Published in final edited form as:

Org Lett. 2008 October 16; 10(20): 4413–4416. doi:10.1021/ol8015429.

A Method for Detecting Water in Organic Solvents

Haoran Sun, Bijia Wang, and Stephen G. DiMagno

Department of Chemistry, University of Nebraska, Lincoln, NE 68588-0304, sdimagno1@unl.edu

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 $\text{S}_{\text{N}}\text{Ar}$ reaction, cogenerated hexacyanobenzene scavenges residual water to form tetrabutylammonium pentacyanophenolate and two equivalents of tetrabutylammonium bifluoride (TBAHF₂). 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 glove box further complicates aquametry.) We sought an alternative general method that would allow 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 SF₄.³¹ We have found that difluoro(phenyl)-λ³-iodane can also be made simply and directly from iodobenzene diacetate (PhI(OAc)₂) by ion exchange under anhydrous basic conditions. When a CD₃CN solution of carefully dried PhI(OAc)₂ is treated with anhydrous TBAF at room temperature, an instantaneous ion exchange occurs to form PhIF₂ and TBAOAc in nearly quantitative yield (Scheme 1). If excess added fluoride is present it associates with PhIF₂ to form the complex anion PhIF₃[−], as is indicated by a broad and shifting signal in the ¹⁹F 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 ¹⁹F chemical shift values are referenced to δ = 0 for CFC1₃, used as an external standard.) Analyses of the ¹⁹F, ¹³C and ¹H NMR spectra of PhIF₂ (¹⁹F NMR: δ = −172 ppm) solutions indicated that small amounts (1–2 %) of bifluoride ion (¹H NMR: δ = 16.4 ppm, t; ¹⁹F NMR: δ = −146.5 ppm, d, J_{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 PhIF₂ under these conditions.

PhIF₂ reacts slowly with water under acidic or neutral conditions, in keeping with the observation that difluoro(aryl)-λ³-iodanes can be prepared with aqueous HF. However, NMR titration experiments revealed that PhIF₂ is hydrolyzed immediately and quantitatively to form HF₂[−] and iodosobenzene (PhIO) in the presence of basic fluoride reagents. The characteristic ¹⁹F NMR signal of HF₂[−] resonates near that of the BF₄[−] ion (δ = −151 ppm) permitting TBABF₄ to be used as a convenient internal standard.³² Comparative integration of the TBABF₄ and TBAHF₂ 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, TBAF, TBABF₄ (internal standard) and CD₃CN, sealed, and baseline ¹⁹F NMR spectra of the samples were obtained. For titration experiments involving large amounts of added water (100 to 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 minutes. The change in the integrated peak areas for the BF₄[−] and HF₂[−] signals confirmed that 2 equivalents of HF₂[−] were generated for each equivalent of added H₂O (Figure 2). Interestingly, no H-D exchange is observed under these anhydrous conditions, indicating that anhydrous solutions of TBAPhIF₃ are significantly less basic than TBAF solutions. Because 1) the TBA cation is susceptible to fluoride-induced E2 elimination in CD₃CN upon long standing, and 2) this elimination reaction is suppressed by the weakly basic PhIF₃[−] complex anion, the dehydrating reagent is best prepared with a 1:1 PhIF₂:TBAF stoichiometry.

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 PhIF₂/TBAF/TBABF₄ reagent is prepared in CD₃CN in a glove box and the modified NMR tube is sealed with a crimp top cap and (new) septum seal. The tube is removed from the glove box and a baseline ¹⁹F 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 glove box) is then injected and a second ¹⁹F 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 [H₂O] = 180 ppm).

Figure 3 shows the result of a single injection water determination experiment involving the addition of 49 μg of water.

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 ($\pm 3\%$) for samples involving measurement of 70 μg of water. Because the NMR method permitted sample preparation in an inert atmosphere glove box, 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 $\text{PhI}(\text{OAc})_2/\text{TBAF}$ reagent is stable in CD_3CN 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 tetramethylammonium³³ or hexamethylpiperidinium³⁴ are used instead of TBA, although these salts prove to be less soluble than TBAF. Conveniently, the stable $\text{TBAF}/\text{PhI}(\text{OAc})_2/\text{TBABF}_4$ 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 ($[\text{H}_2\text{O}] = 3 \text{ ppm}$ in 1 mL solution). ^{19}F NMR sensitivity is sufficient for submicrogram (100 ng) water detection ($[\text{H}_2\text{O}] = 0.1 \text{ ppm}$ 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 $\text{TBAF}/\text{PhIF}_2/\text{TBABF}_4$ solutions that are sufficiently dry ($[\text{H}_2\text{O}] < 1 \mu\text{g}$) 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 $\text{I}=\text{O}$ double bond that drives the dehydration reaction under basic conditions.

