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# Anion Binding of Short, Flexible Aryl Triazole Oligomers

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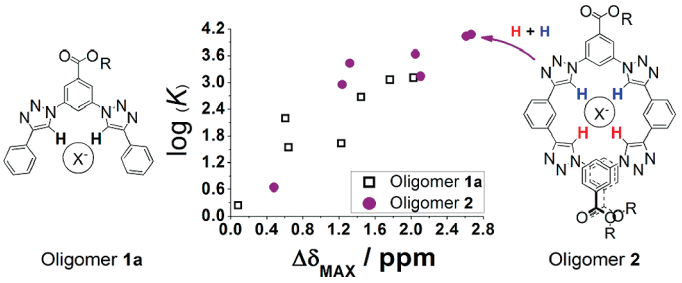


The flexible, electropositive cavity of linear 1,4-diaryl-1,2,3-triazole oligomers provides a suitable host for complexation of various anions. The binding affinities for various combinations of oligomer and anion were determined by $^1$H NMR titrations. Effective ionic radius is found to be a primary determinant of the relative binding interactions of various guests, with small but measurable deviations in the case of nonspherical anions. Solvent effects are significant, and the strength of the binding interaction is found to depend directly on the donor ability of the solvent. A picture emerges in which anion binding can be effectively interpreted in terms of a competition between two solvation spheres: one provided by the solvent and a second dominated by a folded cavity lined with electropositive 1,2,3-triazole CH protons. Implications for rigid macrocycles and other multivalent hosts are discussed.

## Introduction

The collective manipulation of individually weak intermolecular interactions is central to a wide range of molecular phenomena, including ligand−receptor interactions in biology, medicine, and sensors, polymer mechanical and transport properties, and the intra- and intermolecular contacts that guide the secondary structure of natural and synthetic macromolecules. As a result of its strength and directionality, hydrogen bonding from conventional donors (H-X, where X = N, O, or F) is a well-recognized and dominant interaction in many contexts, but it is increasingly clear that other chemical moieties hold promise as important partners in complementary interactions such as cation−$\pi$,[1] $\pi-\pi$,[2] nitrogen−halogen,[3] donor−$\sigma$-acceptor,[4] and hydrogen bonds derived from C-H groups.[5] While not traditionally included in lists of potential hydrogen bond donors, sufficiently polar C−H bonds interact with both anionic and neutral heteroatoms in a manner that places them on the weaker but still useful end of a continuum of hydrogen-bond donors interacting with electron-rich partners.[6]

Recent reports demonstrate that the polarity of neutral 1,4-disubstituted aryl-1,2,3-triazoles (dipole moment ~5 D) and that of the C5-H bond create an electropositive site that can function as an effective hydrogen bond donor for anion binding.[7−9]

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Li and Flood synthesized a tetrameric aryl-1,2,3-triazole macrocycle that demonstrated a high binding affinity ($K = 10^5\ M^{-1}$ in $CD_2Cl_2$) for chloride. A noteworthy feature of the macrocyclic receptor is that it is devoid of conventional H-X hydrogen-bond donors but rather interacts exclusively via C-H chloride contacts.[7] Juwarker et al. demonstrated that when the same aryl triazole functionality is presented in the form of a flexible oligomer, chloride binding induces a pro-helical conformation in the oligomer, a folding pattern that creates an electropositive cavity that is similar to but lacks the preorganization of the macrocycle reported by Li and Flood. The work by Juwarker et al. further demonstrated that the strength of the interaction increases with the generation of triazole-containing oligomer.[8] Also around the same time, Hecht et al. reported on the helicity inversion of a pyridyl 1,2,3-triazole oligomer induced by binding to achiral halides in highly polar solvents.[9]

The practical utility of 1,4-disubstituted-1,2,3-triazoles as functional species in intra- and intermolecular interactions is enhanced by the fact that they are readily accessible through the Cu(I)-catalyzed coupling of azides and alkynes.[10] While triazoles are historically viewed as "stealth" linkages with negligible independent function, these recent reports of anion recognition[11−14] build on a growing body of work regarding the potential functionality of substituted triazoles. For example, the size and dipole moment of 1,2,3-triazoles make them interesting candidates for amide bond surrogates in both a medicinal and structural context.[15] Arora and co-workers have reported the contributions of triazoles to the conformational preferences of mixed amide-triazole oligomers.[16]

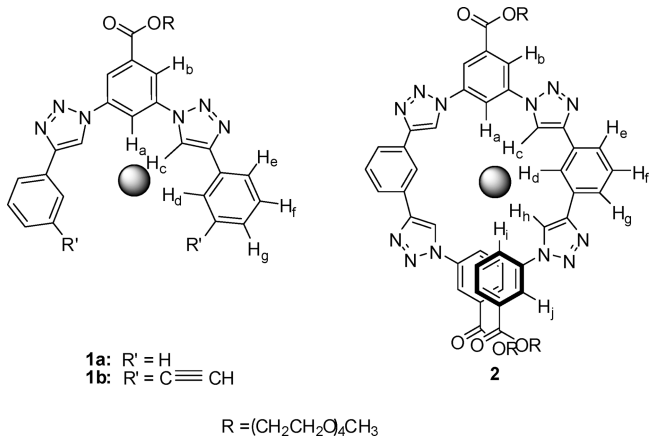


**FIGURE 1.** Oligo(aryl-1,2,3-triazoles) **1** and **2** depicted in their inferred anion binding conformations. Cavity binding triazole protons ($H_c$, $H_h$) and aryl protons ($H_a$, $H_d$) are labeled.

Given the utility of triazole CH−anion interactions in these and other contexts, we therefore set out to establish the structure−activity relationships that guide these interactions in more detail. This manuscript extends our earlier report to the interactions of short aryl-1,2,3-triazole oligomers with a range of anionic guests. The use of flexible hosts of various lengths provides an opportunity to evaluate the *intrinsic* properties of triazole−anion interactions, thus providing a baseline from which to evaluate the effects of size and shape complementarity found in increasingly ordered receptors. The size of the anions, as described by their effective ionic radii, are found to be primary determinants of the strength of binding by the flexible oligomers, with small but measurable deviations in the case of nonspherical anions. Further, the affinity of the receptors for a given anion is typically well correlated with the downfield shifts of the 1,2,3-triazole CH protons upon binding. This correlation provides a useful method for deconvolving the contributions to multivalent binding in the longer oligomers. An unexpected fluoride-catalyzed proton exchange reaction is observed in $d_6$-acetone. Finally, solvent effects on the binding of chloride are presented, and the CH−chloride interaction is found to depend directly on the donor ability of the solvent. A picture emerges in which anion binding can be effectively interpreted in terms of a competition between two solvation spheres: one provided by the solvent and a second dominated by a folded cavity lined with 1,2,3-triazole CH protons.

## Results and Discussion

When tetrabutylammonium salts of various anions are added to $d_6$-acetone solutions of **1a** and **2** (Figure 1), downfield shifts of the $^1$H NMR resonances of the 1,2,3-triazole CH protons and inner cavity aryl protons are observed, indicating a polarizing interaction in the oligomer cavity that we have previously attributed to anion binding.[8] Specifically for oligomer **1a**, addition of anion induces downfield shifts of triazole protons $H_c$ and inner cavity aryl protons $H_a$. Similarly, for oligomer **2**, titration with anion induces downfield shifts of triazole protons $H_c$, $H_h$ and inner cavity aryl proton $H_a$, suggesting in all cases a binding mode similar to that established previously for chloride and fluoride (Figure 2).

