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Bistable Cucurbituril Rotaxanes Without Stoppers

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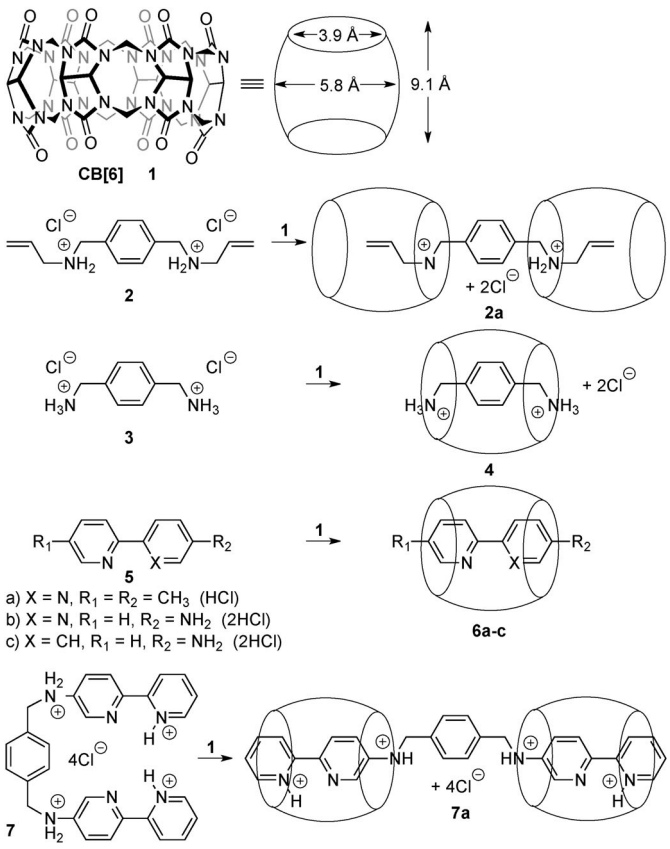
Abstract: Bistable rotaxanes are important design elements of molecular devices for a broad range of applications, such as controlled drug release, molecular rotary motors, and chemical sensors. The host–guest complexes of cucurbit[6]uril and 1,4-bis(alkylaminomethyl)benzene were found to exhibit two stable binding modes with an unexpectedly high barrier between them. Their structural and dynamic properties, kinetic and thermodynamic parameters, as well as different chemical reactivity towards the azide–alkyne [3+2] cycloaddition reaction (click chemistry), were discovered by NMR spectroscopy, X-ray crystallography, and isothermal titration microcalorimetry. The highly stable 2:1 complex, which is formed at room temperature, was found to be a kinetic product, which may be converted to the thermodynamic 1:1 complex upon prolonged heating to 100 °C. The latter is a very stable rotaxane despite the fact that it lacks bulky end groups.

Keywords: click chemistry · cucurbituril · molecular threading · pseudorotaxanes · rotaxanes

Introduction

The chemistry and physical properties of mechanically interlocked molecules, and bistable rotaxanes in particular, are important design elements of molecular devices for a broad range of applications, such as controlled drug release,[1] molecular rotary motors,[2] and chemical sensors.[3] For such applications the ability of the cucurbiturils to form host–guest complexes with diammonium salts is highly attractive.[4] Indeed, cucurbit[6]uril (**1**; Scheme 1), has been widely used for the construction of pseudorotaxanes and rotaxanes that exhibited interesting dynamic, structural, and functional properties.[4a,5,6] In particular, linear aliphatic diammonium salts readily form stable host–guest complexes of **1**.[7] By contrast, the ability of **1** to host aromatic compounds has been less obvious. For example, it was reported that **1** and the dihydrochloride salt of bis-1,4-(allylaminomethyl)benzene (**2**), form exclusively the [3]pseudorotaxane **2a**.[8] This mode of binding with two molecules of **1** hosting the allylic



Scheme 1.

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side chains of **2** was well determined by ^{1}H NMR spectroscopy, electron-spray mass spectrometry, and molecular-mechanical calculations. These observations led to the interpretation that the aromatic moiety in **2** is too big to be encapsulated in the cavity of **1**.[8] However, compound **1** and *p*-xylylenediammonium salt, **3**, are long known to form a stable inclusion complex, **4**, the structure of which was confirmed by single-crystal X-ray crystallography.[9] Furthermore, 5,5′-dimethyl-2,2′-bipyridine, **5a**, was reported to bind to either tetramethyl- or dicyclohexyl-CB[6], and their 1:1 binding mode was predicted by quantum-mechanical calculations and confirmed by X-ray crystallography.[10] Our studies with either 4-aminobipyridine (**5b**) or 4-(2-pyridyl)aniline (**5c**) showed that they form strong 1:1 inclusion complexes with **1** at room temperature (**6b** and **6c**), whereas the bifunctional analogue **7**, forms a strong 1:2 complex with **1** at room temperature, which exhibits remarkably large enhancements of fluorescence intensity and quantum yields.[11]

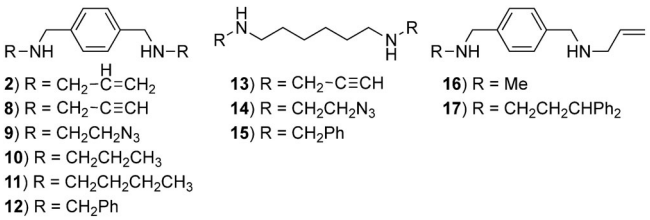
These observations led us to speculate that the aromatic part of **2** can be accommodated within the inner cavity of **1** and this binding mode may even be thermodynamically favored, but may involve unexpectedly high kinetic barriers. To investigate this issue we prepared a series of guest molecules and studied their behavior by using temperature-dependent NMR spectroscopy, X-ray crystallography, isothermal titration microcalorimetry (ITC), as well as by employing the azide–alkyne cycloaddition reaction (click chemistry)[12] as a chemical probe. Here we report that indeed, several 2:1 host–guest complexes, such as **2a** that are formed at room temperature, are kinetic products that may be converted to the thermodynamic 1:1 complexes upon prolonged heating to 100 °C. The latter are very stable rotaxanes despite the fact that they lack bulky end groups.

Abstract in Hebrew:

רוטקסאנים ביסטביליים הם מרכיבים חשובים בתכנון ובבניה של התקנים מולקולריים שונים, המיועדים למגוון רחב של יישומים, כגון שחרור מבוקר של תרופות, מנועים מולקולריים סיבוביים, חיישנים כימיים ועוד. נמצא כי קומפלכסים מסוג של אורח-מארח בין קוקורביט[6]אוריל לבין 1,4-ביס(אלקילאמינומתיל)בנזן, מציגים שני צורוני קישור, אשר מחסום האנרגיה ביניהם גבוה באופן בלתי צפוי. המבנה של שני הצורונים הללו, המאפיינים הדינמיים שלהם, הפרמטרים התרמודינמיים והקינטיים שלהם, וכן פעילותם השונה בתגובת הסיפוח מסוג ציקלואדיציה[2+3] שבין אצטילן טרמינלי ואלקיל אזיד (תגובת קליק), התגלו באמצעות ספקטרוסקופית תמ״ג, קריסטלוגרפיה בקרני רנטגן, ומיקרוקלורימטריה באמצעות טיטרציה איזותרמית. התברר כי הקומפלכס היציב, בעל יחס של 2:1 בין האורח למארח, אשר נוצר בטמפרטורת החדר, הוא תוצר קינטי. הקומפלכס הזה יכול לעבור לתוצר התרמודינמי, שבו היחסים הם 1:1, באמצעות חימום ממושך לטמפרטורה של 100 מעלות צלסיוס. הקומפלכס התרמודינמי הזה הוא רוטקסאן יציב מאד, אף על פי שאיננו מכיל קבוצות קצה נפחיות.

Results and Discussion

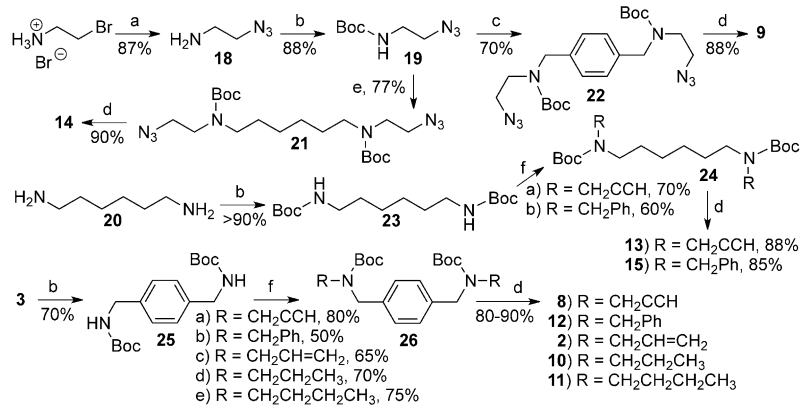
Synthesis of guest molecules: A series of guest molecules, compounds **2** and **8**–**17**, were prepared for this study (Scheme 2). Although compounds **13** and **14** were reported



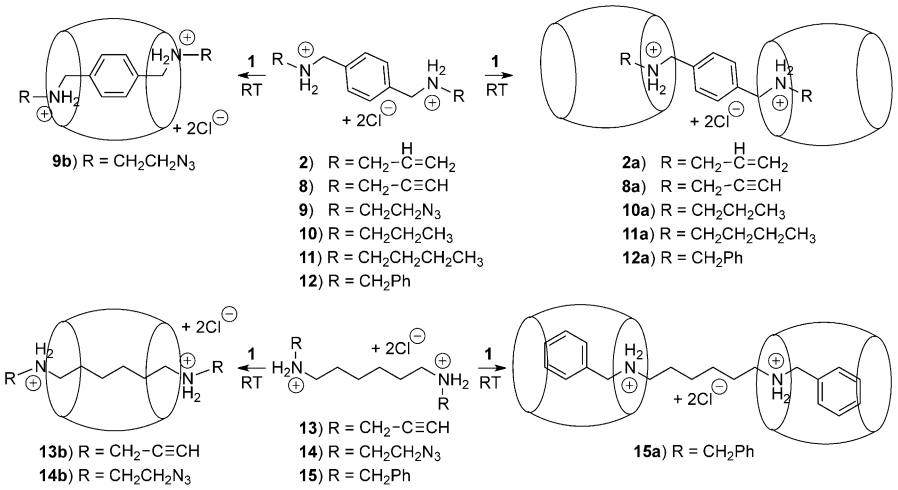
Scheme 2.

earlier,[13] we prepared them in higher yields (Scheme 3), 57 and 53 % rather than the reported 17 and 36 %, respectively (for further experimental details, see the Supporting Information). For example, for the synthesis of **9** and **14** we used 2-azidoethylamine (**18**), which was prepared from bromoethylamine hydrobromide and NaN_3 in water. Protection of **18** with *tert*-butoxycarbonyl (Boc) to produce **19** followed by *N*-alkylation with 1,6-diaminohexane (**20**) afforded **21**. Removal of the Boc groups with ethanolic HCl produced **14** in the form of its dihydrochloride salt in 53 % overall yield. Similarly, *N*-alkylation of **19** with 1,4-bis(bromomethyl)benzene afforded compound **22**, which, upon deprotection, yielded **9** in the form of a dihydrochloride salt in 47 % overall yield. The propargylamine derivatives, compounds **8** and **13**, were prepared in three steps from **3** and **20**, respectively. Similar procedures were applied for the conversion of **23** and **25** to their bis-alkylamine analogues **24** and **26**, respectively. Finally, deprotection under acidic conditions afforded guest molecules **2**, **8**, **10**–**12**, and **15** in the form of their dihydrochloride salts in 30–50 % overall yield. The non-symmetric guest molecules **16** and **17**, were prepared by reacting a 1:1:1 mixture of 1,4-bis(bromomethyl)benzene, Boc-protected allylamine, and either Boc-protected methylamine or Boc-protected 3,3-diphenylpropylamine. Chromatographic separation of the product mixture afforded **16** and **17** in 40 and 20 % yields, respectively.

Inclusion complexes: To study the stoichiometry of the inclusion complexes, an acidic aqueous solution (D_2O–DCl, pH 6) of each of the protonated guests, **2**, **8**–**15**, was mixed with solid **1** (2 equiv) and the mixture was kept at room temperature for 16 h. Quantitative formation of the corresponding inclusion complexes (Scheme 4) was evident by their ^{1}H NMR spectra, which exhibited significant changes in the chemical shifts of the guest molecules (see the Supporting Information). Consistent with the early observations of Mock et al. for other inclusion complexes of **1**,[7a,14] all protons of the guest molecule that reside in the host interior underwent significant upfield shifts. This shielding effect re-



Scheme 3. Synthesis of all symmetrical guest molecules, **2**, **8**–**15**. All final products were isolated in the form of their hydrochloride salts. Reagents and conditions: a) NaN_3, H_2O, 80 °C, 24 h; b) $(Boc)_2O$, Et_3N, CH_2Cl_2, RT, 12 h; c) 1,4-bis(bromomethyl)benzene, NaH, *N*,*N*-dimethylformamide, RT, 48 h; d) 4 N HCl, EtOH, RT, 16 h; e) 1,6-dibromohexane, NaH, *N*,*N*-dimethylformamide, RT, 48 h; f) propargyl bromide (for the synthesis of **24a** and **26a**), benzyl bromide (for the synthesis of **24b** and **26b**), allyl bromide (for the synthesis of **26c**), 1-bromopropane (for the synthesis of **26d**), 1-bromobutane (for the synthesis of **26e**), NaH, *N*,*N*-dimethylformamide, RT, 24–36 h.



Scheme 4. Formation of either 1:2 or 1:1 complexes between various diamine guest molecules and host **1** in water, pH 5, at room temperature.

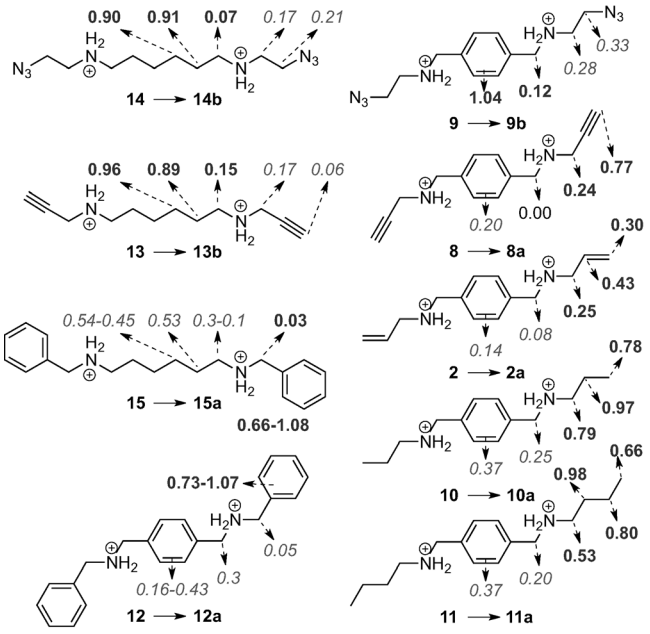
flected the cumulative influence of the urea units, which form a hydrophobic wall of filled π orbitals. The CB hydrophobic interior is remarkably different from the acidic aqueous medium that solvates the free guests.[15] In contrast, all protons of the guest molecule that reside outside the cavity in the vicinity of the portal carbonyl groups underwent deshielding, probably due to the strong anisotropic effect exerted by the strong combined dipole of those carbonyl groups. Thus, the mode of the inclusion complexation could be unequivocally concluded from the sign of the induced chemical shifts (Scheme 5).

