



Research paper

Cyclodextrins enable indirect ultrasensitive Raman detection of polychlorinated biphenyls captured by plasmonic bubbles

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ABSTRACT

Capture, detection and removal of persistent organic pollutants (POPs) from water, air and soil are among the hot topics of research in environmental science.

Here we report the first example of indirect ultrasensitive detection of polychlorinated biphenyls in water, obtained by analysing the Raman signals of silver-cyclodextrin supracrystals resulting from drying-induced aggregation of plasmonic alginate bubbles. Principal component analysis allowed to extend the detection limit to the level of 1 ng/L, which is two orders of magnitude lower than that requested by current legislation.

The presence of persistent organic pollutants (POPs) in water, air and soil has a dramatic impact on ecosystems and human health [1]. Raman spectroscopy has been extensively investigated as an alternative or complementary tool to conventional, yet cumbersome, laboratory techniques, such as chromatography and mass spectrometry, as it provides the chemical fingerprint of POPs and can be easily implemented to the analysis of aqueous solutions because, unlike infrared spectroscopy, it is almost insensitive to water [2,3]. However, trace-level Raman detection of these types of molecular targets in aqueous matrices is usually hampered by their low Raman cross-section. The use of plasmonic metal nanoparticles allowed to exploit Surface Enhanced Raman Scattering (SERS) and extend the analytical capability of Raman-based assays to the level of single molecule, yet these impressive results have been reported only for organic dyes characterized by high Raman cross-section and optical absorption in resonance with the Raman laser source [4,5].

Novel strategies based on pre-concentrating the analytical target on SERS-active omniphobic substrates have been recently developed, in order to further increase sensitivity [6–8]. These methods are very promising for *ex-situ* Raman sensing. However, the development of

reliable probes capable of a simultaneous label-free detection and efficient removal of POPs under real working conditions is still an urgent and unmet goal [9]. We recently demonstrated that alginate-based hydrogels loaded with β -cyclodextrin-capped silver nanoparticles (Ag@ β -CD NPs) are efficient tools for encapsulation, detection and removal of different types of organic pollutants, including dyes and pharmaceutical compounds, without need of any microfluidic chip or superhydrophobic platforms [10]. The working principle of these plasmonic bubbles consists in the synergistic interaction of multiple components (Fig. 1). The silver nanoparticles are utilized for amplifying Raman scattering, while β -CD as silver nanoparticle stabilizers and molecular pan-specific receptors for a large variety of pollutants. Finally, alginate bubbles are environment-friendly, dispersible hydrogel capsules for encapsulating the SERS-active receptors and further capturing/preconcentrating the pollutant targets.

Here we explore the possibility to extend the application of these type of plasmonic bubbles to other classes of POPs, through a novel, radically different approach based on indirect Raman analysis.

In this work, the molecular targets are represented by polychlorinated biphenyls (PCBs), which have been recognized as very

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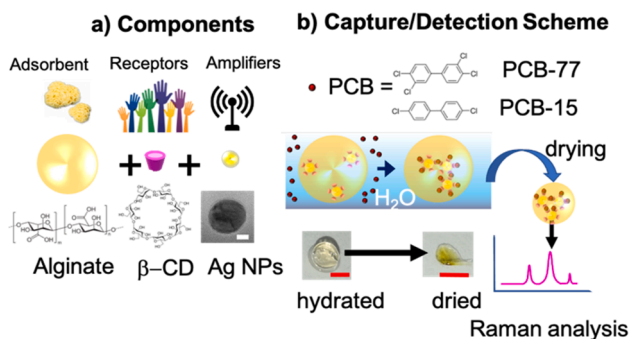


Fig. 1. A) Individual building blocks utilized to fabricate the plasmonic bubbles: adsorbent (alginate hydrogel bubbles), PCB-receptors (β -CD) and optical antennas for amplification of the Raman signal (Ag NPs, scale bar: 5 nm); b) scheme of capture and detection of PCBs. The optical images of plasmonic bubbles in hydrated and dried form are shown (Scale bars: 1 mm).

dangerous carcinogenic agents and endocrine disruptors even at level of traces [11] and are among the most challenging types of POPs in terms of detection. Due to the low solubility of PCBs in water, the possibility to achieve reliable detection at low concentration is very important. In drinking water, the maximum level of PCBs allowed by the U.S. Environmental Protection Agency (EPA) is 0.5 mg/L [12].

