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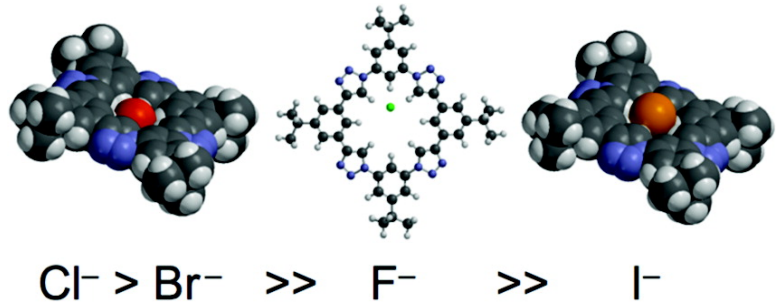

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Strong, Size-Selective, and Electronically Tunable C−H···Halide Binding with Steric Control over Aggregation from Synthetically Modular, Shape-Persistent [3$_4$]Triazolophanes

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Abstract: A series of shape-persistent [3$_4$]triazolophanes bearing *t*-butyl or triethylene glycol (OTg) substituents on the phenylene linkers have been prepared in a modular manner from simple building blocks. Triazolophane−halide binding affinities were determined using UV titrations in order to help in understanding the driving forces behind the large receptor−anion binding strengths supported solely by CH hydrogen-bond donors. The fixed size of the central cavity provides a means for selective recognition of Cl^- and Br^- anions with large binding strengths (K_a > 1 000 000 M^{-1}; ΔG > −8.5 kcal mol^{-1}). The smaller F^- and larger I^- anions are bound less tightly by ∼1 and ∼3 orders of magnitude, respectively. The four triazole-based H-bond donors are believed to be of primary importance, while the four phenylene CH H-bond donors take on a secondary role. Consistent with this idea, the binding affinity can be tuned by as much as 1 kcal mol^{-1} by changing the character of the four phenylene-based substituents from more (OTg) to less (*t*-butyl) electron-donating. Preorganization was also found to play a central role, on the basis of comparisons with a foldamer analogue that shows much-reduced binding. Aggregation was facilitated as the substituents were changed from *t*-butyl to OTg, increasing the degree of self-association from $K_E \approx 0$ to 230 M^{-1} in CD_2Cl_2. Diffusion NMR experiments established aggregation as opposed to dimerization. These findings indicate the importance of the cavity size for selective anion recognition as well as the role of the phenylene linkers in tuning the binding strengths and modulating the aggregation of the [3$_4$]triazolophanes.

Introduction

Effective anion receptors are often constructed from a combination of strong hydrogen-bond donors, positively charged moieties, and Lewis acid metal ions.[1] The associated H-bonding building blocks are classified according to their functional groups; for example, the first recognized anion receptor made use of ammonium groups,[2] and more recently, bioinspired ureas,[3] amides,[4] and guanidiniums[5] as well as synthetically derived polypyrroles[6] have been widely employed. Each of these moieties incorporates strong NH H-bond donors. Far fewer receptors make use of CH H-bond donors,[2e,7] with the exception of the positively charged imidazolium ions.[8] More generally, however, neutral CH H-bonds are less commonly recognized[9] in molecular systems on account of their weakness,[10] even though the CH unit is present in the majority (97%) of chemical

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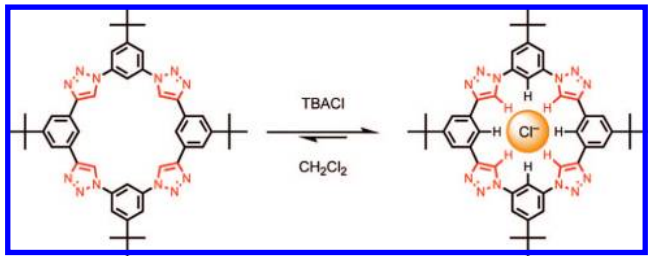
Scheme 1. [3$_4$]Triazolophanes Tightly Encapsulate Cl^- Ions in CH_2Cl_2



compounds.[11] Their relative importance in biological[10] and artificial[1] anion recognition is the topic of ongoing studies, with efforts focusing on experimental[7] and computational[9b,12] evaluation. The investigation of weak noncovalent interactions can be facilitated by studying a closely related series as well as by employing a receptor with an unambiguous structure. Our discovery[13] of the tight binding between a Cl^- anion and a [3$_4$]triazolophane[14] attributable entirely to aromatic CH H-bonds (Scheme 1) presented a means of participating in the reexamination of the hierarchy of H-bond donors. In addition, the shape-persistent[15] character of the macrocyclic structure provided a basis for evaluating how a well-defined cavity[16] can dictate anion-size selectivity.

The triazolophane allows us to investigate the relative importance of two classes of H-bond donors, one involving the CH of the 1,4-disubstitued 1,2,3-triazoles and the other based on the phenylene CH. Although the 1,2,3-triazole has only recently been prepared[17] using Cu-catalyzed 1,3-dipolar cycloadditions,[18] this synthesis has been carried out on a wide scale,[19] leading to functional molecules[20] of increasing complexity. Recent communications making use of a 1,2,3-triazolium cation for phosphate anion recognition,[21] a flexible triazolophane,[14e] and a triazole-based cyclic peptide[22] showing self-assembly as well as the anion-binding properties of foldamers[23] all demonstrate 1,2,3-triazoles participating in noncovalent interactions. In particular, a crystal structure of the triazole-based foldamer[23a] that contains five of the eight rings of the [3$_4$]triazolophane core clearly shows C−H···Cl^- contacts. All of these cases provide cause for examining the triazole subunits more closely when they are employed in artificial anion receptors.

In the first reported example[24,25] where nonaromatic CH units were solely responsible for F^- binding, proximal CF_2 units were believed to aid in polarizing the CH bond of an adjacent methylene group. More recently,[26] polarization of methylene CH H-bonds was found to play a major role in facilitating anion recognition by resorcinarene cavitands. Anion binding has also been observed by taking advantage of non-H-bonding dipoles preorganized into a bowl-shaped receptor.[27] On the basis of these observations, we believe that there are two sources of anion affinity that emerge from the 1,2,3-triazole structure. First, the electronegativities of the three nitrogens combine to polarize the CH bond.[14d,22,23] Second, the lone pairs of electrons on the nitrogen atoms act to establish and orient along the CH bond a

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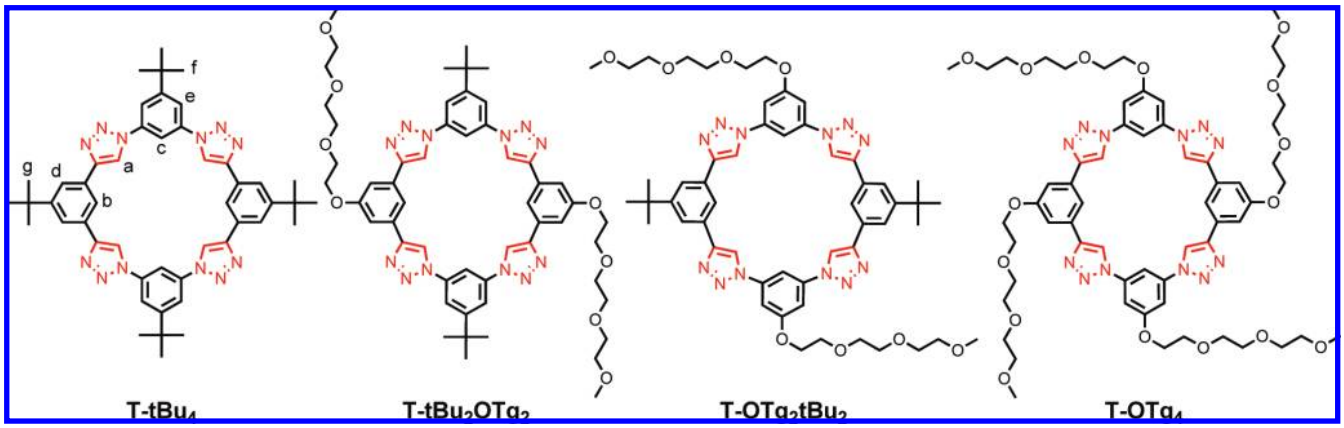
Scheme 2. Structural Formulas of [3$_4$]Triazolophanes Bearing a Variety of Substituents



large (5 D) dipole[28] whose positive end points toward the H atom. These multiple effects contribute to the triazole's unexpectedly strong H-bonding capabilities. This dipolar character is consistent with an increasing number of reports[14e,22] of the H-bond acceptor and Lewis base[29] properties of the triazole nitrogens as well as of the 1,2,3-triazole unit serving as a surrogate for amide bonds.[22,30]

The phenylene groups are believed to be less intrinsically polarized than triazoles, but they are expected to aid in both stabilizing and encapsulating the anion.[12] The H-bond donor properties of phenyl CH have been the topic of a greater number of studies,[12] on the basis of which the binding contributions are believed to be half those of an NH H-bond donor. In addition to their donor abilities, however, they also provide indispensable structural features in triazolophanes. First, they contribute to structural rigidity, reinforcing the preorganization[31] of pairwise interactions between host and guest. Second, they help to define the size of the cavity (internal diameter ~3.8 Å) by virtue of the space they occupy. To investigate the role of size, we employed the series of halides F^-, Cl^-, Br^- and I^-, which have a variety of ionic radii (1.30, 1.81, 1.96, and 2.20 Å, respectively[32]), and made use of molecular models to predict that the halides with the best match to the cavity size will display the strongest binding.

