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Simultaneous Identification of Neutral and Anionic Species in Complex Mixtures without Separation

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Abstract

A chemosensory system is reported that operates without the need for separation techniques and is capable of identifying anions and structurally similar bioactive molecules. In this strategy, the coordination of analytes to a metal complex with an open binding cleft generates “static structures” on the NMR time scale. Unique signals are created by strategically placing fluorine atoms in close proximity to bound analytes so that small structural differences induce distinct ^{19}F NMR shifts that can be used to identify each analyte. The utility of this method is illustrated by quantifying caffeine levels in coffee, by identifying ingredients in tea and energy drinks, and by discriminating between multiple biogenic amines with remote structural differences 6 carbons away from the binding site. We further demonstrate the simultaneous identification of multiple neutral and anionic species in a complex mixture.

Keywords

^{19}F NMR; chemosensing; biogenic amine; palladium; pincer complex

Reliable detection methods that operate on real-world complex mixtures without pre-treatment are highly desirable for many fields ranging from health care and biomedical research to food and beverage quality control because they can reduce costs and simplify the detection process.[1] Unfortunately, frequently utilized informative techniques, including mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopy are not ideal for the analysis of complex mixtures without separation because signals from each individual analyte may overlap with one another and be obscured by unwanted background signals.[2] Various chemosensory platforms have been used to make the analyte signals immune from species that do not participate in recognition; however, closely related analytes with similar binding behaviors are usually undistinguishable. We have recently demonstrated that encapsulating the analyte in a molecular container coated with fluorine probes induces changes in ^{19}F NMR signals useful for identification.[3] The sterically constrained env ironment defined by the container enables size discrimination for the selective detection of less sterically hindered molecules such as nitriles, but limits the implementation of this method to a diverse array of analytes. We now report a chemosensory platform that addresses this limitation and is capable of simultaneously identifying various neutral and

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anionic species in complex mixtures. By design, various analytes are immobilized within an open binding cleft to generate “static complexes” on the NMR timescale. Fluorine atoms appended to the cleft are strategically positioned proximate to the bound analyte to distinguish between closely related analytes (Scheme 1a). The high sensitivity of fluorine NMR shifts to the local environment and the low level of interfering background signals allows this chemosensory platform to operate on complex mixtures without the need of separation, wherein both neural and ionic species with minute structural differences are simultaneously identified in complex mixtures.[4-6]

We view the amide-based palladium pincer complexes (Scheme 1b) to be versatile scaffolds because metallation of the ligand creates a confined binding cleft with a Lewis acidic metal, and also has a structure wherein fluorine probes can be positioned in close proximity to analytes bound in the cleft.[7] Another appealing feature of these complexes is the ability to undergo facile ligand exchange at only one coordination site, but also exhibit analyte bound complexes that are static on the NMR timescale. The complexes are synthesized with a weakly bound acetonitrile that is rapidly replaced by stronger ligands such as pyridine.[8] The wide analyte scope provided by this motif allows for the simultaneous detection of multiple species. As a result of the well-defined coordination chemistry displayed by these complexes, they have been investigated as recognition elements for chemical warfare agents and used to construct functional molecular assemblies.[9] Furthermore, we have shown that chiral fluorinated palladium pincer complexes are capable of differentiating pairs of enantiomeric amines in complex mixtures.[10]

We initially prepared palladium complexes with ligands composed of aryl-groups bearing CF_3 and OCF_3 groups with the aim of differentiating closely related analytes (Scheme 1b, **1**−**4**). Consistent with our design, the X-ray single crystal structure of **2**:CH_3 CN clearly showed that the fluorine probe is pointing towards the analyte and in close proximity to the analyte binding site (Scheme 1c). We are also aware that fluorine groups have low polarizablity as a result of this element's high electronegativity, which limits the chemical shift dispersion. To compensate for this fact, w ehave incorporated a polarizable arylgroup that can be substituted with bromine atoms adjacent to the fluorines to induce more pronounced shifts by the perturbation of polarizable electrons (Scheme 1b, **5** and **6**). We report herein the discriminatory power of these chemosensory constructions for representative neutral bioactive molecules.

