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Intramolecular Hydrogen Bonds Preorganize an Aryl-triazole Receptor into a Crescent for Chloride Binding

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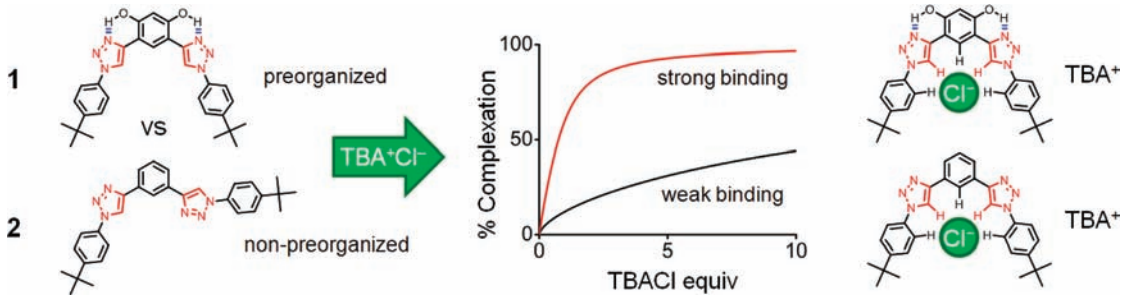
ABSTRACT



Aryl-triazole pentads have been preorganized with intramolecular hydrogen bonds to enhance chloride binding. This outcome highlights the dual hydrogen bond *donor and acceptor* properties of 1,2,3-triazoles.

Recent studies on macrocyclic triazolophanes,[1] aryl-triazole foldamers,[1b,2] and other triazole-containing molecules[3] have shown that C−H•••X⁻ hydrogen bonds are strong enough to play a major role in the field of anion supramolecular chemistry.[4] Triazolophanes have unexpectedly large halide binding constants, which take advantage of macrocyclic preorganization[5] to direct four triazole C−H donors and four phenylene C−H donors into the central cavity. On the other hand, flexible aryl-triazole oligomers containing the same number or more of C−H donors have binding constants that are weaker by orders of magnitude compared to rigid triazolophanes.[1b,2] Such effects were also observed between indole-based macrocycles and foldamers.[6] Thus, preorganizing the conformation of receptors is crucial for obtaining high binding affinities. Herein, we demonstrate a strategy to preorganize the conformations of aryl-triazole pentads using intramolecular hydrogen bonds to increase the Cl^- affinity without forming macrocycles.

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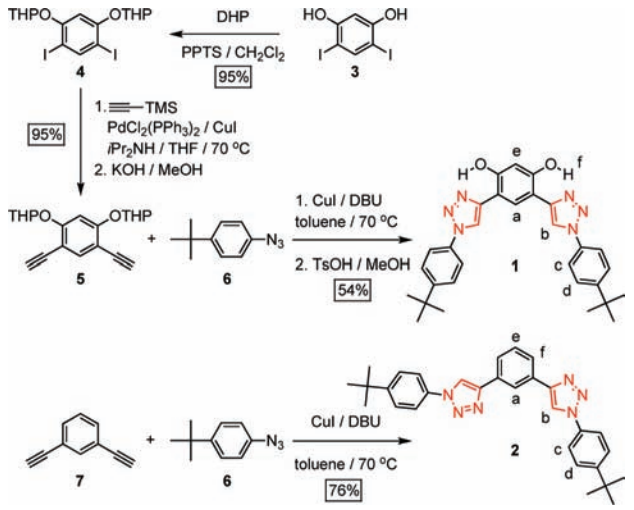
Intramolecular hydrogen bonds have been used in various types of foldamers[7] to preorganize their conformations and assist folding. For instance, aromatic oligo-amide,[8] -urea,[9] and -hydrazide[10] foldamers have been synthesized. Hydrogen bonds have also been used to achieve high yield macrocyclizations.[11] Isophthalamides with intramolecular hydrogen bonds[12] and oligoindoles with metal binding[13] showed an increase in the anion binding constant. Recently, triazole C−H···O hydrogen bonds have been investigated with the aid of X-ray crystallography.[14] Therein, it was also observed that the triazole C−H group forms intermolecular hydrogen bonds with triazole N^2/N^3 atoms in the crystal. It is noteworthy that the N^3 of a triazole could serve as a hydrogen bond acceptor. We envisioned, therefore, that the triazole's N^3 nitrogen could be used as an intramolecular hydrogen bonding site to preorganize aryl-triazole pentads.