On the basis of the preexisting stepwise synthetic methodology,[13] the most straightforward means of conducting a structure−property investigation was to vary the electronic character of the substituents on the phenylene linkers. This approach allowed us to examine how much the phenyl CH H-bond donors can be used to tune the anion binding and also to establish a baseline for how much the polarized and dipole-stabilized triazole CH group contributes to the anion affinity. Furthermore, the differently sized halides provide a means of determining how effective the two classes of H-bond donors are in accommodating alternative binding modes that are expected with poorly encapsulated anions.

The [3$_4$]triazolophanes belong to the D_{2h} point group. This molecular symmetry defines two different phenylenes and gives rise to two different types of phenyl CH H-bond donors for evaluation in this study. The phenylenes that connect to the 1-positions of the triazoles are called N-linked phenylenes, while C-linked phenylenes connect to the 4-positions. Our convention is to orient the triazolophane structures such that the N-linked phenylenes point along the "north" and "south" directions and the C-linked phenylenes lie along the "west" to "east" axis. The modularity of the synthesis[13] allows us to easily change the substituents and therefore to independently evaluate the impacts of the N- and C-linked phenylenes on halide binding, thereby answering the question of which phenylene binds most strongly to the encapsulated anion. For this purpose, we selected the solubility-enhancing methoxy-terminated triethylene glycol (OTg) chain to use in conjunction with the sterically bulky *t*-butyl substituent as a means of designing a series of four [3$_4$]triazolophanes (Scheme 2) with complementary substitution patterns. Our expectation was that the phenylenes with the *t*-butyl substituents would be less electron-donating than the OTg chains and therefore would enhance the polarization of the CH bonds, resulting in larger anion−receptor binding strengths. In addition, the F^- anion appeared to be small enough (see above) to be situated inside the cavity in one of the four directions. Characterization of F^- binding, therefore, provided a means of probing which of the three H-bond donor groups located around the inner surface of the cavity contributes the most to binding. In addition, the ether link of the OTg substituent has a smaller steric size than *t*-butyl group. This size difference effectively extends the planarity of the triazolophane out to the oxygen atoms. Moreover, the long ethylene glycol chains are known to facilitate self-association through solvophobic interactions.[33] As a consequence, we also considered the propensity for the OTg

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substituents to drive aggregation, which is a common feature of shape-persistent macrocycles.[15]

Herein we present the synthesis and characterization of the four [3$_4$]triazolophanes **T-tBu$_4$**,[13] **T-tBu$_2$OTg$_2$**, **T-OTg$_2$tBu$_2$** and **T-OTg$_4$** (Scheme 2). Aggregation behavior was found to be present at higher solution concentrations, as verified using diffusion NMR and quantified in terms of the isodesmic binding model by performing ^{1}H NMR spectroscopy as a function of dilution. The propensity to aggregate increased with OTg substitution. On account of the strong halide binding, the anion association constants could be quantified using UV spectroscopy and titrations between the triazolophanes and tetrabutylammonium (TBA) halide salts at concentrations low enough to exclude any interference from aggregation. In all cases, the too-small F^- and too-large I^- anions were bound less tightly than the snugly fitting Cl^- and Br^- anions. The electronic effects of the substituents were capable of fine-tuning the anion-binding strengths resulting from phenyl-based C−H···anion interactions by ∼10−20%. This modest effect is considered to be indicative of the primary role that the triazoles play in the receptor−halide binding. The structures of the resulting anion−receptor complexes were examined in solution using ^{1}H NMR spectroscopy at modest concentrations. Analyses of the binding strengths for the various halides across the series of triazolophanes as well as of the ^{1}H NMR spectra of the F^- complexes in solution indicated that the N-linked phenylene CH H-bond donors are more important for anion binding than those of the C-linked phenylenes. In the case of the [3$_4$]triazolophanes, we also demonstrated the importance of preorganization in fortifying these aromatic CH H-bonds by utilizing an oligomeric analogue that folds[23,34] around the halide. Taken together, these findings indicate that a cross section of effects come together in the triazolophanes to bind halides size-selectively and with large strengths.

Results and Discussion

Naming and Nomenclature. We have followed the conventions[35] for naming cyclophanes wherever possible. The four triazoles are the persistent feature of the macrocycle, dictating the use of the term "triazolophane" for this class of compound in order to be consistent with other naming schemes incorporating both 1,2,4-[14a,b] and 1,2,3-triazoles.[14c,d] There are three intervening atoms between each triazole and a total of four phenylene linkers, determining the use of the "3" and the italicized subscript "4", respectively, in the prefix [3$_4$]. The core structure should therefore be named [3$_4$](1,4)-1,2,3-triazolophane, which we have shortened to [3$_4$]triazolophane. Descriptive names have been used for the various intertriazole phenylene linkers.

Computer-Aided Design and Synthesis. Previously we reported on the computer-aided design and convergent synthesis[13] of [3$_4$]triazolophane **T-tBu$_4$**, and here we have extended this approach to the preparation of the compounds **T-tBu$_2$OTg$_2$**, **T-OTg$_2$tBu$_2$**, and **T-OTg$_4$**. The abbreviated names for the compounds containing both *t*-butyl and OTg substituents first give the substituents in the north and south phenylene directions and then those in the west and east directions. Briefly, a 1,3-diiodophenylene served as the primary starting material from which 1,3-diazidophenylene and monoethynylphenylene building blocks were prepared. These two components were reacted together in a 1:2 molar ratio, respectively, using click chemistry conditions, generating a "5/8" oligomer (bearing five of the necessary eight ring systems), which was converted into a diethynyl-based 5/8 premacrocycle. This last oligomer was utilized together with a 1,3-diazidophenylene in the final macrocyclization, which was conducted under pseudo-high-dilution conditions to produce **T-tBu$_4$** in good yield (70%). Molecular modeling of the conformations of a key 7/8-oligomer intermediate expected to be present during the final step (Figure 1) was used to verify that the preorganized rotamer (red arrow, Figure 1b) was sufficiently low in energy to allow the final ring-closing reaction to proceed through a Boltzmann-weighted fraction of the reaction mixture. The barriers to rotation were characterized by molecular modeling (HF/3-21G*) to be low (∼4.5 kcal mol^{-1}). Taken together, these semiquantitative models provided a basic evaluation of the reasonably flat potential energy surface for macrocyclization. For the other three triazolophanes studied in this work, further modeling was unnecessary since both the *t*-butyl and OTg substituents on the phenylene linkers were expected to impart similarly small steric factors. A few variations in the synthetic schemes were investigated in order to evaluate alternative pathways for the different building blocks as well as to demonstrate the modularity of the approach.

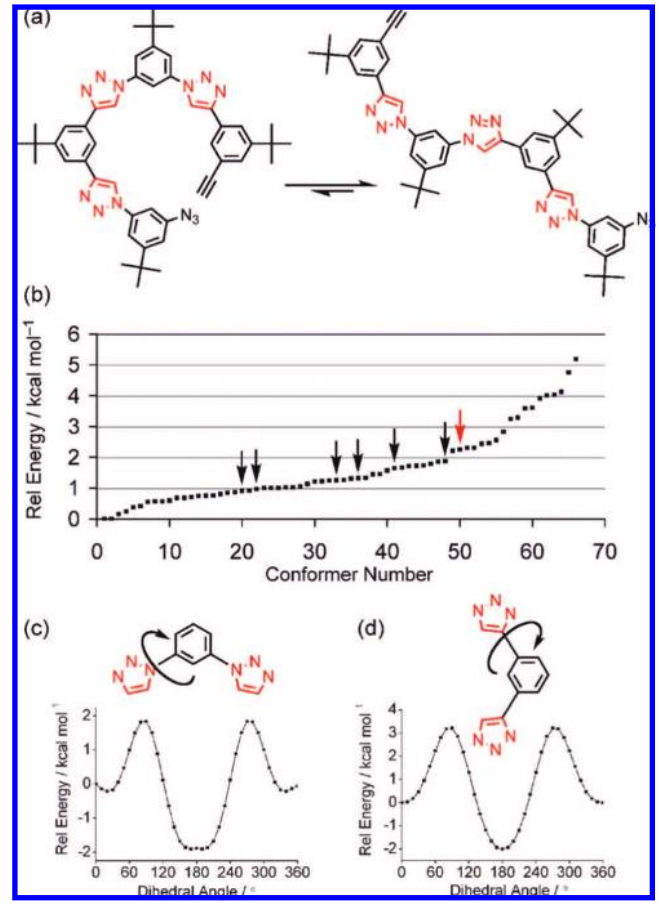

Figure 1. (a) Representation of a hypothetical 7/8-oligomer intermediate expected to exist in a dynamic equilibrium of conformers and (b) a Monte Carlo search (MM2) of its conformer distribution. Arrows indicate conformations that are one bond rotation away from the preorganized conformer (#50, red arrow). Torsion barriers were computed at the HF/3-21G* level for the (c) N-linked and (d) C-linked bis(triazole)benzene model compounds.

