COMMUNICATION

# Chromogenic detection of formaldehyde in water and in gas phase using functionalized silica nanoparticles

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**Sensitive and selective chromogenic detection of formaldehyde, in water and in gas phase, was achieved using functionalized silica nanoparticles.**

Aldehydes are common source of pollution in every-day life since are used in many chemical adhesives and are side-products of many industrial processes or incomplete combustions (automotive exhaust, tobacco smoke, etc.). Among aldehydes, formaldehyde is widely used in household materials, adhesive resins which bind pressed wood products (such as plywood), veneers, and particle board. Formaldehyde is also used in the manufacture of paper, textiles, and paints. However formaldehyde is an intense irritant of eyes and mucous membranes and is therefore highly problematic as indoor pollutant. Moreover, the International Agency for Research on Cancer (IARC) has upgraded the cancer classification of formaldehyde in 2006 to now being clearly “carcinogenic to humans”.[1] Formaldehyde has also been implicated by the IARC as a causative agent of leukemia as well as nasopharyngeal cancer in humans.[2] Formaldehyde levels of 1–3 ppm can cause irritation in eyes and nose, and levels above 10 ppm cause strong discomfort.[3] The US EPA provides a reference dose (RfD) for chronic oral exposure of 0.2 mg/kg bodyweight/day[4] and Feron et al.[5] estimated that formaldehyde intake by food may range between 1.5 and 14 mg/person/day.

Taking into account the above mentioned facts, formaldehyde detection has been explored deeply into the last years. For this purpose several techniques such as cataluminescence,[6,7] different spectroscopies,[8-10] gas chromatography,[11-13] chemoresistivity,[13] organic-inorganic hybrid materials,[14] bio-sensing,[15] field effect gas sensors,[16] quartz micro balances,[17,18] and amperometric electrochemical cells[19] has been developed.

As an alternative to these classical techniques, which are costly and time-consuming, the use of chromogenic and fluorogenic probes for formaldehyde detection has recently emerged.[20-22] All reported probes have been designed using the chemodosimeter paradigm and make use of the well-known reaction between nucleophilic alkyl and aryl amines with the electrophilic carbon of the formaldehyde. These sensing systems were designed in such a way that, upon reaction with formaldehyde, color and/or emission changes were induced. Optical probes are attractive due to their high sensitivity, the use of simple instrumentation, their ability to operate at ambient temperature, and the possibility to measure the target analyte “in situ” using relatively simple assays.[20]

Following our interest in the design and applications of hybrid organic-inorganic materials in sensing and recognition protocols[23,24] we described herein the use of functionalized silica nanoparticles for the chromogenic sensing of formaldehyde both in solution and in air. Among different available silica supports, we decided to use nanoparticles given their easy preparation, straightforward surface functionalization and good stability in both water and organic solvents. The sensory material we have developed employs the well-established ion-channel paradigm introduced by Umezawa some years ago for electrochemical sensors.[25] In our version, the external surface of silica nanoparticles was decorated with thiol moieties as reactive units

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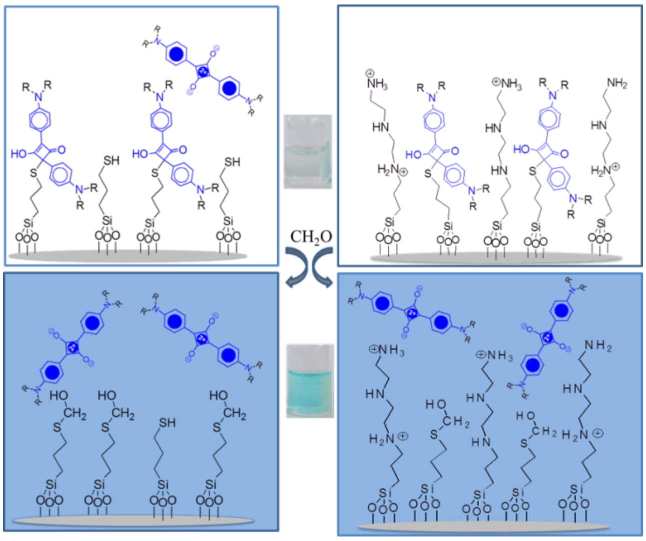
(R) which undergo nucleophilic substitution reaction with formaldehyde. The optical response arises from the competitive reaction of thiols with the electron-deficient 4-membered ring of a blue squaraine dye (SQ) or with formaldehyde. In the absence of formaldehyde the reaction of thiols with SQ results in a loss of π-conjugation of the dye and the subsequent bleaching of the solution. However, in the presence of formaldehyde thiols are expected to react with the –CHO group which would further inhibit SQ-thiol coupling resulting in a chromogenic response (see Scheme 1).



