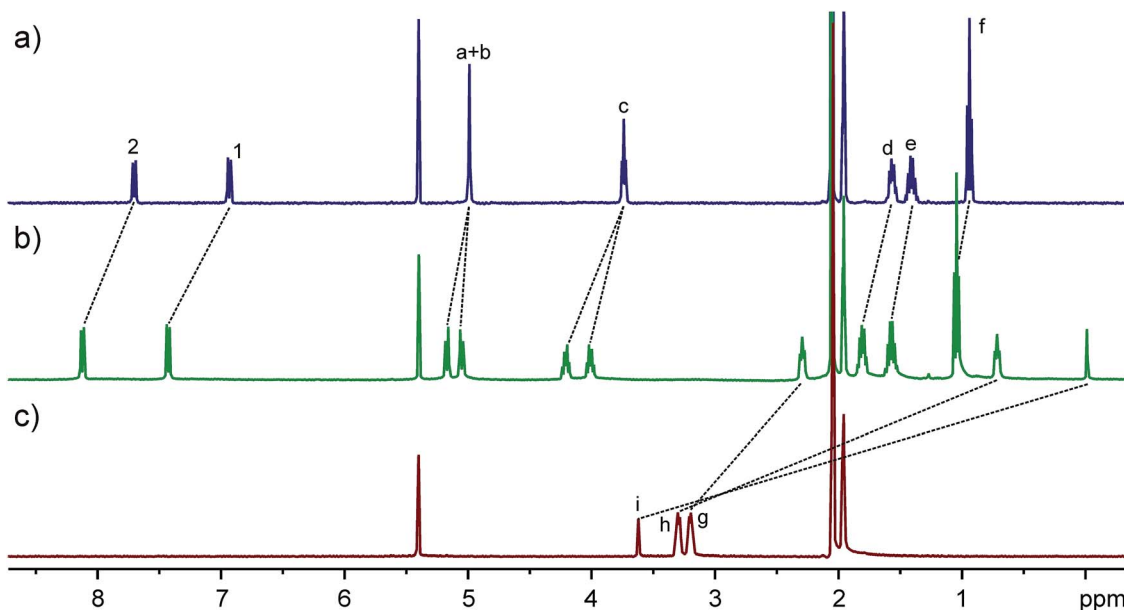
Fig. 2 Full ^{1}H NMR spectra (400 MHz, CD$_2$Cl$_2$: CD$_3$CN = 1 : 1, 2.0 mM, 25 °C) of (a) **TA4**, (c) **D2D^{2+}**, and (b) their equimolar mixture. See Fig. 1 for signal assignments.

peaks of conformer **IV** are all broadened while the peaks of conformer **I** remain sharp, since conformer **IV** has a larger cavity with faster guest exchange kinetics. From guest **D2D^{2+}** to **D5D^{2+}**, conformer **I** was gradually converted to conformer **IV**. With even longer linkers, this trend was reversed (Fig. S5 and S16†). From **1D1^{2+}** to **3D3^{2+}**, conformer **IV** was gradually replaced by conformer **I** and another conformer. This is the conformational response of the host to the structural changes of guests.

