KOH/D₂O, 5 min;
then NMR acquisition

Quantification of Hydrogen Fluoride-Based Reagents using a Bifunctional NMR Internal Standard

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ABSTRACT

A new procedure for quantifying the composition of hydrogen fluoride-based reagents by a combination of ^1H and ^{19}F NMR titration has been developed. An aliquot of a hydrogen fluoride reagent sample and a bifunctional internal standard—ethyl trifluoroacetate, were digested with excess KOH in D_2O , and subjected to quantitative NMR analysis. This procedure provides a more convenient operation and more accurate results than traditional volumetric titration.

Commercially available hydrogen fluoride-based reagents (HF reagents), including Olah's reagent,¹ triethylamine trihydrofluoride,² and the more recently reported HF/DMPU reagent,³ are easy-to-handle and inexpensive nucleophilic fluorinating reagents.⁴ The concentration of these so-called HF reagents is usually

determined by differential weighing, or by volumetric titration. However, the relatively low shelf stability of these reagents, due to the high volatility of hydrogen fluoride, causes the in-bottle concentration of HF solutions to deviate from the labeled content, particularly with aged stocks. In addition, the quality of HF reagents may also vary with different batches and manufacturers. As is the case with other difficult-to-handle stock solution-based reagents such as alkyl lithium and metal amides,⁵ a reliable and practical analytical method to determine the composition of solutions of HF is needed. Herein, we report a quantitative ^1H and ^{19}F NMR titration to determine the composition of HF reagents using a bifunctional internal standard—ethyl trifluoroacetate.⁶ This new protocol enables a rapid triplicate analysis of the composition of an HF reagent using only microliter amounts of such reagent.

The classic volumetric titration of an aliquot of an HF reagent, employing standardized sodium hydroxide solution in the presence of phenolphthalein indicator, is a practical approach, but in practice, particularly in an organic synthesis laboratory, this method is cumbersome. Although the cost of instruments and reagents required by the volumetric titration method is inexpensive, the overall operation, including standardizing the sodium hydroxide solution and conducting the titration, is time-consuming. In addition, handling sub-gram amounts of hydrogen fluoride solution in an open vessel may expose technicians to prolonged HF exposure. To our surprise, an alternative, yet efficient and reliable, quantitative

analysis of the composition of HF reagents is lacking. We surmised that recording the ^1H and ^{19}F spectra of an aliquot of an HF-based reagent in the presence of an internal standard with a known ratio of ^1H and ^{19}F may provide the molar ratio of the corresponding organic stabilizer of HF to the internal standard. Hence, the molar ratio of organic stabilizer to HF and the mass percentage of HF could be obtained. Fortunately, both hydrogen and fluorine, particularly the nuclides ^1H and ^{19}F , can be readily quantified by nuclear magnetic resonance spectroscopy (NMR).

In a typical procedure, 25 μL of an HF reagent (e.g. HF-DMPU) and 15 μL of ethyl trifluoroacetate were digested in 500 μL of 3M KOH solution in D_2O to neutralize HF and to convert ethyl trifluoroacetate into potassium trifluoroacetate and ethanol. The digested sample was transferred into an NMR tube, and its ^1H and ^{19}F NMR spectra was recorded (Figure 1). In the ^{19}F spectrum, the integration of the trifluoroacetate signal (CF_3^-) was calibrated to 3, and integration of the KF signal was recorded as X , thus, the mole ratio of ethyl trifluoroacetate to HF was 1: X . Similarly, in the ^1H spectrum, the integration of ethylene group signal in ethanol was calibrated to 2, and integration of the signal that corresponds to the 2 methyl groups in DMPU was recorded as Y . Thus, the molar ratio of DMPU to ethyl trifluoroacetate is 1:($Y/6$), and the molar ratio of HF to DMPU was $X:(Y/6)$. The mass percentage of HF can be derived from equation 1.

