Molecular Recognition

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1,2,3-Triazole CH···Cl^- Contacts Guide Anion Binding and Concomitant Folding in 1,4-Diaryl Triazole Oligomers**

*Hemraj Juwarker, Jeremy M. Lenhardt, David M. Pham, and Stephen L. Craig**

In memory of Dmitry Rudkevich

Manipulation of weak intermolecular interactions guides the rational design[1] of sensors, drugs, and foldamers-synthetic,[2] nonnatural backbones that fold into an ordered, biomimetic array. 1,4-Substituted 1,2,3-triazoles, which are readily accessible through the Cu^I-catalyzed Huisgen 1,3-dipolar cycloaddition of azides and alkynes,[3] are seemingly universal ligation tools[4] whose capacity for independent function has received far less attention. Recent reports, however, indicate that the size and dipole moment ($\approx$5 D) of triazoles make them interesting candidates for amide bond surrogates,[5] and Arora and co-workers have reported the contributions of triazoles to the conformational preferences of peptido-triazole oligomers.[6]

We hypothesized that oligomer **1** would fold in a manner similar to other linear, flexible oligomers[7] to provide a model cavity by which to explore the intermolecular interactions between the electropositive CH side of 1,4-triazoles and electron-rich guests such as anions (Figure 1). Our expectations were buoyed by previous reports of anion-induced folding,[8,9] in particular by a recent demonstration by Jeong and co-workers[8] that the folding of oligoindoles can be directed through a helical arrangement of NH···anion hydrogen bonds. Herein, we report 1) that 1:1 interactions between diaryl triazoles and chloride ions in acetone are directional and sufficiently strong as to be observable by ^{1}H NMR spectroscopy, 2) that the strength of the interaction increases with the generation of triazole-containing oligomer, and 3) that CH···anion contacts guide the folding of aryl triazole oligomers in solution and in the solid state.

While the "click" coupling of alkyl azides with alkynes is highly efficient,[10] the formation of diaryl triazoles has, until recently, been relatively more difficult and less efficient.[11] Nonetheless, under modified conditions, the Cu^I-catalyzed cycloaddition produces acceptable yields of the desired 1,4-diaryl-1,2,3-triazole-containing compounds **1**–**3**. A tetraethylene glycol unit was introduced outside of the cavity for solubility.

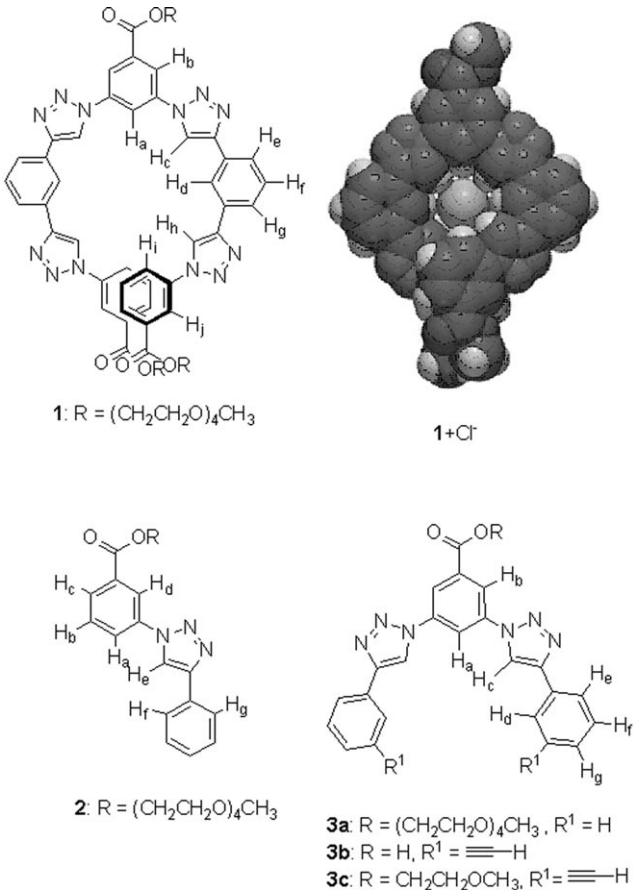

Figure 1. 1,4-Diaryl-1,2,3-triazole oligomers **1**, **2**, and **3** depicted in their inferred chloride binding conformations. Top right: Lowest energy minimization structure (Macromodel 7.0, Amber* force field, $CHCl_3$) of **1**·Cl^-. Side chains are replaced with OCH_3 groups.

