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Dual colorimetric sensoring bis(indolyl)calix[4]crown-6

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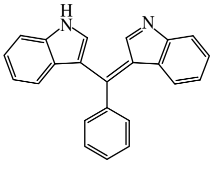
Abstract—Calix-chromophore, bis(indolyl)calix[4]crown-6 (**1**) in an oxidized form showing selective colorimetric changes for both alkaline earth cations and F^- in CH_3CN, has been newly synthesized. It is observed that the binding ability of **1** for the Ca^{2+} binding enhances in the presence of F^-. Compound **1** can operate three independent combinational NOR logic gates toward metal cations and anions.

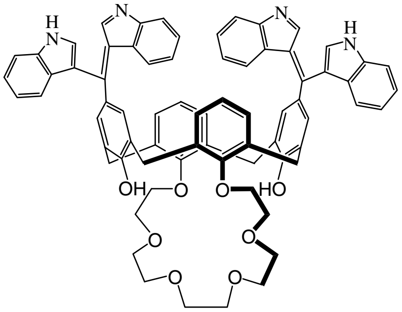
The development of simple chromophore receptors applicable to switches, sensors and 'nano-machines' capable of selectively detecting anions and cations has attracted a great deal of attention in recent years.[1] The chromophore receptor is constructed from two functionally different parts: that is, (1) an ion-recognition part (ionophore) and (2) a signaling part (chromophore) which transforms a chemical information produced by ionophore–ion interaction to an optical signal.[2] As an ion-recognition part, calixarenes have received much interest for the sensing of chemically and biologically important metal cations.[3] In particular, calix[4]crown ethers have been particularly attractive for their unique binding characteristics toward alkali metal, alkaline earth metal, and ammonium ions.[4]

Meanwhile, an oxidized-bisindole compound as below has been found to be useful for anion sensing due to its unique color changes upon anion complexation.[5] The F^- ion, for instance, coordinates to the hydrogen atoms of the bisindole unit by the strong H-bonding interaction followed by deprotonation, resulting in a selective color change of the bisindole group in the UV/vis spectra at 517 nm.[5]



Logic gates, mainly developed by Boolean,[6,7] signaling devices in conjunction with a color change upon any *Input* system, have been of particular interest to organic chemists. There are a number of different kinds of logic algebra such as AND, OR, NAND, NOR, XNOR, and XOR.[8–11] In particular, the NOR gate defined as a combinational OR gate followed by an inverter can be applicable for the ligand color changes upon cation and anion complexation.

Hence, we herein report a synthesis of bisindole bearing calix[4]crown-6 and its selective recognition behaviors toward both cation and anion as well as a design of the corresponding NOR logic gate using the ligand.



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Scheme 1 indicates a synthetic route to sensor **1**. *para*-Diformylated calix[4]crown-6 (**5**) as a starting material was prepared by the selective formylation of calix[4]-crown-6 (**4**) with $SnCl_4/CHCl_2OCH_3$ in $CHCl_3$.[12] The bisindolyl group at the upper rim of the phenolic ring was introduced by the coupling reaction of the indole

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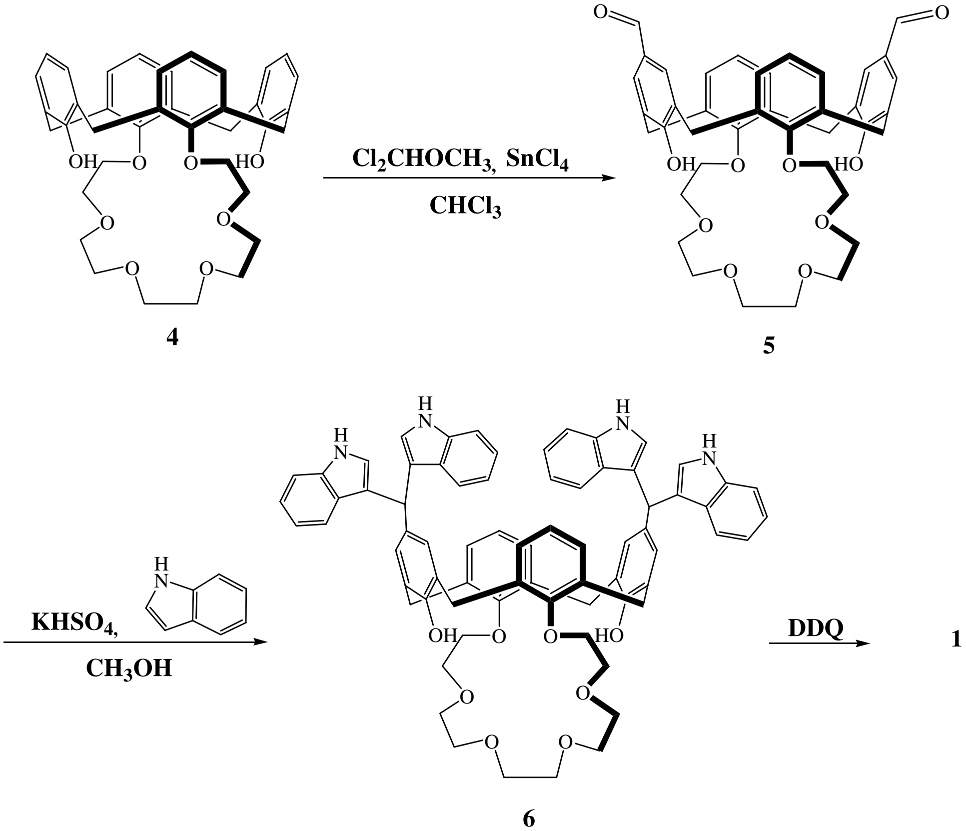


