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First colorimetric sensor array for the identification of quaternary ammonium salts

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ABSTRACT

A colorimetric sensor array based on supramolecular host–guest complexes has been developed for the identification and quantification of quaternary ammonium salts (QAS). QAS are ubiquitous undesirable compounds for which the identification of the individual compounds is not trivial and needs instrumental techniques. The sensor array developed by us is constituted by host–guest complexes formed by the inclusion of tricyclic basic dyes such as proflavine, acridine orange, thionin, and methylene blue inside the hollow space defined by cucurbit[*n*]urils with $n = 7$ and 8. The operation of the sensor array has been demonstrated by differentiating 14 quaternary ammonium salts, some of them differing by a single carbon atom in the alkyl group. The detection limit concentration was 10^{-5} M and the system can also be used to quantify the concentration of the quaternary ammonium ion.

Quaternary ammonium salts (QAS) find massive application as surfactants, particularly in domestic detergent formulations and cleaning products. Other common uses of QAS are as algaecides in pools, as antibacterial agents, and as disinfectants. These compounds are recommended sanitizers in food industry to control *Listeria monocytogenes*, yeasts, molds, and other pathogenous microorganisms.[1] There is a wide range of other relatively minor uses of QAS that expands from electrolytes, electroplating compounds, phase transfer agents, ionic liquids, and templates. Most of the applications of this class of nitrogenated organic compounds involve their direct use in aqueous solutions or, indirectly, their disposal and washouts end in waste waters, producing undesirable contamination. QAS, when in concentrations above a certain limit, can play adverse effects in humans and their presence in food should be avoided. Considering the wide use of QAS and their potential negative effects, there is an increasing attention for their detection as part of environmental monitoring, water analysis, and food quality control. Therefore, it is of interest to develop simple chemical sensors that not only can detect this class of compounds, but also can identify their structure, and quantify their concentration. Sensor systems that are able to give fast and reliable results such as chemical sensor arrays represent one of the rapidly emerging and exciting fields of non-classical analytics.[2] Colorimetric chemosensors for the detection of organic compounds are very practical, rapid, and inexpensive techniques that do not need specially trained personnel or dedicated equipment to use them. Despite the importance and ample use of QAS, the number of analytical techniques applicable to characterize them is very limited, particularly compared to amines and other basic nitrogenated compounds. When the counter ion is devoid of acid–base properties, QAS are pH neutral and apart from the positive charge there are not general structural features such as lone electron pairs and hydrogen bonds that can be used to design specific sensors. Few test methods have been proposed to determine the concentration of QAS either in water[3,4] or in more complex media such as food[1,4,5] and surfactants.[6] Generally, detection and quantification of QAS can be made by chromatography,[6,1] potentiometric[7] or spectroscopic techniques, but these instrumental analytical tools require specific equipments, they are time consuming and need sample pre-treatments. Reverse phase liquid chromatography has been applied to QAS detection in milk.[1] On the other hand, QAS are indirectly titrated sometimes by determining the concentration of the corresponding counter ion. This method is particularly useful when the accompanying anion is a halide or an acid or a base.[8,9] Obviously, this approach, while valid in some cases, suffers from a lack of general applicability because it is not based on the direct detection of the QAS. There are scarce precedents in the literature describing the direct detection of QAS based on colorimetric methods. For example,[3] QAS concentration of cetyltrimethylammonium (CTMA) bromide, tetradecyltrimethylammonium (TDTMA) bromide, and octadecyltrimethylammonium (ODTMA) bromide is determined by titration with sodium tetraphenylboron solution and with methyl yellow as an indicator. Some of the colorimetric methods exploit the ability of these compounds to act as phase-transfer catalysts. Thus, the influence of the presence of quaternary ammonium ions on the partition of a dye between an aqueous and an organic phase is the property used to detect them. However, this methodology suffers from the interference of other phase-transfer agents and also from the fact that quaternary ammonium