For guests **4D4^{2+}–12D12^{2+}** (Fig. S22†), besides the major peaks assigned to conformer **I**, there are many small peaks which have similar intensity and should belong to a single conformer of **TA4**. This conformation can be assigned to conformer **II**, since conformer **II** has the lowest symmetry (C_2) and should show eight doublets for its aromatic protons. This is more clearly seen in the case of **ADA^{2+}** (Fig. 3b and S35†). For all
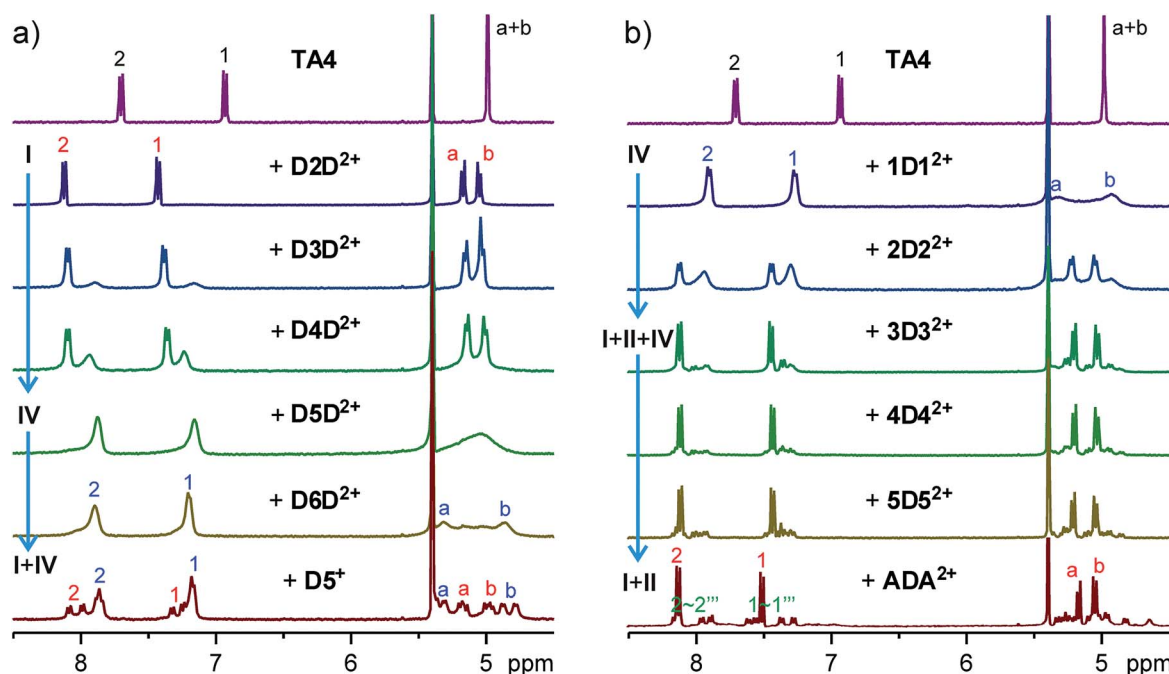

Fig. 3 Partial ^{1}H NMR spectra (400 MHz, CD$_2$Cl$_2$: CD$_3$CN = 1 : 1, 2.0 mM, 25 °C) of **TA4** in the presence of one equivalent (a) guest series **D2D^{2+}–D6D^{2+}** and **D5$^+$** or (b) guest series **1D1^{2+}–5D5^{2+}** and **ADA^{2+}**.

Fig. 4 Energy-minimized structures and partial ^{1}H, ^{1}H-ROESY NMR spectra (500 MHz, CD$_2$Cl$_2$: CD$_3$CN = 1 : 1, 6.0 mM, 25 °C) of (a) D2D^{2+}@TA4-I, (b) 1D1^{2+}@TA4-IV and (c) D5$^+$@TA4. The protons a, b, a′, b′, 2′ and 2 in the models are rendered to show possible NOE contacts; single crystal structures of (d) MeV^{2+}@TA4-III and (e) 1D1^{2+}@TA4-IV. Butyl groups are removed for viewing clarity.

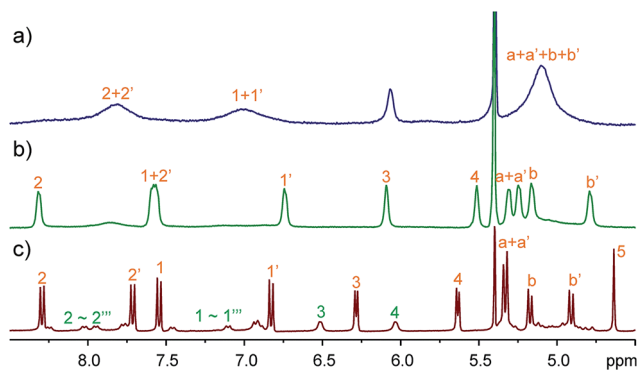**Fig. 5** Partial ^{1}H NMR spectra (CD$_2$Cl$_2$: CD$_3$CN = 1 : 1, 2.0 mM) of an equimolar mixture of TA4 and MeV^{2+} at (a) 25 °C (400 MHz) or (b) −20 °C (600 MHz) and (c) TA4 and AVA^{2+} (400 MHz, 25 °C).

Fig. 6 UV-vis absorption spectra (1.0 mM, 25 °C) of TA4, MeV^{2+}-2PF$_6$, AVA^{2+}-2PF$_6$, MeV^{2+}-2PF$_6$@TA4 and AVA^{2+}-2PF$_6$@TA4. Inset: photos of the above solutions.

these guests, conformer **II** accounts for 45–55% of **TA4** in the solutions.