Scheme 1. Synthetic route to chromogenic **1**.

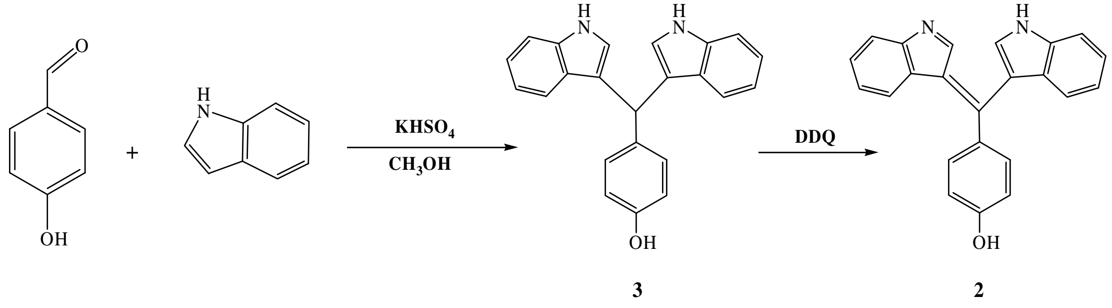
with diformylcalix[4]crown-6 (**5**) in CH_3OH. Compound **1**[13] was then prepared in 38% yield by treating **6**[13] with DDQ in CH_3CN.

Chromogenic **2** as a reference was also synthesized by the pathway shown in Scheme 2. The reaction of indole with 4-hydroxybenzaldehyde in dry CH_3OH gave **3**. Subsequently, the reaction of **3** with DDQ gave oxidized bis(indolyl)phenol **2** in 43% yield.

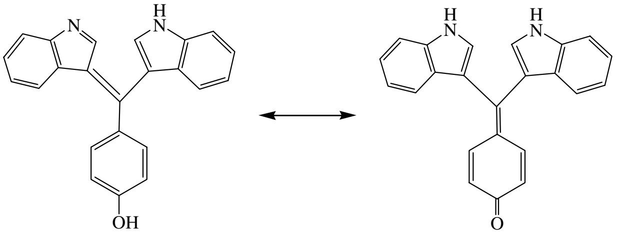
To gain an insight into the spectroscopic behaviors of **1** and **2** toward cations and anions, we initially performed UV/vis spectroscopy experiments of **1** in different solvents, CH_3CN and H_2O/CH_3CN (1:1, v/v). In CH_3CN, absorption band of **1** was observed at $\lambda_{max} = 475$ nm, whereas in H_2O/CH_3CN **1** reveals the absorption band at 556 nm. This is obviously because upon the solvent change from CH_3CN to H_2O/CH_3CN (1:1, v/v), tautomerism involving proton migration could take place to produce a quinone form in polar protic solvents (Fig. 1).[14]

We then investigated absorption band changes of **1** upon addition of various metal perchlorates. As shown in Figures 2 and 3, **1** shows selective color changes from yellow to scarlet and UV/vis bands preferentially move toward alkaline earth metal cations over other alkali and transition metal cations. It is noteworthy that the crown-6 of the calix[4]arene along with two phenol units plays a critical role in the selective encapsulation of the alkaline earth metal cations.[15]

Figure 3a shows marked absorption band changes of chromogenic receptor **1** with the addition of alkaline



Scheme 2. Synthetic route to reference **2**.