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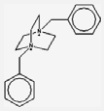
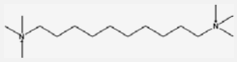
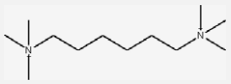
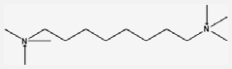
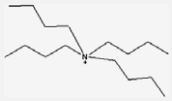
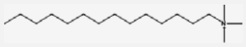
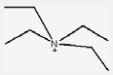
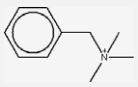
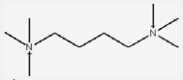
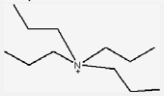
Table 1
Structures, names, and molecular formulae of the 14 QAS used to test the performance of the sensor array with their corresponding structure

Short	Molecular formula	Structure	Full name
CTMA	$C_{19}H_{42}N$		Cetyltrimethylammonium
DABENZ	$C_{20}H_{26}N_2$		1,4,-Dibenzyl-4-aza-1-azonia-bicyclo[2.2.2]octane
DABMET	$C_8H_{18}N_2$		1,4-Dimethyl-1,4diazoniumbicyclo[2.2.2]octane
DDTMA	$C_{15}H_{34}N$		Dodecyltrimethylammonium
DMT	$C_{16}H_{38}N_2$		Decamethonium-*N*,*N*,*N*,*N*′,*N*′,*N*′-hexamethyl-decamethylenediammonium
HMT	$C_{12}H_{30}N_2$		Hexamethonium-*N*,*N*,*N*,*N*′,*N*′,*N*′-hexamethyl-hexamethylenediammonium
OMT	$C_{14}H_{34}N_2$		Octamethonium-*N*,*N*,*N*,*N*′,*N*′,*N*′-hexamethyl-octamethylenediammonium
TBA	$C_{16}H_{37}N$		Tetrabutylammonium
TDTMA	$C_{17}H_{38}N$		Tetradecyltrimethylammonium
TEA	$C_8H_{20}N$		Tetraethylammonium
TMA	$C_4H_{12}N$		Tetramethylammonium
TMB	$C_{10}H_{16}N$		Benzyltrimethylammonium
TMT	$C_{10}H_{26}N_2$		Tetramethonium-*N*,*N*,*N*,*N*′,*N*′,*N*′-hexamethyl-tetramethylenediammonium
TPA	$C_{12}H_{28}N$		Tetrapropylammonium

ions of short alkyl chains do not act as phase-transfer catalysts. In addition, detection based on phase transfer of a dye does not allow to identify unequivocally the chemical structure of the QAS. Other colorimetric protocols are based on the precipitation of an anionic dye, such as eosin, due to the formation of an insoluble salt by ion pairing with quaternary ammonium ions. This procedure using eosin as an indicator has been proposed to detect and quantify quaternary ammonium ions in milk with a detection limit of 5 ppm.[5,9,10] Colorimetric test papers are commercially available to measure the strength of sanitizer solutions and thus to detect quaternary ammonium ions such as alkyldimethylbenzylammonium (benzalkonium bromide),[11–13] and didecyl dimethyl ammonium,[12] in cooking tools and kitchens.[14] However they do not give individual response for different QAS; for example, benzalkonium bromide, CTMA bromide, hexadecylpyridinium chloride, dodecyltrimethylammonium (DDTMA) bromide, and ODTMA chloride will all turn a yellow–green test strip into turquoise-blue as indicated by the provider.[13] The present situation is that there are no available colorimetric chemosensors that are able to identify the individual structure of various quaternary ammonium ions in water. The advantage of sensor arrays in terms of simplicity and accuracy led us to evaluate the potential of our recently presented[15] sensor array based on supramolecular host–guest complexes for the detection and identification of QAS in aqueous media. The results obtained with 14 different QAS (see Table 1) show that our sensor array is particularly suited to detect and identify this type of elusive chemical compounds.

Most approaches on chemical sensing remain largely based on the design of selective sensors for individual organic compounds, requiring dedicated synthesis while frequently showing a very limited solubility in water.[16] On the contrary, we have shown that our system[15] based on the colorimetric response of supramolecular

host–guest complexes is very simple and gives immediate, accurate, and trustworthy results. In addition, no calibration and complicated chemometric procedures are required.