Compared to the 1,4-diazabicyclo[2.2.2]octane (DABCO) guests, viologen **MeV^{2+}** is longer and thinner, and is reasonably expected to select a different host conformation. However, the guest is too thin and undergoes fast exchange at the NMR timescale. This results in broadened NMR signals (Fig. 5a) and thwarts assignment of the host conformation. Two measures
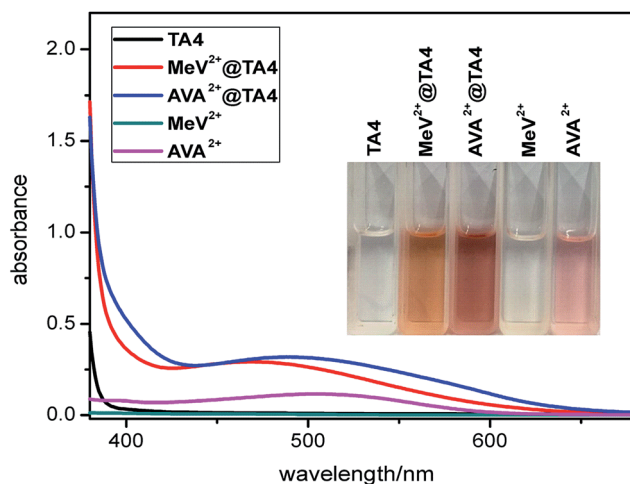
were taken to circumvent this problem: (a) decreasing the temperature; (b) attaching sizable (but not too large) end groups. Both ways worked efficiently to slow down the exchange. At −20 °C, all the peaks become significantly sharpened (Fig. 5b). The peak pattern suggests conformer **III** (C_{2h}
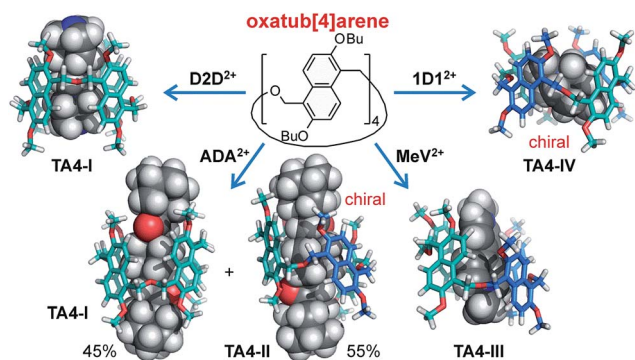
Fig. 7 Summary of guest-selected predominance of one of the four conformers of **TA4**. Butyl groups in the models were abbreviated to methyl groups for viewing clarity.

Table 1 Association constants K_a to **TA4** in 1,2-dichloroethane–MeCN (1 : 1) at 25 °C as determined by ITC

Guests	K_a (10^5 M^{-1})	ΔG (kJ mol^{-1})	ΔH (kJ mol^{-1})	$-T\Delta S$ (kJ mol^{-1})
1D1^{2+}	0.18 ± 0.03	−24.3 ± 0.7	3.10	−27.3
2D2^{2+}	1.44 ± 0.26	−29.4 ± 0.8	−7.30	−22.1
3D3^{2+}	4.57 ± 0.52	−32.3 ± 0.6	−13.0	−19.3
4D4^{2+}	4.30 ± 0.77	−32.2 ± 0.8	−11.9	−20.2
D2D^{2+}	2.34 ± 0.63	−30.7 ± 0.9	−15.4	−15.2
D3D^{2+}	1.56 ± 0.32	−29.6 ± 0.8	−8.7	−21.0
D4D^{2+}	1.09 ± 0.19	−28.8 ± 0.8	−13.1	−15.6
D5D^{2+}	0.75 ± 0.16	−27.8 ± 0.9	−8.43	−19.4
MeV^{2+}	1.31 ± 0.19	−29.2 ± 0.7	−14.0	−15.2
AVA^{2+}	1.82 ± 0.30	−30.0 ± 0.7	−15.3	−14.8

symmetry) to be the selected conformation. For guest **AVA^{2+}** with bulky end groups (Fig. 5c), the conformer **III** is also the major structure but conformer **II** can be identified to account for 30% of **TA4**. Conformer **III** has a long and narrower cavity and fits perfectly to such thin guests. ROESY NMR of **AVA^{2+}@TA4** (Fig. S41†) supports this assignment and the assignments of **I** and **IV** as well: conformer **III** has both NOEs involved in conformers **I** and **IV**, and the NOEs are exactly the same as those observed in these two conformers.

