ORGANIC LETTERS

2005
Vol. 7, No. 24
5469−5472

New Chromogenic Probes into Nanoscopic Pockets in Enhanced Sensing Protocols for Amines in Aqueous Environments

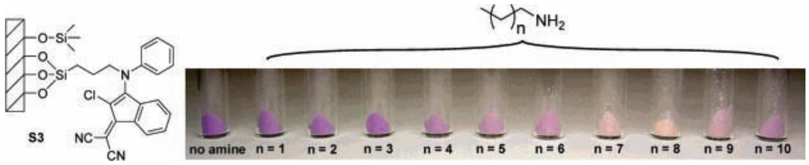
Sara Basurto,[†] Tomás Torroba,*,[†] María Comes,[‡] Ramón Martínez-Máñez,*,[‡]
Félix Sancenón,[‡] Luis Villaescusa,[‡] and Pedro Amorós[§]

Departamento de Química, Universidad de Burgos, Plaza Misael Bañuelos s/n,
09001 Burgos, Spain, Instituto de Investigación en Química Molecular Aplicada,
Departamento de Química, Universidad Politécnica de Valencia, Camino de Vera s/n,
46071 Valencia, Spain, and Institut de Ciència del Materials (ICMUV), Universistat de
València, P.O. Box 2085, 46071 Valencia, Spain

ttorroba@ubu.es; rmaez@qim.upv.es

Received September 22, 2005

ABSTRACT



A new sensory MCM-41-based material for the colorimetric sensing and discrimination of amines has been developed.

The development of molecular chemosensors for sensing protocols for target guests via changes in optical signals is a field of interest.[1] These new methodologies, based on the colorimetric transduction of host−guest interactions, are especially attractive for their potential use in situations where conventional techniques are not appropriate as, for instance, for naked eye screening applications. However, there are still a large number of problems linked to the development of new selective chromogenic probes for sensing applications. This is especially the case for the development of systems for the colorimetric sensing of certain organic species in aqueous environments.[2] In particular, we are interested in developing new and advanced systems for the selective sensing of amines. These are well-known compounds with importance in different areas of chemistry and biochemistry. As a general approach to the particular challenge of developing chromogenic systems for neutral molecules, the reported examples generally relay in the reactivity of certain functional groups. For instance, colorimetric signaling of amines usually involves nucleophilic attack to certain molecular substrates and formation of fluorescent groups in a chemodosimeter fashion. This is an interesting approach that, however, harbors some serious disadvantages. Thus, for instance, many signaling molecules suffer from cross reactivity with several other nucleophiles including the attack of OH^- groups from water. Additionally, many of these systems show signaling events near the UV zone, and there are not many examples of optical transducers of the presence of amines at longer

---

[†] Universidad de Burgos.

[‡] Universidad Politécnica de Valencia.

[§] Universistat de València.

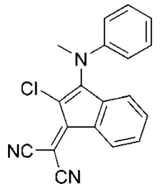
(1) (a) de Silva, A. P.; Gunaratne, H. Q. N.; Gunnlaugsson, T.; Huxley, A. J. M.; McCoy, C. P.; Rademacher, J. T.; Rice, T. E. *Chem. Rev.* **1997**, *97*, 1515. (b) Special Issue on "Luminescent Sensors". *Coord. Chem. Rev.* **2000**, *205*. (c) Beer, P. D.; Gale, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 486. (d) Martínez-Máñez, R.; Sancenón, F. *Chem. Rev.* **2003**, *103*, 4419. (e) Fabbrizzi, L.; Licchelli, M.; Taglietti, A. *Dalton Trans.* **2003**, 3471. (f) Martínez-Máñez, R.; Sancenón, F. *J. Fluoresc*. **2005**, *15*, 267.

