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Nanoscale Supramolecular Probes for the Naked-Eye Detection of Illicit Drugs

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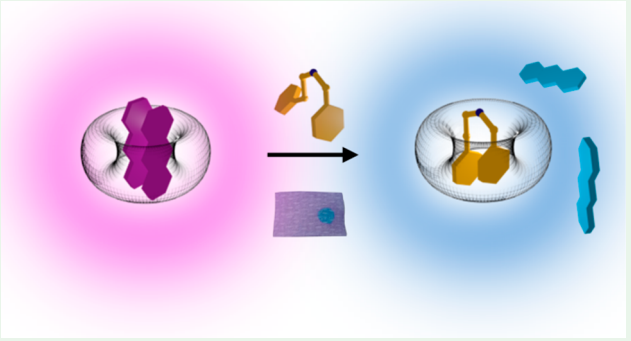
ABSTRACT: The identification of psychoactive substances, in particular of designer drugs, on the site of their discovery is crucial to contrast the diffusion of drugs of abuse. We report here the first example of a nanoscale colorimetric probe, based on the nanoconfinement of a tricyclic dye and the target analytes in the cavity of cucurbit[8]uril. The probe selectively responds to *N*-(2-methoxybenzyl)phenethylamines, with a limit of detection of 3 μM. The sensing system can be deposited on paper, thus obtaining a colorimetric strip test capable of discriminating illegal drugs from other substances of common use.



KEYWORDS: *designer drugs, nanoscale probes, nanoconfinement, indicator displacement assay, paper test*

The diffusion of new psychoactive substances has been continuously increasing in the past decade. Every year, about 50 drugs are detected for the first time in Europe.[1] These substances are often obtained by simple modifications of known drugs and for this reason are named *designer drugs*.[2] They represent a relevant threat because when they first appear on the market, they are not illegal and are difficult to identify with standard analytical methods. In this work, we focused our attention on *N*-(2-methoxybenzyl)phenethylamines (NBOMes). These are powerful 5-HT_{2A} receptor agonists[3] belonging to the same chemical class (psychedelics) as lysergic acid diethylamide (LSD). Recently introduced as recreational drugs, they can produce relevant adverse effects[4,5] and, in selected cases, fatal ones.[6] Risks are increased by the high potency. Indeed, typical reported doses reach 1200 μg, but depending on the administration mode, as little as 50−200 μg is effective.[7] These amounts are difficult to be precisely dosed by common users, and the possibility of overdose is relevant.

Even if other approaches have been proposed,[8−13] the most used detection method for designer drugs is chromatography coupled to mass spectrometry (MS).[14] Analyses of NBOMes have been performed using high-performance liquid chromatography (HPLC)−MS/MS,[15] ultra-HPLC (UHPLC)−MS/MS,[16] gas chromatography (GC)−MS,[17] and PSI-MS.[18] In addition, attenuated-total-reflectance Fourier transform infrared[19] or electrochemical methods[20,21] have been used. All of these techniques require nonportable and expensive instrumentation, sample pretreatment, and well-trained operators, thus limiting the possibility of high-throughput or on-site identification. Presumptive tests of common use (i.e., Marquis, Mecke, and Mandelin among the others) work as well on NBOMes,[22] but they must be used in combination to allow identification, and their interpretation remains user-dependent and often misleading. Moreover, a relatively large amount of substance is needed (milligrams), and the reagents used are harmful chemicals that cannot be handled by untrained personnel.

For these reasons, simple colorimetric detection kits would be of great interest. Recently, a hybrid organic−inorganic nanodevice that uses the 5-HT_{2A} receptor has been developed for the fluorogenic detection of 25I-NBOMe,[23] but to the best of our knowledge, no fully chemical methods have been developed so far for the quick detection of NBOMes.[24]

During the search for a solution to this problem, the peculiar structure of NBOMes attracted our attention. They feature two aromatic moieties connected to an amino group, while most other designer drugs (amphetamines, methamphetamines, phenethylamines, and cathinones) have a single aromatic residue.