A mine and *N*-heterocycle moieties are ubiquitous bioactive molecules with a wide variety of physiological functions.[11] Biogenic amines are key biomarkers for the determination of food freshness and human disease.[12] For instance, a higher-than-normal level of serotonin in serum may indicate carcinoid syndrome.[13] On the other hand, *N*-heterocycles are commonly used in drugs and vitamins, and represent a major class of natural products. Many well-known alkaloids, such as caffeine, nicotine, and morphine contain *N*-heterocyclic units that are suitable ligands to bind to our palladium pincer compounds. As a result, we began by exploring the ^{19}F NMR sensing potential of complex **1**. Our initial results showed that in non-coordinating solvents **1**'s Lewis basic amide group can replace the bound acetonitrile gives rise to self-associated oligomeric species (Figure 1a).[14] To prevent the formation of oligomeric species, an additional 15 equivalent of CH_3CN was added to

chloroform solution of **1**. The monomeric species is stable under this condition with a well-resolved singlet peak observed in ^{19}F NMR (Figure 1b). We then selected a series of amines and *N*-heterocycles as the analytes to evaluate the potential utility in the detection of biologically active compounds. The observation of the discrete signals at precise, concentration-independent chemical shifts indicates the formation of "static" complexes on the NMR time scale for the identification of each analyte. Figure 1 reveals the ability of **1** to discriminate betw een similar analytes. A noteworthy feature is the contrast betw een the new upfield shifted signal observed for benzylamine binding as opposed to the downfield shift for 2-phenethylamine binding, which is caused by the addition of an additional methylene (Figure 1e,f). It is worth noting that the NH_2 group on tryptamine (Figure 1g) is solely responsible for the sensing result as no new peak was observed upon addition of 3-methylindole (Figure 1h). Despite the fact that N-heterocylces, such as pyridine, nicotine and quinoline all coordinate to **1** through a pyridine subunit, distinct shifts were produced (Figure 1j-l). We also find that tertiary amines have a much lower coordinating ability with **1** in comparison with primary amines and the Lew is basic sites on planar *N*-heterocycles. This deduction is based on the fact that the intensity of the generated signal is very low even with analyte at high concentrations (Figure 1m). In contrast, secondary amines have comparable coordinating capabilities as primary amines (for details, see Figure S12 in SI). Interestingly, two new equal intensity peaks were produced by cinchonidine (Figure 1n). This observation is attributed to the steric bulkiness of cinchonidine, which induces the non-equivalence of the two OCF_3 groups (for details, see Figure S9 in SI). The ability to simultaneously identify multiple species is a desired property for chemosensing methods, especially w hen interference is present or more than one analyte is of interest in the system. As a demonstration, a mixture of seven compounds (three amines and four *N*-heterocycles) provides seven new signals with which are uniquely assignable to the corresponding analytes (Figure 1c). It is noteworthy that the receptors **1**-**4** with fluorine probes distinctly arranged as shown in Scheme 1b all displayed different responses for each individual analyte, thus allowing the collection of information of sufficiently many dimensions to unambiguously identify a species (For the multiplexed sensing results using receptors **2**-**4**, see Table S1 in SI).

We next turned our attention to sensor **6** with fluorine probes connected to phenyl group and adjacent to a bromine atom, which is expected to display larger ^{19}F NMR shifts as a result of the polarizable aromatic ring and heavy atom. Sensing experiments shown in Figure 1o confirm the effectiveness of this design, as benzylamine induces a downfield shift of 3.12 ppm w ith **6**, which is much larger than that observed with complex **1** (< 0.2 ppm). Interestingly, the downfield shifts were less pronounced with *N*-heterocycles in comparison to amines (pyridine and caffeine vs. benzylamine and 2-phenethylamine). The nature of the coordination of caffeine to the Pd^{2+} center was confirmed by an X-ray single-crystal structure of the isolated complex **6** (for halogen bonding and π-π stacking interactions in the crystal structure, see Figure S8 in SI).[15]

The rapid differential detection of structurally related organic compounds is crucial to biomedical research and health care and in this context biogenic amines are of particular interest as biomarkers for the disease. The precise identification of specific biogenic amines

is important because of their different physiological functions. However, presently chromatographic separations are necessary when multiple biogenic amines are present in the sample under investigation.[16] To demonstrate the robust discriminatory power of our method, we applied it to the analysis of a mixture of biogenic amines in aqueous solution. Specifically, 2-phenethylamine, tyramine, tryptamine, and serotonin were selected on the basis of their structural similarity. As shown in Figure 2, these analytes were successfully resolved with this method. Moreover, tryptamine and serotonin, which differ by one hydroxyl group, which is 6 carbons away from the binding site, are unambiguously differentiated with well-separated peaks. We emphas ize that the precision provided with this method is difficult to achieve by other non-eluting (chromatographic) methods. In contrast to the well-separated signal obtained with **6**, the palladium complex **5** without the bromine substitution displays inferior discriminatory ability as shown in Figure 2b, which confirms that the polarizable bromine contributes to the induced chemical shifts for a given analyte.