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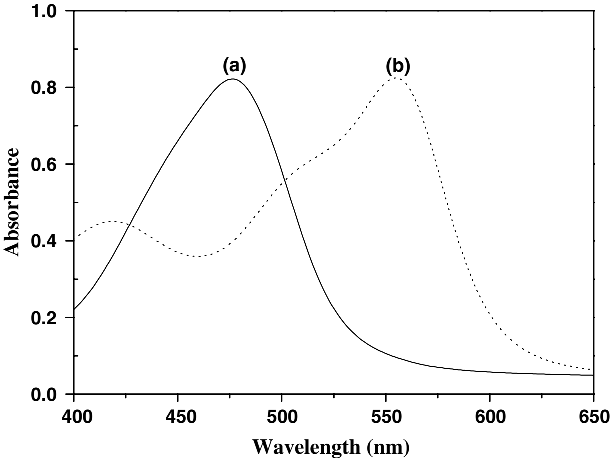


Figure 1. UV/vis spectra of **1** (0.01 mM) (a) in CH_3CN and (b) in H_2O/CH_3CN (1:1 v/v).

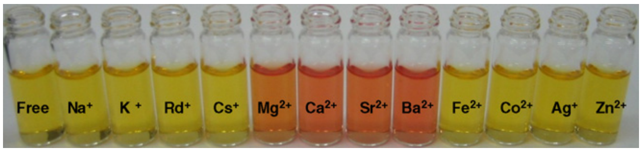


Figure 2. Color changes of **1** upon the addition of 200 equiv of metal cations in CH_3CN.

earth metal cations, where the absorption band with $\lambda_{max} = 475$ nm decreases and the new band $\lambda_{max} = 538$ nm concomitantly enhances. Such a marked red-shift, induced by alkaline earth metal cations accommodated by the crown segment, would involve a shift to quinone form in the tautomerism because alkaline earth metal cations efficiently bind to quinine carbonyl oxygen.[16] Figure 3b illustrates that the titration of Ca^{2+} ion to **1** displays a ratiometry with an isosbestic point centered at 488 nm, informing us the complexation ratio of 1:1.

In contrast, reference **2** in the absence of the crown-6 remains unchanged despite the addition of various cations, directly evidencing that the crown-6 of **1** plays a key role in the cation complexation to give an intramolecular charge transfer (ICT).[16]

To elucidate the role of the calixcrown unit for the Ca^{2+} complexation, ^1H NMR spectroscopy of free **1**, $\mathbf{1}\cdot Ca^{2+}$ and $\mathbf{1}\cdot F^-\cdot Ca^{2+}$ complex in $CDCl_3$ has been taken and the differences are seen in Figure 4a–c, respectively. It is clearly observed that the chemical shift of the calixcrown unit (♣, ∇) is changed by Ca^{2+} ion binding and is further changed by the addition of Ca^{2+} ion in the presence of F^- ion, implicating that the binding property of the crown-6 ring changes to enhance toward Ca^{2+} ion.

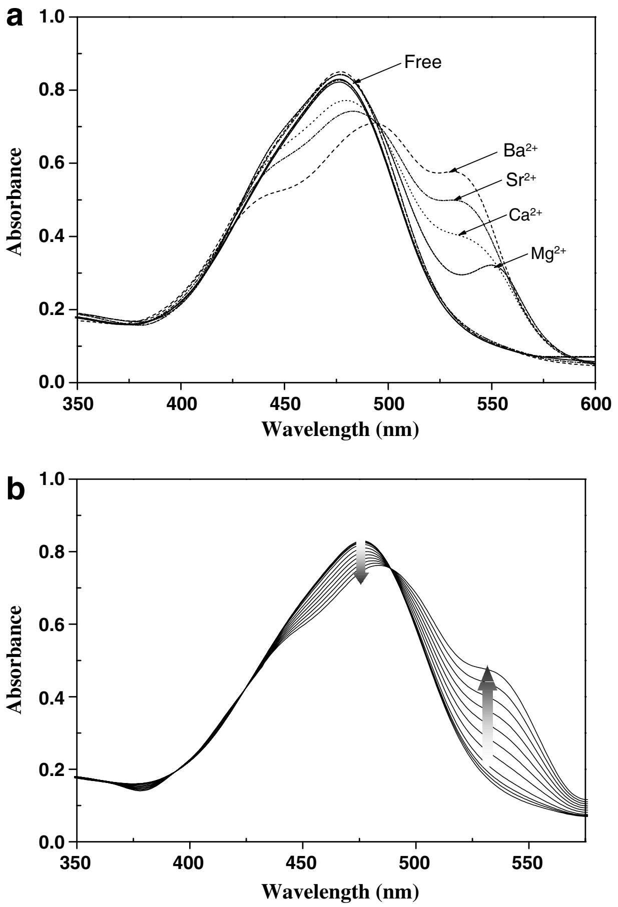


Figure 3. UV/vis spectra of **1** (0.01 mM) in the presence of Na^+, K^+, Rb^+, Cs^+, Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}, Fe^{2+}, Co^{2+}, Ag^+, and Zn^{2+} with perchlorate (200 equiv) in CH_3CN (a). UV/Vis spectra of **1** (0.01 mM) with variable amounts of $Ca(ClO_4)_2$ (b).

