Anion Receptors

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Pure C–H Hydrogen Bonding to Chloride Ions: A Preorganized and Rigid Macrocyclic Receptor**

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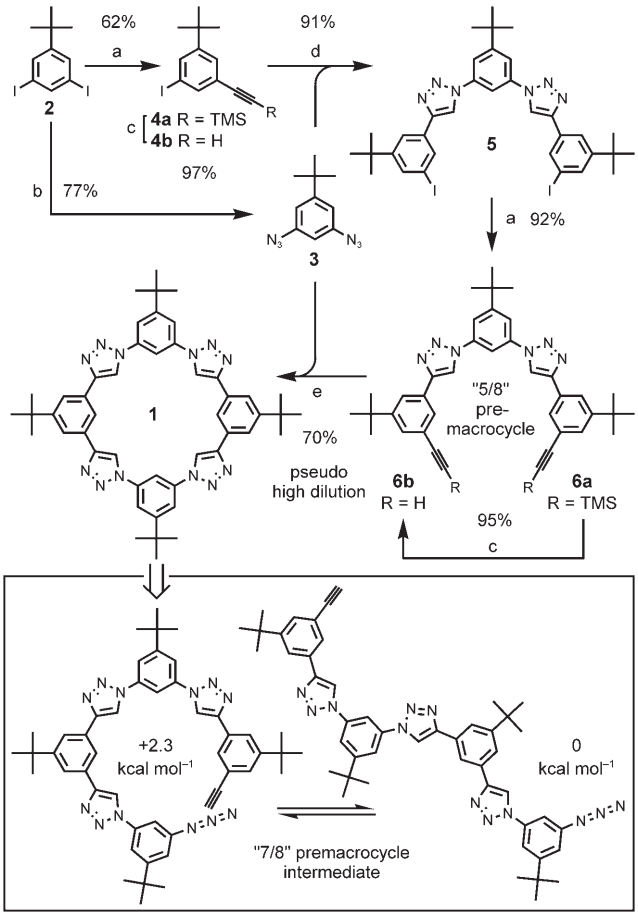
Anions play important chemical and biological roles,[1] and the supramolecular chemistry involving them[2] has grown accordingly.[3] These developments range from fundamental studies on noncovalent bonding[4] to the design of anion receptors[2,5,6] and anion assistance to asymmetric catalysis.[7] A substantial number of artificial organic hosts for anions incorporate strong hydrogen bonds (H-bonds), usually N–H···X^-,[8] e.g., calixpyrrole, or if C–H···X^- H bonds are used, the carbon atom is adjacent to a cationic center, e.g., imidazolium.[9] The strength and the relative significance of weak C–H···X^- H bonds originating from neutral ring systems has been examined recently.[10] Although stronger than previously thought, these H-bonds were only considered as "additional binding sites within a host cavity."[10b] It was surprising, therefore, to discover a break from this dogma when strong chloride binding was displayed by a novel macrocycle described herein, in which there are only aromatic C–H···Cl^- H-bonds.[11] This example appears to strengthen further Cram's idea[12] that a rigid host in which each binding site is preorganized[13] should show the strongest guest binding.

The design for this receptor was originally motivated from the ongoing synthetic developments[14] in shape-persistent macrocycles together with the recognized efficiency of the copper-catalyzed[15] 1,3-dipolar cycloaddition of terminal azides and acetylenes to generate the five-membered 1,2,3-triazole ring system. In recent studies,[16] these triazoles were distinguished from other ring systems by the relief of steric strain provided by the sp^2 nitrogen atoms in the ring system. This observation stimulated the prediction, elaborated herein, that 1,4-disubstitution of triazoles with phenyl rings will produce inter-ring coplanarity that would establish a favorable building block for the preparation of planar macrocycles. To that end, we developed the efficient synthesis (27% yield, seven steps), using click chemistry, of a shape persistent macrocycle incorporating phenylene subunits. It was on the basis of this work that the discovery was made that the macrocycle displays a high affinity for chloride ions supported solely by C–H···Cl^- H-bonds.