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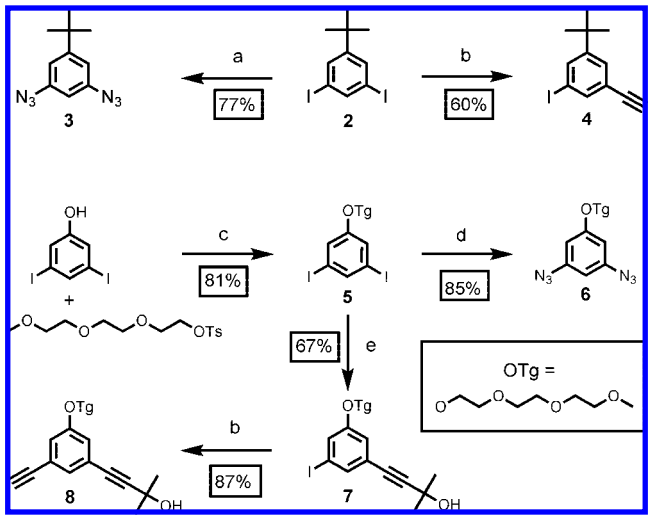
Scheme 3. Synthesis of Monoethynylbenzene **4**, Singly Protected Diethynylbenzene **8**, and Diazides **3** and **6**[a]



[a] a: NaN_3/CuI/*N*,*N*′-dimethylethane-1,2-diamine (DMEA)/sodium ascorbate/7:3:1 EtOH:H_2O:PhMe/reflux/Ar. b: (1) trimethylsilylacetylene/$PdCl_2(PPh_3)_2$/CuI/*i*Pr_2NH/THF/Ar; (2) KF/MeOH/THF. c: K_2CO_3/DMF. d: NaN_3/CuI/DMEA/sodium ascorbate/5:1 DMSO:H_2O/50°C/Ar. e: 2-methyl-3-butyn-2-ol/$PdCl_2(PPh_3)_2$/CuI/*i*Pr_2NH/THF/Ar.

The four building blocks **3**, **4**, **6**, and **8** (Scheme 3) were prepared from the two primary diiodo starting materials **2** and **5**. The 5-*tert*-butyl-substituted 1,3-diiodophenylene **2** was used to prepare the diazido (**3**) and monoethynyl (**4**) building blocks, as previously described.[13] The primary OTg-substituted starting material, 1-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,5-diiodobenzene (**5**), was obtained from the coupling of 3,5-diiodophenol and 2-(2-(2-methoxyethoxy)ethoxy)ethyl-4-methylbenzenesulfonate.[36] Compound **5** was used to obtain the diazide **6** as well as building block **8** as a monoprotected 1,3-diethynylphenylene using sequential Sonogashira reactions. The singly protected diethynylbenzene 4-(3-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-5-ethynylphenyl)-2-methylbut-3-yn-2-ol (**8**) was prepared in 59% yield (three steps) by the successive coupling of **5** with 2-methyl-3-butyn-2-ol and (trimethylsilyl)acetylene followed by desilylation of the diethynylation products using KF in a 1:1 methanol:THF mixture.

All of the [3$_4$]triazolophanes were prepared using the 3,5-diazidobenzene compounds **3** and **6** and the unprotected ethynylbenzenes **4** and **8** as building blocks. Mixing and matching the diazides with the ethynylbenzenes yielded the series of 5/8 oligomers **9a**−**d** via copper-catalyzed cycloadditions. These oligomers were converted into the corresponding diethynyl 5/8 premacrocycles **10a**−**d** either through another Sonogashira reaction followed by deprotection (**10a**, **10c**) or directly by deprotection (**10b**, **10d**). Compounds **10a**−**d** were coupled with diazide **3** or **6** and cyclized using click chemistry under pseudo-high-dilution conditions to generate the corresponding triazolophanes (Scheme 4). Consistent with the reported yield of **T-tBu$_4$** (70%),[13] good yields were obtained for the other three triazolophanes **T-tBu$_2$OTg$_2$** (55%), **T-OTg$_2$tBu$_2$** (60%), and **T-OTg$_4$** (62%).

Structural Characterization of Triazolophanes by Mass Spectrometry and ^{1}H NMR Spectroscopy. All of the triazolophanes were isolated as white solids, but **T-OTg$_2$tBu$_2$** and **T-OTg$_4$** showed slight coloration to a faint red-purple after storage for some time under ambient conditions. MALDI−TOF mass spectrometry of **T-tBu$_4$** showed one peak at *m*/*z* 797.6. High-resolution ESI analysis of triazolophanes **T-tBu$_2$OTg$_2$**, **T-OTg$_2$tBu$_2$**, and **T-OTg$_4$** gave observed (calculated) signals at *m*/*z* 1009.5054 (1009.5048), 1009.5017 (1009.5048), and 1221.5623 (1221.5581), respectively, corresponding to the molecular ions [M + H$^+$] as the major peaks.

The ^{1}H NMR spectra of the triazolophanes in CD_2Cl_2 each displayed five well-separated singlets in the aromatic region (Figure 2). The peaks were assigned with the aid of various 2D NMR spectroscopies in order to distinguish between N- and C-linked phenylene resonances, as exemplified for **T-tBu$_4$**. The single downfield peak at 9.59 ppm corresponds to the four triazole protons (H^a), which reside in identical chemical environments. This peak position is significantly shifted downfield by 1.27 ppm compared to the corresponding peak in the 5/8 oligomeric precursor **10a**.[13] This shift is believed to arise because the triazole protons are located within the greater deshielding environment generated by the ring currents of all four coplanar phenyl rings. The aromatic singlets at 7.93 ppm (H^b) and 7.78 ppm (H^c), each integrating to two protons, were attributed to the inner CH protons of the C-linked and N-linked phenylenes, respectively. The two four-proton singlets resonating at 7.98 ppm (H^e) and 7.87 ppm (H^d) were assigned to the outer protons of the N-linked and C-linked phenylenes, respectively.

The assignments of the proton resonances were verified using 2D NMR experiments. The ^{1}H−^{1}H COSY spectrum of **T-tBu$_4$** in CD_2Cl_2 (Figure S1 in the Supporting Information) showed correlations between the singlet at 7.93 ppm assigned to the inner proton H^b and the peak for the outer proton H^d at 7.87 ppm, tying them into the same phenylene unit. A similar link was observed between the other pair of inner (7.78 ppm, H^c) and outer (7.98 ppm, H^e) proton resonances. Correlations between ^{1}H and ^{13}C peaks were employed to distinguish the N-linked phenylene from the C-linked one. On the basis of a gHMQC experiment in 6:1 CD_2Cl_2:CD_3OD at 298 K (Figure S2 in the Supporting Information), five of the 10 carbon resonances in the 115−125 ppm region were assigned to the corresponding tertiary carbons. The peak at 120.7 ppm was connected to the triazole proton H^a at 9.59 ppm, and the following heteronuclear correlations between (^{1}H, ^{13}C) pairs (ppm) were also found: (7.98, 116.1), (7.93, 122.7), (7.87, 122.0), and (7.78, 107.6). Lastly, a ^{1}H−^{13}C CIGAR map of **T-tBu$_4$** in 6:1 CD_2Cl_2:CD_3OD at 298 K (Figure S3 in the Supporting Information) was recorded in order to identify the connections that occur through multiple bonds, thereby providing a means to make the final assignments. The *t*-butyl protons at 1.63 and 1.58 ppm corresponding to the N- and C-linked phenylene substituents, respectively, showed correlations to the ^{13}C peaks at 155.9 and 152.7 ppm. These assignments left just three remaining unassigned carbon resonances in the aromatic region. A diagnostic connection between the triazole proton H^a at 9.59 ppm and one of the three quaternary carbons at 148.7 ppm was observed in the CIGAR map. This resonance was assigned to the triazole carbon directly bonded with the phenylene ring (C^4) on the basis of its strong correlation with the singlets at 7.93 ppm (H^b) and 7.87 ppm (H^d) previously assigned to the C-linked phenylene. The four- and two-proton singlets at 7.98 and 7.78 ppm (H^e and H^c, respectively) assigned to the N-linked phenylene protons did not show any cross peaks with either of the triazole carbons under these experimental conditions. The remaining assignments of the ^{1}H and ^{13}C

