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ARTICLE

Fluorescent calix[4]arene chemosensor for acidic and basic amino acids in pure aqueous media

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A modified calix[4]arene based receptor **2**, conjugated with four bithiophene-cyanoarylic acid groups, not only recognizes acidic amino acids (Asp and Glu) by quenching fluorescence, but also shows highly selective sensing for basic amino acids (Lys and Arg) by turning on fluorescence in sodium phosphate buffer solution without any organic solvent. The UV-Vis spectroscopy binding analysis and ESI-MS studies indicate that the above complexes have a 1:1 stoichiometry. ^{1}H NMR and molecular modeling studies suggest the supramolecular complex structure like the relation of lid and cup, but not the typical host-guest relation of the cavity. A plausible mechanism involving intramolecular charge transfer (ICT) is proposed.

Introduction

Amino acids and their derivatives are fundamental substrates involved in a wide variety of biological processes, and also play an important role in the area of design and preparation of pharmaceuticals, as they are part of the synthetic process in the production of drug intermediates and protein-based drugs.[1] Therefore the selective recognition of these compounds by synthetic receptors is of particular significance for understanding the interactions between biological molecules as well as design of catalysis systems, new pharmaceutical agents, and separation materials. Of particular relevance are the studies performed in water, where most of the biological processes take place.[2] Recently, considerable efforts have been made to develop macrocyclic receptors with specific properties and functions revealing their affinity and selectivity towards certain amino acids.[3] However, most of these artificial receptors have suffered from low sensitivity and selectivity between various naturally occurring amino acids.[4] Some of them, especially fluorescent chemosensors, achieved high selectivity in their recognition but unsatisfactorily worked in organic or organic-aqueous solution.[5] Thus, the development of synthetic receptors for the recognition of amino acids in aqueous media is highly desirable.

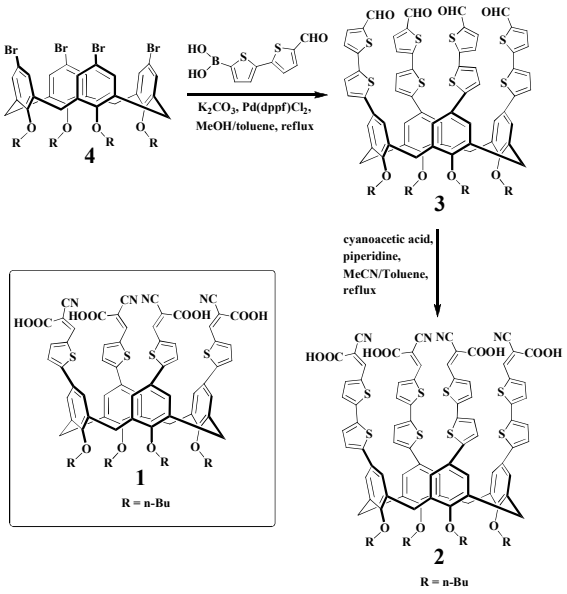
During the last couple of years, we have been interested in preparing and studying new calixarene derivatives, which show interesting properties as molecular receptors, molecular devices, organogelators, and fluorescent chemosensors.[6] On the other hand, organic D-π-A dyes that contain oligothiophene as both donor groups and π bridge, and 2-cyanoacrylic acid as acceptor, are potential fluorescent chemosensors because of their excellent photophysical properties, such as large molar extinction coefficients, long absorption and emission wavelengths, and moderate fluorescence quantum yields. Moreover, the carboxylic acid group of the cyanoacrylic acid acceptor is a representative hydrophilic group and excellent donor/acceptor of hydrogen bonds. When grafted with oligothiophene-cyanoarylic acid groups, calix[4]arene derivatives will become more watersoluble with the potential to recognize amino acids in aqueous media. In a preliminary communication, we reported the ability of a calix[4]arene derivative (**1**) conjugated with four thiophene-cyanoarylic acid groups to act as a selective fluorescent ratiometric chemosensor for acidic amino acids.[7] This led us to undertake an in-depth study of the recognition process by simple structural modification such as variation of the conjugation pathway. Thus, the receptor **2** conjugated with four bithiophene-cyanoarylic acid groups has been designed by addition of a thiophene unit into **1**. The results turn out interestingly that **2** not only recognizes acidic amino acids (Asp and Glu) by fluorescence quenching, but also shows highly selective sensing for basic amino acids (Lys and Arg) by fluorescence turn-on in sodium phosphate buffer solution without any organic solvent. In this paper, we describe a comprehensive study by a multidisciplinary approach using UV-vis absorption and fluorescence spectroscopy, mass spectrometry, nuclear magnetic resonance, and molecular modeling, aiming to propose a binding mode and a reasonable supramolecular structure which can explain the selectivity observed by fluorescence measurements.