Oligomer **1** has appreciable conformational freedom only around the arene–triazole single bonds. Molecular modeling[12] suggested no significant preference for a particular rotamer, a prediction that is supported by NOESY spectra of **1** in [D_6]acetone (Figure 2a). Modeling studies also show that complexation of **1** with Cl^- aligns the electropositive triazole CH units toward the interior of a helix, within which the Cl^- is bound.

The computer modeling holds true in solution, where the chloride-induced folding of **1** is revealed by ^{1}H NMR spectroscopy. The ^{1}H NMR spectrum of **1** changes considerably upon the addition of tetrabutylammonium chloride ($Bu_4N^+Cl^-$). At 1 mM in [D_6]acetone, triazole protons H_c and H_h shift downfield (from δ = 9.5 and 9.3 ppm to 10.9 and

[*] H. Juwarker, J. M. Lenhardt, Dr. D. M. Pham, Prof. S. L. Craig
Department of Chemistry, French Family Science Center
Duke University, Durham, NC 27708-0346 (USA)
Fax: (+1) 919-660-1605
E-mail: stephen.craig@duke.edu

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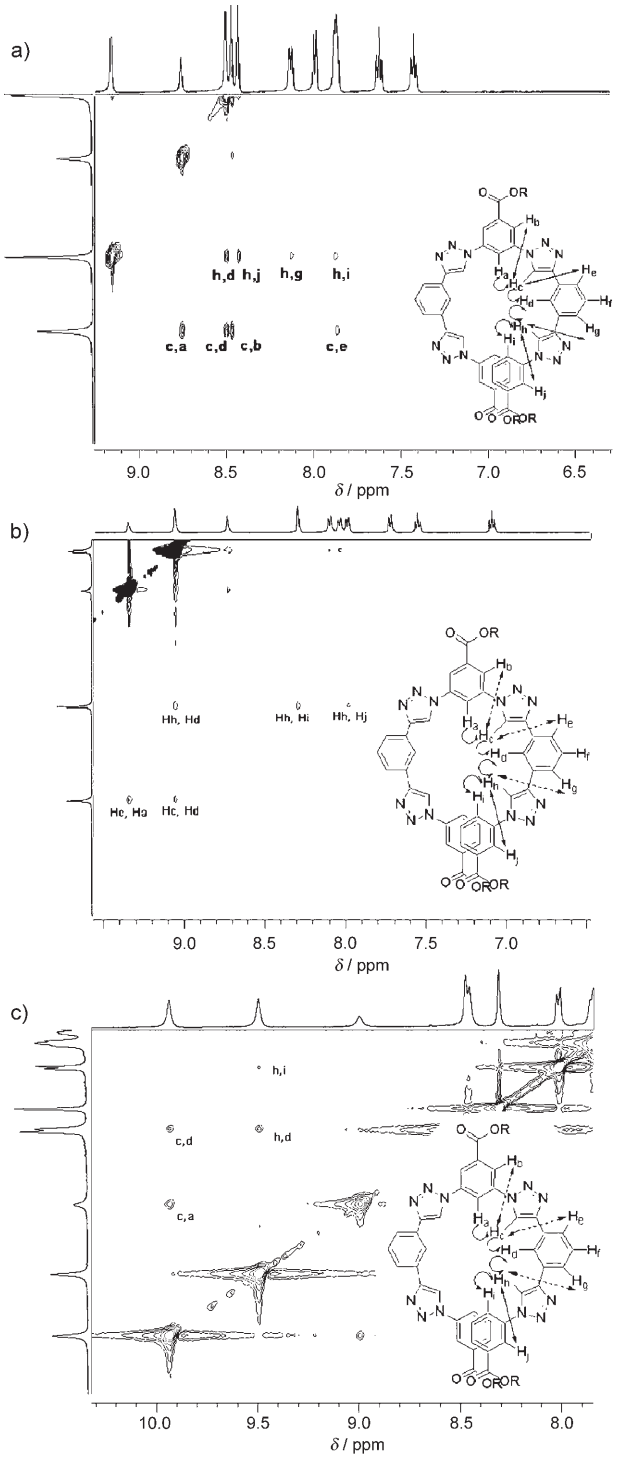