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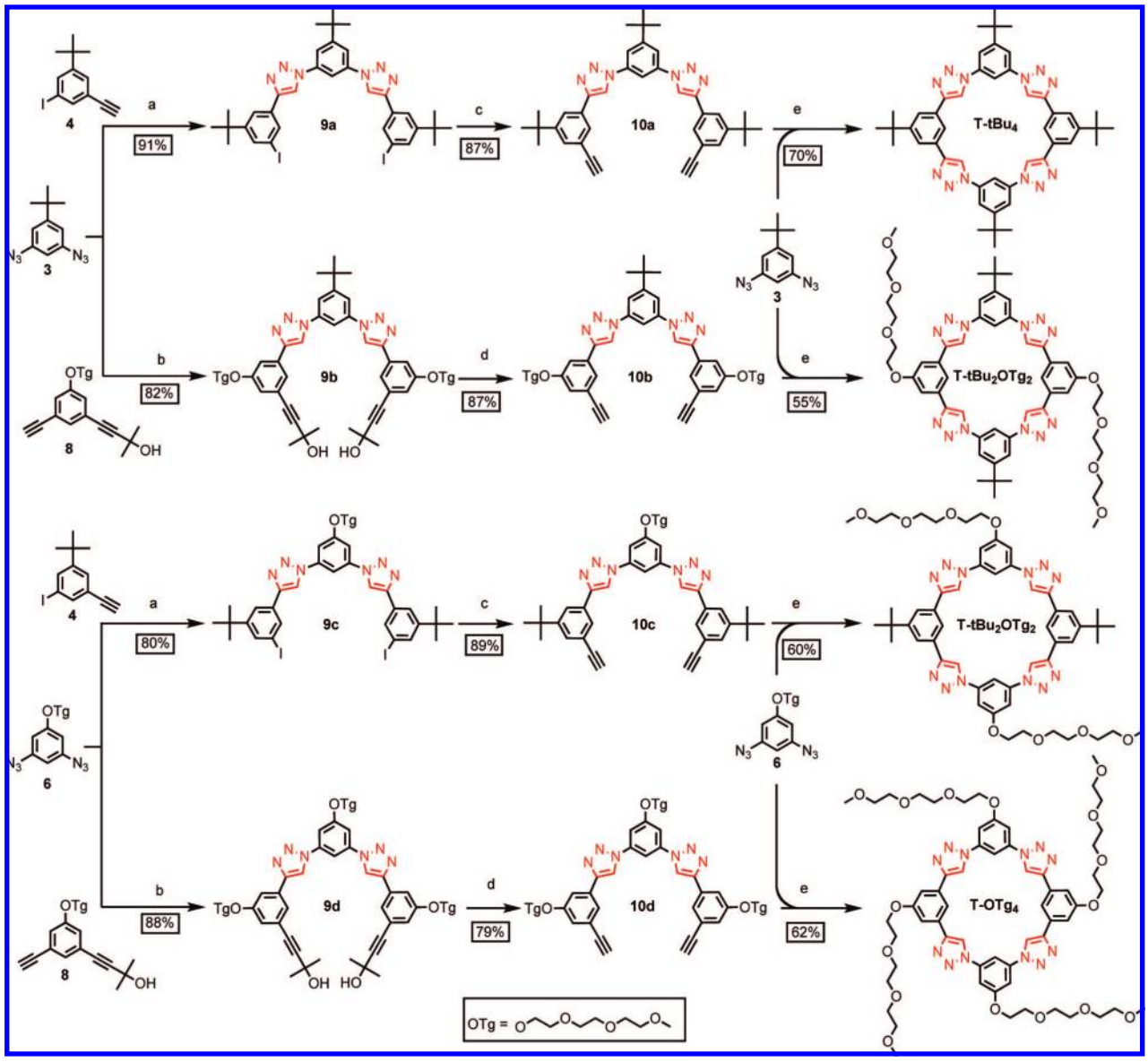
Scheme 4. Synthesis of Diethynyl 5/8 Premacrocycles **9a**−**d** and **10a**−**d** and the Corresponding [3$_4$]Triazolophanes[a]



[a] a: $CuSO_4$/sodium ascorbate/7:3:1 EtOH:H_2O:PhMe. b: CuI/1,8-diaza[5.4.0]bicycloundec-7-ene (DBU)/PhMe/70°C/Ar. c: (1) trimethylsilylacetylene/$PdCl_2(PPh_3)_2$/CuI/iPr_2NH/THF/Ar; (2) KF/MeOH/THF. d: KOH/PhMe/reflux. e: dropwise addition of **10** and either **3** or **6** into CuI/DBU/PhMe/Ar over 10 h followed by stirring for another 4 h.

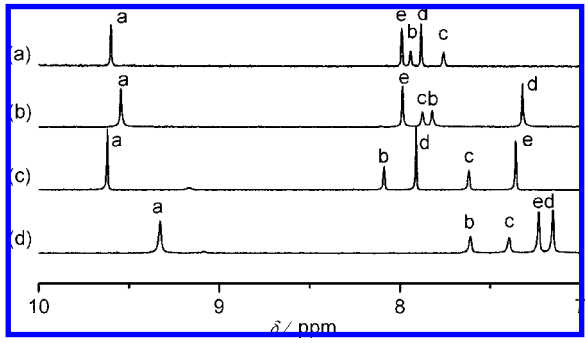


Figure 2. Aromatic region of the ^{1}H NMR spectra (400 MHz, CD_2Cl_2) of (a) **T-tBu$_4$**, (b)**T-tBu$_2$OTg$_2$**, (c) **T-OTg$_2$tBu$_2$**, and (d)**T-OTg$_4$**. All of the spectra were recorded at ∼1 mM.

resonances were made utilizing the CIGAR map and were fortuitously simplified by the fact that the C-linked phenylenes were not strongly coupled with the N-linked ones.

The ^{1}H NMR spectra of the remaining macrocycles were assigned on the basis of the NMR assignments for **T-tBu$_4$**, their 2D COSY spectra (Figures S6−S8 in the Supporting Information), and the substitution patterns of each triazolophane. Principally, the spectrum of **T-tBu$_2$OTg$_2$** showed through-space-coupled inner and outer pairs of singlets that were shifted upfield and thus assigned to the protons at the site of OTg substitution in the C-linked phenylene, while the other pair of singlets were relatively unaffected by this substitution. Conversely, the spectrum of **T-OTg$_2$tBu$_2$** showed that the N-linked phenylene protons were shifted more dramatically upfield compared with those in **T-tBu$_4$**. Consistent with these trends, both sets of resonances were shifted upfield in the spectrum of **T-OTg$_4$** triazolophane.

The NMR data supports the assignment of D_{2h} symmetry, and the 2D NMR (ROESY) spectrum of **T-tBu$_4$** (Figure S4 in the Supporting Information) was found to be consistent with a planar structure. In the case of **T-tBu$_4$**, strong through-space

Table 1. Experimental NMR Diffusion Coefficients (D)[a] of Triazolophanes Recorded as a Function of Concentration (C)

	C (mmol L^{-1})	D (10^{-10} m^2 s^{-1})
T-tBu$_4$	1.0	4.12 ± 0.02
T-tBu$_2$OTg$_2$	1.6	3.16 ± 0.04
	36	2.96 ± 0.01
	72	2.47 ± 0.01
T-OTg$_4$	1.6	2.83 ± 0.02
	34	2.20 ± 0.02
	68	1.95 ± 0.02

[a] Measured in CD_2Cl_2 at 300.3 K.

Table 2. Association Constants (K_E)[a] for Self-Aggregation of the Triazolophanes in Organic Solvents at 298 K As Determined Using ^{1}H NMR Spectroscopy Based on Proton H[d]

	solvent	K_E (M^{-1})	ΔG_E (kcal mol^{-1})
T-tBu$_4$	CD_2Cl_2	−	−
T-tBu$_2$OTg$_2$	CD_2Cl_2	31 ± 4	−2.0
T-OTg$_2$tBu$_2$	CD_2Cl_2	12 ± 2	−1.5
T-OTg$_4$	CD_2Cl_2	230 ± 30	−3.2
	CD_3COCD_3	450 ± 50	−3.6
	CD_3CN	1600 ± 500	−4.4

[a] Determined on the basis of the infinite-association model by the NMR method.

cross peaks were seen between each of the inner protons: triazole proton H^a (9.59 ppm), N-linked phenylene CH proton H^c (7.78 ppm) and C-linked phenylene CH proton H^b (7.93 ppm). Strong cross peaks were also observed between the protons of the *t*-butyl groups and the outer phenylene protons: H^f with H^e from the N-linked phenylenes and H^g with H^d from the C-linked phenylenes. If a nonplanar structure were present to any major extent, other cross peaks would be expected to be evident. For instance, inspection of molecular models that were generated to represent calix[4]pyrrole-like cone structures showed that nonplanarity would have afforded through-space interactions from the triazole protons (H^a) to those on the *t*-butyl groups (H^f and H^g). Moreover, on the basis of molecular modeling, these nonplanar structures were found to be significantly higher in energy (>30 kcal mol^{-1}) than planar ones. Finally, while deviations from complete planarity, such as those evident in the case of porphyrins,[37] cannot be excluded at this stage, these NMR studies strongly support the conclusion that an overall planar structure is present in CD_2Cl_2 solution. These NMR assignments and the planar structures are critical for the interpretation of anion complexation.