Results and discussion

Synthesis

The synthesis of **2** is depicted in Scheme 1. A Suzuki reaction between **4**[5c] and 2TFB (5'-formyl-2,2'-bithiophen-5-yl boronic acid) was successfully executed in the presence of anhydrous K_2CO_3 and $PdCl_2$(dppf) to produce **3**. A Knoevenagel reaction between **3** and cyanoacetic acid then took place under piperidine to finally result in **2** with a high yield. The structures of **2** and **3** were confirmed by ^{1}H NMR, ^{13}C NMR, MS spectra, and EA.

The cone conformation of every compound is clearly shown in the signal pattern of the ^{1}H NMR.[8] Meanwhile, the configuration of the bithiophene-cyanoarylic acid group of **2** can be assigned a Z-geometry since the chemical shift of its alkenic proton is at δ 8.21 ppm in its ^{1}H NMR spectrum.[9]



Scheme 1. Synthesis of **2** and structure of **1**.

The UV spectrophotometric titration of 2 with amino acids

In the absorption spectrum of **2**, maximum bands were observed at 400 nm attributable to the π-π* transition with charge-transfer character. Addition of Asp/Glu resulted in a decrease of the absorption intensity at 500 nm and an increase of the intensity at 400 nm with a slight blue-shift and the isobestic point at 425 nm, which indicates complex formation (Figure 1a and 1b). On the other hand, the titration of **2** with Lys/Arg showed a gradual decrease in absorption at 250-600 nm over an amino acid concentrations range of 50-1000 μM, above which a plateau was achieved, suggesting the presence of equilibrium between **2** and its Lys/Arg complex (Figure 1c and 1d).

The fluorometric titration of 2 with amino acids

In our previous study, calix[4]arene derivative **1** could bind amino acids, which inspired us to test the presence of special amino acids by inspecting the change of fluorescence intensity of **2** in the presence of amino acids. In the fluorescent spectrum of **2**, the maximum excitation and emission wavelengths were observed at 400 and 566 nm, respectively. All titrations of **2** with 20 naturally occurring amino acids revealed that acidic amino acids (Asp/Glu) exhibit a decrease while basic amino acids (Lys/Arg) show an increase in fluorescence intensity, respectively. However, no obvious spectral changes occurred to **2** in the presence of 10 equiv. of Gln, Asn, Phe, His, Ala, Tyr, Gly, Trp, Ser, Met, Cys, Leu, Thr, Ile, Pro, and Val (Figure 2 and S1). These results suggested that acidic and basic amino acids might bind much stronger with **2** than other tested amino acids. Thus, **2** could act as a selective supramolecular fluorescence probe for Asp/Glu and Lys/Arg.

