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Investigation of Anion−π Interactions Involving Thiophene Walls Incorporated Calix[4]pyrroles

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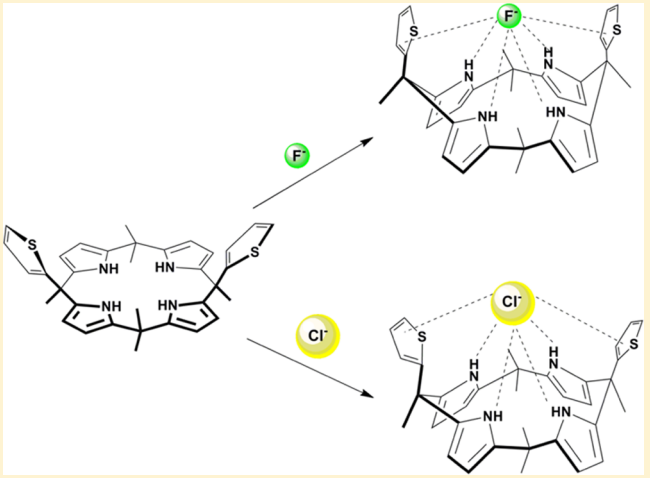
Supporting Information

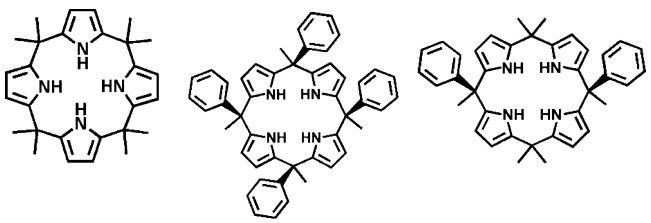
ABSTRACT: Thiophene containing "two-wall" aryl extended calix[4]pyrroles were synthesized for the first time, through acid catalyzed condensation of 2-acetylthiophenes with pyrrole. Isomeric "two-walled" calix[4]pyrroles (**8a−10a** and **8b−10b**) were obtained in satisfactory yields and their halide anion binding strengths were investigated in the solution phase by ^{1}H NMR and in the gas phase by computational methods and mass spectrometry. Change in the chemical shifts of thiophene -CH-protons during the course of NMR titrations entailed participation of the thiophene rings in anion binding; this fact was further substantiated by computational methods. The α,α-(*cis*)-isomers (**8a**, **9a**, and **10a**) showed strong binding toward F^- and Cl^- anions when compared to their isomeric α,β-(*trans*)-isomer (**8b**, **9b**, and **10b**). In both isomers, binding with F^- anion was found to be stronger than that with Cl^- anion. Both the solution-phase and gas-phase results revealed that the thiophene rings stabilize the anions through anion−π interactions.



INTRODUCTION

The realm of supramolecular chemistry lies in the recognition of guest molecules through noncovalent interactions, which are thus considered as the heart of supramolecular chemistry.[1] Among the noncovalent interactions that were established,[2−6] cation−π interactions and anion−π interactions have received considerable attention in current research. These noncovalent interactions are dominated by electrostatic and polarization effects. Cation−π interactions are the strongest noncovalent interactions that depend on the nature of interacting cation and π-system.[7−11] The role and relevance of cation−π interactions are well-demonstrated in several contemporary fields of science.[12] On the other hand, anion−π interactions, which relate to cation−π interactions in an opposite manner (interaction of anionic species with electron deficient aromatic systems) have been recognized as new noncovalent interactions in supramolecular chemistry in recent years.[13] Though there has been a great debate over the existence of anion−π interactions among researchers at primitive stages, theoretical investigations provided clues on the interaction of anions with electron-deficient aromatic rings.[14−16] Further, these investigations were complimented by a few experimental studies as well.[17−20]

Calix[4]pyrroles (Figure 1), the synthetic analogues of porphyrinogens, possess an array of four -NH- groups, due to which they have been explored as supramolecular host molecules for anionic species such as halide anions and some carboxylate group containing organic entities.[21,22] Recently, we



1a **1b** **1c**

Figure 1. Structures of *meso*-octamethylcalix[4]pyrrole (**1a**) and "four-walled" (**1b**) and "two-walled" (**1c**) aryl extended calix[4]pyrroles.

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demonstrated that the calix[4]pyrroles can also bind with cations (alkali metal ions) comparably stronger than calix[4]-arenes,[23] where the cation is stabilized by multiple cation−π interactions involving the π electrons of pyrrole rings in 1,3-alternate conformation (in the gas phase). When calix[4]-pyrroles bind to anionic species, they self-organize into a cone conformation and the anion is stabilized through hydrogen binding with four -NH- groups.

Tuning of the binding properties involves synthetic strategies such as substitution at *meso*/β positions, strapping and appending of aromatic rings at *meso* positions. The aromatic rings at *meso* positions of calix[4]pyrroles supplement further stability to the anion bound calix[4]pyrroles through additional anion−π interactions. Ballester et al. quantified anion−π interactions of four-walled and two-walled phenyl substituted calix[4]pyrroles (Figure 1).[24−26] The two-walled phenyl substitution of calix[4]pyrroles were advantageous over four-walled phenyl substitution because steric interactions among the phenyl rings were minimum in the two-walled phenyl substituted products. Besides, there is a scope to make multiple substitutions on the phenyl rings in two-walled phenyl substituted calix[4]pyrroles that can used in further tuning of anion binding strengths of the host.

To the best of our knowledge, there are no reports in the literature wherein the *meso* positions of calix[4]pyrroles are substituted with aromatic heterocyclic units. This has prompted us to undertake the incorporation of five membered heterocylic thiophene rings at the *meso* position of calix[4]pyrroles and to screen their anion binding strengths, which illuminates the role of anion−π interactions of thiophene units in the stabilization of anions. Further tuning of the electronic density of aromatic rings is also known to be achieved by substituting electron withdrawing groups on the aryl unit at the *meso* position of calix[4]pyrrole. Thus, it has been expanded to include chlorine and bromine substitution on thiophene rings in the current anion binding study.

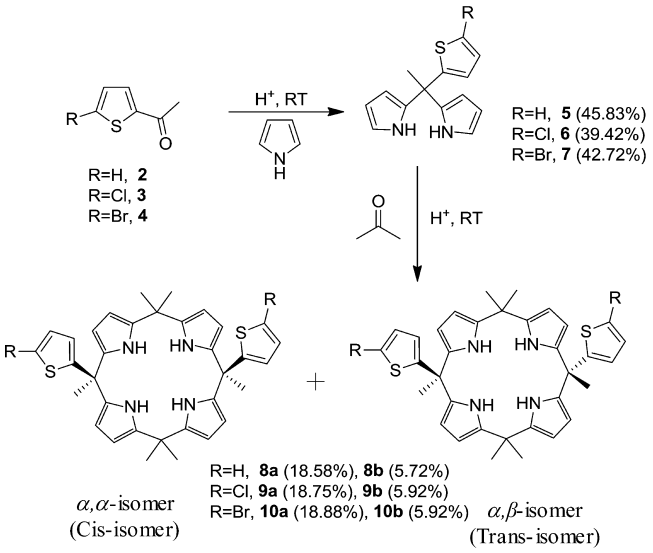
In this study, we report the synthesis of *meso*-1,3-thiophene substituted two-walled calix[4]pyrroles for the first time, and their screening for halide anion binding strength in the solution phase and in the gas phase. The present study also serves as an example for the role of thiophene substituents in anion−π interactions toward stabilizing halide anions.