Figure 1. NMR Titration of HF-DMPU Reagent

$$w(\text{HF}, \%) = \frac{X \times 20.01}{X \times 20.01 + (Y/6) \times 128.18} \times 100\% \quad (\text{eq.1})$$

Three different HF reagents were successfully analyzed by the procedure described above, and these results were compared with the traditional volumetric titration (Table 1). These two methods provided comparable results, although the NMR titration provided lower and more consistent standard deviations, since the visual judgment of the endpoint in volumetric titration was no longer needed. Considering the fact that NMR quantification can be completed in a significantly shorter time span, and that NMR spectrometers are widely available in academia

and industry, the newly developed NMR quantification is a more practical alternative to the traditional volumetric titration approach.

Table 1. Comparison of Results from NMR quantification and Volumetric Titration on the Composition of HF Reagents

Sample	NMR titration (m/m, %) ^a	Volumetric titration (m/m, %) ^{a,b}
HF/DMPU (in-house, <i>ca.</i> 66%)	67.9±0.29%	69.4±2.6%
HF/Pyridine (commercial, <i>ca.</i> 70%)	68.8±0.28%	64.6±0.31%
HF/Triethylamine (commercial, <i>ca.</i> 25%)	23.7±0.38%	23.7±0.86%

^a An average of three trials. ^b Phenolphthalein was used as indicator.

In summary, we have developed an efficient NMR titration procedure that furnished the composition of several hydrogen fluoride-based reagents. Compared to traditional volumetric titration, the NMR titration is more accurate, significantly faster and consumes less sample. Also, the visual judgment of the endpoint in volumetric titration is no longer needed.

EXPERIMENTAL SECTION

Materials and Methods. NMR spectra were recorded on a Varian 400 MR system (400 MHz) with automated sampling, locking, shimming, and tuning. NMR acquisition parameters: for ¹H: number of points = 16k, d1 = 10 s, pw90 = 14.6 μs, pw = 7.3 μs or 45°, 8 scans; for ¹⁹F: number of points = 64k, d1 = 10 s, pw90 = 13 μs, pw = 6.5 μs or 45°, 16 scans.⁷ Chemical shifts of ¹H signals are referenced to residual HOD at 4.75 ppm. Chemical shifts of ¹⁹F signals are referenced to KF at -

125.30 ppm. Ethyl trifluoroacetate (99%), analytical grade sodium hydroxide and potassium hydroxide (85%), and deuterated solvents were obtained from regular commercial sources and used directly. Olah's reagent and triethylamine trihydrofluoride were purchased from a commercial supplier. The HF-DMPU reagent was prepared by condensing gaseous HF dispensed from a PTFE manifold into a cooled PTFE cylinder that contained pre-weighted DMPU. HDPE vials and bottles purchased from VWR. All operations involving HF were conducted in a well-ventilated fumehood.

Preparation of the Digestion Solution. D₂O (10 mL) was added to a 20 mL-scintillation vial that contained KOH (2 g). The solution was homogenized in a vortex mixer and was ready to use.

Representative Procedure: ¹⁹F NMR Titration. An aliquot of the digestion solution (0.5 mL) was added to a 10 mL-HDPE vial equipped with a micro-stirring bar. The vial was chilled in an ice-water bath, and HF/DMPU (25 µL) and ethyl trifluoroacetate (15 µL) were added via an Eppendorf pipette. The vial was capped, and the aliquot was gently stirred for 5 minutes. The aliquot was then transferred into an NMR tube, and its spectrum was recorded. In the ¹⁹F spectrum, the integration of the two signals (δ -79.24 ppm for trifluoroacetate, and δ -125.30 ppm for KF) showed a 1:6.89 molar ratio of ethyl trifluoroacetate to KF. In the ¹H spectrum, the integration of the two signals (δ 3.45 ppm for the ethyl of

trifluoroacetate, and δ 2.66 ppm for the methyl groups of DMPU) showed a 1:0.44 molar ratio of ethyl trifluoroacetate to DMPU. According to equation 1, the mass percentage of HF is 67.8%.

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(6) Several other internal standards were also tested. A combination of methanol and trifluoroacetic acid caused higher standard deviation. p-Trifluoromethyl phenol suffers low solubility and instability in highly basic aqueous solution.

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