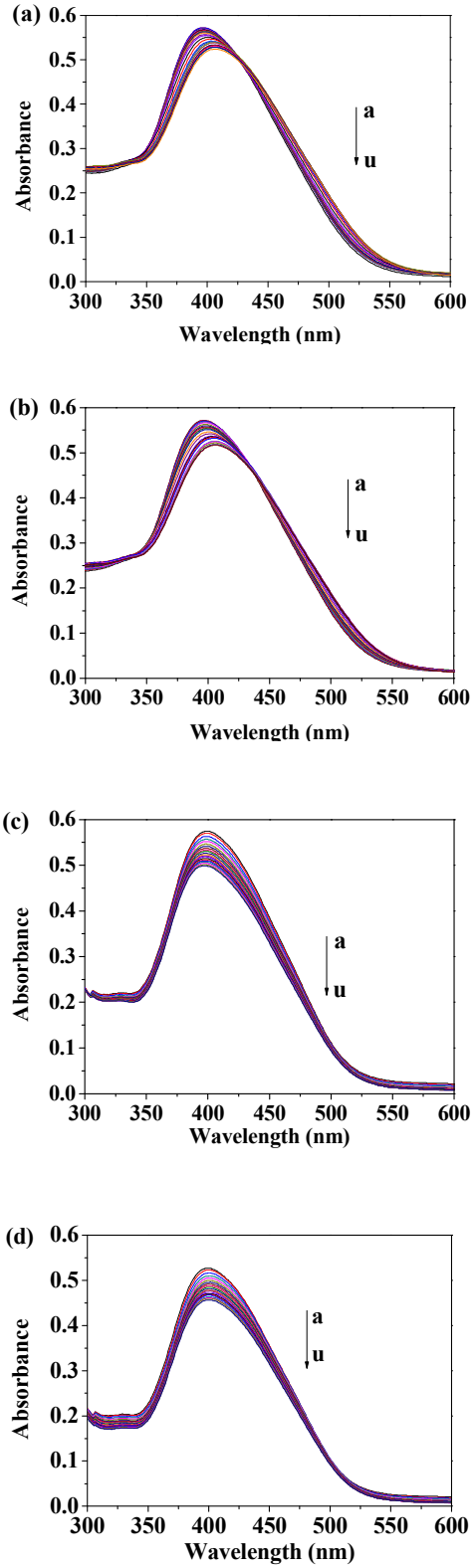


Figure 1. UV-Vis titrations of **2** with (a) Asp, (b) Glu, (c) Lys and (d) Arg in sodium phosphate buffer solution (0.1 M, pH 7.8). [**2**] = 5.0×10^{-6} M, and [Asp] = [Glu] = [Lys] = [Arg] = 0.02 M. From a to u: 0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190 and 200 equiv.

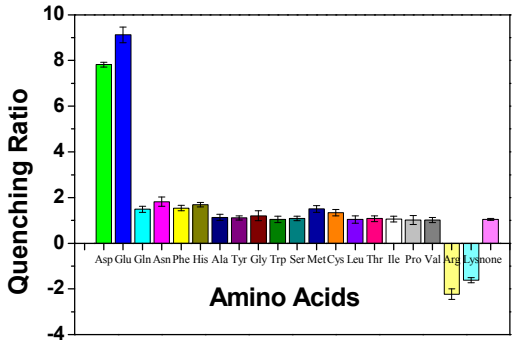


Figure 2. Quenching ratio (F_0/F for Asp, Glu, Gln, Asn, Phe, His, Ala, Tyr, Gly, Trp, Ser, Met, Cys, Leu, Thr, Ile, Pro, Val and None; $-F/F_0$ for Lys and Arg) of **2** (5×10^{-6} M) upon the addition of 10 equiv. amino acids in sodium phosphate buffer solution (0.1 M, pH 7.8). F and F_0 are the fluorescent intensities of **2** with and without amino acid, respectively. λ_{ex} = 400 nm, and λ_{em} = 566 nm.

To gain insight into the recognition behavior of **2** and Asp/Glu, the fluorescence emission spectral titration experiments were carried out. It was found that upon the addition of Asp/Glu to **2**, the emission band at 566 nm gradually decreased with a slight red-shift within 10 nm. When the amino acid concentrations were 10 equiv. of **2**, approximately 87% and 89% fluorescence quenching were observed for Asp and Glu, respectively (Figure 3a and 3b). On the basis of fluorescence emission titrations, the association constants for the 1:1 complexes of **2** and acidic amino acids were calculated to be 7.87×10^4 M^{-1} and 1.36×10^5 M^{-1} for Asp and Glu according to the Stern-Volmer equation, respectively.

To explore the recognition property of **2** to Lys/Arg, we have also carried out similar fluorescence titration experiments. The titration of **2** with basic amino acids showed gradual enhancement in the fluorescence intensity from 1 to 10 equiv. of Lys/Arg, and achieved a plateau afterward (Figure 3c and 3d). The Scatchard-type equation was used to calculate the binding constants between **2** and basic amino acids, which were about 3.48×10^3 M^{-1} and 8.11×10^3 M^{-1} for Lys and Arg, respectively.