Two distinct types of inclusion complex were observed on the basis of their NMR data. Complexes **2a**, **8a**, **10a**, **11a**, **12a**, and **15a** exhibited a 1:2 binding mode with two CB molecules hosting the side groups of the guest and leaving the central part exposed to the solvent. In contrast, molecules **9b**, **13b**, and **14b**, formed 1:1 inclusion complexes with one host molecule accommodating the central part of the guest.

Further support for these two different binding modes was obtained from ITC measurements at room temperature, which afforded the values of binding constant ($\log\beta$)[16] and binding stoichiometry (n). Solutions of **1** were titrated with each of the guest molecules **2**, **8**–**15**, and with **20**. The latter served as a known reference compound for comparison with literature data. All stoichiometry values (Table 1) were consistent with the above-mentioned interpretation of ^{1}H NMR spectra.

We classified the complexes into three groups according to their binding properties (Table 1). The first group (Table 1, entries 1–4) includes the 1:1 complexes, as indicated by their binding stoichiometry of approximately 1. The binding constants of **13** and **14** were found to be an order of magnitude weaker than that of the parent guest **20** ($\log\beta = 6.25 \pm 0.04$).[11] This observation was expected on the basis of the known stronger affinity of **1** to primary versus secondary ammonium ions.[7a] The phenomenon can be understood in terms of higher steric demand of the secondary ammonium ions and their smaller number of hydrogen-bonding opportunities with either the portal carbonyl oxygen atoms or the surrounding water molecules.

Interestingly, guest **9** formed a 1:1 complex (Table 1, entry 4) although all other aromatic guests formed 1:2 complexes (Table 1, entries 6–10). This observation could be understood on the basis of the relative affinities between the side chains in these guest molecules and **1**. The dissociation constant of 2-azidoethyl amine (2.5×10^{-3} M) is much higher than those of propargylamine (6.5×10^{-4} M) and *n*-propylamine (8.2×10^{-5} M).[7a] Thus, both guest molecules bearing azidoethyl groups (**14** and **9**; Table 1, entries 3 and 4) prefer central binding at room temperature. The binding affinity of **14** was found to be an order of magnitude stronger than that of **9**. Apparently, in spite of the entropic advantage of the rigid aromatic core in **9**, it has a much lower enthalpy term, probably reflecting the repulsive interactions between the



Scheme 5. ^{1}H NMR-induced chemical shifts (ppm) upon formation of inclusion complexes of the guest molecules **2a**, **8**–**15** at room temperature in D_2O–DCl solutions containing trace DMSO ($\delta = 2.71$ ppm) as an internal standard. The shielding effect (ppm, upfield shift) is shown in bold, whereas deshielding (ppm, downfield shift) is shown in italic.

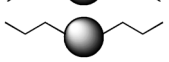
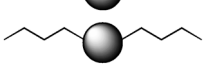
aromatic system and the filled π orbitals of the host urea groups, as well as the steric interactions. The aromatic ring is obviously larger than the optimal space provided by the interior of **1**, with a 3.9 Å portal diameter and interior diameter of 5.8 Å.[15,17] This conflict leads not only to diminished binding affinities but also to a distortion of the host, as seen in the solid-phase structures of these complexes (see below).

The second group (Table 1, entries 5 and 6) includes the two guest molecules bearing benzyl side chains. The benzyl group is known to be a weak binder of **1** in comparison with the small alkyl side chains of the third group (Table 1, entries 7–10).[7a] Yet, both **12** and **15** prefer peripheral binding, probably due to the high kinetic barrier associated with the required threading of the large benzyl group through the polar portal of **1** and moving of the benzyl groups from the hydrophobic interior of **1** to the aqueous medium.

The third group (Table 1, entries 7–10) of guests **2**, **8**, **10**, and **11** exhibits very similar binding parameters. Their relatively high negative entropic terms probably reflect significant restriction of conformational mobility that is not compensated by the release of water molecules from the solvated guest and **1**.[18] One should not be mislead by the fact that both guest molecules bearing propargyl groups (**13** and **8**; Table 1, entries 2 and 8) exhibit very similar enthalpy and entropy terms. They show different binding modes at room temperature, central binding with **13** and peripheral with **8**.

Plotting the thermodynamic data of Table 1 along with previously reported data,[11] revealed an essentially linear correlation between $T\Delta S^0$ and ΔH^0 values (Figure 1). The slope α ($-T\Delta\Delta S^0$), which is the incremental value of the thermodynamic parameter of binding, was found to be 0.92 for this series of host–guest complexes. This value is comparable with the observed known values for complexes of cationic hydrophobic guests with α-, β-, and γ-cyclodextrins (0.79, 0.80, and 0.97, respectively).[19] These values are consistent with the fact that entropy dominates the favorable free energy of mainly hydrophobic interactions.[15] Association of two nonpolar surfaces, that is, the inner cavity of **1** and either the alkyl or aromatic backbone of the diammonium guest, causes the release of structured molecules of water near nonpolar surfaces.[20] The intercept calculated from the regression line ($T\Delta S^0 = 6.1$ kcal mol^{-1}) represents the inherent complex stability (ΔG^0) obtained at a hypothetical case of $\Delta H^0 = 0$. Comparison with the analogous values for crown ethers ($T\Delta S^0 = 2.9$ kcal mol^{-1}) and α-, β-, and γ-cyclodextrins (1.9, 2.6, and 3.6 kcal mol^{-1}, respectively) highlights the high entropy gain.[21]

Table 1. Overall binding constants ($\log\beta$), binding stoichiometry (n, guest/host ratio), enthalpy (ΔH), and entropy (ΔS) of binding between **2**, **8**–**15**, and **20** with **1**. In the graphical representation of the guest molecules the solid bar represents 1,6-diaminohexane and the sphere represents *p*-xylylenediamine. In all experiments 0.13 mM of **1** was titrated with a solution of the guest molecule (1–2 mM) in NH_4Cl buffer (10 mM, pH 4) at 303 K.

Entry	Guest	Complex	$\log\beta$	n	ΔH [kcal mol^{-1}]	ΔS [eu]
1		**20@1**	6.25 ± 0.04	0.91	−11.13 ± 0.01	−8.1 ± 0.1
2		**13@1**	4.95 ± 0.04	0.91	−13.51 ± 0.02	−21.9 ± 0.1
3		**14@1**	5.65 ± 0.02	1.00	−12.39 ± 0.02	−15.1 ± 0.1
4		**9@1**	4.60 ± 0.03	0.88	−8.44 ± 0.15	−6.0 ± 0.1
5		**15@1**	4.31 ± 0.04	0.51	−8.6 ± 0.7	−8.6 ± 0.1
6		**12@1**	4.14 ± 0.05	0.49	−11.2 ± 1.7	−17.9 ± 0.6
7		**2@1**	5.71 ± 0.02	0.53	−15.21 ± 0.01	−24.0 ± 0.1
8		**8@1**	5.26 ± 0.04	0.50	−13.56 ± 0.14	−21.5 ± 0.1
9		**10@1**	5.28 ± 0.03	0.50	−13.8 ± 0.2	−21.5 ± 0.1
10		**11@1**	5.83 ± 0.05	0.51	−16.0 ± 0.3	−26.3 ± 0.1

Kinetic versus thermodynamic control over the binding mode: The observation that many structurally similar guest molecules exhibit either peripheral or central binding modes (Scheme 4) led us to speculate that the 1:2 and the 1:1 complexes could be kinetically interconvertible under appropriate conditions. Consistent with

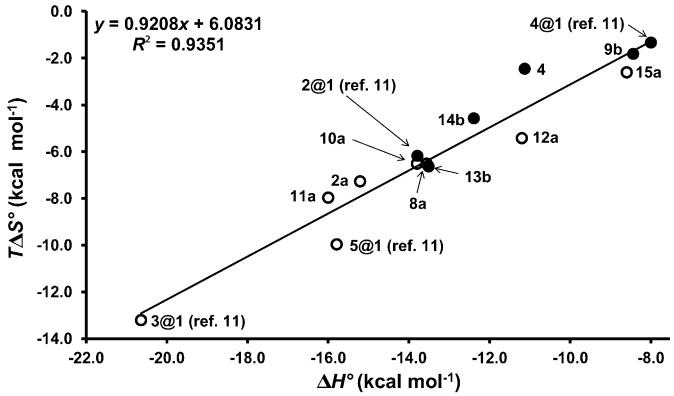
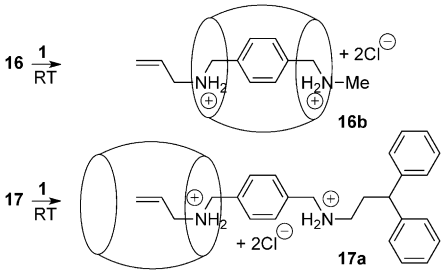


Figure 1. Enthropy–entalpy compensation plot for the complexation of various guests with **1**. Filled and open circles represent the thermodynamic data for 1:1 and 1:2 binding modes, respectively.



Scheme 6. Formation of the inclusion complexes between **1** and non-symmetric guests **16** and **17**.

this notion was the room temperature behavior of the non-symmetric guest molecule **16**, which preferred a central binding mode **16b**, whereas compound **17** preferred the peripheral binding **17a** (Scheme 6). These observations suggested that the central binding mode of the aromatic group is preferred thermodynamically, whereas binding of the allylic side chain is favored kinetically.

Furthermore, since compounds **8** and **9** are structurally similar but exhibit very different complexation behavior with **1**, we suspected that the observed 1:2 complex **8a** is a kinetic product, whereas the 1:1 complex **9b** is a thermodynamic one. To examine this assumption, we monitored the ^{1}H NMR spectrum of **8a** as a function of time and temperature. Mixing **8** and **1** at a 1:2 molar ratio at room temperature for 36 h resulted in the exclusive formation of **8a** (Figure 2b). The 1:2 binding mode was apparent from the downfield shift of the aromatic protons (A, $\Delta\delta = 0.20$), the upfield shift of the propargylic (C, $\Delta\delta = -0.24$) and the acetylenic (D, $\Delta\delta = -0.77$) protons and the essentially unchanged benzylic protons, B. This situation changed dramatically upon heating the mixture to 100 °C for 10 days (Figure 2c–g), leading to essentially quantitative conversion of **8a** to **8b**. The shift from a peripheral to central binding mode was evident from the considerable upfield shift of the aromatic protons (A, $\Delta\delta = -1.36$ ppm) accompanied by a smaller upfield shift of the benzylic signal (B, $\Delta\delta = -0.08$ ppm) and large downfield shifts of the propargylic (C, $\Delta\delta = 0.71$ ppm) and the acetylenic (D, $\Delta\delta =$

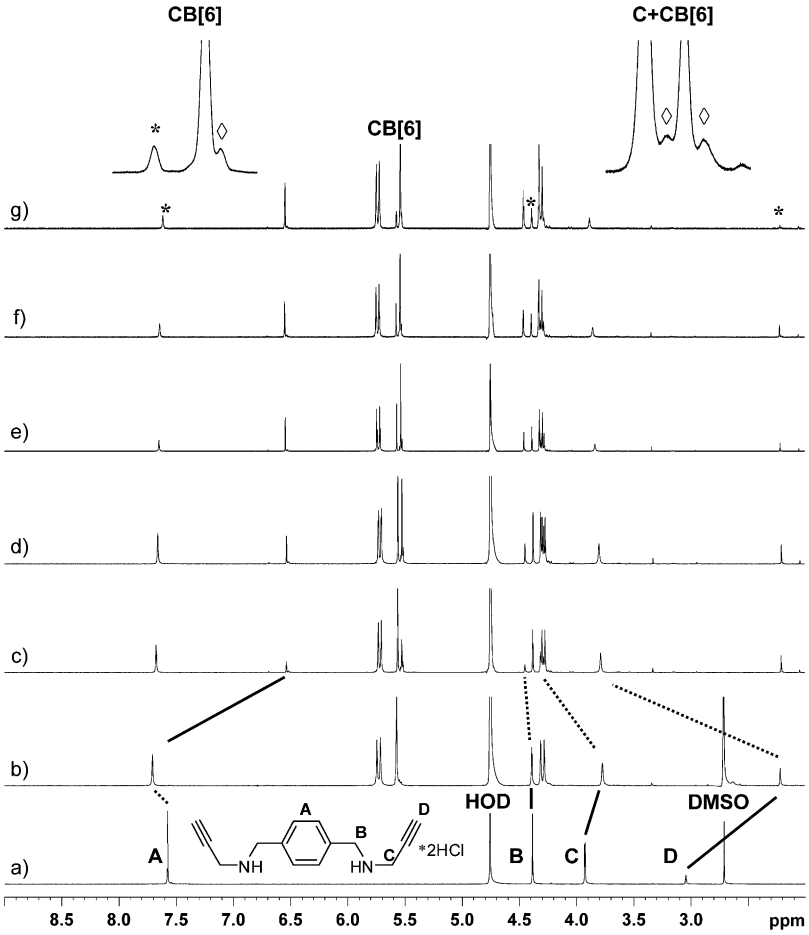


Figure 2. ^{1}H NMR spectra of **8** (600 MHz, D_2O–DCl). Solid and dashed lines represent upfield and downfield shifts, respectively. a) Doubly protonated **8** in the absence of **1** at RT. b) After addition of **1** (2 equiv with respect to **8**), 36 h at RT. c) The mixture (b) after 14 h at 100 °C. d) Mixture (b) after 28 h at 100 °C. e) Mixture (b) after 54 h at 100 °C. f) Mixture (b) after 67 h at 100 °C. g) Mixture (b) after 91 h at 100 °C. The expanded parts of the latter spectrum at $\delta = 5.5$–5.6 (left) and 4.25-4.35 ppm (right) exhibit signals of **1** with the most intense signals representing the 1:1 binding mode, **8b**. The small signals marked with * represent the 1:2 binding mode, **8a**, and those marked with ◇ represent free **1**.

1.57 ppm) signals. Much smaller changes were observed in the signals of the host molecule **1**. The most significant of which was the upfield shift of the methine signal from $\delta = 5.57$ ppm in **8a** to $\delta =$ 5.53 ppm in **8b**. Further confirmation of the structures of the 1:2 and 1:1 binding modes was obtained from single-crystal X-ray crystallography of complexes **8b** and **11a** (see below).