RESULTS AND DISCUSSION

Synthesis. The synthetic scheme for the studied isomeric *meso*-1,3 thiophene substituted two-walled calix[4]pyrroles is shown in Scheme 1, and details are given in the Experimental section. Briefly, the condensation of 2-acetyl thiophene (**2**), 2-acetyl 5-chlorothiophene (**3**), and 2-acetyl 5-bromothiophene (**4**) with pyrrole resulted in the corresponding dipyrromethane intermediates (**5**, **6**, and **7**, respectively) in good yields (~50%). These intermediates were further subjected to condensation with acetone, which afforded a mixture of isomeric *meso*-1,3 thiophene substituted two-walled calix[4]pyrroles (α,α-isomer or *cis* isomer, **8a−10a**, and α,β-isomer or *trans* isomer, **8b−10b**). These isomers were successfully obtained by silica gel column chromatography.

The structures of dipyrromethane intermediates and thiophene substituted two-walled calix[4]pyrroles have been confirmed by their ^{1}H nuclear magnetic resonance (NMR), ^{13}C NMR, and mass spectral data. All the isomers (**8a−10a** and **8b−10b**) are colorless solids and are freely soluble in dichloromethane and chloroform and sparingly soluble in

Scheme 1. Synthetic Scheme for the Isomeric *meso*-1,3-Thiophene Substituted Two-Walled Calix[4]pyrroles (8a−10a and 8b−10b)



acetonitrile, acetone, and methanol. The yields of these isomers (**8a−10a** and **8b−10b**) were 18−20% and 5−8%, respectively. The products due to extended calixpyrroles were not observed under the used reaction conditions.

NMR Binding Studies. The isomeric *meso*-1,3 thiophene substituted two-walled calix[4]pyrroles were screened for their halide anion binding strength by ^{1}H NMR. Preliminary ^{1}H NMR investigation of individual isomeric compounds (**8a−10a** and **8b−10b**) revealed that the spectra contained a number of resonances that were consistent with their stereochemistry. The methyl protons of **8a−10a** were resonated as three signals of equal intensity, whereas the methyl protons of **8b−10b** were resonated as two signals of 1:2 intensities. Bruno et al.[27] and Barattucci et al.[28] made similar observations for the calix[4]-pyrroles with phenyl substitution at *meso*-positions instead of thiophenes. Further, the structures of **8a**, **9a**, and **10a** were confirmed by ^{1}H NMR and NOE studies. For example, ^{1}H NMR spectrum of **8a** showed two triplets at 5.92 and 5.79 ppm (β-pyrrolic protons) with a coupling constant of 3.0 Hz, which included a vicinal coupling to each other and a meta coupling to -NH- proton. Whereas three protons of thiophene appeared as two doublets of doublets at 7.14 and 6.64 ppm due to vicinal and meta couplings and one doublet of doublet at 6.88 ppm due to two vicinal couplings. There was a strong NOE interaction of -NH- protons of pyrrole with methyl protons appeared at 1.98 ppm, and there was no NOE interaction between thiophene protons and the methyl protons at 1.53 and 1.58 ppm, which confirmed its *cis*-structure. Similarly structures of compounds **8b**, **9b**, and **10b** were also confirmed by characteristic NMR data.

Anion (F^-, Cl^-, Br^-, and I^-) binding studies of compounds **8a−10a** and **10b** were carried out in $CDCl_3$ using ^{1}H NMR. The compounds **8b** and **9b** could not be screened for their anion binding abilities due to their low yields. Anions were titrated with the hosts in the form of their tetrabutylammonium salts. Changes in the chemical shifts of different protons of calix[4]pyrroles as a function of anion concentration were used to calculate the binding affinities of anions. Nonlinear curve data indicated a 1:1 binding model for the studied calix[4]-

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pyrroles. F^- and Cl^- anions induced considerable change in the chemical shifts of protons in both the isomeric receptors, whereas larger anions (Br^- and I^-) showed minor/no chemical shift changes in the receptors. Hence, the present study designs are suitable and selective for F^- and Cl^- anions.

Titration of the receptors **8a**−**10a** with tetrabutylammonium fluoride implied that the fluoride anion formed stable complexes with all the receptors. In the compound **10a**, the NH- proton signal, which appeared as a broad singlet at δ = 7.26 ppm in free host, completely disappeared (merged with baseline) after the addition of 0.2 equiv of fluoride. Similarly, the -NH- signal disappeared in the case of **8a** and **9a**, when 0.2 equiv of fluoride was added. Such disappearance of the -NH- proton suggests that these compounds readily form a stable complex with fluorine, which could not be observed on the NMR time scale. In addition to the disappearance of -NH- signal, there was a considerable change in the chemical shifts for both thiophene and pyrrole -CH- protons that indicated the involvement of thiophene and pyrrole rings in binding with fluoride anion (Figure 2). These spectral changes clearly

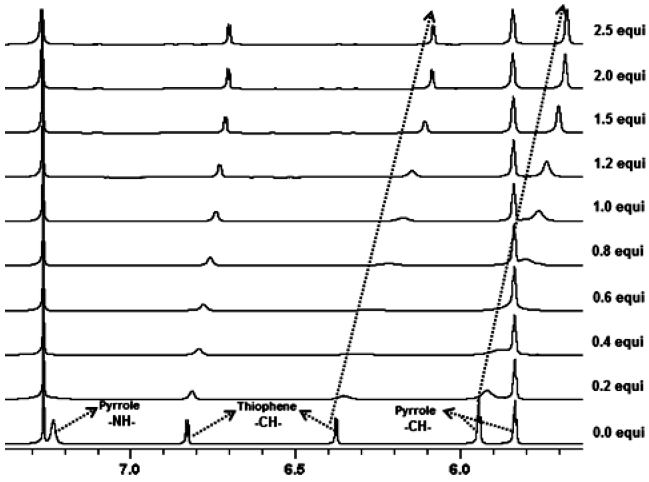

Figure 2. ^{1}H NMR spectra of the receptor **10a** as a result of the titration with fluoride anion.

revealed that fluoride anion bound to receptors (**8a**, **9a**, and **10a**) through a cone conformation having thiophene substitution faced toward the center of the calix[4]pyrrole cavity. The association constant, K_a, value was found to be 10.00 × 10^3 M^{-1} and 13.64 × 10^3 M^{-1} for receptors **8a** and **10a**, respectively. Whereas under studied experimental conditions, the K_a for receptor **1a** was found to be 7.69 × 10^3 M^{-1}. Thus, involvement of two thiophene rings enhanced the stabilization of anion through increased anion−π interactions (as in **10a**).

