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Nanoparticle-Assisted NMR Detection of Organic Anions: From Chemosensing to Chromatography

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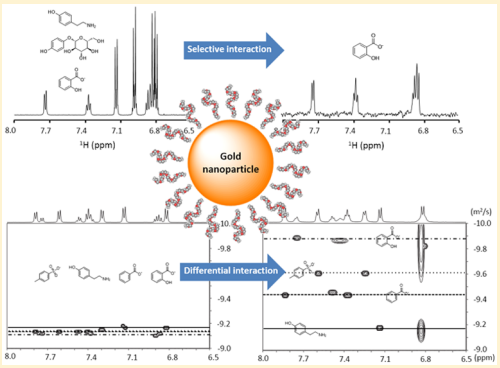
Supporting Information

ABSTRACT: Monolayer-protected nanoparticles provide a straightforward access to self-organized receptors that selectively bind different substrates in water. Molecules featuring different kinds of noncovalent interactions (namely, hydrophobic, ion pairing, and metal−ligand coordination) can be grafted on the nanoparticle surface to provide tailored binding sites for virtually any class of substrate. Not only the selectivity but also the strength of these interactions can be modulated. Such recognition ability can be exploited with new sensing protocols, based on NMR magnetization transfer and diffusion-ordered spectroscopy (DOSY), to detect and identify organic molecules in complex mixtures.

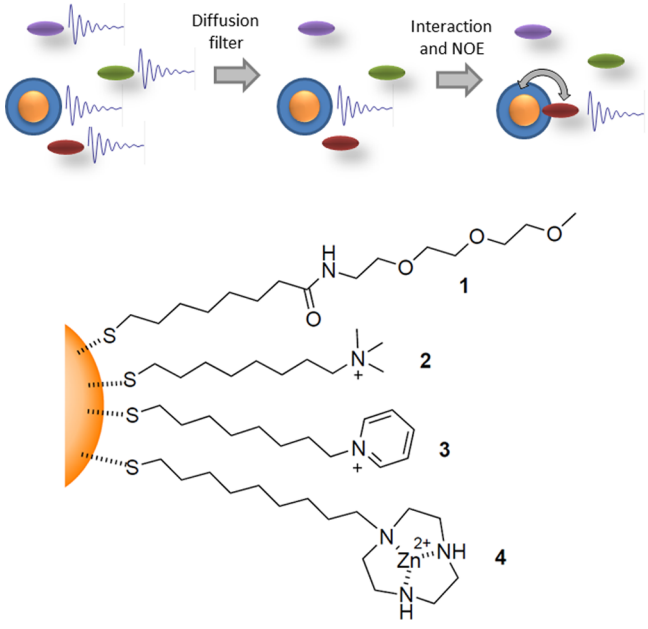


INTRODUCTION

Detection of a selected compound within a complex mixture is a common problem that chemists face every day. Several effective analytical techniques (chromatography, biochemical assays, biosensors, selective electrodes, chemosensors) have been developed, but most of them still suffer from the limitation of providing only indirect or poor information on the identity of the analyte. Indeed, the target molecule is differentiated from other components of the mixture on the basis of its interaction with the detection system and on the property changes it induces. As a result, the information provided (retention time, color change, and current or voltage variation) relies on the selectivity of the detection system and errors due to the presence of known and unknown interfering species in the mixture are always possible.[1]

NMR spectroscopy is probably the most powerful technique for the identification of organic compounds, even when their structure is unknown. Indeed, the amount of information provided by NMR is often sufficient to assign, with relative easiness, the chemical structure of most compounds. Unfortunately, the use of this technique for direct analysis of complex mixtures is generally compromised by the excess of information stemming from the combination of many (and most likely overlapping) spectra. Therefore, detection of the target analyte is often impossible because its signals are masked by those of other components, mainly matrix interferents.[2] We recently proposed "NMR chemosensing" (Chart 1) as a new protocol for analyte identification and quantification in complex mixtures, based on the use of nanoparticle-based receptors.[3] More specifically, this method relies on the ability of monolayer-protected nanoparticles to bind selected substrates by noncovalent interactions,[4] complemented with an inter-

Chart 1. (Top) Nanoparticle-Based NMR Sensing with NOE Pumping Experiments: Working Scheme. (Bottom) Nanoparticle-Coated Thiols Used in This Article



molecular nuclear Overhauser effect (NOE) transfer of magnetization between spins of the monolayer and of the bound analyte.