ESI MS Studies on Formation of the Complexes

The electrospray ionization (ESI) mass spectrometry was also used to characterize the complexes between **2** and amino acids in 1:1 molar ratio. The salient peak at m/z 1832.2 for $[\mathbf{2}\cdot\text{Lys}+\text{H}]^+$ was found by using the solution of **2** and Lys in 8 : 1 : 100 (v/v/v) dimethylacetamide, H_2O, and acetonitrile (Figure 4), which provided further evidence for formation of a 1:1 stable complex between **2** and Lys. Similarly, formation of the 1:1 complexes between **2** and Asp, Glu, and Arg was also evidenced by the ESI mass spectrometry, in which the salient peaks at m/z 1819.1, 1833.2, and 1860.2 for $[\mathbf{2}\cdot\text{Asp}+\text{H}]^+$, $[\mathbf{2}\cdot\text{Glu}+\text{H}]^+$, and $[\mathbf{2}\cdot\text{Arg}+\text{H}]^+$, respectively, were all observed (Figure S2).

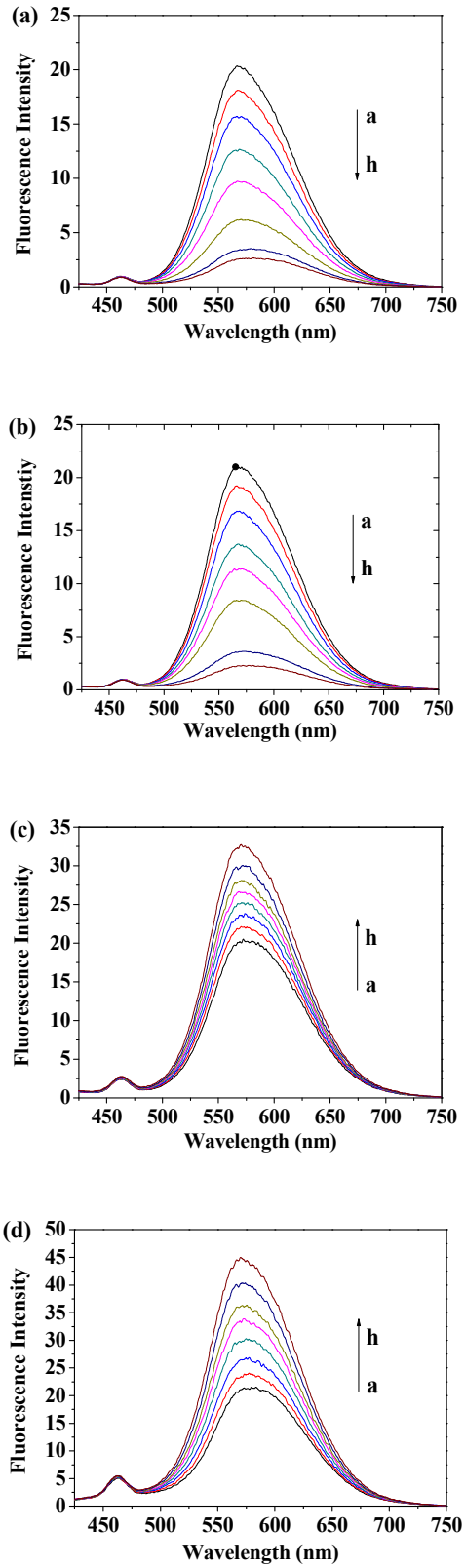


Figure 3. Fluorescent titrations of **2** with (a) Asp, (b) Glu, (c) Lys and (d) Arg in sodium phosphate buffer solution (0.1 M, pH 7.8). λ_{ex} = 400 nm, [**2**] = 5.0×10^{-6} M, and [Asp] = [Glu] = [Lys] = [Arg] = 0.02 M. From a to h: 0, 1, 2, 3, 4, 5, 7 and 10 equiv.

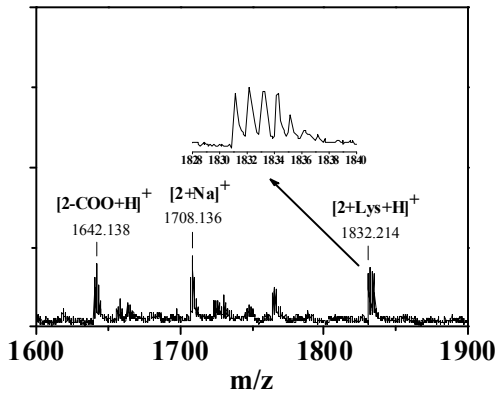


Figure 4. ESI MS spectra of **2** and Lys in 1 : 1 molar ratio.