In anion complexation test, Figure 5 indicates the color changes of **1** upon the addition of F^-, Cl^-, Br^-, I^-, $CH_3CO_2^-$, HSO_4^-, and $H_2PO_4^-$. Receptor **1** shows F^- and $CH_3CO_2^-$ ion selectivity over other anions tested in CH_3CN. On the other hand, in H_2O/CH_3CN (1:1, v/v), **1** reveals a drastic color change with HSO_4^- or $H_2PO_4^-$ ion.

Figure 6 indicates that in CH_3CN, **1** shows selectivity for the F^- and $CH_3CO_2^-$ ions over other anions with which the corresponding wavelength moves from 475 to 517 nm. By contrast, in CH_3CN/H_2O (1:1, v/v), the UV band of **1** moves from 556 to 475 nm by addition of HSO_4^- or $H_2PO_4^-$ anion. It is assumed for this particular observation that in H_2O the absorption band of the bis-indol unit moves bathochromically because of the hydrogen bonding-based ICT, and then the acidic anion in H_2O such as HSO_4^- and $H_2PO_4^-$ ($pK_a = 1.99$ and 3.88, respectively) could disturb the H-bonding between

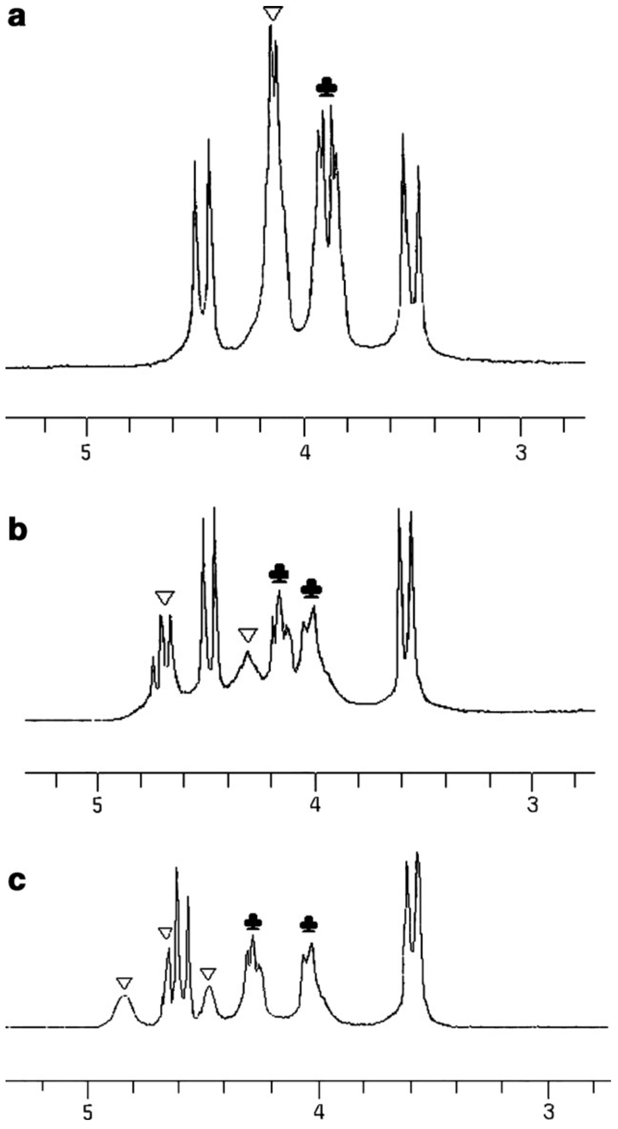


Figure 4. Partial ^1H NMR spectra of (a) free **1** and (b) in the presence of excess $Ca^{2+}(ClO_4)_2$ and (c) addition of $Ca^{2+}(ClO_4)_2$ in the presence of TBAF. ♣ and ∇ represent ethyleneoxy unit of crown-6.

