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Na^+ Triggered Fluorescence Sensors for Mg^{2+} Detection Based on a Coumarin Salen Moiety

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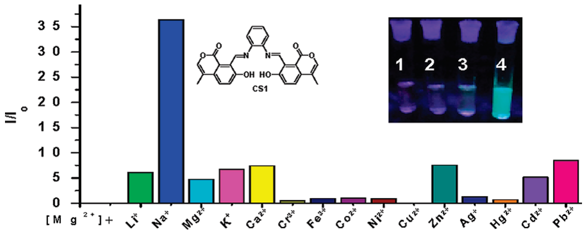
ABSTRACT



Two coumarin salen-based sensors CS1 and CS2 can exhibit a pronounced fluorescence enhancement response toward Mg^{2+} as high as 36-fold (CS1) and 111-fold (CS2) in the presence of Na^+ as a synergic trigger. More importantly, the fluorescent color of CS1 was bright green instead of weak yellow after the addition of Mg^{2+} and Na^+ together, which can be easily detected by the naked eye.

The magnesium ion (Mg^{2+}) is one of the most abundant divalent cations in cells and can play vital roles in many cellular processes, such as enzyme-driven biochemical reactions, proliferation of cells, and stabilization of DNA conformation.[1] Moreover, Mg^{2+} is also believed to be an etiological factor in many pathological processes, such as congestive heart failure, cerebral infarction, lung cancer, and muscle dysfunction.[2] Consequently, the detection of Mg^{2+} has attracted increasing interest in the areas of chemical and biological sciences. In the past few years, many analytical methods have been developed for the detection of Mg^{2+}, including atomic absorption, ion-selective electrodes (ISEs), and NMR.[3] Optical detection, following changes of fluorescence or UV–vis spectroscopy arisen from the Mg^{2+}-induced perturbation of the chromophore, is best suitable for Mg^{2+} detection in biological systems.

Recently, investigations on highly sensitive and selective fluorescent sensors have drawn considerable attention due to its convenience and real-time response. In particular, numerous efforts have been devoted to the design of chemosensory systems with unique electrical and optical properties that are capable of detecting metal ions in both a real-time and reversible fashion. A number of fluorescent sensors for Mg^{2+} detection have been reported in previous

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(1) (a) Rubin, H. *Arch. Biochem. Biophys.* **2007**, *458*, 16–23. (b) Cowan, J. A. *Biometals* **2002**, *15*, 225–235. (c) Shoda, T.; Kikuchi, K.; Kojima, H.; Urano, Y.; Komatsu, H.; Suzuki, K.; Nagano, T. *Analyst* **2003**, *128*, 719–723. (d) Wolf, F. I.; Torsello, A.; Fasanella, A.; Cittadini, A. *Mol. Aspects Med.* **2003**, *24*, 11–25. (e) Saris, N. E. L.; Mervaala, E.; Karppanen, H.; Khawaja, J. A.; Lewenstam, A. *Clin. Chem. Acta* **2000**, *294*, 1–26. (f) Rubin, H. *Bioessays* **2005**, *27*, 311–320. (g) Moll, J. R.; Acharya, A.; Gal, J.; Mir, A. A.; Vinson, C. *Nucleic Acids Res.* **2002**, *30*, 1240–1246.

(2) (a) Stepura, O. B.; Martynow, A. I. *Int. J. Cardiol.* **2009**, *134*, 145–147. (b) Larsson, S. C.; Virtanen, M. J.; Mars, M.; Männistö, S.; Pietinen, P.; Albanes, D.; Virtamo, J. *Arch. Intern. Med.* **2008**, *168*, 459–465. (c) Mahabir, S.; Wei, Q. Y.; Barrera, S. L.; Dong, Y. Q.; Etzel, C. J.; Spitz, M. R.; Forman, M. R. *Carcinogenesis* **2008**, *29*, 949–956. (d) Nielsen, F. H.; Lukaski, H. C. *Magnesium Res.* **2006**, *19*, 180–189.