Single-crystal structures

Single crystals of **MeV^{2+}@TA4** and **1D1^{2+}@TA4** were obtained by slow vapor diffusion of diethyl ether into the solutions in the 1 : 1 mixture of MeCN and CH$_2$Cl$_2$. The structures of **TA4** (Fig. 4d and e and S54–S62†) were clearly shown to be in conformations **III** and **IV** for **MeV^{2+}@TA4** and **1D1^{2+}@TA4**, respectively. This further consolidates the above assignments. For conformer **IV**, both enantiomers appear in pairs in the solid state (Fig. S61†). The binding mode is almost the same as those revealed by molecular modelling: **1D1^{2+}** is nested and tipped in the cavity; **MeV^{2+}** is threaded through and forms a [2]pseudo-rotaxane. In both structures, the oxygen atoms of CH$_2$–O–CH$_2$ are inwardly directed and multiple C–H⋯O hydrogen bonds[27] are detected, supporting a non-innocent role for these linkers.

In addition, C–H⋯π[28] and cation⋯π interactions[29] are also observed. Charge-transfer interactions were detected for **MeV^{2+}@TA4** by UV-vis spectroscopy (Fig. 6 and S63†).

Thermodynamic parameters

For all the guests shown above, one conformer or a combination of two or three conformers of **TA4** is selected, and some examples are shown in Fig. 7. That is, different conformers have different binding affinities towards the same guest. The host also shows conformational responses to the structural change of guests. What are the thermodynamic consequences for such conformational responses? In order to answer this question, the association constants with selected guests were determined using isothermal titration calorimetry (ITC, see ESI†). A 1 : 1 binding stoichiometry for all these guests was obtained by ITC and ESI-MS. The data in Table 1 show that almost all the association constants are of the same order of magnitude, that is, 10^5 M^{-1}, except for **1D1^{2+}** and **D5D^{2+}**. From **D2D^{2+}** to **D5D^{2+}**, the host conformation gradually changes from **I** to **IV**, and the association free energy only decreased by *ca.* 3 kJ mol^{-1}. In view of the conformational equilibrium, the association free energy surely would undergo a larger decrease were the conformation fixed. From **1D1^{2+}** to **4D4^{2+}**, the association free energy increased by 8 kJ mol^{-1}, accompanied by a gradual conformational change from **IV** to a mixture of **I** and **II**. If the conformation is fixed, the increase should be smaller. In the case of **MeV^{2+}** and **AVA^{2+}**, **MeV^{2+}** induces mainly conformer **III**; while **AVA^{2+}** selects 30% conformer **II** and 70% conformer **III**. However, their association free energies are not very different. Consequently, the conformational reservoir of the host shows conformational responses to different guests and thus maximizes the association free energy. Although the association free energies were changed only slightly, the binding entropies and enthalpies show much more drastic changes. In addition, the entropic contribution is large for all the guests, presumably due to the release of the solvent molecules in the host and the solvated guest during binding.

Conclusions

In summary, we report a new smart macrocyclic receptor, namely oxatub[4]arene. This macrocycle has four representative conformations, resulting from the flipping of naphthalene panels. Each conformer possesses a deep, well-defined cavity but their cavity sizes are different. Different guests select a single host conformer or a combination of conformers. All four conformers have been observed when different guests are applied, and characterized by 2D NMR and X-ray single crystallography. In the crystal structures, the oxygen atoms of CH$_2$–O–CH$_2$ are directed into the cavities and multiple C–H⋯O hydrogen bonds are detected, supporting a non-spectator role for the linkers. In addition, C–H⋯π, cation⋯π, and charge-transfer interactions are observed. Thermodynamically, the differences in association constants for different conformers to the same guest are greater than one order of magnitude. The host shows conformational responses to the structural changes

of guests, which maximizes the association free energy compared to that expected for those macrocycles with a single cavity.