Concerning our sensor array, despite the individually low selectivity of each component of the system, the cross-analysis is of outstanding capability. Such impressive performance is achieved owing to a set of non-specific, but cross-effective basic dyes and organic capsules. This is illustrated by the perfect discrimination of 14 different QAS. The sensor array is able to discriminate among QAS showing only very subtle dissimilarities. Such strength is mainly due to the diversity of interactions between the analytes and the host–guest complexes. The colorimetric test described here is based on the positive charge borne by the quaternary ammonium ion and on the size and polarity of the overall molecule to differentiate among different quaternary ammonium ions. Specifically our chemosensor is based on the influence of quaternary ammonium ions on the host–guest complex of cucurbit[n]urils, more precisely CB[7] and CB[8], with basic dyes,[17] namely proflavine (PF), oxonine (OX), pyronine (PY), methylene blue (MB), thionine (TH), and acridine orange (AO). Due to the affinity of the portal carbonyl groups of CBs for positively charged organic species, QAS interact with CBs and disturb the dye–CB complex leading to changes in color or fluorescence emission. The binding of the analyte to the receptor affects the host–guest complex triggering a response which is reported through colorimetric and fluorimetric color changes. As an example Figure 1 shows the response of the 14 QAS under study for the host–guest complex of PF with CB[7] and CB[8]. Thus, processing the colorimetric–fluorimetric variations through simple Euclidian distances calculation inside the Red–Green–Blue (RGB) space allows a perfect identification and discrimination.

The sensor array in which this application of identifying QAS is based has been already reported by us for the detection of amines.[15] In a 3×7 well plate, each of the rows receives one of the six common over-the-counter tricyclic basic dyes, while only two host capsules (CB[7] and CB[8] (among the seven employed in our precedent work)),[15] and water are distributed in columns. The capsule-free column provides a reference that shows the relevance of the complexation between capsules and dyes in the discrimination process. Multi-well plates are identically prepared with 200 µl of water or capsule solution (1×10^{-4} M), and 70 µl of dye (3.86×10^{-4} M). Each of the plates is employed for one given QAS, each well being filled with 30 µl of analyte in aqueous solution producing the color alteration which is examined by placing the plates into a black chamber illuminated under 'white' (400–700 nm) or quasi monochromatic UV light (330 nm). When illuminating with UV light, the image is due to the fluorescence emission of the dyes.

For both types of illumination, a picture is taken with a CCD camera from which RGB values are extracted. Then, various statistical analyses of all collected color components are performed. Finally different algorithms,[18,19] such as classification trees and principal component analysis (PCA), are employed in order to highlight the colorimetric features that make each analyte unique. Other algorithmic approaches[18,20] such as support vector machine (SVM) and neural networks (NNs) could be employed, but the relative low number of wells needed to discriminate QAS makes these

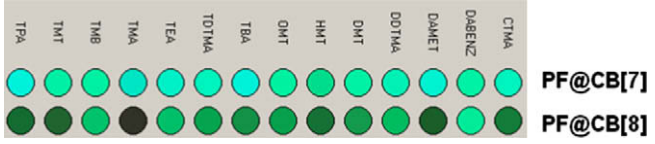


Figure 1. Colorimetric response of 14 QAS with PF@CB[7] or PF@CB[8] (line) at 10^{-3} M under UV light illumination. For QAS codes and structures see Table 1.

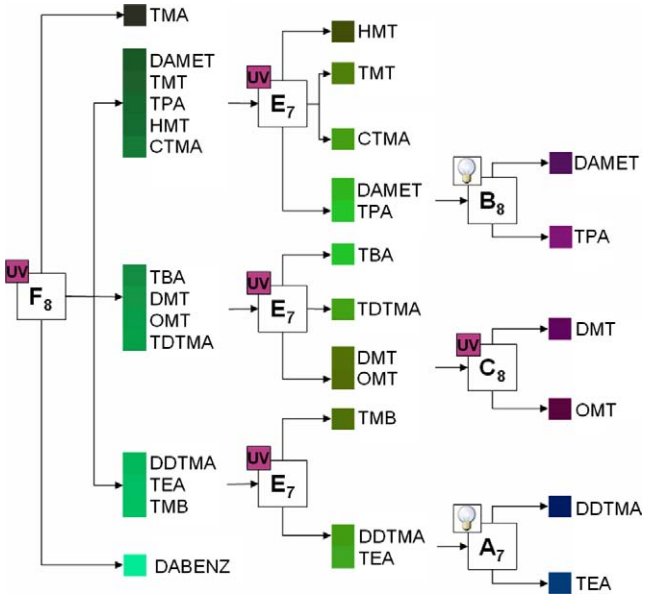


Figure 2. Example of discrimination tree where each node corresponds to a given complex, that is, the letter refers to the dye (A: MB, B: TH, C: OX, E: AO, F: PF), while the number in subscript corresponds to CB[n] with $n = \{7 \text{ or } 8\}$. In each node is reported the light, which is employed for the detection: either UV or 'white' light. The squares are painted with the observed color.