Coffee represents a complicated mixture, the primary constituents of which are water, carbohydrates, fiber, proteins, free amino acids, lipids, minerals, organic acids, chlorogenic acid, trigonelline, and caffeine.[17] To illustrate the precise identification and quantification of a target species achievable with our sensing scheme, we demonstrate the detection of caffeine in regular and decaffeinated coffee without pre-treatment.[18] In this experiment, untreated coffee and non-volatile 4-nitrobenzotrifluoride (internal standard) was added to **1** in methanol for ^{19}F NMR analysis. It is noteworthy that the association of caffeine in almost quantitative in methanol (see Figure S6 in SI) such that the concentration of caffeine can be easily determined from the integration of the corresponding ^{19}F NMR signal. As shown in Figure 3, although a number of unidentified species are observed, the signal produced at the distinctive chemical shift allows for the unambiguous identification of caffeine in an extremely complex background. The concentrations of caffeine in regular and decaffeinated coffee were determined to be 612 and 29 mg/L, respectively.[19] Notably, the precision of this method can be evaluated by concurrently adding another analyte of comparable coordinating ability and known concentration (quinoline and caffeine have a similar association to **1**, see Figure S5 in SI for details). The deviation of the concentration of the added quinoline calculated from ^{19}F NMR is found to be less than 3%, thus suggesting the matrices of coffee have a negligible impact on our sensing result (for the differentiation of caffeine analogues, see Figure S14 in SI).

We next extended this strategy to the identification of ingredients of tea, artificial sweetener, and energy drinks. In these experiments, an untreated solution of the commercial product was directly mixed with **6** for ^{19}F NMR analysis. As shown in Figure 4, caffeine, aspartame, acesulfame K, taurine and niacinamide were unambiguously identified, thus demonstrating the wide applicability of this approach to the direct analysis of samples with complex ingredients. Our identifications were corroborated by the ingredient lists provided by the product manufacturers. (See Figure S13 in SI for details.)

In addition to neutral organic molecules, the identification of various anions by chemosensing methods is also challenging. In contrast to cations, the charge on the anions is often more diffuse, which decreases the electrostatic interactions between the receptor and the anions. Moreover, the solvation energy in water tends to be higher for anions than

cations with comparable size, w hich requires a receptor design that can mitigate the competition from the solvent.[20] We envisioned that the pincer ligand will encapsulate the anions in a hydrophobic pocket, thus mitigating some of the solvation and encouraging a static association on the NMR time scale between the palladium complex and the anions. Furthermore, the anions bound to the Pd^{2+} should be differentiable by their distinct shape and size. As shown in Figure 5, complex **6** is capable of simultaneously identifying neutral and anionic species in a complex mixture. In this case we display ^{1}H coupled spectra, to shown that the shifts cause by simple anion binding still produces adequate shifts. Anions bound to **6** induce a significant upfield shift, while neutral species tend to induce a significant downfield to slight upfield shift. This dichotomy enables the peaks to be easily assigned and the identities of the analytes to be unambiguously determined. A species with ^{19}F NMR signal at –109.55 ppm issometimes observed when the experiment is performed in THF/D_2 O, and is likely due to an oligomeric palladium complex as the intensity of this peak decreased upon addition of excess amount of amine. This behavior has been previously investigated, and a cyclic hexamer of a palladium pincer complex has been reported and characterized by X-ray crystallography.[9f] It is noteworthy that the ability to simultaneously identify anions and bioactive organic molecules by chemosensing methods has not been demonstrated before and could be very useful for diagnostic test wherein a comprehensive detection of multiple characteristic species is needed for disease determination.

