รีเซพเตอร์สำหรับไอออนลบจากคอลิกเอซิดที่มี NH-คาร์บาโมซัลโฟนาไมด์เป็นหน่วยจับ

Cholic Acid Based Anion Receptor Containing NH-Carbamosulfonamide Binding Units.

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บทคัดย่อ

ทำการออกแบบและสังเคราะห์รีเซพเตอร์จากคอลิกเอซิด (**S2L**) ที่มีการต่อหมู่ NH-คาร์บาโมซัลโฟนาไมด์จำนวน 2 หมู่ที่ตำแหน่ง C7 และ C12 บนโมเลกุลคอลิกเอซิดเพื่อใช้ในการศึกษาความสามารถในการจับกับไอออนลบชนิดต่างๆ ประกอบด้วยฟลูออไรด์ คลอไรด์ โบรไมด์ แอซีเตต เบนโซเอท ไซยาไนด์ ไดไฮโดรเจนฟอสเฟต ไบซัลเฟต เปอร์คลอเรต และไนเทรต ด้วยเทคนิคโปรตอนเอ็นเอ็มอาร์ ยูวี-วิสิเบิล และการคำนวณทางคอมพิวเตอร์ ผลจากเทคนิคโปรตอนเอ็นเอ็มอาร์พบว่าไอออนลบเข้าไปเกิดพันธะไฮโดรเจนกับรีเซพเตอร์ที่ตำแหน่ง NH-คาร์บาโมซัลโฟนาไมด์ซึ่งเป็นหน่วยจับไอออนลบ ส่วนผลจากเทคนิคยูวี-วิสิเบิลและการคำนวณทางคอมพิวเตอร์พบการหลุดออกของโปรตอนที่หมู่ NH-คาร์บาโมซัลโฟนาไมด์เมื่อจับกับไอออนลบที่มีความเป็นเบสสูง ได้แก่ ไซยาไนด์ ฟลูออไรด์ แอซีเตต เบนโซเอท และไดไฮโดรเจนฟอสเฟต อัตราส่วนการจับกันระหว่างรีเซพเตอร์กับไอออนลบพบว่าจับกันในอัตราส่วน 1:1 ผลการคำนวณค่าคงที่การจับกันระหว่างรีเซพเตอร์กับไอออนลบพบว่าไซยาไนด์จะให้ค่าสูงสุดที่ log K = 6.08

ABSTRACT

A synthetic receptor (**S2L**) based on cholic acid and possessing two NH – carbamosulfonamide binding sites at C7 and C12 positions was designed and synthesized. The binding abilities toward various anions (F^-, Cl^-, Br^-, I^-, AcO^-, BzO^-, CN^-, $H_2PO_4^-$, HSO_4^-, ClO_4^- and NO_3^-)

were investigated using ^{1}H-NMR spectroscopy, UV-Vis spectrophotometry, and computer simulations. Changes in the ^{1}H-NMR spectra revealed the binding with anions occurring at the NH - carbamosulfonamide binding sites via a hydrogen bonding formation. Results from UV-Vis spectra, and optimized structures of the **S2L**-halide anion complexes exhibited a possibility to deprotonation at one of the NH-carbamolsulfonamide group in the case of the binding with strong basic anions (CN^-, F^-, AcO^-, BzO^- and $H_2PO_4^-$). Job plot analysis indicated the formation of 1:1 host - guest complexation. The highest binding constant was obtained from CN^- anion (log *K* = 6.08).