High sensitivity in PCB detection, up to 10^{-6} – 10^{-7} M, was reported for conventional plasmonic SERS substrates in the absence of receptors [13–17]. However these approaches can be utilized only in lab-scale experiments as they do not allow for a direct capture of PCBs in water under real world conditions. For example, Bantz and Haynes demonstrated the detection of PCBs by partition layer-modified SERS substrates [18]. This method relies on the spectral subtraction of signals of decanethiols utilized for coating Ag NPs before and after addition of PCB solutions, which exposes it to pitfalls due to the presence of other possible apolar interfering species.

Affinity agents can help addressing these issues. β -CDs have been widely utilized as abiotic receptors to bind a large variety of molecular guests, by taking advantage of their hydrophobic inner cavity, which makes them suitable to host any apolar moiety (e.g. phenyl groups, hydrophobic chains...) of a given molecular guest with a size compatible with that of the cavity (0.65 nm) [19]. For this reason, β -CDs have been successfully utilized as receptors for PCBs [10]. Depending on matching between the size of the β -CD cavity and that of a given PCB, the host-guest complexation energy can be slightly different, ranging from 20 to 40 Kcal mol⁻¹ in water solutions [20].

However, the SERS sensitivity of β -CD-functionalized plasmonic substrates towards PCBs has been limited to 10^{-4} – 10^{-5} M [21,22].

Here we aim at exploiting the pivotal role of β -CDs in inducing self-assembly of silver nanoparticles in response to analyte-receptor binding events, to create Ag@ β -CD supracrystals and aggregates able to keep the information of the presence of PCBs. β -CD-mediated self-assembly has been already utilized for controlling nanoparticle aggregation and for UV-Vis detection of analytes [23] but not for Raman sensing. In fact, most of the organic molecules, including PCBs, exhibit Raman signals that fall in the same spectral region (400–1800 cm⁻¹) of Raman modes originated from intermolecular interactions among the metal@ β -CD nanoparticles. Thus, at low concentration, the spectral features of the analyte are completely hidden by the Raman modes of the hybrid aggregates [21]. However, these Raman modes could be influenced by the presence of analytes and give rise to spectra that can be utilized for indirect sensing. We tested our hypothesis through preliminary experiments that compared the Raman spectra of tetrachlorobiphenyl (PCB-77) captured by plasmonic bubbles with or without β -CD receptors. Both types of bubbles were extracted from water contaminated by PCBs and dried at room temperature. All experimental details are reported in ESI 1. Upon drying, the bubbles shrink up to ~70% and their average

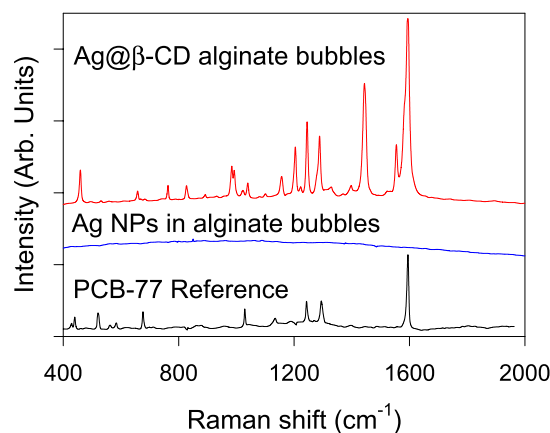


Fig. 2. Raman detection and analysis of the captured PCBs. Raman spectra of PCB-77 adsorbed from an aqueous solution at the initial concentration of 3.4×10^{-4} M by either Ag@ β -CD or β -CD-free plasmonic alginate dried bubbles. The reference spectrum is also shown for comparison.

weight is reduced by two orders of magnitude, from about 10 to 0.1 mg, which means that water contribute by 99% to the overall mass of the original bubble. As a result of drying, the silver nanoparticles are induced to aggregate.

Fig. 2 shows the Raman spectra of PCB-77 captured by soaking the plasmonic bubbles for 16 h in polluted aqueous solutions at a nominal concentration of 3.4×10^{-4} M, corresponding to 100 mg/L. The Raman spectra acquired from analogous bubbles made with naked Ag NPs (i.e. in the absence of β -CD receptors) do not show any signal associated to the presence of the PCB. On the other hand, the Raman spectra acquired from the Ag@ β -CD alginate bubbles contain the main spectral features of the pollutant, such as the stretching peaks of both the biphenyl rings around 1600 cm⁻¹, the stretching on bridge at 1294 cm⁻¹, C-H wagging at 1240 cm⁻¹, trigonal stretching ring at 1028 cm⁻¹ and C-Cl stretching and deformation ring modes at 1134 and 674 cm⁻¹. In comparison to the reference spectrum, we also observe the signal of the β -CD receptors [10], as well as extra Raman modes (see, for example the peak splitting in the 1570–1600 cm⁻¹ region) that suggest the formation of β -CD:PCB host-guest complex aggregates.