Starting from this observation, our idea was to exploit nanoconfinement to obtain target selectivity and color variation of the sample. We reasoned that a nanosized host could act as a selective receptor for NBOMes by encapsulating in the cavity both aromatic moieties (Figure 1). Cucurbiturils

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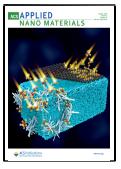

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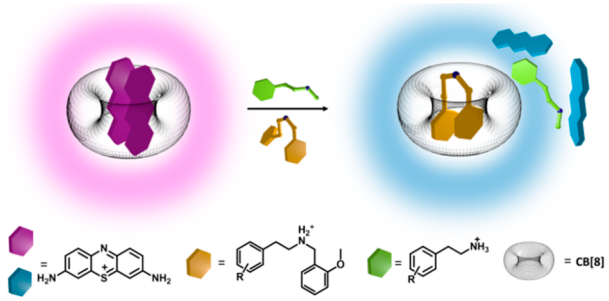

Figure 1. Scheme of the indicator displacement essay approach used in this paper. On the left, two thionine (TH) molecules are hosted as dimers inside the CB[8] cavity. The complex TH_2·CB[8] gives the solution a purple color. When analytes are added, NBOMes can disrupt the TH_2·CB[8] complex with a remarkable selectivity, forming the 1:1 complex CB[8]·NBOMe. The TH molecules that at this point are free give a blue color to the solution.

are well-studied hosts for amphiphilic organic cations and have been used for the recognition of phenethylamine derivatives.[10,25] In particular, cucurbit[8]uril (CB[8]; Figure 2) has a

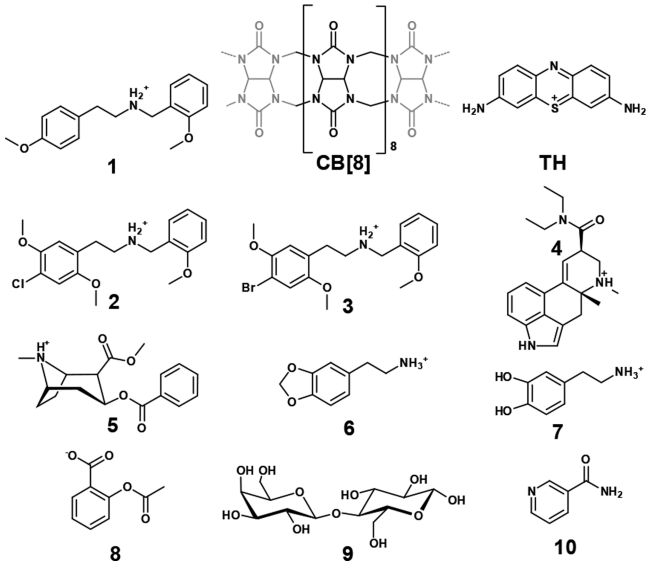

Figure 2. Chemical structures of CB[8] and the analytes used in this work.

strong preference toward the inclusion of two aromatic guests in its large cavity[26] and the ability to selectively form 1:1 inclusion complexes with dibenzyl-substituted amines.[27] This nanoconfinement ability can be exploited both to achieve selectivity, because only a large guest will be able to efficiently fill the nanometer-sized cavity, and to generate a signal, because the forced proximity of two dye molecules modifies their electronic properties. Indeed, CB[8] was used by Garcia et al.[28] for the colorimetric detection of γ-hydroxybutyric acid. We, hence, decided to explore the design of a CB[8]-based selective nanosensor for the detection of NBOMes.