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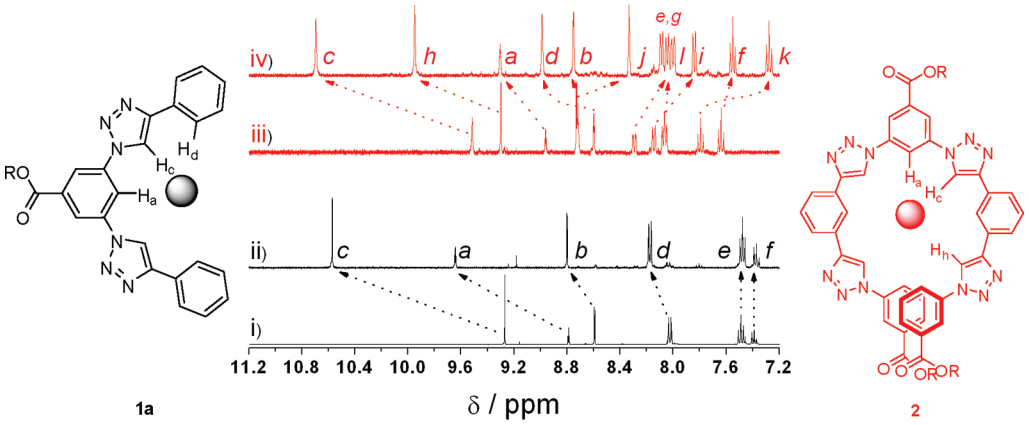


**FIGURE 2.** Partial $^1$H NMR spectra (400 MHz, $d_6$-acetone, 298 K) of oligo(aryl-1,2,3-triazoles) with and without $Bu_4N^+Cl^-$: (i) 1 mM **1a**, (ii) 1 mM **1a** + 1 mM $Bu_4N^+Cl^-$, (iii) 1 mM **2**, and (iv) 1 mM **2** + 1 mM $Bu_4N^+Cl^-$. Downfield shifts of binding protons are denoted by dashed lines. Similar effects of varying magnitude are observed for all of the ions reported.

**TABLE 1. Anion Binding Constants of Oligo(aryl-1,2,3-triazoles) 1·X$^-$ and 2·X$^-$ Obtained from $^1$H NMR Titration (1 mM, $d_6$-acetone, 298 K) with $(Bu)_4N^+X^-$**[a]

| anion ($X^-$) | $K$ (**1a**·$X^-$) ($M^{-1}$) | $\Delta\delta_{max}$ (ppm) | $K$ (**2**·$X^-$) ($M^{-1}$) | $\Delta\delta_{max(i)}$ (ppm) | $\Delta\delta_{max(o)}$ (ppm) |
|---|---|---|---|---|---|
| $Cl^-$ | 1260 (30) | 2.03 (0.02) | 1.2 (0.4) × $10^4$ | 1.63 (0.03) | 1.08 (0.03) |
| $Br^-$ | 470 (30) | 1.45 (0.05) | 1.1 (0.2) × $10^4$ | 1.52 (0.01) | 1.11 (0.01) |
| $I^-$ | 43 (1) | 1.23 (0.02) | 1.4 (0.2) × $10^3$ | 1.21 (0.01) | 0.91 (0.01) |
| $PhCO_2^-$ | 1150 (70) | 1.77 (0.02) | 4.3 (0.2) × $10^3$ | 1.34 (0.06) | 0.76 (0.04) |
| $HSO_4^-$ | 160 (30) | 0.61 (0.03) | 2.7 (0.6) × $10^3$ | 0.67 (0.01) | 0.67 (0.02) |
| $NO_3^-$ | 35 (3) | 0.64 (0.02) | 910 (50) | 0.63 (0.01) | 0.60 (0.01) |
| $PF_6^-$ | 1.7 (0.6) | 0.08 (0.02) | 4 (2) | 0.30 (0.07) | 0.32 (0.07) |

[a] $\Delta\delta_{max}$ (ppm) = calculated maximum change ($\Delta$) in chemical shift ($\delta$) of 1,2,3-triazole proton $H_c$ upon anion binding. Subscripts denote inner (i) and outer (o) 1,2,3-triazole protons for oligomer **2** ($H_c$ and $H_h$). The titration data were fit by Benesi−Hildebrand, Scatchard, and nonlinear regression methods.[18] All three methods gave similar results, and the individual fits are provided in the Supporting Information. For convenience and clarity, the average binding constants and variation due to choice of method (in parentheses) are presented here. None of the conclusions of this work rely on the choice of fitting method. Absolute uncertainties arise from uncertainties in the concentrations and the possibility of subtle aggregation and/or dielectric effects on chemical shift as a function of salt concentration. These absolute uncertainties are estimated to be less than 50% in $K$ and less than 5% in $\Delta\delta_{max}$. Binding constants reported for oligomer **2** are the average of binding constants derived from fits of both the inner and outer triazole protons.

In all cases, a 1:1 binding stoichiometry is determined by Job's Method of Continuous Variation.[17] The anion-binding strength of oligo(aryl-1,2,3-triazoles) **1a** and **2** were determined in $d_6$-acetone from titrations with seven different anions of varying size, geometries, and basicities (Table 1). Trends in the binding affinities of each oligomer are discussed sequentially, below, followed by comparisons between the two.

**Oligo(aryl-1,2,3-triazole) 1a·X$^-$.** Oligomer **1a** displays a 1:1 binding stoichiometry with all of the studied anions (Figure 3). The relative anion binding strengths of **1a** in $d_6$-acetone (Table 1) are

$$Cl^- \sim C_6H_5CO_2^- > Br^- > HSO_4^- > I^- \approx NO_3^- > PF_6^-$$

It is evident that as the size of the anion increases, the binding strength decreases, a correlation that is consistent with the expected electrostatic nature of the ion binding interaction (Figure 4). Small deviations are observed, however, in the case of benzoate (a tighter binder than expected from its size) and nitrate (a weaker binder than expected from its size). The magnitude of these deviations is rather small (~1 kcal mol$^{-1}$), but they indicate a subtle contribution from geometric complementarity between host and guest. In the case of benzoate in particular, the distribution of negative charge is not isotropic but is concentrated in the plane of the carboxylate group and away from the formally uncharged phenyl group (Figure 5). Etter has pointed out that this electrostatic distribution favors *anti* hydrogen bonding patterns that are well met in this case by host **1a** (Figure 5),[19] a feature that has been exploited in oxoanion receptors previously[20] and which reinforces the hypothesis of a geometric origin to the deviation in Figure 4. The concentrated charge in benzoate relative to the spherical halides is also related to its high $\beta$ value (2.01), where $\beta$ reflects the hydrogen-bonding proton acceptor ability relative to hydrogen ion as obtained from Kamlet−Taft parameters.[21] We do find a rather weak correlation between binding affinity and $\beta$ (data not shown), although we note that $\beta$ and ionic radius will share an intrinsic correlation that complicates an efficient separation of the two effects. Couching the apparent intrinsic selectivity of **1a** for benzoate in terms of geometric complementarity seems, therefore, to be more appropriate.