Aggregation Investigation using Variable-Concentration ^{1}H NMR Spectroscopy. The presence of aggregation in samples of the triazolophanes in CD_2Cl_2 was evident from the concentration-dependent chemical shifts in the ^{1}H NMR spectra (Figures S9−S12 in the Supporting Information) and verified from diffusion NMR experiments. The largest effect was seen for **T-OTg$_4$**, wherein the triazole H^a proton peak moved upfield from 9.54 to 9.06 ppm and that for the inner H^b protons of the C-linked phenylene rings from 7.36 to 6.88 ppm as the concentration was increased from 0.082 to 71 mM (CD_2Cl_2, 25 °C). The upfield shifts indicate that the aggregates adopt a structure in which the macrocyclic frameworks stack in a face-to-face geometry, as reported frequently in self-association phenomena arising from $\pi-\pi$ stacking interactions.[15,38−40]

In order to distinguish between the monomer−dimer equilibrium and equilibria involving more highly aggregated species[41] in the solution phase, diffusion NMR experiments were performed.[42] The diffusion coefficient D of a spherical molecule in solution can be described by the Stokes−Einstein equation:

$$D = \frac{k_B T}{6\pi\eta r_s}$$

where η is the viscosity and r_s is the molecular dimension.[43] Thus, the average sizes of the aggregated species in solution can be compared on the basis of their diffusion coefficients. If only a monomer−dimer equilibrium exists, the D values for the monomer and dimer species should be nearly identical.[44] On the other hand, for highly aggregated species, which have much larger r_s values than monomers, a change in D values should be observable as a function of concentration. Triazolophane **T-tBu$_4$**, which does not aggregate because of its bulky substituents, has a diffusion coefficient of 4.12×10^{-10} m^2 s^{-1} at 1 mM. As shown in Table 1, for **T-OTg$_4$** and **T-tBu$_2$OTg$_2$**, diffusion coefficients of 2.83×10^{-10} and 3.16×10^{-10} m^2 s^{-1}, respectively, were observed at a concentration of 1.6 mM. The large difference between the D values of **T-OTg$_4$** or **T-tBu$_2$OTg$_2$** and monomeric **T-tBu$_4$** indicates that the hydrodynamic radius of the species present in solution for **T-OTg$_4$** or **T-tBu$_2$OTg$_2$** is much larger than that of the reference compound. These data evidently show formation of extended aggregates in CD_2Cl_2. A gradual decrease in the D value was observed when the concentration of the solution was increased, indicating an increase of the hydrodynamic radius of the aggregates. Triazolophane **T-OTg$_4$** showed a greater decrease in the diffusion constant than **T-tBu$_2$OTg$_2$**, which agrees with the association constants obtained by ^{1}H NMR fitting (see below). These concentration- and structure-dependent properties are consistent with the formation of higher-order aggregates.

The self-association behavior of these triazolophanes is sensitive to the polarity of the solvent, akin to that of phenylacetylene[15b] and other related macrocycles.[38] In more-polar solvents, such as CD_3CN, the chemical shifts of the outer protons on the C-linked phenylenes of **T-OTg$_4$** (Figure 3a) moved upfield from 6.99 to 6.15 ppm as the concentration was increased from 0.17 to 75 mM at 25 °C. More evidently, the seven resonances of the protons in the OTg chain moved upfield, became broadened, and eventually merged together. The association constants (K_E) for the formation of higher-order aggregate species[45] (Table 2) were obtained by analyzing the concentration-dependent ^{1}H NMR data (Figure 3b). The aggregation was quantified using the outer protons from the C-linked phenylenes (H^d). Only **T-tBu$_4$** showed a negligible propensity to aggregate in CD_2Cl_2; the other triazolophanes showed increasing aggregation strengths as the number of OTg

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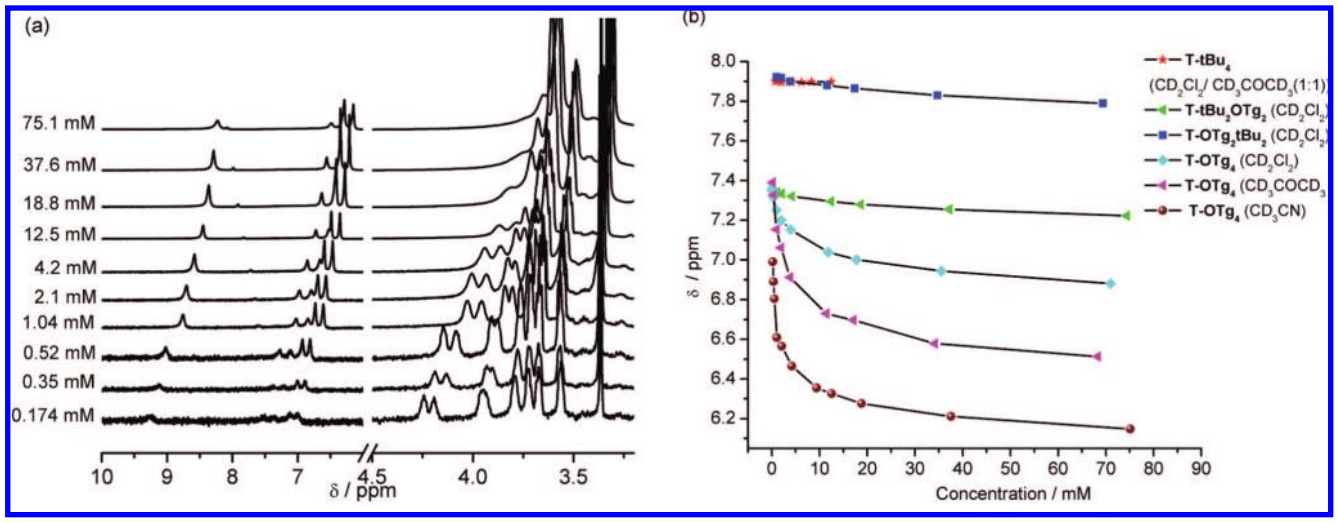

Figure 3. (a) Selected region of the ^{1}H NMR spectra (400 MHz) of **T-OTg$_4$** in CD_3CN at 25 °C, in which the peaks show concentration-dependent chemical shifts. (b) Concentration dependence of ^{1}H NMR chemical shifts for the outer protons H^d of **T-tBu$_4$**, **T-tBu$_2$OTg$_2$**, **T-OTg$_2$tBu$_2$**, and **T-OTg$_4$** in CD_2Cl_2 and of **T-OTg$_4$** in CD_3COCD_3 and CD_3CN at 25 °C.

substitutions increased. On the basis of the free energy changes, the self-association affinity almost doubled with each addition of a pair of OTg chains, reaching $\Delta G_E = -3.2$ kcal mol^{-1} ($K_E = 230 \pm 30$ M^{-1}) for **T-OTg$_4$**. We attribute the aggregation to an increase in the $\pi-\pi$ interactions between macrocyclic faces that is facilitated by the reduction of steric bulk, leading to the proposed stacking arrangement. Additionally, increased numbers of OTg chains on adjacent stacked pairs of triazolophanes are expected to enhance stacking.[33] The extent of aggregation of **T-OTg$_4$** was seen to increase in more polar solvents, consistent with a solvophobic triazolophane-based core.

Halide-Binding Investigations. The spherical F^-, Cl^-, Br^-, and I^- anions were tested for binding to the triazolophanes using UV titrations, and the structures of the anion complexes were characterized with the aid of changes in the chemical shifts in the ^{1}H NMR spectra. To take advantage of their good solubilities in organic solvents and to minimize possible effects of ion-pair formation,[1] TBA salts were used in the titration experiments. Ab initio modeling (HF/3-21G*) of the host−guest complexes formed between **T-tBu$_4$** and the halides (Figure 4) revealed three different binding modes. Both the Cl^- and Br^- ions lie coplanar with the triazolophane structure; however, the F^- ion is small enough to sit in one corner of the central cavity, and the I^- anion is too large to penetrate inside the cavity. On the basis of these models, we expected size-selective binding between the halides and the triazolophane's central cavity to be displayed.