Figure 2. Partial ^{1}H-^{1}H NOESY spectra (500 MHz, [D$_6$]acetone, 298 K, 0.45 ms mixing time) of a) **1** (7.0×10^{-3} M), b) **1** (7.0×10^{-3} M) and $Bu_4N^+Cl^-$ (7.3×10^{-3} M), and c) **1** (7.0×10^{-3} M) and $Bu_4N^+F^-$ (7.3×10^{-3} M). Strong (solid arrows) and weak or absent contacts (dashed lines) indicate a preference for a helical conformation in the presence of the ions.

10.2 ppm, respectively) upon addition of 1 equivalent $Bu_4N^+Cl^-$, indicative of a polarizing, hydrogen-bonding-like interaction. The Cl^- concentration dependence of the chemical shift of H_c in **1** is substantially different from that of the corresponding protons in **2** and **3** (vide infra), showing that these shifts are due to tight, directional binding of Cl^- rather than a bulk dielectric effect. Similar, but less dramatic, downfield shifts are observed in the aryl protons H_a and H_d, which are expected constituents of the cavity interior. Importantly, the putative peripheral protons of the helix (H_b, H_e, H_f, and H_g) feature *upfield* shifts, indicating increased shielding as the electron density of **1** is polarized away from the helix interior.

The chloride-induced folding is confirmed by 2D NOESY experiments.[8,13] While the various rotamers of **1** are equally populated, NOESY contacts in the presence of $Bu_4N^+Cl^-$ indicate that the folding depicted in Figure 1 is operative. Specifically, upon Cl^- binding, H_c has a strong contact with H_a rather than H_b, as well as a stronger contact with H_d than H_e. Similarly, triazole proton H_h has a stronger contact with H_d than H_g (Figure 2b).

We expected that individual triazole–anion interactions would be too weak to be observed in polar solvents outside of multivalent hosts such as **1**. On the contrary, titration of **2** with $Bu_4N^+Cl^-$ in [D$_6$]acetone leads to a gradual downfield ^{1}H NMR shift in the triazole proton H_e. A Job's plot[14] confirms a 1:1 binding stoichiometry, and a fit to the chemical shift titration data gives a binding constant of $12\pm0.3\,M^{-1}$ and an endpoint for the completely complexed proton of $\delta=$ 10.8 ppm (Table 1). The binding is a factor of ca. 10 smaller than that of the conventional NH hydrogen bond donor 1,4-diphenylpyrrole ($140\,M^{-1}$).[15]

Table 1: Bu_4N^+ halide binding constants and changes in chemical shift of H_c (for **1** and **3a**) or H_e (for **2**) upon binding, as determined from 1:1 Benesi–Hildebrand fits to ^{1}H NMR titration data in [D$_6$]acetone.

Aryl triazole	Anion[a]	K [M^{-1}]	$\Delta\delta_{max}$ [ppm][b]
1	Cl^-	1.7×10^4	1.60
1	Br^-	1.2×10^4	1.52
1	I^-	1.3×10^2	1.20
2	Cl^-	1.2×10^1	1.61
3a	Cl^-	1.3×10^3	2.03

[a] Accurate fluoride binding constants could not be obtained due to apparent aggregation with excess fluoride. [b] Difference in chemical shift of triazole proton for free vs. complexed triazole.

Similar downfield shifts, although of smaller magnitude, are observed for H_a and H_f, protons that would also contact Cl^- in the binding mode shown in Figure 1. The chemical shifts of protons that are not involved in the expected anion complexation are observed to move either very little or upfield. Binding constants determined from the H_a and H_f titration data agree within experimental error with that from H_e (Supporting Information). That the $\Delta\delta$ of H_a is threefold greater than that of H_d suggests an orientation preference of the ester group away from the bound chloride ion. This preference is also observed in the NOESY spectrum of **2**·Cl^-; the H_a–H_e contacts are greater than H_d–H_e. Importantly, the conformational preference is a consequence of Cl^- binding, as **2** alone in [D$_6$]acetone exhibits stronger H_d–H_e contacts (Supporting Information).