(3) (a) Zmozinski, A. V.; de Jesus, A.; Vale, M. G. R.; Silva, M. M. *Talanta* **2010**, *83*, 637–643. (b) de Jesus, A.; Zmozinski, A. V.; Barbar, J. A.; Vale, M. G. R.; Silva, M. M. *Energy Fuels* **2010**, *24*, 2109–2112. (c) Kilic, Z.; Acar, O.; Ulasan, M.; Ilim, M. *Food Chem.* **2002**, *76*, 107–116. (d) Luo, Y.; Zhang, B.; Chen, M.; Wang, J.; Zhang, X.; Gao, W. Y.; Huang, J. F.; Fu, W. L. *J. Agric. Food Chem.* **2010**, *58*, 9396–9400. (e) Shim, J. H.; Jeong, I. S.; Lee, M. H.; Hong, H. P.; On, J. H.; Kim, K. S.; Kim, H. S.; Kim, B. H.; Cha, G. S.; Nam, H. *Talanta* **2004**, *63*, 61–71. (f) Zhu, J. W.; Qin, Y.; Zhang, Y. H. *Anal. Chem.* **2010**, *82*, 436–440. (g) Hamdi, A.; Kim, S. H.; Abidi, R.; Thuéry, P.; Kim, J. S.; Vicens, J. *Tetrahedron* **2009**, *65*, 2818–2823. (h) Hifumi, H.; Tanimoto, A.; Citterio, D.; Komatsu, H.; Suzuki, K. *Analyst* **2007**, *132*, 1153–1160. (i) Ishida, M.; Naruta, Y.; Tani, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 91–94. (j) Patra, S.; Paul, P. *Dalton Trans.* **2009**, 8683–8695.

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works, such as diketone,[4] crown ether,[5] polymer based ligands,[6] and nanoparticles.[7] However, some available Mg^{2+} sensors have difficulty in distinguishing Mg^{2+} and Ca^{2+},[8] so it is still interesting and of importance to design a highly selective and sensitive fluorescent sensor that can recognize Mg^{2+} without the interference from other metal ions, especially Ca^{2+}.

Salen-based ligands have the potentially tetradentate N_2O_2 donor and can form stable complexes with various metal ions. There are many reports on these salen-based fluorescent sensors for metal ions detection.[9] As a better fluorophore, coumarin derivatives have been widely used for constructing sensory systems due to their desirable photophysical properties with a large Stock shift and visible emission wavelength.[10] In this paper, we designed two coumarin salen-based ligands as fluorescence sensors for Mg^{2+} recognition. The fluorescence intensities of the two sensors are enhanced by mixing Na^+ and Mg^{2+} together, and the fluorescence color is bright green, which can be easily detected by the naked eye. The results indicate that two coumarin salen-based sensors can exhibit high sensitivity and selectivity for Mg^{2+} recognition in the presence of Na^+ as the coexisting cation.

The synthesis protocol of two sensors is outlined (SI, Scheme 1). 8-formyl-7-hydroxy-4-methylcoumarin was prepared according to reported procedures.[11] CS1 and CS2 could be obtained by condensation of *o*-phenylenediamine and (*R*,*R*)-1,2-diaminocyclohexane with 8-formyl-7-hydroxyl-4-methyl-coumarin via a nucleophilic addition–elimination reaction in 81.9% and 86.8% yields, respectively.

The fluorescence response behaviors of sensors CS1 and CS2 on various metal ions have been investigated. CS1 and CS2 can display weak and broad emission bands centered at 550 and 510 nm, respectively. Figure 1a and 1b show the fluorescence spectra of CS1 and CS2 (10 μM in THF) upon the addition of various metal ions in aqueous solution with the excitation at 360 and 352 nm. As shown in Figure 1a, obvious fluorescence enhancement could be observed as high as 4.7-fold (SI 4a) upon the addition of Mg^{2+} at a 1:1 molar ratio, and the addition of other selected metal ions, such as Li^+, Na^+, K^+, Ca^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Ag^+, Hg^{2+}, and Pb^{2+}, causes almost no fluorescence response. But Cr^{3+}, Ni^{2+}, and Cd^{2+} cause limited fluorescence quenching under the same conditions ($I/I_0 < 0.7$). Meanwhile, Cu^{2+} can lead to almost complete quenching of CS1 (Supporting Information, SI 4a), which can be attributed to the energy or electron-transfer reactions arisen from the strong metal–ligand orbital interaction upon the formation of binding metal complexes.[12] In addition, the maximum emission wavelength of CS1 appears remarkably blue-shifted from 550 to 490 nm. As shown in Figure 1b, Mg^{2+} (10 μM) can lead to the pronounced fluorescence enhancement of CS2 as high as 9.8 (SI 4b) at a 1:1 molar ratio. Moreover, a blue shift is also observed from 510 to