คำสำคัญ: คอลิกเอซิด รีเซพเตอร์ การจับไอออนลบ NH-คาร์บาโมซัลโฟนาไมด์

Keywords: Cholic acid, Receptor, Anion binding, NH-carbamosulfonamide

INTRODUCTION

Cholic acid, a member of steroid group of compounds, has been explored as a potential scaffold in receptor design and guest recognition for many years (Davis et al, 1997; Li and Dias, 1997; Wallimann et al, 1997; Davis 2003; Davis, 2007). Due to their structural preorganization receptors based on cholic acid are endowed with well-defined shape and complementary binding sites for binding with various guests. The first advantage of cholic acid as a scaffold in host-guest chemistry, especially in the area of anion recognition, is its structure containing polar functional groups suitable for anion binding sites. Furthermore, cholic acid possesses lipophilic surfaces, which permit solubility of the receptors in non-polar media (Davis, 1999). The second advantage is a good framework for multiple binding sites. Three secondary hydroxyl groups (3α-OH, 7α-OH and 12α-OH) on the cholic acid building block were substituted with a variety of functional groups to provide two distinct classes of anion receptors; (a) electroneutral anion receptors and (b) positively charged receptors. The electroneutral anion receptors are gaining increasing attention (Antonisse and Reinhoudt, 1998; Gale, 1998) because they have several potential applications for example membrane transport (Davis, 2006; Davis, 2007), phase transfer (Ayling et al, 2002), and sensing devices (Buhlmann et al, 1998; Jadhav et al, 2011; Nayal and Pandey, 2015). Hydrogen bonding is the main interaction for the anion binding in the electroneutral receptors. The binding units, which act as neutral hydrogen bond donor groups, could be amide (Bondy and Loob, 2003; Chmielewski et al, 2004), urea (Hughes et al, 1996; Gale, 2003), thiourea (Nie et al, 2004), sulfonamide (Shin-ichi et al, 2002; Shang et al, 2007; Mammoliti et al, 2009) or carbamate (Kavallieratos et al, 1997; Siracusa

et al, 2002; Fang et al, 2005) based. The positively charged receptors for anion binding containing ammonium, guanidinium, imidazolium and pyridinium groups have been reported (Best et al, 2003; Llinares et al, 2003; Chahar and Pandey, 2008; Chhatra et al, 2011; Tripathi and Pandey, 2011).

Receptors based on cholic acid are prepared by attaching electroneutral H-bond donor groups to 3α-OH, 7α-OH, and 12α-OH moieties. Modifications of binding sites at both 7α-OH and 12α-OH groups have been shown to be beneficial for anion recognition because they are co-directed for guest binding. Most of the hydroxyl groups were modified, multiple H-bond donor units could be incorporated resulting in an improvement of guest binding ability. Davis group and many researchers (Hughes et al, 1996; Davis et al, 1997; Ayling et al, 2001; Gale, 2003; del Amo et al, 2004; Nie et al, 2004; Davis, 2007) have reported the introduction of urea and thiourea as NH hydrogen bond donors for anion recognition and shown their higher efficiency for anion binding in comparison to amide and carbamate. This has been rationalized by the higher number of hydrogen bond donors in the urea and thiourea systems. To promote an acidity of NH-urea and NH-carbamate, electron withdrawing groups such as $-NO_2$ and $-CF_3$ were added to the binding site resulting in an increasing of anion binding affinities (Clare et al, 2005). Deprotonation of relatively acidic protons of the receptor binding unit after binding with basic anions such as F^-, $H_2PO_4^-$, AcO^- and OH^- has been reported for various types of artificial receptors which contain a labile NH-group for example azobenzene (Ros-Lis et al, 2007; Niu et al, 2008), imidazole (Goswami and chakrabarty, 2011; Batista et al, 2004), indole (Lee et al, 2010) and hydrazone (Kigga and Trivedi, 2014; Gupta et al, 2014). This phenomenon is accompanied by visual color changes of the receptor resulting in selective recognition of these anions. The characteristic change in photochemical properties can be used for "naked-eye" detection.

In aim of the present work is to synthesize a receptor based on cholic acid containing NH-carbamosulfonamide binding site for anions. The NH-carbamate groups at positions 7α- and 12α- of the receptor were expectly more acidic by attachment of the *p*-toluenesulfonyl group. The effect of the NH-carbamosulfonamide groups on the binding ability with anions was investigated by using both experimental and computational methods.