As shown in ESI 2, both types of plasmonic bubbles (with or without β -CD) exhibit a comparable adsorption capability. The slight increase in PCB absorption observed in β -CD-functionalized bubbles is not sufficient to justify such a remarkable difference in Raman response, which might originate from the key role of β -CD in driving the formation of silver aggregates with an efficient distribution of the plasmonic hot-spots. The fact that these signals were only observed in this concentration range, which corresponds to a nearly-stoichiometric ratio between host and guest molecules, confirms previous computational studies on the formation of β -CD-PCB complexes [20].

On the other hand, higher concentration (3.4×10^{-3} M) of the analyte did not result in any significant enhancement of the Raman spectra, which are similar to that of the PCB-77 reference solutions (ESI 3-1). This is due to the fact that SERS is a surface effect, which is maximized only when the analytical targets are in close proximity to the plasmonic metal nanoparticles and typically vanishes out for distances exceeding 5–10 nm. As expected, at low concentration ($<3.4 \times 10^{-5}$ M), direct detection of the PCB Raman modes is hampered by the high density of Raman modes resulting from aggregated Ag@ β -CD nanoparticles, which are not observed in either β -CD-free or pure alginate bubbles (Fig. 3a). The strong influence of non-covalent interactions on the Raman spectra of organic and hybrid organic-inorganic crystals has been extensively investigated in previous studies [24]. In particular, Loftsson and co-workers and Baglioni and co-workers elucidated the complexity of β -CD crystallization [25,26]. For sensing purposes, it would be important to evaluate whether these aggregates can be

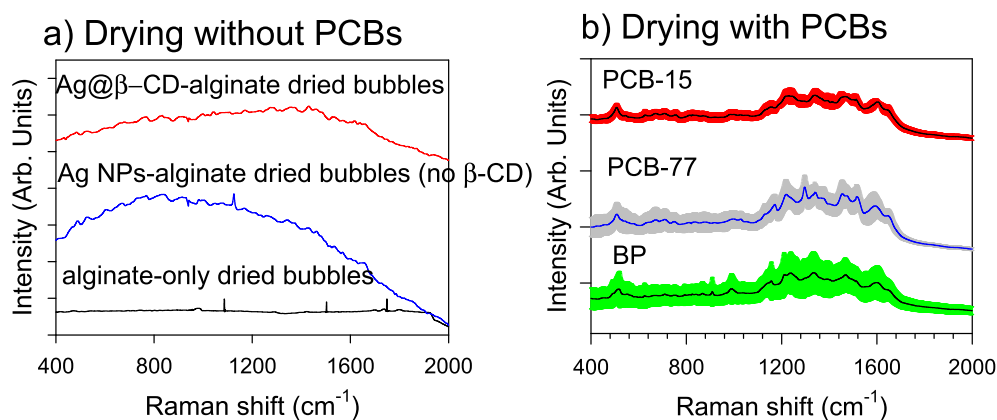


Fig. 3. a) Examples of Raman spectra of pure alginate, and β -CD-free alginate and Ag@ β -CD alginate dried bubbles obtained from water without PCBs. b) Examples of Raman spectra obtained from Ag@ β -CD alginate bubbles that have been extracted and dried from water containing BP, PCB-77 and PCB-15. The plasmonic bubbles were soaked for 2 weeks in PCB solutions (10 μ g/L). The continuous line represents the averaged spectrum, the shaded contour is formed by standard deviation of the spectra (an enlarged view is shown in Fig. ESI 3.4).