In the case of receptor **10b** (an isomeric compound of the receptor **10a**), the -NH- protons also appeared as a broad singlet at 7.29 ppm in free host and this signal disappeared when 0.4 equiv of fluoride anion was added. In addition, there was a significant shift in the signals of pyrrole -CH- protons, but to a lesser extent when compared to that observed in its isomer **10a**. There was no considerable change in the chemical shifts of thiophene -CH- protons, but broadening of one of the thiophene -CH- protons at 6.52 ppm was observed during the course of titrations (Figure 3). This spectral behavior implied that **10b** also bound to fluoride anion but to a lesser extent when compared to its isomer **10a**. The K_a was found to

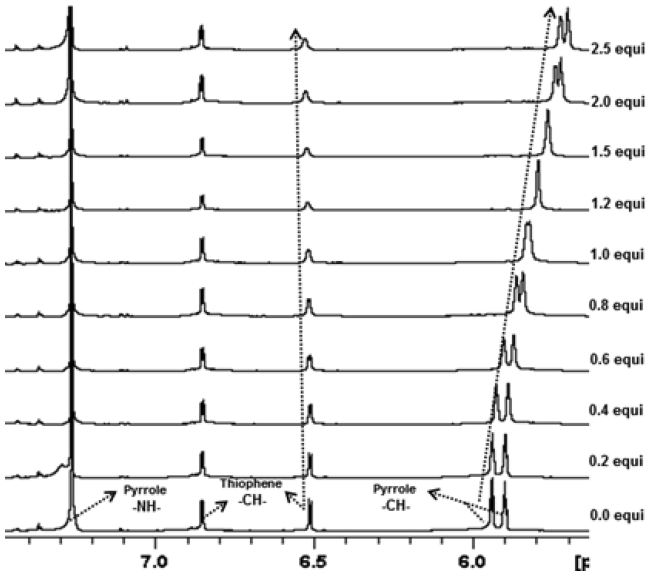

Figure 3. ^{1}H NMR spectra of the receptor **10b** as a result of titration with fluoride anion.

be 1.34 × 10^3 M^{-1} for receptor **10b**. The weaker binding of fluoride anion with **10b** must be due to orientation of thiophene substituents, because in any of its conformations only one thiophene was involved in the stabilization of anion.

Titration of chloride anion with receptors **8a**, **9a**, and **10a** did not show significant change in chemical shifts. In complexes of **8a**.Cl^-, **9a**.Cl^-, and **10a**.Cl^-, the -NH- protons were marginally affected with respect to the free receptor, which indicated existence of slow complexation−decomplexation equilibrium in these complexes on an NMR time scale (titration of Cl^- with receptors **8a** and **9a** are shown in Supporting Information Figure S19−20). There was no change in the chemical shifts of either thiophene -CH- protons or pyrrole -CH- protons. This data suggested that the binding of chloride anion with the receptors was not that effective as found with fluoride anion. The lower binding with chloride anion may arise from two situations. In one situation, the chloride anion, due to its bigger size, may bind to these receptors on to the face that does not contain the thiophene substitution through "*cone flipping*" (Scheme 2). In another situation, the thiophene rings might move away from the center of calix[4]pyrrole cavity; therefore the thiophene rings interact very weakly with the chloride anion (Scheme 2). Titration of chloride anion with receptor **10b** also showed similar chemical shifts with K_a, of 0.28 × 10^3 M^{-1} (Supporting Information Figure S21). The binding of the studied receptors was much weaker for the bromide and iodide anions than chloride anion due to their larger size. Construction of jobs plot indicated 1:1 binding model for both fluoride and chloride anions with the studied receptors (the plots of **8a**−**10a** with fluoride anion are shown in Supporting Information Figure S22).

Mass Spectrometry. Electrospray ionization mass spectrometry (ESI-MS) is a soft technique, which preserves the solution-phase molecular architecture in the gas phase and provides direct measurement of stoichiometry of the supramolecular assemblies. In order to elucidate the stoichiometry of anion complexes of the studied calix[4]pyrroles, we performed ESI-MS experiments under negative mode. The stock solutions of the receptor (**8a**−**10a** and **8b**−**10b**) and anion were mixed such that their final concentrations were in the ratio of 1:50 μM

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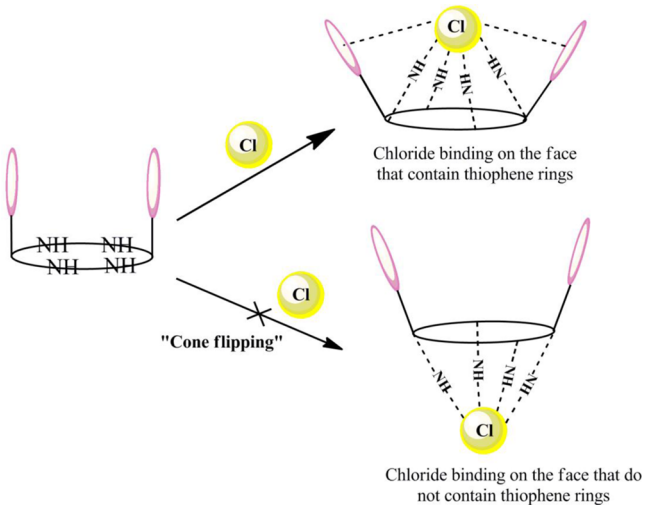
Scheme 2. Probable Modes of Chloride Anion Binding in *cis*-Isomer of 1,3-Thiophene Substituted Two-Walled Calix[4]pyrrole



(Receptor, R; Anion, X). The negative ion ESI mass spectra showed $[R-H]^-$ and $[R+X]^-$ ions, (where X = F^- and Cl^-). As an example, the ESI mass spectra of the receptor **8a** with fluoride and chloride anions are shown in Figure 4 and Supporting Information Figure S23, respectively. Formation of these ions was confirmed by high resolution mass spectral data and isotopic distribution patterns. The ions due to higher aggregates like $[2R+X]^-$ and $[R+2X]^{2-}$ were absent in the spectra, which indicates that both isomeric receptors show 1:1 complexes with anions.