Li and Flood have reported halide binding studies of a related acyclic oligo(aryl-1,2,3-triazole) that displays size

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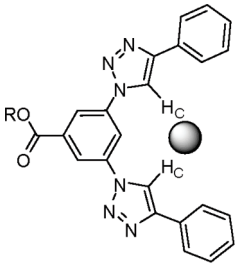



**1a**

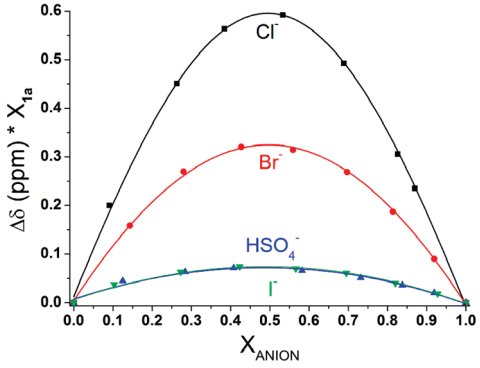
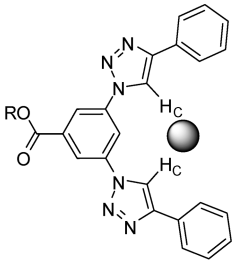



**FIGURE 3.** Job's plots of **1a**·$X^-$ displaying 1:1 binding stoichiometries with the $Bu_4N^+$ salts of $Cl^-$, $Br^-$, $I^-$, and $HSO_4^-$ ($d_6$-acetone, 298 K). $PhCO_2^-$, $NO_3^-$, and $PF_6^-$ also display similar binding stoichiometries and are omitted for clarity but included in the Supporting Information. Gaussian fit of data points was performed using Origin 7.0. Inner triazole proton $H_c$ displays a 1:1 binding stoichiometry with all measured $X^-$. $\Delta\delta$ (ppm) = change in $^1$H chemical shift of monitored protons $H_c$. $X_1$ = mole fraction of oligomer **1a**. $X_{anion}$ = mole fraction of anion during data collection.




**1a**

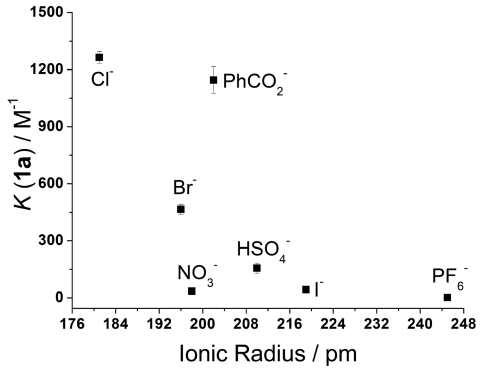



**FIGURE 4.** Correlation of anion binding strength to ionic radius for oligomer **1a**. Ionic radii obtained from Goldschmidt and Pauling crystal data correlations as compiled by Marcus.[21] Error bars reflect the uncertainty associated with choice of binding isotherm.

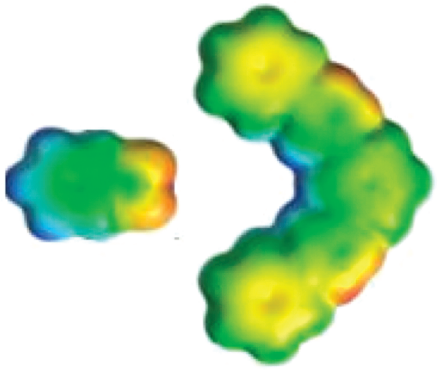


**FIGURE 5.** Electrostatic potential maps (Spartan) of benzoate (left) and an aryl triazole trimer (right) showing the complementarity of the anisotropic electrostatic distributions, each of which is concentrated in the plane. Red denotes regions of negative charge, and blue denotes regions of positive charge.

selectivity for the larger $Br^-$ and $I^-$ over $Cl^-$ and $F^-$ in $CD_2Cl_2$, a trend that differs from that found here for **1a** in $d_6$-acetone as a solvent.[7b] The selectivity observed in Li and Flood's linear oligomers further differs from that reported by the same authors for an aryl-1,2,3-triazole macrocycle in which the fixed cavity favors $Cl^-$ and $Br^-$. Together, these differences indicate that anion selectivity is not an intrinsic property of aryl-1,2,3-triazole functional groups but rather a confluence of geometric and solvation effects, which we explore further below.

Differences in anion binding strengths reflect differences between electrostatic interactions (ion−dipole, ion−induced dipole) and geometric distortions of the host−guest system.[22] Electrostatic effects are reflected by the magnitude of the induced downfield shifts in the CH proton resonances of the fully bound hosts ($\Delta\delta_{max}$), and we find for **1a** a reasonable correlation between $\Delta\delta_{max}$ and the anion binding constant $K$ (Figure 6). Chloride, for example, is the best guest and induces the largest difference in CH chemical shift between the fully complexed and uncomplexed species ($\Delta\delta_{max}$ = 2.03 ppm) compared to the weak binding of $PF_6^-$ ($\Delta\delta_{max}$ = 0.08 ppm), with the other anions in between. The larger, spherical halides $Br^-$ and $I^-$ bind more weakly than $Cl^-$ and have lower induced chemical shifts ($\Delta\delta_{max}$ of 1.45 and 1.23 ppm, respectively). This correlation between magnitude of chemical shift and binding strength is similar to that which forms the basis of the Guttman acceptor number,[23] and similar correlations have been reported previously, for example, in a recent study by Jeong and coworkers.[24] For the triazole oligomers, a respectable linear free energy relationship is observed (Figure 6). It is of interest to note that benzoate fits the chemical shift trend quite well ($\Delta\delta_{max}$ = 1.8 ppm, $K = 10^3$ $M^{-1}$), in comparison to its deviation with respect to ionic radius (Figure 4). The good fit of benzoate with respect to induced chemical shift (Figure 6) further supports that its higher affinity relative

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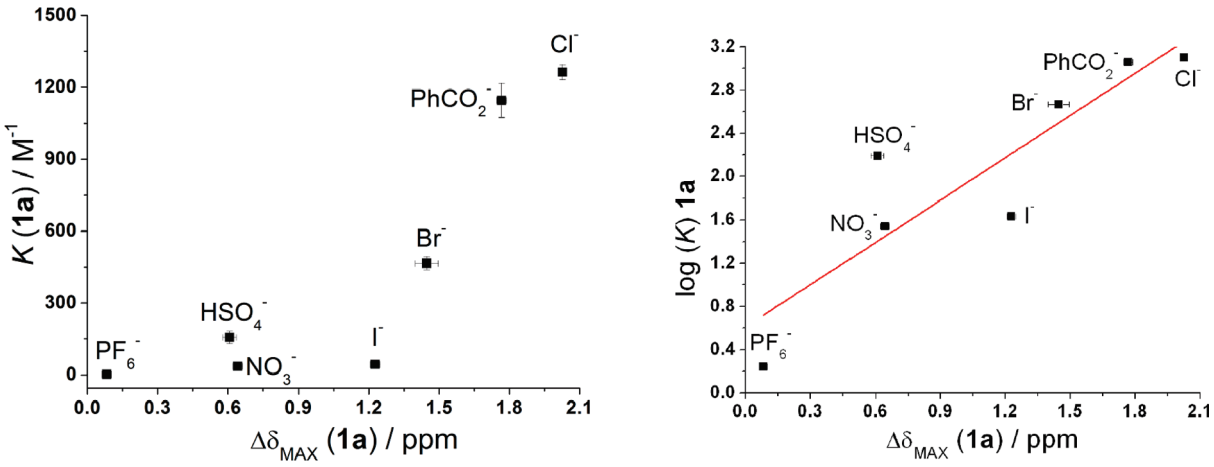


**FIGURE 6.** Correlation of calculated chemical shift change ($\Delta\delta_{max}$) with anion binding strength ($K$) of oligomer **1a**. Data obtained by $^1$H NMR titration of **1a** (1 mM; $d_6$-acetone, 298 K) and calculation of $\Delta\delta_{max}$ performed by nonlinear regression curve fitting of $^1$H NMR data by Origin 7.0. $\Delta\delta_{max}$ is the calculated induced chemical shift of triazole proton $H_c$ (ppm) when bound to anion. Error bars denote the uncertainty associated with the choice of isotherm fitting method.