The complexation behavior of **15** was similarly monitored by ^{1}H NMR spectroscopy. Mixing solutions of **15** and **1** at a 1:2 molar ratio at room temperature for 36 h resulted in the exclusive formation of **15a** (Figure 3b). The 1:2 binding mode was apparent from the upfield shift of the aromatic protons (A, from $\Delta\delta = -0.66$ to -1.08 ppm) accompanied by a smaller upfield shift of the benzylic signal (B, $\Delta\delta =$ -0.03 ppm), whereas all signals of the alkyl chain exhibited large downfield shifts (C–E, from $\Delta\delta = 0.1$ to 0.54 ppm). This situation changed dramatically upon heating to 100 °C for 5 days (Figure 3c and d), leading to conversion of **15a** to **15b**. Interestingly, the reaction of **15** with **1** was found to be incomplete at room temperature, affording **15a** in approximately 45 % yield. After heating to 100 °C for 92 h the 1:1 complex **15b** was obtained in 55 % yield.

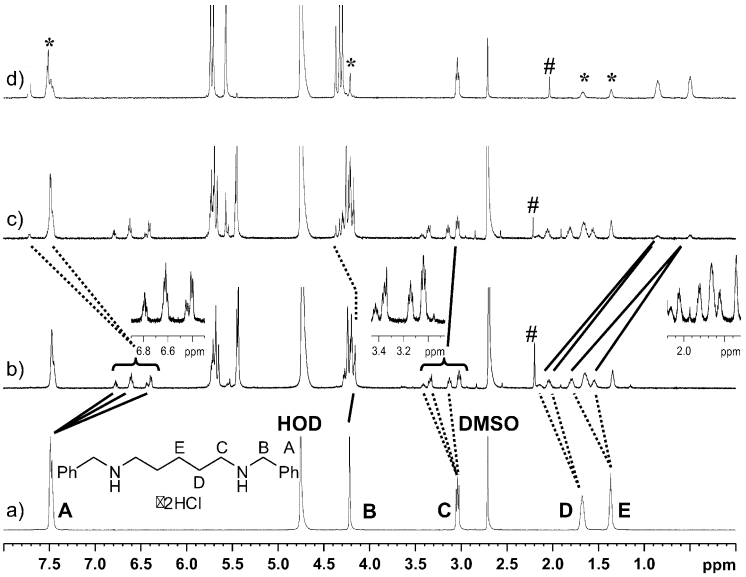
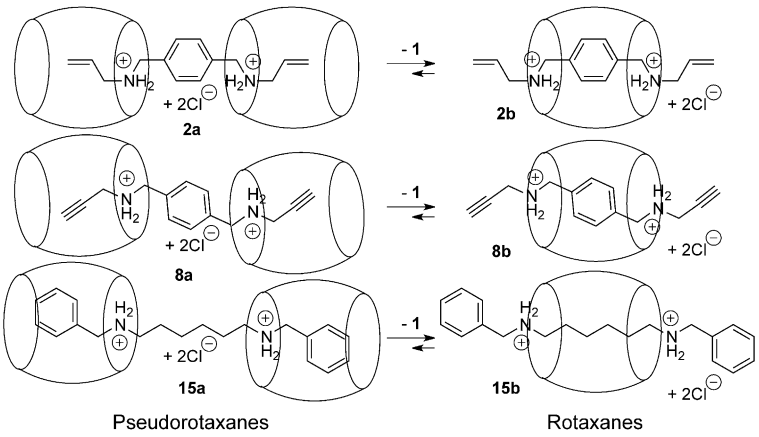


Figure 3. ^{1}H NMR spectra of **15** (500 MHz, D_2O–DCl). Solid lines represent upfield shifts, whereas dashed lines represent downfield shifts. a) Doubly protonated **15** in the absence of **1** at RT. b) After addition of **1** (2 equiv with respect to **15**) and 36 h at RT. c) Mixture (b) after 3 h at 100 °C. d) Mixture (b) after 92 h at 100 °C. The expanded parts of spectrum (b) at $\delta = 6.9$–6.3 (left), 3.5–2.9 (middle), and 2.2–1.5 ppm (right) exhibit signals of the 1:2 binding mode, **15a**. The small signals marked with * represent free **15** and those marked with # refer to acetone impurity.

Interestingly, similar threading processes upon thermal treatment were recently reported with analogues of guest **15**, with either pyridyl[22] or 4-carboxaldehydephenyl[23] instead of the phenyl groups. In both cases the conversion of the host–guest complex from its kinetically stable peripheral binding mode to the thermodynamically stable central binding mode occurred in acidic water upon reflux for several hours. Another case of threading under thermodynamic control at high temperatures was reported for *N*,*N*′-diisobutylspermine.[24]



Scheme 7. Interconversion between the peripheral and central complexes at elevated temperatures.

The experiment described in Figure 2 allowed for a qualitative assessment of the apparent rate constant for the conversion of **8a** to **8b**. Analogous experiments were carried out to monitor the conversion of **2a** to **2b** and of **15a** to **15b**. The progress of this isomerization process (Scheme 7) was determined by measuring the relative integration values of the methine proton signal of **1** at $\delta = 5.57$ ppm in complexes **2a**, **8a**, and **15a** and at $\delta = 5.53$ ppm in **2b**, **8b**, and **15b**. The conversion (%) was plotted versus time (Figure 4 and Figure S4 in the Supporting Information) indicating apparent first-order kinetics in all three cases with the apparent rate constants as follows: compound **2a**: $k = 3.6 \pm 0.3 \times 10^{-5}\ s^{-1}$; compound **8a**: $k = 1.17 \pm 0.07 \times 10^{-4}\ s^{-1}$; compound **15a**: $k = 1.18 \pm 0.08 \times 10^{-4}\ s^{-1}$.

The thermodynamic parameters for the transition from **8a** to **8b** were determined by monitoring the progress of the reaction at 70, 80, 90, and 100 °C by ^{1}H NMR spectroscopy. The resultant first-order rate constants were used in an Eyring plot (Figure 5). The enthalpy of activation, $\Delta H^{\neq} = 4.4 \pm 0.2$ kcal mol^{-1}, was calculated from the slope. The activation entropy, $\Delta S^{\neq} = -67.4 \pm 0.5$ cal mol^{-1} K^{-1}, was calculated from the intercept with the y axis. These values were used to determine the Gibbs free energy difference, $\Delta G^{\neq} = 24.4 \pm 0.2$ kcal mol^{-1} at 298 K.

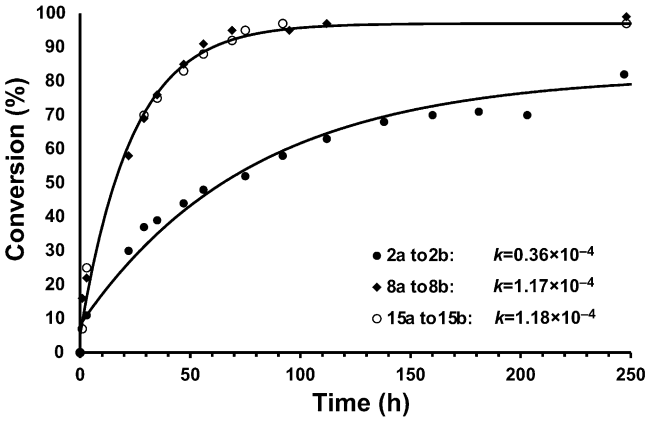


Figure 4. Observed transition between 2:1 and 1:1 binding mode upon heating complexes (**2a**, **8a**, and **15a**) at 100 °C. The solid line represents the data fitting according to an apparent first order rate equation (s^{-1}).

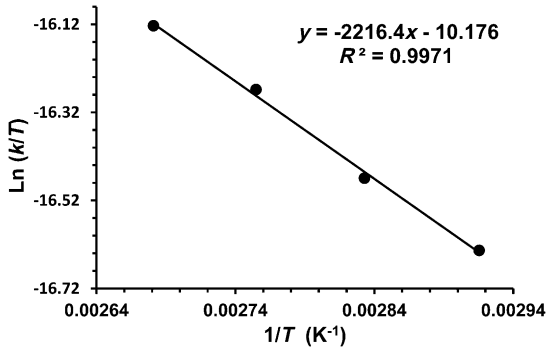


Figure 5. Eyring plot for the transition from **8a** to **8b**: the transition rates ($k\times10^{-5}$, s^{-1}), 2.05 ± 0.21, 2.49 ± 0.81, 3.12 ± 0.41, and 3.71 ± 0.44 were determined at $T=343$, 353, 363, and 373 K respectively, and plotted to give the kinetic energy parameters. The Gibb's free energy of the transition state was calculated at 298 K using the Gibb's free energy function $\Delta G^{\ddagger}=\Delta H^{\ddagger}-T\Delta S^{\ddagger}$. The values obtained from this plot were $\Delta H^{\ddagger}=(4.4\pm0.2)$ kcal mol^{-1}, $\Delta S^{\ddagger}=(-67.4\pm0.5)$ cal mol^{-1}K^{-1}, and $\Delta G^{\ddagger}=(24.4\pm0.2)$ kcal mol^{-1} at 298 K.

These results indicate that the transformation of **8a** to **8b** involves very common value[25] of the enthalpy of activation but the entropy term is outstandingly high. The latter could be expected since the process involves loss of one host molecule as well as release of the two side chains from rigid complexation to free movement. This large entropy of activation is unprecedented for threading processes with the cucurbituril guest. The closest examples of large entropic gain in the kinetics of the threading and sliding processes are the threading of viologen polymers within toroidal porphyrin ($\Delta S^{\ddagger}=21$–23 cal mol^{-1}K^{-1}), which involves stretching of the polymeric chains,[26] and the threading of viologen chains within calix[6]arene ($\Delta S^{\ddagger}=30.1$ cal mol^{-1}K^{-1}), which involves reversible formation of hydrogen bonds.[25]

X-ray crystallography: The solid-state structures of representative complexes **4**, **8b**, **9b**, and **11a**, all crystallized from an acidic (pH 6) aqueous solution, provided valuable information about the binding interactions of these inclusion complexes. We compared the structures of the new 1:1 complexes **8b** and **9b** and the 1:2 complex **11a** (Figure 6), with the structure of the parent system, **4**, which was found to be identical with the one reported by Freeman.[9a] The single-crystal X-ray crystallographic data and refinement details of all four complexes are provided in Table 2.

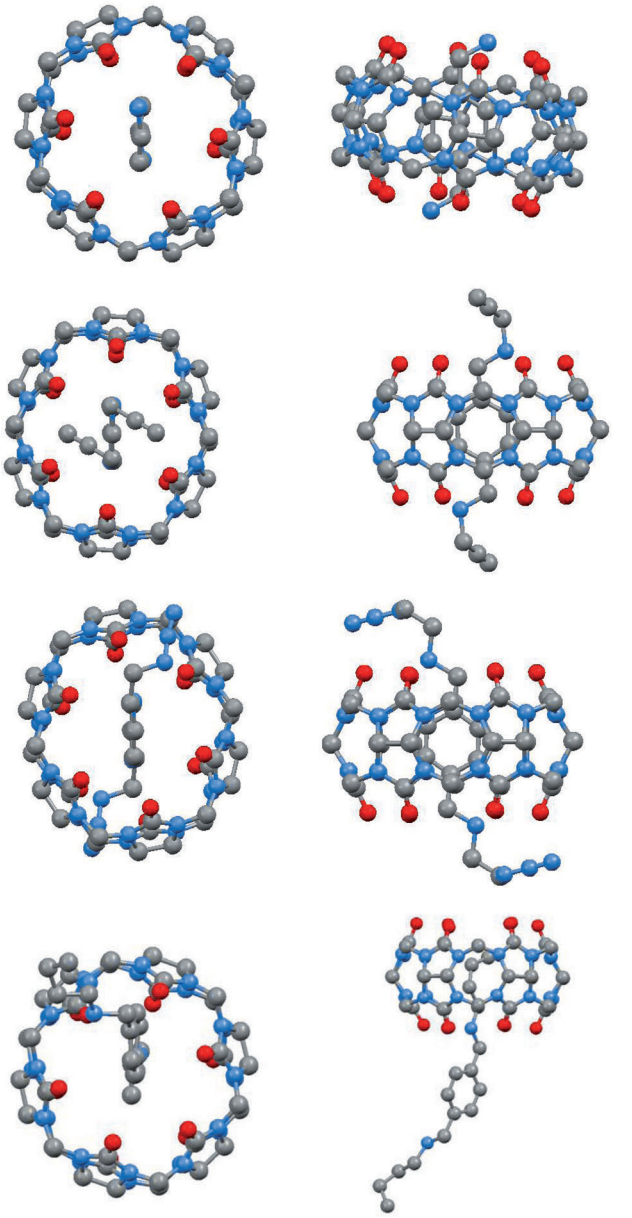


Figure 6. Stereoviews of the X-ray crystal structures (top to bottom) of **4**, **8b**, **9b**, and **11a** (with one cucurbituril unit being omitted for clarity): left: top view, right: side view. Color code: C, gray; N, blue; O, red. Hydrogen atoms, water molecules, and counteranions were omitted from all structures.

A common feature of all crystal structures is the presence of large number of water molecules occupying the intermolecular space within the unit cell in addition to the chloride counteranions. The ratio between the actual complex and

Table 2. Crystallographic data and refinement details.

	4	**8b**	**9b**	**11a**
formula	$C_{44}H_{50}N_{26}O_{12}$·2Cl·10H_2O	$C_{50}H_{52}N_{26}O_{12}$·2Cl·18H_2O	$C_{48}H_{56}N_{32}O_{12}$·2Cl·12H_2O	$C_{88}H_{100}N_{50}O_{24}$·2HCl·29$H_2O$
formula weight	1204.35	1550.47	1560.64	2837.4
density [g cm^{-3}]	1.670	1.497	1.604	1.339
T [K]	293(2)	240(1)	293(2)	293(2)
diffractometer	KappaCCD	KappaCCD	KappaCCD	APEX2 DUO
scan mode	ω and ϕ scans	ω and ϕ scans	ω and ϕ scans	ω scans
crystal size [mm]	0.45×0.36×0.05	0.35×0.18×0.14	0.55×0.30×0.25	0.44×0.16×0.02
crystal system	monoclinic	monoclinic	triclinic	monoclinic
space group	$P2_1/n$	$C2/c$	$P\bar{1}$	Cc
a [Å]	12.078(2)	27.465(5)	11.357(2)	25.398(3)
b [Å]	15.819(3)	20.600(4)	12.191(2)	47.898(4)
c [Å]	14.438(3)	12.510(2)	13.036(3)	12.873(10
α [°]	90	90	109.54(3)	90
β [°]	91.974(2)	96.15(3)	97.84(3)	116.826(2)
γ [°]	90	90	102.69(3)	90
V [Å^3]	2756.9(9)	7037(2)	1615.6(7)	13975(2)
Z	2	4	1	4
F(000)	1452	3336	818	5900
θ_{max} [°]	25.05	25.05	25.02	25.25
unique reflns	4877	6202	5703	24853
$I>2\sigma(I)$	3537	4513	4526	18548
R-factor (all data)	0.0921	0.1067	0.0708	0.1042
R-factor ($I>2\sigma(I)$)	0.0693	0.0813	0.0565	0.0851
S	1.063	1.051	1.079	1.145

these localized water molecules ranges from 1:10 in **4**, 1:12 in **9b**, 1:17 in **8b**, and 1:29 in **11a**, (1:14.5 per cucurbituril unit). Expectedly, these water molecules are interconnected through a network of hydrogen bonds that also includes the carbonyl oxygen atoms of **1** and, in the case of **4**, the ammonium groups of the guest molecule.