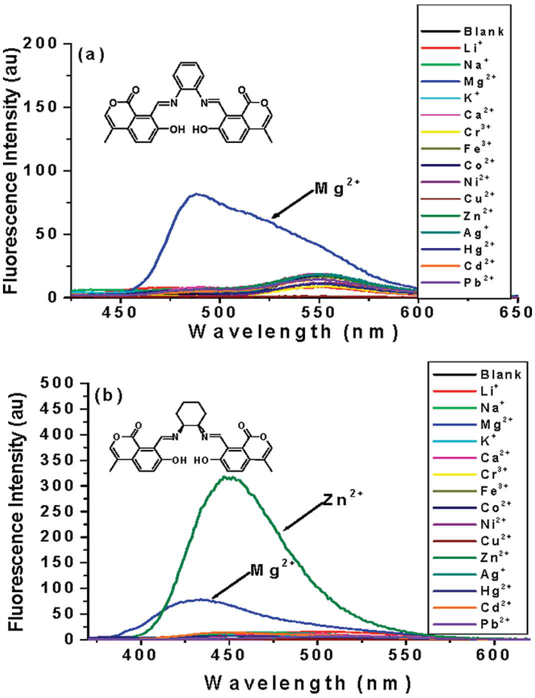

Figure 1. Selectivity of sensors (a) CS1 and (b) CS2 toward Mg^{2+} and other metal ions: fluorescence spectra of the ligand–metal ion complexes.

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[4] (a) Suzuki, Y.; Komatsu, H.; Ikeda, T.; Saito, N.; Araki, S.; Citterio, D.; Hisamoto, H.; Kitamura, Y.; Kubota, T.; Nakagawa, J.; Oka, K.; Suzuki, K. *Anal. Chem.* **2002**, *74*, 1423–1428. (b) Shoda, T.; Kikuchi, K.; Kojima, H.; Urano, Y.; Komatsu, H.; Suzuki, K.; Nagano, T. *Analyst* **2003**, *128*, 719–723. (c) Komatsu, H.; Iwasawa, N.; Citterio, D.; Suzuki, Y.; Kubota, T.; Tokuno, K.; Kitamura, Y.; Oka, K.; Suzuki, K. *J. Am. Chem. Soc.* **2004**, *126*, 16353–16360. (d) Kim, H. M.; Yang, P. R.; Seo, M. S.; Yi, J. S.; Hong, J. H.; Jeon, S. J.; Ko, Y. G.; Lee, K. J.; Cho, B. R. *J. Org. Chem.* **2007**, *72*, 2088–2096. (e) Kim, H. M.; Jung, C.; Cho, B. R. *Angew. Chem., Int. Ed.* **2007**, *46*, 3460–3463. (f) Valeur, B.; Leray, I. *Coord. Chem. Rev.* **2000**, *205*, 3–40.

[5] (a) Farruggia, G.; Iotti, S.; Prodi, L.; Montalti, M.; Zaccheroni, N.; Savage, P. B.; Trapani, V.; Sale, P.; Wolf, F. I. *J. Am. Chem. Soc.* **2006**, *128*, 344–350. (b) Liu, Y.; Han, M.; Zhang, H. Y.; Yang, L. X.; Jiang, W. *Org. Lett.* **2008**, *10*, 2873–2876. (c) Kim, J.; Morozumi, T.; Nakamura, H.; Nakamura, H. *Org. Lett.* **2007**, *9*, 4419–4422. (d) Bronson, R. T.; Montalti, M.; Prodi, L.; Zaccheroni, N.; Lamb, R. D.; Dalley, N. K.; Izatt, R. M.; Bradshaw, J. S.; Savage, P. B. *Tetrahedron* **2004**, *60*, 11139–11144.