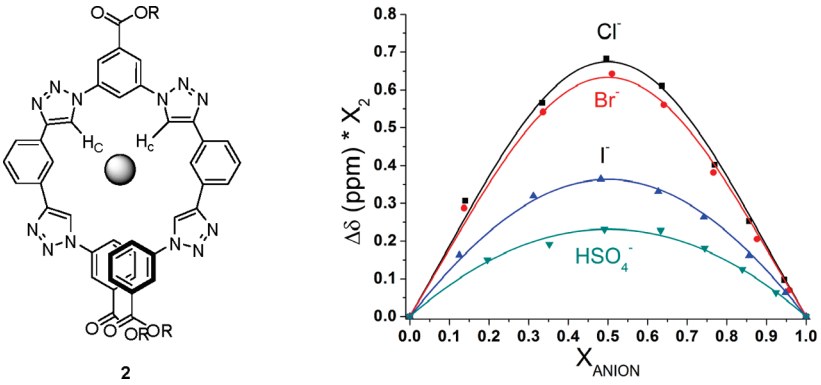


**FIGURE 7.** Job's plots of $2\cdot X^-$ ($d_6$-acetone, 298 K) displaying 1:1 binding stoichiometries with the $Bu_4N^+$ salts of $Cl^-$, $Br^-$, $I^-$ and $HSO_4^-$. Benzoate, $NO_3^-$ and $PF_6^-$ also display 1:1 binding but are omitted for clarity and included in the Supporting Information. $X_2$ = mole fraction of oligomer **2**. $X_{anion}$ = Mole fraction of anion. $\Delta\delta$ is the induced change in $^1$H NMR chemical shift of triazole protons $H_c$ upon anion binding (ppm).

to ionic radius is due to stronger electrostatic interactions between the negative charge of the guest and partial positive charge distribution in the host, rather than an effect due to, for example, interactions between the host and the aromatic ring of the guest. The only apparent exception to the correlation between binding strength and induced chemical shift is hydrogen sulfate ($K = 140$ M$^{-1}$, $\Delta\delta_{max} = 0.62$ ppm), which has a lower $\Delta\delta_{max}$ and higher $K$ than iodide ($K = 48$ M$^{-1}$, $\Delta\delta_{max} = 1.16$ ppm). We note that weak binding interactions are potentially more susceptible to systematic uncertainty, for example, due to minor contributions from aggregation, and that erroneously low $\Delta\delta_{max}$ will lead to erroneously high $K$, exaggerating apparent differences. Even if both the precision and accuracy of the measured values were certain, however, the magnitude of the deviations are sufficiently small ($< 1.5$ kcal mol$^{-1}$ per ion from the values expected from the remainder of the series) that they defy a meaningful explanation.

**Oligo(aryl-1,2,3-triazole) 2.** We next consider the extent to which these same trends in binding extend to the longer oligomer **2**. The concentration of oligomer **2** was kept at 1 mM in order to overcome the formation of $\pi$-stacked aggregates at higher concentrations. Such aggregation is evident by $^1$H NMR through extreme broadening and eventual coalescence of the aromatic protons. At the lower concentrations, Job's plots confirmed a 1:1 binding stoichiometry for all anions with oligomer **2** (Figure 7).

$^1$H NMR titration with the corresponding $Bu_4N^+$ salts and subsequent nonlinear regression curve fitting enabled the quantitative determination of binding affinities, which are reported in Table 1. The relative anion binding affinities of **2** were determined to be

$$Cl^- > Br^- > C_6H_5CO_2^- > HSO_4^- > I^- \approx NO_3^- > PF_6^-$$

The trend in anion binding observed for **2** is similar to that observed for **1a**, in that larger anions lead to weaker binding. As seen for **1a**, a reasonable correlation between induced chemical shift ($\Delta\delta_{max}$) and binding affinity $K$ is found (Figure 8). The magnitude of the induced chemical shift provides an interesting insight into the nature of these multivalent interactions. When the *total* chemical shifts (e.g., in $H_c + H_h$ for **2** versus $H_c$ only in **1a**) are considered, the binding data versus induced chemical shift for **1a** and **2** collapse reasonably well onto a single master curve (Figure 8, right).

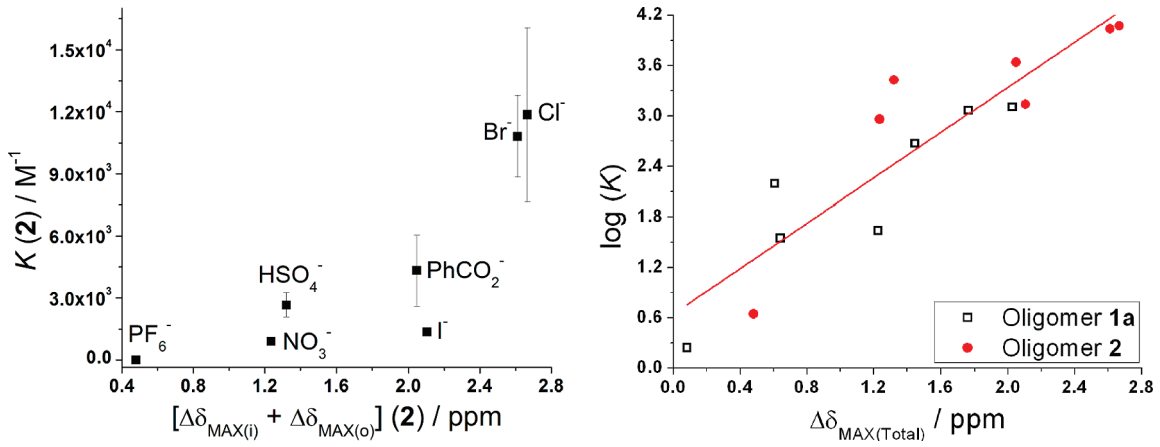


**FIGURE 8.** (Left) Correlation of the sum of the calculated chemical shift changes ($\Delta\delta_{max}$) of the outer and innter triazole protons upon anion binding with anion binding strength ($K$) of oligomer **2**. Data obtained by $^1$H NMR titrations of **2** with $Bu_4N^+X^-$ (1 mM; $d_6$-acetone, 298 K) and calculation of $\Delta\delta_{max}$ obtained by nonlinear regression curve fitting of $^1$H NMR data by Origin 7.0. (Right) Correlation of total chemical shift change of triazole protons upon anion binding with anion binding strength for oliomers **1a** and **2**. Error bars denote the uncertainty associated with the choice of isotherm fitting method.