Complex **11a** exhibits two modes of hydrogen bonding with the water molecules. One mode involves a water molecule that bridges two carbonyl oxygen atoms on two different cucurbituril units, C=O(10)-O(81)-(06A)O=C), 2.84–2.97 Å with an angle of 135°. The other mode involves two water molecules that bridge the two cucurbituril units, C=O(8)-O(68)-O(70)-(04A)O=C, 2.73–2.88 Å (Figure 7). These attractive interactions could explain the asymmetry observed in the structure of **11a** with the two CB units forming an angle of 42.56° (Figure 6). A similar situation was observed with the [2]pseudorotaxane of CB[7] with bispyridinuim ethane. In that case, however, the non-symmetrical orientation of the cucurbiturils was explained by a repulsive interaction between the cations.[4b]

These observations are reminiscent of the recently reported complexation of thioflavin T (ThT) with CB[7].[27] Geometry optimization calculations revealed that the two CB[7] units in the 1:2 binding mode were not parallel, and slightly moved away from the N atom of the guest in comparison with the 1:1 binding mode.[27a] This geometry was interpreted in terms of the repulsive interaction between the carbonyl portals of both CB[7] units, but compensated by hydrogen-bonding interactions between the charged *N*-methyl group of the guest and the carbonyl oxygen atoms of both CB units, resulting in a non-symmetrical orientation of the CB units. The 1:2 complexation mode was reinforced by cooperative binding of calcium cations.[27b]

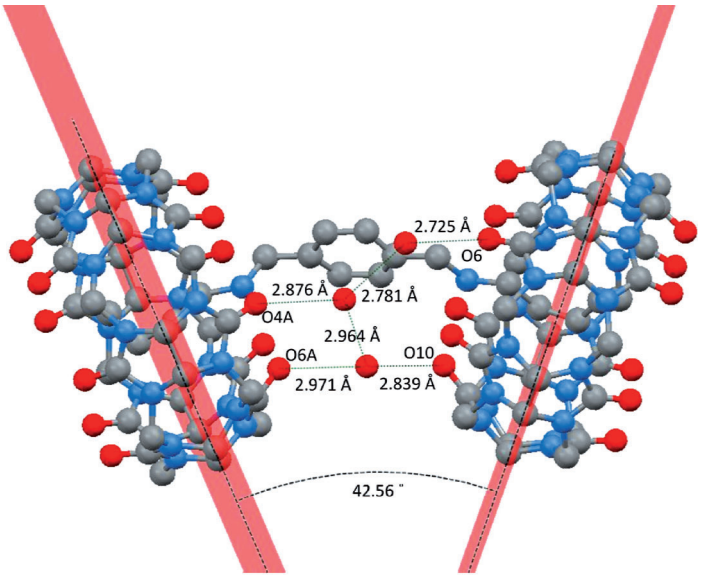


Figure 7. Crystal structure of **11a** exhibiting a network of three water molecules that interconnect the two cucurbituril units.

All the 1:1 complexes **4**, **8b**, and **9b**, exhibited two types of hydrogen bonding between the carbonyl oxygen atoms of **1** and the guest. The more obvious bonds involve the ammonium hydrogen atoms NH-O=C, 1.980(3)–2.420(3) Å. Less obvious, but quite visible, are the hydrogen bonds between the carbonyl oxygen atoms and the benzylic methylene hydrogen atoms of the guest CH-O=C, 2.317(3)–2.508(2) Å.

In most of the reported solid state structures of host–guest complexes of the cucurbit[*n*]urils, particularly with the larger members of the family ($n=7$, 8, and 10), no distortion of the host was noticed, as reflected by nearly ideal circular

portals, as well as a circular equator line, which accommodates all methine groups. However, in complexes **4**, **8b**, and **9b**, for which the size of the aromatic guest is relatively large with respect to the cavity of **1**, considerable distortions of the host were observed. The ellipsoid shape of the portals could be defined by the intercage distances between opposite pairs of oxygen atoms. In **4** these distances are 6.581(3), 7.014(3), and 7.244(3) Å. In **8b** they are 6.554(4), 6.673(4), and 7.615(4) Å, whereas in **9b** they are 6.518(4), 6.726(4), and 7.608(4) Å. These numbers represent a significant deviation from the nearly symmetrical circle that characterizes **1** hosting two water molecules: 6.710(7), 6.710(7), and 6.683(6) Å.[28]

We found that the relative orientation of a guest within **1** varies among the complexes, as reflected by the angles between the plane defined by the aromatic carbons and the planes accommodating opposite carbonyl oxygen atoms (Figure 8). In complex **4** the aromatic plane is almost perpendicular to plane produced by O1-O4-O1′-O4′ (85°) and bisects the remaining two planes, O2-O5-O2′-O5′ (24°) and O3-O6-O3′-O6′ (32°). In **8b**, the aromatic guest is almost parallel to the plane of O3-O6-O3′-O6′ (3.2°) and bisects the two remaining planes O2-O5-O2′-O5′ (52°) and O1-O4-O1′-O4′ (59°). The corresponding angles in **9b** are 8.9°, 45°, and 65°, respectively.

The ellipsoid geometry of **1** in the 1:1 complexes is also manifested by the variations in distance between the opposite methine groups on the equator. In an ideal circular structure of **1** with nearly D_{6h} symmetry these carbon atoms are 10.15–10.20 Å apart, that is, $\Delta d = 0.05$ Å. The largest deviation of $\Delta d = 1.31$ Å was reported for a complex of 4-methylpyridinium with **1**.[29] Similarly large distortions were observed with **4**, **9b**, and **8b**, with Δd being 0.60, 1.21, and 1.29 Å, respectively. Following the method of Farrugia,[30] we calculated the expanded cavity volume[15] of **1** in complexes **4**, **8b**, **9b**, and **11a** (327.2, 355.2, 369.1, and 398.3 Å^3, and found that these cavities increase with the steric demands of the side chains.

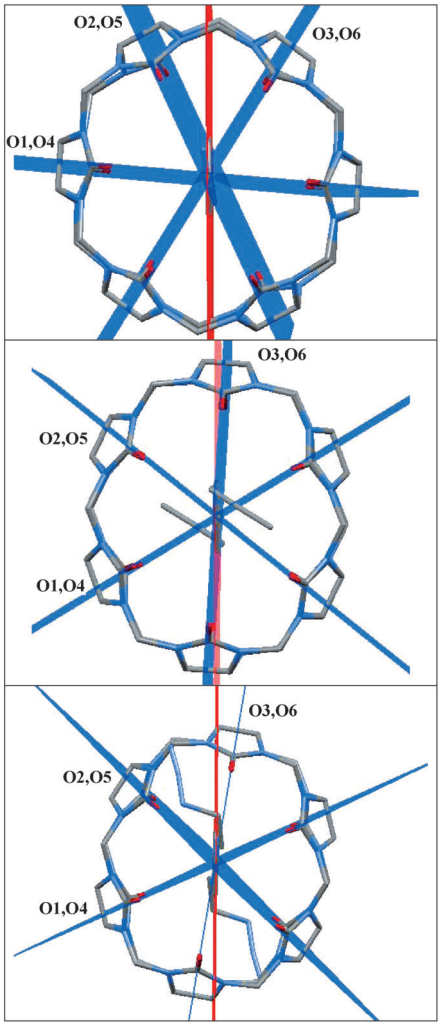
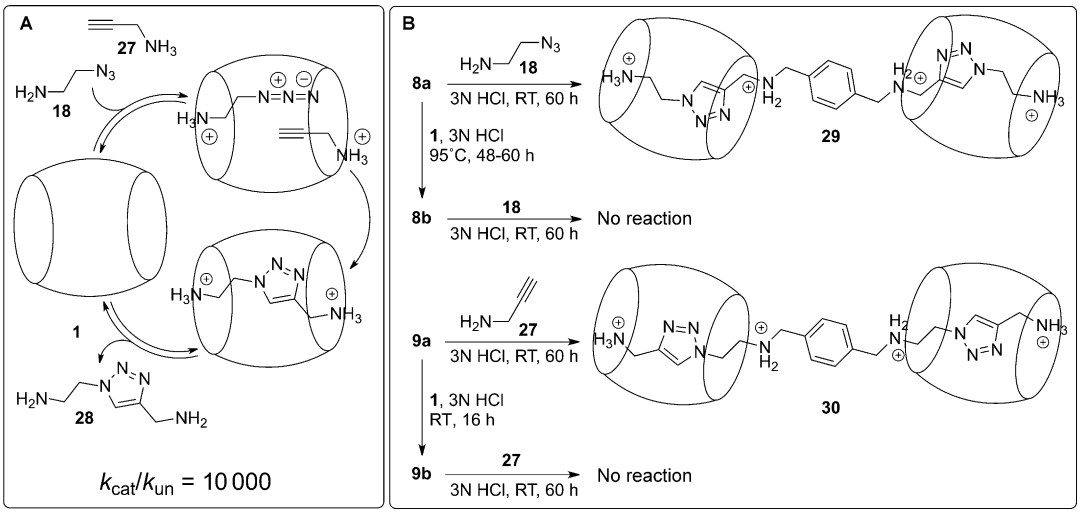


Figure 8. Crystal structures in top view of **4** (top), **8b** (middle), and **9b** (bottom), show the orientation of the guest with respect to the carbonyl oxygen portals of **1**. The red line represents the plane produced by the phenyl backbone of the guest and the blue lines are the planes formed by the opposite pairs of oxygen atoms of **1**. Color code: C, gray; N, blue; O, red. Hydrogen atoms water molecules, and counteranions were omitted for clarity.

The 1,3-dipolar cycloaddition reaction as a chemical probe of the binding mode: The azide–alkyne cycloaddition reaction, known as the click reaction,[12,31] produces a thermally and hydrolytically stable triazole group, which has been extensively utilized for conjugations of various chemical and biological entities.[32] The reaction can be catalyzed by **1** provided that both reactants are equipped with ammonium end groups that render them guest molecules of **1**.[7d,33] For example, the cycloaddition reaction between 2-azidoethylamine (**18**) and propargyl amine (**27**) to produce 2-(4-(aminomethyl)-1*H*-1,2,3-triazol-1-yl)ethanamine (**28**) is accelerated 10000-fold when the reaction is carried out in acidic water with catalytic amounts of **1** (Scheme 8A). The catalytic mechanism is understood in terms of a proximity effect with both reactants being concomitantly encapsulated within the cavity of **1**, thus gaining high effective molarity.[7c] This catalytic reaction is practically irreversible, proceeding in quantitative yield to produce a single regioisomer without side products. The reaction has been utilized for the preparation of pseudorotaxanes,[1b,34] self-threading rotaxanes,[3,35] polypseudorotaxanes, and polyrotaxanes.[36]

We anticipated that the catalytic effect of **1**, which is very sensitive to the relative positioning of the host and guest molecules, could be exploited as a chemical probe for reporting on the binding mode between **1** and the above-mentioned guest molecules. For example, in the reaction between **8** and **18** at room temperature, if **1** binds the side chains of **8** to form **8a**, the host molecule can concomitantly accommodate the acetylenic unit of **8** and the azide portion of **18** and therefore is expected to catalyze their cycloaddition reaction (Scheme 8B, top). In contrast, with the central complexation mode, **8b**, this reaction would be inhibited because in this mode **1** does not only reside away from the



Scheme 8. A) The proposed catalytic cycle of the cycloaddition reaction between 2-azidoethylamine **18** and propargyl amine **27** to form triazole **28**. B) The chemical reactivity of either **8** or **9** in the cycloaddition reaction represents a chemical probe of the complexation mode with **1**, either peripheral (**8a**, **9a**), which is active, or central binding (**8b**, **9b**), which is inactive. Chloride counter anions were omitted for clarity.

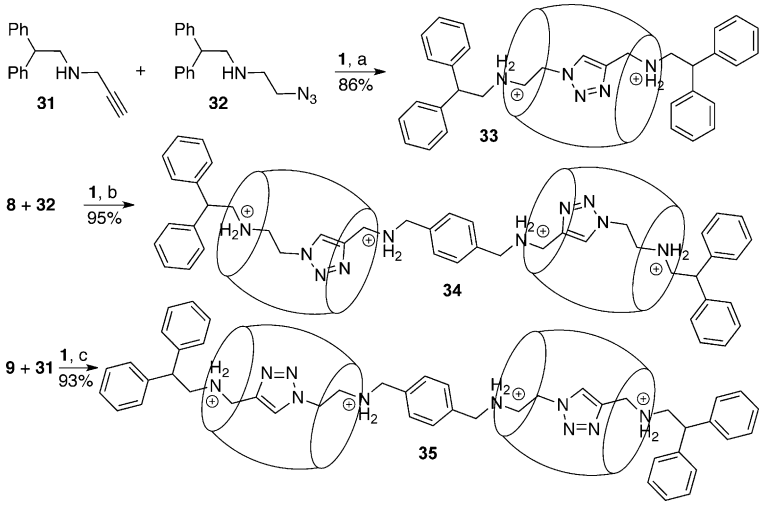
acetylene side chain, but also deters another molecule of **1** from accommodating the acetylenic unit.

Indeed, addition of azide **18** to an acidic solution of **8** and **1** under conditions that usually lead to the exclusive formation of **8a** (3 N aq HCl, room temperature, 48 h) afforded triazole **29** in 90% yield. In contrast, addition of **18** to the same mixture after heating (95 °C, 5 days) and cooling back to room temperature, conditions that usually lead to **8b**, did not result in any observable cycloaddition products (Scheme 8B, top).

Similarly, addition of acetylene **27** to an acidic solution of **9** and **1** at a molar ratio of 2:1:2 in 3 N HCl and stirring the mixture at room temperature for 60 h afforded **30** in 90% yield. The formation of triazole **30** under these circumstances is remarkable because these conditions usually lead to the exclusive formation of **9b**, which is expected to be inactive in the cycloaddition reaction. The formation of **30** in high yields under these conditions indicates that the cycloaddition reaction is faster than the conversion of **9a** to **9b**. To rule out an alternative explanation that **9b** forms first and then interconverts to **9a** under the reaction conditions we carried out a control experiment. Premixing of **9** and **1** for 16 h at room temperature in the absence of **27** (conditions that lead to the quantitative formation of **9b**) followed by the addition of **27**, did not result in any detectable reaction (Scheme 8B, bottom).

