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Carbonyl Groups as Molecular Valves to Regulate Chloride Binding to Squaramides

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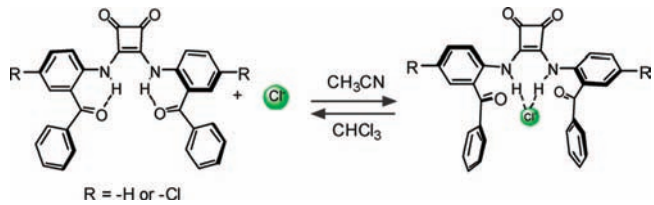
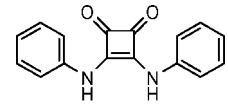
ABSTRACT



Environment-sensitive binding of anions to synthetic receptors is important for the functional mimicry of ion channels. We describe new squaramide-based chloride ion receptors whose anion binding cavity can be opened and closed by using carbonyl groups as valves. In nonpolar solvents, the carbonyls preclude chloride binding via intramolecular hydrogen bonding with the squaramide NHs. In polar solvents, disruption of the intramolecular hydrogen bonds reorients the carbonyl groups and opens the anion-binding cavity.

Artificial receptors for chloride ions are increasingly sought after as mimics of anion channels.[1] In diseases such as cystic fibrosis that are caused by mutations in chloride channels, artificial receptors could potentially serve as surrogate chloride transporters for rectifying defective ion transport.[1b] However, in the synthetic Cl^- ion receptors reported so far,[2] the incorporation of an environment-dependent switching/gating mechansim has rarely been attempted.[2h,3] This is rather surprising since gating is an integral feature of all ion channels.[4] "Smart" artificial chloride ion receptors whose binding cavities can be opened and closed in response to changes in the environment can be useful in regulating ion transport[1] as well as in other areas including environmental remediation[5] and sensor design.[6]

In our strategy (Scheme 1) to regulate chloride binding, we envisioned a molecular valve approach.[7] We sought to exploit secondary diphenyl squaramides, which are known to prefer the extended ZZ conformation,[8] as the anion-binding scaffold.[9] We reasoned that introduction of *o*-carbonyl substituents capable of intramolecular hydrogen



ZZ conformer

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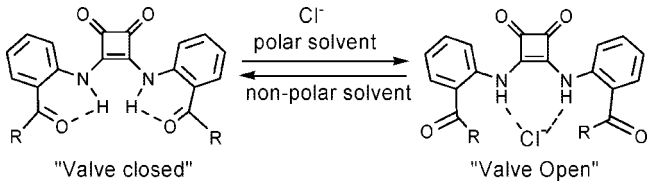
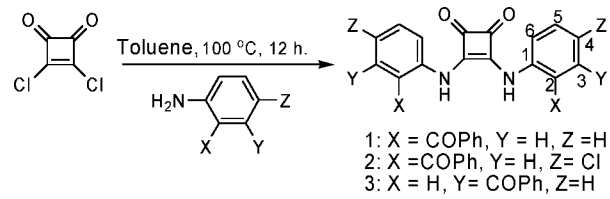
Scheme 1. Proposed Molecular Valve Approach



Scheme 2. Synthesis of Secondary Squaramides



bonding with the squaramide NHs would preclude anion binding. We anticipated further that a combined solvent-induced disruption[2h] of the intramolecular hydrogen bond and anion-induced reorientation of the carbonyls[3f,10] would facilitate binding. We wish to describe in this paper the use of carbonyl groups as molecular valves to regulate chloride ion binding to squaramides. The opening and closing of the carbonyl valves is controlled by solvent-polarity dependent intramolecular hydrogen bonding.

The key distinguishing feature of our work is that we exploit the rigid preorganized anion-binding cavity in squaramides and use intramolecular hydrogen bonding to open and close the cavity. Our approach complements that of Santacroce et al.,[3a] who used intramolecular hydrogen bonding as a tool for preorganizing the anion-binding cavity of isophthalimides.

Benzoyl-substituted squaramides **1**−**3** were chosen as the chloride ion receptors and were synthesized (Scheme 2) by reaction of squaric acid chloride with the appropriate substituted aniline.[11] The crude squaramides were purified by chromatography followed by repeated recrystallization.