Increasing the number of triazoles results in the formation of a more positive cavity, and stronger interactions are observed with trimer **3a**. A Job's plot again confirms a 1:1 interaction, and the best fit to the ^{1}H NMR titration of **3a** with $Bu_4N^+Cl^-$ gives an association constant of $1.3\times10^3\,M^{-1}$ (Table 1). Similarly to **1** and **2**, upon chloride binding the triazole proton H_c exhibits the strongest NOESY contacts with aryl protons H_a and H_d, consistent with the expected orientation shown in Figure 1. Solid state data provide further support for a pro-helical conformation in **3a**·Cl^-; the mode of binding deduced from the NMR spectra is observed in crystallography data obtained for the Bu_4N^+ salt of acid **3b** complexed with Cl^- (Figure 3).[22]

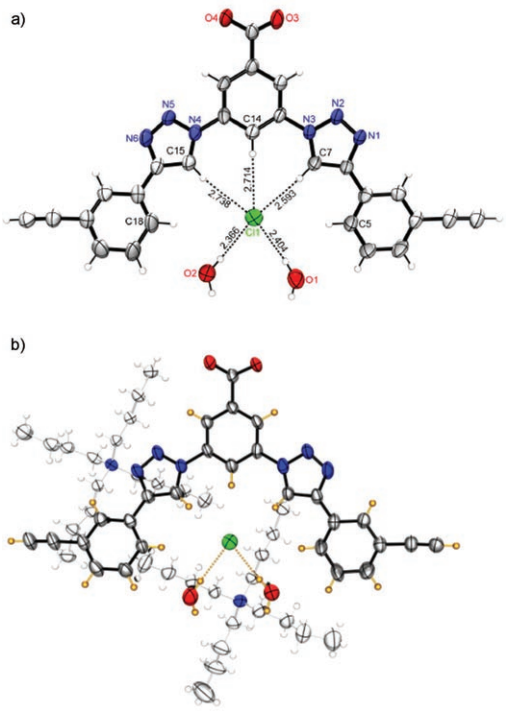

Figure 3. The crystal structure of **3b**·Cl^- shows a crescent-shaped conformation in which the triazole protons face inward to form a half-ring with five CH···Cl^- contacts. Crystal structure (a) shows interatomic distances with Cl^- while (b) depicts the position of Bu_4N^+ counter ions. Note the presence of water molecules hydrogen-bonding to the anion.

As expected, the four triazoles of **1** result in stronger chloride binding than for **2** or **3**. A Job's plot confirms 1:1 binding in this case as well, and fits to titration data give a binding constant of $1.7\times10^4\,M^{-1}$. While the chloride ion is a good guest and an effective inducer of folding, however, it is not unique. Similar folding (Figure 2c) and binding (Table 1) are observed with other Bu_4N^+ halides.

Taken together, these results demonstrate that triazoles have potentially important interactions with ions, and that these interactions guide the folding of aryl triazole-based oligomers. The potency of these interactions places them in good company relative to other CH sources,[16] and triazoles therefore provide an alternative to conventional protic hydrogen bonds and coordination complexes as functional components in anion receptors.[17] Potential advantages are likely to be situational rather than general, for example, synthetic accessibility and chemical compatibility. Ongoing work in our lab suggests that similar interactions with triazoles may be important for a variety of electron-rich guests, particularly when presented in a multivalent fashion. We expect that the intrinsic electronic properties of triazoles (e.g., large dipole moment, electropositive CH) will lead to their increasing use as functional units, including but extending beyond their utility as amide surrogates,[18] the basis for new classes of foldamers,[2] or components of polymers with new properties.[19] On the basis of strong anion binding, one can also imagine triazoles as potential aprotic, organic Lewis acid catalysts.[20,21]

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[22] CCDC-663329 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