(2) (a) Bell, T. W.; Hext N. M. *Chem. Soc. Rev.* **2004**, *33*, 589. (b) Mohr, G. J. *Chem. Eur. J.* **2004**, *10*, 1082. Ros-Lis, J. V.; García, B.; Jiménez, D.; Martínez-Máñez, R.; Sancenón, F.; Soto, J.; Gonzalvo, F.; Valldecabres, M. C. *J. Am. Chem. Soc.*, **2004**, *126*, 4064. Ros-Lis, J. V.; Martínez-Máñez,R.; Soto, J. *Org. Lett.* **2005**, *7*, 2337.

10.1021/ol052298+ CCC: $30.25

wavelengths. And finally, probably the most serious drawback from a molecular recognition point of view is that these protocols are designed for signaling families of compounds and not to sense a certain member within a set of molecules having the same functional group.

We are interested not only in developing new amine chromogenic sensors but also in designing standard routes to enhance the capability to distinguish within a complex family of compounds. With these previous ideas in mind, we report here the development of a new reagent for the colorimetric detection of primary amines based on 1-dicyanomethylene-2-chloro-3-(*N*-methyl-*N*-phenylamino)indene **I** (see Figure 1).



I

Figure 1. 1-Dicyanomethylene-2-chloro-3-(*N*-methyl-*N*-phenylamino)indene (**I**).

Compound **I** can be obtained readily by simple amination of 1-dicyanomethylene-2,3-dichloroindene.[3] Compound **I** is highly colored ($\epsilon = 8935$ L mol^{-1} cm^{-1}) with an intense absorption centered at 552 nm which should most likely be ascribed to a charge-transfer band due to the presence of the donor amine group and the dicyanomethylene acceptor moiety. In fact, coordination of metal cations to the amino group in **I** (unpublished results) results in a hypsochromic shift of the absorption band as would be expected in these donor−acceptor-type dyes.[4] Additionally, preliminary studies on the reactivity of **I** with nucleophiles revealed chromogenic changes in the presence of primary amines, whereas no changes were found for secondary or tertiary amines (see the Supporting Information). Despite this interesting result, this product displays drawbacks similar to those described above as it is capable of signaling primary aliphatic amines but not able to sense a certain member within this very large family of compounds. Additionally, **I** is not water soluble and also undergoes cross reactivity in the presence of an excess of amines to produce complex uncharacterized mixtures most likely containing oligomeric derivatives that limit their use as chromochemodosimeters.

To overcome these problems, it is necessary to couple the specific reactivity of the amine group with additional interactions in order to enhance selectivity. Several approaches have been developed, but most of them are involved with the use of sophisticated molecular host receptors. As an alternative approach, we are interested in exploring the potential use of predefined nanoscopic inorganic structures that when conveniently functionalized can result in an enhancement of the selectivity observed. Prominent examples of enhanced selectivity using nanoscopic inorganic solids can, for instance, be observed using gold nanoparticles,[5] SAMs,[6] and, more recently, mesoporous materials.[7] Specifically, the use of mesoporous solids is highly tempting because of the recent reported examples suggesting that their use as rigid 3D scaffoldings can mimic simple features of more complex biological structures. Thus, for instance, conveniently hydrophobed pores containing additional reactive sites can be archaic prototypes of very complex "binding pockets" in biological systems.[7] This confinement feature might also bring in collateral beneficial attributes as, for instance, chemical stability of the "active sites".

In an attempt to enhance the response of **I** toward primary amines in terms of both selectivity and stability, we designed a route to covalently anchor the chromogenic probe onto suitable nanoscopic hydrophobic pockets. The synthetic route is shown in Scheme 1. In a first step, the *N*-methyl-*N*-(propyl-3-trimethoxysilyl)aniline derivative was used together with TEOS, CTAB, and TEA to prepare, using a co-condensation protocol, the UVM-7[8] mesoporous functionalized solid **S1**. This solid was further reacted with hexamethyldisilazane in order to "block" the dangling −OH groups introducing highly hydrophobic $-CH_3$ moieties in **S2**. Finally, reaction of **S2** with 1-dicyanomethylene-2,3-dichloroindene gave the purple