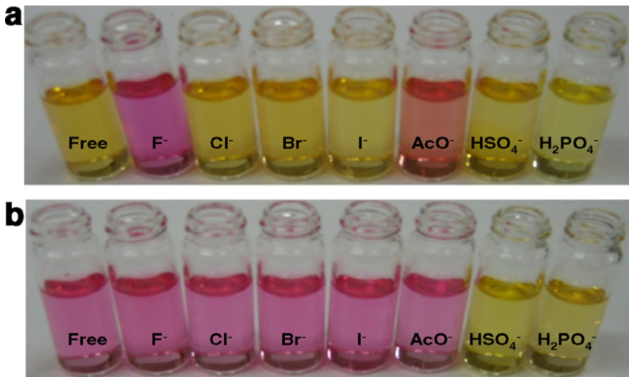


Figure 5. (a) Color changes of **1** upon the addition of 200 equiv of tetrabutylammonium salt of anions in CH_3CN and (b) in H_2O/CH_3CN (1:1 v/v).

the N–H and H_2O molecule to give rise to a hypsochromical shift of the absorption band.

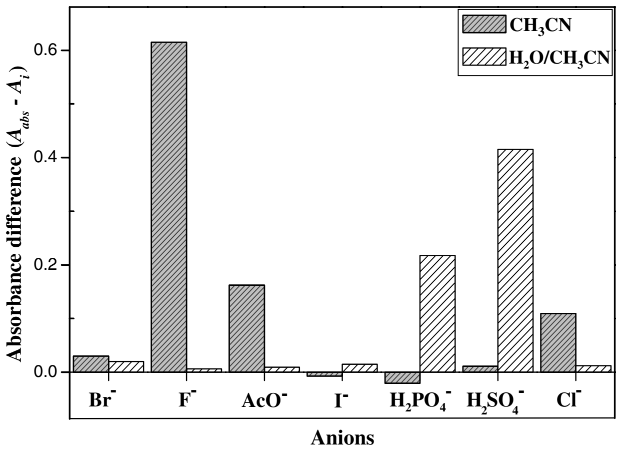


Figure 6. Bar profiles for fluorescence changes ($A_{abs} - A_i$) of 0.01 mM solutions of **1** in CH_3CN (517 nm) and H_2O/CH_3CN (475 nm).

During the titration of F^- to a solution of **1**, we observed band changes in a function of $[F^-]$ (Fig. 7). Addition of F^- to a CH_3CN solution of **1** caused a band at 475 nm to decline and concomitantly a new band at 517 nm increased. In the end, the color of **1** is found to change from yellow to red. This new band with $\lambda_{max} = 517$ nm would originated from the deprotonated ligand $[L^-]$ of oxidized bisindole parts.[17,18] In addition, the Job's plot analysis exhibited a maximum at 0.36 mol fraction of F^-, indicating the formation of 1:2 (ligand: metal) complexes. On the other hand, the addition of anions (F^-, Cl^-, Br^-, I^-, $CH_3CO_2^-$, HSO_4^-, $H_2PO_4^-$) to the non-conjugated **6** induces neither a color change nor a modification of the corresponding absorption spectral changes in CH_3CN.

In the other aspect of the complexation study, we tested anion-induced metal binding ability of **1** where both cation and anion binding sites are available. The interaction of Ca^{2+} with free **1** and with $1{\cdot}F^-$ was investigated through the titration experiments. We

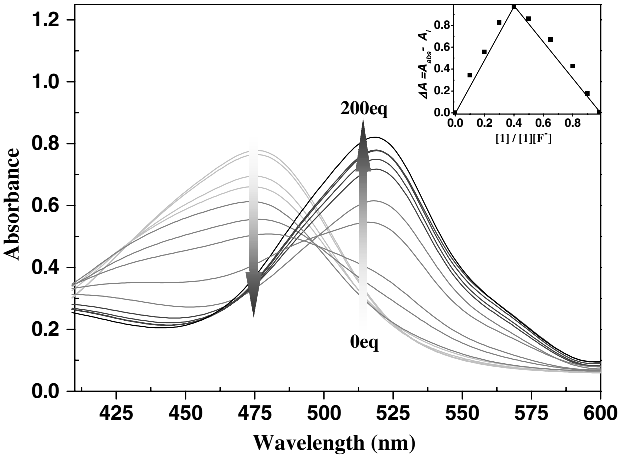
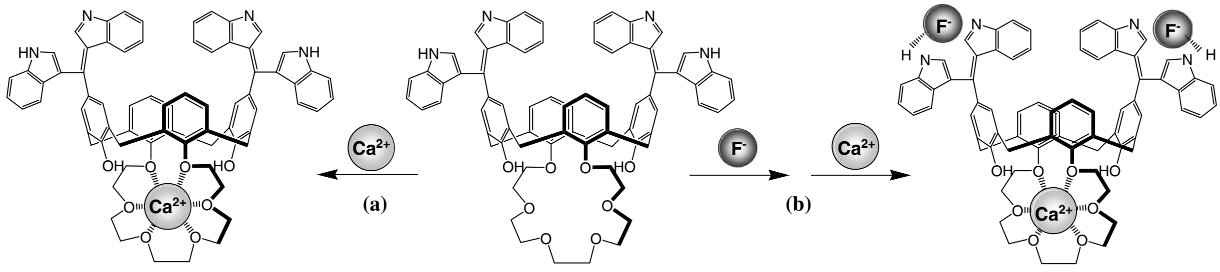


