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A Method for Detecting Water in Organic Solvents

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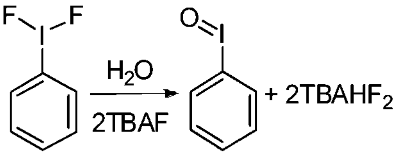
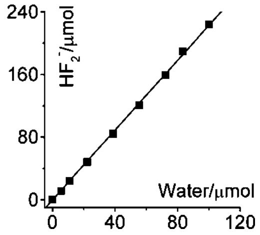
ABSTRACT





The potent dehydrating ability of difluoro(aryl)-λ^3-iodanes is exploited to develop a convenient ^{19}F-NMR-based aquametry method that is more sensitive than coulometric Karl Fischer titration. The key difluoro(aryl)-λ^3-iodane reagents are synthesized readily from commercially available and inexpensive precursors.

In modern synthetic chemistry, significant effort may be expended to exclude moisture from reactions. Dehydration procedures are often performed to ensure experimental reproducibility when water-sensitive reagents are used. However, water's ubiquity, solubility, and propensity to physisorb on reaction vessel surfaces often leave the experimentalist to question if putatively anhydrous conditions actually are. The fundamental question "How dry is dry?" proves to be devilishly difficult to answer if an accurate determination of trace water contaminant at the μg level is required.

We reported recently the synthesis of anhydrous fluoride salts, such as tetrabutylammonium fluoride (TBAF), from hexafluorobenzene and tetraalkylammonium cyanides.[1−3] Concurrent with this preparative $\mathrm{S_N}$Ar reaction, cogenerated hexacyanobenzene scavenges residual water to form tetrabutylammonium pentacyanophenolate and two equivalents of tetrabutylammonium bifluoride ($TBAHF_2$). Thus, the anhydrous fluoride reagents prepared and used in situ are exceptionally dry. Upon isolation of the fluoride salts for storage, the dehydrating agent is removed leaving the reagents susceptible to trace water contamination from solvents and vessels when the salts are redissolved for synthetic chemistry. Existing physical and chemical aquametry methods for quantitative measurement of water in organic solvents (GC,[4−7] IR,[8−13] and Karl Fischer titration[14,15]) are not well suited for rapid trace water analysis at the scale (1 mL total solvent volume) or under the conditions used for fluorination. (Sample preparation in an inert atmosphere glovebox further complicates aquametry.) We sought an alternative general method that would allow

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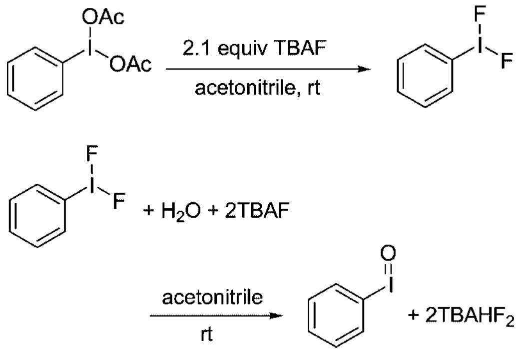
us to determine directly the amount of water in solutions containing dry fluoride salts. We have found that ^{19}F NMR spectroscopy in conjunction with the reagent combination TBAF/PhI(OAc)$_2$ offers a rapid, convenient, general, and exquisitely sensitive (100 ng detection limit) aquametry method.[16,17]