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The NMR strategy we used to detect the analyte is the "NOE pumping" experiment,[5] which is divided in two blocks (Chart 1). First, a diffusion filter is applied to dephase (cancel) the signals of the fast diffusing, small molecules in the sample. Only the magnetization of the large species, in this case the nanoparticles, survives after this step. Second, a NOE experiment is started immediately after the diffusion filter. During this step, the magnetization is transferred from the nanoparticles to the interacting molecules (in fast exchange regime) and the corresponding signals are detected. The strength of this method rests on its ability to extract the relevant information directly from the analyte in the form of an NMR spectrum of the interacting molecule. Hence, the target molecule can be detected, unambiguously identified, and even quantified using a proper calibration curve.

In our previous report,[3] we demonstrated that NMR chemosensing performed with ultrafine (1.8 nm core diameter) gold nanoparticles coated with a monolayer of amphiphilic neutral molecules (**1**, Chart 1) was able to selectively detect salicylate in water in the presence of several other aromatic anions of similar structure. Such selectivity was ascribed to hydrophobic interactions, since the nanoparticle coating monolayer forms a self-organized hydrophobic pseudophase and salicylate has the highest *n*-octanol/water partition coefficient among the tested molecules. Target detection was also possible in urine, again in the presence of overlapping interferents. In this case, the NMR-chemosensing techniques also allowed the detection and identification of the salicyluric acid which, albeit structurally similar to salicylate, has a different NMR spectrum.

In this paper, we extend the scope of nanoparticle-based NMR detection by showing how the self-organized nature of nanoparticles can be exploited to design binding sites tailored at the detection of different analytes. This also allows tuning the selectivity and increasing the sensitivity of NMR chemosensing. Finally we will show that the affinity modulation also allows the use of nanoparticles in the context of "chromatographic NMR",[6] another technique for the simultaneous identification of multiple analytes in complex mixtures.

RESULTS AND DISCUSSION

Owing to the ease of preparation and modification of monolayer protected nanoparticles, the potential applications of NMR chemosensing are quite broad. Nanoparticle preparation simply requires the mixing of functional thiols with a gold salt and a reducing agents (or with preformed nanoparticles).[7] Such simple operation leads to the formation of defined objects (the gold nanocrystals) coated with an ordered 3D monolayer of organic molecules. Even when the molecular structure of the coating thiols is relatively simple, as for those reported in Chart 1, cooperation between the functional groups may create recognition patterns for selected molecules.[8] Consequently, nanoparticles capable of recognizing and binding different substrates can be easily designed, prepared, and used.

Early NMR chemosensing experiments were characterized by high selectivity but suffered from a relatively low sensitivity. Indeed, for sodium salicylate a limit of detection (LOD) of 2.5 mM was achieved using **1**-coated nanoparticles at 70 μM concentration.[3] Such a low sensitivity stems from the moderate affinity of the analyte for the nanoparticles monolayer (an apparent association constant, K_{assoc}, of 120 M^{-1} was measured),[3] which in turn is due to the fact that binding is based only on hydrophobic interactions.

In this context, a first rationale of the NOE pumping experiment can be drawn in close parallel to the theory of relaxation developed for liable water spins in proteins hydration (see the Supporting Information).[9] The NOE-pumping experiment probes the intermolecular cross-relaxation rates, σ, between protons of the analytes and protons on the monolayer. In turn, the quantity σ results from a linear combination of spectral density functions (SDFs) calculated at different Larmor frequencies. By assuming that the analyte exchange on the monolayer and the nanoparticle rotation are statistically independent processes, it is possible to define a characteristic correlation time $\tau_{c,k}$ which depends on both the rotational correlation time τ_c of the nanoparticle and on the mean residence time $\tau_{M,k}$ of the analyte spin in the monolayer. In this theoretical framework, it can be shown that the effect of the correlation time $\tau_{c,k}$ on the SDFs is such that the absolute values of the cross relaxation rates rapidly increase as $\tau_{M,k} > \tau_c$ (see the Supporting Information for examples). In other words, the stronger the interactions between the analytes and the monolayer, the larger will be the analytes signals emerging from NOE pumping experiments. Consequently, higher affinity of the nanoparticle for the analyte should result in lower detection limits.

Starting from these considerations, we decided to verify how the nanoparticle affinity for the substrate could be improved by introducing a second effective interaction that adds to the hydrophobic one.[8e] Since salicylate is negatively charged, the use of electrostatic ion pairing as the additional interaction was quite a logical choice. In this view, thiols **2**−**4** (Chart 1), bearing different positively charged headgroups, were synthesized by standard or literature procedures (see the Supporting Information). Gold nanoparticles (AuNps) (1.7 nm average gold core diameter, see the Supporting Information) coated with thiols **1**−**4** (**1**−**4**−AuNp) were then prepared and tested as anions receptors for NMR chemosensing.