^{1}H NMR studies on Formation of the Complexes

To gain a better understanding for the interaction of these four amino acids with the sensor, we have conducted a ^{1}H NMR spectroscopic investigation. From the ^{1}H NMR spectra of **2**, substrates, and their mixtures at 1:1 molar ratio, it is found that one H signal of $C^{\beta}H_2$ in Lys undergoes an obvious downfield shift from 1.64 ppm to 1.71 ppm (marked by black dot in Figure 6), contrarily, the $C^{\varepsilon}H_2$ signal in Lys undergoes an obvious upfield shift from 3.06 ppm to 2.77 ppm (marked by white dot in Figure 6), respectively. The CH_2 group signal of Asp undergoes a slight downfield shift from 2.83, 2.77 ppm to 2.85, 2.79 ppm (marked by white and black dots in Figure S3). The $C^{\alpha}H$ group signal of Glu undergoes an obvious downfield shift from 3.31 ppm to 3.40 ppm (marked by white dot in Figure S4). One H signal of $C^{\delta}H_2$ in Arg undergoes an obvious downfield shift from 2.92 ppm to 3.10 ppm (marked by white dot in Figure S7). Moreover, partial signal of the other two CH_2 groups, $C^{\beta}H_2$ and $C^{\gamma}H_2$, in Arg also undergoes an obvious downfield shift from 1.43 ppm to 1.74 ppm (marked by black dot in Figure S5).

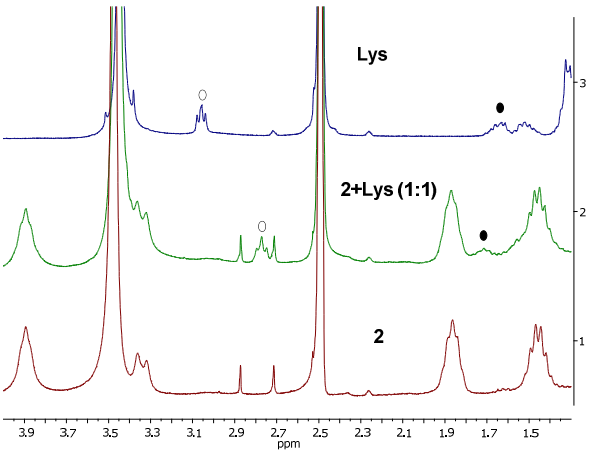


Figure 6. Partial ^{1}H NMR spectra of **2**, Lys and a 1 : 1 mixture of **2** and Lys in DMSO-d_6/D_2O.

The downfield shift of CH or CH_2 in Asp, Glu, Lys and Arg shows that significant interaction exists between these molecules and **2**, but they are not included by the cavity of **2**. The upfield shift of $C^{\varepsilon}H_2$ in Lys may result from two interaction modes: (i) its branched NH_2 exists as NH_3^+ and is included by cavity of **2**; (ii) its branched NH_2 changes into NH_2 from NH_3^+, then interacts with the carboxylic and amino groups of **2**. The second mode embodies the actual existing state of the branched NH_2 of Lys under its UV and Fluorescent titration condition. Coleman reported that calix[4]arene sulphonate includes the branched NH_3^+ of Lys with its cavity and induces an obvious upfield shift ($\Delta\delta > 1.5$ ppm at pH =5, $\Delta\delta > 1.0$ ppm at pH =1) of $C^{\varepsilon}H_2$ when host and gust was mixed at 1:1 molar ratio.[10] Although the cavity structure of **2** can't be wholly equated to that of the reported calix[4]arene sulphonate, the comparable slight upfield ($\Delta\delta$ = 0.29 ppm) is subjective to result from the second factor. Noticeably, ^{1}H NMR spectrum of **2** has no distinct change on the addition of these four substrates, implying acidic and basic amino acids can be only caught by bithiophene-cyanoarylic acid groups at the upper rim of **2**, such as the relation of lid and cup, but not included by its cavity.[11] Based on the NMR analysis, it can be deduced that the selectivity toward amino acid of **2** could be improved when the dimension of its "cup" is changed to fully match that of one "lid".