[6] (a) Ding, A. L.; Pei, J.; Yu, W. L.; Lai, Y. H.; Huang, W. *Thin Solid Films* **2002**, *417*, 198–201. (b) Pei, J.; Yu, W. L.; Ding, A. L.; Yu, W. L.; Lai, Y. H. *Macromol. Rapid Commun.* **2002**, *23*, 21–25.

[7] Park, E. J.; Brasuel, M.; Behrend, C.; Philbert, M. A. *Anal. Chem.* **2003**, *75*, 3784–3791.

[8] (a) Pesco, J.; Salmon, J.; Vigo, J.; Viallet, P. *Anal. Biochem.* **2001**, *290*, 221–231. (b) Kim, J.; Morozumi, T.; Kurumatani, N.; Nakamura, H. *Tetrahedron Lett.* **2008**, *49*, 1984–1987. (c) Dubonosov, A. D.; Minkin, V. I.; Bren, V. A.; Shepelenko, E. N.; Tsukanov, A. V.; Starikov, A. G.; Borodkin, G. S. *Tetrahedron* **2008**, *64*, 3160–3167. (d) Gromov, S. P.; Ushakov, E. N.; Fedorova, O. A. *J. Org. Chem.* **2003**, *68*, 6115–6125.

[9] (a) Cozzi, P. G. *Chem. Soc. Rev.* **2004**, *33*, 410–421. (b) Pucci, D.; Aiello, I.; Bellusci, A.; Crispini, A.; Ghedini, M.; Deda, M. L. *Eur. J. Inorg. Chem.* **2009**, 4274–4281. (c) Chu, Z. L.; Huang, W.; Wang, L.; Gou, S. H. *Polyhedron* **2008**, *27*, 1079–1092. (d) Xu, Y.; Meng, J.; Meng, L. X.; Dong, Y.; Cheng, Y. X.; Zhu, C. J. *Chem.—Eur. J.* **2010**, *16*, 12898–12903.

[10] (a) Trenor, S. R.; Shultz, A. R.; Love, B. J.; Long, T. E. *Chem. Rev.* **2004**, *104*, 3059–3077. (b) Suresh, M.; Das, A. *Tetrahedron Lett.* **2009**, *50*, 5808–5812. (c) Komatsu, K.; Urano, Y.; Kojima, H.; Nagano, T. *J. Am. Chem. Soc.* **2007**, *129*, 13447–13454. (d) Lim, N. C.; Schuster, J. V.; Porto, M. C. *Inorg. Chem.* **2005**, *44*, 2018–2030. (e) Ray, D.; Bharadwaj, P. K. *Inorg. Chem.* **2008**, *47*, 2252–2254. (f) Lim, N. C.; Brückner, C. *Chem. Commun.* **2004**, 1094–1095. (g) Hanshaw, R. G.; Hilkert, S. M.; Jiang, H. *Tetrahedron Lett.* **2004**, *45*, 8721–8724.

430. Meanwhile, CS2 shows much more sensitivity toward Zn^{2+} (39.3-fold), which is in accordance with our previous report.[9d] The obvious fluorescent enhancement responses can be attributed to two reasons: (1) the decrease of the HOMO of the conjugated segment of the ligand when the Salen-based N_2O_2 receptor coordinates with Mg^{2+} or Zn^{2+};[13] (2) upon binding Mg^{2+} or Zn^{2+}, a coordination-enhanced fluorescence process happens, meanwhile the intramolecular electron-transfer process is forbidden. So an enhancement in the emission spectrum and a red shift in the absorption spectrum are observed simultaneously. (SI 6).[14]

Inspired by the above results, we further investigated the fluorescent response behaviors of two coumarin salen-based sensors CS1 and CS2 toward Mg^{2+} under a Na^+ triggered synergistic effect. The fluorescence titration of CS1-Na^+ with Mg^{2+} was presented in Figure 2a. The fluorescent intensities of a Na^+–ligand complex show a gradual enhancement as high as 36-fold upon the addition of Mg^{2+} from 0.1 to 1.2 equiv. Moreover, the maximum emission wavelength of sensor CS1 is also blue-shifted from 550 to 490 nm, which is induced by the well-known ICT mechanism.[14c] Figure 2b shows a gradual fluorescence enhancement of the CS2–Na^+ complex upon addition of Mg^{2+} from 0.1 to 1.2; a much larger enhancement efficiency that reaches 111-fold is observed when 1.0 equiv of Mg^{2+} is added. Meanwhile the maximum emission wavelength of sensor CS2 is blue-shifted from 510 to 430 nm. The interesting results suggest that the effects of Na^+ and Mg^{2+} ions are synergistic, because the presence of 10 μM Mg^{2+} alone does not induce such a large fluorescence enhancement in this recognition event.