**Scheme 1**. Colorimetric protocol for the chromogenic detection of formaldehyde using **N1** and **N2** nanoparticles.

Coated silica nanoparticles (**N1**) were prepared using the commercially available trialcoxysilane derivative (3-mercaptopropyl) trimetoxysilane following the procedure reported by Montalti and co-workers.[26] In this synthetic protocol, silica nanoparticles were heated at 80 ºC in a water:ethanol:acetic acid (1:2:1) mixture in the presence of coating subunits (see Supporting Information for details). Solid **N1** was characterized using standard procedures. Thiol content was determined by elemental analysis and thermogravimetric measurements and amounted to 1.10 mmol/g SiO$_2$.

The reactivity of solid **N1** with SQ was tested in the absence and the presence of formaldehyde. In a typical experiment **N1** was suspended in PBS (0.01 M, pH 7.0, 10 mL). Then, 2 mL of the suspension of the nanoparticles were mixed with 0.1 mL of formaldehyde (0.1 mM in water) and stirred for 5 min. Finally, 0.18 mL of an acetonitrile solution of SQ (1.0 x 10$^{-4}$ M) was added and the changes in the visible band of the dye at 642 nm as a function of time monitored. The same protocol was carried out with **N1** suspensions in the absence of formaldehyde. The obtained results are shown in Figure 1. As seen, in the absence of formaldehyde, there is a gradually decrease of the absorbance at 642 nm indicating that reaction between thiols and SQ occurs. However, in the presence of formaldehyde the thiol-SQ reaction was highly inhibited. This inhibition is ascribed to the reaction of thiols with formaldehyde that yielded weakly nucleophilic (alkylthio) methanol moieties that are unable to react with SQ.

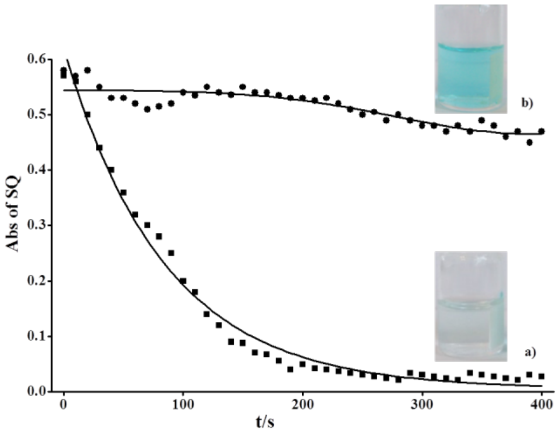


**Figure 1**. Absorbance at 642 (SQ band) versus time for PBS (0.01 M, pH 7.0) suspensions of **N1** and SQ alone (a) and in the presence of formaldehyde 0.1 mM (b).

