ORGANIC LETTERS

2005
Vol. 7, No. 14
2857−2859

Single Molecular Multianalyte Sensor: Jewel Pendant Ligand

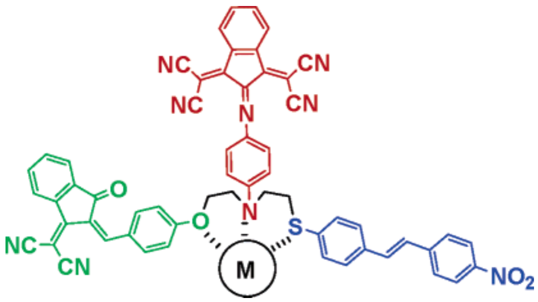
Hirokazu Komatsu,[†] Daniel Citterio,[†] Yukio Fujiwara,[†] Katsuya Minamihashi,[†] Yoshio Araki,[‡] Masafumi Hagiwara,[‡] and Koji Suzuki*,[†,§]

Department of Applied Chemistry and Department of Information and Computer Science, Keio University, Yokohama 223-8522, Japan, and JST-CREST, Saitama 332-0012, Japan

suzuki@applc.keio.ac.jp

Received April 5, 2005

ABSTRACT



The jewel pendant ligand has multiple chromogenic units combined in a single molecule with the dyes linked to a semiselective binding site by three heteroatoms (O, N, S) having different HSAB characteristics, to indicate diverse response to individual transition metal ions. Using a single-molecular multianalyte sensor, multiple analytes could be determined with a minimal sensing system.

A number of molecular optical sensors (chromoionophores, fluoroionophores) have been developed that focus on the selective binding to an analyte.[1] Those molecules are used in many fields, such as bioimaging,[2] and clinical and environmental analysis with fiber-optic sensors.[3] They are composed mainly of a binding site and a transducer site (chromophore) combined in one molecule. The molecular design of the sensor molecules that show selective binding to an analyte has been well established especially for alkaline[4,5] (Na^{I}, K^{I}, etc.) and alkaline-earth metals[6,7] (Ca^{II}, Mg^{II} etc.). Since the selective ion−ligand complexes for those ions are charge-interaction dominated, the search for selective binding sites has focused on the ion-size recognition properties of the ligands. These selectivities have been investigated in our laboratories for the molecular design of ionophores and fluorescent probes.[8] Recently, optical molecular sensors with specific response to heavy- and transition-metal ions[9] such as Hg^{II}, Cu^{II}, and Zn^{II} have been reported. However, for ionophore design,[10] the selective binding to these metals is a challenging issue; thus, not only the selective binding

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[†] Department of Applied Chemistry, Keio University.
[‡] Department of Information and Computer Science, Keio University.
[§] JST-CREST.

(1) (a) de Silva, A. P.; Gunaratne. H. Q.; Gunnlaugsson, T.; Huxley, A. J. M.; McCoy, C. P., Rademacher J. T.; Rice, T. E. *Chem. Rev.* **1997**, *97*, 1515−1566. (b) Fabbrizzi, L.; Poggi, A. *Chem. Soc. Rev.* **1995**, 197−202.

(2) Haugland, R. P. *Handbook of Fluorescent Probes and Research Chemicals*, 9th ed.; Molecular Probes: Carlsbad, CA, 2002.

(3) (a) Hisamoto, H.; Suzuki, K. *Trends Anal. Chem.* **1946**, *18*, 513−524. (b) Suzuki, K. *Asahi Garasu Zaidan Josei Kenkyu Seika Houkoku* **1995**, 237−244. (c) Spichiger-Keller, U. E. *Chemical Sensors and Biosensors for Medical and Biological Applications*; Wiley-VCH: New York, 1997.

(4) (a) Minta, A.; Tsien, R. Y. *J. Biol. Chem.* **1989**, *264*, 19449−19457. (b) He, H.; Mortellaro, M. A.; Leiner, M. J. P.; Young, S. T.; Fraatz, R. J.; Tusa, J. K. *Anal. Chem.* **2003**, *75*, 549−555.

(5) He, H.; Mortellaro, M. A.; Leiner, M. J. P.; Fraatz, R. J.; Tusa, J. K. *J. Am. Chem. Soc.* **2003**, *125*, 1468−1469.