EXPERIMENTAL

1. General

All reactions were carried out under nitrogen atmosphere. Unless otherwise noted, materials were obtained from commercial

suppliers and used without further purification. Dichloromethane and acetonitrile (AR grade) were used without further distillation. ^{1}H and ^{13}C-NMR spectra were recorded on 400 MHz NMR spectrometer, model Ultrashield Advance 400 from Bruker and chemical shifts were given in ppm relative to tetramethylsilane (TMS). All NMR spectra were measured in either $CDCl_3$ or acetone-d_6. FT-IR was recorded on Fourier Transform Infrared Spectroscopy, model Spectrum GX from Perkin Elmer using KBr as a matrix. Mass spectrum (ESI) was recorded on Bruker Daltonics Maldi-TOF. UV-Vis spectra were recorded on UV- Vis Spectrophotometer, model Jasco V-650 (double beam). All spectra were recorded in acetonitrile.

2. Synthesis of methyl 3α-acetoxy-7α, 12α-bis[toluenesulfonylcarbamate]-5β-cholan-24-oate (S2L)

In a 100 mL two-necked round-bottomed flask, methyl 3α-acetoxy-7α, 12α-dihydroxy-5β-cholan-24-oate (**C1**) (0.50 g, 1.08 mmol) was dissolved in dichlromethane (50 mL). Then *p*-toluenesulfonylisocyanate (0.40 mL, 2.69 mmol) was added and the mixture was stirred at room temperature for 24 h. The solvent in the reaction mixture was evaporated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with ethyl acetate : hexane = 2:1 to provide the desired product as a white solid (R_f = 0.61)

Compound **S2L**; Yield 31.52%. ^{1}H-NMR (acetone-d_6) δ 10.19 (1H, *bs*, NH-carbamosulfonamide), 7.92 (3H, *t*, J = 8.4 Hz, aromatic H_a), 7.77 (1H, *d*, J = 8.4 Hz, aromatic H_a), 7.45 (3H, *dd*, J = 8.0, 3.6 Hz, aromatic H_b), 7.36 (1H, *d*, J = 8.4, Hz, aromatic H_b), 6.55 (1H, *bs*, NH- carbamosulfonamide), 4.91 (1H, *bs*, H_{12}), 4.78 (1H, *bs*, H_7), 4.45 (1H, *m*, H_3), 3.64 (3H, *s*, $COOCH_3$), 2.46 (6H, *d*, J = 2 Hz, aromatic CH_3), 2.03 (3H, *s*, CH_3COO), 0.94 (1H, *s*, H_{21}), 0.68 (3H, *s*, H_{19}), 0.47 (3H, *2s*, H_{18}). ^{13}C-NMR ($CDCl_3$) δ 12.05, 17.48, 21.73, 21.82, 22.39, 22.74, 25.28, 26.66, 27.28, 28.34, 30.67, 31.41, 34.43, 34.61, 34.85, 38.14, 40.73, 42.76, 45.05, 47.26, 51.66, 74.11, 74.27, 79.48, 126.64, 127.92, 128.31, 129.75, 129.91, 130.13, 136.10, 136.14, 145.51, 149.96, 150.46, 170.89, 174.45. FT-IR (KBr); 3593, 3234, 2955, 2872, 1739, 1162 cm^{-1}. MS (ESI) m/z calcd for $C_{43}H_{58}N_2O_{12}S_2$ $[M + Na]^+$ 881, found 881.273.

3. Anion recognition studies

Anions recognition abilities of **S2L** were investigated using ^{1}H-NMR and UV-Vis titration experiments. A study of the binding with anions by ^{1}H-NMR was performed using solutions of **S2L** in acetone-d_6. The solution of **S2L** for UV-Vis titration with all guests was prepared in acetonitrile. The concentrations of **S2L** solutions are $3.0x10^{-3}$ M and $4.5x10^{-4}$ M for NMR and UV-Vis experiments, respectively. All

anions are in a form of tetrabutylammonium salts.

4. Halide anion recognition by computational method

All possible starting geometries of steroidal-based receptor for anion substrates were constructed using experimental data. Anion targets were located in the middle of two functional groups, which are electron deficient and can form hydrogen bonds. Semi-empirical methods (AM1, PM6 and PM7) were used in the geometry optimizations for all steroidal-based receptors and complexes with anion guests. The interaction energies were calculated follow the equation

$$E_{int} = E_{S-A} - (E_S + E_A)$$

Where E_{int} = interaction energy (kJ/mol)

E_{S-A}, E_S, and E_A = heat of formation of anion-receptor complexes, receptors and anions (kJ/mol), respectively.