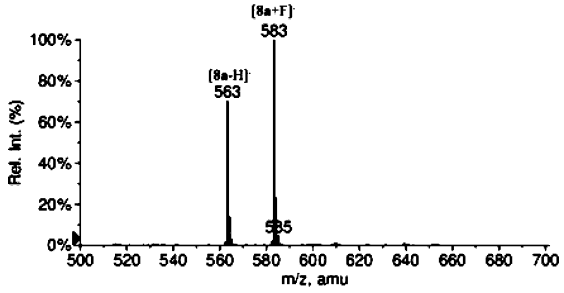


Figure 4. Negative ion ESI mass spectrum of **8a** with F^- anion.

Computational Studies. In order to draw further insights into the true nature of interactions between the studied receptors and anions, we have carried out density functional theory (DFT) calculations over the anion bound calix[4]-pyrroles. As it is evident from the NMR studies that the receptors showed strong affinity toward F^- and Cl^- anions, the DFT calculations were restricted to the complexes of these two anions.

DFT studies on anion bound calix[4]pyrroles indicated that the anion complexes of all the receptors (**8a−10a** and **8b−10b**) were stabilized in cone conformation by an array of four intramolecular hydrogen bonding interactions (NH···F^-/Cl^-) or anion−π (π···F^-/Cl^-) and both. Binding of F^- anion to the receptors **8a−10a** leads to the identification of two different types of complexes, i.e., **I−F** and **II−F**, while receptors **8b−10b** lead to the formation of only one complex, **III−F**. The optimized 3D structures of F^- bound complexes (**I−F**, **II−F**, **III−F**) for receptors **8a** and **8b** are shown in Figure 5 and the computed energetic details were summarized in Table 1.

In complexes **I−F**, the two thiophene rings were above the core of calix[4]pyrrole cavity, whereas in complexes of **II−F**, the two thiophene rings were in the plane of the calix[4]pyrrole cavity. Further, in the case of complexes of **III−F**, one thiophene ring was in the plane of calix[4]pyrrole cavity, while the other was above/below to this plane.

In each complex of **8a.I−F**, **8a.II−F**, and **8b.III−F**, all four hydrogen bonds (NH···F^-) were equivalent with a bond distance of about 1.71, 1.77, and 1.74 Å, respectively. These hydrogen bonds are slightly larger than those reported for F^--bound *meso*-octamethylcalix[4]pyrrole (**1a**, Figure 1). Fluoride anion was located at about 1.46 to 1.50 Å over the centroid of four nitrogen atoms of pyrrole rings (Figure 7). The complexation energies for the complexes **8a.I−F** and **8a.II−F** were found to be −76.41 and −67.16 kcal/mol, respectively,

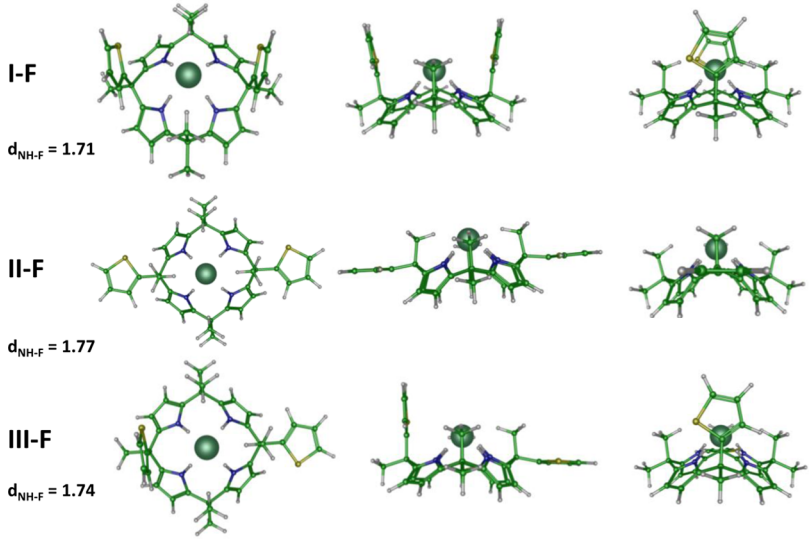


Figure 5. Top, side, and front views of DFT optimized structures of the fluoride bound complexes of the receptors **8a** and **8b** (average hydrogen bond distances in Å).

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Table 1. Complexation Energies (ΔE_{comp}), Deformation Energies (E_{deform}), Anion Binding Energies (E_{Anbind}), and Average Hydrogen Bond Strength (E_{hy}) (in kcal/mol) of Fluoride and Chloride Complexes of the Receptors 8a−10a and 8b

receptor	complex	ΔE_{comp}	E_{deform}	E_{Anbind}	E_{hy}
		Fluoride Binding			
8a	**I−F**	−76.41	21.37	−97.78	−24.44
8a	**II−F**	−67.16	34.02	−101.18	−25.29
8b	**III−F**	−71.51	27.66	−99.17	−24.79
9a	**I−F**	−80.00	21.61	−101.61	-
10a	**I−F**	−80.18	21.69	−101.86	-
		Chloride Binding			
8a	**I−Cl**	−48.65	17.00	−65.65	−16.41
8a	**II−Cl**	−41.12	29.98	−71.10	−17.77
8b	**III−Cl**	−45.08	22.41	−67.49	−16.87
9a	**I−Cl**	−51.98	17.42	−69.40	-
10a	**I−Cl**	−52.08	17.36	−69.44	-

besides having similar average hydrogen bonding strength (~25 kcal/mol) (Table 1). Further, energy decomposition analysis indicated that during the formation of complex **8a.II−F** a large amount of conformational penalty/deformation energy (34.02 kcal/mol) was paid compared to that of complex **8a.I−F** (21.37 kcal/mol). In the case of complex **8b.III−F**, the complexation and deformation energy was found to be −71.51 and 27.66 kcal/mol, respectively (Table 1). The average hydrogen bonding strength was found to be in the range of 24−25 kcal/mol (Table 1). From the total binding energy, the stability order of the F^- bound complexes was found to be **I−F** > **III−F** > **II−F**. The difference in the relative stability of these complexes could be attributed to the difference in the anion−π interactions. In the complex of **8a.II-F**, fluoride anion was not stabilized by anion−π interactions due to the absence of thiophene rings above the calix[4]pyrrole cavity. However, in the complexes of **8a.I−F** and **8b.III−F** the fluoride anion was stabilized by anion−π interactions by 2-fold (9.25 kcal/mol) and 1-fold (4.25 kcal/mol, Table 1), respectively.