---

(3) *N*-Methylaniline (0.5 mL, 4.63 mmol) was added to a solution of 1-dicyanomethylene-2,3-dichloroindene[11] (30 mg, 0.122 mmol) in CH_2Cl_2 (10 mL) and the mixture stirred at room temperature for 15 min. Workup and column chromatography (silica, hexane/CH_2Cl_2 1:1 to CH_2Cl_2) gave **I** as a purple-bluish solid (35 mg, 90%): mp 175−176 °C (CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.15 (d, $J = 7.6$ Hz, 1H, ArH), 7.40 (m, 3H, ArH), 7.23 (m, 2H, ArH), 7.17 (t, $J = 7.7$ Hz, 1H, ArH), 6.97 (t, $J = 7.7$ Hz, 1H, ArH), 5.98 (d, $J = 7.6$ Hz, 1H, ArH), 3.89 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.04, 155.57, 144.58, 135.59, 133.30, 130.88, 129.75, 129.43, 127.59, 125.17, 123.19, 122.95, 115.64, 114.05, 104.35, 67.00, 43.58; IR (KBr, cm^{-1}) 2920, 2210 (CN), 1518, 1390; MS (EI) *m/z* 319 ($M^+ + 2$, 5), 317 ($M^{\bullet+}$, 15), 282 ($M^+ - Cl$, 39), 267 (39), 207 (14), 149 (14), 85 (67), 83 (100); HRMS calcd for $C_{19}H_{12}ClN_3$ 317.07198, found 317.07199; UV−vis (CH_2Cl_2, 25 °C) λ_{max}, nm (ϵ, L mol^{-1} cm^{-1}) 552 (8935), 368 (12896), 250 (14379).

(4) Valeur, B.; Leray, I. *Coord. Chem. Rev.* **2000**, *205*, 3.

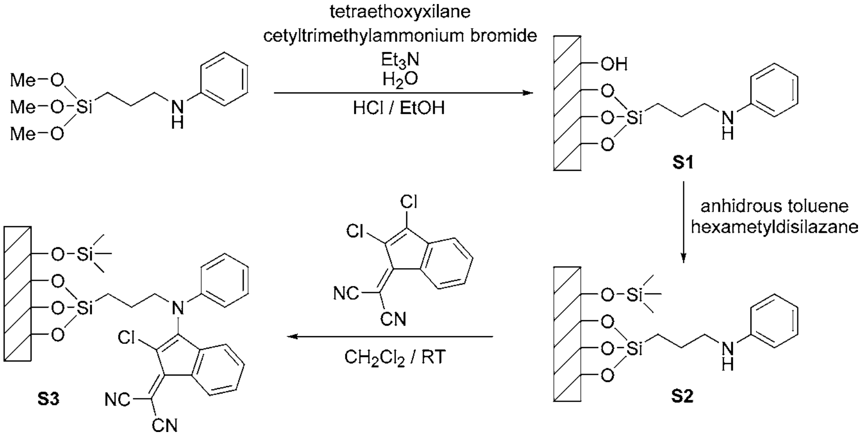
(5) (a) Lin, S.-Y.; Liu, S.-W.; Lin, C.-M.; Chen, C. *Anal. Chem.* **2002**, *74*, 330. (b) Watanabe, S.; Sonobe, M.; Arai, M.; Tazume, Y.; Matsuo, T.; Nakamura, T.; Yoshida, K. *Chem. Commun.* **2002**, 2866. (c) Brasola, E.; Mancin, F.; Rampazzo, E.; Tecilla, P.; Tonellato, U. *Chem. Commun.* **2003**, 3026. (d) Beer, P. D.; Cormode, D. P.; Davis, J. J. *Chem. Commun.* **2004**, 414. (e) Drechsler, U.; Erdogan, B.; Rotello, V. M. *Chem. Eur. J.* **2004**, *10*, 5570.