In conclusion, we have found that the $\text{TBAF}/\text{PhI}(\text{OAc})_2/\text{TBABF}_4$ 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 glove box and inert atmosphere work; it is relatively rapid, and it needs no calibration other than the acquisition of a baseline ^{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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank the National Science Foundation (CHE 0717562) for support and the National Institutes of Health (RR016544-01) for infrastructure to conduct this research. We thank Dr. John Erickson and Novartis for the use of an electrochemical Karl Fischer titrator.

References

1. Sun H, DiMagno SG. *J Am Chem Soc* 2005;127:2050–2051. [PubMed: 15713075]
2. Sun H, DiMagno SG. *Angew Chem, Int Ed* 2006;45:2720–2725.
3. Sun H, DiMagno SG. *Chem Commun* 2007:528–529.
4. Nussbaum R, Lischke D, Paxmann H, Wolf B. *Chromatographia* 2000;51:119–121.
5. Hogan JM, Engel RA, Stevenson HF. *Anal Chem* 1970;42:249–52.
6. Pasika WM, West AC III. *Anal Chem* 1971;43:275–6.
7. Knight HS, Weiss FT. *Anal Chem* 1962;34:749–51.
8. van de Voort FR, Sedman J, Cocciardi R, Juneau S. *Talanta* 2007;72:289–295. [PubMed: 19071616]
9. Li M, Pacey GE. *Talanta* 1997;44:1949–1958. [PubMed: 18966939]
10. Garrigues S, Gallignani M, de la Guardia M. *Anal Chim Acta* 1993;281:259–64.
11. Meeker RL, Critchfield FE, Bishop ET. *Anal Chem* 1962;34:1510–1511.
12. Forbes JW. *Anal Chem* 1962;34:1125–1128.
13. Streim HG, Boyce EA, Smith JR. *Anal Chem* 1961;33:85–89.
14. Scholz, E. *Karl Fischer Titration*. Springer; Berlin: 1984.
15. Mitchell, J., Jr; Smith, DM. *Aquametry: A Treatise on Methods for the Determination of Water*, Pt. 1. 2. Wiley; New York: 1977.
16. Although ^{19}F NMR spectroscopy has been used previously for aquametry, see reference 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..
17. Ho FFL, Kohler RR. *Anal Chem* 1974;46:1302–1304.
18. Zhdankin VV. *Science of Synthesis* 2007;31a:161–233.
19. Sawaguchi M, Ayuba S, Hara S. *Synthesis* 2002:1802–1803.
20. Naumann D, Ruether G. *J Fluorine Chem* 1980;15:213–22.
21. Ruppert I. *J Fluorine Chem* 1980;15:173–8.
22. Sket B, Zupan M, Zupet P. *Tetrahedron* 1984;40:1603–6.
23. Gregorcic A, Zupan M. *J Chem Soc, Perkin Trans 1*;1977:1446–9.
24. Zupan M. *Collect Czech Chem Commun* 1977;42:266–74.
25. Gregorcic A, Zupan M. *Bull Chem Soc Jpn* 1977;50:517–20.
26. Zupan M, Pollak A. *J Fluorine Chem* 1976;7:445–7.
27. Zupan M, Pollak A. *J Org Chem* 1976;41:2179–2182.
28. Zupan M, Pollak A. *J Chem Soc, Perkin Trans 1*;1976:1745–8.
29. Bailly F, Barthen P, Breuer W, Frohn HJ, Giesen M, Helber G, Henkel G, Priwitzer A. *Zeitschrift Anorg Allgem Chem* 2000;626:1406–1413.
30. Ye C, Twamley B, Shreeve JnM. *Org Lett* 2005;7:3961–3964. [PubMed: 16119942]
31. Lyalin VV, Orda VV, Alekseeva LA, Yagupol'skii LM. *Zh Org Khim* 1970;6:329–32.
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.
33. Christe KO, Wilson WW, Wilson RD, Bau R, Feng JA. *J Am Chem Soc* 1990;112:7619–25.
34. Mahjoub AR, Zhang X, Seppelt K. *Chem Eur J* 1995;1:261–5.

Figure 1.

Graphical representation of the water determination experiment. From left to right: 1) TBAF/ $\text{PhI}(\text{OAc})_2$ /TBABF₄ mixture in a reaction tube; 2) assay mixture dissolved in CD_3CN ; 3) side (bottom) and top (top) views of a customized 5 mm NMR tube featuring a fused crimp cap vial septum seal; 4) tube containing solid reagents (TBAF, TBABF₄, $\text{PhI}(\text{OAc})_2$), CD_3CN and sample after the addition of the solvent being tested. The process arrows indicate a) addition of CD_3CN , b) installation of the cap, c) collection of the background ^{19}F NMR spectrum, d) injection of the solvent being tested, e) collection of the final ^{19}F NMR spectrum.

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

Figure 3. Single injection water determination by ^{19}F NMR: bottom, background spectrum before the addition of “wet” CH_3CN ; top, spectrum collected after the injection of a CH_3CN sample containing 49 μg of H_2O .

Scheme 1.
Preparation and reaction of PhIF₂.