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Detection and Differentiation of Neutral Organic Compounds by ^{19}F NMR with a Tungsten Calix[4]arene Imido Complex

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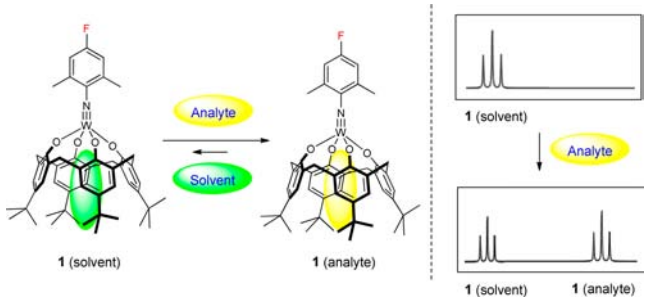
Supporting Information

ABSTRACT: Fluorinated tungsten calix[4]arene imido complexes were synthesized and used as receptors to detect and differentiate neutral organic compounds. It was found that the binding of specific neutral organic molecules to the tungsten centers induces an upfield shift of the fluorine atom appended on the arylimido group, the extent of which is highly dependent on electronic and steric properties. We demonstrate that the specific bonding and size-selectivity of calix[4]arene tungsten−imido complex combined with ^{19}F NMR spectroscopy is a powerful new method for the analysis of complex mixtures.

The selective detection and identification of organic compounds is of fundamental importance in environmental monitoring and biological studies.[1,2] The desire for rapid and reliable analytical methods has led to extensive studies of chemical sensors that rely on changes in fluorescence,[3] resistance[4] or other properties in response to a target analyte. However, the difficulty in direct conversion of a sensor response to precise structure and concentration information limits the use of these methods in the detection and differentiation of analytes in complex mixtures. Therefore, it is highly desirable to develop sensing platforms that provide outputs that are effectively analyte fingerprints. Herein, we report such a method by combining a calix[4]arene tungsten−imido receptor with ^{19}F NMR for the selective detection and differentiation of organic molecules in complex mixtures.[5]

Calixarenes have found wide application in molecular recognition and sensing as a result of their utility as rigid scaffolds that present diverse functionality and encapsulate molecules.[6] The interactions between unfunctionalized calixarenes and neutral organic molecules are weak, and their host−guest complexes are best characterized in the solid state.[7] In contrast, metalated calixarene complexes tend to be higher affinity receptors as a result of the presence of the Lewis acidic metal centers.[8] Among the various metalated calixarene complexes, tungsten−oxo complex stands out as being particularly stable and has a restrictive binding site capable of binding small Lewis basic organic molecules.[9] Despite the highly specific recognition properties of these complexes, their application in sensing is largely unexplored. In 2002, we reported a conducting polymer incorporated with calixarene tungsten−oxo complex and observed a change of polymer's conductivity in the presence of certain organic molecules.[10] However, differentiation of various analytes, especially in complex mixtures, would still be challenging using that method. Put simply, more information from a sensor than a change in the intensity of an single observable signal is often needed to precisely identify an analyte in a confounding environment. To address this challenge, we have designed a fluorinated tungsten−imido calix[4]arene receptor/chemosensor. Our hypothesis is that the binding of a Lewis basic organic molecule will induce an increase of the electron density on tungsten thereby changing the chemical shift of the fluorine that is connected by π-conjugation. Critical to the success of this method is the fact that the chemical shift range of ^{19}F NMR spectroscopy is very large (>300 ppm), thereby allowing subtle differences in the electronic structure to produce observable changes (Scheme 1).[11] Furthermore, the lack of organic fluorine compounds in nature combined with the highly specific recognition ability of calixarene tungsten−imido complex precludes interfering background signals and enables the analysis of complex mixtures.

Scheme 1. General Illustration of ^{19}F NMR Spectroscopy Detection of Organic Molecules



We began our investigations by preparing the *t*-Bu-calix[4]arene tungsten−imido complex (**1**). Calix[4]arene tungsten−imido complexes were previously synthesized from the reaction of W(VI)(=NR)$_2$Cl$_2$ with calix[4]arene or the reaction of calix[4]arene tungsten(IV) olefin adduct with organic azides.[12] These methods necessitated the preparation of air-sensitive intermediates, and as an alternative, we attempted to incorporate the imido moiety by direct imination of the corresponding calix[4]arene tungsten−oxo which is stable and readily prepared.[9] Although $WOCl_4$ can be transformed to W(=NR)Cl$_4$ by reaction with isocyanates,[13] no conversion was observed under the same conditions with