Molecular Modeling and Proposal of a Supramolecular Complex Structure

The binding mechanism of **2** toward Asp, Glu, Lys, and Arg was further investigated through molecular modeling with the Gaussian 03 package.[12] Because a branched carboxylic group or amino group exists in these four amino acids, it is speculated that these additional groups should play an important role in the high selectivity through H-bond interactions with the cyanoarylic acid groups on **2**, cooperating with the characteristic groups of amino acids. Based on this deduction and the NMR analysis results, the optimization of the complexes was executed by placing a corresponding amino acid in a position maximally close to two opposite cyanoarylic acid groups pointing inward of **2**. Compound **2**, **2**–Asp, **2**–Glu, **2**–Lys and **2**–Arg complex were optimized at the level of B3LYP/6-31G, the results of which are shown in Figure 7 and Table S1-7. **2** has an elongated shape, and its four bithiophene-cyanoarylic acid groups are almost coplanar with their corresponding benzene rings. In the four complexes, amino acids are bridged on the top of **2** by catching its three bithiophene-cyanoarylic acid groups with different number of H-bonds: O198–H207···O116, O115–H1927···O201, O102–H188···O200, N194–H202···O198 and N194–H203···N80 (**2**–Asp complex); O199–H200···O116, O115–H192···O210, O102–H188···O201, O202–H211···O102, and N194–H203···N80 (**2**–Glu complex); N200–H214···O116, O102–H188···O201, O202–H216···O102, and N194–H203···N80 (**2**–Lys complex); N203–H217···O116 , O102–H188···O201, O202–H215···O102, O115–H192···N199, and N194–H205···N80 (**2**–Arg complex). Under these H-bonding interactions from amino acids, the bithiophene rings

on three bridged "arms" of **2** are promted to rotate far away from their conjoint benzene rings. In all of complexes, the branched carboxylic or amino group expectedly cooperates with the characteristic groups of amino acids in multiple H-bond formations and thereof strengthens the interaction with **2**. The difference of H-bond fashion in four complexes results in different stabilization energy (Table S5: 26.6 kcal/mol of **2**–Asp complex; 33.5 kcal/mol of **2**–Glu complex; 20.5 kcal/mol of **2**–Lys complex; and 31.6 kcal/mol of **2**–Arg complex), suggesting the interaction between **2** and Glu is slightly stronger than that between **2** and Asp and the interaction between **2** and Arg is slightly stronger than that between **2** and Lys, which is consistent with the results from fluorescence and UV-Vis titrations.

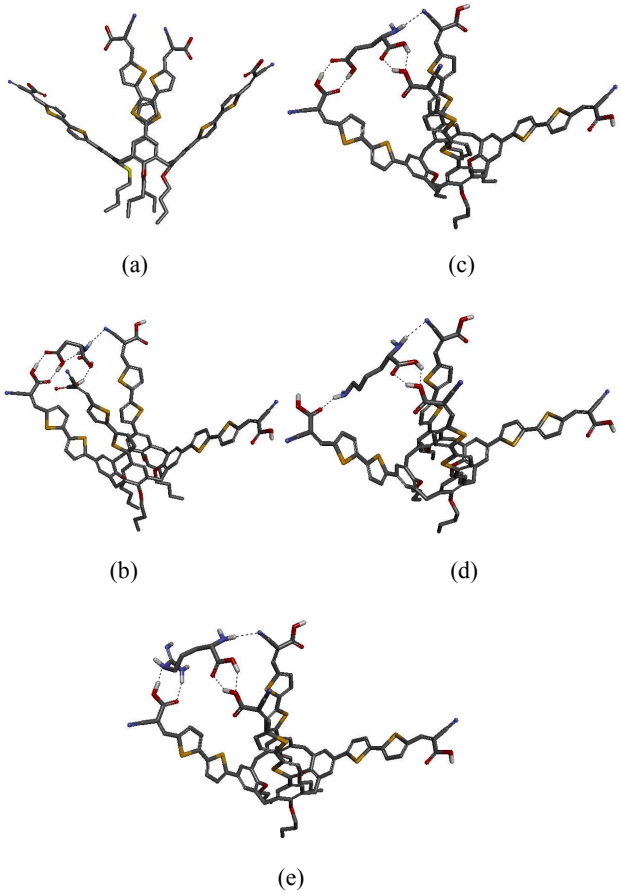


Figure 7 Optimized structures of (a) **2**, (b) **2**–Asp complex, (c) **2**–Glu complex, (d) **2**–Lys complex, and (e) **2**–Arg complex. H-bonds are shown as dotted lines. Nonpolar hydrogen atoms are omitted for clarity.