In a second step, the chromogenic response of **N1** nanoparticles in the presence of formaldehyde, acetaldehyde, propionaldehyde, butyraldehyde, acetone, salicylaldehyde and 4-aminobenzoic acid was tested following the same protocol described above. As seen in Figure 2, the four aliphatic aldehydes tested were able to inhibit to some extent the thiol-SQ reaction whereas a more pronounced bleaching of the solution was observed in the presence of acetone, salicylaldehyde and 4-aminobenzoic acid. The different degree of thiol-SQ reaction inhibition is tentatively attributed to the different electrophilic character of the carbonyl moiety in the tested aldehydes (formaldehyde > acetaldehyde > propionaldehyde > butyraldehyde).

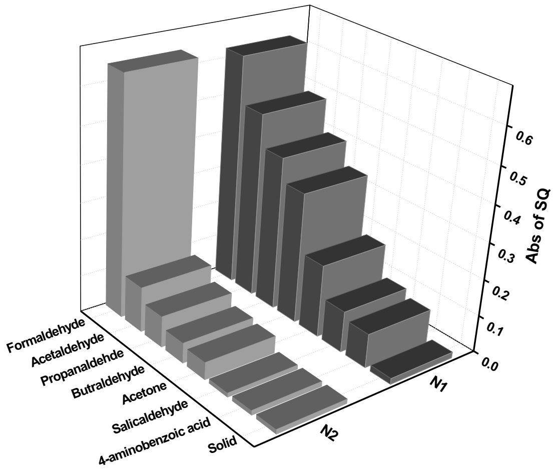


**Figure 2**. Absorbance at 642 (SQ band) nm for PBS (0.01 M, pH 7.0) suspensions of **N1** and **N2** nanoparticles in the presence of selected aldehydes, ketones and carboxylic acids (0.1 mM) after 10 min.

In order to improve the selectivity of our material toward formaldehyde a second solid **N2** was prepared. It was envisioned that grafting bulky polar molecules onto the nanoparticle's surface would enhance the reactivity of the thiol groups toward sterically less hindered aldehydes. For this purpose we selected 3-[2-(2-aminoethylamino)ethylamino]propyltrimethoxysilane as polar group. We are aware that amines are also able to react with aldehydes yielding the corresponding imines. However, the higher nucleophilic character of thiols was expected to occur preferentially. Moreover amines are expected to be partially protonated under the experimental conditions (neutral pH) making them less nucleophilic.

**N2** nanoparticles were obtained upon reaction with 3-[2-(2-aminoethylamino)ethylamino] propyltrimethoxysilane and (3-mercaptopropyl) trimetoxysilane in a 10:1 molar ratio. Other molar ratios were tested but the final supports were less selective. The organic contents in the final **N2** nanoparticles were determined by elemental analysis and thermogravimetric studies and amounted to 0.54 mmol/g of $SiO_2$ for polyamine and 0.033 mmol/g of $SiO_2$ for thiols. The average coverage on solid **N2** was about 1.75 molecules/$nm^2$ (1.65 of which are triamines and 0.10 are thiols). From the organic matter content and the value of the specific surface of the silica nanoparticles (ca. 200 $m^2$ $g^{-1}$) an average distance between anchored molecules of about 5.7 Å was calculated.

Selectivity studies with **N2** nanoparticles, using the same procedure described above for **N1**, revealed a clear different response than that obtained for the thiol-functionalized solid (see Figure 2). The response obtained using **N2** nanoparticles was highly selective and only addition of formaldehyde was able to inhibit the thiol-SQ reaction. The selectivity of **N2** toward formaldehyde could be explained bearing in mind that grafting of polyamines into the nanoparticle surface generate a highly polar environment around thiols and as a consequence, only formaldehyde, i.e. the more polar and smallest of the aldehydes tested, was able to access to the nanoparticle's surface and react with the grafted thiols.

Once probed the selective response of **N2** nanoparticles toward formaldehyde the sensitivity of the sensory solid was assessed. For this purpose, the chromogenic response of PBS suspensions of **N2** nanoparticles upon addition of increasing quantities of formaldehyde was studied. The absorption of SQ dye at 642 nm was gradually enhanced upon increasing formaldehyde concentration (see Supporting Information). From the titration profile a limit of detection of 1.2 μM (36 ppb) for formaldehyde was determined.