As expected, when used in NOE pumping experiments, **2**−AuNp proved to be highly effective in detecting salicylate in water (or buffered solutions), with a sizable sensitivity improvement as compared to **1**−AuNp. Figure 1 reports the results of NOE pumping experiments performed with AuNp 15 μM and salicylate 1 mM. While in the spectrum recorded with **1**−AuNp (Figure 1c) the salicylate signals are undetectable, they clearly emerge in the NOE pumping spectrum recorded with **2**−AuNp (Figure 1b, S/N = 5.3). By defining the limit of detection (LOD) as the analyte concentration that produces signals whose intensity is greater than 3 times the standard deviation of the noise, we could determine a LOD of 0.5 mM for salicylate detection with **2**−AuNP.

The higher affinity of these nanoparticles for salicylate was confirmed with a titration experiment (Figure 2a) wherein NOE pumping experiments were run on a series of samples containing **2**−AuNp with increasing concentrations of salicylate. The integrated intensities of the salicylate signals increase with the concentration, reaching a plateau at about 2 mM. A fit of the integrated intensities versus the analyte concentration with a 1:1 binding model[10] provides an apparent association constant (K_{assoc}) of ~4×10^4 M^{-1}, a value which is above the limit that can be precisely determined by NMR. If we compare this figure with the value of 120 M^{-1} previously obtained with **1**-coated nanoparticles,[3] where the interaction is prevalently hydrophobic, it appears that the additional ion

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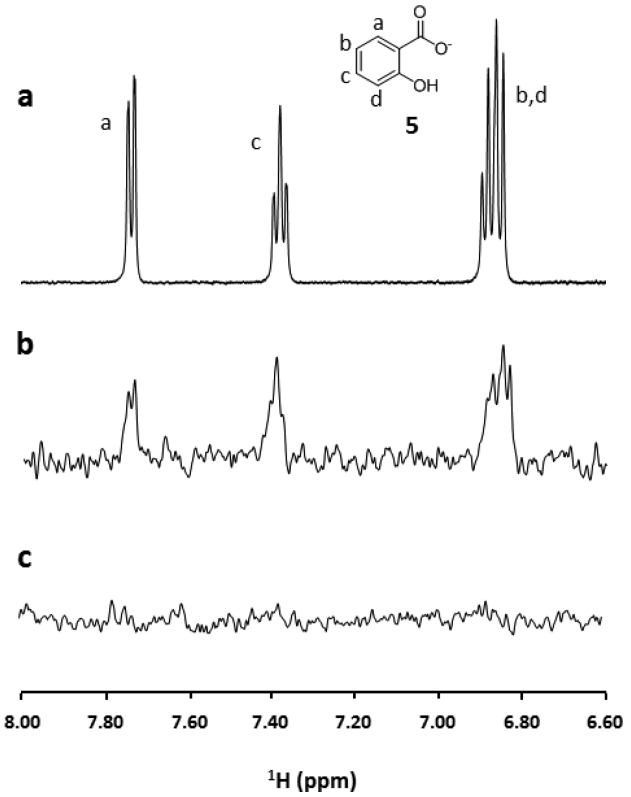

Figure 1. (a) ^{1}H NMR subspectrum of 1 mM sodium salicylate (**5**) in D_2O. (b) NOE-pumping subspectrum of the same sample in the presence of **2**−AuNp. (c) NOE-pumping subspectrum of the same sample in the presence of **1**−AuNp. Conditions: [AuNp] = 15 μM, carbonate buffer 20 mM, pD = 10, 28 °C.

pairing in **2**−AuNp contributes at least as effectively as the hydrophobic interaction ($10^2 \times 10^2$) to the substrate binding. Such a hypothesis was confirmed by a second titration experiment performed using acetate (**6**) as substrate (Figure 2b). Here, the hydrophobic contribution to the substrate binding is negligible and ion pairing is the sole interaction at play. In line with the previous analysis, the determined binding constant is 140 ± 20 M^{-1}.

To further investigate how the concurrence of both the electrostatic ion pairing and the hydrophobic interaction ensures a higher substrate affinity (and consequently lower detection limits), we applied NMR chemosensing to a series of carboxylic acids featuring different chain lengths (Figure 3). In this case, the nanoparticles residual signals, which are normally present in the NOE pumping spectrum, were removed by background subtraction. As expected, using **2**−AuNp at 15 μM and carboxylic acids at 2 mM concentration, no signals were detected in the NOE-pumping experiment when acetate was the analyte. Very weak signals were found with butyrate (**7**), with just the triplet of the terminal methyl group (0.8 ppm) appearing in the spectrum. Finally, all the signals relative to sodium hexanoate (**8**) were clearly visible in the spectrum. Hence, low concentration recognition requires the presence in the substrate of both an anionic charge and an alkyl chain containing at least five carbon atoms.