The selectivity was calculated using the interaction energy of each complex divided by the interaction energy of the complex with lowest interaction energy. All calculations were performed with the program package MOPAC2012 (James, 2012). The molecular geometries were drawn with the program MOLDEN (Schaftenaar and Neodik, 2000).

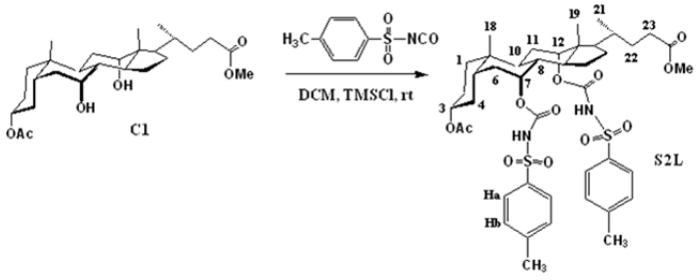
RESULTS AND DISCUSSION

1. Synthesis of S2L receptor (Scheme 1)

Compound **C1** was prepared according to literature procedures (Davis et al, 1997; Davis and Perez-Payan, 1999) by simultaneous esterification of both the hydroxyl group at position C_3 and carboxylic group at position C_{24} of cholic acid using *p*-toluenesulfonic acid and methyl acetate. The coupling reaction between **C1** and toluenesulfonyl isocyanate at room temperature for 24 h afforded the desired product (**S2L**) in 31.52% yield after purification by column chromatography using ethyl acetate : hexane = 2:1 as eluent. The reaction of two hydroxyl groups at positions C_7 and C_{12} with isocyanate group of *p*-toluenesulfonyl isocyanate compound yielded two carbamosulfonamide groups, which were designed as binding sites for anion recognition. The final product was characterized by ^{1}H-NMR and ^{13}C-NMR spectroscopy, FT-IR and high resolution mass spectrometry.

2. Anions Recognition Studies by ^{1}H-NMR Titration

The binding of **S2L** with anions (F^-, Cl^-, Br^-, I^- AcO^-, BzO^-, CN^-, $H_2PO_4^-$, HSO_4^-, ClO_4^- and NO_3^-) was investigated using ^{1}H-NMR titration. As shown in Figure 1, the aromatic protons (H_a and H_b) at 7.00-8.00 ppm were displayed.



Scheme 1. Synthesis and numbering system for S2L.