Pentad **1** (Scheme 1) was designed to have two hydroxyl groups on the central phenylene that could form hydrogen bonds with the triazoles on either side. Although electron-donating groups on phenylene have been shown[15] to decrease the binding affinity in previous studies on triazolophanes,[1b] we assumed that preorganization would be the dominant factor in this case. *t*-Butyl groups were used on the terminal phenyls for the purpose of solubility. Pentad **2**, which does not have hydroxyl groups, was prepared as a control.

Scheme 1. Syntheses of Pentads **1** and **2**



Synthetic routes for pentads **1** and **2** are shown in Scheme 1. Diiodoresorcinol (**3**) was protected with tetrahydropyran (THP) groups using dihydropyran (DHP) with a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) to give **4**. Sonogashira coupling of **4** with trimethylsilylacetylene followed by desilylation provided diacetylene **5** in 95% yield. **5** was "clicked"[16] with aryl azide **6**, and then the THP groups were removed to afford pentad **1** in a moderate yield. Aryl triazole pentad **2** was prepared by click reaction between **6** and **7**. All compounds were fully characterized.[17] 2D NOESY studies on **1** (strong $H^{a,b}$ and $H^{b,c}$ cross peaks) and **2** (medium $H^{a,b}$, $H^{b,c}$, and $H^{b,f}$ cross peaks) are consistent with greater preorganization of **1**.[17]

The ^{1}H NMR titration (Figure 1) of **1** and **2** with tetrabutylammonium chloride (TBACl) in CD_2Cl_2 provides insight into the structures of the resulting complexes in solution. The downfield position of the −OH ^{1}H NMR signal in pentad **1** (10.9 ppm), compared to **3** (5.4 ppm), indicates that it is deshielded by hydrogen bonding. Upon addition of TBACl, pentads **1** and **2** both showed large downfield shifts of the triazoles' H^b and central phenylene's H^a protons. The α-CH_2 proton of the TBA^+ cation peak also shifted in both titrations indicating that TBA^+ is involved in the solution-phase equilibria. Additionally, the −OH signal of **1** did not have a large peak shift, which implies that it does not have a direct interaction with Cl^-.

Quantitative analysis of the ^{1}H NMR titration data was achieved using combinations of the following equilibria

$$\mathrm{P} + \mathrm{Cl}^- = \mathrm{P}\cdot\mathrm{Cl}^- \quad K_a \tag{1}$$

$$\mathrm{TBA}^+ + \mathrm{Cl}^- = \mathrm{TBA}^+\cdot\mathrm{Cl}^- \quad K_{ion} \tag{2}$$

$$\mathrm{P} + \mathrm{TBA}^+\cdot\mathrm{Cl}^- = \mathrm{P}\cdot\mathrm{Cl}^-\cdot\mathrm{TBA}^+ \quad K_{ipc} \tag{3}$$

$$\mathrm{P}\cdot\mathrm{Cl}^- + \mathrm{TBA}^+ = \mathrm{P}\cdot\mathrm{Cl}^-\cdot\mathrm{TBA}^+ \quad K_{ipc}' \tag{4}$$

(P: Pentad **1** or **2**)

In addition to formation of the 1:1 complex ($P\cdot Cl^-$, K_a), we included the ion pairing,[18] both competitive with TBACl

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(17) Supporting Information.