On the basis of such information, we tested the selectivity of the sensing system on a mixture of salicylate (**5**), tyramine (**9**), and arbutin (**10**). All these molecules have an amphiphilic structure including a negatively charged (**5**), positively charged (**9**),[11] or neutral (**10**) polar moiety and an aromatic nonpolar

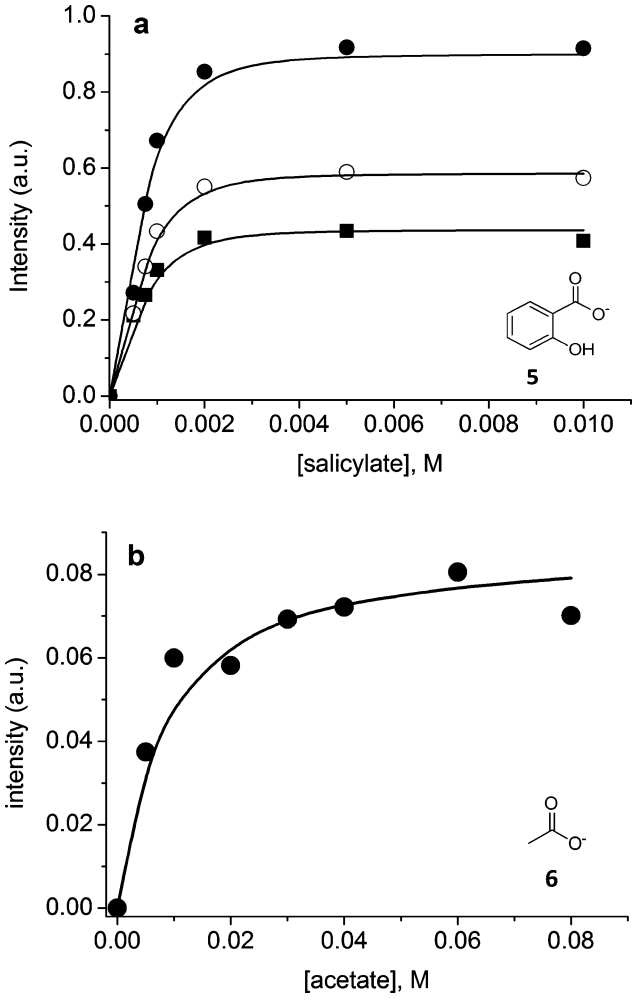

Figure 2. Integrated intensities of the different salicylate (a, ● = 6.8 ppm, ○ = 7.4 ppm, □ = 7.75 ppm) or acetate (b, ● = 1.98 ppm) signals in NOE-pumping experiments with **2**−AuNp, as a function of the analyte concentration. Solid line: best fit of the data. Conditions: [AuNp] = 15 μM, carbonate buffer 20 mM, pD = 10, temp = 28 °C.

tail. This ensures that, while hydrophobic interaction is possible with the aromatic portion of all the three substrates, electrostatic ion-pairing interaction is available only to salicylate. Indeed, only salicylate was detected in the NMR chemosensing experiment (Figure 4), confirming that a simultaneous hydrophobic and electrostatic interaction is a prerequisite for successful detection. In addition, the spectrum reported in Figure 4 nicely highlights the advantages and potentials of NMR chemosensing. Looking just at the 6.9−6.8 ppm region, the presence of salicylate in the mixture is hardly assessed by standard NMR experiments due to the signal overlap. However, the salicylate signals nicely stand out in the NOE pumping spectrum, allowing for unambiguous identification of the analyte.

More insight into the behavior of the sensing system was obtained by investigating the detection of other potential analytes featuring negatively charged groups. As reported in Figure 5, when a mixture of salicylate (**5**), benzoate (**11**), tosylate (**12**), and tyramine (**9**, as negative control) is analyzed by NOE pumping, the signals of all the three anionic species are present in the NOE pumping spectrum. In line with our expectations, **2**−AuNp nanoparticles also detect other and more hydrophilic aromatic anions, besides salicylate, that were

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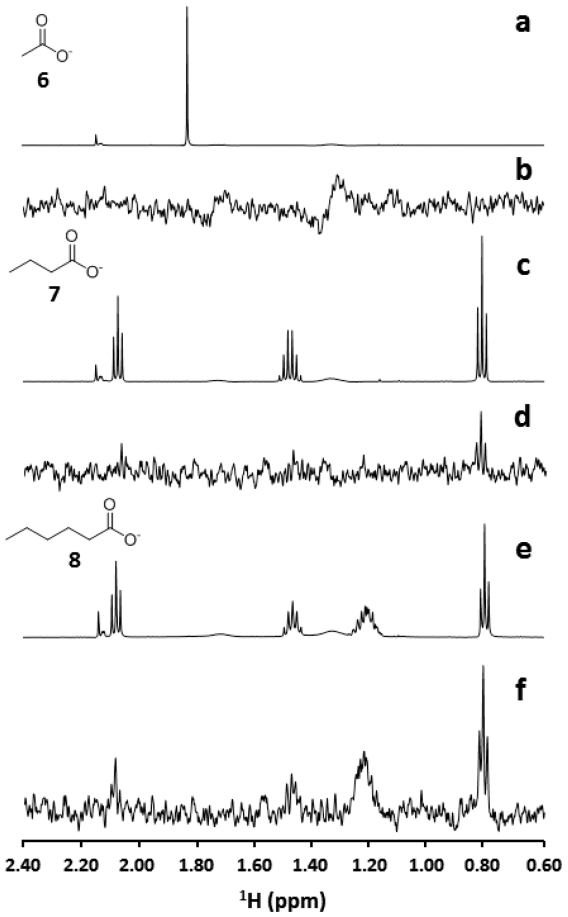