So far there has been no report on the pronounced response behavior toward Mg^{2+} detection based on the fluorescence sensor under the Na^+ triggered synergistic effect. This may be due to the building blocks of salen receptors of CS1 and CS2 fitting well for the formation of the stable Mg^{2+}–ligand and Zn^{2+}–ligand complexes. On the other hand, Na^+ can still interact with another lone pair of electrons on the oxygen atom of OH groups after Mg^{2+} has coordinated with one lone pair of electrons on the oxygen atom of a N_2O_2 group, which can reduce the nonradiative decay of the excited state and lead to the pronounced fluorescence enhancement.

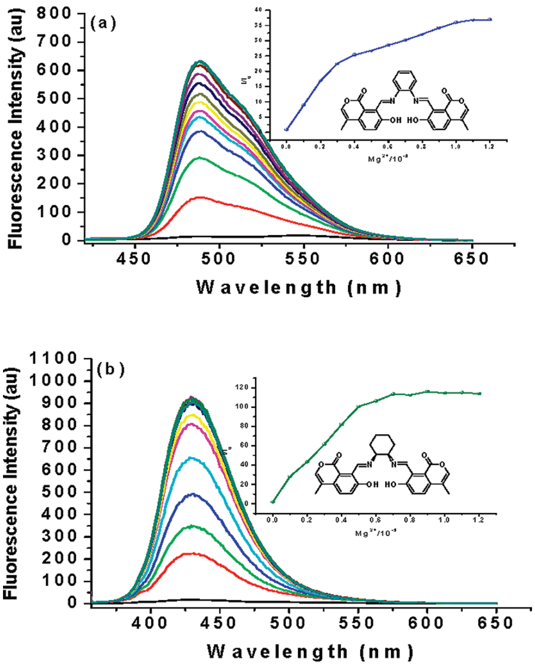

Figure 2. Fluorescence spectra of (a) CS1 and (b) CS2 (10 μM) + 1.0 equiv of Na^+ in THF with increasing amounts of Mg^{2+} ((0, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 11.0, 12.0) × 10^{-6} mol/L) ((a): $\lambda_{ex} = 360$ nm; (b): $\lambda_{ex} = 352$ nm); inset: Plot of the concentration of Mg^{2+} vs I/I_0, where I is the fluorescence intensity of (a) CS1 or (b) CS2 with the addition of Mg^{2+} at (a) $\lambda_{em} = 490$ nm or (b) 430 nm and I_0 is the fluorescence intensity of (a) CS1 or (b) CS2 without Mg^{2+} at (a) 550 nm or (b) 510 nm.

In this paper, we proceeded to further evaluate their selectivity of CS1 and CS2 toward Mg^{2+}. The results indicate that Li^+, K^+, Ca^{2+}, Zn^{2+}, Hg^{2+}, and Pb^{2+} can also slightly trigger the fluorescent enhancement of CS1-Mg^{2+} as high as 6.1-, 6.7-, 7.4-, 7.5-, 5.2-, and 8.5-fold (Figure 3a). In parallel, Li^+, K^+, Ca^{2+}, and Zn^{2+} can also increase the fluorescence intensities of CS2-Mg^{2+} by 12.6-, 16.4-, 13.7-, and 47.5-fold (Figure 3b), respectively. Other metal ions, such as Cr^{3+}, Cd^{2+}, and Cu^{2+} can cause different content fluorescence quenchings of CS1-Mg^{2+} and CS2-Mg^{2+} (see SI 3).