In summary, we have reported a chemosensory platform wherein analytes are immobilized through coordination to a metal, and fluorine probes are located in c lose proximity to the analyte to produce precise ^{19}F NMR shifts that can be used to identify the analyte. The robust detection power of this strategy is demonstrated by the quantification of caffeine content in coffee, identification of ingredients in beverages, and differentiation of structurally similar biogenic amines. The simultaneous identification of multiple neutral and anionic species is also achieved. The method of using palladium pincer complexes and ^{19}F NMR to precisely probe local structures that we have illustrated here is only a representative example of the more general chemosensory strategy we will continue to develop. The method is not restricted to metal-ligand coordination, and chemosensing using ^{19}F NMR represents a powerful general method for analyzing complex mixtures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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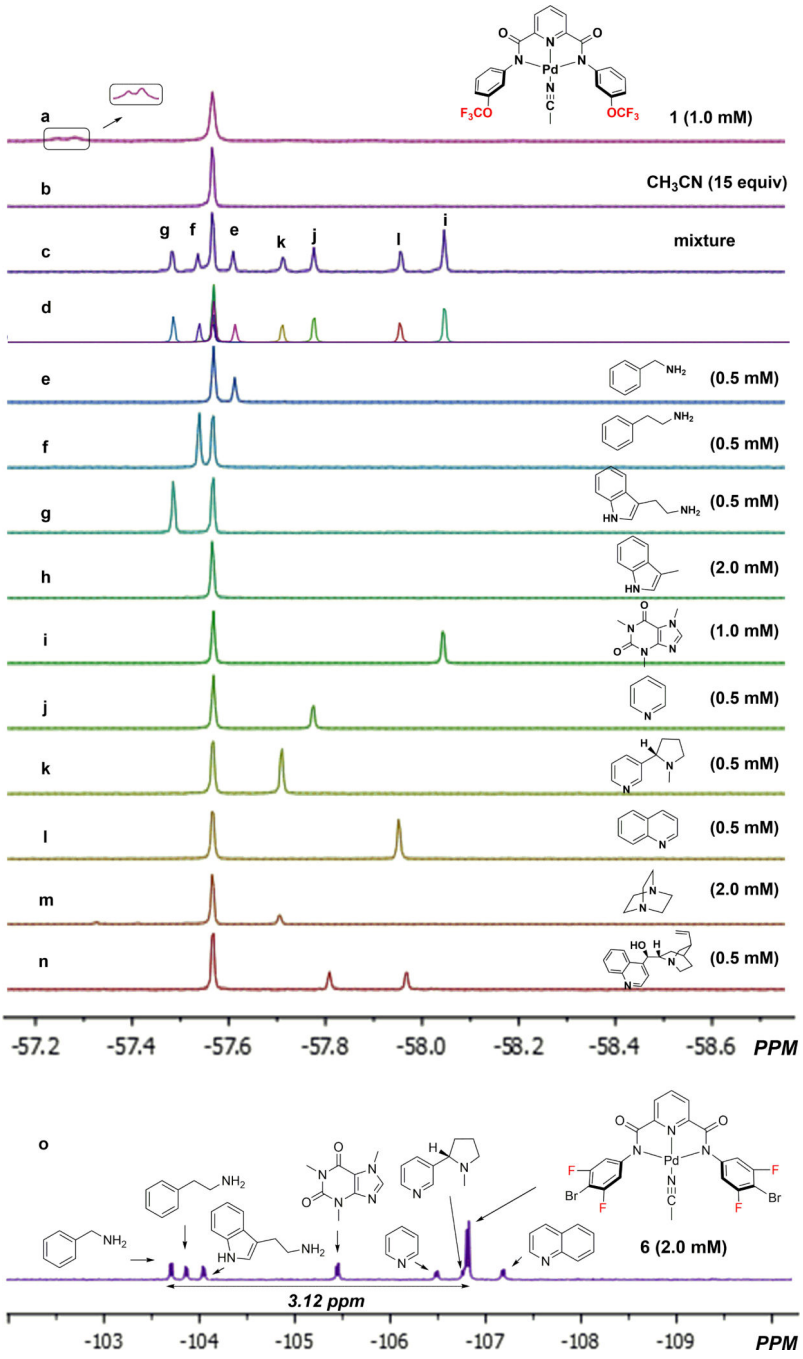

Scheme 1.

a) Cartoon representation of the chemosensory method reported herein. Structurally similar analytes bind to a metal complex, inducing distinct ^{19}F NMR shifts in fluorine atoms placed in close proximity to the bound analyte. b) Palladium pincer complexes with fluorine probes at different locations. c) X-ray single crystal structure of **2**:CH_3CN