Figure 3. (a) ^{1}H NMR subspectrum of sodium acetate (**6**). (b) NOE-pumping subspectrum of **6** in the presence of **2**−AuNp. (c) ^{1}H NMR subspectrum of sodium butanoate (**7**). (d) NOE-pumping subspectrum of **7** in the presence of **2**−AuNp. (e) ^{1}H NMR subspectrum of sodium hexanoate (**8**). (f) NOE-pumping subspectrum of **8** in the presence of **2**−AuNp. Conditions: [carboxylates] = 2 mM, [AuNp] = 15 μM, carbonate buffer 20 mM, pD = 10. **2**−AuNp signals were removed by subtraction of a NOE pumping spectrum obtained in the absence of analytes.

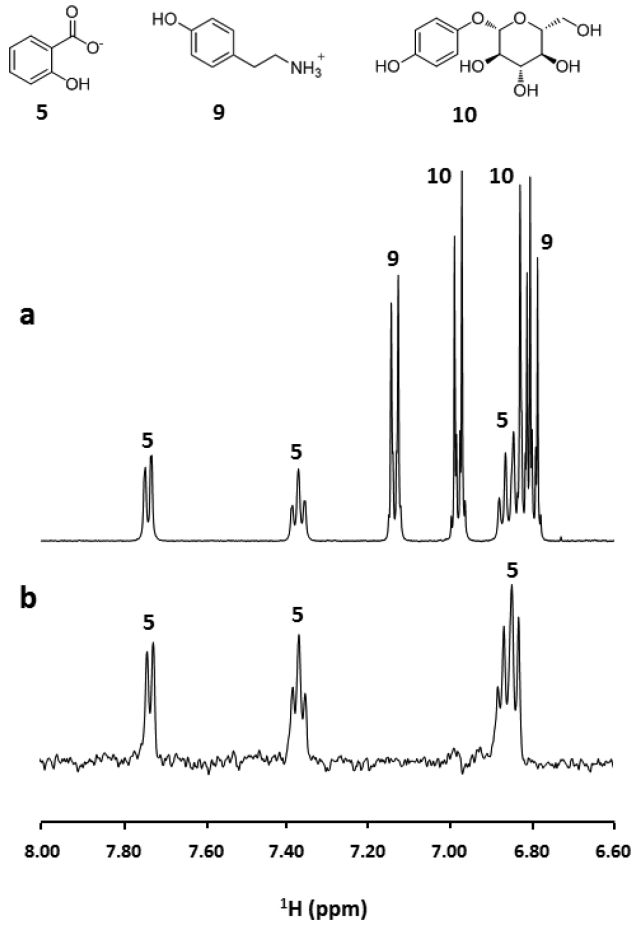

Figure 4. (a) ^{1}H NMR subspectrum of sodium salicylate (**5**), tyramine (**9**), and arbutin (**10**), 2 mM each in D_2O. (b) NOE-pumping subspectrum of the same sample in the presence of **2**-coated gold nanoparticles. Conditions: [AuNp] = 15 μM, HEPES buffer 10 mM, pD = 7.0.

not detected by **1**−AuNp nanoparticles.[3] Signal intensities in the NOE pumping spectrum (Figure 5b) are, however, different for each analyte, roughly following the order **5** > **12** > **11**. This trend indeed suggests a parallel binding affinity, with salicylate interacting more strongly than tosylate and benzoate. Within this series the ion-pairing interaction can be considered similar for each anionic analyte, and the affinity modulation is likely due to a different strength of the hydrophobic interaction. However, the computationally predicted *n*-octanol/water partition coefficients at pH 7.4 (log D) for **5**, **11**, and **12** are, respectively, −1.14, −0.98 and −2.57.[13] At difference from what we reported previously for **1**−AuNp,[3] and also here in the case of linear carboxylic acids, there is not a clear correlation between log *D* values and nanoparticles affinity, indicating that the interaction with the nanoparticle-coating monolayer is different from the simple partition into a hydrophobic phase.