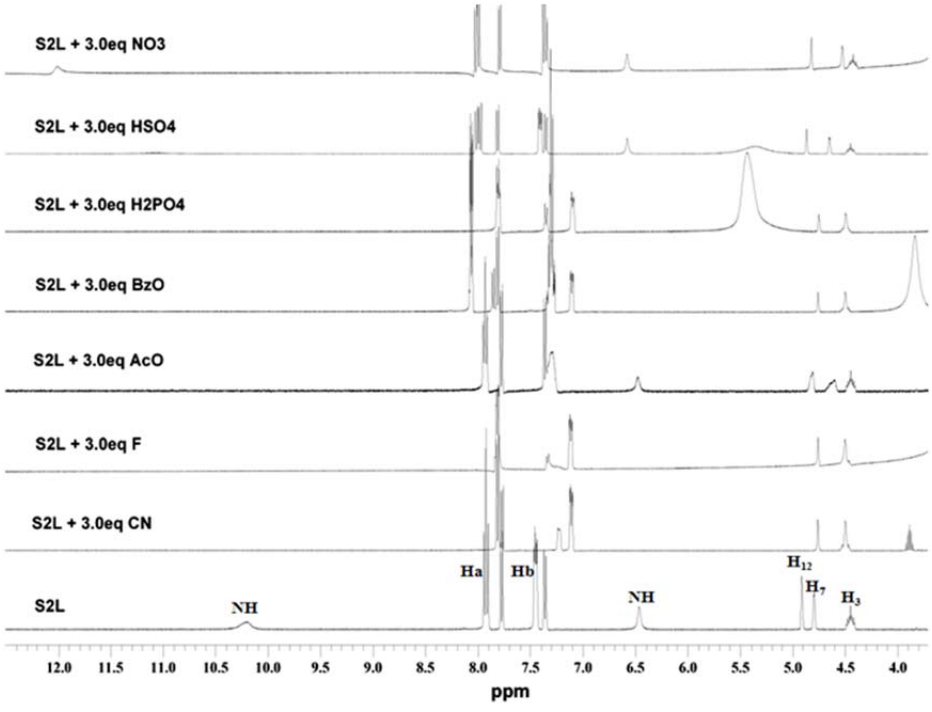


Figure 1. Partial ^{1}H-NMR spectra of **S2L** in acetone-d_6 with 3 equivalents of anions.

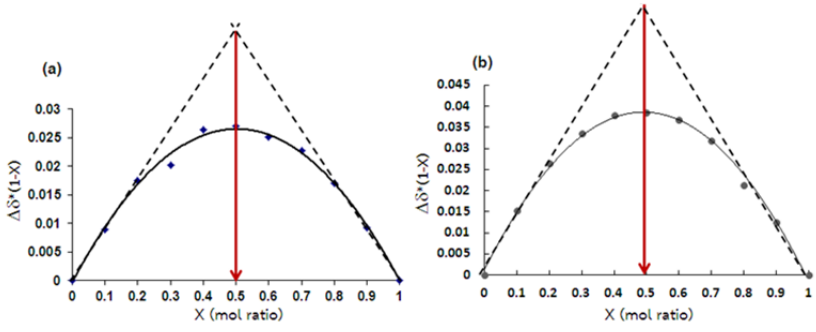


Figure 2. Job's plot for the complex between **S2L** and (a) fluoride ion and (b) cyanide ion (^{1}H NMR experiments by monitoring the shift of H_7 proton).

The signals of H_3, H_7 and H_{12} were observed in the range of 4.40 – 5.00 ppm. The aliphatic protons, H_7 and H_{12} on carbons were adjacent to the carbamate binding sites. Two peaks at 10.19 and 6.55 ppm were assigned to NH-carbamosulfonamide. One NH peak appeared at more downfield position due to a formation of intramolecular hydrogen bond between the near two adjacent carbamosulfonamide groups. This intra-molecular bond was proven by a computational optimization of **S2L** structure using PM7 method as shown in Figure 6a. Considerably, binding affinity of **S2L** with anions remarkably exhibited the spectral changes of aromatic protons (H_a and H_b) and aliphatic protons (H_7 and H_{12}) as shown in Figure 1. In the case of NO_3^- and HSO_4^-, the peak of NH at 10.19 ppm exhibited a large downfield shift to 12.10 ppm while another NH peak at 6.55 ppm showed a small shift to downfield. The aromatic H_a and H_b protons at 7.00 – 8.00 ppm were also shifted to downfield while the aliphatic protons (H_7 and H_{12}) at 4.70 and 4.90 ppm shifted to upfield. These results indicated the formation of hydrogen bonding interactions occurred between NH-carbamosulfonamide and the anions. In the case of Cl^-, Br^- and I^- which studied in $CDCl_3$ solution, similar ^{1}H-NMR results were observed. Unfortunately, the expected downfield shift of the NH-carbamosulfonamide proton has not been detected in $CDCl_3$ solvent.