More generally, there are several consequences for the macrocycles with multiple interconvertible cavities: (a) the combination of several cavities into one macrocycle certainly expands its guest binding scope and improves the tolerance of structural change of guests. But low guest selectivity can also be expected; (b) at least three of the four conformations can be selected to predominate by appropriate guests for oxatub[4] arene. The alkyl groups on oxatub[4]arene are oriented in different patterns for different conformers. Thus, the guest-controlled transition among these conformations causes the allosteric change[30] of the alkyl groups on the host. When replacing the alkyl groups with functional groups, this may be applied to the construction of molecular machines and devices and stimuli-responsive supramolecular materials; (c) the present macrocycle is not just another flexible macrocycle whose conformation can be tuned during binding through an induced-fit mechanism.[31] Once the cavities are occupied by guests, these conformers cannot interconvert, since the flipping of naphthalene has to occur through the cavity which has little free space; (d) in the context of systems chemistry,[32] the multiple conformations constitute a complex network, providing the possibility for complex functions. In summary, we believe this unique macrocyclic receptor further enriches the toolbox of supramolecular chemistry and may find wide applications in the near future.

Acknowledgements

Notes and references

1 (a) *Macrocyclic Chemistry: Current Trends and Future Perspectives*, ed. K. Gloe, Springer, Dordrecht, 2005; (b) F. Davis and S. Higson, *Macrocycles: Construction, Chemistry and Nanotechnology Applications*, Wiley, Chichester, 2011.

2 (a) J.-M. Lehn, *Supramolecular Chemistry: Concepts and Perspectives*, Wiley-VCH, Weinheim, 1995; (b) J. W. Steed and J. L. Atwood, *Supramolecular Chemistry*, Wiley, Chichester, 2nd edn, 2009.

3 (a) V. Balzani, A. Credi, F. M. Raymo and J. F. Stoddart, *Angew. Chem., Int. Ed.*, 2000, **39**, 3348–3391; (b) E. R. Kay, D. A. Leigh and F. Zerbetto, *Angew. Chem., Int. Ed.*, 2007, **46**, 72–191; (c) E. R. Kay and D. A. Leigh, *Angew. Chem., Int. Ed.*, 2015, **54**, 10080–10088.

4 (a) B. Zheng, F. Wang, S. Dong and F. Huang, *Chem. Soc. Rev.*, 2012, **41**, 1621–1636; (b) D.-S. Guo and Y. Liu, *Chem. Soc. Rev.*, 2012, **41**, 5907–5921; (c) X. Ma and H. Tian, *Acc. Chem. Res.*, 2014, **47**, 1971–1981.

5 (a) Z. Qi and C. A. Schalley, *Acc. Chem. Res.*, 2014, **47**, 2222–2233; (b) S. Dong, B. Zheng, F. Wang and F. Huang, *Acc. Chem. Res.*, 2014, **47**, 1982–1994.

6 X. Ma and Y.-L. Zhao, *Chem. Rev.*, 2015, **115**, 7794–7839.

7 (a) M.-X. Wang, *Chem. Commun.*, 2008, 4541–4551; (b) M.-X. Wang, *Acc. Chem. Res.*, 2012, **45**, 182–195.

8 (a) T. Ogoshi, S. Kanai, S. Fujinami, T.-A. Yamagishi and Y. Nakamoto, *J. Am. Chem. Soc.*, 2008, **130**, 5022–5023; (b) For reviews: M. Xue, Y. Yang, X.-D. Chi, Z.-B. Zhang and F. Huang, *Acc. Chem. Res.*, 2012, **45**, 1294–1308; (c) D.-R. Cao and H. Meier, *Asian J. Org. Chem.*, 2014, **3**, 244–262; (d) P. J. Cragg and K. Sharma, *Chem. Soc. Rev.*, 2012, **41**, 597–607; (e) T. Ogoshi and T. A. Yamagishi, *Eur. J. Org. Chem.*, 2013, 2961–2975; (f) H. Zhang and Y.-L. Zhao, *Chem.–Eur. J.*, 2013, **19**, 16862–16879; (g) N. L. Strutt, H. Zhang, S. T. Schneebeli and J. F. Stoddart, *Acc. Chem. Res.*, 2014, **47**, 2631–2642; (h) C. Li, *Chem. Commun.*, 2014, **50**, 12420–12433; (i) M.-C. Xia and Y.-W. Yang, *Progr. Chem.*, 2015, **27**, 655–665; (j) Z. Zhang, Y. Luo, J. Chen, S. Dong, Y. Yu, Z. Ma and F. Huang, *Angew. Chem., Int. Ed.*, 2011, **50**, 1397–1401.