**Figure 3**. Photographs of a 1.0 x 2.0 cm silica dipstick immersed in a 2 ml of PBS (0.01 mM, pH 7.0) and with 0.18 ml of SQ (acetonitrile, 1.0 x $10^{-4}$ M). The right-handed stick was previously immersed in formaldehyde (1 mM) for 5 min, whereas de left-handed foil was directly dipped into PBS-SQ solution.

In order to enhance the applicability of our chromogenic system to detect formaldehyde we prepared test strips by simple functionalization of coated silica PET films with 3-[2-(2-aminoethylamino)ethylamino] propyltrimethoxysilane and (3-mercaptopropyl) trimethoxysilane (see Supporting Information for details). In a typical test, functionalized sticks were immersed in 2 mL of PBS (pH 7.4) alone or containing 0.1 ml of formaldehyde (0.1 mM) for 5 min. Then, SQ was added and the solution stirred for 15 min. As seen in Figure 3, solution of the stick that was reacted with formaldehyde remained blue whereas a clear bleaching was observed for the untreated foil.

Additional experiments to test the possible use of **N2** nanoparticles for the chromogenic recognition of formaldehyde in gas phase were carried out. For this purpose, **N2** nanoparticles were directly exposed to an atmosphere containing different quantities of formaldehyde gas for 20 min. Then, the nanoparticles exposed to formaldehyde were suspended in PBS buffer, SQ was added and the intensity of the band at 642 nm measured after 15 min. As seen in Figure 4, a progressive increase of the absorbance at 642 nm upon increasing formaldehyde concentration was observed. Following this protocol a LOD of 17 ppm for the detection of formaldehyde in air was determined.

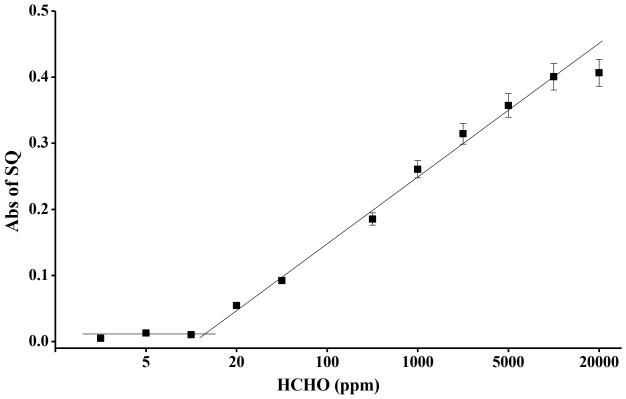


**Figure 4**. Absorbance at 642 nm for PBS (0.01 M, pH 7.0) suspensions of **N2** exposed to different formaldehyde gas concentrations (during 20 min) and after 15 min of SQ addition.

The mechanism of the formaldehyde-selective chromogenic response observed was assessed by $^{13}C$ MAS NMR measurements carried out with **N1** nanoparticles which were selected for the sake of clarity due to the absence of polyamine moieties. As seen in Figure 5 $^{13}C$ MAS NMR of **N1** showed two signals centered at 11.5 ($-Si-\underline{C}H_2-CH_2-CH_2-SH$) and 28.2 ppm (two carbons overlapped $-Si-CH_2-\underline{C}H_2-\underline{C}H_2-SH$). When **N1** reacted with formaldehyde the signal centered at 28.2 ppm splitted into two new signals at 23.4 and 33.9 ppm and a new carbon appeared at 70.0 ppm (see Figure 5). The signal centered at 70.0 ppm was ascribed to a carbon of the alkylthio methanol group. Similar information was obtained from NMR studies for **N2** (see Supporting Information).