The possibility of easily modifying and optimizing the monolayer binding properties is clearly a fundamental advantage of using monolayer-protected nanoparticles, which behave as scaffolds to self-organize molecular binding sites. Hence, we decided to reverse the previous approach and search for nanoparticles capable to detect hydrophilic carboxylates such as acetate at low concentrations. To this end, **3**−AuNp and **4**−AuNp nanoparticles were screened, together with **2**−AuNp, for their ability to detect 10 mM sodium acetate in water. The NOE pumping experiment performed with **3**−AuNp does not reveal the presence of acetate (see the Supporting Information). In the case of **2**−AuNp only a weak signal, just above the detection limit, emerges in the spectrum. On the other hand, a large signal is seen in the NOE pumping experiment performed with **4**−AuNp. The different behavior of the three nanoparticles reveals that the higher sensitivity of **4**−AuNp is likely due to an additional interaction besides those already examined. Indeed, while trimetylammonium and *N*-alkylpyridinium headgroups are expected to provide only electrostatic interactions, Zn(II) ions may contribute with additional metal−ligand coordination interactions. Moreover, cooperative binding of the carboxylate group to two metal centers can be postulated.[8]

The ability of **4**-coated nanoparticles to detect small-molecule organic anions was then tested by analyzing via NMR chemosensing a mixture containing sodium acetate (**6**), sodium dimethylphosphate (**13**), ethanol (**14**), methanol (**15**), and DMF (**16**). As expected, only the two anions emerge from the NOE pumping experiment (Figure 6). The intensity of the dimethyl phosphate signal is larger than that of acetate, suggesting a greater affinity of **4**-coated nanoparticles for the

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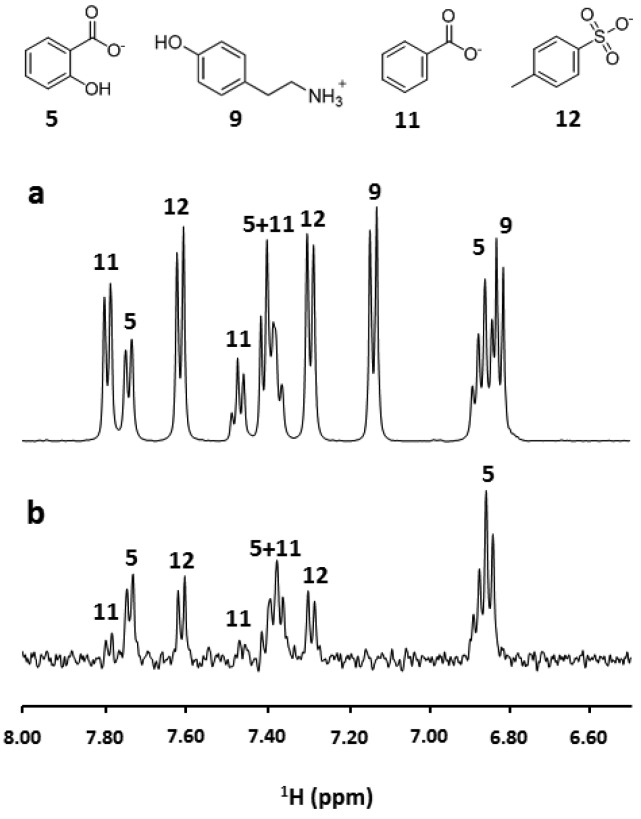

Figure 5. ^{1}H NMR subspectrum of sodium salicylate (**5**), sodium benzoate (**11**), potassium tosylate (**12**), and tyramine (**9**), 2 mM each in D_2O. (b) NOE-pumping subspectrum of the same sample in the presence of **2**-coated gold nanoparticles. Conditions: [AuNp] = 15 μM, HEPES buffer 10 mM, pD = 7.0.