In a structural context, the planar 1,2,3-triazole ring system defines a nonlinear interconnection geometry. The triazole bears one sterically active C^5-H hydrogen. With these features and the hypothesized coplanarity in mind, a computer-aided approach using molecular mechanics (MM2) was employed in the design of a planar macrocycle **1** (Scheme 1). Eight ring systems are linked together, wherein four triazoles alternate with four phenyl rings. This design allows for minimal deviations from ideal bond angles and minor steric interactions between hydrogens on adjacent ring systems. The



Scheme 1. Synthesis and partial retrosynthetic analysis (inset) of **1**: a) TMSC≡CH, $[PdCl_2(PPh_3)_2]$, CuI, iPr_2NH, THF, Ar, 8 h; b) NaN_3, CuI, DMEA, sodium ascorbate, EtOH/H_2O/PhMe (7:3:1), reflux, Ar, 1 h; c) KF, MeOH, THF, 8 h; d) $CuSO_4$, sodium ascorbate, EtOH/H_2O/PhMe (7:3:1), Ar; e) dropwise addition of **3** and **6b** over 10 h to CuI, DBU, PhMe, Ar, stirring, 4 h. TMS = trimethylsilyl; DMEA = *N*,*N*′-dimethylenthylenediamine; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

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structure is two-fold symmetric, with one pair of facing phenyl rings having N^1-bound triazoles, whereas the other pair are C^4-bound. The calculated size of the central cavity of **1** (HF/3-21G*) is determined by the 5.38, 5.90, and 5.96-Å internuclear distances between facing pairs of hydrogen atoms on triazole groups, and on the nitrogen-linked and carbon-linked phenyl groups, respectively. These endocyclic hydrogen atoms define a space-filling cavity with a diameter of about 3.8 Å, sufficient to contain a chloride ion (ionic radius = 1.81 Å).[2,17] Based on the shorter of the three interhydrogen distances, the calculated distance from the triazole hydrogen to the center of the cavity is 2.69 Å. This is long enough to support a linear C–H···Cl^- interaction based on an analysis of 8537 observed C–H···Cl^- interactions[18] from which circa 11% display similar or shorter interatomic distances. Finally, a range of substituents on the phenyl ring were screened computationally from which it was hypothesized that meta substitution with *tert*-butyl groups would enhance solubility and inhibit π-stacking while retaining planarity.[14]

A convergent synthesis by a "5/8" pre-macrocyclic oligomer, wherein five of the eight ring systems are present, was considered as the initial cyclization strategy.[14] Macrocyclization will be facilitated if the immediate precursor to **1** is preorganized. To investigate the energy landscape leading to **1**, a model of this likely precursor was obtained by disconnecting the macrocycle through one of the triazole linkages to generate a "7/8" oligomer with a terminal alkyne and azide functionality (Scheme 1, inset). A Monte Carlo simulation (MM2) of the possible conformations returned 66 low-energy conformers, each showing little deviation from inter-ring coplanarity. The single conformer (50th based on relative energy) that is preorganized to resemble the macrocycle is seen at + 2.3 kcal mol^{-1}. Although the statistical population of this conformer will be relatively low, we considered employing pseudo-high-dilution reaction conditions to mitigate this nonideal situation. Furthermore, the energy profile (HF/3-21G*) generated by rotating one of the N^1- or C^4-bound triazole groups past the central phenylene unit in both N^1- and C^4-bound 1,3-bis(triazole)benzene models produces torsion barriers of 6 and 4 kcal mol^{-1}, respectively (see Supporting Information). These analyses suggested that, for the hypothetical 7/8 premacrocyclic intermediate, this potential energy surface could be rapidly traversed, allowing the reaction to funnel towards the final copper-catalyzed macrocyclization rather than generating oligomeric byproducts.[14c]