(6) (a) Grynkiewicz, G.; Poenie M.; Tsien, R. Y. *J. Biol. Chem.* **1985**, *260*, 3440−3450. (b) Minta, A.; Kao, J. P.; Tsien, R. Y. *J. Biol. Chem.* **1989**, *264*, 8171.

(7) (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) 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.

10.1021/ol0507219 CCC: $30.25

but also the optical discrimination of the cations is discussed for the development of new chromoionophores. On the other hand, the multisensor array approach, consisting of the combination of multiple nonselective transition-metal chromoionophores and mathematical analysis systems[11] (such as PLS, ANNs) has been investigated for the simultaneous determination of several heavy-metal ions. In these systems, sensors are not required to indicate high selectivity to a single analyte but should be semiselective (i.e., selective to several analytes of interest and no response to analytes out of interest) and show a discriminating response to many analytes.

Here, we demonstrate that a minimal multisensor can consist of one single molecule. The goal of our research is the development of a single-molecular sensor for multiple analytes. This concept has to our best knowledge not been reported to date. For establishing our goal, we propose a novel molecular design called a “jewel pendant ligand”.

The jewel pendant ligand possesses multiple chromogenic subunits in one molecule with the dyes linked to a semiselective binding site with three heteroatoms (N, O, S) having different hard−soft acid−base (HSAB) characteristics.[12] The molecule is designed to indicate a diverse response to individual cations.

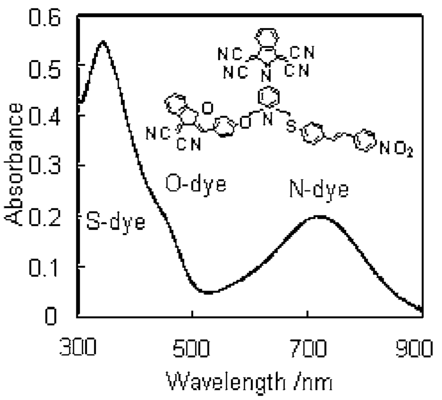

Figure 1. Structure and spectra of JPL-1 (10 μM) in MeCN.

An open-shaped ligand was selected for JPL-1 (Figure 1) to show semiselectivity to cations. The three chromophoric units were chosen to have different λ_{max} values. They were selected from indan or stilbene derivatives, since those dyes do not have substituents acting as potential binding sites to metal ions such as phenol, carboxyl, or diazo groups. Therefore, all chromophore−ion interactions can be assumed to occur at the heteroatomic binding sites connected to the different chromophoric units.

The nitrogen-linked dye (N-dye) used for JPL-1 is an aza analogue of the dicyanovinyl indan derivatives,[13] having a peak of maximum absorbance at 710 nm. The oxygen-linked dye (O-dye) is a dicyanovinyl indan derivative with a λ_{max} value at 460 nm. The sulfur-linked dye (S-dye) is stilbene[14] with λ_{max} at 380 nm.

The organic synthesis of JPL-1 (refer to Scheme 1 in the Supporting Information) was performed starting from a commercially available aniline derivative by first connecting a part of the S-dye via the tosylate followed by the final S-dye synthesis via the Heck reaction.[15] The next steps were the connection of a part of the O-dye via the methylate and the synthesis of the final O-dye by a coupling reaction. Finally the synthesis of JPL-1 was completed by coupling of the N-dye (overall 2.4% yield).

The absorbance spectra of JPL-1 measured in acetonitrile solution are shown in Figure 1. The absorbance peak near 710 nm originates from the N-dye, and the shoulder near 460 nm results from the O-dye overlapping to some extent with the S-dye. The observed λ_{max} value in the 340 nm region is composed of the combined peak of the O-dye, S-dye, and the second absorbance band of the N-dye.

The change in the absorbance spectra of JPL-1 in the presence of 10 equiv of 12 metal cations (Mg^{II}, Ca^{II}, Mn^{II}, Co^{II}, Ni^{II}, Zn^{II}, Ag^{I}, Hg^{II}, Cu^{II}, Fe^{III}, Al^{III}, Cr^{III}, and Pb^{II}) was measured in acetonitrile solution. For Cu^{II}, Fe^{III}, Al^{III}, Pb^{II}, and Cr^{III}, the absorbance spectra showed changes compared to the ion-free solution (Figure 2), where the changes for the band of the N-dye were most significant and varied with those ions (see Figure S1 in the Supporting Information). The response of the absorbance from the O- and S-dyes was minor, but apparently different for Cu^{II}. The apparent binding constants with those ions calculated by curve fitting are listed in Table S1 (Supporting Information). The binding constants K are on the order of 10^5-10^6 M^{-1} and not significantly different for the metals. Thus, JPL-1 appears to interact “semiselectively” with a series of metal ions.