As a first step, we confirmed the ability of CB[8] to bind NBOMes. To enable detailed studies, which are limited by restrictions on the purchase of psychoactive substances, we synthesized the model compound **1** (F-NBOMe; Figure 2) as a structural analogue of NBOMes devoid of psychotropic effects. The affinity of CB[8] for **1** was investigated by ^{1}H NMR titration (Figure 3). Several effects were observed upon the

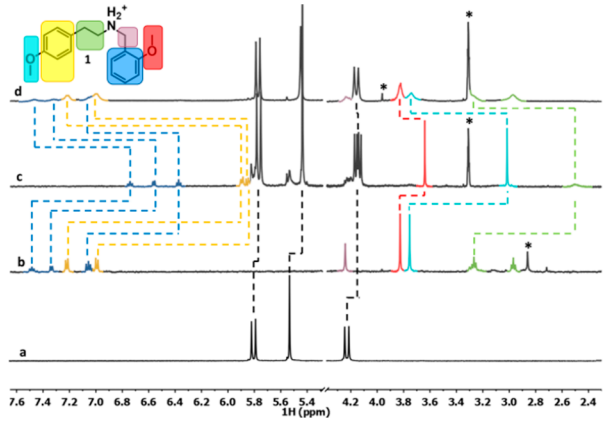

Figure 3. (a) ^{1}H NMR spectrum of CB[8]. (b) ^{1}H NMR spectrum of **1**. (c) ^{1}H NMR spectrum of a mixture of CB[8] and a substoichiometric amount of **1** added. (d) ^{1}H NMR spectrum of CB[8] in the presence of excess of **1**. All spectra are recorded at 500 MHz in D_2O (p*D* = 5.5, acetate buffer). Asterisks denote unknown impurities and solvent isotopic impurities.

addition of increasing amounts of **1** to a solution of CB[8]. When less than 1 equiv of **1** was added, a new set of signals appeared, in a regime of slow exchange with free CB[8] (Figure 3c). Some of these signals could be assigned to CB[8] in the inclusion complex. They were slightly downfield with respect to those of free CB[8], and the signal at 4.1 ppm was split into two sets (Figure 3, black lines). The remaining signals were produced by encapsulated **1**, again downfield-shifted with respect to the free molecule. In particular, a relevant 1.3 ppm shift was observed for the signals produced by the phenethyl residue (Figure 3, yellow signals). These effects strongly suggested coencapsulation of both the benzyl and phenethyl moieties in the CB[8] cavity. When an excess of **1** was added (Figure 3d), all of the signals underwent a progressive broadening. Chemical shifts of the CB[8] signals were almost unaffected. On the other hand, the signals of encapsulated **1** progressively disappeared, and a new set of broad signals from **1** appeared at chemical shift values similar to those of a free molecule (Figure S15). Hence, in these conditions, a 2:1 complex in fast exchange with free **1** is likely the prevalent species.

A similar behavior was observed for the 25C-NBOMe molecule (**2**), even if the small amount of compound available prevented us from a detailed investigation (Figure S16). The formation of 1:1 encapsulation complexes of **1** and **2** with CB[8] was confirmed by electrospray ionization mass spectrometry (ESI-MS) experiments (Figures S18 and S26). In the case of **1**, also traces of the 2:1 complex could be detected (Figure S20).

To gain further insight into the difference of the complexation capability of CB[8] toward different substances of abuse, we used isothermal titration calorimetry (ITC) to measure the affinity constants for analytes **2** and **4**–**6** (Figures S10–13 and Table S1). Results confirmed the proposed complexation mode (the formation of 1:1 and 2:1 complexes was determined for **2** and **6**, while in the case of **4** and **5**, only 1:1 complexes were detected) and the greater affinity of CB[8] for NBOMes. The only interferent with similar affinity is cocaine (**5**). However, simulations performed with the obtained affinity values (Table S1) at different CB[8]/analyte ratios confirmed that the fraction of **2** encapsulated by the cavitand is

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significantly greater than that in the case of the other analytes (Table S2).