NMR analysis showed that the H_6 doublet was consistently the most deshielded signal in the benzoyl squaramides **1**−**3**. This indicated a preference for the extended ZZ conformation with the deshielding attributable to the proximity of H_6 to the cyclobutene dione carbonyl.[8a] In the case of the ortho-substituted derivatives **1** and **2**, the ZZ conformation is further reinforced by intramolecular hydrogen bonding between the carbonyl of the ortho benzoyl groups and the squaramide N-Hs.[12] This is suggested by the following: (a) the 2 ppm downfield shift of the N−H signal for the ortho isomers (11.4 and 11.3 ppm, respectively, for **1** and **2** in $CDCl_3$) relative to the meta derivative **3** (9.2 ppm in $CDCl_3$); (b) in the ^{13}C NMR spectra, the benzoyl carbonyl in the ortho derivative **1** is deshielded by ∼4 ppm compared to the meta isomer **3**; and (c) in IR spectra, in $CHCl_3$, the benzoyl carbonyl signal of **1** and **2** appears at lower frequencies (1641 cm^{-1} and 1644 cm^{-1} respectively) than that for the meta derivative **3** (1660 cm^{-1}).

The interactions of the *o*-benzoylsquaramides **1** and **2** with chloride ions[13] were dependent on solvent polarity (Figure 1). In nonpolar solvents such as toluene, methylene chloride, and chloroform, there was no observable interaction of the squaramides with chloride ions despite addition of a large excess. In contrast, in polar solvents such as acetonitrile, addition of Cl^- ion led to a downfield shift of the N−H peak along with changes[14] in the aromatic region of the NMR spectrum, suggestive of a hydrogen-bonded supramolecular complex. The alternative possibility of covalent attachment of the chloride to the benzoyl carbony[15] was considered

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(13) The addition of Br^- or I^- to **1** (or **2**) did not lead to any solvent-polarity dependent NMR spectral shifts. For F^-, $CH_3CO_2^-$, and $H_2PO_4^-$ there were no spectral changes in $CHCl_3$ but in CH_3CN, a 77 nm bathochromic shift in the UV−vis spectra was identical to that generated by the addition of OH^- indicating deprotonation of the squaramide (see the Supporting Information).

(14) Similar spectral shifts were observed in solvent mixtures such as 9:1 (v/v) CD_3CN/DMSO-d_6 or $CD_3CN/CDCl_3$ (9:1) but not in neat DMSO-d_6 or pyridine-d_5. Compounds **1** and **2** were insoluble in methanol-d_4.

(15) The resulting tetrahedral intermediate would be stabilized by intramolecular hydrogen bonding: Kim, Y. K.; Lee, Y.-H.; Lee, H.-Y.; Kim, M. K.; Cha, G. S.; Ahn, K. H *Org. Lett.* **2003**, *5*, 4003–4006.

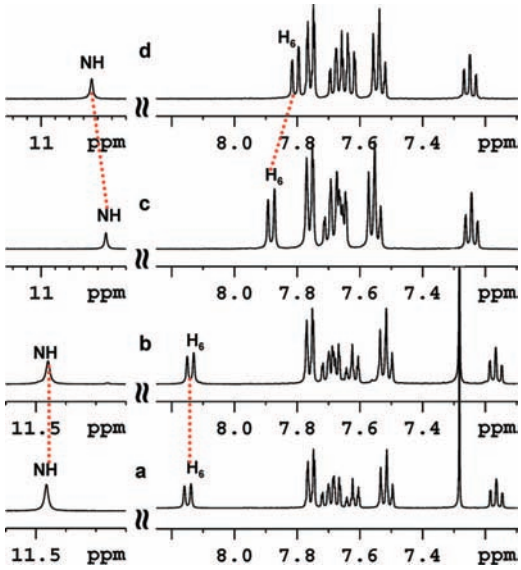


Figure 1. NMR spectra of the *o*-benzoylsquaramide **1** (2×10^{-3} M) in (a) $CDCl_3$, (b) $CDCl_3$ with 1 equiv of tetrabutyl ammonium chloride (TBACl), (c) CD_3CN, and (d) CD_3CN with 1 equiv of TBACl.

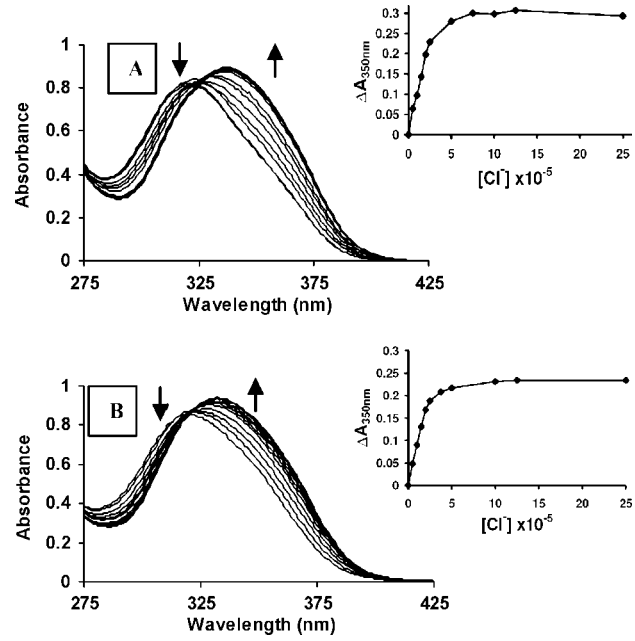


Figure 2. Interactions of *m*-benzoylsquaramide **3** (2.5×10^{-5} M) with TBACl in (A) $CHCl_3$ and (B) CH_3CN. The binding isotherms are shown in the insets.