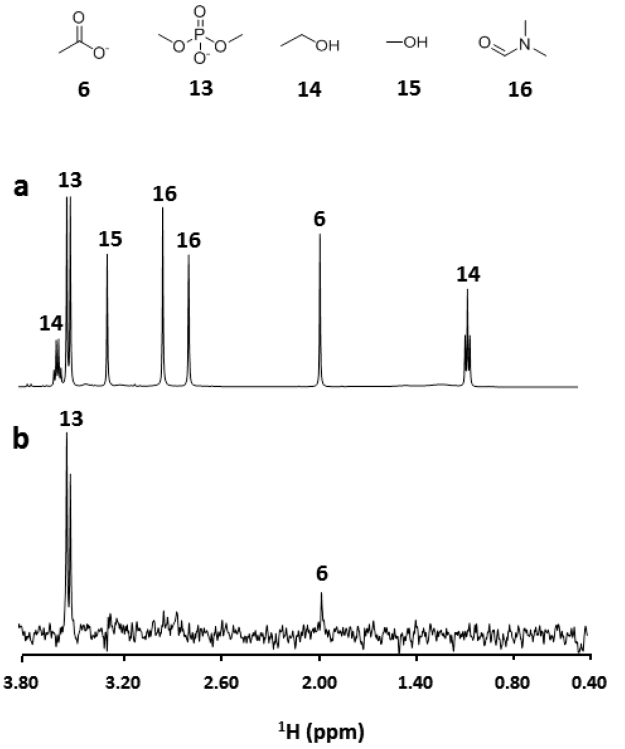

Figure 6. (a) ^{1}H NMR subspectrum of sodium acetate (**6**), sodium dimethylphosphate (**13**), ethanol (**14**), methanol (**15**), and DMF (**16**) each at 10 mM concentration in D_2O. (b) NOE-pumping subspectrum of the same sample in the presence of **4**-coated gold nanoparticles. Conditions: [AuNp] = 15 μM. The NOE pumping pulse scheme was complemented with a CPMG*z* filter[12] to improve the baseline.

former. Such evidence is in line with the recent observations by Prins and co-workers, who demonstrated that polyphosphate ions bind more strongly to **4**-coated nanoparticles than polycarboxylates.[14]

All of the above experiments demonstrate that monolayer-protected nanoparticles can be easily tailored to change their affinity toward selected substrates. Hydrophobic, ion-pairing, and metal–ligand coordination interactions can be combined to provide stronger interaction and/or different selectivity. In summary, **1**-coated nanoparticles detect only highly hydrophobic species, **2**-coated nanoparticles detect moderately (and highly) hydrophobic organic anions, and **4**-coated nanoparticles can be used for highly hydrophilic organic anions.

The peculiar recognition properties found for monolayer-protected nanoparticles promptly suggest their use in combination with other analytical techniques based on NMR. A few years ago, Caldarelli and co-workers introduced the idea of "chromatographic NMR"[6] to analyze complex mixtures of organic molecules, extending to solid phases the principle of "affinity NMR" championed by Shapiro.[15] In this technique, interactions with a solid stationary phase (silica gel) are used to perturb the diffusion coefficients of dissolved analytes in such way that their NMR signals can be conveniently separated by diffusion-ordered spectroscopy (DOSY).[16] However, because of the sample heterogeneity, all spectra must be acquired under magic-angle spinning conditions to reduce the anisotropy of the magnetic susceptibility. An alternative approach to reduce the magnetic field inhomogeneity across the sample consists in matching the magnetic susceptibility of the silica gel with that of proper mixtures of deuterated solvents[17] or in the use of soluble stationary phases.[18] In this intriguing context, we reasoned that most of such problems could be overcome by use of nanoparticles as a pseudostationary phase. In fact, 2 nm gold core nanoparticles are small enough to not perturb the magnetic field homogeneity across the sample (thus allowing the use of solution-state NMR), yet they are large enough to have quite low diffusion coefficients. Most importantly, the nanoparticles affinity toward a specific class of molecules can be tuned by the proper choice of the monolayer, as already demonstrated. Combined together, such features could potentially allow a pseudochromatographic resolution of very complex mixtures by solution-state NMR, even on spectrometers of moderate field strengths.

Starting from such premises we decided to test this idea on the **2**–AuNp, salicylate (**5**), benzoate (**11**), tosylate (**12**), and tyramine (**9**) mixtures previously investigated via NMR chemosensing. In this case, the single components cannot be easily isolated with a standard ^{1}H spectrum, NOE pumping (Figure 5b), or even DOSY (Figure 7a). However, if the DOSY experiment is repeated in the presence of **2**–AuNp (Figure 7b), each component is easily identified on the basis of its altered diffusion coefficient, which is directly related to the affinity for the nanoparticles monolayer. It is evident from Figure 7b that salicylate (**5**) diffusion coefficient is the most reduced: indeed, salicylate interacts with **2**–AuNp so strongly that a chemical shift perturbation is also observed. Regrettably, such perturbation results in a superposition of the signals of salycilate and tyramine at 6.84 ppm, but the difference in diffusion coefficients induced by the nanoparticles allows to