The individual interactions, insofar as they are accurately reported by the induced chemical shifts, therefore are additive and can be compared from one oligomer to another. For example, the $\Delta\delta_{max}$ differences associated with chloride binding in **1a** and **2** (2.03 ppm for **1a** versus 1.63 ppm for the inner triazole proton and 1.08 for the outer triazole proton of **2**) can be used to infer further structural details of multivalent binding.[25] The fact that oligomer **2** has a larger binding affinity for chloride ($K > 10^4$ M$^{-1}$ for **2** versus $K = 1280$ M$^{-1}$ for **1a**) is not due to tighter interactions of chloride with individual triazole CH protons; on the contrary, the individual interactions appear to be weaker (the individual $\Delta\delta_{max}$ values for both the inner and outer triazole CH resonances are smaller for **2** than for **1a**). Instead, the weakening of individual contacts is overcome by the increased number of triazole CH donors.

The major difference in binding trends between the two oligomers is the relative binding strengths of bromide and benzoate. In the smaller oligomer **1a**, benzoate binds more tightly than bromide (1150 versus 470 M$^{-1}$), whereas in the longer oligomer **2**, bromide binds more tightly than benzoate ($1.1 \times 10^4$ versus $4.3 \times 10^3$ M$^{-1}$). Notably, that difference is consistent with the differences in $\Delta\delta_{max}$, which is smaller for **2**·benzoate than **1a**·benzoate, implying a poorer fit of benzoate within the pseudocircular cavity of **2**. Oligomer **2** is longer than its counterpart, and in order to simultaneously maximize CH−anion contacts and preserve planarity, it must wrap around anions to form a cavity that is at least partially "closed off" by the terminal aryl groups. It can therefore be envisioned that in a fully "wrapped" oligomer **2**, benzoate must bind perpendicularly to the plane of the triazoles, as the overall size of benzoate would disallow planar entry into the binding cavity that is allowed by **1a**. The perpendicular binding of benzoate in the cavity of calixpyrroles has been reported previously by Sessler,[26] and it is well-known from Etter's seminal work that such a binding mode is not optimal for hydrogen-bonding-type interactions.[19] Even if benzoate were able to maintain a coplanar binding geometry with host **2**, however, the nonsymmetrical distribution of negative charge in the carboxylate would prevent simultaneous CH−anion interactions between the effectively circularly symmetric host and unsymmetric guest. This effect of uneven charge distribution is similar to that observed in trends in the progressive aqueous solvation of carboxylates. The addition of a first molecule of water to acetate *in vacuo*, for example, is more exothermic than the addition of a single molecule of water to chloride, although the overall bulk aqueous solvation energy of acetate is considerably lower than that of chloride.[27] One (and potentially a second) directional, hydrogen-bonding-type interaction interacts strongly with the concentrated, directional charge distribution of the carboxylate, but subsequent solvating interactions have significantly less effect relative to spherical anions of comparable size. Here, the crescent-shaped host **1a** effectively saturates the preferred, "specific" binding region on benzoate, and increasing the generation of the host generates rapidly diminishing returns in binding constant, a picture that is supported by the significant difference in induced $\Delta\delta_{max}$ values for the inner (1.31 ppm) and outer (0.74 ppm) triazole CH protons upon binding to benzoate. Therefore, in terms of geometric complementarity, the isotropic charge distribution on bromide is a better fit for **2** than is the anisotropic charge distribution on benzoate, while the reverse is true for **1a**. Overall, the effect of size/shape complementarity on binding in the linear oligomers is much less than that in the rigid macrocycles reported by Li and Flood, but these results suggest that the onset of some geometric effects occurs in linear oligomers of comparable size, without the need for covalent conformational restraints.

**Fluoride Binding.** Fluoride is a common and important target for anion binding, and its absence from the previous discussion is likely conspicuous. Studying fluoride binding in heterocyclic anion receptors is often problematic because of

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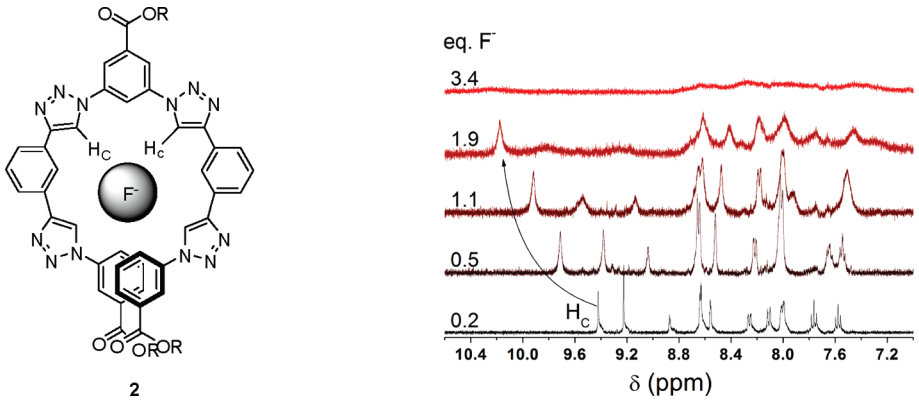


**FIGURE 9.** Aggregation effects indicated by $^1$H NMR spectra upon addition of $Bu_4N^+F^-$ to a 1 mM solution of oligomer **2** in $d_6$-acetone. Addition of > 1 equiv of $F^-$ results in severe peak broadening.

the inherent basicity of the fluoride anion ($\beta = 2.88$, compared to 1.67 for $Cl^-$), and such is the case here. The fluoride anion can form very stable hydrogen bonds, for example, in polynuclear aggregates such as $HF_2^-$. Hydrofluoric acid is a relatively weak acid ($pK_a = 3.2$), and in urea-based and pyrrole-based anion receptors, fluoride has been shown to deprotonate the acidic NH hydrogen bond donor to form two separate species, $L^-$ and $HF_2^-$, according to the reaction[28]

$$HL + 2F^- \rightarrow L^- + HF_2^-$$

where HL is the protic fluoride receptor, a role filled here by the triazoles (*vide infra*).

In the case of oligomer **2**, the use of $Bu_4N^+F^-$ complicates quantitative study by inducing aggregation to a much greater extent than the other salts (Figure 9). Nonetheless, at low concentrations of $F^-$ in $d_6$-acetone, a reasonable $^1H-^1H$ NOESY spectrum has previously been reported that indicates a $\mathbf{2}\cdot F^-$ binding mode similar to that of $\mathbf{2}\cdot Cl^-$.[8] Aggregation is less problematic for the shorter oligomer **1a** and diaryltriazole **3**, but the addition of more than 1 equiv of $F^-$ leads to deprotonation of the triazole CH protons (Figures 10 and 11). For example, while there is no substantial change in the intensity of the triazole CH proton resonance upon addition of 0.8 equiv of $Bu_4N^+F^-$ to **1a**, the addition of 3 equiv results in a pronounced loss of intensity over a few hours (Figure 11). A similar effect is noticed upon the addition of 1.2 equiv; however, the loss of the CH resonances takes considerably longer. For both **3** and **1a** (Figure 12), the triazole CH proton resonance is not restored when $AgNO_3$ is added to precipitate $F^-$ as the silver salt, indicating a chemical change in the triazoles.