Mechanism of amino acid sensing

To account for the observed sensing of acidic and basic amino acid ion by **2**, a plausible mechanism involving intramolecular charge transfer (ICT) is proposed. When a fluorophore contains an electron donating group conjugated to an electron-withdrawing group, it undergoes ICT from the donor to the acceptor upon excitation by light. The consequent change of the dipole moment leads to a larger Stokes shift, which is influenced by the microenvironment of the fluorophore. **2**, which consists of a *n*-butyl substituted calix[4]arene donor, a 2-cyanoacrylic acid acceptor, and an oligothiophene spacer, is an ideal fluorescent chemosensor. Intramolecular charge transfer (ICT) occurs from a *n*-butyl substituted calix[4]arene donor to 2-cyanoacrylic acid acceptor upon photoexcitation of **2**. The hydrogen bonding with the electron acceptor could increase or decrease the flow of charge from the donor to the acceptor, thereby affecting the ICT process. When one NH_2 groups and two electron-withdrawing COOH groups in an Asp/Glu interact with the acceptor groups, the excited state is more stabilized by the Asp/Glu than the ground state, which leads to a red shift of the absorption and emission spectra. Moreover, the interaction between **2** and Asp/Glu provides a fluorescence quenching pathway. The fluorescence quenching of **2** may occur by the excitation energy transfer or charge transfer from **2** to the Asp/Glu. Conversely, the binding between **2** and Lys/Arg involves simultaneous coordination by two electron-donating NH_2 groups and one COOH group. The consequent electron-donating effect by interaction with NH_2 groups depolarizes the *n*-butyloxy group through 2-cyanoacrylic acid of the oligothiophene group leading to a decreased ICT emission band which consequently results in a blue shift of 5 nm (peak shift from 576 to 571 nm). This is also supported by fluorescence titration studies involving Asp/Glu and Lys/Arg. In the case of other amino acids, the absence of significant binding with the 2-cyanoacrylic acid is the main reason for the absence of any significant emission response.

Conclusions

In summary, a fluorescent chemosensor based on calix[4]arene derivative **2** conjugated with four bithiophene-cyanoarylic acid groups at the upper rim can selectively recognize acidic amino acids (Asp and Glu) by fluorescence quenching, but also shows highly selective sensing for basic amino acids (Lys and Arg) by fluorescence turn-on over a wide range of naturally occurring amino acids in sodium phosphate buffer solution, without any organic solvent, which may result from multiple H-bond interactions between them. This outstanding property of **2** may prompt it to be widely applied in the analysis of acidic and basic amino acids in pure aqueous media.

Acknowledgment

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details of syntheses of **2** and **3**; UV-Vis titrations of **2** with Glu and Arg; fluorescent titrations of **2** with Glu and Arg; ESI-MS spectra of **2** and Asp, **2** and Glu, **2** and Arg; ^{1}H NMR spectra of **2** and Asp, **2** and Glu, **2** and Arg; Cartesian coordinates of **2**, **2** and Asp, **2** and Glu, **2** and Lys, **2** and Arg from B3LYP/6-31G optimization; hydrogen bonds and energies in **2** and Asp, **2** and Glu, **2** and Lys, **2** and Arg based on computational study (B3LYP/6-31G). See DOI: 10.1039/b000000x/

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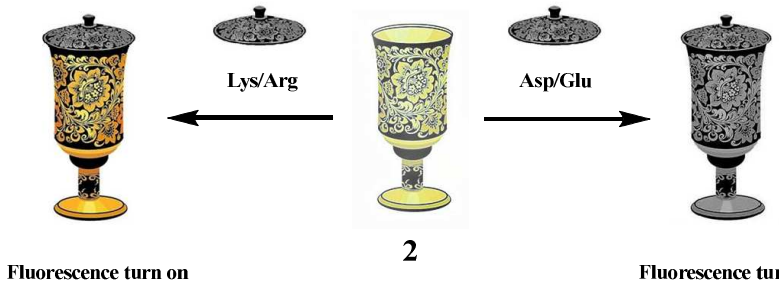
Graphical Abstract

Fluorescent calix[4]arene chemosensor for acidic and basic amino acids in pure aqueous media

Yao-Wei Xu[a], Li-Lin Tan[a], Jun-Min Liu*[a],Li-Min Xiao[c], Shao-Yong Li*[b], Cheng-Yong Su*[a]



A fluorescent calix[4]arene chemosensor **2** displays high sensitivity toward acidic and basic amino acids in aqueous media through multiple H-bond interactions.