Difluoro(aryl)-λ^3-iodanes are recognized as being remarkably water sensitive under basic conditions.[18] Difluoro(aryl)-λ^3-iodanes have been prepared from ArIX$_2$ compounds and aqueous HF,[19] by oxidation of iodoarenes with electrophilic fluorine sources (F$_2$,[20,21] XeF$_2$,[22−28] ClF,[29] Selectfluor[30]) and by treatment of iodosoarenes or bis(trifluoroacetoxy)iodo arenes with SF$_4$.[31] We have found that difluoro(phenyl)-λ^3-iodane can also be made simply and directly from iodobenzene diacetate (PhI(OAc)$_2$) by ion exchange under anhydrous basic conditions. When a CD$_3$CN solution of carefully dried PhI(OAc)$_2$ is treated with anhydrous TBAF at room temperature, an instantaneous ion exchange occurs to form PhIF$_2$ and TBAOAc in nearly quantitative yield (Scheme 1). If excess added fluoride is present, it associates with PhIF$_2$ to form the complex anion PhIF$_3$$^-$, as is indicated by a broad and shifting signal in the ^{19}F NMR spectrum. If a slight molar excess of fluoride is present, the signal resonates at approximately −13 ppm; further additions of TBAF shift the fluoride signal upfield. (All ^{19}F chemical shift values are referenced to $\delta = 0$ for CFCl$_3$, used as an external standard.) Analyses of the ^{19}F, ^{13}C, and ^{1}H NMR spectra of PhIF$_2$ (^{19}F NMR: $\delta = -172$ ppm) solutions indicated that small amounts (1−2%) of bifluoride ion (^{1}H NMR: $\delta = 16.4$ ppm, t; ^{19}F NMR: $\delta = -146.5$ ppm, d, $J_{\mathrm{H-F}} = 121$ Hz) and PhIO were also formed. We suspected that these impurities arose from trace water contamination (Scheme 1) and sought to investigate and exploit the water sensitivity of PhIF$_2$ under these conditions.

Scheme 1. Preparation and Reaction of PhIF$_2$



PhIF$_2$ reacts slowly with water under acidic or neutral conditions, in keeping with the observation that difluoro-(aryl)-λ^3-iodanes can be prepared with aqueous HF. However, NMR titration experiments revealed that PhIF$_2$ is hydrolyzed immediately and quantitatively to form HF$_2$$^-$ and iodosobenzene (PhIO) in the presence of basic fluoride reagents. The characteristic ^{19}F NMR signal of HF$_2$$^-$ resonates near that of the BF$_4$$^-$ ion ($\delta = -151$ ppm) permitting TBABF$_4$ to be used as a convenient internal standard.[32] Comparative integration of the TBABF$_4$ and TBAHF$_2$ signals allows water-generated bifluoride ion to be quantified easily. To test the accuracy and reproducibility of the TBAF/PhI(OAc)$_2$ method for water detection, we constructed specialized reaction vessels by fusing crimp-top autosampler vials (2.0 mL, borosilicate glass, PTFE/silicone/PTFE septum seal) to the open ends of standard (5 mm) NMR tubes (Figure 1). These customized tubes were charged with PhI(OAc)$_2$,

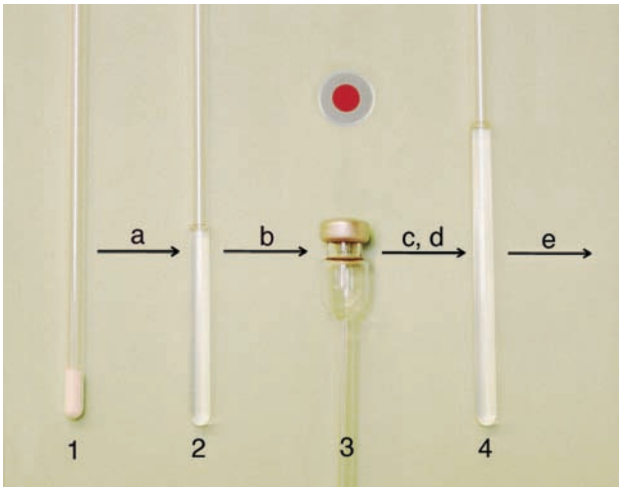


Figure 1. Graphical representation of the water determination experiment. From left to right: (1) TBAF/PhI(OAc)$_2$/TBABF$_4$ mixture in a reaction tube; (2) assay mixture dissolved in CD$_3$CN; (3) side (bottom) and top (top) views of a customized 5 mm NMR tube featuring a fused crimp cap and septum seal; (4) tube containing solid reagents (TBAF, TBABF$_4$, PhI(OAc)$_2$), CD$_3$CN and sample after the addition of the solvent being tested. The process arrows indicate (a) addition of CD$_3$CN, (b) installation of the cap, (c) collection of the background ^{19}F NMR spectrum, (d) injection of the solvent being tested, and (e) collection of the final ^{19}F NMR spectrum.

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(16) Although ^{19}F NMR spectroscopy has been used previously for aquametry, see ref 17, the fluorinated probe used earlier, hexafluoroacetone, offers clear disadvantages in terms of safety, sensitivity, chemical compatibility, and speed compared to the TBAF/PhI(OAc)$_2$ reagent.