(6) (a) Crego-Calama, M.; Reinhoudt, D. N. *Adv. Mater.* **2001**, *13*, 1171. (b) Basabe-Desmonts, L.; Beld, J.; Zimmerman, R. S.; Hernando, J.; Mela, P.; García-Parajó, M. F.; van Hulst, N. F.; van der Berg, A.; Reinhoudt, D. N.; Crego-Calama, M. *J. Am. Chem. Soc.* **2004**, *126*, 7293.

(7) (a) Lin, V. S.-Y.; Lai, C.-Y.; Huang, J.; Song, S.-A.; Xu, S. *J. Am. Chem. Soc.* **2001**, *123*, 11510. (b) Descalzo, A. B.; Jiménez, D.; Marcos, M. D.; Martínez-Máñez, R.; Soto, J.; El Haskouri, J.; Guillem, C.; Beltrán, D.; Amorós, P.; Borrachero, M. V. *Adv. Mater.* **2002**, *14*, 967. (c) Descalzo, A. B.; Jiménez, D.; El Haskouri, J.; Beltrán, D.; Amorós, P.; Marcos, M. D.; Martínez-Máñez, R.; Soto, J. *Chem. Commun.*, **2002**, 562. (d) Comes, M.; Marcos, M. D.; Martínez-Máñez, R.; Sancenón, F.; Soto, J.; Villaescusa, L. A.; Amorós, P.; Beltrán, D. *Adv. Mater.* **2004**, *16*, 1783. (e) Radu, D. R.; Lai, C.-Y.; Wiench, J. W.; Pruski, M.; Lin, V. S.-Y. *J. Am. Chem. Soc.* **2004**, *126*, 1640. (f) Descalzo, A. B.; Rurack, K.; Weisshoff, H.; Martínez-Máñez, R.; Marcos, M. D.; Amorós, P.; Hoffmann, K.; Soto, J. *J. Am. Chem. Soc.* **2005**, *127*, 184. (g) Comes, M.; Rodríguez-López, G.; Marcos, M. D.; Martínez-Máñez, R.; Sancenón, F.; Soto, J.; Villaescusa, L. A.; Amorós, P.; Beltrán, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 2918. (h) Descalzo, A. B.; Marcos, M. D.; Martínez-Máñez, R.; Soto, J.; Beltrán, D.; Amorós, P. *J. Mater. Chem.* **2005**, *15*, 2721.

(8) El Haskouri, J.; Ortiz de Zarate, D.; Guillem, C.; LaTorre, J.; Caldés, M.; Beltrán, A.; Beltrán, D.; Descalzo, A. B.; Rodriguez-López, G.; Martínez-Máñez, R.; Marcos, M. D.; Amorós, P. *Chem. Commun.* **2002**, 330.

Scheme 1. Synthetic Route to the Formation of Solid **S3**



solid **S3** (see Scheme 1). The final **S3** solid was exhaustively washed and dried and used as sensory material for amine-sensing protocols (see below).

The rationalization of the chemical composition of the solids was calculated from thermogravimetric and elemental analysis, and the results are summarized in Table 1, which shows the molar ratios with respect to SiO_2 of anilinium groups, the final anchored 1-dicyanomethylene-2-chloro-3-(*N*-alkyl-*N*-phenylamino)indene dye, and CH_3 groups in the surface after the hydrophobation process with hexamethyldisilazane.

Table 1. Chemical Composition of Solids **S1**, **S2**, and **S3**

solid	aniline/SiO_2[a]	dye/SiO_2[a]	CH_3/SiO_2[a]
S1	4.53×10^{-3}		
S2	3.57×10^{-3}		0.63
S3	3.57×10^{-3}	3.35×10^{-3}	0.63

[a] Molar ratios.