Comforted by the facts that CB[8] was effective in coencapsulating both of the NBOMes aromatic moieties and that nanoconfinement generates a difference in the affinity for the different analytes, we proceeded to assess the ability of an inclusion complex of CB[8] with an environmentally sensitive dye to signal the presence of NBOMes according to the indicator displacement approach (Figure 1). We selected thionine acetate (TH; Figure 2), a cheap, not harmful, and commercially available blue dye that is reported to undergo pronounced absorption changes upon inclusion in CB[8].[29] Indeed, when free in solution at pH = 5.5 and 10 μM concentration, its absorption spectrum featured, in the visible region, a main band at 599 nm accompanied by a shoulder at 558 nm (Figure 4). The addition of CB[8] caused a blue shift

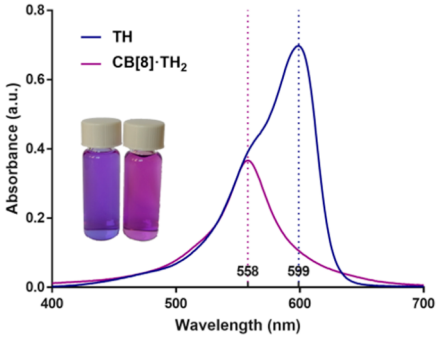

Figure 4. UV-Vis spectrum of 20 μM TH in buffered water (acetate buffer, pH = 5.5, blue solution, and λ_{MAX} = 599 nm) and of 10 μM CB[8]·TH_2 in buffered water (acetate buffer, pH = 5.5, purple solution, and λ_{MAX} = 558 nm).

of the main band and shoulder to 557 and 521 nm, respectively (Figure 4), likely a result of the formation of a plane-to-plane dimer (H-dimer) inside the cavity.[30] The appearance of the shorter-wavelength band at the expense of the longer-wavelength one can be detected by the naked eye as a change of color from blue to violet (Figure 4). The absorption intensity at 599 nm linearly decreased by increasing the concentration of CB[8] to sharply level off after the addition of 0.5 equiv of cucurbituril, suggesting the formation of a TH_2·CB[8] species with high affinity (Figure S4). [The formation of the inclusion complexes was further investigated by ^{1}H NMR and ESI-MS, confirming the presence of both TH_2·CB[8] and TH·CB[8] (Figures S14 and S17).]

Subsequently, we tested the ability of the TH_2·CB[8] complex to act as a colorimetric chemosensor for NBOMes. A titration experiment (Figure 5) was performed by adding increasing amounts of a F-BOMe solution (in 1:1 water/methanol) to TH_2·CB[8] (5 μM) in buffered water (acetate buffer, pH = 5.5). [The addition of methanol during the titration experiment, as well as the dilution of TH_2·CB[8], does not affect the complexation equilibrium (Figures S5–S8).] Remarkably, we observed the appearance of the absorption band at 599 nm, relative to free TH, even at the lowest concentration of **1** added (5 μM). A 50% TH displacement was reached at a 20 μM concentration of analyte, and the formation of the free TH band was complete at 550 μM (Figure 5). ESI-MS experiments confirmed the displacement of TH from the inclusion complex, revealing the

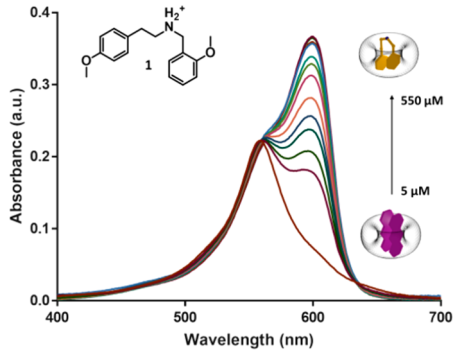

Figure 5. UV-Vis spectra of a solution of 5 μM TH_2·CB[8] complex upon subsequent additions of **1** in buffered water at pH 5.5 (acetate buffer). Inset: Chemical structure of **1** at pH = 5.5.

presence of the species TH_2·CB[8], $\mathbf{1}_2$·CB[8], TH·**1**·CB[8], and **1**·H·CB[8] (Figures S21–S25).