advanced techniques unnecessary, while the tree representation is preferred due to its obvious clarity. The specific response of the array for each compound at six different concentrations 10^{-x} M, with $x = [1–6]$ is digitalized.

Among the numerous possible sequences of wells allowing a perfect discrimination, the tree presented in Figure 2 is chosen as CTMA, DDTMA, TDTMA are discriminated after one single well observation. Note that TMA, TBA, TPA, and TEA are also discriminated by the first split as each compound belongs to separated leaves. Consequently, our sensor is able to discriminate and identify various QAS with the slightest structural changes, that is, a single carbon difference.

The response to each analyte varies in a certain range as a function of its concentration. Figure 3 shows the case of TMA and DABENZ with AO@CB[7] to illustrate the variations observed as a function of the concentration. It can be observed that overlapping in the images of different analytes may occur, usually either when

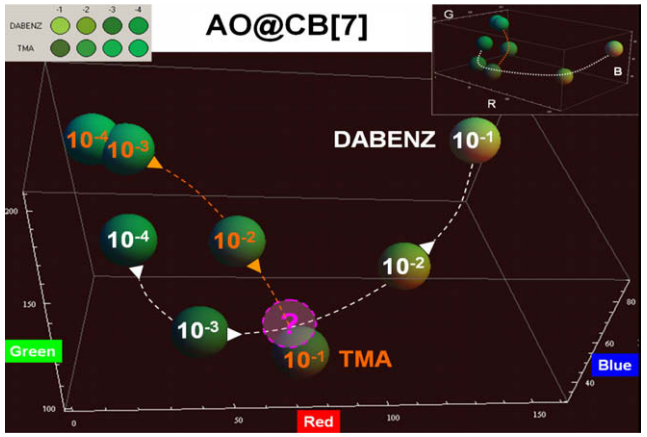


Figure 3. Variation of the concentration of DABENZ and TMA with AO@CB[7]. The inset shows the digitalized colors of AO@CB[7] at concentrations ranging from 10^x M, with $0 \leqslant x \leqslant -4$.

the concentration reaches a lower threshold (due to the fact that all the images, independently of the analyte, tend to converge to the images in the absence of analyte when the dilution is sufficiently high),or for a few cases where trajectories are crossed as pointed out in Figure 3. Under our operation conditions, we have been able to distinguish the presence of analytes for concentrations above 10^{-5} M. This sensitivity limit is certainly remarkable and outperforms the current colorimetric tests.

In conclusion, the above results show an original and innovative colorimetric sensor array for QAS in water based on a library built by combining a series of guest dyes with cucurbiturils. Taking into account the numerous potential applications, and also because of its simplicity and efficiency, the presented sensor array appears as very promising. As far as we know, this is the first sensor that is able to discriminate and identify various QAS.