A stepwise approach (Scheme 1) was employed to prepare the macrocycle **1**. The diiodo compound **2**[19] served as an excellent starting material to access building blocks **4a**,**b**, using Sonogashira conditions, as well as the diazide **3**. The latter diazide is itself utilized in two different steps. The first, using click chemistry conditions, with the trimethylsilyl-protected monoethynyl **4b** leads to the diiodo 5/8 oligomeric intermediate **5**, which was converted into the diethynyl 5/8 premacrocycle using standard Sonogashira conditions and deprotected to afford **6b** in excellent yields. The second use of diazide **3** is in the final one-pot intermolecular coupling followed by unimolecular cyclization to generate **1**. Pseudo-high-dilution conditions are employed for the macrocyclization, wherein a 1:1 mixture of **3** and **6b** (0.2 mmol, PhMe) is added dropwise over 10 h to a heated solution (70 °C) of CuI (0.03 mmol) with the base DBU (1,8-diazo-[5.4.0]bicycloundec-7-ene) in PhMe. During the addition of each drop (ca. 200 μL) to the reaction mixture, there is an approximate 200-fold excess of Cu^I catalyst. This situation is believed to favor the formation of a copper-acetylide[20] of **6b** that can react with **3** under the pseudo-high-dilution conditions to generate, by an intermolecular coupling, the 7/8 premacrocyclic intermediate followed by the final unimolecular cyclization. Initially, the product was isolated in a 50% yield after chromatographic separation (SiO_2) as a white solid. An improved yield, 70%, which was obtained after exhaustive degassing of the reaction mixture with argon, indicates that the macrocyclization does in fact occur faster than the reaction of a terminal copper acetylide with another incoming (di)azide.

The identity of the macrocycle was confirmed from a single peak in the MALDI-TOF mass spectrum with *m*/*z* 797.6. The ^{1}H NMR spectrum (CD_2Cl_2) displays five well-separated singlets in the aromatic region (Figure 1). The single downfield peak at $\delta = 9.59$ ppm corresponds to the four

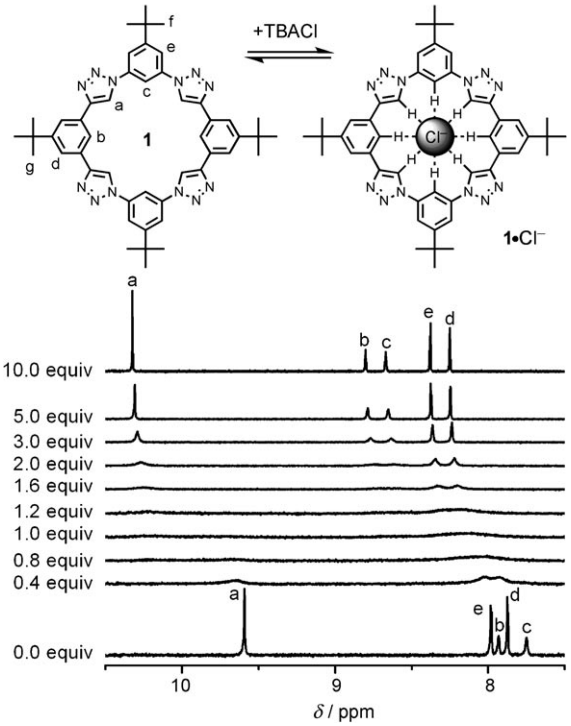

Figure 1. ^{1}H NMR spectra (aromatic region) of **1** upon titration with tetrabutylammonium chloride (TBACl); CD_2Cl_2, 298 K.

H^5 triazole hydrogen atoms residing in identical chemical environments. This position is significantly shifted 1.27 ppm downfield compared to **6b** (see Supporting Information). This shift arises when the triazole hydrogen atoms are located within the greater deshielding environment generated by the ring currents of all four phenyl rings. The ^{1}H NMR data were assigned with the aid of 2D experiments (see Supporting Information), and are consistent with the two-fold symmetry. The through-space couplings measured using 2D NMR

(ROESY) spectroscopy are consistent with the predicted planar structure, although deviations from complete planarity cannot be excluded at this stage.

The host–guest chemistry between the macrocycle and the chloride anion is immediately detected by a dramatic increase in the solubility of the macrocycle beyond 1 mM (CH_2Cl_2) upon the addition of tetrabutylammonium chloride (TBACl). More quantitatively, a solution of **1** (2 mM, CD_2Cl_2) was titrated with up to 10 equivalents of TBACl with concomitant downfield shifts (Figure 1) in all aromatic hydrogen signals. The triazole hydrogen signal shifts downfield by 0.73 ppm, the endocyclic hydrogen atoms of the N^1- and C^4-linked phenyl units shift 0.92 and 0.87 ppm, respectively. The exocyclic hydrogen atoms of the phenyl rings distal from the central cavity shift only half as much (ca. 0.4 ppm). The retention of the simple peak pattern and the similar magnitude of the shifts in all the endocyclic hydrogen atoms are consistent with the macrocycle maintaining its shape[14] and with the localization of the chloride ion inside the cavity. A geometry optimization (HF/3-21G*) supports this interpretation and shows that the chloride ion is held within the plane of the macrocycle, which is consistent with the circa 3.7-Å cavity diameter. The observation of extensive line broadening after the addition of one equivalent of the chloride ion is consistent with binding dynamics occurring on the same timescale as the ^{1}H NMR experiment. A preliminary variable temperature analysis (see Supporting Information) places the barrier for this process at around 14.5 kcal mol^{-1}.