9 (a) J. Svec, M. Necas and V. Sindelar, *Angew. Chem., Int. Ed.*, 2010, **49**, 2378–2381; (b) M. A. Yawer, V. Havel and V. Sindelar, *Angew. Chem., Int. Ed.*, 2015, **54**, 276–279.

10 (a) H.-Y. Gong, B. M. Rambo, E. Karnas, V. M. Lynch and J. L. Sessler, *Nat. Chem.*, 2010, **2**, 406–409; (b) B. M. Rambo, H.-Y. Gong, M. Oh and J. L. Sessler, *Acc. Chem. Res.*, 2012, **45**, 1390–1401.

11 (a) S. Lee, C.-H. Chen and A. H. Flood, *Nat. Chem.*, 2013, **5**, 704–710; (b) A. Singharoy, B. Venkatakrishnan, Y. Liu, C. G. Mayne, S. Lee, C.-H. Chen, A. Zlotnick, K. Schulten and A. H. Flood, *J. Am. Chem. Soc.*, 2015, **137**, 8810–8818.

12 (a) S. T. Schneebeli, M. Frasconi, Z. Liu, Y. Wu, D. M. Gardner, N. L. Strutt, C. Cheng, R. Carmieli, M. R. Wasielewski and J. F. Stoddart, *Angew. Chem., Int. Ed.*, 2013, **52**, 13100–13104; (b) Z. Liu, G. Liu, Y. Wu, D. Cao, J. Sun, S. T. Schneebeli, M. S. Nassar, C. A. Mirkin and J. F. Stoddart, *J. Am. Chem. Soc.*, 2014, **136**, 16651–16660.

13 (a) J. C. Barnes, M. Juríček, N. L. Strutt, M. Frasconi, S. Sampath, M. A. Giesener, P. L. McGrier, C. J. Bruns, C. L. Stern, A. A. Sarjeant and J. F. Stoddart, *J. Am. Chem. Soc.*, 2013, **135**, 183–192; (b) M. Juríček, J. C. Barnes, E. J. Dale, W.-G. Liu, N. L. Strutt, C. J. Bruns, N. A. Vermeulen, K. Ghooray, A. A. Sarjeant, C. L. Stern, Y. Y. Botros, W. A. Goddard III and J. F. Stoddart, *J. Am. Chem. Soc.*, 2013, **135**, 12736–12746; (c) E. J. Dale, N. A. Vermeulen, A. A. Thomas, J. C. Barnes, M. Juríček, A. K. Blackburn, N. L. Strutt, A. A. Sarjeant, C. L. Stern, S. E. Denmark and J. F. Stoddart, *J. Am. Chem. Soc.*, 2014, **136**, 10669–10682.

14 Y. Chun, N. J. Singh, I. C. Hwang, J. W. Lee, S. U. Yu and K. S. Kim, *Nat. Commun.*, 2013, **4**, 1797.

15 (a) H. Chen, J. Fan, X. Hu, J. Ma, S. Wang, J. Li, Y. Yu, X. Jia and C. Li, *Chem. Sci.*, 2015, **6**, 197–202; (b) J. Zhou, G. Yu, L. Shao, B. Hua and F. Huang, *Chem. Commun.*, 2015, **51**, 4188–4191; (c) J. Ma, H. Deng, S. Ma, J. Li, X. Jia and C. Li, *Chem. Commun.*, 2015, **51**, 6621–6624.

16 (a) Q.-H. Guo, Z.-D. Fu, L. Zhao and M.-X. Wang, *Angew. Chem., Int. Ed.*, 2014, **53**, 13548–13552; (b) Q.-H. Guo, L. Zhao and M.-X. Wang, *Angew. Chem., Int. Ed.*, 2015, **54**, 8386–8389.

17 (a) C.-F. Chen, *Chem. Commun.*, 2011, **47**, 1674–1688; (b) P. Xin, L. Zhang, P. Su, J.-L. Hou and Z.-T. Li, *Chem. Commun.*, 2015, **51**, 4819–4822; (c) J.-H. Wang, H.-T. Feng and Y.-S. Zheng, *Chem. Commun.*, 2014, **50**, 11407–11410; (d) H.-J. Zhou, Y.-S. Zhao, G. Gao, S.-Q. Li, J.-B. Lan and J.-S. You, *J. Am. Chem. Soc.*, 2013, **135**, 14908–14911.