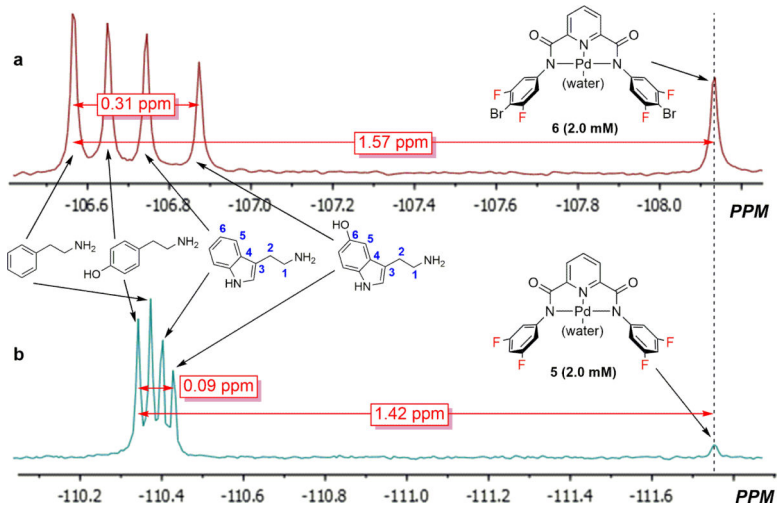

Figure 1.

^{19}F NMR spectra (64 scans each) of a) complex **1** alone (1.0 mM in $CDCl_3$) showing the formation of oligomeric products, b–n) a mixture of complex **1** (1.0 mM in $CDCl_3$), CH_3CN (15 mM) and different analytes (0.5–2.0 mM), b) no analyte, c) mixture of seven analytes, d) superimposition of the spectra of complex **1** with each of the seven analytes collected independently, e–n) complex **1** bound to various analytes. o) ^{19}F NMR spectrum (64 scans) of a mixture of complex **6** (2 mM in $CDCl_3$), CH_3CN (30 mM) and different analytes (0.5–2.0 mM).

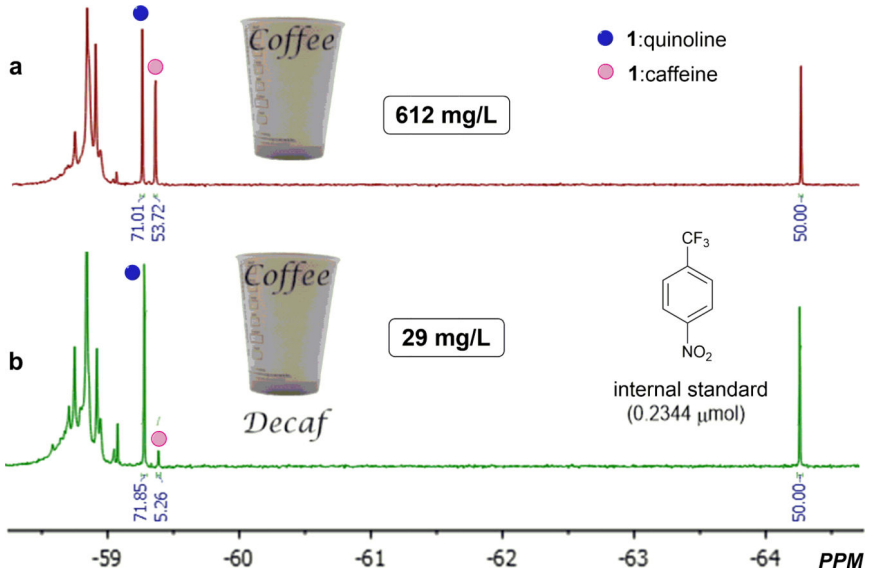

Figure 2.

^{1}H-decoupled ^{19}F NMR spectra (128 scans) of mixtures of a) complex **6** and b) complex **5** (ca. 2.0 mM each), with (from left to right) 2-phenethy lamine, tyramine, tryptamine, and serotonin (ca. 0.25 mM each) in THF/D_2O. The spectra are aligned with respect to the receptor peak so that the magnitudes of the chemical shift dispersions of **5** and **6** may be directly compared.