Ensured that TH_2·CB[8] could detect **1**, we moved to check whether the system could work with a real representative of the N-BOMes family. Titrations with 25C-NBOMe (**2**; Figure 2) showed that the system responded also to this molecule, albeit with a smaller affinity than that of **1**. The detection limit for this analyte, determined on the linear portion of the plot, was 3 μM (Figure S33). To further validate the method, we also tested the response of the sensor toward a street sample (R-25C-NBOMe) suspected to contain NBOMe. [The permission to use small quantities of the illicit drugs used in this work was granted to F.M. by the Italian Ministero della Salute (Permission No. SP/001 of 10.01.2019). The street sample was an aliquot of a casework file.]

The sample was formulated as a small piece of blotter paper (approximately 5 × 7 mm) with a smiling face of the comic character "Felix the cat" printed on it. The blotter paper was extracted with ethanol (see the Supporting Information), and the residue obtained by evaporation of the solvent was dissolved in a 1:1 water/methanol mixture and used to titrate TH_2·CB[8]. The response obtained matched that of the standard molecule **2** (Figures 6 and S31). ^{1}H NMR and ESI-MS analysis of the extract (Figures S27–S30) confirmed indeed that the substances contained in the blotter paper were NBOMes and, in detail, an almost equimolar mixture of 25C

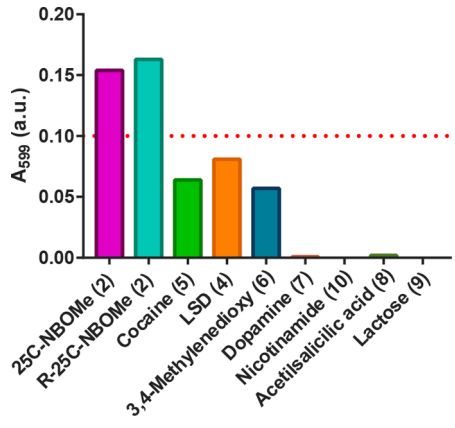

Figure 6. Plot of the absorbance at 599 nm recorded for all of the molecules tested after a 100 μM addition. The red dotted line at A_{599} = 0.10 represents the threshold value for discrimination of the NBOMes from the other molecules.

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and 25B-NBOMe (**3**; Figure 2). Hence, the sensing system responded in a similar way to different NBOMes, and its performance was not perturbed by additives possibly present in the formulation.

Eventually, we tested the selectivity of the sensing system toward other psychoactive substances and possible excipients or nonpsychoactive drugs (Figure 2). In particular, we selected LSD (**4**), cocaine (**5**), and (3,4-methylenedioxy)-phenethylamine [**6**, a phenethylamine very similar to (3,4-methylenedioxy)methamphetamine (MDMA), ecstasy] as representative psychoactive substances and dopamine (**7**), acetylsalicylic acid (**8**), lactose (**9**), and nicotinamide (**10**) as possible excipients and negative controls (Figure 2). The response of the sensing system to these analytes is reported in Figure 6. Psychoactive substances such as **4**–**6** produced a response that was significantly smaller than that obtained with **1**, **2**, and the street sample. In addition, nonpsychoactive substances did not produce any spectral change. Figure 6 summarizes the selectivity of the sensing system by plotting the absorbance at 599 nm recorded for the different analytes at 100 μM, which roughly correspond to analyzing 50–100 μg of a substance.

Inspection of Figure 6 clearly revealed that N-BOMes are the only substances that produce a 599 nm absorption larger than 0.15, while absorption values obtained with other psychoactive substances were around 0.05 and nonpsychoactive substances gave absorbances close to 0. In this way, by setting a decisional limit at an absorbance of 0.1, it is possible, once the concentration is set, to discriminate 25C-NBOMe from the other drugs. On the other hand, the simple appearance of the 599 nm band is enough to assess the detection of a psychoactive substance.