The relative changes in absorbance of JPL-1 with these ions are compared at the characteristic wavelengths of the three chromophores of JPL-1 in Figure 3 (see Table S3 in the Supporting Information for details). In the presence of Cu^{II}, all dye units showed a change in absorbance, to Fe^{III}, the N- and O-dyes, to Pb^{II}, the N- and S-dyes, and to trivalent Al^{III} and Cr^{III}, the N-dye only. The proposed coordination models, based on the observed spectral changes, are schematically shown in Figure 4.

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(8) (a) Suzuki, K.; Sato, K.; Hidamoto, H.; Siswanta, D.; Hayashi, K.; Kasahara, N.; Watanabe, K.; Yamamoto, N.; Sasakura, H. *Anal. Chem.* **1996**, *68*, 208−215. (b) Suzuki, K.; Watanabe, K.; Matsumoto, Y.; Kobayashi, M.; Sato, S.; Siswanta, D.; Hisamoto, H. *Anal. Chem*. **1995**, *67*, 324−334. (c) Suzuki, K.; Yamada, H.; Sato, K.; Watanabe, K.; Hisamoto, H.; Tobe, Y.; Kobiro, K.. *Anal. Chem.* **1993**, *65*, 3404−3410.

(9) (a) Rurack, K.; Kollmannsberger, M.; Resch-Genger, U.; Daub, J. *J. Am. Chem. Soc.* **2000**, *122*, 968−969. (b) Fabbrizzi, L.; Licchelli, M.; Pallavicini, P.; Sacchi, D.; Taglietti, A. *Analyst* **1996**, 121, 1763−1768. (c) Prodi, L.; Bolletta F.; Montalti, M.; Zacheroni, N. *Coord.Chem.Rev.* **2000**, *205*, 59−83.

(10) (a) Bühlmann P.; Pretsch E.; Bakker, E. *Chem. Rev.* **1998**, *98*, 1593−1687. (b) Siswanta, D.; Nagatsuka., K.; Yamada, H.; Kumakura, K.; Hisamoto, H.; Shichi, Y.; Toshima, K., Suzuki, K. *Anal. Chem.* **1996**, *68*, 4166−4172.

(11) (a) Raimundo, I. M.; Narayanaswamy R. *Sens. Act. B* **2003**, *90*, 189−197, (b) Mikami, D.; Ohki, T.; Yamaji, K.; Citterio, D.; Ishihara, S.; Hagiwara, M.; Suzuki, K. *Anal. Chem.* **2004**, *76*, 5726−5733.

(12) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533−3539.

(13) Bello, K. A.; Cheng, L.; Griffiths, J. *J. Chem. Soc., Perkin Trans. 2* **1987**, 815−818.

(14) Noyce, D. S.; Hartter, D. R.; Miles, F. B. *J. Am. Chem. Soc.* **1968**, *90*, 4633−4637.

(15) Patel, P. A.; Ziegler, C. B.; Cortese, N. A.; Zebovitz, T. C.; Terpko, M.; Heck, R. F. *J. Org. Chem.* **1977**, *42*, 3903−3907.