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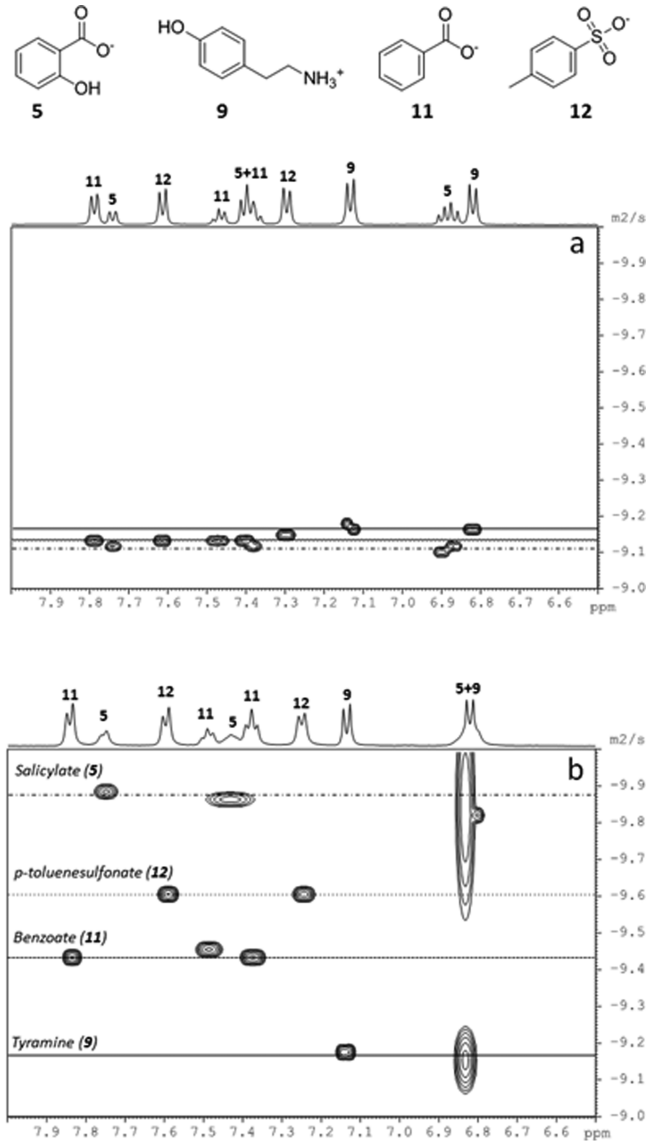

Figure 7. DOSY experiment performed on a mixture of sodium salicylate (**5**), sodium benzoate (**11**), potassium tosylate (**12**), and tyramine (**9**) in water in the absence (a) or in the presence (b) of **2**–AuNp. Conditions: [AuNp] = 90 μM, HEPES buffer 10 mM, pD = 7.0.

resolve the overlap in the diffusion dimension, epitomizing the major advantage of chromatographic NMR. A decrease of the tosylate (**12**) and benzoate (**11**) apparent diffusion coefficients is also noticed, yet to a lesser extent due to their smaller interaction with the nanoparticles. As expected from the outcome of the NOE pumping experiment, the DOSY map shows no change for tyramine (**9**) diffusion coefficient in the absence and in the presence of nanoparticles.

NMR diffusometry further corroborates what has been observed so far in NOE-pumping experiments (Figure 5b): that is, monolayers of organic molecules coating gold NPs can effectively interact with small molecules via noncovalent interactions. Indeed, cases exist where a NOE-pumping experiment is not selective enough because of the strong interactions at play (Figure 5b), whereas a diffusion coefficient change is generally not observed for weak interactions.[5] In this respect, NOE pumping and nanoparticles-assisted DOSY can be seen as complementary techniques.

CONCLUSION

The results here reported nicely demonstrate how the combination of monolayer-protected nanoparticles with NMR can disclose new detection protocols and improve existing ones. We have shown that noncovalent interactions between AuNp coating monolayers and analytes can be exploited to label and detect the interacting molecules either by magnetization transfer or by a perturbation of their diffusion coefficient. The self-organized and multifunctional nature of nanoparticles allows for an easy design and construction of new receptors where the substrate affinity can be tailored by modulating and combining different interactions. When the interaction is selective and the exchange is fast on the diffusion time scale, the spins located on the NPs monolayer can be used as a magnetization source to be selectively transferred to the interacting analytes via NOE. In such way, only the signals of the interacting species are found in the final spectrum and the NOE pumping experiment easily allows to probe the affinity of different substrates for the nanoparticles. On the other hand, when the interactions are strong, a variation of the analytes diffusion coefficient can be observed, which allows for optimal separation in diffusion-ordered spectra. A problem that still needs to be addressed is the presence of residual nanoparticles signals in the NOE pumping spectrum. This drawback can be partially overcome by appropriately designing the nanoparticle coating monolayer, i.e., by pairing, as in the case of salicylate detection, nonaromatic monolayers with aromatic substrates. Other solutions of more general application may involve a fine-tuning of the experimental parameters or the development of NMR editing techniques capable to suppress the background signal. Several potential applications are at reach of these methods and their development is ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Synthesis and characterization of new organic compounds and nanoparticles; additional NMR experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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