Binding of chloride anion to the receptors **8a−10a** also lead to the identification of two different types of complexes (**I−Cl**, **II−Cl**), whereas chloride binding to receptors **8b−10b** lead to identification of one type of complex (**III−Cl**) similar to that of fluoride ion binding. The optimized 3D structures of Cl^- bound complexes for receptors **8a** and **8b** (**I−Cl**, **II−Cl**, **III−Cl**) are shown in Figure 6 and the computed energetic details were summarized in Table 1. The hydrogen bond distances in these complexes were found to be larger (2.25−2.35 Å) than those of the F^- complexes. Chloride anion was located at about 2.27−2.29 Å over the centroid defined by the nitrogen atoms of pyrrole rings. This lower movement (about 0.80 Å) of chloride anion compared to fluoride anion in the cavity (Figure 7) may

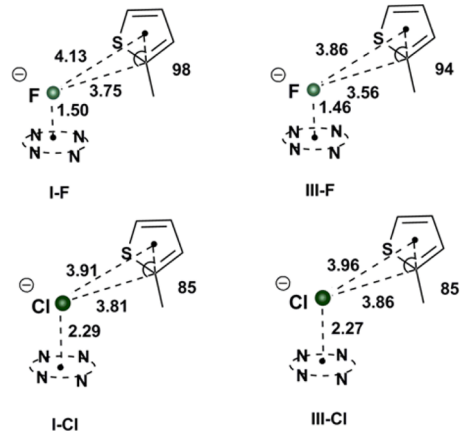

Figure 7. Important geometrical parameters between the anions (F^- and Cl^-) and the thiophene ring (distances and angles in Å and degrees, respectively).

be due to its weaker hydrogen bonding strength and larger size. The average hydrogen bonding strength was found to be about ~17 kcal/mol, which was about 7.82 kcal/mol lower compared to that of F^- bound complexes (Table 1). Further, energy decomposition analysis showed that chloride complexes **I−Cl**, **II−Cl**, and **III−Cl** also follow same pattern of deformation and complexation energies, as found in the case of fluoride complexes. However, the strength of average complexation energy was found to be 26.74 kcal/mol lower than that of fluoride complexes. This decrease in the binding affinity could

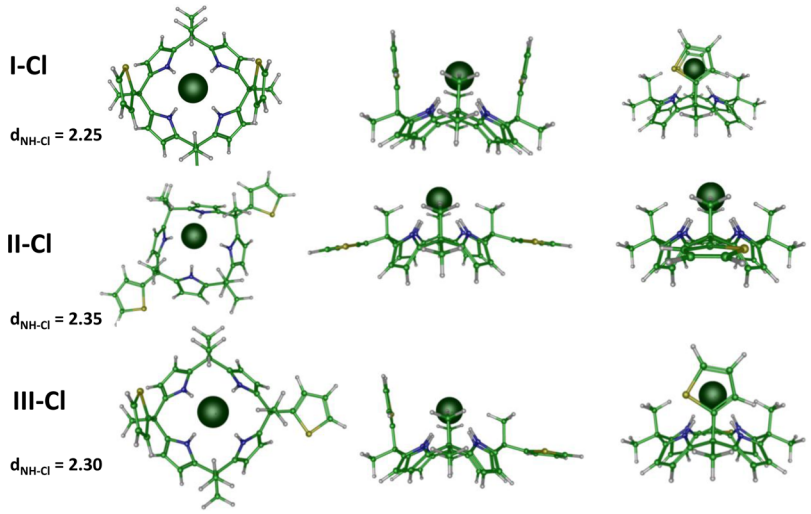

Figure 6. Top, side, and front views of DFT optimized structures of the chloride bound complexes of the receptors **8a** and **8b** (average hydrogen bond distances in Å).

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be attributed to the larger size of chloride anion and decrease in its hydrogen bonding strength compared to that of fluoride anion. Moreover, the strength of $\pi\cdots Cl^-$ interaction was found to be about 3.95 and 7.53 kcal/mol, in the complexes of **8b.III−Cl** and **8a.I−Cl**, respectively. This also indicated that an increase in the size of anion from fluoride to chloride reduces the anion$\cdots\pi$ interaction.

During the course of NMR titrations of chloride anion with receptors **8a−10a**, there was a small/no change in chemical shift values of -CH- protons of pyrrole ring and/or thiophene rings. This may be due to the interaction of chloride anion on the face of calix[4]pyrrole cavity that did not contain thiophene rings on the same face (a conformation after cone flipping; Scheme 2). We have made several efforts to get an energy-minimized structure of "*cone flipping*" conformation using the computational model. However, all the attempts toward optimizing this complex lead to the formation of **I−Cl** complex. This implied that the receptors prefer to bind chloride anion on to the face which contains the thiophene rings rather than in the conformation undergoing "*cone flipping*". Hence, the possibility of "*cone flipping*" for accommodating larger chloride anions could be ruled out. In the case of isomeric receptors **8b−10b**, such a situation did not arise.

On the comparative scale, the deformation energy associated with fluoride anion was more than that with chloride anion, which induced huge changes in geometry of receptors to make proper binding. The larger size and poor hydrogen bond strength of chloride anion lead to the lower binding affinity compared to the fluoride anion. Substitution on the thiophene ring altered the electronic properties of the thiophene ring. On the substitution of chlorine or bromine in the thiophene rings, the binding affinity for fluoride and chloride anions increased in the range of 3.33−3.77 kcal/mol. This improvement in the binding affinity arose as a result of an increase in the anion$-\pi$ interaction due to the electron withdrawing nature of chlorine and bromine atom. Due to these substitutions, deformation energy did not change significantly, however; only anion binding affinity increased, and therefore complexation energy was raised. Among the studied receptors, the receptors **9a** and **10a** showed almost equal and stronger binding ability and receptor **8a** followed next in the order.

CONCLUSIONS

Thiophene containing "two-walled" calix[4]pyrroles were successfully synthesized for the first time and the isomeric (*cis* and *trans*) compounds were well separated in satisfactory yields. The two-walled calix[4]pyrroles were screened for their anion binding ability by means of NMR, mass spectrometry, and computational methods. Anion induced chemical shift changes of -CH- protons of thiophene and pyrrole rings in receptors **8a−10a** (*cis* isomers) during the course of NMR titrations indicated that the thiophene rings were involved in stabilizing the anion through anion$-\pi$ interactions. In the receptors **8b−10b** (*trans* isomers), only one thiophene ring participated in the stabilization of the anion. Further, jobs plots and negative ion ESI mass spectral data indicated that these new receptors form 1:1 stoichiometric complexes. Computational investigation of anion-bound receptors indicated that two different anion-bound complexes were possible for receptors **8a−10a**, wherein the orientation of thiophene rings differ with respect to central cavity of receptors. Optimization of anion-bound complexes of the receptors **8b−10b** generated only one type of complex. The possibility of interaction of larger chloride anion onto the face that did not contain thiophene rings through "cone flipping" could be ruled out since optimization led to the **I−Cl** complex only. Among the studied receptors, **9a** and **10a** showed strong binding ability when compared to receptor **8a**. Thus, two-walled thiophene substituted calix[4]-pyrroles strongly interact with halide/anions through anion$-\pi$ interactions and show enhanced binding over that of *meso*-octamethyl calix[4]pyrroles (**1a**) which is evident from both NMR and computational studies.