18 (a) J.-M. Lehn, *Chem.–Eur. J.*, 1999, **5**, 2455–2463; (b) P. T. Corbett, J. Leclaire, L. Vial, K. R. West, J.-L. Wietor, J. K. M. Sanders and S. Otto, *Chem. Rev.*, 2006, **106**, 3652–3711; (c) J.-M. Lehn, *Chem. Soc. Rev.*, 2007, **36**, 151–160; (d) J. N. H. Reek and S. Otto, *Dynamic Combinatorial Chemistry*, Wiley-VCH, Weinheim, 2010; (e) F. B. L. Cougnon and J. K. M. Sanders, *Acc. Chem. Res.*, 2012, **45**, 2211–2221; (f) J. Li, P. Nowak and S. Otto, *J. Am. Chem. Soc.*, 2013, **135**, 9222–9239.

19 (a) Z. He, G. Ye and W. Jiang, *Chem.–Eur. J.*, 2015, **21**, 3005–3012; (b) G. Huang and W. Jiang, *Progr. Chem*, 2015, **27**, 744–754.

20 G. Huang, Z. He, C.-X. Cai, F. Pan, D. Yang, K. Rissanen and W. Jiang, *Chem. Commun.*, 2015, DOI: 10.1039/c5cc06768e.

21 For reviews: (a) V. Böhmer, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 713–745; (b) A. Ikeda and S. Shinkai, *Chem. Rev.*, 1997, **97**, 1713–1734; (c) For recent examples: C. Talotta, C. Gaeta, Z. Qi, C. A. Schalley and P. Neri, *Angew. Chem., Int. Ed.*, 2013, **52**, 7437–7441; (d) C. Talotta, N. A. de Simone, C. Gaeta and P. Neri, *Org. Lett.*, 2015, **17**, 1006–1009.

22 B.-L. Poh, C. S. Lim and K. S. Khoo, *Tetrahedron Lett.*, 1989, **30**, 1005–1008.

23 G. D. Andreetti, V. Boehmer, J. G. Jordon, M. Tabatabai, F. Ugozzoli, W. Vogt and A. Wolff, *J. Org. Chem.*, 1993, **58**, 4023–4032.

24 (a) P. E. Georghiou and Z. Li, *Tetrahedron Lett.*, 1993, **34**, 2887–2890; (b) P. E. Georghiou, Z. Li, M. Ashram, S. Chowdhury, S. Mizyed, A. H. Tran, H. Al-Saraierh and D. O. Millera, *Synlett*, 2005, 879–891; (c) A. H. Tran, D. O. Miller and P. E. Georghiou, *J. Org. Chem.*, 2005, **70**, 1115–1121; (d) T. A. AlHujran, L. N. Dawe and P. E. Georghiou, *Org. Lett.*, 2012, **14**, 3530–3533; (e) H.-A. Tran, J. Collins and P. E. Georghiou, *New J. Chem.*, 2008, **32**, 1175–1182.

25 (a) B. J. Shorthill, C. T. Avetta and T. E. Glass, *J. Am. Chem. Soc.*, 2004, **126**, 12732–12733; (b) C. T. Avetta, B. J. Shorthill, C. Ren and T. E. Glass, *J. Org. Chem.*, 2012, **77**, 851–857.

26 K. Cottet, P. M. Marcos and P. J. Cragg, *Beilstein J. Org. Chem.*, 2012, **8**, 201–226.

27 R. K. Castellano, *Curr. Org. Chem.*, 2004, **8**, 845–865.

28 M. Nishio, M. Hirota and Y. Umezawa, *The CH/π Interaction: Evidence, Nature, and Consequences*, Wiley, Chichester, 1998.

29 D. A. Dougherty, *Acc. Chem. Res.*, 2013, **46**, 885–893.

30 (a) C. Kremer and A. Lützen, *Chem.–Eur. J.*, 2013, **19**, 6162–6196; (b) P. C. Knipe, S. Thompson and A. D. Hamilton, *Chem. Sci.*, 2015, **6**, 1630–1639.

31 D. E. Koshland Jr, *Proc. Natl. Acad. Sci. U. S. A.*, 1958, **44**, 98–104.

32 (a) R. F. Ludlow and S. Otto, *Chem. Soc. Rev.*, 2008, **37**, 101–108; (b) J. R. Nitschke, *Nature*, 2009, **462**, 736–738; (c) E. Mattia and S. Otto, *Nat. Nanotechnol.*, 2015, **10**, 111–119.