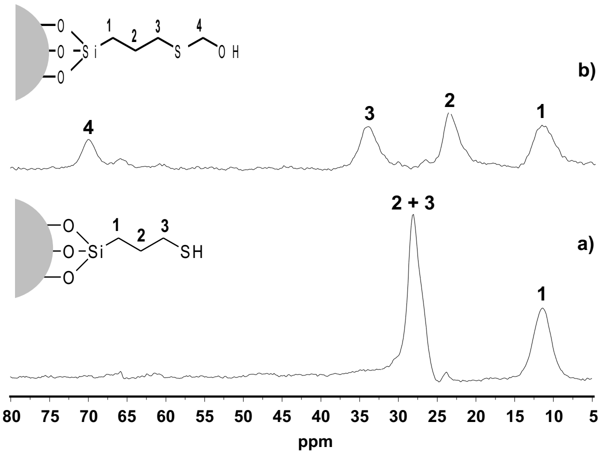


**Figure 5**. $^{13}$C MAS NMR spectra of **N1** nanoparticles (a) before and (b) after exposed to formaldehyde.

In summary, we have prepared silica nanoparticles (**N1** and **N2**) functionalized with thiols and polyamines for the chromogenic recognition of formaldehyde in water or in gas phase. The sensing mechanism arises from the formaldehyde-induced inhibition of a thiol-SQ reaction after reaction of formaldehyde with thiol groups. The sensing material **N2** showed LOD for formaldehyde of 36 ppb in water and 17 ppm in gas phase. The probe is very easy to prepare yet it is highly selective to the detection of formaldehyde.

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## References

[1] “Formaldehyde, 2-butoxyethanol and 1-tert- butoxypropan-2-ol” IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, **2006**, 88, 39.

[2] R. Baan, Y. Grosse, K. Straif, B. Secretan, F. El Ghissanni, V. Bouvard, L. Benbrahim-Tallaa, N. Guha, C. Freeman, L. Galichet, V. Collagno, *Lancet Oncol.*, **2009**, 10, 1143.

[3] J. Wang, L. Liu, S. -Y. Cong, J. -Q. Qi, B. -K. Xu, *Sens. Actuat. B*, **2008**, 134, 1010.

[4] “Formaldehyde (CASRN 50-00-0). Integrated Risk Information System,” Document 0419, U.S.-E.P.A., Washington, DC, USA, **1998**.

[5] V. J. Feron, H. P. Til, F. DeVrijer, R. A. Woutersen, F. R. Cassee, P. J. Van Bladeren, *Mutat. Res.*, **1991**, 259, 363.

[6] P. Yang, C. W. Lau, J. Y. Liang, J. Z. Lu, X. Liu, *Luminescence*, **2007**, 22, 473.

[7] X. O. Can, Z. Y. Zhang, X. R. Zhang, *Sens. Actuat. B*, **2004**, 99, 30.

[8] D. Bicanic, S. Persijn, A. Taylor, J. Cozijnsen, B. van Veldhuyzen, G. Lenssen, H. Wegh, *Rev. Sci. Instrum.*, **2003**, 74, 690.

[9] B. W. M. Moeskops, M. M. L. Steeghs, K. van Swam, S. M. Cristescu, P. T. J. Scheepers, F. J. M. Harren, *Physiol. Meas.*, **2006**, 27, 1187.

[10] O. Bunkoed, F. Davis, P. Kanatharana, P. Thavarungkul, S. P. J. Higson, *Anal. Chim. Acta*, **2010**, 659, 251.

[11] H. Ohata, M. Otsuka, S. Ohmori, *J. Chromatogr., Biomed. Appl.*, **1997**, 693, 297.

[12] Z. Li, L. K. Jacobus, W. P. Wuelfing, M. Golden, G. P. Martin, R. A. Reed, *J. Chromatogr. A*, **2006**, 1104, 1.

[13] D. Shi, L. Wei, J. Wang, J. Zhao, C. Chen, D. Xu, H. Geng, Y. Zhang, *Sens. Actuat. B*, **2013**, 177, 370.