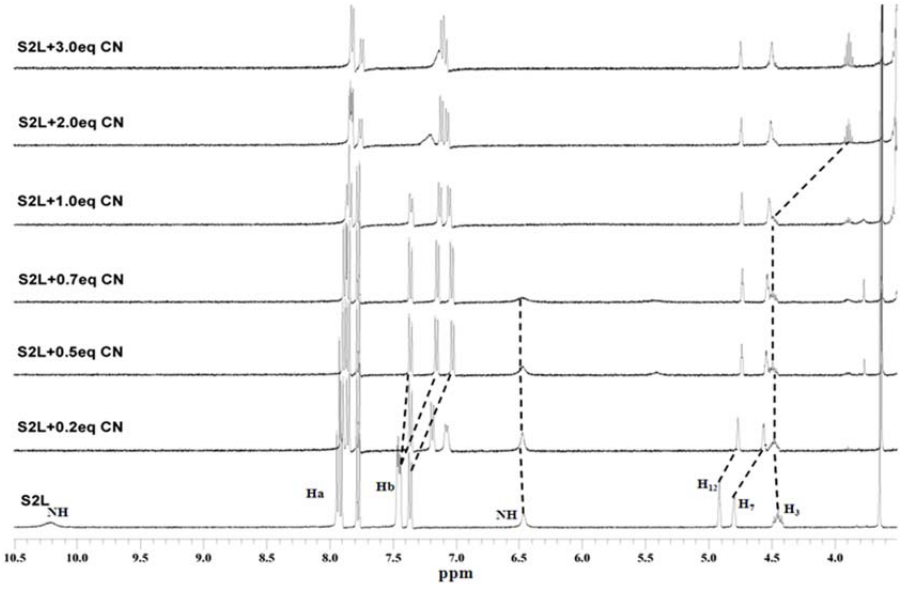


Figure 3. Partial ^{1}H NMR titration spectra of **S2L** in acetone-d_6 upon adding cyanide ion from 0.2 to 3.0 equivalents.

Compared to other anions, the different changes of **S2L** protons including NH, H_a, H_b, H_7, H_{12} and H_3 were observed upon the addition of strong basic anions (F^-, AcO^-, BzO^-, CN^- and $H_2PO_4^-$), for instance a disappearance of the NH proton at 10.19 ppm and an upfield shift of H_a, H_b, H_7, H_{12} signals. These observations implied that the binding properties of **S2L** toward strong basic anions are different from those with other halide anions, NO_3^- and HSO_4^-. Results from ^{1}H-NMR titration showed that strong bases of CN^- and F^- could strongly affect to the shifts of all protons, neighboring the anion binding site. This means that **S2L** binds strongly with CN^- and F^-. In case of CN^-(Figure 3), the peak of NH proton at 10.19 ppm simultaneously disappeared after adding 0.1 equivalents of CN^- but another NH proton at 6.55 ppm exhibited a downfield shift upon the addition of 0.1 – 0.7 equiv of CN^- and then thoroughly disappeared with the increase of CN^- to 1.0 equiv. The disappearance of both NH protons could not observe in the case of 1.0 equiv. F^- addition. This means that CN^- which is a stronger base than F^-, deprotonated both NH-carbamosulfonamide groups. Interestingly, a significant upfield shift of aliphatic proton (H_3) at 4.45 ppm was also found. The reason may be electron density increasing of the deprotonated form of **S2L** induced shielding effect. Job's plot based on the ^{1}H-NMR titration data obtained by monitoring H_7 proton signal supports a 1:1 host-guest stoichiometric ratio in all cases (Figure 2a and 2b).

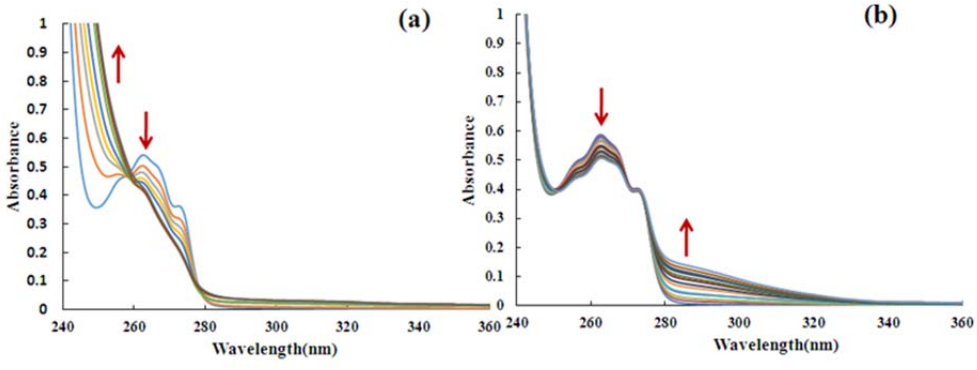


Figure 4. Changes in the absorption spectra of **S2L** ($4.5x10^{-4}$ M) upon addition of (a) fluoride ion and (b) nitrate ion (0-10 equiv) in acetonitrile