The same modes of reactivity were observed in the reaction of acetylene **31** and azide **32** in the presence of **1** at room temperature to produce rotaxane **33** in 86% yield (Scheme 9). As expected, the room temperature reaction between **8** and **32** in the presence of **1** afforded the [3]rotaxane **34** in 90% yield. Consistent with the above-described experiments, no reaction occurred upon addition of **32** to a thermally treated mixture of **8** and **1** (95 °C, 48 h). Similarly, the isomeric [3]rotaxane **35** was obtained at room temperature in 93% yield by mixing **9**, **31**, and **1** in a 1:2:2 ratio. Again, this reaction was completely inhibited when **31** was added to a premixed (16 h at room temperature) solution of **9** and **1**.

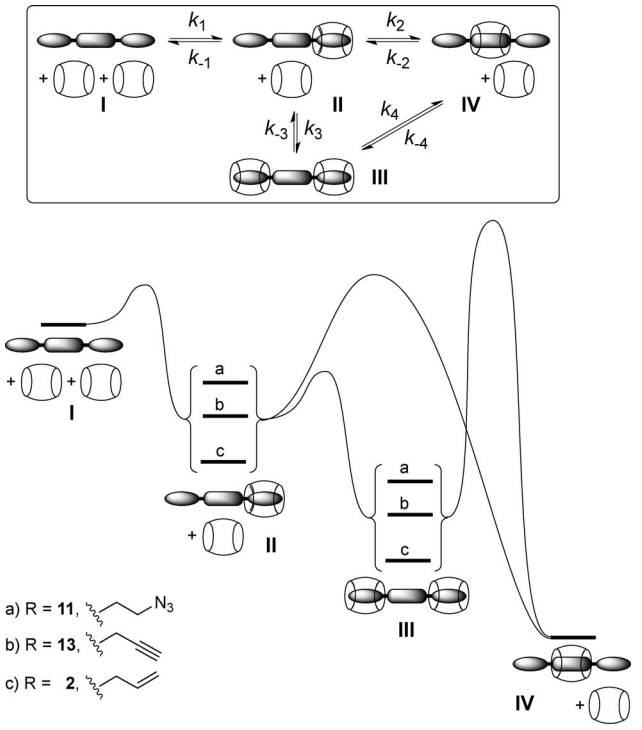
The structures of these new rotaxanes were confirmed by ^{1}H NMR spectroscopy, the spectra of which exhibited a sig-



Scheme 9. Synthesis of rotaxanes **33**–**35**. Reagents and conditions: a) **1** (1 equiv), 3 N HCl, 50 °C, 48 h, b) **8** (2 equiv), **32** (2 equiv), **1** (2 equiv), 6 N HCl, RT, 60 h, c) **9** (2 equiv), **31** (2 equiv), **1** (2 equiv), 6 N HCl, RT, 60 h. Chloride counter anions were omitted for clarity.

nificant upfield shift ($\Delta\delta = -2.3$ ppm) of the encapsulated triazole proton ($\delta = 4.08$ ppm) in comparison with free triazole ($\delta = 6.38$ ppm) in agreement with previously reported complexes.[37] The specific encapsulation of the triazole units in **34** and **35** was evident from the upfield shift of the triazole protons ($\delta = 4.34$ ppm) and downfield shift of the aromatic ring protons ($\delta = 7.90$ rather than $\delta = 7.16$ ppm in the free guest).

Mechanistic considerations: The fact that all of the above-mentioned guests have three binding sites for the host molecule renders their host–guest chemistry a non-trivial sequence of binding events depicted by a postulated equation (Scheme 10, top) and a schematic energy profile (Scheme 10, bottom). The first event involves the formation of a non-symmetrical complex **II** from **I** with the relevant rate constants k_1 and k_{-1} for the forward and backward reactions. Complex **II** can accommodate a second host molecule to form the 1:2 complex **III** with the relevant rate constants k_3 and k_{-3}. Alternatively, **II** can undergo isomerization to the symmetrical, 1:1 complex **IV** involving rate constants k_2 and k_{-2}. The key question of the entire mechanism concerns the transition from **III** to **IV**. One possible route involves a stepwise mechanism: first, release of one host molecule to form complex **II**, and then sliding of the remaining host to its new location to form **IV**. An alternative route involves a concerted mechanism with simultaneous sliding of both hosts, so that the shift of one CB is associated with the expulsion of the other, with the relevant rate constants k_4 and k_{-4}. All steps are quite complex because they involve desolvation and reorganization of hydrogen-bonded water molecules around the ammonium groups of the guest and the carbonyl groups at the portals of **1**.



Scheme 10. A qualitative free energy diagram depicting the various binding modes of **1** with the various guest molecules.

At this point we can only speculate on the physical cause of the kinetic barrier for going from the peripheral to central binding mode. The concerted transition from **III** to **IV** seems to involve higher activation energy in comparison with the stepwise mechanism that goes through **II**. There is no apparent synergism between the two binding events that could award the concerted mechanism with a kinetic advantage over the stepwise process.

Theoretical[38] and experimental[39] studies have revealed that filling the cavity of a host molecule by a molecular chain is relatively fast in comparison with the subsequent movement of the chain through the cavity. This effect has recently been discussed in the context of the threading mechanism of a polymeric chain through a macrocyclic ring. The first event was termed the "entron effect".[40] Thus, in our case the filling of **1** with the side chain of one of our guests is expected to be faster than the subsequent threading, namely, k_1 and k_3 are expected to be larger than k_2 and k_4. The entron effect was recently observed in the threading of a spermine derivative through **1**.[41]

We expected that the interconversion between the peripheral and central binding modes would be pH dependent because the threading of ammonium guest molecules into **1** is known to involve proton dissociation–association steps.[42] A qualitative confirmation of this notion was obtained from monitoring the conversion of **8a** to **8b** under pH 2, 4, and 6 at 100 °C (Figure S5 in the Supporting Information). Although at either pH 4 or 6 the conversion was essentially complete in 12 days, at pH 2 the reaction progressed significantly slower reaching only 45 % in the same period of time. The comparison between pH 4 and 6 was less conclusive due to the poorer solubility of **1** at pH 6.

Conclusion

The dynamic properties of several host–guest complexes of CB[6] with 1,4-bis(alkylaminomethyl)benzene were discovered by temperature-dependent NMR spectroscopy, X-ray crystallography, isothermal titration microcalorimetry, as well as by their reactivity in the azide–alkyne [3+2] cycloaddition reaction (click chemistry). The 2:1 complexes that are formed at room temperature, were found to be kinetic products that may be converted to the thermodynamically more stable 1:1 complexes upon prolonged heating to 95 °C. The latter are very stable rotaxanes despite the fact that they lack bulky end groups.

Multiple binding modes within a given pair of host and guest molecules is a widely known phenomenon in biology, in which the two partners adopt different conformations by induced fit to accommodate two or more binding modes. Biological systems often harness this opportunity for regulatory functions, such as switching between different modes of chemical reactivity.[43] The two binding modes of **1** with vari-

ous guest molecules, which may switch their chemical reactivity, as is the case with the two complexes **8a** and **8b** with respect to the click reaction, demonstrate that this behavior is not limited to biological macromolecules and can occur with small molecules as well. The significance of these observations stems from the importance of the chemistry and physical properties of mechanically interlocked molecules, as design elements of molecular devices for a broad range of applications, such as controlled drug release, molecular rotary motors, and chemical sensors.

Experimental Section

General methods: All reactions were carried out in anhydrous solvents under inert atmosphere. Starting materials such as methyl amine (33% in ethanol), α,α′-diamino- and dibromo-*p*-xylene, 1,6-diamino- and dibromohexane, 2-bromoethylamine hydrobromide salt, allyl and propargyl amine **27**, allyl, propargyl, benzyl, propyl, and butyl bromides were purchased from Aldrich Chemicals. CB[6] **1** was prepared as described previously.[2] Flash chromatography was performed on Merck silica gel 60 (230–400 mesh). ^{1}H and ^{13}C NMR spectra were recorded in the solvents indicated by using either AVIII400 or AV500 Bruker spectrometers. Chemical shifts (δ) are given in ppm relative to TMS. The residual solvent signals were used as references and the chemical shifts were converted to the TMS scale: $CDCl_3$: $\delta_H = 7.26$ ppm, $\delta_C = 77.16$ ppm, D_2O–DCl: (with trace DMSO) $\delta_H = 2.71$ ppm, $\delta_C = 39.4$ ppm. The following abbreviations or combinations thereof were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, qu = quintet, m = multiplet, br = broad. Mass spectra were recorded by using either Waters MALDI microMX (TOF) or Waters LCT Premier microMax spectrometers (TOF-ESI, with MeCN/water, 1:1). ITC measurements were performed at 303 K by using a VP-ITC instrument (MicroCal, USA). Repeat experiments indicated errors of 1–3% in the values of binding stoichiometry (n), enthalpy (ΔH) and entropy (ΔS) of binding, and binding constant (K) over the most favorable concentration range. Each experiment consisted of 20–35 consecutive injections (6–9 μL each) of guest solutions into micro-calorimetric reaction cell (1.4 mL) charged with a solution of **1**. To maximize heat evolution (≥ 2 μcal s^{-1}) in the ITC experiments, **1** was employed at 0.13 mM, which is close to its saturation concentration. All solutions were degassed prior to the titration experiment according to procedures recommended by MicroCal, Inc. Curve fitting was performed using ORIGIN 7.0 software adapted for ITC data analysis. In all cases the single set of identical sites model was applied (Table 1). Crystals of all four complexes, **4**, **8b**, **9b**, and **11a** were obtained by slow diffusion of isopropanol into aqueous solutions of the complexes. The single crystals were mounted on a Nonius KappaCCD diffractometer (**4**, **8b**, **9b**) or APEX2 DUO diffractometer (**11a**) and data was collected using graphite monochromatized $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$) at 293 8 K (**4**, **9b**, **11a**) and 240 K (**8b**). The following program was used for data collection and reduction: Nonius 1997 Collect,[44] HKL DENZO, and Scalepack.[45] The structures were solved by direct methods using the program package maXus[46] and refined in the usual way using SHELXL97.[47] Non-hydrogen atoms were refined anisotropically and hydrogen atoms isotropically.

Kinetic experiments: ^{1}H NMR experiments were recorded on Bruker AVIII600 spectrometer operating at 600 MHz using Bruker 5 mm broad band observe (BBO) Z gradient probe, with ^{2}H lock channel and the sample not spinning. All NMR experiments were carried out in D_2O–DCl (pH 5, 0.1 M) with a trace of DMSO as an internal calibration. NMR dynamic processes were quantitatively determined by variable temperature measurements for a solution containing 1.75 mM of both the guest **8**, and host **1** at a given temperature. For each set of experiments, the temperature was stabilized by Bruker BVT-3000 temperature control unit and the temperature of the probe was calibrated with ethylene glycol. For each slow exchange experiment, the resulting solutions were allowed to equilibrate for at least 30 min before the spectrum was acquired at RT. The ratio between the signals corresponds to the methylene bridge protons of **1** in its 1:2 binding mode and the 1:1 binding mode was measured and plotted over time. The curves followed first-order kinetics and the rate constant was determined by fitting to an exponential growth function with the program Origin8.1. The activation energy parameters were determined by employing the rate constants versus temperature according to the Eyring equation: $\mathrm{Ln}(k/T) = -\Delta H^{\#}/RT + \mathrm{Ln}(k_B/h) + \Delta S^{\#}/RT$, in which R is the universal gas constant (1.986 cal mol^{-1} K^{-1}), k_B is the Bolzmann constant (3.298×10^{-24} cal K^{-1}) and h is the Plank constant (1.584×10^{-34} cal s). k and T are the reaction rate constant (s^{-1}) and temperature (K), respectively. $\Delta G^{\#}$ was calculated by the Gibb's free energy function: $\Delta G^{\#} = \Delta H^{\#} - T\Delta S^{\#}$.

2-Azidoethylamine (18): A mixture of 2-bromoethylamine hydrobromide (3 g, 14.6 mmol), NaN_3 (2.86 g, 44 mmol), and H_2O (15 mL) was heated at 80 °C for 30 h. After being cooled to RT, the mixture was quenched with slow addition of KOH (4.8 g) and washed with Et_2O (20 mL). The aqueous phase was extracted twice with Et_2O and the combined organic phases were washed with brine and dried over $MgSO_4$. After removal of the solvent, column chromatography of the residue (silica gel, hexane/EtOAc, 9:1) afforded **18** as viscous oil (1.1 g, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 3.36$ (t, $J = 5.7$ Hz, 2H), 2.87 (t, $J = 5.7$ Hz, 2H), 1.43 ppm (br s, NH, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 54.6$, 41.3 ppm; MS (MALDI-TOF): m/z: calcd for $C_2H_7ClN_4$: 122.6; found: 87.1 $[M-Cl]^+$.

***N*-Boc-2-azidoaminoethane (19)**: A solution of **18** (0.5 g, 5.8 mmol) and Et_3N (1.2 mL, 8.7 mmol) in THF (20 mL) was stirred for 30 min at RT. $(Boc)_2O$ (1.3 g, 5.9 mmol) was added and the mixture was stirred overnight at RT, then quenched with aq NH_4Cl and extracted with Et_2O. The organic phase was separated and washed with H_2O and brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel, hexane/EtOAc, 9:1) to give **19** as viscous oil (0.94 g, 88% yield). ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 4.8$ (br s, NH), 3.41 (t, $J = 5.5$ Hz, 2H), 3.29 (t, $J = 5.5$ Hz, 2H), 1.45 ppm (s, 9H); MS (MALDI-TOF): m/z: calcd for $C_7H_{14}N_4O_2$: 186; found: 209 $[M+Na^+]$.

***N,N′*-Di-Boc-bis(azidoethyl)-1,6-diaminohexane (21)**: NaH (60% suspended in oil, 360 mg, 9 mmol) was added to a stirred solution of **19** (0.613 g, 3.3 mmol) in DMF (15 mL) at 0 °C, and the mixture was stirred at RT for 1 h. 1,6-Dibromohexane (0.267 g, 1.1 mmol) was added and the mixture was stirred at RT overnight, then quenched with aq NH_4Cl solution, extracted with Et_2O, washed with H_2O, brine, and dried over Na_2SO_4. Removal of the solvent followed by column chromatography (hexane/EtOAc 8:2) afforded **21** as colorless viscous oil (1.15 g, 77%). ^{1}H NMR (500 MHz, $C_2D_2Cl_4$ at 355 K) $\delta = 3.41$ (t, $J = 5.5$ Hz, 2H), 3.38 (t, $J = 5.5$ Hz, 2H), 3.25 (t, $J = 7$ Hz, 2H), 1.57 (m, 2H), 1.51 (s, 9H), 1.33 ppm (m, 2H); ^{13}C NMR (500 MHz, $C_2D_2Cl_4$ at 355 K) $\delta = 155.25$, 79.8, 50.1, 48.2, 46.8, 28.6, 28.5, 26.6 ppm; MS (ESI): m/z: calcd for $C_{20}H_{38}N_8O_4$: 454; found: 455 $[M+H^+]$.