EXPERIMENTAL SECTION

General Methods and Instrumentation. Dry $CaCO_3$ was used for distillation of acetone. Pyrrole was also subjected to distillation prior to use. All commercial reagents were used as received without further purification unless specified and the solvents used were distilled before use. The moisture/air sensitive reactions were performed under dry nitrogen atmosphere. The retention factor (R_f) values were determined using analytical thin layer chromatography (TLC) with silica gel 60 and F_{254} precoated plates (0.25 mm thickness). Spots on the TLC plates were visualized using ultraviolet light (254 nm), iodine, or charging solution. Flash column chromatography was performed with silica gel 60 (100−200 mesh). Melting points were determined in capillaries and were uncorrected. All the NMR spectra were recorded on 300 and 600 MHz NMR spectrometers. Proton and ^{13}C chemical shifts are reported in ppm (δ) relative to the internal standard, tetramethylsilane (TMS, δ 0.00). Mass spectra were recorded on a Q-TOF mass spectrometer.

NMR Titrations. All the halides were taken in their tetrabutylammonium salt forms. Due to their hygroscopic nature, all the salts were dried in a vacuum oven for at least 24 h before use. All the experiments were carried out at room temperature in $CDCl_3$ solvent and care was taken to minimize exposure to atmosphere during sample preparation and titration. A solution of calix[4]pyrrole receptor (5 mM) in $CDCl_3$ (0.5 mL) was prepared first in NMR tube. Aliquots of tetrabutylammonium halide salt solutions (500 mM) in $CDCl_3$ were added to produce solutions containing 0, 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.5, 2.0, 2.5, 3.0, 5.0, 8.0, and 10.0 equiv of the halide concentration. ^1H NMR spectra were acquired after each addition of halide solution. Affinity constants for the studied receptors toward halides were obtained from nonlinear regression fits of the chemical shift changes against the concentration of halide anion. The data was processed by using *Origin 8* software.

Mass Spectrometry. All the experiments were performed using QSTAR XL mass spectrometer equipped with an ESI source. The optimized conditions for all the experiments were as follows: capillary voltage −4.0 kV; declustering potential −60 V; mass resolution 10 000 (fwhm). Nitrogen was used as the curtain and collision gas. The data acquisition was under the control of Analyst QS software. All the samples were introduced into the source by direct infusion at the rate of 15 μL/min using built-in syringe pump. All the spectra reported were averages of 25 to 30 scans.

Computational Methodology. Quantum chemical calculations for all the receptors and their anionic complexes were carried out using the Jaguar suite of programs.[29,30] The geometry optimizations of all host−guest complexes $[R{-}X]^-$ (where X = F^- and Cl^-) were carried out using the M06-D3/6-31+G(d,p) level of theory.[31,32] This function captures the weak interaction (noncovalent interactions). For Br substituted systems the LACP+G(d,p) basis set was used for Br atom, and for the rest of the elements 6-31+G(d,p) was employed. The total binding energies (complexation energy ($\Delta E_{comp/total\ bind}$), deformation energies (ΔE_{deform}), anion binding energies (ΔE_{anbind})) were obtained using Scheme 3.[33] The "$[R{-}X]^-$" is an optimized structure of anion bound R, "R*" is a conformation identical with that in the optimized complex $[R{-}X]^-$ from which anion is removed. It means "R*" is formed by removing the anion from the complex without any other change in its structure; "R" is a global minimum 1,3-alternate conformation. Anion binding energy is the absolute binding strength

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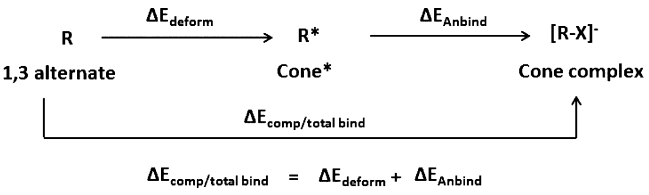
Scheme 3. General Steps Involved in Anion Binding by Two-Walled Calix[4]pyrroles



between R and anion. This is the energy which is involved in binding of anion to R by means of hydrogen bonding and anion−π interactions. It is calculated by the difference in energy of "[R−X]$^-$" with sum of energies of "R*" and optimized anion "X$^-$". Deformation energy is the energy which is lost in converting the most stable conformation (1,3-alterate) to the cone conformation. It is calculated by difference of energy of "R*" and energy of the most stable conformation.

Synthesis. *Synthesis of Dipyrromethanes (**5**−**7**).* TFA (3 equiv) was added to a solution of **2**−**4** (1 equiv) in pyrrole (12 equiv), at 0 °C. The mixture was stirred under inert nitrogen atmosphere at room temperature for 3 h, then neutralized (NaOH 1 M) and extracted (2 × 25 mL CH_2Cl_2). The organic phase was dried (Na_2SO_4) and concentrated. The crude brown oil was subjected to column chromatography (SiO_2, hexane/EtOAc 3:1).

*Compound **5**.* Yield: 45.83% (1.76 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (s, br, 2H), 7.14 (dd, J = 5.2,1.2 Hz, 1H), 6.87 (dd, J = 5.2, 3.6 Hz, 1H), 6.72 (dd, J = 3.6, 1.2 Hz, 1H), 6.61−6.52 (m, 2H), 6.12−6.04 (m, 2H), 6.03−5.95 (m, 2H), 2.07 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.2, 136.9, 126.3, 124.9, 124.3, 116.9, 108.1, 105.8, 42.4, 30.4. IR (KBr) 3420, 3097, 2967, 2927, 1549, 1455, 1402, 1258, 1226, 1093, 1029, 710 cm^{-1}. MS (ESI) m/z 243 [M + H]$^+$; HR-MS (ESI) Calcd for $C_{14}H_{15}N_2S$ [M + H]$^+$: 243.0951 found: 243.0949.

*Compound **6**.* Yield: 39.42% (1.35 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (s, br, 2H), 6.68 (d, J = 3.7 Hz, 1H), 6.59 (dt, J = 1.72.6 Hz, 2H), 6.48 (d, J = 3.7 Hz, 1H), 6.09 (td, J = 2.6 3.5, 2H), 6.05−5.99 (m, 2H), 2.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.0, 136.1, 128.5, 125.4, 124.0, 117.2, 108.3, 106.2, 42.7, 30.0. IR (KBr) 3421, 2255, 2128, 1647, 1025, 999, 825, 765 cm^{-1}. MS (ESI) m/z 277 [M + H]$^+$; HR-MS (ESI) Calcd for $C_{14}H_{13}ClN_2S$ [M + H]$^+$: 277.0588, found: 277.0561.