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References and notes

1. Valladao, M.; Sandine, W. E. *J. Dairy Sci.* **1994**, *77*, 1509–1514.
2. Anslyn, E. V. *J. Org. Chem.* **2007**, *72*, 687; Wright, A. T.; Anslyn, E. V. *Chem. Soc. Rev.* **2006**, *35*, 14; Albert, K. J.; Lewis, N. S.; Schauer, C. L.; Sotzing, G. A.; Stitzel, S. E.; Vaid, T. P.; Walt, D. R. *Chem. Rev.* **2000**, *100*, 2595; Ciosek, P.; Wroblewski, W. *Analyst* **2007**, *132*, 963.
3. Narasimham, K. C.; Vasundara, S.; Udupa, H. V. K. *Analyst* **1972**, *97*, 260–262.
4. Furlong, T. E.; Elliker, P. R. *J. Dairy Sci.* **1953**, *36*, 225.
5. Miller, D. D.; Elliker, P. R. *J. Dairy Sci.* **1951**, *34*, 273–278.
6. Boccacci Mariani, M.; Milana, M. R.; Giamberardini, S.; Cavalli, S. *Chromatographia* **1993**, *36*, 362–364.
7. See ASTM Standard Test Method for QAS in Fabric Softeners. http://www.astm.org/standards/D5070.htm.
8. Flanagan, T. L., Jr; Drennen, T. J.; Goetchius, G. R. *Soap San. Chem.* **1948**, *24*, 163–165.
9. Wilson, J. B. *J. Assoc. Off. Agric. Chem.* **1946**, *29*, 311–327.
10. Wilson, J. B. *J. Assoc. Off. Agric. Chem.* **1948**, *31*, 480–484.
11. MicroEssential Laboratory QUAT Test paper Cat# QT-10. https://www.microessentiallab.com.
12. http://sciencelab.com.
13. http://www.galladechem.com.
14. See also http://allqa.com.
15. Montes-Navajas, P.; Baumes, L. A.; Corma, A.; Garcia, H. *Tetrahedron Lett.* **2009**, *50*, 2301–2304.
16. Potyrailo, R. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 702; Gale, P. A. *Acc. Chem. Res.* **2006**, *39*, 465; Kuswandi, B.; Nuriman; Verboom, W.; Reinhoudt, D. N. *Sensors* **2006**, *6*, 978.
17. Lagona, J.; Mukhopadhyay, P.; Chakrabarti, S.; Isaacs, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4844; Lee, J. W.; Samal, S.; Selvapalam, N.; Kim, H. J.; Kim, K. *Acc. Chem. Res.* **2003**, *36*, 621; Mock, W. L. In *Supramolecular Chemistry Ii—Host Design and Molecular Recognition*, Springer Verlag: Berlin, **1995**; Vol. 175, p 1.; Rudkevich, D. A. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 393; Fathallah, M.; Fotiadu, F.; Jaime, C. *J. Org. Chem.* **1994**, *59*, 1288; Montes-Navajas, P.; Teruel, L.; Corma, A.; Garcia, H. *Chem. Eur. J.* **2008**, *14*, 1762; Koner, A. L.; Nau, W. M. *Supramol. Chem.* **2007**, *19*, 55; Nau, W. M.; Mohanty, J. *Int. J. Photoenergy* **2005**, *7*, 133.
18. Baumes, L. A.; Serra, J. M.; Serna, P.; Corma, A. *J. Comb. Chem.* **2006**, *8*, 583–596; Serra, J. M.; Baumes, L. A.; Moliner, M.; Serna, P.; Corma, A. *Comb. Chem. High Throughput Screening* **2007**, 13–24; Corma, A.; Moliner, M.; Serra, J. M.; Serna, P.; Díaz-Cabañas, M. J.; Baumes, L. A. *Chem. Mater.* **2006**, *18*, 3287–3296.
19. Palacios, M. A.; Nishiyabu, R.; Marquez, M.; Anzenbacher, P. *J. Am. Chem. Soc.* **2007**, *129*, 7538–7544; Meier, M. A. R.; Schubert, U. S. *Chem. Commun.* **2005**, *36*, 4610–4612; Fernandez, Y. D.; Gramatges, A. P.; Amendola, V.; Foti, F.; Mangano, C.; Pallavicini, P.; Patroni, S. *Chem. Commun.* **2004**, 1650–1651; Wang, Z.; Palacios, M. A.; Zyryanov, G. V.; Montes, V. A.; Anzenbacher, P. *J. Am. Chem. Soc.* **2008**, *130*, 10307–10314.
20. Baumes, L. A.; Farruseng, D.; Lengliz, M.; Mirodatos, C. *QSAR Comb. Sci.* **2004**, *29*, 767–778; Klanner, C.; Farrusseng, D.; Baumes, L. A.; Lengliz, M.; Mirodatos, C.; Schüth, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 5347–5349; Baumes, L. A.; Moliner, M.; Corma, A. *QSAR comb. Sci.* **2007**, *26*, 255–272; Serna, P.; Baumes, L. A.; Moliner, M.; Corma, A. *J. Catal.* **2008**, *258*, 25–34.