Because the signal produced by the sensing system is a variation of the absorption spectrum in the visible region, the corresponding color change from purple (TH_2·CB[8]) to blue (free TH) can be detected also by the naked eye. For this reason, we decided to support the sensor on a paper strip to obtain a handy material that could allow on-site detection. We prepared a 100 μM solution of TH_2·CB[8] in buffered water (acetate buffer, pH = 5.5), and we soaked filter paper in it. An excess of solution was removed with absorbent paper, and the stripes were further dried in air at room temperature for 15 min. Drug testing was as simple as dropping on the stripe a small drop (1 μL) of a 10 mM aqueous (or methanol) solution of the sample to be analyzed. The response was considered positive when the wetted region of the stripe turned immediately to light blue. The color change persisted even when the test stripe dried again. Figure 7 reports the pictures of the test stripes after the deposition of different analytes and interferents. The test gives positive responses to 25C-NBOMe (**2**), LSD (**4**), cocaine (**5**), and the MDMA analogue (**6**). On the other hand, it is not sensitive to variations of the pH of the analyte solution, and it gives negative responses to acetylsalicylic acid (**8**), sugars (as lactose, **9**), and nicotinamide (**10**). Importantly, the extracts from the street sample gave, as expected, a positive response as well (Figure S32). Drug concentrations as low as 0.3 mM can be detected (Figure S34). Most of the selectivity featured by the sensing system in solution is matched by the strip test because psychoactive substances were easily discriminated from nonpsychoactive substances. However, the strip test did not maintain the ability to distinguish NBOMes from other psychoactive amines because this would require fine control of the drug concentration that could not be possible in an on-site test. In addition, diffusion of water in the wetted paper likely results in an increase of the local concentration of the analytes.

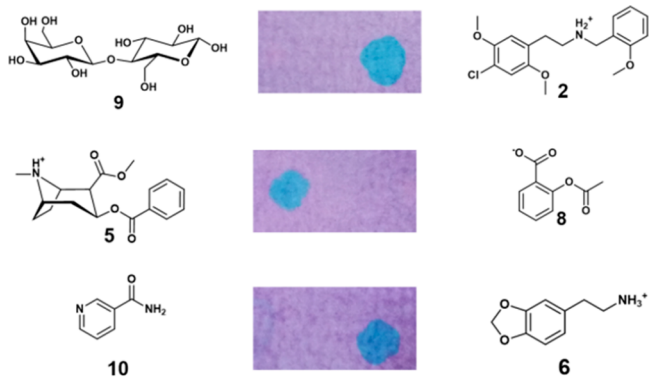

Figure 7. Detail of colorimetric strip tests upon exposition to different substances. The unreacted strip test has a purple color, which turns to light blue upon exposure to a small drop (1 μL) of drug (10 mM water or methanol).

The diffusion of drugs is an urgent problem, and the threat they represent is increased by designer drugs. For these reasons, the possibility of identifying potential illicit drugs with colorimetric methods and on-site tests is of great importance. Rapidity, low cost, the absence of harmful reagents, and simple or even no instrumentation needed are features that could allow a relevant increase of the number of tests performed and give a substantial contribution to effectively limit this phenomenon. In this paper, we have shown that the nanoconfinement properties of the supramolecular host CB[8] can be used to develop a colorimetric indicator for the selective detection of 25-NBOMes. The reason for the selectivity observed lies in the ability of the nanosized CB[8] cavity to induce cooperative coinclusion of the two aromatic moieties of the drug in the host cavity. In addition, the sensing nanosystem can be immobilized on paper to produce fast test strips allowing the on-site quick detection of potential illicit drugs. Of course, false positives may occur because of the ability of CB[8] to include several chemical species, but this test would allow one to screen potential candidates to be submitted to more accurate analysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsanm.0c02370.

Experimental procedures, details on the standardization of CB[8] and TH solutions, UV–vis titration curves for all of the analytes, ITC titrations and binding data, NMR and ESI-MS characterizations, and calculation of the detection limit (PDF)

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Author Contributions

‡These authors contributed equally.

Notes

The authors declare no competing financial interest.

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