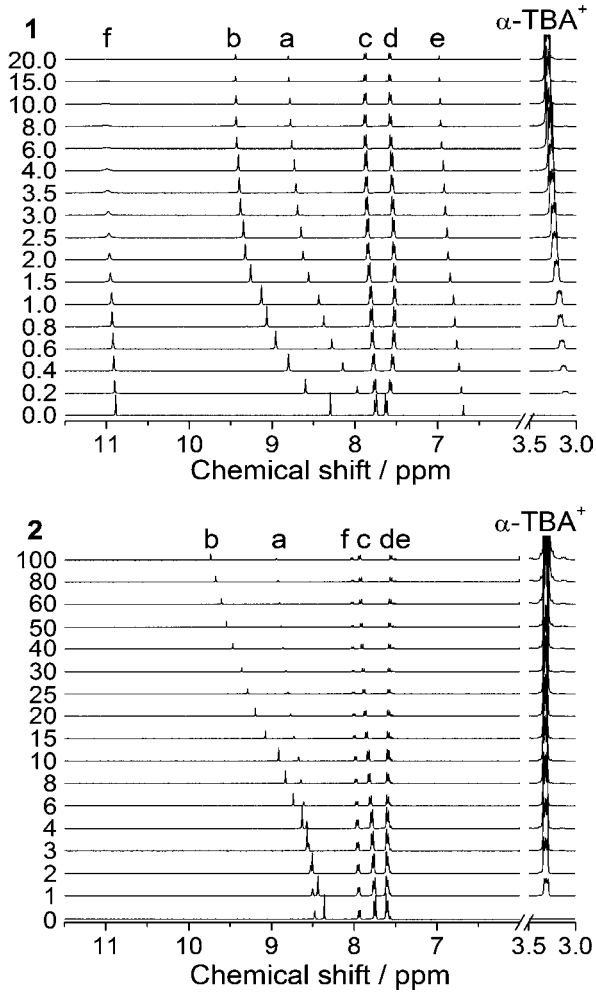

Figure 1. ^{1}H NMR titration (5 mM CD_2Cl_2, 298 K) of **1** and **2** with increasing equivalents of TBACl.

(K_{ion})[19] and as the ion-paired complex (P•Cl^-•TBA^+, K_{ipc} or K_{ipc}'). The latter was inferred from peak shifts of the TBA^+ signal.[17] Data fittings (Table 1)[17] were conducted using HypNMR.[20] Fitting of the data for **2** is based on the

Table 1. Equilibrium Constants (M^{-1}) and Free Energies (kJ•mol^{-1}) Obtained from Fitting the ^{1}H NMR Data

	K_a (ΔG)	K_{ion} (ΔG)	K_{ipc} (ΔG)	K_{ipc}' (ΔG)
1	46800 ± 2500 (−26.6)	72000 ± 5000 (−27.7)	360 ± 10 (−14.6)	550 ± 80 (−15.6)
2	1000 ± 250 (−17.1)	72000 ± 5000 (−27.7)	8 ± 1 (−5.2)	550 ± 80 (−15.6)

assumption that K_{ipc}' (**1**) is equal to K_{ipc}' (**2**), i.e., complexes **1**•Cl^- and **2**•Cl^- have similar structures.

The anion binding strength (Table 1) of preorganized pentad **1** is ~50 times greater than **2** ($\Delta\Delta G$ = 9.5 kJ mol^{-1}). This enhancement is similar to isophthalamide ($\Delta\Delta G$ = 8.2 kJ mol^{-1})[12] and indole ($\Delta\Delta G$ = 9.1 kJ mol^{-1})[13] receptors. All three systems are consistent with the entropy content of rotation about sp^2-sp^2 single bonds.[21] While the C−H hydrogen bond of **1** will also be enhanced by polarization,[17] preorganization seems to dominate.

The intramolecular hydrogen bond is observed in the X-ray crystal structure of pentad **8** (Figure 2)[17] where the backbone

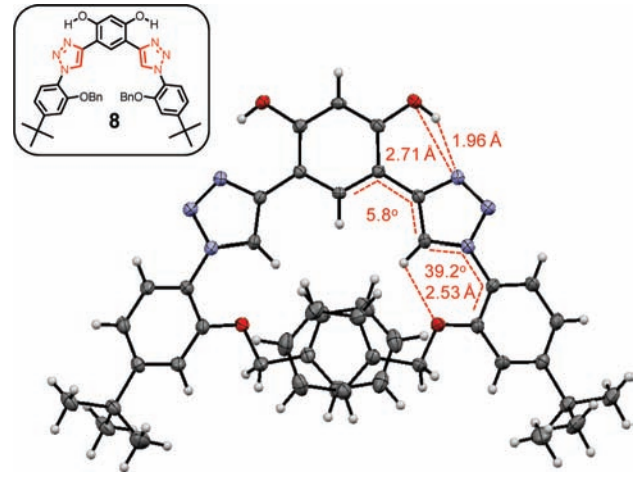

Figure 2. Crystal structure of pentad **8**. Non-hydrogen atoms are drawn with 50% probability ellipsoids.

is preorganized into a crescent. Two OH···N^3 hydrogen bonds are formed, and the triazole C−H forms a hydrogen bond with the benzylether's oxygen atom.[14]

In conclusion, intramolecular hydrogen bonds between hydroxyl groups and triazole N^3 preorganize the pentad backbone for Cl^- binding to enhance the binding constant. Such intramolecular hydrogen bonds could be further extended to preorganize foldamers and receptors.

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Note Added after ASAP Publication. Scheme 1 contained errors in the version published ASAP April 7, 2010; the correct version reposted April 12, 2010.

Supporting Information Available: Syntheses, experimental procedures, tables of X-ray crystallography, and titration data. This material is available free of charge via the Internet at http://pubs.acs.org.

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