Figure 7. UV/vis spectral changes of **1** in CH_3CN (0.01 mM) in the presence of 0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 1, 10, 20, 40, 60, 80, 100 and 200 equiv of tetrabutylammonium salt of F^-. Inset: Job's plot for $1{\cdot}F^-$ (0.01 mM) in CH_3CN.



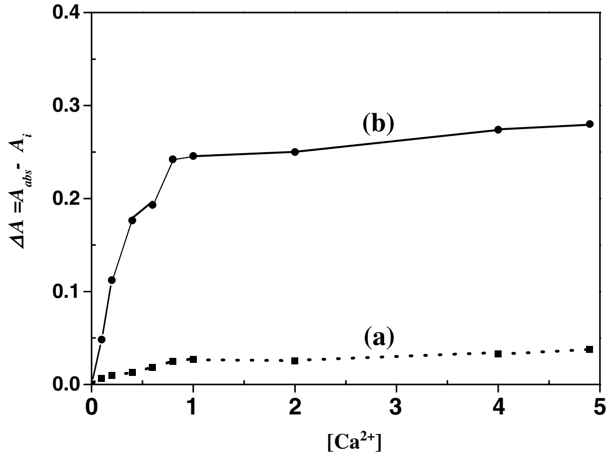


Figure 8. (a) UV/vis spectra of **1** (0.01 mM) with variable mounts of $Ca(ClO_4)_2$ corresponding changes in $A_{abs} - A_i$ ratio represented by the intensity at 535 nm in CH_3CN. (b) UV/vis spectra of $\mathbf{1}{\cdot}F^-$ (0.01 mM, 200 equiv of F^-) with variable mounts of $Ca(ClO_4)_2$ corresponding changes in $A_{abs} - A_i$ ratio represented by the intensity at 535 nm in CH_3CN.

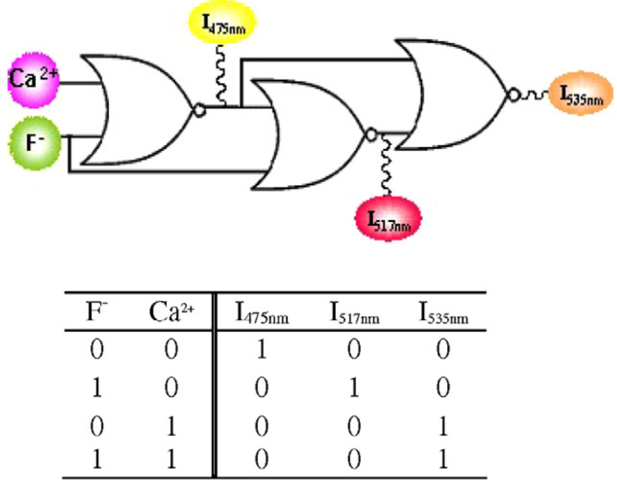
found that the binding ability of **1** for the Ca^{2+} cation enhances in the presence of F^- anion as shown in Figure 8 and Table 1,[19] which is in good agreement with the observation of the chemical shift changes in ^1H NMR spectra (Fig. 4) in which upon adding 5 equiv of $Ca(ClO_4)_2$ into a chloroform-d solution of the receptor $\mathbf{1}{\cdot}F^-$, proton peaks of calixcrown are observed to be more shifted than those of **1**·F.

As a consequence of the UV/vis spectral behavior of **1** in the presence of Ca^{2+} or F^-, the probe molecule mimics the function of combinational NOR logic gate.[20] As seen in Figure 9, we constructed three logic circuits along with the truth tables for the absorption band at 475 nm, 517 nm and 535 nm upon the addition of two input signals (F^- and Ca^{2+}). The NOR gate can be executed only when neither of the two inputs are present, which is consistent with the result of the absorption band at 475 nm (output 1) when neither Ca^{2+} nor F^- is added. However, when one of the two or both inputs is operated, the absorption band of **1** at 475 nm declines, refereeing to as the NOR logic gate. Besides, there appears also an event switching ON at 517 nm (output 2) when neither Ca^{2+} nor output 1 using as the other input signal is added. Finally, there is another ON with an absorption band at 535 nm (output 3) when neither output 1 nor output 2 is added. It should be noted that new synthetic sensor **1**, to the best of our knowledge, is the first example capable of computing combinational three NOR logic gates. This will be useful in more complex algorithm systems and its interpretation, and furthermore can speed up the computing operation associated with digital computers.