***N, N′*-Di-Boc-di-(azidoethyl)-*p*-xylylenediamine (22)**: The synthesis was performed by using **19** (0.1 g, 0.53 mmol), NaH (60%, suspended in oil, 80 mg, 2 mmol), α,α-dibromo-*p*-xylylene (64 mg, 0.24 mmol), and DMF (5 mL), and by following the above-described procedure for the preparation of **21**, and gave **22** as a white solid (0.176 g, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 7.18$ (s, 4H), 4.48 (s, 4H), 3.40–3.30 (br m, 8H), 1.50 (s, 9H) 1.45 ppm (s, 9H).

***N,N′*-Bis-Boc-1,6-diaminohexane (23)**: The synthesis was performed by using **20** (0.5 g, 5.8 mmol), $(Boc)_2O$ (2.2 g, 10 mmol), Et_3N (2.1 mL, 15 mmol), and THF (20 mL and by following the above-described procedure for the preparation of **19**, and gave **24** as a white solid (1.76 g) quantitatively following column chromatography (silica gel, hexane/EtOAc 7:3). ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 4.52$ (s, 2NH), 3.09 (d, $J = 6.5$ Hz, 4H), 1.46–1.31 ppm (m, 26H).

***N,N′*-Bis-propargyl-*N,N′*-di-boc-1,6-diaminohexane (24a)**: The synthesis was performed by using **23** (1 g, 3.2 mmol), NaH (60%, suspended in oil, 0.76 g, 19 mmol), propargyl bromide (1.5 g, 12.6 mmol), and DMF (15 mL), and by following the above-described procedure for the preparation of **21**, and gave **24a** as a white solid (0.87 g, 70%) following column chromatography (silica gel, hexane/EtOAc 8:2). ^{1}H NMR

(500 MHz, $CDCl_3$) δ 4.04 (brs, 4H), 3.3 (t, $J=7.5$ Hz, 4H), 2.18 (s, 2H), 1.56–1.25 ppm (m, 26H).

***N,N′*-Bis-benzyl-*N,N′*-di-boc-1,6-diaminohexane (24b)**: The synthesis was performed by using **23** (0.275 g, 0.87 mmol), NaH (60%, suspended in oil, 0.28 g, 7 mmol), benzyl bromide (0.45 g, 2.6 mmol), and DMF (10 mL), by following the above-described procedure for the preparation of **21**, and gave **24b** as a white solid (0.26 g, 60%) after column chromatography (silica gel, hexane/EtOAc 8:2). ^{1}H NMR (500 MHz, $CDCl_3$) $\delta=$ 7.35–7.28 (m, 5H), 7.19 (brs, 4H), 4.42 (s, 4H), 4.34 (brs, 4H), 1.51 ppm (s, 18H); MS (ESI): *m/z*: calcd for $C_{30}H_{44}N_2O_4$: 496.7; found: 497.3 [M+H$^+$], 519.3 [M+Na$^+$], 535 [M+K$^+$].

***N,N′*-Di-Boc-*p*-xylylene diamine (25)**: The synthesis was performed by using **3** (2 g, 14.7 mmol), $(Boc)_2O$ (6.4 g, 29.4 mmol), Et_3N (6 mL, 44 mmol), and CH_2Cl_2 (50 mL), and by following the above-described procedure for the preparation of **19** to afford **25** as a white solid (4.45 g, 90%) after column chromatography (silica gel, hexane/EtOAc 7:3). ^{1}H NMR (500 MHz, $CDCl_3$) $\delta=7.24$ (s, 4H), 4.82 (brs, NH), 4.28 (s, 4H), 1.45 ppm (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=155.9$, 138.1, 127.7, 79.5, 44.4, 28.4 ppm. MS (MALDI-TOF): *m/z*: calcd for $C_{18}H_{28}N_2O_4$: 336.4; found: 254 [M+H3O$^+$], 359 [M+Na$^+$], and 375 [M+K$^+$].

General procedure for *N*-alkylation: The synthesis was performed by using **25** (1 g, 3.2 mmol), NaH (60%, suspended in oil, 1 g, 24 mmol), DMF (20 mL), and bromide (propargyl, benzyl, allyl, propyl, and butyl; 12.6 mmol) by following the above-described procedure for the preparation of **21**, and gave **24a–e** respectively after column chromatography (silica gel, hexane/EtOAc 9:1).

***N,N′*-Bis-propargyl-*N,N′*-di-boc-*p*-xylylene diamine (26a)**: Compound **27a** was obtained as a white solid (1.05 g, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) $\delta=7.22$ (s, 4H), 4.53 (s, 4H), 3.96 (brd, $J=6.4$ Hz, 4H), 2.2 (s, 2H), 1.48 ppm (s, 18H); MS (ESI): *m/z*: calcd for $C_{24}H_{32}N_2O_4$: 412; found: 413 [M+H$^+$], 435 [M+Na$^+$].

***N,N′*-Bis-benzyl-*N,N′*-di-boc-*p*-xylylene diamine (26b)**: Compound **26b** was obtained as pale yellow crystals (0.83 g, 50%). ^{1}H NMR (300 MHz, $CDCl_3$) $\delta=7.35$ (m, 10H), 7.19 (brs, 4H), 4.42 (brs, 4H), 4.34 (brs, 4H), 3.13 (brd, 4H), 1.50 ppm (brs, 18H); ^{13}C NMR (100.7 MHz, $CDCl_3$) $\delta=$ 155, 138, 137, 128.5, 127.2, 80, 49, 48.8, 28.5; MS (ESI): *m/z*: calcd for $C_{32}H_{40}N_2O_4$: 516.7; found: 517.3 [M+H$^+$].

***N,N′*-Bis-allyl-*N,N′*-di-boc-*p*-xylylene diamine (26c)**: Compound **26c** was obtained as pale yellow oil (0.87 g, 65%). ^{1}H NMR (500 MHz, $CDCl_3$) $\delta=7.20$ (brs, 4H), 5.76 (brs, 2H), 5.13 (brs, 4H), 4.41 (brs, 4H), 3.8 (d, $J=5$ Hz, 4H), 1.6 ppm (brs, 18H); MS (ESI): *m/z*: calcd for $C_{24}H_{36}N_2O_4$: 416; found: 434 [M+H$_2$O], 439 [M+Na$^+$].

***N,N′*-Bis-propyl-*N,N′*-di-boc-*p*-xylylene diamine (26d)**: Compound **26d** was obtained as colorless oil (0.81 g, 60%). ^{1}H NMR (300 MHz, $CDCl_3$) $\delta=7.16$ (s, 4H), 4.39 (bd, $J=7.2$ Hz, 4H), 3.13 (brd, 4H), 1.43 (brs, 18H), 1.37 (brs, 4H), 0.83 ppm (t, $J=7.5$ Hz, 6H); ^{13}C NMR (100.7 MHz, $CDCl_3$) $\delta=156.2$, 137.5, 127.8, 127.2, 79.5, 49.6, 48.2, 28.5, 21.4, 11.3 ppm; MS (MALDI-TOF): *m/z*: calcd for $C_{24}H_{40}N_2O_4$: 420; found: 443 [M+Na$^+$] and 459 [M+K$^+$].

***N,N′*-Bis-butyl-*N,N′*-di-boc-*p*-xylylene diamine (26e)**: Compound **26e** was obtained as pale yellow oil (0.72 g, 50%). ^{1}H NMR (300 MHz, $CDCl_3$) $\delta=7.16$ (brs, 4H), 4.39 (brs, 4H), 3.13 (brd, 4H), 1.43 (brs, 22H), 1.19 (m, 4H), 0.87 ppm (t, $J=3$ Hz, 6H); ^{13}C NMR (100 MHz, D_2O–DCl) $\delta=132.1$ 130.5, 50.3, 47.0, 27.4, 19.1, 12.7 ppm; MS (MALDI-TOF): *m/z*: calcd for $C_{16}H_{28}N_2$: 248; found: 249 [M+H$^+$].

General procedure for the removal of Boc protecting group: A mixture of each starting material, that is, **21–22, 24a,b**, and **26a–e** (0.5–1.5 mmol) in EtOH (10 mL) and 4 N HCl (4 mL) was stirred overnight at RT. After removal of the solvent the residue was dissolved in hot MeOH and upon standing overnight the resultant precipitate was collected. If precipitation did not occur addition of Et_2O to the hot methanolic solution resulted in precipitation upon cooling and the precipitate was collected.

***N,N′*-Bis-allyl-*p*-xylylene diammonium chloride (2)**: Compound **2** was obtained as an off-white solid (0.37 g, 85%). ^{1}H NMR (500 MHz, D_2O–DCl) $\delta=7.55$ (s, 4H), 5.92 (m, 2H), 5.32 (d, $J=6$ Hz, 2H), 5.5 (s, 2H), 4.27 (s, 4H), 3.71 ppm (d, $J=6.5$ Hz, 4H); ^{13}C NMR (125 MHz, D_2H-DCl) $\delta=132.8$, 131.2, 127.9, 124.7 50.4, 49.8, 39.4 ppm; MS (ESI): *m/z*: calcd for $C_{14}H_{22}Cl_2N_2$: 289; found: 217 [M−Cl$^-$−HCl].

***N,N′*-Bis-propargyl-*p*-xylylene diammonium chloride (8)**: Compound **8** was obtained as an off-white solid (0.36 g, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) $\delta=7.57$ (s, 4H), 4.38 (s, 4H), 3.92 (d, $J=2.5$ Hz, 4H), 3.04 ppm (t, $J=2$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) $\delta=132.5$, 131.4, 79.1, 73.6, 50, 36.4 ppm; MS (ESI): *m/z*: calcd for $C_{14}H_{18}Cl_2N_2$: 285; found: 213 [M−Cl$^-$−HCl].

***N,N′*-Bis-(azidoethyl)-*p*-xylylene diammonium chloride salt (9)**: Compound **9** was obtained as an off-white solid (0.16 g, 88%). ^{1}H NMR (500 MHz, D_2O–DCl) $\delta=5.75$ (s, 4H), 4.32 (s, 4H), 3.77 (t, $J=5.5$ Hz, 4H), 3.28 ppm (t, $J=5.5$ Hz, 4H); ^{13}C NMR (125 MHz, D_2O–DCl) $\delta=$ 132.6, 131.3, 51.2, 47.4, 46.5 ppm; MS (ESI): *m/z*: calcd for $C_{12}H_{20}Cl_2N_8$: 347; found: 275 [M−Cl$^-$−HCl].

***N,N′*-Bis-propyl-*p*-xylylene diamine (10)**: Compound **10** was obtained as an off-white solid (0.37 g, 85%). ^{1}H NMR (300 MHz, D_2O–DCl) $\delta=7.54$ (s, 4H), 4.25 (s, 4H), 3.03 (t, $J=7.6$ Hz, 4H), 1.69 (sextet, $J=7.6$ Hz, 4H), 0.94 ppm (t, $J=7.6$ Hz, 4H); ^{13}C NMR (100 MHz, D_2O–DCl) $\delta=$ 132.9, 131.3, 51.2, 49.6, 19.9, 11.0 ppm; MS (MALDI-TOF): *m/z*: calcd for $C_{16}H_{30}Cl_2N_2$: 321.3; found: 221 [M−HCl−Cl$^-$]$^+$, 162 [M−2HCl−CH$_2$NHBu]$^+$.

***N,N′*-Bis-butyl-*p*-xylylene diamine (11)**: Compound **11** was obtained as an off-white solid (0.4 g, 85%). ^{1}H NMR (300 MHz, D_2O–DCl) $\delta=7.54$ (s, 4H), 4.25 (s, 4H), 3.06 (t, $J=7.8$ Hz, 4H), 1.64 (quintet, $J=7.5$ Hz, 4H), 1.35 (sextet, $J=7.5$ Hz, 4H), 0.89 ppm (t, $J=7.5$ Hz, 6H); ^{13}C NMR (100 MHz, D_2O–DCl) $\delta=132.1$, 130.5, 50.3, 47.0, 27.4, 19.1, 12.7 ppm; MS (MALDI-TOF): *m/z*: calcd for $C_{16}H_{28}N_2$: 248; found: 249 [M+H$^+$].

***N,N′*-Bis-benzyl–*p*-xylylene diammonium chloride (12)**: Compound **12** was obtained as an off-white solid (0.47 g, 85%). ^{1}H NMR (500 MHz, D_2O–DCl) $\delta=7.52$ (s, 4H), 7.49 (m, 10H), 4.30 (s, 4H), 4.28 ppm (s, 4H); ^{13}C NMR (125 MHz, D_2O–DCl) $\delta=132.8$, 131.3, 131.3, 130.5, 130.4, 129.9, 51.4, 50.7 ppm; MS (ESI): *m/z*: calcd for $C_{22}H_{26}Cl_2N_2$: 389.4; found: 316.2 [M−Cl$^-$−HCl].

***N,N′*-Bis-propargyl-hexane-1,6-diammonium chloride salt (13)**: Compound **13** was obtained as an off-white solid (0.12 g, 85%). ^{1}H NMR (500 MHz, D_2O–DCl) $\delta=3.91$ (d, $J=2$ Hz, 4H), 3.14 (t, $J=7.5$ Hz, 4H), 2.97 (t, $J=2.5$ Hz, 4H), 1.70 (brs, 4H), 1.42 ppm (brs, 4H); ^{13}C NMR (125 MHz, D_2O–DCl) $\delta=78.6$, 73.8, 47.2, 36.9, 25.8, 25.7 ppm; MS (ESI): *m/z*: calcd for $C_{12}H_{22}Cl_2N_2$: 265; found: 193 [M−Cl$^-$−HCl].

***N,N′*-Bis-(2-azidoethyl)-1,6-hexane diammonium chloride (14)**: Compound **14** was obtained as an off-white powder (160 mg, 90%).^{1}H NMR (400 MHz, D_2O–DCl) $\delta=3.75$ (t, $J=5.5$ Hz, 4H), 3.22 (t, $J=5.5$ Hz, 4H), 3.06 (t, $J=7.5$ Hz, 4H), 1.71 (brm, 4H), 1.42 ppm (brm, 4H); ^{13}C NMR (125 MHz, D_2O–DCl) $\delta=47.8$, 47.1, 46.5, 25.5, 25.4 ppm; MS (ESI): *m/z*: calcd for $C_{10}H_{24}Cl_2N_8$: 327; found: 255 [M−Cl$^-$−HCl].

***N,N′*-Bis-benzyl-hexane-1,6-diammonium chloride salt (15)**: Compound **15** was obtained as an off-white solid (0.14 g, 52%). ^{1}H NMR (500 MHz, D_2O–DCl) $\delta=7.49$ (brs, 10H), 4.22 (s, 4H), 3.04 (t, $J=7.5$ Hz, 4H), 1.68 (brs, 4H), 1.37 ppm (brs, 4H); ^{13}C NMR (125 MHz, D_2O–DCl) $\delta=$ 131.4, 130.4, 130.3, 129.9, 51.6, 47.5, 2×25.9 ppm; MS (ESI): *m/z*: calcd for $C_{20}H_{30}Cl_2N_2$: 369.4; found: 297 [M−Cl$^-$−HCl].