The solids were characterized following standard solid-state procedures. For instance, X-ray diffraction and electron microscopy (SEM and TEM) confirmed the presence of the MCM-41 (UVM-7-type) structure. The powder X-ray diffraction patterns of the obtained hybrid solids show that these materials keep the characteristic intense peak at ca. $2\theta = 2°$ (indexed to the (100) reflection assuming the existence of a MCM-41-like hexagonal cell), indicating that the different synthetic steps did not affect substantially the structure of the silica matrix. In addition to this intense peak, a wide and small signal that could be assigned to the overlapped (110) and (200) reflections of the typical hexagonal cell can also be observed in those structures with lower numbers of organic groups. This feature can be associated to an intraparticle porous topology characteristic of MCM-41-like disordered hexagonal silicas. Additionally, the solid is organized in nanometric particles that are glued forming micrometric aggregates. This forms a bimodal hierarchic pore organization that can be appreciated through TEM and porosimetry measurements. For instance, the nitrogen adsorption−desorption isotherm of solid **S3** (714.1 $m^2\ g^{-1}$) shows two well-defined steps, one at intermediate relative pressure ($0.2 < P/P_0 < 0.4$) due to condensation of N_2 inside the mesopores and another at higher relative pressures associated to the filling of textural interparticle pores. From the first step, a pore diameter of 2.45 nm and a pore volume of 0.52 $cm^3\ g^{-1}$ was obtained, whereas from the second step a volume of 0.96 $cm^3\ g^{-1}$ and a diameter of 65.2 nm for the textural porosity was obtained. The first interval at intermediate pressures occurs with absence of hysteresis loop suggesting the existence of uniform and cylindrical mesopores.

S3 is a hybrid material containing signaling amine probes embedded onto hydrophobic 2.45 nm nanoscopic pockets. As a testing assay of its chromogenic sensing properties, **S3** was studied in water in the presence of certain primary amines of increasing hydrophobicity and size. In a typical assay, 4 mg of the solid **S3** was was soaked for 5 min with water containing a certain amine at a concentration of ca. 7 $\times 10^{-3}$ mol dm^{-3} at pH ca. 11.2. The solid was then filtered under vaccum and dried. The results are shown in Figure 2.

Figure 2. Color change in **S3** in the presence of primary aliphatic amines. From left to right: no amine, *n*-propylamine, *n*-butylamine, *n*-pentylamine, *n*-hexylamine, *n*-heptylamine, *n*-octylamine, *n*-nonylamine, *n*-decylamine, *n*-undecylamine, and *n*-dodecylamine.

There is a very remarkable difference between the response of the solid **S3** and that found for **I** in solution (see above). Thus, whereas the probe in solution is unspecific and poorly applicable to real samples, the hybrid sensory material **S3** is highly selective and reacts preferentially with the not too large but lipophilic enough amines *n*-nonylamine and *n*-

decylamine (also partially with *n*-undecylamine), whereas **S3** remains silent in the presence of small hydrophilic or very large aliphatic amines. Figure 3 shows the diffuse reflectance of solid **S3** before and after reaction with *n*-decylamine. **S3** presented the characteristic charge-transfer band centered at 554 nm that undergoes a blue shift to 445 nm upon reaction with the amine. As a result of the probe confinement onto nanopores, an enhanced selective chromogenic response is found, and solid **S3** is capable of chromogenically discriminating certain member within a set of similar organic molecules having the same functional group.