We attribute the loss of the CH resonance to fluoride-catalyzed proton/deuteron exchange between the aryl-1,2,3-triazoles and $d_6$-acetone, a hypothesis supported by repetition of the $F^-/AgNO_3$ sequence in protio acetone, after which **3** is isolated and returned to deuterated solvent, and the triazole CH resonance is found intact (Figure 12). In addition, mass spectrometry of **3** after exposure to > 1 equiv

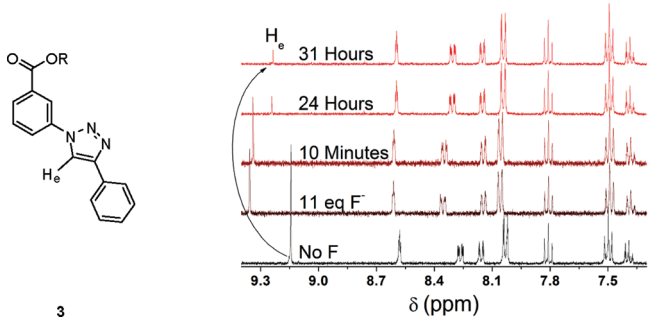


**FIGURE 10.** Effect of high fluoride concentration (55 mM, 11 equiv) on disappearance of the $^1$H NMR resonance of the triazole proton of **3** (5 mM) in $d_6$-acetone. The effect is quite extreme, as seen from the drastic reduction in intensity over time of the sharp 1,2,3-triazole CH singlet that is originally at $\delta = 9.15$ ppm.

of $F^-$ in $d_6$-acetone reveals an increase of 1 Da in the parent ion peak (from 456.21 to 457.21), consistent with a single H/D exchange. The combination of proton transfer and the apparent requirement of > 1 equiv of $F^-$ for host deprotonation supports an $HF_2^-$ mediated pathway (with possible contributions from $H_2OF^-$ through adventitious water) similar to that observed previously in ureas and calixpyrroles.[28] We note that similar processes may contribute to the aggregation of **2**, which is more pronounced when > 1 equiv of $Bu_4N^+F^-$ is used (Figure 9). These behaviors present obvious challenges to quantifying $F^-$ binding, resulting in its omission from our binding studies.

**Solvent Effects.** Molecular recognition in any solvated environment depends on the nature of the interactions between host and guest, but it also involves at least partial desolvation of both the free host and the free guest in order to facilitate the host:guest interactions.[29] When ionic species are present, these desolvation penalties can be enormous: in the case of anionic guests, the desolvation penalty is especially severe in protic solvents. We anticipated that anion (de)solvation would be a major factor in the present systems, and we therefore investigated the solvent dependency of chloride recognition by $^1$H NMR titration experiments of **1a** with $(Bu)_4N^+Cl^-$ in $d_6$-acetone, $CD_2Cl_2$, $CD_3CN$,

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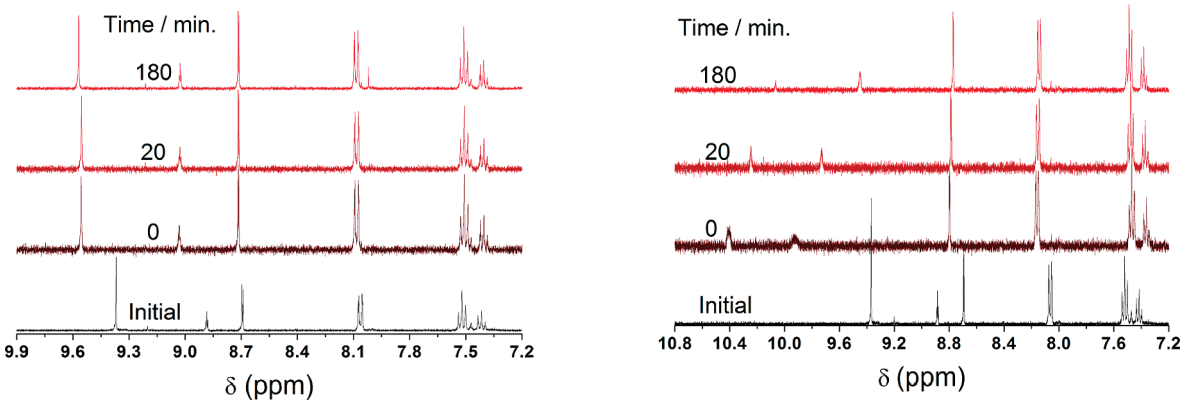


**FIGURE 11.** (Left) 1 mM **1a** + 0.8 equiv of $Bu_4N^+F^-$ shows no pronounced decrease in the intensity of the triazole CH proton. (Right) 1 mM **1a** + 3 equiv of $Bu_4N^+F^-$ shows a gradual disappearance of the triazole CH proton resonance.

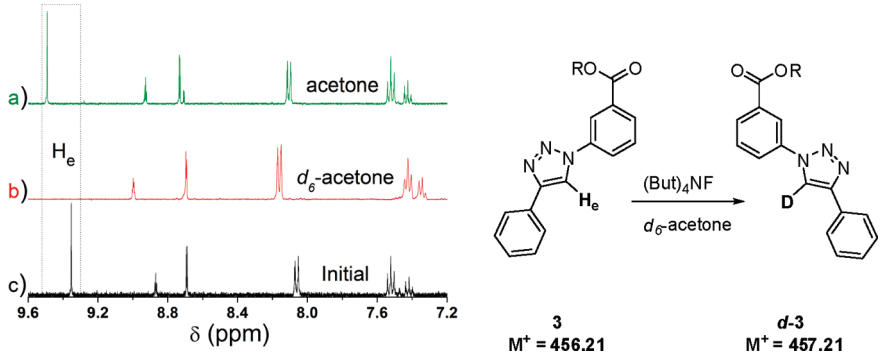


**FIGURE 12.** $^1$H NMR spectra of **3**·$F^-$ showing that triazole proton disappearance is reliant upon acetone being in the deuterated form. (a) In protic acetone solvent, the triazole CH $^1$H NMR resonance ($H_e$) persists after 24 h with excess fluoride. (b) Upon switching to deuterated solvent, the triazole CH $^1$H NMR resonance ($H_e$) completely disappears. (c) Excess fluoride in conjunction with deuterated acetone is necessary to cause the triazole CH $^1$H NMR resonance to disappear, as **3** in $d_6$-acetone without fluoride yields no change in the $^1$H NMR resonance of triazole CH proton $H_e$. The slight downfield shift of the CH resonance in (a) relative to (c) is attributed to partial association with residual nitrate. Mass spectral data (see Supporting Information) support the assignment of deuterated oligomer **3** (right) after fluoride treatment in $d_6$-acetone.