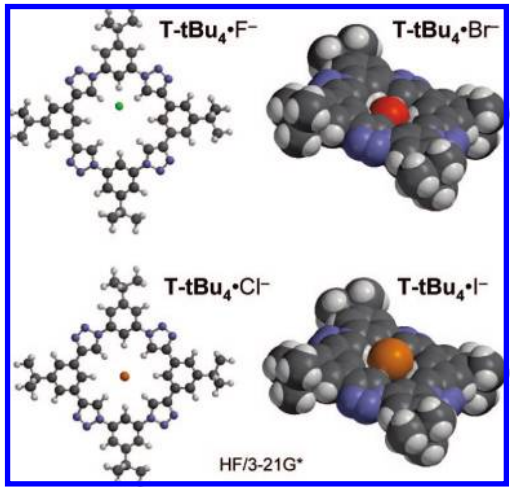

Figure 4. Models (HF/3-21G*) of the structures for halide complexation with **T-tBu$_4$**.

Accurate values of the association constants (K_a) were determined using standard UV-titration methods at concentrations below 10 μM. The binding isotherms were generated by recording the modest changes in the UV absorption as a function of halide concentration (shown for **T-tBu$_2$OTg$_2$** in Figure 5a). On the basis of the confirmation (via Job's plot) of 1:1 binding stoichiometry determined previously[13] for the **T-tBu$_4$**•Cl^- complex in solution, the data were fitted to a 1:1 binding isotherm (Figure 5b), providing the calculated K_a values (Table 3). The binding constants are the results of duplicate determinations that were conducted at sufficiently low concentrations to ensure that the degree of binding was less than 80% at 1:1 molar ratios of host and guest.[46]

An extremely strong binding affinity ($K_a = 1.1 \times 10^7$ M^{-1}) was observed for Cl^- with **T-tBu$_4$**,[47] while the affinity of Br^- for the same receptor ($K_a = 7.5 \times 10^6$ M^{-1}) placed a close second. In line with the molecular modeling results, the too-small F^- and too-large I^- anions ($K_a = 2.8 \times 10^5$ and 1.7×10^4 M^{-1}, respectively) did not bind as tightly as the ideally sized Cl^- and Br^- anions. As predicted, sequential replacement of *t*-butyl by the more strongly electron-donating OTg group reduced the binding affinity across the series of triazolophanes. On the basis of the substitution patterns, it was observed that substitution of OTg onto the N-linked phenylenes as opposed to the C-linked ones had a larger effect in weakening the binding affinities toward all of the halides.

The ^{1}H NMR spectra of the halide titrations are consistent with the picture generated from the binding affinities. All of the ^{1}H NMR titrations were conducted at ~1 mM in order to help suppress the effect of aggregation on chemical-shift positions while maintaining good signal intensity. Titrations with

(46) Hirose, K. In *Analytical Methods in Supramolecular Chemistry*; Schalley, C. A., Ed.; Wiley-VCH: Weinheim, Germany, 2007.
(47) This value is more accurate than the one reported previously in ref 13.

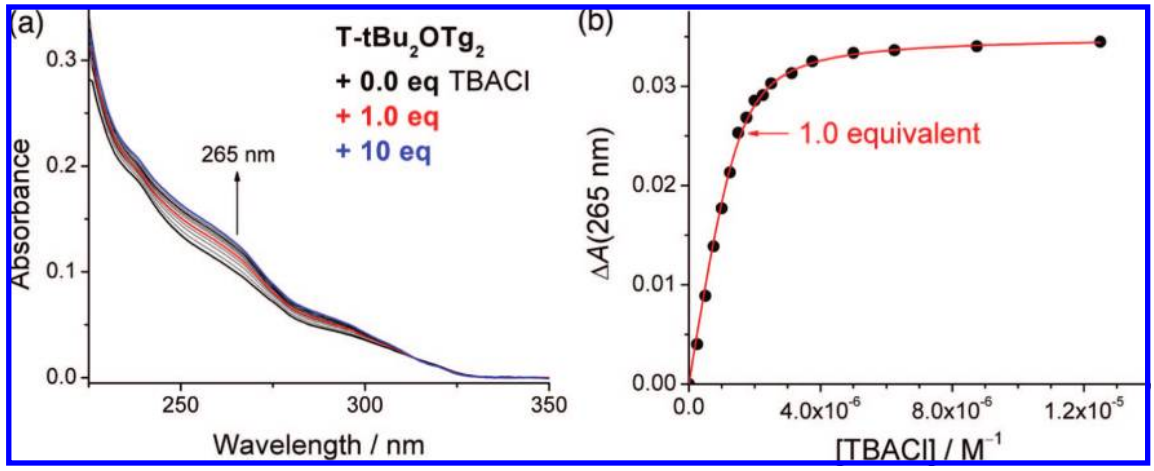

Figure 5. (a) Representative UV changes upon titration of triazolophane **T-tBu$_2$OTg$_2$** (1.5 μM, CH_2Cl_2) with TBACl and (b) the fit of the absorption changes at 265 nm to a 1:1 isotherm.

Table 3. Association Constants (K_a) for Halide Binding with the Triazolophanes (Determined Using UV Spectroscopy) and with Oligomer **11** (Determined Using ^{1}H NMR Spectroscopy) in CH_2Cl_2 at Room Temperature

	K_a(UV) (M^{-1})[a]				K_a(NMR) (M^{-1})[b]
halide	**T-tBu$_4$**	**T-tBu$_2$OTg$_2$**	**T-OTg$_2$tBu$_2$**	**T-OTg$_4$**	**11**
F^-	280 000 ± 30 0000	230 000 ± 20 000	150 000 ± 5000	200 000 ± 20 000	42 ± 4
Cl^-	11 000 000 ± 2 000 000	5 100 000 ± 400 000	3 700 000 ± 700 000	2 900 000 ± 300 000	6.9 ± 0.3
Br^-	7 500 000 ± 900 000	4 200 000 ± 300 000	1 900 000 ± 200 000	1 700 000 ± 200 000	268 ± 6
I^-	17 000 ± 1000	19 000 ± 2000	5000 ± 200	4000 ± 400	210 ± 10

[a] Errors were obtained from the fits to the isotherms. [b] Obtained from ^{1}H NMR titrations of **11** with TBA halide salts in CD_2Cl_2 and based on the shift of triazole proton H^a. Errors were obtained from the fits to the isotherms.

T-OTg$_2$tBu$_2$ (Figure 6) are representative of the features observed for all of the triazolophanes. The F^- anion was seen to engage almost exclusively with the N-linked phenylenes (H^c) and the triazoles (H^a) and seemed to ignore the C-linked phenylenes (H^b). This positional selectivity persisted even in the case of **T-OTg$_2$tBu$_2$**, where the F^- anion could have become bound with the C-linked phenylene bearing the less-electron-donating *t*-butyl groups, which were found to strengthen overall anion binding. For this small halide, the triazole and inner N-linked phenylene resonances retained their singlet splitting patterns, and both were observed to shift during the titration, indicating that the F^- oscillates between the north and south poles within the cavity faster than the ^{1}H NMR time scale at 298 K. These observations are in agreement with the picture generated by modeling (Figure 4), which shows that the F^- ion is always engaged with two triazole units and just one phenylene. This picture is consistent with the primary role that the triazoles serve in binding the F^- anion.

In the case of the Cl^- and Br^- anions, all of the proton resonances were shifted upfield by greater (~1 ppm) and lesser (~0.5 ppm) amounts for the inner and outer protons, respectively. These peak shifts and the concerted impact of substitution on K_a (Table 2) are consistent with halide encapsulation inside the triazolophane cavity (Figure 4). The chemical shifts upon complexation of Br^- were all greater by ~20% than those for Cl^-, even though the association constant is less than that for Cl^-. This difference is attributed to the larger size of the halide, which exerts a steric pressure on the CH hydrogens, rather than to larger binding strength. In addition, the peaks were observed to broaden during the addition of 0.2−1.0 equiv of Cl^- and Br^-, indicating that the kinetics of complexation are on the same time scale as the ^{1}H NMR experiment, consistent with strong anion binding.[48]

In the case of I^-, the chemical shifts indicated a different mode of binding than for the other two sets of halides. Contrary to the encapsulation behavior observed for both Cl^- and Br^-, the triazole protons were shifted to a greater extent than the phenylene protons, and the N- and C-linked phenylene protons were all shifted by the same amount. Taken together, these features suggest that the I^- anion is symmetrically docked with the triazolophanes, that the triazoles are mostly responsible for binding I^-, and that the phenylene protons contribute to enhancing the complexation efficiency in a manner similar to that for Cl^- and Br^-.

The different association strengths can be rationalized from the three binding modes. The strengths of ion−dipole interactions are governed by the following relationship:

$$E = \frac{q_1 \mu_2 \cos\theta}{4\pi\varepsilon_0 \varepsilon r^2}$$

where q_1 is the charge on the anion, μ_2 is the dipole moment, θ is the angle specifying the relative orientation of the anion to the dipole, r is the distance between the centers of the anion and the dipole, and ε is the dielectric constant. In an analysis of the binding modes, the dipoles from all sources are valid for interpretation. In the context of this relationship and the measured binding affinities, the magnitudes of these interactions are consistent with encapsulation for Cl^- and Br^- ions. For these two halides, optimal close contacts (small r) and orientations ($\theta \approx 180°$) can be achieved with both types of phenylene

(48) Piatek, P.; Lynch, V. M.; Sessler, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 16073–16076.