The optical output signals of a salen-based ligand in response to metal ion binding have been used to develop AND and INHIBIT logic gates.[15] The AND gate is a digital logic gate that implements logical conjunction, which results in a HIGH output (1) only if both of the inputs are simultaneously applied as HIGH. In another sense, the function of AND can effectively find the "minimum" between two binary digits, just as the OR function finds the "maximum". The fluorescence of CS2

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(11) (a) Kulkarni, A.; Patil, S. A.; Badami, P. S. *Eur. J. Med. Chem.* **2009**, *44*, 2904–2912. (b) Kulkarni, A.; Patil1, S. A.; Badami, P. S. *J. Enzyme Inhib. Med. Chem.* **2010**, *25*, 87–96. (c) Hu, Y.; Li, Q. Q.; Li, H.; Guo, Q. N.; Lu, Y. G.; Li, Z. Y. *Dalton Trans.* **2010**, *39*, 11344–11352. (d) Yıldırım, M.; Kaya, İ. *J. Fluoresc.* **2010**, *20*, 771–777.

(12) (a) Pina, F.; Bernardo, M. A.; GarcÍa-España, E. *Eur. J. Inorg. Chem.* **2000**, 2143–2157. (b) Xu, Z. C.; Yoon, J.; Spring, D. R. *Chem. Soc. Rev.* **2010**, *39*, 1996–2006. (c) Bozdemir, O. A.; Guliyev, R.; Buyukcakir, O. *J. Am. Chem. Soc.* **2010**, *132*, 8029–8036. (d) de Silva, A. P.; McClenaghan, N. D. *Chem.—Eur. J.* **2002**, *8*, 4935–4945.

(13) (a) Liu, Y.; Zhang, S. W.; Miao, Q.; Zheng, L. F.; Zong, L. L.; Cheng, Y. X. *Macromolecules* **2007**, *40*, 4839–4847. (b) Liu, Y.; Miao, Q.; Zhang, S. W.; Huang, X. B.; Zheng, L. F.; Cheng, Y. X. *Macromol. Chem. Phys.* **2008**, *209*, 685–694.

(14) (a) Zhang, Y.; Guo, X. F.; Si, W. X.; Jia, L. H.; Qian, X. H. *Org. Lett.* **2008**, *10*, 473–476. (b) Liu, Z. P.; Zhang, C. L.; Li, Y. L.; Wu, Z. Y.; Qian, F.; Yang, X. L.; He, W. J.; Gao, X.; Guo, Z. J. *Org. Lett.* **2009**, *11*, 795–798. (c) Wang, Y. W.; Yu, M. X.; Yu, Y. H.; Bai, Z. P.; Shen, Z.; Li, F. Y.; You, X. Z. *Tetrahedron Lett.* **2009**, *50*, 6169–6172.

(15) (a) de Silva, A. P.; Gunaratne, H. Q. N.; McCoy, C. P. *Nature* **1993**, *364*, 42–44. (b) Coskun, A.; Deniz, E.; Akkaya, E. U. *Org. Lett.* **2005**, *7*, 5187–5189. (c) Irie, M.; Fukaminato, T.; Sasaki, T.; Tamai, N.; Kawai, T. *Nature* **2002**, *420*, 759. (d) Montenegro, J. M.; Perez-Inestrosa, E.; Collado, D. *Org. Lett.* **2004**, *6*, 2353–2355. (e) Joseph, R; Ramanujam, B.; Acharya, A.; Rao, C. P. *J. Org. Chem.* **2009**, *74*, 8181–8190. (f) Pischel, U. *Angew. Chem., Int. Ed.* **2007**, *46*, 4026–4040. (g) Saha, A.; Manna, S.; Nandi, A. K. *Soft Matter* **2009**, *5*, 3992–3996.