***p*-Xylylenediammonium hydrochloride (3)**: To a solution of α,α-diamino-*p*-xylylene (0.5 g, 3.6 mmol) in MeOH (2 mL) a few drops of concentrated HCl were added and the resulting white precipitate was washed with Et_2O to give **3** (0.75 g) in quantitative yield. ^{1}H NMR (500 MHz, D_2O–DCl) $\delta=7.35$ (s, 4H), 4.25 (s, 4H) ppm; MS (ESI): *m/z*: calcd for $C_8H_{14}N_2Cl_2$: 209.1; found: 137 [M−HCl−Cl]$^+$.

General procedure for the complex formation of guests with 1

*Synthesis of complexes **4**, **9b**, **13b**, and **14b***: Compound **1** (0.1 mmol) was added to a solution of selected guest (0.05 mmol) in acidic H_2O (25 mL, pH 5–5.5) and stirred at RT for 16 h. The resulting mixture was filtered and the solvent of the filtrate was removed under reduced pressure. The residue from the filtrate was dissolved in H_2O (10 mL), and acetone was added and the resulting precipitate was washed with MeOH and Et_2O to give a 1:1 complex in quantitative yield with respect to the guest. Single crystals of **4** and **9b** were obtained by recrystallization from H_2O with few drops of isopropanol and subjected to X-ray analysis.

Synthesis of complexes ***2a, 8a, 10a–12a****, and* ***15a***: Compound **1** (0.1 mmol) was added to a solution of selected guest (0.05 mmol) in acidic H_2O (25 mL, pH 5.5–6) and stirred at RT for 16 h. The resulting mixture was filtered and acetone was added to the filtrate. The resulting precipitate was collected and washed with MeOH and Et_2O to afford 1:2 complexes in >90% yield. A single crystal of **11a** was obtained by recrystallization from H_2O with few drops of isopropanol and subjected to X-ray analysis.

Synthesis of complexes ***2b, 8b****, and* ***15b***: A solution of selected complex, **2a**, **8a**, and **15a** (0.05 mmol) in acidic H_2O (25 mL, pH 5.5–6) was heated to 100 °C for several days. After being cooled, acetone was added to the filtrate, and the resulting precipitate was collected and washed with MeOH and Et_2O to afford 1:1 complexes in >90% yield. A single crystal of **8b** was obtained by recrystallization from H_2O with few drops of isopropanol and subjected to X-ray analysis.

Compound 2a: ^{1}H NMR (500 MHz, D_2O–DCl) δ=7.69 (s, 4H), 5.75 (d, J=15.5 Hz, 12H), 5.58 (s, 24H), 5.20 (brs, 4H), 4.74 (2H olefin inside DHO), 4.36 (s, 4H), 4.31 (d, J=15.5 Hz, 12H), 3.45 ppm (brs, 4H).

Compound 2b: ^{1}H NMR (500 MHz, D_2O–DCl) δ=6.51 (s, 4H), 6.28 (m, 4H), 5.78 (m, 2H), 5.75 (d, J=15.5 Hz, 12H), 5.51 (s, 24H), 4.36(s, 4H), 4.31 (d, J=15.5 Hz, 12H), 4.04 ppm (d, J=7.0 Hz, 4H).

Compound 4: ^{1}H NMR (500 MHz, D_2O–DCl) δ=6.53 (s, 4H), 5.75 (d, J=15.5 Hz, 12H), 5.51 (s, 24H), 4.35 (s, 4H), 4.32 ppm (d, J=15.5 Hz, 12H); ^{13}C NMR (125 MHz, D_2O–DCl) δ=157, 133.3, 124.6, 70.6, 51.9, 41.6 ppm; MS (ESI): m/z: calcd for $C_{44}H_{50}Cl_2N_{26}O_{12}$: 1206; found: 1133 [$M$−HCl−$Cl^-$].

Compound 8a: ^{1}H NMR (500 MHz, D_2O–DCl) δ=7.77 (s, 4H), 5.73 (d, J=15.5 Hz, 24H), 5.56 (s, 24H), 4.38 (s, 4H), 4.29 (d, J=15.5 Hz, 24H), 3.68 (s, 4H), 2.21 ppm (s, 2H).

Compound 8b: ^{1}H NMR (500 MHz, $CDCl_3$) δ=6.54(s, 4H), 5.73 (d, J=15.5 Hz, 12H), 5.53 (s, 12H), 4.45 (s, 4H), 4.32–4.28 (m, 4H), 3.8 ppm (s, 2H); MS (MALDI-TOF): m/z: calcd for $C_{50}H_{52}D_2Cl_2N_{26}O_{12}$: 1284; found: 1212 [$M$−$Cl^-$−DCl].

Compound 9b: ^{1}H NMR (500 MHz, D_2O-DCl) δ=6.53 (s, 4H), 5.74 (d, J=16 Hz, 12H), 5.53 (s, 12H), 4.4 (s, 4H), 4.29 (d, J=16 Hz, 12H), 4.1 (t, J=5.5 Hz, 4H), 3.56 ppm (t, J=5.5 Hz, 4H).

Compound 10a: ^{1}H NMR (400 MHz, D_2O–DCl) δ=7.91 (brs, 4H), 5.75 (d, J=16 Hz, 12H), 5.59 (s, 12H), 4.50 (brs, 4H), 4.33 (brd, 12H), 2.24 (brs, 4H), 0.73 (brs, 4H), 0.17 (brs, 6H); MS (ESI): m/z: calcd for $C_{86}H_{98}Cl_2N_{50}O_{24}$: 2284.7; found: 1108.8 [M−2Cl^-]$^{+2}$; HRMS (ESI): m/z: calcd for $C_{43}H_{49}N_{25}O_{12}$: 1108.4086; found: 1108.4071.

Compound 11a: ^{1}H NMR (400 MHz, D_2O–DCl) δ=7.91 (s, 4H), 5.75 (2×d, J=9 Hz, 12H), 5.58 (s, 12H), 4.44 (s, 4H), 4.31 (2×d, J=16 Hz, 12H), 2.53 (t, J=7.6 Hz, 4H), 0.67 (m, 4H), 0.55 (sextet, J=7.2 Hz, 4H), 0.23 ppm (t, J=7.2 Hz, 6H); MS (ESI): m/z: calcd for $C_{88}H_{102}Cl_2N_{50}O_{24}$: 2312.8; found: 1121.8 [M−2Cl^-]$^{+2}$; HRMS (ESI): m/z: calcd for $C_{44}H_{51}N_{25}O_{12}$: 1122.4227; found: 1122.4204.

Compound 12a: ^{1}H NMR (500 MHz, D_2O–DCl) δ=7.91 (d, J=8 Hz, 2H), 7.63 (d, J=8 Hz, 2H), 6.75 (m, 2H), 6.57 (t, J=8 Hz, 4H), 6.41 (d, J=8 Hz, 4H), 5.63 (d, J=15 Hz, 12H), 5.4 (s, 12H), 4.36 (d, J=15 Hz, 12H), 4.20–4.14 ppm (s, 8H); MS (ESI): m/z: calcd for $C_{56}H_{66}Cl_2N_{26}O_{12}$: 1366.4; found: 1293.6 [M−Cl^-−HCl].

Compound 13b: ^{1}H NMR (500 MHz, D_2O–DCl) δ=5.75 (d, J=16 Hz, 12H), 5.6 (s, 12H), 4.32 (d, J=15.5 Hz, 12H), 4.08 (d, J=1.5 Hz, 4H), 3.03–2.97 (m, 6H), 0.8 (brs, 4H), 0.46 ppm (brs, 4H); MS (MALDI-TOF): m/z: calcd for $C_{48}H_{58}Cl_2N_{26}O_{12}$: 1262; found: 1190 [$M$−$Cl^-$−HCl].

Compound 14b: ^{1}H NMR (500 MHz, D_2O–DCl) δ=5.77 (d, J=15.5 Hz, 12H), 5.60 (s, 12H), 4.35 (d, J=15.5 Hz, 12H), 3.95 (t, J=5.5 Hz, 4H), 3.39 (t, J=5.5 Hz, 4H), 2.99 (t, J=7.5 Hz, 4H), 0.79–0.75 (m, 4H), 0.53–0.49 ppm (m, 4H); MS (MALDI-TOF): m/z: calcd for $C_{46}H_{60}Cl_2N_{32}O_{12}$: 1324; found: 1251 [$M$−$Cl^-$−HCl].

Compound 15a:^{1}H NMR (500 MHz, D_2O–DCl) δ=6.65–6.42 (m, 10H), 5.72 (m, 12H), 5.45 (s, 12H), 4.29 (s, 4H), 4.22 (m, 12H), 3.35–3.0 (m, 4H), 2.3–2.1 (m, 4H), 1.8–1.55 ppm (m, 4H).

Compound 15b: ^{1}H NMR (500 MHz, D_2O–DCl) δ=7.72 (brs, 4H), 7.51 (s, 6H), 5.72 (d, J=15.5 Hz, 12H), 5.6 (s, 12H), 4.37 (s, 4H), 4.32 (d, J=15 Hz, 12H), 3.04 (t, J=7.5 Hz, 4H), 0.85 (t, J=7.5 Hz, 4H), 0.49 (brs, 4H); MS (ESI): m/z: calcd for $C_{56}H_{66}Cl_2N_{26}O_{12}$: 1366.4; found: 1293.6 [M−Cl^-−HCl].

Preparation of asymmetric guests 16 and 17: The synthesis of *N*-Boc-methylamine, *N*-Boc-allylamine, and *N*-boc-(3,3-diphenyl)propylamine was performed by addition of $(Boc)_2O$ (2 equiv) and Et_3N (3.5 equiv) to a solution of either methyl ammonium chloride (1 g, 14.8 mmol), allyamine (3 g, 0.05 mol), or 3,3-diphenylpropyl amine (1 g, 4.7 mmol) in CH_2Cl_2 (0.3 M amine concentration), and by following the above-described procedure for the preparation of **19**, the *N*-protected products were obtained as white solids (average yield: 90%) following column chromatography (silica gel, hexane/EtOAc 8:2).

***N*-Boc-methylamine**: ^{1}H NMR (400 MHz, $CDCl_3$) δ=4.50 (brs, NH), 2.72 (s, 3H), 1.44 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=156.6, 79.1, 31.2, 28.4 ppm.

***N*-Boc-allylamine**: ^{1}H NMR (400 MHz, $CDCl_3$) δ=5.83 (ddt, J=16.8 Hz, J=10.0 Hz, J=4.8 Hz, 1H), 5.17 (dq, J=16.8 Hz, J=1.6 Hz, 1H), 5.09 (dq, J=10 Hz, J=1.6 Hz, 1H),4.64 (brs, NH), 3.74 (brs, 2H), 1.44 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=155.8, 134.9, 115.7, 79.3, 43.1, 28.4 ppm.

***N*-Boc-(3,3-diphenyl)propylamine**: ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.30–7.17 (m, 10H), 4.50 (brs, NH), 3.97 (t, J=8 Hz, 1H), 3.08 (brq, 2H), 2.26 (q, J=8 Hz, 2H), 1.43 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=153, 128.6, 127.8, 126.3, 78, 48.8, 39.4, 35.7, 28.4 ppm.

A general procedure for non-symmetric *N*-alkylation: The synthesis was performed by using a mixture of either *N*-Boc-methylamine(0.33 g, 2.6 mmol) and *N*-Boc-allylamine (0.4 g, 2.6 mmol), or a mixture of *N*-Boc-(3,3-diphenyl)propylamine (0.4 g, 1.3 mmol) and *N*-Boc-allylamine (0.2 g, 1.3 mmol), NaH (60%, suspended in oil, 6 equiv), DMF (140 mL), and α,α′-dibromo-*p*-xylylene (1 equiv) by following the above-described procedure for the preparation of **21** and gave *N*-allyl, *N*′-methyl- and *N*-allyl, *N*′-(3,3-diphenyl)propyl-*N*,*N*′-di-Boc-*p*-xylylenediamine, respectively, after column chromatography (silica gel, hexane/EtOAc 9:1):

***N*-Allyl, *N*′-methyl-*N*,*N*′-di-Boc-*p*-xylylenediamine**: The compound was isolated as a pale yellow oil from a mixture of all three possible products (0.24 g, 25%). ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.19 (brs, 4H), 5.75 (brs, 1H), 5.12 (brs, 2H), 4.40 (brs, 4H), 3.78 (brs, 2H) 2.81 (s, 3H), 1.43 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=155.8, 137.3, 137, 133.7, 127.5, 116.9, 116.4, 79.6, 52.3, 49, 48.6, 33.9, 28.4 ppm; MS (MALDI-TOF): m/z: calcd for $C_{22}H_{34}N_2O_4$: 390.52; found: 413.16 [M+Na].

***N*-Allyl, *N*′-(3,3-diphenyl)propyl-*N*,*N*′-di-boc-*p*-xylylenediamine**: The compound was isolated from a mixture of all three possible products as a white powder (0.34 g, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.30–7.17 (m, 14H), 5.75 (brs, 1H), 5.12 (brs, 2H), 4.39 (brs, 4H), 3.78 (brs, 2H) 3.08 (brs, 2H), 2.27 (brs, 2H), 1.43 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=155.8, 144.2, 137.2, 133.7, 128.51, 128.47, 127.72, 127.65, 126.2, 125.5, 116.6, 115.9, 79.7, 71.8, 59.0, 48.8, 28.4 ppm.

***N*-Allyl, *N*′-methyl-*p*-xylylenediammonium chloride (16)**: The synthesis was performed by using *N*-allyl, *N*′-methyl–*N*,*N*′-di-boc-*p*-xylylenediamine (0.17 g, 0.44 mmol), EtOH (35 mL), and HCl (14 mL, 4 M) and following the above-described general procedure for the removal of the Boc protecting group. The product was obtained as a white solid (0.11 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (brs, 4H), 5.91 (m, 1H), 5.51 (d, J=4.8 Hz, 1H), 5.48 (brs, 1H), 4.25 (brs, 4H), 3.69 (d, J=6.8 Hz, 2H) 2.22 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=131.1, 130.8, 129.24, 129.22, 126.1, 122.5, 50.5, 48.5, 47.9, 30.9, 28.4 ppm; MS (MALDI-TOF): m/z: calcd for $C_{12}H_{20}N_2Cl_2$: 263.2; found: 191.2 [M−HCl−Cl]$^+$.