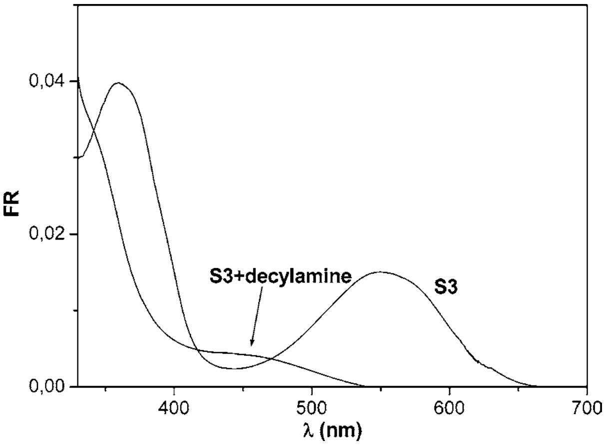


Figure 3. Diffuse reflectance of **S3** and **S3** + *n*-decylamine.

Furthermore, the confinement of the probe into the pores also has beneficial features in terms of stability: (i) solid **S3** is stable at basic pH due to their hydrophobic nature and (ii) there is no presence of cross reactivity to form oligomeric derivatives as **I** does in solution (see above). Additionally, whereas **I** reacts with cyanide and also changes color in the presence of certain metal cations in nonaqueous environments, the sensing material **S3** remains entirely silent to those species.[9] A comparison between the reactivity of solid **S3** and the molecule **I** is shown in Table 2.

This behavior is somewhat reminiscent of the structure–activity links in certain proteins that base their selectivity in the confinement of the active site in complex superstructures. This confinement entails additional recognition advantages as consequence of the coupling of two consecutive processes “extraction” + “recognition” resulting in an overall enhancement of selectivity toward certain guests. Additionally, in preliminary competitive experiments it was found that **S3** responded selectively to the *n*-decylamine even in complex mixtures containing other amines.[10] It is also remarkable that the selective pattern shown by **S3** is hardly reachable with synthetic analogous receptors in solution.

Table 2. Comparison of the Chromogenic Sensing Properties of **S3** and **I**[a]

	$CH_3(CH_2)_nNH_2$												
n	2	3	4	5	6	7	8	9	10	11	CN^-	OH^-	M^{2+}
S3	–	–	–	–	–	–	(x)	x	(x)	–	–	–	–
I	x	x	x	x	x	x	x	x	x	x	x	x	x

[a] x = strong response; (x) = weak response; – = no response.

In summary, we have shown here the use of a new colorimetric probe for the sensing of primary aliphatic amines. The compound **I** can be used for colorimetric detection of primary amines and their performance can be enhanced in terms of stability and selectivity by anchoring the probe into suitable nanoscopic pores. These results show that the combination of molecular concepts and 3D solid-state preorganized architectures are suitable hetero-supramolecular synergic routes to enhance recognition/sensing properties for chemosensing protocols.

Acknowledgment. We thank the Ministerio de Ciencia y Tecnología (Project Nos. REN2002-04237-C02-01, MAT2003-08568-C03-02, PPI-06-03, and BQU2001-0258) and Junta de Castilla y León, Consejería de Educación y Cultura, y Fondo Social Europeo (Project No. BU01/03) for support. M.C. and S.B. thank Caja de Ahorros del Mediterráneo (CAM) and Universidad de Burgos, respectively, for Doctoral Fellowships. F.S. thanks the Ministerio de Ciencia y Tecnología for a Ramón y Cajal contract.

Supporting Information Available: Structure **I** and a figure showing color changes of **I** in the presence of amines. This material is available free of charge via the Internet at http://pubs.acs.org.

OL052298+

---

[9] This was most likely due to the hydrophilic character of these species that avoids extraction to the nanoscopic pores where the probe is anchored.

[10] To the best of our knowledge, there are very few examples of neat chromogenic discrimination of similar amines. See, for instance: (a) Reference 7d. (b) Rakow, N. A.;, Suslick, K. S. *Nature* **2000**, *406*, 710. (c) Mertz, E.; Zimmerman, S. C. *J. Am. Chem. Soc*. **2003**, *125*, 3424.

[11] Konstantinova, L. S.; Rakitin, O. A.; Rees, C. W.; Souvorova, L. I.; Torroba, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1023