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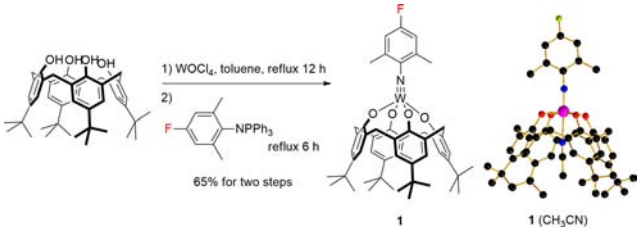
calix[4]arene tungsten−oxo as a result of the increased electron density on tungsten metal and rigid geometry imposed by the calix[4]arene. In analogy to Wittig reactions, which are driven to completion by the strong phosphorus oxygen bond,[14] we envisioned the direct imination of the calix[4]arene tungsten−oxo could be achieved by an analogous iminophosphorane ($Ph_3P{=}NR$) reagent.[15] To our delight, the reaction proceeded smoothly in refluxed toluene, and **1** is obtained in good yield using a "one pot" method from *t*Bu-calix[4]arene (Scheme 2).

Scheme 2. Preparation of Fluorinated Calix[4]arene Tungsten Complex 1 and an X-ray Structure of 1 (1:1 Cocrystal with CH_3CN)[a]



[a]Black = carbon, green = fluorine, blue = nitrogen, red = oxygen, purple = tungsten.

It should be mentioned that the presence of the two methyl groups on the arylimido ligand is crucial to the success of the reaction.[16] The structure of **1** was further confirmed by X-ray crystallography (Scheme 2, right).

With **1** in hand, we explored its sensing potential with ^{19}F NMR spectroscopy by adding various analytes to chloroform solutions of **1** at ambient temperature. Complex **1** only allows endo-coordination of analytes and the size selectivity of the bowlic calix[4]arene eliminates interference from larger analyte.[8] Additionally, our approach is selective to strong binding of Lewis basic analytes that produce static structures on the NMR time scale and peaks at precise chemical shifts. This latter feature is important because we seek to differentiate between analytes wherein their dissociation is very fast and/or they have weak interactions with the tungsten. In these cases, the ^{19}F NMR shift caused by the presence of the molecule could be considered as a solvent effect, which does not interfere with the sensing of the target molecule. As shown in Figure 1, only a single triplet is observed in ^{19}F NMR experiments with ethyl acetate, acetone, and ethanol, which suggested that these analytes do not bond strongly to tungsten metal and/or the binding is too dynamic to induce a shift in ^{19}F NMR (Figure 1a−d). In presence of a large excess of ethanol, an upfield shift was observed which can be considered as a solvent effect (Figure 1e,f). In contrast, a new upfield peak was observed in the experiment with dimethyl sulfoxide (DMSO) indicating the association of DMSO and **1** in solution. The upfield shift is consistent with the assumption that the electron density on tungsten metal increases upon the coordination of analyte. Increasing the concentration of the DMSO led to the disappearance of the signal for **1** indicating full conversion to the inclusion complex. The chemical shift of the new peak remains at constant chemical shift, thereby indicating that the shift is not caused by a solvent effect. Furthermore, the binding with DMSO and *N*,*N*-dimethylformamide (DMF) produces much larger upfield shifts than acetonitrile (CH_3CN) (Figure 1g,i,q), which indicates the response is highly dependent on the electron donating ability of the analyte. This hypothesis is