Table 1. Binding constants (K_a, M^{-1}) of **1** (0.01 mM) in the presence of anions and cations in CH_3CN

Host	Ca^{2+}	F^-	Ca^{2+} in F^-	F^- in Ca^{2+}
1	4.98×10^3	6.02×10^3	6.95×10^3	4.36×10^3

For F^- ion, the K_a was obtained on the basis of 1:2 complex ratio.



F^-	Ca^{2+}	I_{475nm}	I_{517nm}	I_{535nm}
0	0	1	0	0
1	0	0	1	0
0	1	0	0	1
1	1	0	0	1

Figure 9. NOR gates with **1** under the action of two chemical inputs (200 equiv of F^- and Ca^{2+}).

In conclusion, we firstly synthesized new di(bisindolyl) calix[4]crown-6 (**1**) which modulates an ICT to give a dramatic color change upon the addition of alkaline earth metal cations and F^-. In H_2O/CH_3CN (1:1 v/v), **1** exhibits a selective color change with HSO_4^- and $H_2PO_4^-$ ion. The binding ability of **1** for the Ca^{2+} cation binding enhances in the presence of F^- anion. Sensor **1** also plays a role in three combinational NOR logic gates.

Acknowledgments

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References and notes

1. Nishiyabu, R.; Anzenbacher, P. *J. Am. Chem. Soc.* **2005**, *127*, 8270.
2. Inoue, Y.; Gokel, G. W. *Cation Binding by Macrocycles: Complexation of Cationic Species by Crown Ethers*; Marcel Dekker: New York, 1990.
3. (a) Asfari, Z.; Böhmer, V.; Harrowfield, J.; Vicens, J. *Calixarenes*; Kluwer: Dordrecht, 2001; (b) Gutsche, C. D. *Calixarenes Revisited*; The Royal Society of Chemistry: Cambridge, 1998.
4. (a) Kubo, Y.; Obara, S.; Tokita, S. *Chem. Commun.* **1999**, 2399; (b) Kubo, Y.; Maeda, S.; Tokita, S.; Kubo, M. *Nature* **1996**, *382*, 552.
5. He, X.; Hu, S.; Liu, K.; Guo, Y.; Xu, J.; Shao, S. *Org. Lett.* **2006**, *8*, 333.
6. Langford, S. J.; Yann, T. *J. Am. Chem. Soc.* **2003**, *125*, 11198.
7. Ji, H.-F.; Dabestani, R.; Brown, G. M. *J. Am. Chem. Soc.* **2000**, *122*, 9306.
8. de Silva, A. P.; Gunaratne, H. Q. N.; McCoy, C. P. *J. Am. Chem. Soc.* **1997**, *119*, 7891.
9. Credi, A.; Balzani, V.; Langford, S. J.; Stoddart, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 2679.
10. (a) de Silva, A. P.; Dixon, I. M.; Gunaratne, H. Q. N.; Gunnlaugsson, T.; Maxwell, P. R. S.; Rice, T. E. *J. Am. Chem. Soc.* **1999**, *121*, 1393; (b) de Silva, A. P.; Gunaratne, H. Q. N.; McCoy, C. P. *Nature* **1993**, *364*, 42; (c) de Silva, A. P.; McClenaghan, N. D. *J. Am. Chem. Soc.* **2000**, *122*, 3965.
11. Saghatelian, A.; Volcker, N. H.; Guckian, K. M.; Lin, V. S. Y.; Ghadiri, M. R. R. *J. Am. Chem. Soc.* **2003**, *125*, 346.
12. Kim, Y. H.; Cha, N. R.; Chang, S. K. *Tetrahedron Lett.* **2002**, *43*, 3883.