The binding strength of **1** for chloride ions was determined by recording the changes (Figure 2a) in the UV absorption (265 nm) as a function of chloride-ion concentration. Based on the Job-plot determination of 1:1 binding stiochiometry, the data were fitted to a binding isotherm (Figure 2b) providing the calculated association constant of $K_a = (130000 \pm 30000)\,\text{M}^{-1}$; $\Delta G = -7.0$ kcal mol^{-1} (CH_2Cl_2, 298 K). Potential aggregation effects[14] were excluded on the basis of a UV dilution study (see Supporting Information), substantiating 1:1 binding. The strength of the binding is comparable to a wide range of receptors.[5,6,8,9] What is remarkable, however, is that this association occurs solely with the use of C–H···Cl$^-$ H-bonds, and arises from within a neutral receptor. Triazole-based C^5–H H-bonds or close contacts have been seen in many solid-state structures.[21] In those instances, and presumably here, the H-bonds are aided by the relatively large 5-Debye dipole,[15c,22] with its positive end directed almost in line with C^5–H bond. Furthermore, on account of the shape persistence, there is a negligible energy cost that is often associated with a change in the conformation of the receptor.[12] The dominant role of preorganization was confirmed using a model compound, produced by click chemistry between **6b** and phenylazide, which contains the four triazole units but delivers significantly reduced binding affinity ($K_a = 7\,\text{M}^{-1}$).

In summary, good yields of a shape-persistent macrocycle have been established based upon a sequence of Sonogashira and click-chemistry reactions. The collective effect of the preorganized shape of the macrocycle, the ideal size of the inner cavity, and the cumulative result of multiple weak C–H hydrogen bonds determine a relatively strong affinity for chloride ions. This discovery highlights the broader strategy of bringing efficient reaction chemistries into synergy with the intrinsic properties of the resulting chemical functionality, in this case, the 1,2,3-triazole ring system.

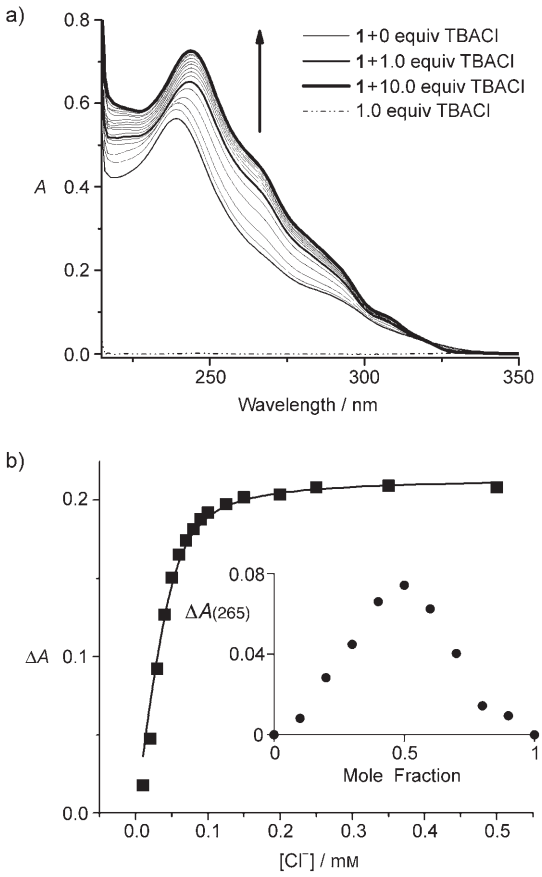

Figure 2. a) UV titration of **1** with TBACl (CH_2Cl_2, 100 μM) and b) the fitting analysis (Job Plot: inset) obtained from UV spectroscopy.

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