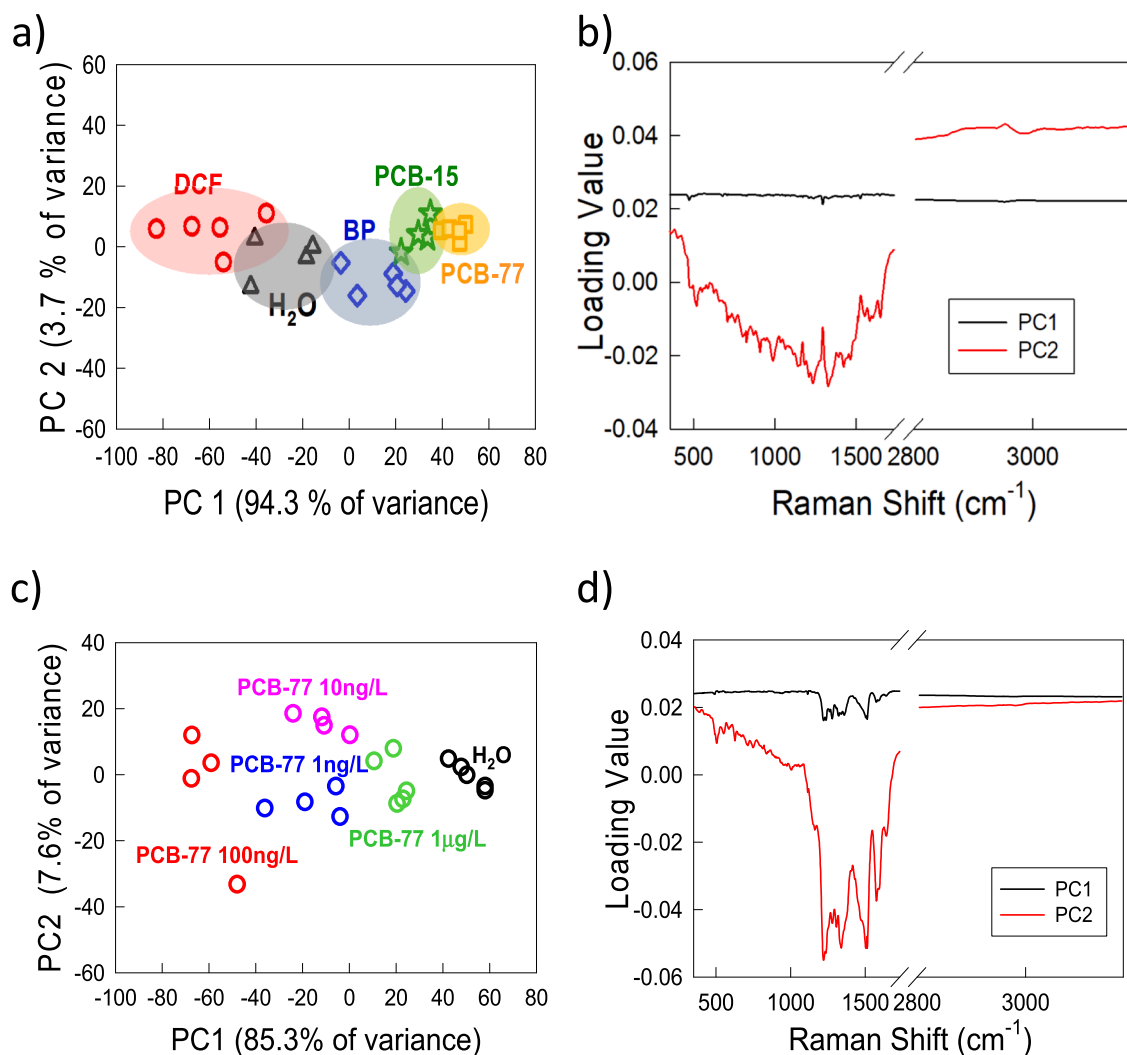


Fig. 4. a) PCA score plot and b) PCA loading plot based on the PC1 e PC2 components for the dataset of PCBs and other organic pollutants (DCF) captured by Ag@ β -CD plasmonic bubbles from 10 μ g/L solutions after 2 weeks; c) PCA score plot and d) PCA loading plot based on the PC1 e PC2 components for the dataset of Raman spectra of PCB-77 solutions at different concentration. Pure water is also reported for reference. The limit of detection is extended to 1 ng/L.

distinguished on the basis of the analytes that have or have not been captured and distinguish among different types of PCBs and between PCBs and other types of compounds captured by β -CD receptors. In order to investigate these points, in addition to PCB-77, other two different types of biphenyl compounds, *i.e.* non-chlorinated biphenyl (BP) and 1,4 dichlorobiphenyl (PCB-15), were analysed using the same

procedure. Fig. 3b shows examples of Raman spectra of the three different biphenyl compounds that have been captured by plasmonic bubbles after the same soaking time (two weeks) and at the same nominal concentration of the PCB-contaminated solution (10 mg/L). For simplicity, we report the averaged Raman spectra of the PCBs. The standard deviation is indicated by the shaded averaged

spectrum. At least 30 measurements per specimen have been carried at different soaking time (16 h, 4 days, 1, 2, 3 and 4 weeks). In general, at any given soaking time the spectra of the different biphenyl compounds exhibit the Raman modes of β -CDs, with variations of intensity and positions that reflect their local order of aggregation.