unlikely since all carbonyl signals are intact in the ^{13}C NMR spectra even after addition of excess chloride. Aggregation of the squaramides[16] was also excluded since identical chloride-induced spectral shifts were observed over a concentration range of 0.5 to 5 mM.

Job plots[17] confirmed 1:1 stoichiometry for the chloride complexes. The binding constants for compounds **1** and **2** were determined[18] by NMR spectroscopy; no apparent chloride-induced changes were seen in the absorption spectra in either $CHCl_3$ or CH_3CN. The K_a for the ortho benzoyl derivative **1** (Table 1) was comparable to the catechol derivatives[2h] as well as some of the isophthalimides[3a]

Table 1. Chloride Ion Association Constants (K_a) of Squaramides **1**−**3**

compd	solvent	K_a (M^{-1})
1	$CHCl_3$	
1	CH_3CN	84 ± 8^a
2	$CHCl_3$	
2	CH_3CN	517 ± 34^a
3	$CHCl_3$	$(7.8 \pm 1.4) \times 10^{5b}$
3	CH_3CN	$(4.1 \pm 0.6) \times 10^{5b}$

[a] The K_a values were determined by NMR. [b] The K_a values were determined by UV−vis spectroscopy. In each case, the reported K_a values are the average of three independent measurements.

reported recently. Interestingly, introduction of a chloro substituent led to a 5-fold increase in the binding affinity for squaramide **2** (Figure 2).

In contrast to the ortho isomers, a chloride-induced bathochromic shift of ~10 nm (in both $CHCl_3$ and CH_3CN) allowed us to use absorption spectroscopy for determining the binding constants for **3**. The K_a values for the meta isomer were independent of solvent polarity and were considerably larger than the ortho isomers **1** and **2**, presumably due to steric hindrance in the latter.

The observation that Cl^- binding to the *o*-squaramides occurs only in CD_3CN led us to examine the NMR spectra of the uncomplexed squaramides in different solvents. We found that for the ortho derivatives the N−H signal shifted upfield with increasing solvent polarity. For instance, for squaramide **1**, the N−H signal is shifted upfield (relative to $CDCl_3$) by ~1 ppm in CD_3CN and by 1.5 ppm in DMSO. In contrast, there was no clear trend for the meta isomer: the N−H peak was shifted upfield in CD_3CN but was deshielded in DMSO. The trend mentioned above for the ortho squaramides is likely due to disruption of the intramolecular hydrogen bond in polar competitive solvents such as CH_3CN. In fact, similar acetonitrile-induced upfield shifts of the NH peaks, observed in carbamoyl squaramides, have also been attributed to disruption of N·H···O═C hydrogen bonds.[12a,19] In the ^{13}C NMR spectrum of squaramide **1**, an upfield shift of the benzoyl carbonyl signal by ~0.9 ppm in CH_3CN, relative to $CHCl_3$, is also consistent with disruption (or weakening) of the intramolecular hydro-

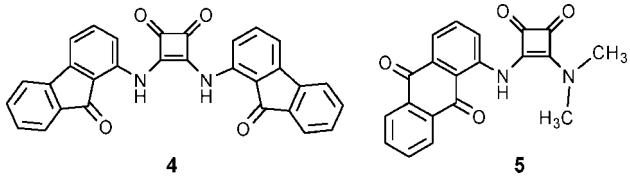
(16) Aggregation of the uncomplexed squaramides was examined separately but was considered unlikely since in the NMR spectra of **1** and **2** only minor changes ($\Delta\delta < 0.01$) were observed over a 10-fold (0.5−5 mM) variation in concentration in both $CDCl_3$ and CD_3CN. For **3**, a linear relationship between absorbance and concentration (20−2 μM) excluded aggregation.

(17) Job, P. *Compt. Rend.* **1925**, *180*, 928–930.