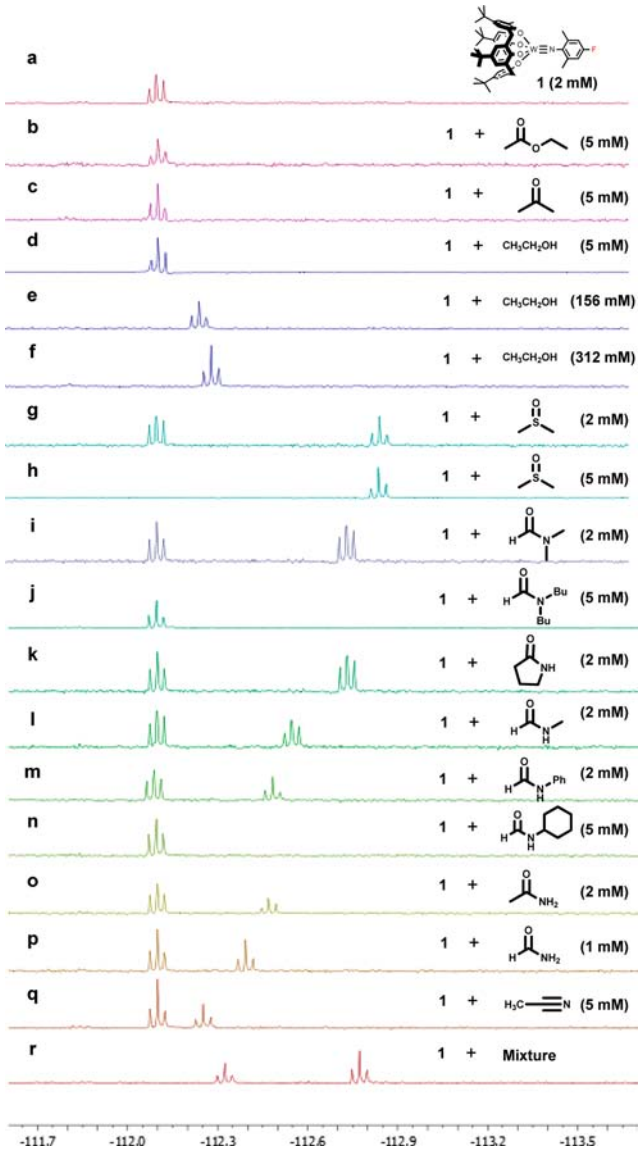


Figure 1. ^{19}F NMR spectrum (typically 64 scans) of a mixture of complex **1** (2 mM in $CDCl_3$) and different analytes (1.0−5.0 mM). (e and f) A total of 5 and 10 μL of ethanol was added to complex **1** (2 mM) in 0.55 mL $CDCl_3$, respectively. (r) Ethyl acetate, acetone, ethanol, and *N*,*N*-dibutylformamide (each 10 μL) were added to a mixture of complex **1** (2 mM) and DMF (5 mM) in $CDCl_3$.

further supported by experiments with various structurally diverse amides. The amide with more electron donating substituents on carbonyl group and nitrogen atom induced a more pronounced upfield shift (Figure 1i−p). DMF and 2-pyrrolidinone, which possess similar electron density on oxygen and steric bulk, resulted in similar shifts (Figure 1i,k). Another observation from Figure 1 is that DMSO and amides show better coordinating ability than CH_3CN which is consistent with a previous study.[17] *N*,*N*-Dibutylformamide failed to show a response with **1** because it is too bulky to bind in the cavity (Figure 1j). The precise size selectivity of this method was further demonstrated by the different behavior between *N*-phenylformamide and *N*-cyclohexylformamide wherein only *N*-phenylformamide induced a change in the ^{19}F NMR (Figure 1m,n). Clearly, the cavity effect of calix[4]arene enables the size discrimination of analytes with the same function group. To test the application of the method in the analysis of complex

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mixture, **1** was mixed with DMF and an excess amount of acetone, ethanol, ethyl acetate and *N*,*N*-dibutylformamide in chloroform. As shown in Figure 1, only complex **1** and its adduct with DMF were observed in ^{19}F NMR (Figure 1r).

Considering the diverse methods to elaborate calixarenes,[6,18] tuning the selectivity of the method should be readily achieved by modifying the upper rim of calixarene. To test the feasibility of this idea, tungsten calixarene−imido **2** without *t*-Bu group was prepared using the same method as shown in Scheme 1. Indeed, **2** displays different selectivity and is capable of hosting larger molecules such as *N*-cyclohexylformimade and *N*,*N*-dibutylformamide, which failed to coordinate to **1** (Figure 2b,c).

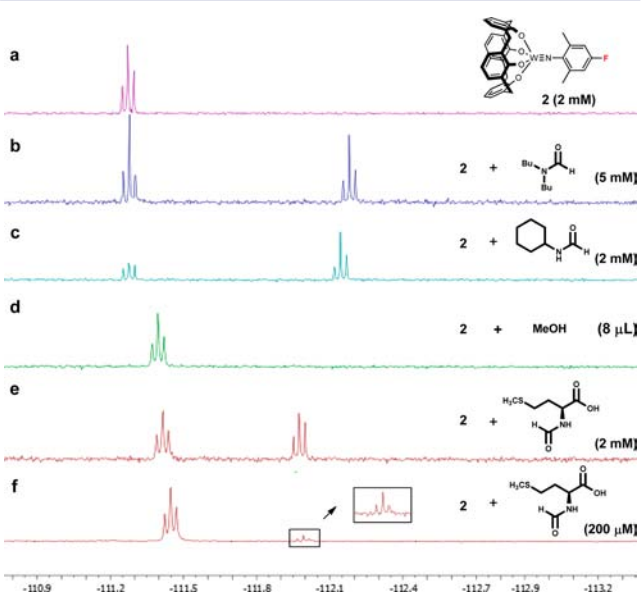

Figure 2. ^{19}F NMR spectrum (typically 64 scans) of a mixture of **2** (2 mM) and different analytes (2.0−5.0 mM). (d−f) Methanol (ca. 8 μL) was used as a cosolvent to dissolve *N*-formylmethionine. (f) An acquisition time of 24 min (800 scans) was employed.