***N*-Allyl, *N*′-(3,3-diphenyl)propyl-*p*-xylylenediammonium chloride (17)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.55 (s, 4H),7.48–7.27 (m, 10H), 5.92 (m, 1H), 5.525 (d, J=3.6 Hz, 1H), 5.505 (d, J=10.8 Hz, 1H), 4.27 (s, 2H), 4.25 (2H), 4.09 (dt, J=8 Hz, 2H), 3.68 (m, 2H), 2.93 (m, 2H), 2.46 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=144, 143.7, 132.4, 132.1, 130.8, 129.3, 127.77, 127.75, 127.5, 127.3, 127.2, 124.2, 50.0, 49.9, 49.4, 49.3, 48.2, 38.6, 32.3, 30.9 ppm; MS (ESI): m/z: calcd for $C_{26}H_{32}Cl_2N_2$: 443.5; found: 371.1 [M−Cl^-−HCl]$^+$, HRMS (ESI): m/z: calcd for $C_{26}H_{31}N_2$: 371.2487; found: 371.2448.

Complexes 16b and 17a: Compound **1** (0.01 mmol) was added to a solution of selected guest (0.01 mmol) in acidic H_2O (25 mL, pH 5–5.5) and stirred at RT for 16 h. The resulting mixture was filtered and the solvent of the filtrate was removed under reduced pressure. The residue from the filtrate was dissolved in H_2O (10 mL), and acetone was added and the resulting precipitate was washed with MeOH and Et_2O to give a 1:1 complex in quantitative yield with respect to the guest.

Compound 16b: ^{1}H NMR (400 MHz, D_2O–DCl) $\delta = 6.53$ (br d, $J = 8$ Hz, 4H), 6.28 (m, 1H), 5.73 (m, 2H), 5.71 (d, $J = 13.6$ Hz, 12H), 5.53 (s, 12H), 4.38 (s, 4H), 4.31 (d, $J = 13.6$ Hz, 12H), 4.05 (d, $J = 6.8$ Hz,4H), 3.12 ppm (s, 3H); MS (MALDI-TOF): *m/z*: calcd for $C_{48}H_{56}Cl_2N_{26}O_{12}$: 1258; found: 1223.2 $[M-Cl]^+$, 1187.4 $[M-Cl^- -HCl]^+$; HRMS (ESI): *m/z*: calcd for $C_{48}H_{55}N_{26}O_{12}$: 1187.4493; found: 1187.4496.

Compound 17a: ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.62$ (s, 4H), 7.46–7.27 (m, 10H), 5.71 (m + d, $J = 15.6$ Hz, 1H + 12H), 5.525 (d, $J = 3.6$ Hz, 1H), 5.36 (s, 12H), 5.33 (d, $J = 10.2$ Hz, 1H), 4.31 (s, 2H), 4.29 (s, 2H), 4.27 (d, $J = 3.6$ Hz, 12H), 3.58 (d, $J = 6.4$ Hz, 2H) 2.94 (m, 2H), 2.46 ppm (m, 2H).

Preparation of [3]pseudorotaxanes

N,N′-*(1,4-phenylenebis(methylene))bis(2-(4-(aminomethyl)-1*H*-1,2,3-triazol-1-yl)ethan-amine) (**29**)*: A mixture of **8a** (80 mg, 0.035 mmol) and **18** (9.5 mg, 0.077 mmol) in 3 N HCl (10 mL) was stirred at RT for 60 h, and then the solvent was removed under reduced pressure. The solid residue was dissolved in H_2O (10 mL) and acetone was added. The resultant precipitate was collected by filtration and redissolved in H_2O (10 mL) and MeOH. The resultant precipitate was collected by filtration and found to be pure **29** as a white solid (75 mg, 95%). ^{1}H NMR **(**500 MHz, D_2O–DCl**):** $\delta = 7.97$ (s, 4H), 6.57 (s, 2H), 5.73 (dd, $J = 15.1$ Hz, 24H), 5.51 (s, 24H), 4.56 (s, 4H), 4.34 (s, 4H), 4.28 (dd, $J = 7.5$, 16 Hz, 24H), 4.19 (t, $J = 6$ Hz, 4H), 3.56 ppm (t, $J = 6$ Hz, 4H); MS (ESI^+): *m/z*: calcd for $C_{90}H_{104}Cl_4N_{58}O_{24}$: 2524; found: 1226 $[M-2Cl]^{2+}$; MS (ESI^-): *m/z*: calcd for $C_{90}H_{106}Cl_6N_{58}O_{24}$: 2597; found: 1297 $[M-2H]^{2-}$.

N,N′-*(1,4-phenylenebis(methylene))bis(*N,N-*(2-(aminoethyl)-1*H*-1,2,3-triazol-4,1-diyl) methylamine) (**30**)*: The synthesis was performed by using **9a** (68 mg, 0.029 mmol) and propargyl amine (6 mg, 0.065 mmol) by following the above-described procedure for the preparation of **29** and gave **30** as a white solid (69.5 mg, 95%). ^{1}H NMR (500 MHz, D_2O–DCl): $\delta = 7.86$ (s, 4H), 6.55 (s, 2H), 5.72 (2 × d, $J = 15.5$, 27.5 Hz, 24H), 5.52 (s, 24H), 4.67 (s, 4H), 4,28 (2 × d, $J = 12$ Hz, 24H), 4.21 (t, $J = 6.5$ Hz, 4H), 4.20 (s, 4H), 3.85 ppm (t, $J = 6.5$ Hz, 4H); MS (ESI^+): *m/z*: calcd for $C_{90}H_{104}Cl_4N_{58}O_{24}$: 2524; found: 1226 $[M-2Cl]^{2+}$; MS (ESI^-): *m/z*: calcd for $C_{90}H_{106}Cl_6N_{58}O_{24}$: 2597; found: 1297 $[M-2H]^{2-}$.

Preparation of [*n*]rotaxanes

N-*(Propargyl)-2,2-diphenylethanamonium chloride (**31**)***:** Diphenyl acetaldehyde (0.25 g, 1.3 mmol), propaygyl amine (82 mg, 1.5 mmol), and 3 Å molecular sieves (0.5 5 g) in MeOH (5 mL) were stirred at RT for 1 h, then cooled to 0 °C, $NaBH_4$ (76 mg, 2 mmol) was added portionwise and the reaction mixture was stirred for an additional 1 h at RT. To the mixture water was added and filtered. The solid was washed with Et_2O (5 × 10 mL) and combined with the separated organic layer from the filtrate. The combined organic layers were washed with brine, dried over MgSO4, filtered and concentrated to afford *N*-(propargyl)diphenylethylimine (260 mg, 1.1 mmol) as a pale yellow oil. The crude product was used in the following reaction without further purification. The imine was dissolved in CH_2Cl_2 (10 mL) and then Et_3N (0.3 mL, 1.7 mmol), $(Boc)_2O$ (288 mg, 1.3 mmol), and DMAP (20 mg) were added. The resultant mixture was stirred at RT for 48 h, quenched with aq NH_4Cl and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. *tert*-Butyl-*N*-(propargyl)diphenylethylamine was obtained after column chromatography (silica gel, hexane/EtOAc 9:1) as colorless oil (0.2 g, 55%). ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.3$–7.2 (m, 10H), 4.35 (m, 1H), 3.98 (d, $J = 8$ Hz, 2H), 3.85–3.68 (br s, 2H), 2.2 (br s, 1H), 1.41 ppm (s, 9H). Removal of Boc protecting group was achieved by following the above-described general procedure using *tert*-butyl-*N*-(propargyl)diphenylethylamine, 4 N HCl and EtOH. Compound **31** was obtained in quantitative yield as a white solid. ^{1}H NMR (500 MHz, D_2O–DCl): $\delta = 7.43$–7.35 (m, 10H), 4.45 (t, $J = 8$ Hz, 2H), 3.95 (d, $J = 2$ Hz, 2H), 3.92 (d, $J = 8$ Hz, 2H), 3.00 ppm (br s, 1H); ^{13}C NMR (125 MHz, D_2O–DCl): $\delta = 140.4$, 130.1, 128.6, 128.3, 79.1, 73.5, 51, 48.4, 37.6 ppm; HRMS (ESI-TOF): *m/z*: calcd for $C_{17}H_{18}N$: 236.1434; found: 236.1439 $[M+H]^+$.

N-*(2-azidoethyl)-2,2-diphenylethanamonium chloride (**32**)*: A mixture of diphenyl acetaldehyde (0.5 g, 2.5 mmol), 2-amino-1-azidoethane (**18**; 0.9 g, 10.2 mmol), sodium triacetoxyborohydride (4.3 g, 20.5 mmol), and AcOH (0.1 mL) in 1,2-dichloroethane (10 mL) was stirred at RT for 48 h. Then, a solution of aq NH_4Cl (10 mL) was added and the mixture was extracted with EtOAc. The combined organic layer was washed with brine, dried with Na_2SO_4, filtered, and the solvent was removed to afford *N*-(2-azidoethyl)diphenylethylimine (650 mg, 2.44 mmol) as a colorless oil. The crude product was used in the following reaction without further purification. The imine was dissolved in CH_2Cl_2 (10 mL) and then Et_3N (0.6 mL, 3.66 mmol), $(Boc)_2O$ (640 mg, 2.93 mmol), and DMAP (50 mg) were added. The reaction mixture was stirred at RT for 48 h and then quenched with aq NH_4Cl and extracted with CH_2Cl_2. The organic layer was washed with brine, dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure to afford *tert*-butyl-2-azidoethyl(diphenylethyl)carbamate after column chromatography (silica gel, hexane/EtOAc 9:1) as a colorless oil (0.6 g, 66%). ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.3$–7.21 (m, 10H), 4.28 (t, $J = 8$ Hz, 1H), 3.90 (d, $J = 8$ Hz, 2H), 3.25 (t, $J = 5.5$ Hz, 2H), 3.06 (t, $J = 5.5$ Hz, 2H), 1.44 ppm (s, 9H); MS (ESI): *m/z*: calcd for $C_{21}H_{26}N_4O_2$: 366.5; found: 389 $[M+Na]^+$. Removal of the Boc protecting group was achieved by following the above-described general procedure using *tert*-butyl-2-azidoethyl(diphenylethyl)carbamate, 4 N HCl, and EtOH. Compound **32** was obtained in quantitative yield as a white solid. ^{1}H NMR (500 MHz, D_2O–DCl): $\delta = 7.43$–7.33 (m, 10H), 4.46 (t, $J = 8$ Hz, 1H), 3.86 (d, $J = 8$ Hz, 2H), 3.73 (t, $J = 5.5$ Hz, 2H), 3.27 ppm (t, $J = 5.5$ Hz, 2H); ^{13}C NMR (125 MHz, D_2O–DCl): $\delta = 140.6$, 130.1, 128.6, 128.3, 51.6, 48.3, 47.3, 47 ppm; MS (ESI): *m/z*: calcd for $C_{16}H_{19}ClN_4$: 302; found: 275 $[M-Cl]^+$.

*[2]Rotaxane (**33**)*: A mixture of **31** (13 mg, 0.05 mmol), **32** (15 mg, 0.05 mmol), and **1** (50 mg, 0.05 mmol) in 3 N HCl (10 mL) was stirred at 50 °C for 48 h. Then the water was removed under reduced pressure and the resultant solid was washed with cold MeOH. The solid was dissolved in boiling MeOH and filtered. Et_2O was added to the filtrate and the material was precipitated and collected through filtration. The rotaxane **33**, was obtained as a white solid (53 mg, 67%). ^{1}H NMR (500 MHz, D_2O–DCl): $\delta = 7.62$–7.24 (m, 20H), 6.38 (s, 1H), 5.64–5.54 (2 × d, $J = 15.5$ and 14.5 Hz, 12H), 5.34 (s, 12H), 4.87 (t, $J = 7.5$ Hz, 1H), 4.74 (m, 1H), 4.33 (s, 2H), 4.15 (br t, 12H + 4H), 3.97 (t, $J = 7$ Hz, 2H), 3.64 (t, $J = 7$ Hz, 2H).

*[3]Rotaxane (**34**)*: Compound **1** (35 mg, 0.035 mmol) was added to a mixture of *N,N′*-bis-propargyl-*p*-xylylene diammonium chloride (**8**; 3.6 mg, 1.25 μmol) and *N*-(2-azidoethyl)-2,2-diphenylethanamonium chloride (**32**; 9.5 mg, 0.03 mmol) in 6 N HCl (5 mL) and the reaction mixture was heated at 50 °C for 48 h. The rotaxane precipitated during the reaction and was filtered and washed with 6 N HCl (2 mL), acetone (5 mL), and Et_2O (5 mL) to afford a white solid (3.5 mg, 1.2 μmol). ^{1}H NMR (500 MHz, D_2O–DCl): $\delta = 7.94$ (s, 4H), 7.57 (d, $J = 7.5$ Hz, 8H), 7.43 (t, $J = 7.5$ Hz, 8H), 7.35 (t, $J = 7.5$ Hz, 4H), 6.5 (s, 2H of Tr), 5.66 (dd, $J = 3$, 15.5 Hz, 24H), 5.48 (s, 24H), 4.73 (t, $J = 8$ Hz, 2H), 4.54 (t, $J = 6$ Hz, 4H), 4.36–4.33 (m, 2H), 4.23 (dd, $J = 2$, 15.5 Hz, 24H), 4.18–4.13 (m, 8H), 3.79 ppm (t, $J = 7$ Hz, 4H); MS (ESI): *m/z*: calcd for $C_{118}H_{130}Cl_6N_{58}O_{24}$: 2957; found: 1370 $[M-4HCl-2Cl]^{+2}$.

*[3]Rotaxane (**35**)*: The synthesis of rotaxane **35** was performed by using *N,N′*-bis-(2-azidoethyl)-*p*-xylylene diammonium chloride (**9**; 5.8 mg, 1.6 μmol), *N*-propargyl-2,2-diphenylethanamonium chloride (**31**; 13.6 mg, 0.05 mmol), and **1** (55 mg, 0.05 mmol) by following the above-described procedure for the preparation of [3]rotaxane **34**, and gave [3]rotaxane **35** as a white solid (4.7 mg, 1.6 μmol). ^{1}H NMR (500 MHz, D_2O–DCl): $\delta = 7.87$ (s, 4H), 7.66 (d, $J = 7.5$ Hz, 8H) 7.38 (t, $J = 7.5$ Hz, 8H), 7.25 (t, $J = 7.5$ Hz, 4H), 6.44 (s, 2H of Tr), 5.63 (dd, $J = 15$, 69 Hz, 24H), 5.37 (s, 24), 4.88 (t, $J = 7$ Hz, 2H), 4.64 (s, 4H), 4.35 (s, 4H), 4.24–4.07 (m, 28H), 4.08 (t, $J = 6$ Hz, 4H), 7.74 ppm (t, $J = 6$ Hz, 4H); MS (ESI^-): *m/z*: calcd for $C_{118}H_{130}Cl_6N_{58}O_{24}$: 2957; found: 1477 $[M-H]^-$, (ESI^+): 1406 $[M-2HCl-2Cl^-]^{+2}$, 926 $[M-2HCl-3Cl^-]^{+3}$.

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