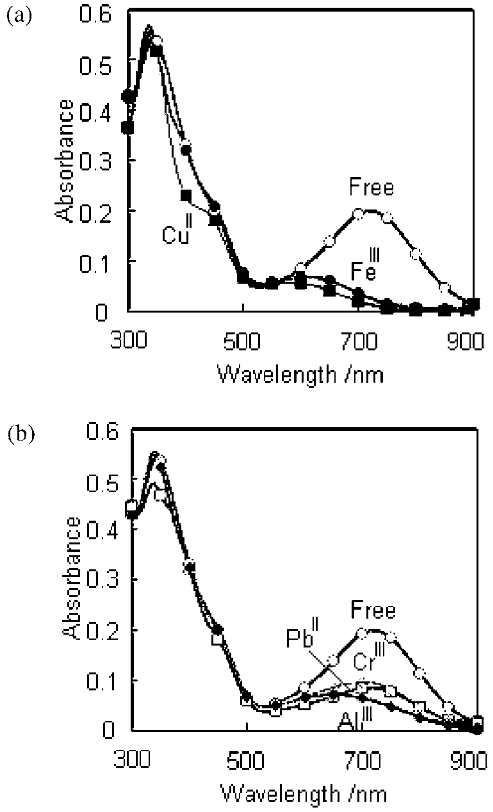

Figure 2. Absorbance spectra of JPL-1 (10 μM) in the presence of 10 equiv of various metal cations: (a) Fe^{III}, Cu^{II}; (b) Al^{III}, Cr^{III}, Pb^{II} in MeCN (○, free; ●, Fe^{III}; ■, Cu^{II}; ◆, Al^{III}; ◇, Cr^{III}; □, Pb^{II}).

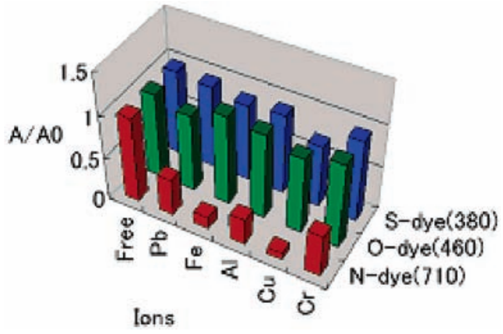

Figure 3. Comparison of the response (A/A_0) of JPL-1 (10 μM) at different wavelengths (380, 460, 710 nm) to 10 equiv of various metals (Pb^{II}, Fe^{III}, Al^{III}, Cu^{II}, Cr^{III}).

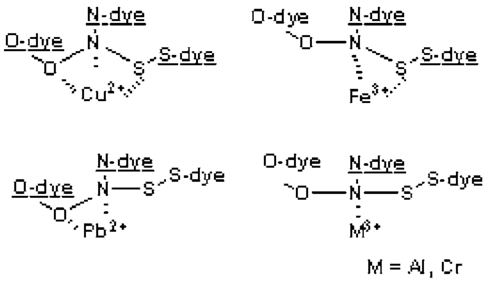

Figure 4. Proposed model for response of JPL-1. Interacting dyes are underlined, and interaction is shown as a dashed line.

The different optical response reflects different complex formations in correspondence to the molecular design concept. However, the differences in response behavior can only be partially accounted for by the HSAB principle. Other assumed influencing factors are solvent effects and ion size.

With this molecular discrimination ability of JPL-1, the simultaneous determination of multiple cations was demonstrated for mixed sample solutions of Fe^{III} and Cu^{II} as a first model of a simple application.

The absorbance spectra of 5 × 5 combinations of concentrations of Fe^{III} and Cu^{II} in the 3−50 μM range in the mixture with JPL-1 were measured in acetonitrile. The experimental data was analyzed with a back-propagation artificial neural network (BP-ANN)[16,17] that has already been reported for the simultaneous determination of metal ions in mixed solution.[11]

With the BP-ANNs, the concentrations of Cu^{II} and Fe^{III} in mixtures were simultaneously estimated. For Cu^{II}, a root-mean-square error of prediction (RMSEP) of 4.3 mM was achieved ($R = 0.94$) and for Fe^{III} the RMSEP was found to be 5.0 μM ($R = 0.90$). (Table S2, Supporting Information).

We have proposed a novel strategy to determine heavy- and transition-metal ions with a single-molecular multianalyte sensor having a unique molecular design concept. JPL-1 has the capability of determining multiple metal ions with the spectral diversity of three heteroatom-linked dyes, based on the nature of the heteroatoms and their interaction with the cations. The simultaneous determination of Fe^{III} and Cu^{II} was achieved by analysis with BP-ANNs as an example. By using this concept of the jewel pendant ligand as a multianalyte sensor, we have demonstrated a way to determine multiple analytes with a single-molecular sensor component.

Supporting Information Available: Experimental details, figures and tables, and analysis by ANNs. This material is available free of charge via the Internet at http://pubs.acs.org.

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[16] Zupan, J.; Gasteiger, J. *Neural Networks for Chemists An Introduction*; VCH Verlag: Weinheim, 1993; pp 318−362.

[17] Lachenbruch, P.; Mickey, M. Estimation of Error Rates in Discriminant Analysis. *Technometrics* **1968**, 1−111.