13. Preparation of **6** (5,17-di[bis(indolyl)phenyl]calix[4]arene-crown-6), concd. $KHSO_4$ (0.16 g, 1.18 mmol) was added to a mixture of indole (0.28 g, 2.4 mmol) and **5** (0.4 g, 0.59 mmol) in dry methanol (20 mL) and the reaction was stirred at room temperature for 10 h. A small amount of water was added to quench the reaction and the aqueous phase was extracted with CH_2Cl_2 (30 mL) twice. The organic layer was collected, washed with water, and dried over anhydrous $MgSO_4$. Column chromatographic separation (eluent was a 2:1 mixture of ethyl acetate and hexane) gave 280 mg of **6** in 43.2% yield with a crystalline solid. Mp 138–140 °C. IR (KBr pellet, cm^{-1}): 3450, 3200, 1200. ^1H NMR (200 MHz, $CDCl_3$): δ 8.2 (br s, 4H, NH), 7.8 (d, 4H), 7.45 (d, 4H), 7.22–7.14 (m, 8H), 7.1 (d, 4H), 6.7 (d, 4H), 6.5 (s, 4H), 5.86 (s, 2H), 4.42 (d, 4H, ArCH_2Ar), 3.5 (d, 4H, ArCH_2Ar), 4.12 (m, 8H, OCH_2-CH_2O), 3.8 (m, 8H, OCH_2CH_2O). ^{13}C NMR ($CDCl_3$): 170.78, 170.76, 155.3, 155.1, 147.9, 129.61, 128.08, 122.43, 121.05, 119.91, 116.56, 114.32, 112.71, 111.61, 107.99, 103.95, 71.82, 71.80, 71.79, 70.62, 70.60, 69.82, 69.01, 41.91, 32.03 ppm. FAB MS mass spectra, JEOL-JMS-HX 110A/110A High resolution Tandem Mass Spectrometry in Seoul Nat'l University (Korea). FAB MS m/z (M^+): calcd 1115.32. Found: 1115.00. Preparation of **1** (oxidized 5,17-di[bis(indolyl)phenyl]calix[4]crown-6), cone. Compound **6** (0.27 g, 0.25 mmol) was dissolved in CH_3CN (10 mL). DDQ (0.045 g, 0.2 mmol) solution of CH_3CN was added dropwise to the solution. This reaction was allowed to stir for 5 h to give a dark red precipitate, which was filtered and washed with CH_3CN. Recrystallization from ethyl ether gave **1** in 38% yield. Mp 248–250 °C. IR (KBr pellet, cm^{-1}): 3445, 3200, 1205. ^1H NMR (200 MHz, $CDCl_3$): δ 7.9 (d, 4H), 7.54 (d, 4H), 7.25–7.18 (m, 8H), 6.98–6.78 (d, 8H), 6.75–6.4 (t, 4H), 4.40 (d, 4H, ArCH_2Ar), 3.6 (d, 4H, ArCH_2Ar), 4.1 (t, 8H, OCH_2-CH_2O), 3.78 (t, 8H, OCH_2CH_2O). ^{13}C NMR ($CDCl_3$): 160.24, 159.98, 152.01, 151.87, 147.45, 147.28, 147.1, 138.36, 134.22, 132.56, 132.54, 131.93, 130.11, 129.43, 129.23, 128.52, 127.17, 125.41, 124.58, 121.01, 120.94, 116.28, 98.39, 71.97, 71.83, 71.71, 70.58, 70.52, 69.98, 69.37, 42.21, 31.95 ppm. FAB MS m/z (M^+): calcd 1111.58. Found: 1112.02.
14. Zhao, Y. B.; Guo, X. Q.; Yang, X. F. *Talanta* **2002**, *57*, 883.
15. (a) Pearson, A. J.; Xiao, W. *J. Org. Chem.* **2003**, *68*, 5369; (b) Yamaguchi, T.; Ito, T.; Sato, T.; Shinbo, T.; Nakao, S. I. *J. Am. Chem. Soc.* **1999**, *121*, 4078.
16. (a) Kim, S. K.; Kim, S. H.; Kim, H. J.; Lee, S. H.; Lee, S. W.; Ko, J.; Bartsch, R. A.; Kim, J. S. *Inorg. Chem.* **2005**, *44*, 7866; (b) Mallick, A.; Haldar, B.; Chattopadhyay, N. *J. Phys. Chem. B* **2005**, *109*, 14683.
17. Gunnlaugsson, T.; Kruger, P. E.; Jensen, P.; Tierney, J.; Ali, H. D. P.; Hussey, G. M. *J. Org. Chem.* **2005**, *70*, 10875.
18. Shenderovich, I. G.; Tolstoy, P. M.; Golubev, N. S.; Smirnov, S. N.; Denisov, G. S.; Limbach, H. H. *J. Am. Chem. Soc.* **2003**, *125*, 11710.
19. (a) Association constants were obtained using the computer program ENZFITTER, available from Elsevier-BIOSOFT, 68 Hills Road, Cambridge CB2 1LA, United Kingdom; (b) Connors, K. A. *Binding Constants*; Wiley: New York, 1987.
20. Lee, S. H.; Kim, J. Y.; Kim, S. K.; Lee, J. H.; Kim, J. S. *Tetrahedron* **2004**, *60*, 5171.