A direct comparison of Fig. 3 a and b shows that the Raman spectra of Ag@ β -CD aggregates either in the presence or absence of PCBs are significantly different. On the other hand, the spectra of Ag@ β -CD aggregates soaked in solutions with different types of PCBs are quite similar and their distinction is not trivial, as the PCB-specific Raman modes are not detectable and information about their presence and identity is convoluted in the signals of the β -CD aggregates. For this reason, in order to assess the applicability of plasmonic bubbles for a fast and reliable detection of PCBs and, in general, organic pollutants, at very low concentration, we processed the Raman data through principal component analysis (PCA). PCA is a well-known chemometric technique utilized to extract few variables from a high dimensional data set and visualize them in a lower dimensional space of uncorrelated variables, which are linear combinations of the original ones, the so-called Principal Components (PCs) [27]. This type of multivariate analysis is particularly useful to disentangle the most significant information contained in the spectra. Fig. 4a shows the results of PCA on Raman spectra acquired from Ag@ β -CD plasmonic bubbles that have been soaked in solutions containing PCB-15, PCB-77, BP and diclofenac (DCF) in the low concentration range, as well as in non-contaminated mineral water. PCA operates a clear distinction among the samples. In particular, DCF is clearly separated from biphenyl compounds, which are in turn distinguished on the basis of the number of chlorine atoms. Moreover, both types of POPs (biphenyls and diclofenac) are distinguished from mineral water. This approach allows to take advantage of indirect information from the Raman spectra of Ag@ β -CD nanoparticle aggregates to rapidly detect the presence of different POPs. Fig. 4b shows the evaluation of the detection limit for PCB through PCA in a low concentration range (1 mg–1 ng/L). PCA enabled to sort data in distinguishable groups. This strategy allows for a reliable detection of PCBs from aqueous solutions in the order of 1 ng/L, a concentration that is two orders of magnitude lower than the EPA limit (0.5 mg/L) [12].

In summary, this study shows that the Raman modes of β -CD receptors coupled to Ag NPs in dried plasmonic bubbles containing low concentration (from mg/L to ng/L) of PCBs can be differentiated from those of reference, pollutant-free bubbles. Moreover, different types of PCBs can be distinguished on the basis of PCA analysis. Further differentiations between the Raman spectra of PCB-loaded and bubbles carrying pharmaceutical compounds were also assessed. These experiments suggest that, at low concentration, all information about the identity of different analytes is encoded in Raman spectra of the Ag@ β -CD aggregates and can be revealed through this indirect approach. The origin of the different, non-covalent interactions between the analytes and Ag@ β -CD nanoparticles, which occur during complexation and drying, is still unclear and deserves further investigation. These studies are challenging and could include the use of cryo-TEM and synchrotron radiation techniques to characterize the hybrid aggregates. In fact, conventional TEM analysis does not allow to include alginate bubbles and gives rise to artifacts.

A hypothesis is that small amounts of PCBs might be sufficient to reduce the number of water molecules associated with the β -CD receptors, with direct consequences on the non-covalent interactions that drive the drying-induced aggregation of Ag@ β -CD nanoparticles.

However, from a sensing viewpoint, a full understanding of the mechanism of aggregation is not mandatory at this stage of the research, as the significance of the experiments has been assessed by PCA, which enabled to manage the complexity and variability of Raman data at low concentration ranges, sorting out similar spectra originated from different analytes. Notably, in the case of PCBs investigated in the present work, the limit of detection has been lowered by two orders of magnitude with reference to the current legislation limits. The concept

of indirect Raman detection is quite general and versatile. It does not need of using any dyes, labels or Raman reporters and could be extended and suitably adapted to the detection of many other target species by means of novel strategies of sensing that have been recently developed [28–33]. Moreover, it offers a large variety of applications that are not limited to environmental analysis and remediation, but can be extended to forensics, medicine and, in general, molecular diagnostics.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cplett.2021.138674>.

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