DMSO, $CDCl_3$, and 1:1 $d_6$-acetone:cosolvent mixtures. As expected, the choice of solvent exerts a large effect on the affinity of the aryl-1,2,3-triazole receptor for the anionic guest (Table 2); the magnitude of the stability constants varies by over 2 orders of magnitude across the series, and **1a** shows the highest chloride binding constant in $d_6$-acetone. There is no quantitative correlation between binding constant and either dielectric constant and dipole moment, but a good correlation was found with the Gutmann acceptor number (AN) of the solvents, which gives a quantitative measure of the solvent's ability to accept and/or donate electron density, for example, through hydrogen-bonding-type electrostatic interactions.[23,30]

Table 2 shows that as AN decreases, the anion binding affinity $K$ increases.[32] The trend includes 1:1 solvent mixtures of acetone with high AN solvents, for which the binding strength is larger than that of the pure solvents themselves. The exceptions to the trend are DMSO and the 1:1 acetone/DMSO cosolvent. We note that DMSO is an excellent acceptor of localized positive charge (e.g., that of a hydrogen bond proton donor) and hypothesize that it competes with chloride for the triazole CH donors. Support for this hypothesis is found in the downfield shift of the triazole CH protons in DMSO (9.642 ppm) relative to the other solvents (8.42−9.35 ppm), consistent with the acidic nature of the $C_4$-H proton.[33] Anion complexation, therefore, is dominated by a competition between the electrostatic interactions between solvent and anion versus those between the host and anion. These trends readily explain the apparent discrepancy in anion selectivity observed here for host **2** and reported previously by Li and Flood for a related, acyclic triazolophane.[7b] In our experiments, conducted in $d_6$-acetone,

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**TABLE 2. Effect of Solvent on the Chloride Binding Affinity of 1**

| solvent | $K$ ($M^{-1}$)[a] | $\Delta\delta_{max}$ (ppm) | acceptor number (AN)[b] |
|---|---|---|---|
| acetone | 1260 (30) | 2.03 (0.02) | 12.5 |
| 1:1 acetone/DMSO | 27 (1) | 1.48 (0.03) | 17.3 |
| 1:1 acetone/$CD_2Cl_2$ | 110 (3) | 1.95 (0.01) | 18.7 |
| 1:1 acetone/$CD_3CN$ | 100 (3) | 2.03 (0.01) | 19.2 |
| DMSO | 5.1 (0.4) | 1.34 (0.08) | 19.3 |
| 1:1 acetone/$CDCl_3$ | 61 (6) | 1.40 (0.08) | 20.3 |
| $CD_2Cl_2$ | 34 (1) | 2.37 (0.04) | 20.4 |
| $CDCl_3$ | 18 (1) | 2.6 (0.1) | 23.1 |

[a]Binding constants obtained from $^1$H NMR titration of oligomer **1** (1 mM, 298 K) with $Bu_4N^+Cl^-$. The titration data were fit by Benesi–Hildebrand, Scatchard, and nonlinear regression methods.[18] All three methods gave similar results, and the individual fits are provided in the Supporting Information. For convenience and clarity, the average binding constants and variation due to choice of method (in parentheses) are presented here. None of the conclusions of this work rely on the choice of fitting method. Absolute uncertainties arise from uncertainties in the concentrations and the possibility of subtle aggregation and/or dielectric effects on chemical shift as a function of salt concentration. These absolute uncertainties are estimated to be less than 30% in $K$ and less than 5% in $\Delta\delta_{max}$. [b]Acceptor numbers for pure solvents obtained from Gutmann et al.[23] For 1:1 solvent mixtures, AN is calculated from Dimroth–Reichardt parameters $E_T$.[30] $E_T$ values for 1:1 solvent mixtures were derived from linear solvation energy relationships of solvatochromic parameters described in detail by Kamlet and Taft.[31]

chloride is found to be a better guest than bromide, whereas Li and Flood observed that a similar acyclic receptor bound bromide more tightly than chloride in $CD_2Cl_2$. The change in anion selectivity can be attributed to differential solvation; the smaller chloride ion is better solvated than bromide. When the binding studies are conducted in $CD_2Cl_2$ versus $d_6$-acetone, therefore, the increased donor ability of the $CD_2Cl_2$ will stabilize the free chloride more than its bromide counterpart. The magnitude of the selectivity for chloride over fluoride in the macrocyclic receptors of Li and Flood is similarly expected to have a significant solvent dependency, as solvation energies of fluoride are much larger than those of chloride.[27,30a]

**Implications for Receptor Design.** When considering anion binding in the acyclic receptors **1a** and **2**, perhaps the most significant conclusion is the lack of major surprises. The identified trends in binding are largely valid across the entire series of anion guests with only a few deviations, which are typically of a fairly small magnitude. Anion binding varies relatively smoothly with ion size, the number and strength of individual triazole–anion contacts in the host, and the donor ability of the solvent. Even in cases where deviations are observed, they are relatively minor (generally ~1 kcal $mol^{-1}$ or less). These results suggest a model of anion binding in which the host–guest interaction can be thought of in terms of a transfer of anion from the solvation sphere provided by the solvent to a partial solvation sphere provided by the aryl triazole host. Any contributions from shape- or size-complementary "molecular recognition" are relatively minor. As shown in our prior work, for example, the host **2** can wrap neatly around the chloride ion to form a pseudocircular cavity for binding that is reminiscent of the macrocycles of Li and Flood. The ability to do so, however, presents no great advantage: iodide is incapable of fitting into the planar binding site, but it (presumably) accesses another host conformation that provides high-quality CH contacts and results in a binding affinity only 1 order of magnitude lower than that of chloride, despite its more diffuse charge distribution. There is no evidence from the trends that the pseudocircular cavity presents a "special" binding arrangement for appropriately sized ions.

These results prompt an interesting question: if a tightly enforced circular cavity is not particularly advantageous for anion binding, why are the anion binding affinities of the macrocyclic receptors reported by Li and Flood up to 5 orders of magnitude stronger than those of the related acyclic oligomers?[7b] The entropic benefits of preorganization must surely play a role, but the number of conformational degrees of freedom that are lost upon anion binding is rather modest. Because the orientation of the terminal aryl groups in **2** is likely to be a minor contributor to binding, there are only six aryl-triazole single bond torsions that are expected to be restricted upon anion complexation. Each of these torsions would be expected to be dominated by two fairly narrow regions of values centered at 0° and 180° in the unbound oligomer, and each would be limited to only one of those ranges upon idealized anion binding. The entropic penalty associated with that reduced conformational freedom is seemingly inadequate to explain a difference in binding affinity of several orders of magnitude between the macrocyclic and acyclic triazole oligomers.[34] For comparison, the complete loss of torsional entropy upon binding has been calculated for similar rotors to be ~11 eu.[34a] Even if all six rotors were completely frozen upon anion binding (which surely overestimates the actual entropic loss), then the total cost in free energy of just over 4 kcal $mol^{-1}$ is not sufficient to account for the reported differences between the rigid macrocycles and acyclic oligomers.

A complementary effect could be that the macrocyclic receptor preorganizes the triazoles not so that they are well-positioned to maximize the interactions between the receptor and the anionic guests; after all, the charge distribution in most of the ions is not heavier within an equatorial plane. Rather, the macrocycles might achieve higher affinity by preorganizing the electropositive C-H end of the triazole dipoles so that they create repulsive interactions in the unbound host (that is, whereas the unbound state of the acyclic receptor can relax to a lower-energy conformation, the shape-persistent macrocycle can not) and/or a cavity that can only be filled at additional entropic and enthalpic penalty by the surrounding solvent.[35] In other words, macrocyclization might *destabilize the unbound state of the host* rather than stabilizing the bound host:guest complex. This type of contribution, while often less discussed than contributions due to favorable preorganization, is a well-known contributor to the macrocyclic effect and similar multivalent binding processes.[36] Support for the importance of destabilization in the unbound host in these systems comes from several sources. For example, we note that in the crystal structure of the triazole oligomer **1b** (Figure 13), the triazoles