3. Anions Recognition Studies by UV-Vis Titration

The studies of binding of **S2L** with anions were performed in acetonitrile. The titration studies of **S2L** with all anions demonstrated the spectral changes in UV-Vis spectra in three different regions. In acetonitrile, the spectrum of **S2L** showed a peak with λ_{max} at 263 nm. Titration with CN^-, F^-, AcO^- and $H_2PO_4^-$ caused a decreasing in the absorption band at 263 nm while a new band at λ_{max} of 250 nm was developed. An isosbestic point at 254 nm was observed (Figure 4a). This indicates the formation of a new product, which was proposed to be the deprotonated form of **S2L**. This result was in agreement with a computational simulation result, which indicated the deprotonation at NH-carbamate binding site after the addition of F^-. To confirm the deprotonation of **S2L** at the NH-carbamate binding site by strong basic anion, a titration with OH^-, was performed. Similar changes in the UV-Vis spectra of **S2L**, upon the increment of CN^-, F^-, AcO^- and $H_2PO_4^-$, were obtained. Unlikely, the UV-Vis spectral change of **S2L** in the case of NO_3^-, Cl^-, Br^- and ClO_4^- (Figure 4b and 5a) displayed a slow decrease of the absorption band at 263 nm without a new absorption band and isosbestic point but a new band around 300 nm was observed upon increase amount of NO_3^- and ClO_4^-.

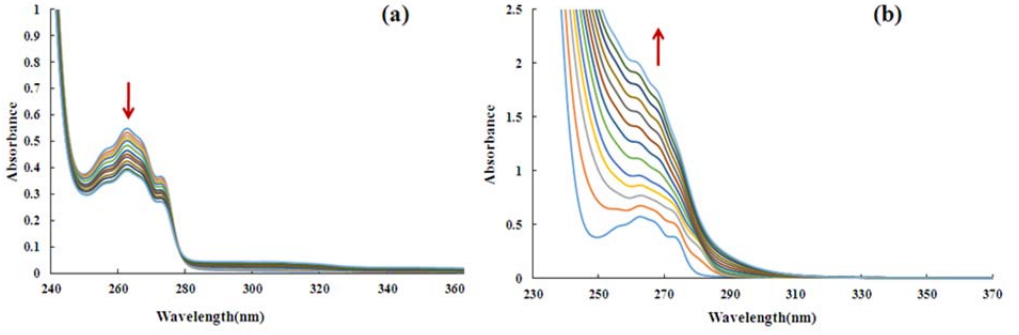


Figure 5. Changes in the absorption spectra of **S2L** ($4.5x10^{-4}$ M) upon addition of (a) perchlorate ion and (b) benzoate ion (0-10 equiv) in acetonitrile

In the presence of I^-, the characteristic absorption band at 263 nm of **S2L** remained unchanged but we found an appearance of the characteristic band of I^- and BzO^- at 250 nm and 265 nm, respectively. Concerning the aromatic guests; BzO^- (Figure 5b), the absorbance at 263 nm of **S2L** was slightly increased possibly caused by the complementary $\pi - \pi$ stacking interactions with the receptor.

To investigate the binding affinity of **S2L**, the log *K* values calculated using the Specfit 32 program and according to the Benesi-Hilderbrand equation of 1:1 host-guest complexation (Hirose, 2001) from UV-vis titration data, were evaluated. As shown in Table 1, the highest log *K* value of 6.08 was obtained for the complex with CN^-. The low log *K* values obtained in the case of Cl^-, Br^-, I^-, BzO^-, NO_3^-, HSO_4^- and ClO_4^- binding related to a low anion basicity and large ionic radii. These properties indicated that these anions did not prefer to bind with **S2L**. Surprisingly, the induced-fit binding involving both H-bonds and **π–π** stacking interactions in the complexe of **S2L** with BzO^-, provided the lowest log *K* values of 4.11. From all results, it can be explained that a large size and steric guest gave the promising influence of binding affinity.