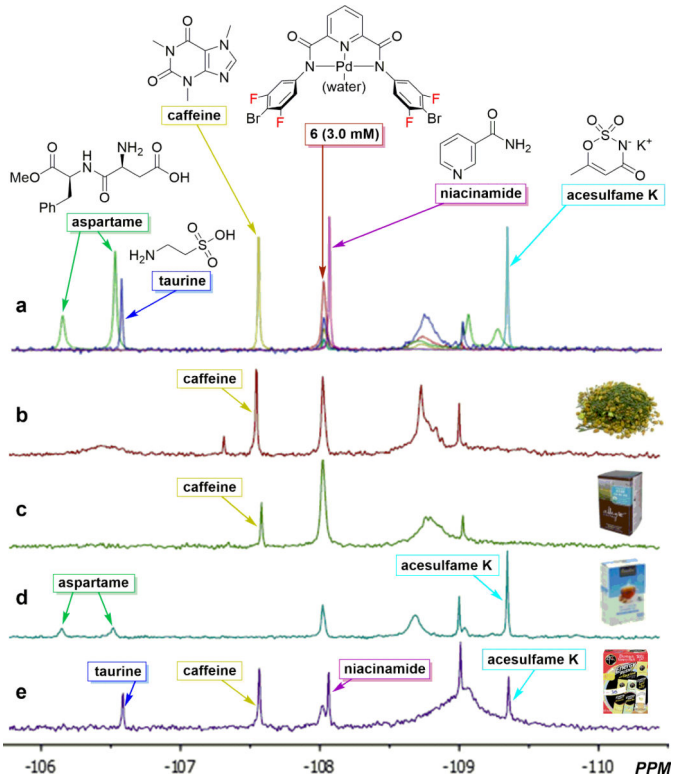

Figure 3.

^{19}F NMR spectra (128 scans) of a mixture of complex **1** (ca. 3.0 mM in MeOH/D_2O/H_2O), internal standards (molar ratio of 4-nitrobenzotrif luoride:quinoline = 50:35.1) and coffee. a) 40 μL of regularly brewed coffee was added. b) 80 μL of decaffeinated coffee was added.

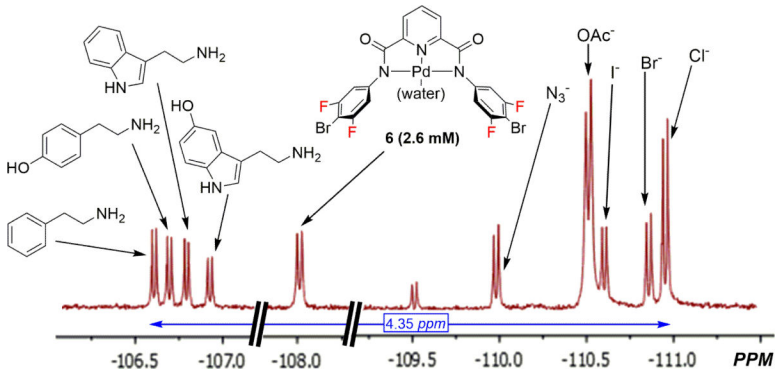

Figure 4.

^{1}H-decoupled ^{19}F NMR spectra (64-128 scans each): a) superimposed spectra of mixtures of complex **6** (ca. 2.8 mM) with aspartame (ca. 4.1 mM), taurine (ca. 4.1 mM), caffeine (ca. 2.0 mM), niacinamide (ca. 2.0 mM), and acesulf ame potassium (ca. 2.0 mM) in MeOH/D_2O/H_2O, each collected independently. Spectra of b) tea brewed f rom loose *genmaicha* green tea, c) tea brewed from Allegro brand *Asian Gen Mai Cha* tea bag, d) Essential Everyday brand *No Calorie Sweetener*, and e) 4C brand *Energy Rush Tea2Go* energy drink, respectively, with complex **6** (ca. 2.8 mM) in MeOH/D_2O/H_2O, with identif iable ingredients labelled.

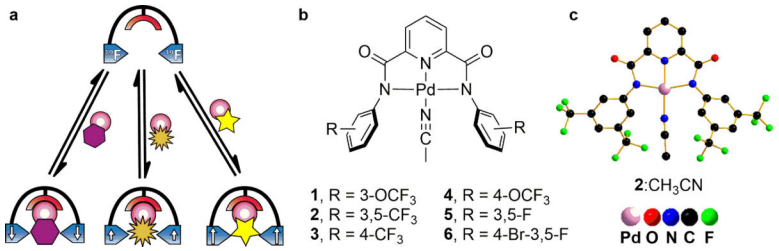

Figure 5.

^{19}F NMR spectrum (128 scans) of a mixture of complex **6** (ca. 2.6 mM), 2-phenethy lamine (ca. 0.1 mM), tyramine (ca. 0.1 mM), tryptamine (ca. 0.1 mM), serotonin (ca. 0.1 mM), tetrabuty lammonium azide (ca. 0.2 mM), tetrabuty lammonium acetate (ca. 1.1 mM), tetrabuty lammonium iodide (ca. 0.2 mM), tetrabuty lammonium bromide (ca. 0.2 mM), and tetrabuty lammonium chloride (ca. 0.2 mM) in THF/D_2O. The distance between the most upfield and most downfield signals is 4.35 ppm.