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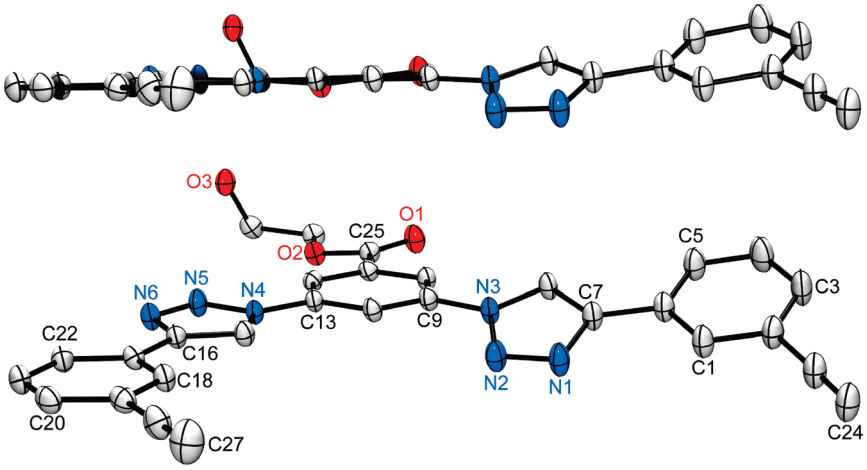



**FIGURE 13.** Partial crystal structure of oligomer **1b** (oligoethyleneglycol units truncated for clarity; see Supporting Information for complete structure), showing the alternating orientation of the triazole dipoles.

adopt a zigzag "anti" conformation that minimizes the internal dipole of the molecule in a way that is obviously inaccessible to the macrocycle. Arora and co-workers[16] have previously noted similar conformational preferences in oligomeric triazoles, and calculations on the macrocyclic receptors reveals puckering of the unbound (but not anion-complexed) planar macrocycle, presumably to relieve hydrogen−hydrogen repulsions.[22] The conformation of the oligomer without anion is in marked contrast to the crystal structure of a related oligomer:chloride complex reported previously,[8] in which the triazoles neatly wrap around the anion partner in the expected geometry.

This qualitative structural evidence is supported by previously reported calculations from Li and Flood,[7b] in which the "anti" arrangement of unrestricted triazoles is favored by ~2 kcal $mol^{-1}$ over the "syn" conformation that is preorganized for anion binding. The ability of the unbound acyclic host to "relax" into more stable, anti conformations might therefore be expected to contribute up to 5−6 kcal $mol^{-1}$ of stability to the unbound state of **2** versus the macrocyclic host (~2 kcal $mol^{-1}$ for each of three sequential triazole pairs). The actual contribution due to such conformational relaxations to the free energy of the unbound state might be either higher or lower than this crude estimate, depending on entropic penalties and interactions between nonadjacent triazoles, but it demonstrates that enforced dipolar repulsion in the unbound macrocycle is capable of making up the difference between the observed differences in binding constants and those expected on the basis of purely entropic grounds. Finally, the induced chemical shifts, $\Delta\delta_{max}$, whose correlation to the strength of individual interactions has been discussed above, are *greater* for the acyclic rather than the macrocyclic hosts, suggesting that, if anything, the flexibility of the linear oligomers facilitates rather than inhibits favorable CH−anion contacts. While a quantitative breakdown of the contributions from these competing mechanisms is not within the scope of this work, this analysis may be useful in the design of future triazole-based receptors.

## Conclusion

The 1:1 binding affinities of short, oligomeric aryl-1,2,3-triazoles for various anions have been investigated in multiple solvents. Over much of the series, the strength of the interaction is well-correlated with the effective ionic radius of the anion (smaller anions are bound more tightly), the total induced chemical shifts of all interacting triazole CH protons (greater shifts are associated with stronger interactions), and the Gutmann number of the solvent (better hydrogen bond donors lead to weaker binding). Increasing the number of triazoles in the linear oligomers leads to a decrease in the magnitude of the individual CH−anion contacts, but overcomes that penalty through the multivalent presentation of additional hydrogen-bond-type donors. Geometric complementarity appears to have a modest but measurable effect on the binding of benzoate, but in general these results suggest a model in which the host−guest interaction is dominated by what can be thought of as a partial transfer of anion from one amorphous solvation sphere provided by the solvent to another provided by the aryl triazole host. The nonspecific nature of the binding suggests that favorable contacts provided by the preorganization of a macrocyclic triazole-containing host are unlikely to account for the increased affinity observed in those receptors and, together with the magnitude of the difference in binding constants between the rigid and flexible hosts, suggests that a significant fraction of the binding affinity of macrocyclic hosts arises from the destabilization of their unbound state relative to that of the flexible analogues. Finally, fluoride ion is observed to catalyze proton/deuteron exchange between the host triazoles and $d_6$-acetone in a process that appears to be mediated by the formation of $HF_2^-$. The proton transfer reactions are inhibited by the presence of host that apparently sequesters fluoride ion.

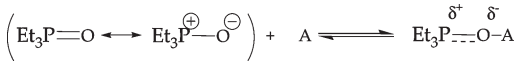
## Experimental Section

The synthesis and characterization of aryl-1,2,3-triazole oligomers **1a,b**, **2**, and **3** have been reported previously.[8] $^1$H NMR titration experiments were carried out with the corresponding tetrabutylammonium salts of bromide, hydrogen sulfate, iodide, nitrate, benzoate, and hexafluorophosphate.

**$^1$H NMR Titrations.** Host oligomer concentrations were kept to 1 mM by weighing out appropriate amounts of host and dissolving in either 500 $\mu$L or 1 mL of deuterated solvent. These stock solutions were diluted to 1 mM concentrations in 2 mL samples by pipet. Weighing an appropriate amount of the respective tetrabutylammonium chloride salt and dissolving in

1 mL of the 1 mM host solution yielded chloride stock solutions. Subsequent additions of anion from this stock solution enabled the host oligomer concentration to remain constant throughout the titration experiments, with the only possibleperturbation of concentration coming from evaporation of deuterated solvent. Anion was added sequentially to an initial 600 $\mu$L volume of the host by micropipet, and $^1$H NMR of the solution was recorded with chemical shifts of the 1,2,3-triazole CH proton recorded versus $d_6$-acetone (2.05 ppm).

**Acceptor Number of Binary Solvent Mixtures.** The Gutmann acceptor number (AN) of a solvent gives a quantitative measure of the solvent's ability to accept negative charge (for example, through hydrogen bonding). Acceptor numbers were derived by Gutmann and co-workers as empirical quantitites for characterizing the electrophilic properties of electron pair acceptor solvents. These unitless numbers are obtained from the relative $^{31}$P NMR chemical shifts produced by the electrophilic actions of acceptor solvents (A) in triethylphosphine oxide, described below:



The relative $^{31}$P NMR chemical shift values $\delta_{corr}$ (*n*-hexane as reference solvent, arbitrarily assigned 0) are related to those of the 1:1 complex $Et_3PO-SbCl_5$ ($\delta_{corr}(Et_3PO-SbCl_5)$) dissolved in 1,2 dichloroethane, which was arbitrarily assigned the value of 100. This empirical solvent parameter can be mathematically described by the following relationship:

$$\text{acceptor number (AN)} = [\delta_{corr\_}/\delta_{corr}(Et_3PO-SbCl_5)] \times 100 = \delta_{corr} \times 2.348$$

The acceptor numbers are dimensionless numbers describing the acceptor property of a given solvent relative to those of $SbCl_5$.[21,23a]

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**Supporting Information Available:** Additional spectra, titration data, and binding constant fits. This material is available free of charge via the Internet at http://pubs.acs.org.