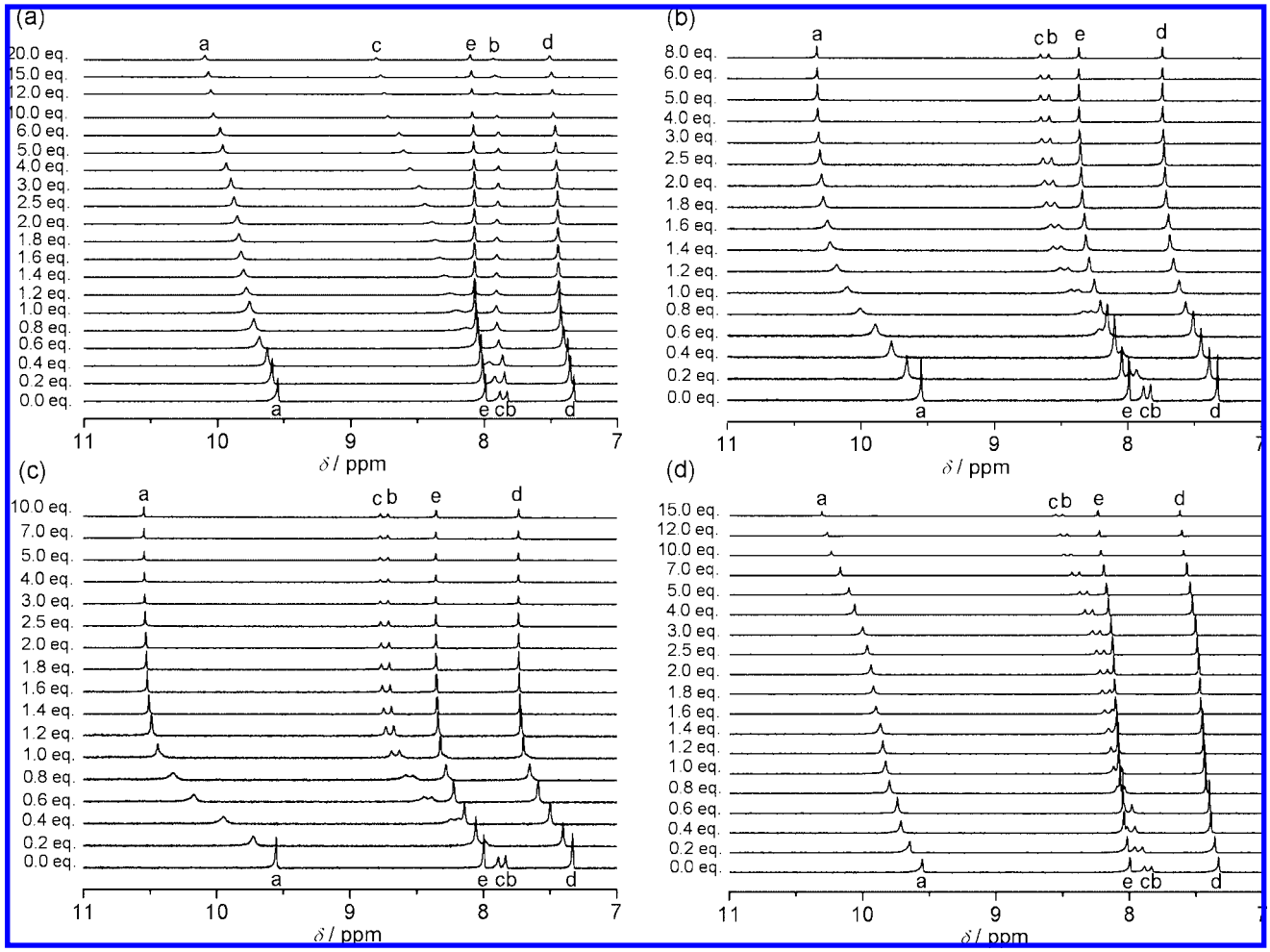

Figure 6. ^{1}H NMR spectra (aromatic region) of **T-tBu$_2$OTg$_2$** in CD_2Cl_2 at 298 K upon titrational addition of (a) TBAF, (b) TBACl, (c) TBABr, and (d) TBAI (H^a, triazole; H^b, C-linked phenylene; H^c, N-linked phenylene).

H-bond donors and the triazole-based dipoles. It is possible that the slightly larger size of the Br^- anion (ionic radii: 1.96 Å for Br^- and 1.80 Å for Cl^-) accounts for the modest differences in binding free energy ($\leq$0.4 kcal mol^{-1}) indicated by the K_a values in Table 3. For the two poorly fitting halides, F^- appears to have an advantage over I^- by being partially encapsulated (Figure 4). The smaller F^- anion can (i) engage with two triazole and one N-linked phenylene H-bond donor with close contacts (it has the smallest possible r of any halide, given its ionic radius of 1.30 Å) and at ideal geometries ($\theta \approx 180°$) and (ii) interact with the five other H-bond donors with less-ideal geometries. In contrast, while I^- can form close van der Waals contacts with all eight H-bond donors, it is forced to do so over longer distances (I^- ionic radius = 2.20 Å) and at nonideal geometries ($\theta \neq 180°$).

Convergent and Preorganized Hydrogen Bonding: Control Experiments. An acyclic analogue of **T-tBu$_4$** was synthesized and tested for anion binding in order to study the importance of binding-site preorganization. Oligomer **11** (Figure 7), prepared from **10a** and azidobenzene (see the Supporting Information), has four triazole units, three *t*-butyl-substituted phenylene groups, and two terminal phenyl rings. This oligomer can be considered as a ring-opened foldamer[23] form of macrocycle **T-tBu$_4$** having the same types and almost the same number of H-bond donors. Even though the molecule produced a more complex ^{1}H NMR spectrum because of its lower symmetry, the proton signals could be assigned using the same 2D NMR techniques employed for the assignment of the triazolophane spectra. Each proton was then assigned specifically utilizing the through-space cross peaks seen with the aid of 2D NOESY experiments.

NMR titration experiments involving **11** and the halides (shown for TBABr in Figure 7) were performed under the same conditions used for the triazolophanes. The chemical shifts were sensitive to the size and shape of the anion. In the case of Cl^-, Br^-, and I^-, the chemical-shift patterns of the protons expected to engage in H bonding were shifted downfield by the largest amounts. The central triazole protons H^a were shifted the most, although not to the extent shown by any of the triazolophanes. Interestingly, both the central N-linked phenylene proton (H^c) and the spacer C-linked phenylene protons (H^e) were shifted into the same peak position. For the **11**$\cdot F^-$ complex, the halide binding appears to engage with the three rings in the core. This interpretation is based upon the greater downfield shift of the "inner" proton H^c on the central phenylene than of the "inner" protons H^e on the spacer phenylenes. This selective binding is consistent with the picture generated for binding of F^- to the triazolophanes. For all of the halide complexes, the protons H^h and H^i on the phenyl endgroups were shifted upfield. These facts indicate that the acyclic molecule **11** binds halides in a manner similar to that of the triazolophanes and that the final complex results in a folded structure consistent with that found

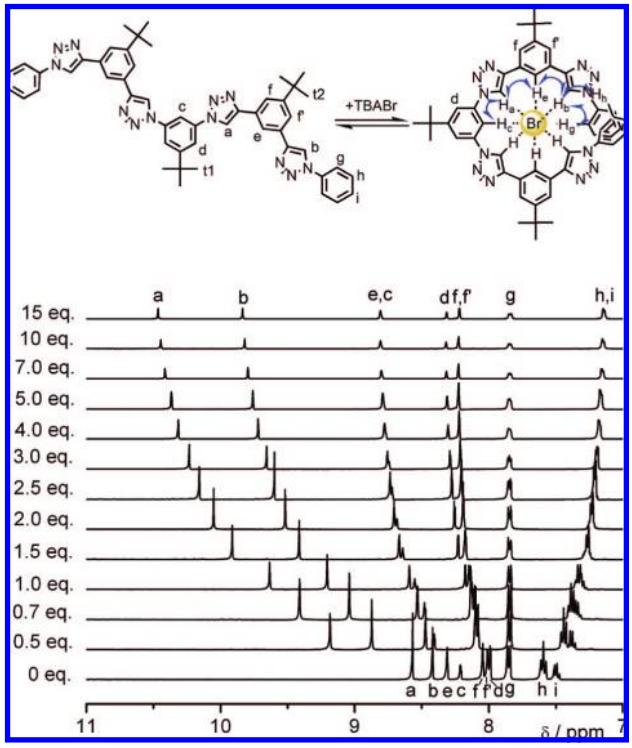

Figure 7. ^{1}H NMR spectra (aromatic region) of **11** in CD_2Cl_2 at 298 K upon titrational addition of TBABr .

in studies[23] conducted on a similar oligomeric structure bearing ester-linked tetraethylene glycol substituents on the central and terminal phenyl units.