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TBAF, TBABF$_4$ (internal standard) and CD$_3$CN, sealed, and baseline ^{19}F NMR spectra of the samples were obtained. For titration experiments involving large amounts of added water (100−2000 μg), NMR spectra were gathered and analyzed after multiple measured additions of standardized water solutions through the septum cap of a single tube. The time elapsed between injection and completion of each NMR data acquisition was less than 10 min. The change in the integrated peak areas for the BF$_4^-$ and HF$_2^-$ signals confirmed that 2 equiv of HF$_2^-$ were generated for each equivalent of added H$_2$O (Figure 2). Interestingly, no H−D exchange is observed under these anhydrous conditions, indicating that anhydrous solutions of TBAPhIF$_3$ are significantly less basic than TBAF solutions. Because (1) the TBA cation is susceptible to fluoride-induced E2 elimination in CD$_3$CN upon long standing and (2) this elimination reaction is suppressed by the weakly basic PhIF$_3^-$ complex anion, the dehydrating reagent is best prepared with a 1:1 PhIF$_2$/TBAF stoichiometry.

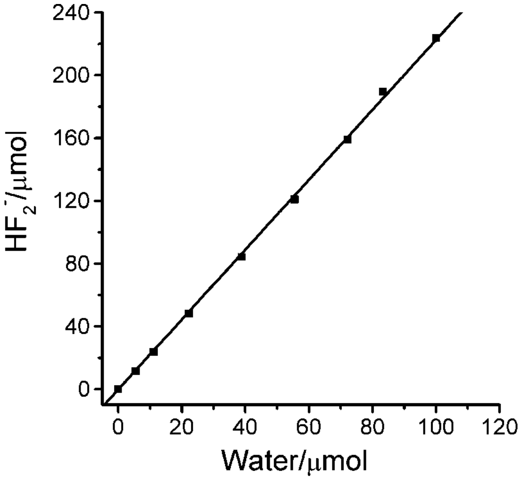

Figure 2. Results from the titration of a PhIF$_2$/CD$_3$CN solution with standardized aqueous acetonitrile.

For solutions containing very low water concentrations (less than 10 ppm), we were concerned that sample manipulation could introduce significantly more water than that being measured; thus, we sought to develop a reproducible "single injection" method. The rationale for this method is that if the septum is only pierced once, all operations may be performed under the inert atmosphere conditions required for very careful work. In the single injection method, the PhIF$_2$/TBAF/TBABF$_4$ reagent is prepared in CD$_3$CN in a glovebox and the modified NMR tube is sealed with a crimp top cap and (new) septum seal. The tube is removed from the glovebox and a baseline ^{19}F NMR spectrum is recorded to establish the amount of background bifluoride ion present. (Background bifluoride ion arises from traces of water in the NMR solvent, salts, and from physisorbed water on the glass vessel.) The sample solution to be tested (either within or outside of the glovebox) is then injected and a second ^{19}F NMR spectrum is obtained. To illustrate and test the reproducibility of the single injection technique, a series of sample tubes was prepared, baseline spectra were gathered, and each tube was treated with a weighed amount of commercially obtained "dry" acetonitrile (measured [H$_2$O] = 180 ppm). Figure 3 shows the result of a single injection water determination experiment involving the addition of 49 μg of water.

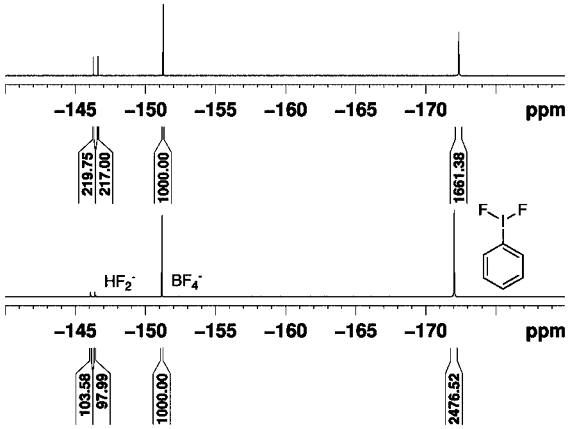

Figure 3. Single injection water determination by ^{19}F NMR: bottom, background spectrum before the addition of "wet" CH$_3$CN; top, spectrum collected after the injection of a CH$_3$CN sample containing 49 μg of H$_2$O.