*Compound **7**.* Yield:42.72% (1.33 g). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (s, 2H), 6.82 (d, J = 3.7 Hz, 1H), 6.62−6.54 (m, 2H), 6.47 (d, J = 3.7 Hz, 1H), 6.13−6.05 (m, 2H), 6.05−5.97 (m, 2H), 2.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.8, 136.1, 129.2, 125.1, 117.2, 110.8, 108.3, 106.1, 42.7, 30.0. IR (KBr) 3421, 3387, 3101, 2974, 2925, 2855, 1545, 1418, 1252, 1090, 1008, 798, 730 cm^{-1}. MS (ESI) m/z 321 [M + H]$^+$; HR-MS (ESI) Calcd for $C_{14}H_{13}BrN_2S$ [M + H]$^+$: 321.0056, found: 321.0050.

*Synthesis of α,α and α,β-Isomeric Calix[4]pyrroles **8a**−**10a** and **8b**−**10b**.* TFA (3 equiv) was added to compounds **5**−**7** (1 Equiv) in dry acetone (50 mL), at 0 °C. The mixture was stirred under nitrogen atmosphere at room temperature for 4 h. The reaction mixture was neutralized (NaOH, 1 M) and then extracted with DCM twice in 25 mL aliquots. The organic phase was dried (Na_2SO_4), concentrated, and subjected to column chromatography (SiO_2, hexane/EtOAc, 97:3).

*Compound **8a**.* Yield: 18.58% (0.43 g); mp 235−238 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 (s, br, 4H), 7.14 (dd, J = 5.0, 1.2 Hz, 2H), 6.88 (dd, J = 5.0, 3.4 Hz, 2H), 6.64−6.53 (dd, J = 3.4, 1.2 Hz, 2H), 5.92 (t, J = 3.0 Hz, 4H), 5.79 (t, J = 3.0 Hz, 4H), 1.98 (s, 6H), 1.58 (s, 6H), 1.53 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5, 138.6, 136.4, 126.0, 124.5, 123.6, 105.5, 103.2, 42.2, 35.2, 29.8, 29.4, 28.2. IR (KBr) 3407, 3303, 3105, 2969, 2927, 1705, 1571, 1370, 1260, 1221, 1040, 762, 708 cm^{-1}. MS (ESI) m/z 563 [M-H]$^-$; HR-MS (ESI) Calcd for $C_{34}H_{36}N_4S_2$ [M-H]$^-$: 563.2303, found: 563.2294.

*Compound **8b**.* Yield: 5.72% (0.13 g); mp 211−213 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (s, br, 4H), 7.15 (dd, J = 5.0, 1.2 Hz, 2H), 6.90 (dd, J = 5.0, 3.6 Hz, 2H), 6.76 (dd, J = 3.6, 1.2 Hz, 2H), 5.92 (t, J = 3.0 Hz, 4H), 5.86 (t, J = 3.0 Hz, 4H), 1.95 (s, 6H), 1.51 (s, 12H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.8, 138.7, 136.3, 126.1, 124.5, 123.6, 105.3, 103.1, 42.3, 35.2, 30.2, 29.6, 29.1 IR (KBr) 3424, 3352, 3101, 2968, 2926, 1648, 1574, 1415, 1225, 1039, 764, 705 cm^{-1}. MS (ESI) m/z 563 [M-H]$^-$: HR-MS (ESI) Calcd for $C_{34}H_{36}N_4S_2$ [M-H]$^-$: 563.2303, found: 563.2318.

*Compound **9a**.* Yield: 18.75% (0.42 g); mp 166−168 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.18 (s, 4H), 6.65 (d, J = 3.7 Hz, 2H), 6.33 (d, J = 3.7 Hz, 2H), 5.87 (t, J = 3.0 Hz, 4H), 5.79 (t, J = 3.0 Hz, 4H), 1.89 (s, 6H), 1.57 (s, 6H), 1.53 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 138.8, 135.6, 127.9, 125.1, 123.7, 105.8, 103.4, 42.5, 35.2, 29.9, 29.0, 28.1. IR (KBr) 3457, 3416, 3100, 2969, 2926, 1705, 1572, 1445, 1418, 1222, 1021, 765 cm^{-1}. MS (ESI) m/z 667 [M+Cl]$^-$; HR-MS (ESI) Calcd for $C_{34}H_{34}Cl_2N_4S_2$ [M+Cl]$^-$: 667.1290, found: 667.1275.

*Compound **9b**.* Yield: 5.92% (0.13 g); mp 153−155 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24 (s, 4H), 6.67 (d, J = 3.7 Hz, 2H), 6.47 (d, J = 3.7 Hz, 2H), 5.94 (t, J = 3.0 Hz, 4H), 5.90 (t, J = 3.0 Hz, 4 Hz), 1.91 (s, 6H), 1.52 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.4, 138.9, 135.5, 125.2, 125.0, 123.7, 105.6, 103.4, 42.6, 35.3, 32.1, 30.0, 29.2. IR (neat) 3427, 3328, 3109, 2968, 2926, 2857, 1705, 1447, 1220, 1025, 763 cm^{-1}. MS (ESI) m/z 667 [M+Cl]$^-$; HR-MS (ESI) Calcd for $C_{34}H_{34}Cl_2N_4S_2$ [M+Cl]$^-$: 667.1290, found: 667.1306.

*Compound **10a**.* Yield: 18.88% (0.42 g); mp 175−178 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 (s, 4H), 6.79 (d, J = 3.7 Hz, 2H), 6.33 (d, J = 3.7 Hz, 2H), 5.91 (t, J = 3.0 Hz, 4H), 5.79 (t, J = 3.0 Hz, 4H), 1.90 (s, 6H), 1.57 (s, 6H), 1.53 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1, 138.8, 135.5, 128.9, 124.7, 110.2, 105.8, 103.4, 42.5, 35.2, 29.9, 29.0, 28.1. IR (KBr) 3393, 2966, 2922, 2857, 1668, 1566, 1426, 1214, 1038, 770 cm^{-1}. MS (ESI) m/z 755 [M+Cl]$^-$; HR-MS (ESI) Calcd for $C_{34}H_{34}Br_2N_4S_2$ [M+Cl]$^-$: 755.0280, found: 755.0326.