Table 1. Binding constants calculated from UV-Vis titration of receptor **S2L** for all anions

Anions	Log K[a]	Log K[b]	Anions	Log K[a]	Log K[b]
CN^-	-	6.08	BzO^-	-	4.11
F^-	5.82	5.57	$H_2PO_4^-$	-	5.43
Cl^-	4.05	c	HSO_4^-	-	4.62
Br^-	2.69	c	ClO_4^-	-	5.36
AcO^-	-	5.16	NO_3^-	-	4.24

[a] log K values are calculated from Specfit32 program, [b] log K values are calculated from Benesi-Hilderbrand equation, [c] could not be calculated

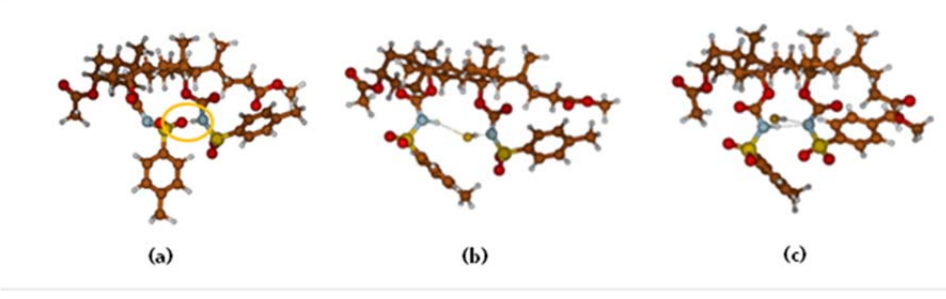


Figure 6. The optimized geometry of (a) **S2L** showing an intramolecular hydrogen bonding between two carbamosulfonamide binding units, the fluoride-**S2L** based complex using semi-empirical methods (b) PM6 and (c) PM7 showing the deprotonation at one of NH-carbamosulfonamide binding unit by F^-.

4. Anions Recognition Studies by Computational Simulation

The optimized structure of **S2L** (Figure 6a) was observed the intramolecular hydrogen bonds between the near sulfonamide group and NH group. The optimized geometries of halide-**S2L** complexes showed that two NH-carbamosulfonamide binding sites in **S2L** formed hydrogen bond with the halide anions. The halide anions located in the middle of two NH-carbamosulfonamide groups and were stabilized by the hydrogen bond. Interestingly, it was found that fluoride anion removed one of hydrogen from one NH-carbamosulfonamide group in the fluoride-**S2L** complex, shown in Figures 6b and 6c. This simulated complex structure supported our hypothesis about the possibility of deprotonation at the NH-carbamate of the receptor by basic anions such as fluoride. Similar results have been reported by many research groups (Camiolo et al, 2003; Kim and Kim, 2005; Panzella et al, 2009; Bhardwaj et al, 2011). The optimized structures of **S2L** complexes with Cl^-, Br^-, and I^-, revealed that they preferentialy formed only hydrogen bonds with both NH-carbamosulfonamide binding sites.

CONCLUSION

The cholic acid receptor **S2L** containing two NH-carbamosulfonamide binding sites has been successfully designed and synthesized. Its recognition properties toward anions were investigated. The interaction with cyanide, fluoride, acetate and dihydrogenphosphate displayed deprotonation at the NH-carbamosulfonamide binding site. These complexes also exhibited highest binding strength. The stiochiometry of 1:1 was determined using Job's method from the ^{1}H-NMR data for all anions. The optimized geometry of the fluoride-**S2L** complex revealed the formation of hydrogen bonding and deprotonation at one side of the NH-carbamosulfonamide binding unit while other halide anions formed only hydrogen bonding with the NH-carbamosulfonamide of **S2L**. Distinct changes in the UV-Vis spectra of **S2L** comfirmed the performance of guests in three categories such as deprotonating anion (CN^-, F^-, AcO^- and $H_2PO_4^-$), $\pi - \pi$ stacking binding guests (BzO^-), and H-bond forming guests (Cl^-, Br^-, I^-, NO_3^-, HSO_4^- and ClO_4^-).

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