To test the reproducibility and accuracy of the measurement technique, we measured water concentrations in 15 samples by conventional coulometric Karl Fischer titration and by ^{19}F NMR spectroscopy. For the NMR procedure, the reproducibility was equal to that of Karl Fischer titration (±3%) for samples involving measurement of 70 μg of water. Because the NMR method permitted sample preparation in an inert atmosphere glovebox, sample handling errors for Karl Fischer titration were larger than those intrinsic to the NMR experiments. Notably, for "dry" THF we were able to measure easily and accurately the addition of 5 μg of water to a sample. In contrast, the detection limit for coulometric Karl Fischer titration using typical commercial equipment is 10 μg of added water.

Reasonable system stability is required for practical application of this water detection method. Since precise evaluation of water concentration relies on an accurate determination of bifluoride ion concentration, it is important to minimize any side reactions that might generate HF$_2^-$. Control experiments showed that the PhI(OAc)$_2$/TBAF reagent is stable in CD$_3$CN solution for several hours, long enough for baseline and sample NMR spectra to be gathered. After this time, small amounts of cation decomposition produce detectable amounts of HF$_2^-$. The long-term stability of the system can be improved substantially if more robust cations, such as tetramethylammonium[33] or hexamethylpi-

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(32) The long T1 relaxation time for tetrafluoroborate necessitated single scan acquisitions. If better signal-to-noise ratios are required, fluorinated benzenes may be used as internal standards.

peridinium[34] are used instead of TBA, although these salts prove to be less soluble than TBAF. Conveniently, the stable TBAF/PhI(OAc)$_2$/TBABF$_4$ salt mixture can be preweighed and sealed in the NMR tube so that deuterated solvent and liquid samples can be added through the septum subsequently (Figure 1, left). Like TBAF itself, the reagent mixture is stable in the solid state for months at −40 °C under an inert atmosphere.

Using typical instrumentation (Bruker Avance 400 MHz, QNP probe) and a single scan acquisition, the signal-to-noise ratio is sufficient to measure accurately the addition of 3 μg of water ($[H_2O] = 3$ ppm in 1 mL solution). ^{19}F NMR sensitivity is sufficient for submicrogram (100 ng) water detection ($[H_2O] = 0.1$ ppm in 1 mL) with more sophisticated equipment (600 MHz spectrometer, dedicated H/F probe) and a longer acquisition time; however, we have found it a significant challenge to prepare TBAF/PhIF$_2$/TBABF$_4$ solutions that are sufficiently dry ($[H_2O] < 1$ μg) to provide the low background necessary for submicrogram water detection.

The scope of the NMR aquametry technique is relatively broad, although it is limited by the basicity and nucleophilicity of weakly coordinated fluoride ion. Halogenated alkanes and enolizable ketones and aldehydes are incompatible with these conditions, but measurement of trace water contamination in a wide range of alcohols and aprotic solvents (DMF, CH_3CN, DMSO, benzene, toluene, ether, THF, pyridine) is possible. Although it may seem surprising that the water content in alcohols can be measured by this technique, the iodonium ligand exchange reaction of an alcohol for fluoride is strongly disfavored. It is only the formation of the I═O double bond that drives the dehydration reaction under basic conditions.

In conclusion, we have found that the TBAF/PhI(OAc)$_2$/TBABF$_4$ reagent combination removes water quantitatively from organic solvents and generates the easily detectable bifluoride ion in the process. ^{19}F NMR spectroscopy of these solutions permits water concentration to be assessed sensitively and accurately for a relatively broad range of solvents. The aquametry technique is compatible with glovebox and inert atmosphere work; it is relatively rapid, and it needs no calibration other than the acquisition of a background ^{19}F NMR spectrum. Moreover, it can be performed with dried, commercially available salts and NMR solvents. The difluoro(aryl)-λ^3-iodane-based procedure is a convenient alternative to Karl Fischer titration wherever NMR infrastructure is available.

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Supporting Information Available: Experimental procedures for sample preparation and water determination. This material is available free of charge via the Internet at http://pubs.acs.org.

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