*Compound **10b**.* Yield: 5.92% (0.13 g); mp 161−163 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.19 (s, 4H), 6.80 (d, J = 3.7 Hz, 2H), 6.46 (d, J = 3.7 Hz, 2H), 5.90 (t, J = 3.0 Hz, 4H), 5.84 (t, J = 3.0 Hz, 4H), 1.91 (s, 6H), 1.52 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3, 138.9, 135.5, 129.0, 124.8, 110.3, 105.6, 103.4, 42.6, 35.3, 30.0, 29.6, 29.2. IR (neat) 3427, 2969, 2925, 2860, 1658, 1574, 1413, 1219, 1041, 765 cm^{-1}. MS (ESI) m/z 755 [M+Cl]$^-$; HR-MS (ESI) Calcd for $C_{34}H_{34}Br_2N_4S_2$ [M+Cl]$^-$: 755.0280, found: 755.0335.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}CNMR spectra for synthesized compounds **5**−**7** and **8a**−**10b**, titration curves for receptors (**8a**, **9a**, and **10b**) with chloride anion, jobs plots for titration of fluoride with receptors **8a**, **9a**, and **10a** and negative ion ESI mass spectrum of **8a** with chloride anion. Cartesian coordinates of the complexes considered in the study are given in Table S1. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Lehn, J. -M. *Supramolecular Chemistry: Concepts and Perspectives*; VCH: Weinheim, 1995.
(2) Lodish, H.; Berk, A.;. Zipursky, S. L.; Matsudaria, P.; Baltimore, D.; Darnell, J. *Molecular Cell Biology*, 4th ed.; W. H. Freeman: New York, 2000.
(3) Arunan, E.; Desiraju, G. R.; Klein, R. A.; Sadlej, J.; Scheiner, S.; Alkorta, I.; Clary, D. C.; Crabtree, R. H.; Dannenberg, J. J.; Hobza, P.; Kjaergaard, H. G.; Legon, A. C.; Mennucci, B.; Nesbitt, D. J. *Pure Appl. Chem.* **2011**, *83*, 1619−1636.
(4) Ciferri, A.; Perico, A. *Ionic interactions in natural and synthetic macromolecules*; John Wiley & Sons, Inc.: Hoboken, NJ, 2012.
(5) Israelachvill, J. N. *Intermolcular and Surface Forces*, 3rd ed.; Academic Press: Waltham, 2011.
(6) Chandler, D. *Nature* **2005**, *437*, 640−647.
(7) Sayyed, F. B.; Suresh, C. H. *J. Phys. Chem. A* **2000**, *115*, 11414−11419.
(8) Mecozzi, S.; West, A. P.; Dougherty, D. A. *J. Am. Chem. Soc.* **1996**, *118*, 2307−2308.
(9) Cubero, E.; Luque, F. J.; Orozco, M. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 5976−5980.
(10) Alkorta, I.; Rozas, I.; Elguero, J. *J. Am. Chem. Soc.* **2002**, *124*, 8593−8598.
(11) Wheeler, S. E.; Houk, K. N. *J. Am. Chem. Soc.* **2009**, *131*, 3126−3127.
(12) Mahadevi, A. S.; Sastry, G. N. *Chem. Rev.* **2013**, *113*, 2100−2138.
(13) Frontera, A.; Gamez, P.; Mascal, M.; Mooibroek, T. J.; Reedijk, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 9564−9583.
(14) (a) Mascal, M.; Armstrong, A.; Bartberger, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 6274−6276. (b) Quinonero, D.; Garau, C.; Rotger, C.; Frontera, A.; Ballester, P.; Costa, A.; Deya, P. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3389−3392.
(15) Berryman, O. B.; Bryantsev, V. S.; Stay, D. P.; Johnson, D. W.; Hay, B. P. *J. Am. Chem. Soc.* **2007**, *129*, 48−58.
(16) (a) Kim, D.; Tarakeshwar, P.; Kim, K. S. *J. Phys. Chem. A* **2004**, *108*, 1250−1258. (b) Estarellas, C.; Frontera, A.; Quinonero, D.; Deya, P. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 415−418. (c) Garau, C.; Quinonero, D.; Frontera, A.; Ballester, P.; Costa, A.; Deya, P. M. *J. Phys. Chem. A* **2005**, *109*, 9341−9345.
(17) Mooibroek, T. J.; Black, C. A.; Gamez, P.; Reedijk, J. *Crys. Growth Des.* **2008**, *8*, 1082−1093.
(18) Rosokha, Y. S.; Lindeman, S. V.; Rosokha, S. V.; Kochi, J. K. *Angew. Chem.* **2004**, *116*, 4750−4752; *Angew. Chem., Int. Ed.* **2004**, *43*, 4650−4652.
(19) Berryman, O. B.; Hof, F.; Hynes, H. J.; Jhonson, D. W. *Chem. Commun.* **2006**, 506−508.
(20) Wang, D.-X.; Zheng, Q.-Y.; Wang, Q.-Q.; Wang, M.-X. *Angew. Chem.* **2008**, *120*, 7595−7598.
(21) Gale, P. A.; Sessler, J. L.; Karl, V.; Lynch, V. *J. Am. Chem. Soc.* **1996**, *118*, 5140−5141.
(22) Gale, P. A.; Sessler, J. L.; Karl, V. *Chem. Commun.* **1998**, 1−8.
(23) Dinesh Kumar, Ch.; Bhaskar, S.; Soujanya, Y.; Naresh Chary, V.; Santhosh Reddy, P.; Srinivas, K.; Sastry, G. N.; Prabhakar, S. *Phys. Chem. Chem. Phys.* **2014**, *16*, 17266−17271.
(24) Gil-Ramirez, G.; Escudero-Adan, E. N.; Benet-Buchholz, J.; Ballester, P. *Angwew. Chem., Int. Ed.* **2008**, *47*, 4114−4118.
(25) Adriaenssens, L.; Estarellas, C.; Jentzsch, A. V.; Belmonte, M. M.; Matile, S.; Ballester, P. *J. Am. Chem. Soc.* **2013**, *135*, 8324−8330.
(26) Adriaenssens, L.; Gil-Ramirez, G.; Frontera, A.; Quinonero, D.; Eduardo, C.; Escudero-Adan; Ballester, P. *J. Am. Chem. Soc.* **2014**, *136*, 3208−3218.
(27) Bruno, G.; Cafeo, G.; Kohnke, F. H.; Nicolo, F. *Tetrahedron* **2007**, *63*, 10003−10010.
(28) Barrattucci, A.; Bonaccorsi, P.; Cafeo, G.; Kohnke, F. H.; Papalia, T. *Tetrahedron* **2011**, *67*, 7548−7556.
(29) Bochevarov, A. D.; Harder, E.; Hughes, T. F.; Greenwood, J. R.; Braden, D. A.; Philip, D. M.; Rinaldo, D.; Halls, M. D.; Zhang, J.; Friesner, R. A. *Int. J. Quantum Chem.* **2013**, *113*, 2110−2142.
(30) *Jaguar*, v 8.1; Schrodinger, LLC: New York, 2013.
(31) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215−241.
(32) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. *J. Chem. Phys.* **2010**, *132*, 154104−154119.
(33) Wu, Y. D.; Wang, D. F.; Sessler, J. L. *J. Org. Chem.* **2001**, *66*, 3739−3746.

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