We next explored potential applications of the method to detect biologically relevant amides. *N*-Formylmethionine is known to play an important role in the protein synthesis of bacteria and is recognized by the human body to stimulate immune defense.[19] The detection of *N*-formylmethionine is of interest as it is a characteristic structure motif of prokaryotic proteins.[20] Both **1** and **2** were tested, and only **2** binds *N*-formylmethinine (Figure 2e). The slight shift of the signal of unbound **2** is a result of the use of methanol as a cosolvent to dissolve *N*-formylmethionine. With an acquisition time of 24 min (800 scans), a detection limit of 200 μM could be achieved using this method (Figure 2f).

To further demonstrate applications in the analysis of complex mixtures, we have applied our method to the direct analysis of a crude reaction mixture. The complexity of reaction mixtures typically necessitates gas chromatography or liquid chromatography−mass spectrometry to provide detailed information. However, these schemes require time-consuming prepurification steps, and therefore, alternatives are desirable. As chemical reactions are accompanied by the bond cleavage and formation, the electronic properties and the size of the product are usually different from the starting material. To illustrate that subtle differences in a complex background can be observable by our tungsten−imido sensor, we selected the Suzuki−Miyaura reaction as a model system. This complex mixture contains aryl halide, organoboronic acid, palladium metal, phosphine ligand, inorganic base and water.[21] Moreover, side reactions, such as protonation or homocoupling of organoboronic acid and the overlap of signals at aromatic range, can make the crude proton NMR difficult to interpret. The Suzuki−Miyaura coupling with 4-cyanobenzenitrile and phenyl boronic acid was carried out using $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ as the catalyst with a mixture of DME and 2 M Na_2CO_3 as the solvent. Small aliquots were taken and mixed with **1** in chloroform for ^{19}F NMR analysis. As shown in Figure 3, only

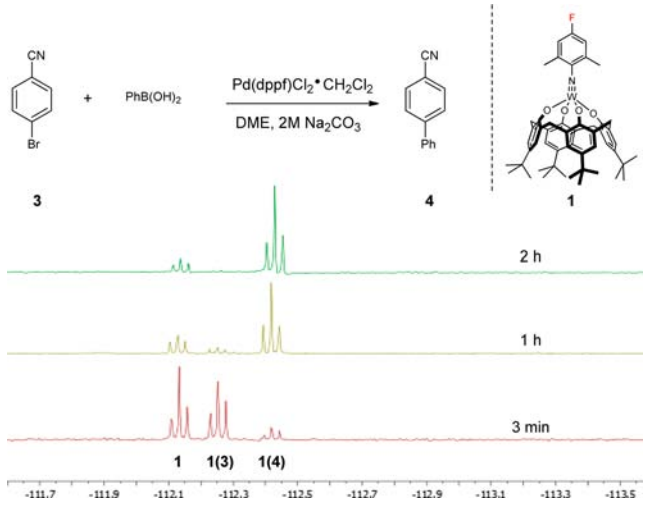

Figure 3. ^{19}F NMR spectrum (typically 128 scans) of a mixture of **1** (3 mM, 0.55 mL) and crude reaction mixture (60 μL) taken after reaction was carried out for 3 min, 1 h, and 2 h, respectively.

three species were observed in ^{19}F NMR spectrum, which were identified as unbound **1**, and adducts of **1** with the starting material **3** and product **4**. As the reaction proceeded, the starting material decreased with a concurrent increase of product. The simplicity of the spectrum allowed for a clear monitoring of the reaction.

In summary, we have demonstrated a new sensing scheme based on fluorinated calixarene imido complexes and their applications in the detection and differentiation of neutral organic molecules. The upfield shift of ^{19}F NMR upon binding to the tungsten center is self-consistent and supports our model of coordination of Lewis bases to the tungsten centers transmitting greater electron density at the fluorine center. The power of this method is a clear and unambiguous detection of target molecules in complex mixtures and we have demonstrated the robust sensing in complex organic reactions. The combination of molecule recognition with ^{19}F NMR technology not only allows the analysis of complex mixture but also provides valuable structure information. The application of this method can be easily widened by designing more fluorinated receptors.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization data for all new compounds. 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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