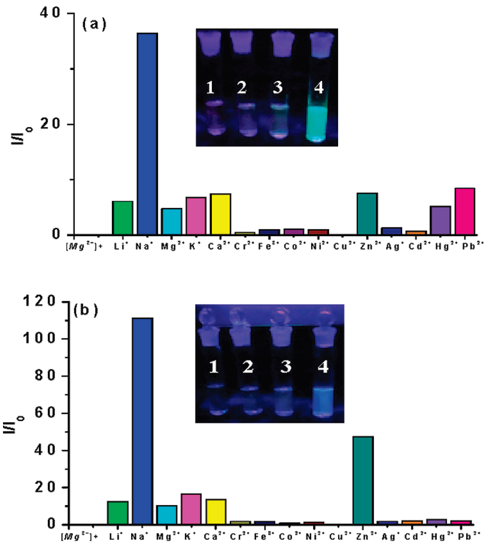
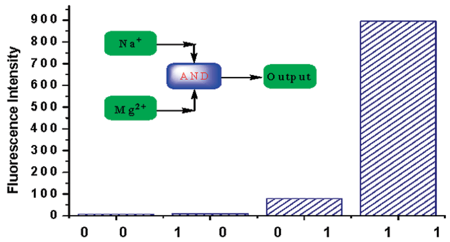
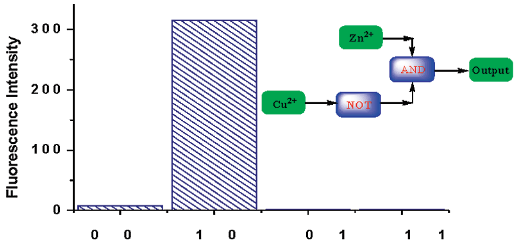


Figure 3. Selectivity of the CS1 (a) and CS2 (b) toward Mg^{2+} and other metal ions. In these experiments, the fluorescence measurement was taken at $\lambda_{ex} = 360$ nm (for CS2, $\lambda_{ex} = 352$ nm) from 10 μM of the sensor in THF at room temperature and in the absence and presence of 1.0 equiv of a metal ion. Inset: The fluorescence image of a solution of the sensors (10 μM) plus 1.0 equiv of a metal ion excited by a commercially available UV lamp ($\lambda_{ex} = 365$ nm) (**1**: None; **2**: Na^+; **3**: Mg^{2+}; **4**: $Na^+ + Mg^{2+}$).



input		output	
Na^+	Mg^{2+}	AND fluorescence	
0	0	low (**8.02**)	0
1	0	low (**9.71**)	0
0	1	low (**79.8**)	0
1	1	high (**894.4**)	1

Figure 4. Fluorescence output of ligand CS2 (10 μM) in the presence of chemical inputs, Na^+ (10 μM) and Mg^{2+} (10 μM), and the truth table of the **AND** gate.



input		output	
Zn^{2+}	Cu^{2+}	INH fluorescence	
0	0	low (**8.02**)	0
1	0	high (**315.6**)	1
0	1	low (**1.02**)	0
1	1	low (**1.21**)	0

Figure 5. Fluorescence output of ligand CS2 in the presence of chemical inputs, Zn^{2+} (10 μM) and Cu^{2+} (10 μM), and the truth table of the **INH** gate.

(10 μM) at 430 nm (Output 1) would be largely enhanced only if 1.0 equiv of Na^+ (Input 1) and 1.0 equiv of Mg^{2+} (Input 2) are combined with CS2 in a THF solution (Figure 4).

An INH logic gate can be basically understood as an AND operation with one of the inputs being reversed. That is, INH can be integrated by incorporating a NOT and an AND gate.[16] A basic two-input INHIBIT action can be obtained for CS2 (10 μM) with Zn^{2+} (10 μM) and Cu^{2+} (10 μM) as inputs (Figure 5). Fluorescence enhancement of CS2 at 450 nm is observed only in the presence of 1.0 equiv of Zn^{2+} and the absence of Cu^{2+}, leading to the output as “1”. Under other conditions the fluorescence of CS2 is quenched, resulting in output “0”.

In summary, two salen-based ligands can act as excellent fluorescent sensors for the detection of Mg^{2+}. Mg^{2+} can produce a pronounced fluorescence enhancement response under a Na^+ triggered synergistic effect. Two fluorescence-based logic gates can be used as potential candidates for a molecular logic circuit.

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Supporting Information Available. synthetic procedures, characterization, and additional spectra data. This material is available free of charge via the Internet at http://pubs.acs.org.

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[16] (a) Kluciar, M.; Ferreira, R.; de Castro, B.; Pische, U. *J. Org. Chem.* **2008**, *73*, 6079–6085. (b) 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*, 1393–1394.