We therefore concur[23] that the halides form primary hydrogen bonds with the triazole protons, facilitating the formation of the weaker hydrogen bonds with inner phenylene protons H^c and H^e and ultimately driving a folded structure upon halide binding. The small F^- anion binds with only part of the molecule, while for Cl^- and particularly for the larger Br^- and I^- anions, the oligomer **11** can wrap around the anion reasonably well. Consequently, the induced hydrogen bonds of the phenylene units (H^c/H^e···anion), which prefer to shift downfield and merge together, suggest that they are in very similar chemical environments upon anion complexation. The upfield shifts of the H^h and H^i protons can be ascribed to the $\pi-\pi$ stacking interaction between the two terminal phenyl rings that takes place as **11** wraps around the anion. As a result of this conformational change, the triazole protons (H^a and H^b) and the protons para to the *t*-butyl groups are projected inward, with the two terminal phenyl rings overlapping to generate a folded structure that resembles the conformation of the triazolophanes.

The binding constants of **11** with these halides (Table 3) were obtained from an analysis of the ^{1}H NMR titration data using a 1:1 binding model (see the Supporting Information). This acyclic reference compound showed much weaker binding to all of the anions tested than did the triazolophanes. The weaker affinities for **11** confirm that the rigid display of functional groups in the preorganized triazolophane receptors makes a significant contribution to the binding energy. Compared to that for the macrocyclic forms, however, the size selectivity in **11** shifted in favor of the larger Br^- and I^- halides over Cl^-. Consequently, where the macrocyclic structure enforces close H···anion contacts, the helical oligomer **11** likely folds up to define a slightly expanded cavity. The related work by Craig and co-workers[23a] revealed that larger binding strengths [$K_a(Cl^-) = 1.7 \times 10^4$ M^{-1}] are obtained with the ester-substituted phenylenes. The ester functionality is likely to exert a stronger polarizing effect on the CH H-bonds by virtue of its electron-withdrawing character. Moreover, given the propensity for the OTg groups to facilitate aggregation in the triazolophanes, the ester-linked tetraethylene glycol chains might favor a folded structure, particularly in the more-polar solvent in which the K_a values were determined (CD_3COCD_3). On the basis of the much-reduced binding affinities for the *t*-butyl-substituted oligomer **11** [$K_a(Cl^-) = 7$ M^{-1} in CD_2Cl_2], NMR experiments were conducted to corroborate that the folded structure is present upon anion complexation.

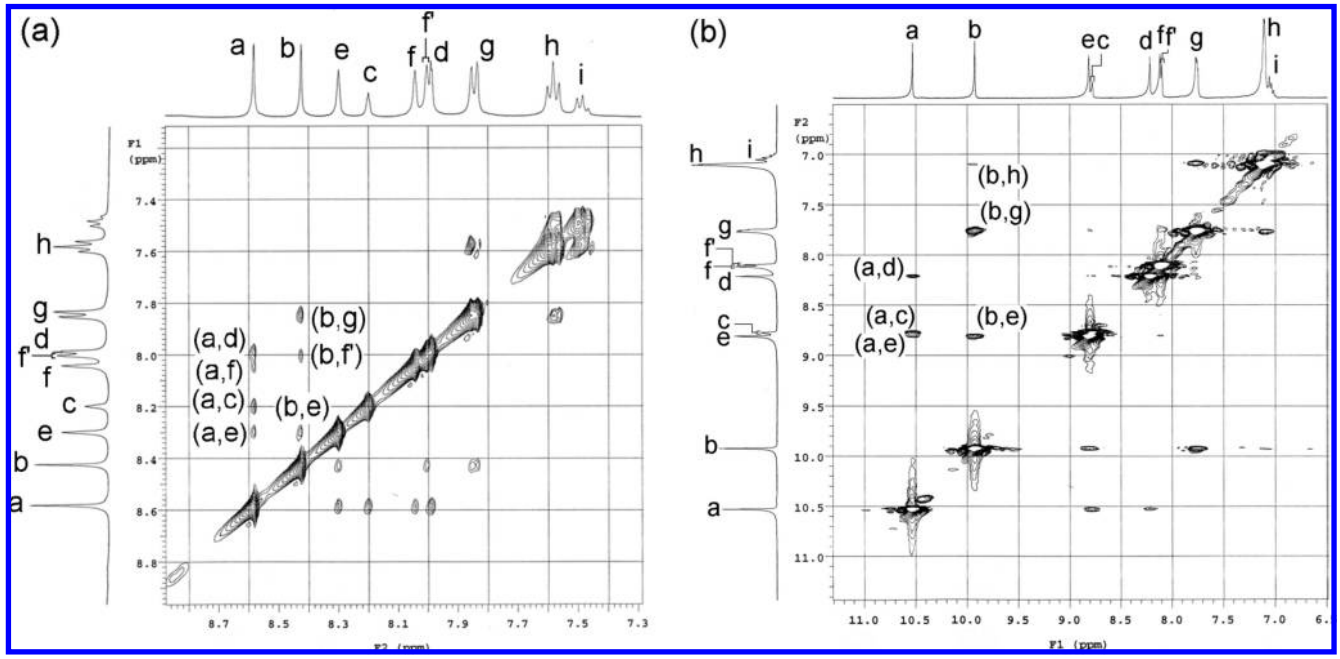

Figure 8. 2D ^{1}H−^{1}H NOESY spectra of **11** in CD_2Cl_2 at 298 K (a) before and (b) after addition of TBACl.

The folded conformation of **11**·Cl^- was verified on the basis of cross peaks observed in 2D NOESY experiments. The NOESY spectrum of the uncomplexed oligomer **11** (Figure 8a) shows connectivities from both sets of triazole protons to the phenylene-ring protons that can be grouped into two sets, the first linking triazole proton H^a to phenylene protons H^c, H^d, H^e, and H^f and the second connecting triazole proton H^b to phenylene protons H^e, $H^{f'}$, and H^g. When TBACl was added (Figure 8b), the NOE cross peaks connecting H^a to H^f and H^b to $H^{f'}$ originally seen in the spectrum of uncomplexed **11** disappeared. The associated changes in through-space proximity arise from the conformation changes in **11** upon halide binding and indicate that the interproton distances $H^a \cdots H^f$ and $H^b \cdots H^{f'}$ have become larger on average. These data are similar to those observed for the ester-substituted foldamer[23] and in this case support the change in conformation into a folded structure upon anion complexation.

Conclusions

A series of substituted [3_4]triazolophanes have been prepared in good yields from simple building blocks, demonstrating the facile modularity of the synthetic approach. Size-selective halide recognition was observed to distinguish Cl^- or Br^- anions from the too-small F^- anion by 1.5 orders of magnitude and the too-large I^- anion by almost 3 orders of magnitude. A remarkably large binding strength with Cl^- ion [$K_a = (1.1 \pm 0.2) \times 10^7$ M^{-1}, equivalent to $\Delta G_a = -9.6$ kcal mol^{-1}] was observed with the use of four *t*-butyl substituents on the triazolophane in nonpolar solvents. The majority of the binding arises from the preorganized structure, in which the four triazoles are responsible for focusing their polarized CH H-bonds and the positive ends of their 5 D dipoles into the central cavity. Consistent with this idea, the CH H-bond donor strength of the intervening phenylene linkers can be utilized to tune the receptor's binding strength by an amount (1 kcal mol^{-1}) that accounts for ~10−20% of the receptor's underlying anion affinity (>7 kcal mol^{-1}). Each electron-donating group weakens the anion-binding affinity, but this effect was greatest when the substituent was on the phenylene group linked to the triazoles through the nitrogens. These results suggest the following order of CH H-bond donor strengths: triazole > N-linked phenylene > C-linked phenylene. Consistent with this ranking, the F^- anion was found to bind in a tridentate manner with two flanking triazoles and a central N-linked phenylene. The Cl^- and Br^- anions were encapsulated inside the cavity, allowing ideal geometries for ion−dipole stabilization. The I^- ion, however, is proposed to dock with an open face of the central cavity with much-reduced affinity. An analogous open-chain form folds up around the anion templates with much-reduced binding strengths, emphasizing the extreme importance of preorganization. The triazolophanes were also found to aggregate together with moderate strengths, and the propensity increased with an increase in the number of triethylene glycol chains present and with increasing solvent polarity. Finally, the triazolophanes appear to be well-suited for fundamental studies of CH H-bonding, with the present study clearly showing the importance of aromatic CH H-bond donors in binding anions when these donors are preorganized into a shape-persistent macrocyclic structure.

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Supporting Information Available: Synthetic procedures, compound characterization, NMR spectroscopy, UV titrations, binding isotherms, NMR titrations, and aggregation isotherms. This material is available free of charge via the Internet at http://pubs.acs.org.

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