(18) Although significant changes were observed in both the NH and the aromatic regions of the NMR spectra, tracking of the latter signals was difficult due to peak overlap.

gen bond in the former solvent. The chemical shift of benzoyl carbonyl of the meta isomer, **3**, is unaffected by changes in solvent polarity. Therefore, based on our spectral data and literature precedence, we infer that in squaramides **1** and **2**, disruption[20] of intramolecular hydrogen bonding in CD_3CN facilitates chloride binding while in the nonpolar $CHCl_3$, anion binding is precluded due to a strong preference for the intramolecularly hydrogen bonded form.

To address the issue of whether disruption of intramolecular hydrogen bonding alone was important or whether carbonyl group reorientation was also required, we prepared the fluorenone squaramide **4**.



4 **5**

The N−H signal for **4** in $CHCl_3$ was found to be significantly upfield (10.4 ppm) relative to **1** and **2** (11.2 and 11.3 ppm, respectively) as well as the constrained anthraquinone squaramide **5** (12.6 ppm). This suggests a considerably weakened[21] intramolecular hydrogen bond in the fluorenone squaramide **4** relative to **1**, **2**, and **5**. However, despite the weakened intramolecular hydrogen bonding, no chloride-induced spectral changes in $CHCl_3$ were detected for **4**, thereby underscoring the requirement for carbonyl reorientation. Attempts to further confirm the necessity of carbonyl reorientation in CH_3CN were not successful, however, due to the insolubility of **4** in that solvent.

Nevertheless, gas-phase DFT calculations supported the idea of a conformational change. In the uncomplexed form, the intramolecularly hydrogen-bonded conformer is preferred with each *o*-benzoyl carbonyl group coplanar with the nearest squaramide NH. The N−H···O=C distance was calculated to be 1.76 Å, while the hydrogen bond angle was found to be 140°.[22] In the chloride complex,[23] the intramolecular hydrogen bonding is disrupted (the N−H···O=C distance increases to 2.84 Å) and the carbonyl groups pivot out of plane with each pointing in opposite directions and nearly perpendicular to the cyclobutene dione ring. This pivoting of the carbonyls is presumably triggered by unfavorable ion dipole interactions between the carbonyl of the ortho benzoyl group and the incoming chloride ion.[24] Thus, the carbonyl groups indeed function as "valves" to open and close the anion-binding cavity of squaramides-.(Figure 3).

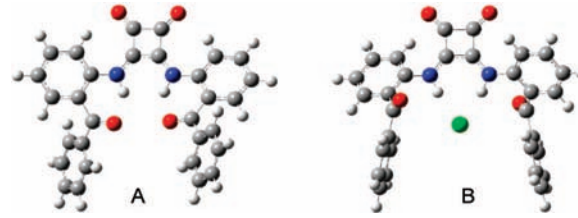


Figure 3. DFT (B3LYP/6-31+G**)-minimized structures of (A) uncomplexed squaramide **1** and (B) the chloride complex.

In summary, we have developed a unique class of squaramides whose binding to chloride can be "gated" by using carbonyl groups as environment-responsive molecular valves. The binding of Cl^- in polar medium and its release in a nonpolar environment establishes a new paradigm in the design of synthetic anion channel mimics. Future studies will focus on examining the generality of the molecular valve approach in other ortho substituted squaramides as well as the design of new chloride receptors that are functional in aqueous medium.

Acknowledgment. We thank Dr. Clifford Soll of the CUNY Mass Spectrometry Facility at Hunter College for the HRMS data and acknowledge the Department of Chemistry, Queens College, for partial funding.

Supporting Information Available: Experimental details, compound characterization data, Job plots, and Cartesian coordinates of squaramide **1** and the chloride complex. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) For acetonitrile-induced weakening of the intramolecular hydrogen bond in ortho-substituted anilines, see: Denisov, G. S.; Kuzina, L. A *J. Mol. Struct.* **1992**, *271*, 9–18.

(20) Numerous attempts to record IR spectra of **1** and **2** in CH_3CN, as additional evidence for hydrogen bond disruption, were not fruitful. Due to low solubility of the squaramides, concentrated solutions (> 5 mM) in CH_3CN could not be prepared.

(21) Structural constraints enforce an increase in the hydrogen bond distance in **4** relative to **5**: Baumstark, A. L.; Graham, S. S.; Boykin, D. W *Tetrahedron Lett.* **1990**, *31*, 957–960.

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(24) Unfavorable nonbonded interactions between Cl^- and the carbonyl dipoles are likely to be severe since the distance between the oxygen atoms of the two benzoyl carbonyls in compound **1** (3.57 Å) is about the same as the ionic radius of Cl^- (3.31 Å); see: Paula, S.; Volkov, A. G.; Deamer, D. W *Biophys. J.* **1998**, *74*, 319–327.