[14] T. Itoh, I. Matsubara, W. Shin, N. Izu, M. Nishibori, *Sens. Actuat. B*, **2008**, 128, 512.

[15] K. Mitsubayashi, H. Matsunaga, G. Nishio, S. Toda, Y. Nakanishi, H. Saito, M. Ogawa, K. Otsuka, *Sens. Actuat. B*, **2005**, 108, 660.

[16] M. Lofdahl, C. Utaiwasin, A. Carlsson, I. Lundstrom, M. Eriksson, *Sens. Actuat. B*, **2001**, 80, 183.

[17] Y. Zhu, H. Li, Q. Zheng, J. Xu, X. Li, *Langmuir*, **2012**, 28, 7843.

[18] C. Heil, G. R. Windscheif, S. Braschohs, J. Florke, J. Glaser, M. Lopez, J. Muller-Albrecht, U. Schramm, J. Bargon, F. Vogtle, *Sens. Actuat. B*, **1999**, 61, 51.

[19] P. Jacquinot, A. W. E. Hodgson, B. Muller, B. Wehrli, P. C. Hauser, *Analyst*, **1999**, 124, 871.

[20] Z. Li, Z. Xue, Z. Wu, J. Han, S. Han, *Org. Biomol. Chem.*, **2011**, 9, 7652.

[21] W. Zhoua, H. Dong, H. Yan, C. Shi, M. Yu, L. Wei, Z. Li, *Sens. Actuat. B.*, **2015**, 209, 664.

[22] T. F. Brewer, C. J. Chang, *J. Am. Chem. Soc.*, **2015**, 137, 10886.

[23] a) S. El Sayed, C. de la Torre, L. E. Santos-Figueroa, C. Marín-Hernández, R. Martínez-Máñez, F. Sancenón, A. M. Costero, S. Gil, M. Parra, *Sens. Actuat. B.*, **2015**, 207, 987. b) S. El Sayed, L. Pascual, A. Agostini, R. Martínez-Máñez, F. Sancenón, A. M. Costero, M. Parra, S. Gil, *ChemistryOpen*, **2014**, 3, 142. c) S. El Sayed, C. de la Torre, L. E. Santos-Figueroa, R. Martínez-Máñez, F. Sancenón, M. Orzáez, A. M. Costero, M. Parra, S. Gil, *Supramol. Chem.*, **2015**, 4. 244. d) A. Agostini, I. Campos, M. Milani, S. El Sayed, L. Pascual, R. Martínez-Máñez, M. Licchelli, F. Sancenón, *Org. Biomol. Chem.*, **2014**, 12, 1871.

[24] a) E. Climent, A. Agostini, M. E. Moragues, R. Martínez-Máñez, F. Sancenón, T. Pardo, M. D. Marcos *Chem. Eur. J.* **2013**, 19, 17301. b) E. Climent, A. Martí, S. Royo, R. Martínez-Máñez, M. D. Marcos, F. Sancenón, J. Soto, A. M. Costero, S. Gil, M. Parra, *Angew. Chem. Int. Ed.*, **2010**, 49, 5945. c) S. El Sayed, M. Milani, M. Licchelli, R. Martínez-Máñez, F. Sancenón, *Chem. Eur. J.*, **2015**, 21, 7002. d) S. El Sayed, C. Giménez, E. Aznar, R. Martinez-Manez, F. Sancenón, M. Licchelli., *Org. Biomol. Chem.*, **2015**, 13, 1017.

[25] a) M. Sugawara, K. Kojima, H. Sazawa, Y. Umezawa, *Anal. Chem.*, **1987**, 59, 2842. b) H. Aoki, K. Hasegawa, K. Tohda, Y. Umezawa, *Biosens. Bioelectron.*, **2003**, 18, 261.

[26] M. Montalti, L. Prodi, N. Zaccheroni, G. Falini, *J. Am. Chem. Soc.*, **2002**, 124, 13540.