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Determination of the Hammett acidity of HF/base reagents

Mélissa Longuet, Kassandra Vitse, Agnès Martin-Mingot, Bastien Michelet,* Frédéric Guégan,* and Sébastien Thibaudeau*

Université de Poitiers, UMR-CNRS 7285, IC2MP, 4 rue Michel Brunet, TSA 51106, 86073 Poitiers Cedex 9, France

ABSTRACT: Harnessing the acidity of HF/base reagents is of paramount importance to improve the efficiency and selectivity of fluorination reactions. Yet, no general method has been reported to evaluate their acidic properties and experimental designs are still relying on trial-and-error approach. We report a new method based on ^{19}F NMR spectroscopy which allows highly sensitive measures and short-time analyses. Advantageously, the basic properties of the indicators can be determined upstream by DFT calculations affording a simple yet robust semi-empirical approach. In particular, the indicators used in this study were rationally-designed to fit on the conceptually-appealing and commonly-used Hammett scale. This method has been applied to commercially-available and recently developed HF/base reagents.

INTRODUCTION

After decades of research on the development of fluorination methods, the selective incorporation of a fluorine atom into organic molecules still remains a synthetic challenge.¹ To this end, an important number of fluorinating reagents have been developed, all originating from a single source of fluorine that is hydrogen fluoride.² Thus, HF would appear to be the most ideal fluorinating reagent in terms of cost and atom-economy. To overcome the difficulty and the safety hazard associated with the handling of anhydrous hydrogen fluoride, it is better used as a complex with an organic base.³ A wide array of HF/base combinations have been reported as fluorinating reagents over the past decades such as HF/pyridine⁴ or HF/ Et_3N ⁵ to mention but two examples. One of the most representative applications of such HF/base reagents in recent years is certainly the fluoro-functionalization of olefins and alkynes. This includes hydrofluorination (olefins,⁶ alkynes⁷), halofluorination (olefins),⁸ difluorination (olefins),⁹ hetero(S, Se, O, N)-fluorination (olefins),¹⁰ oxofluorination (alkynes)¹¹ and other fluoro-cyclization/rearrangement.¹² In many cases, a careful screening of HF/base reagents were necessary to improve the efficiency of these transformations. Moreover, the acidity of such reagents can also play a crucial role in the regio-,^{9f,9g,9i} chemo-^{9k,9o} or enantioselectivity^{12h,12i} of fluorination reactions. This phenomenon, first reported by Gilmore,^{9b,9g} was then also observed by other authors during the development of fluorinative transformations of olefins (Figure 1). Thus, harnessing the Brønsted acidity of HF/base reagents appears essential for full exploitation of their synthetic potential.

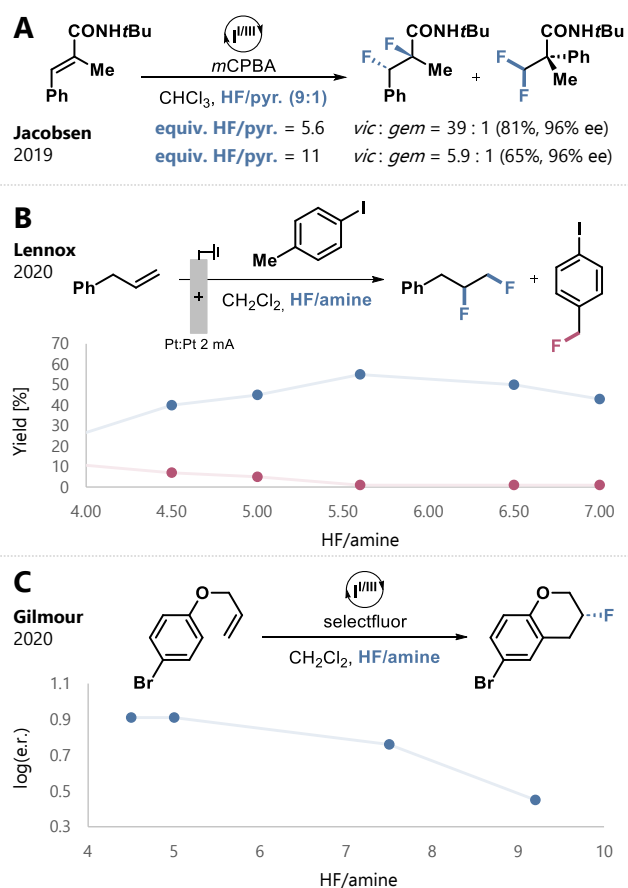


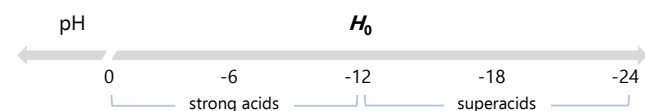
Figure 1. Impact of the acidity of HF/base reagents on the regio- (A, ref 9i), chemo- (B, ref 9k) or enantioselectivity (C, ref 12i) of olefin fluorofunctionalization.

However, unlike dilute aqueous acids whose acidity can be easily determined using the pH scale, evaluating the acidity of HF-based solutions is still a major challenge and no general methods have been developed so far. This prompted us to develop a new strategy for the acidity evaluation of such media. In strong acids, the pH scale becomes inadequate due to the high concentration of active species. These acids are more generally characterized by the Hammett acidity function $H_0 = \text{p}K_{\text{BH}^+} - \log([\text{BH}^+]/[\text{B}])$ where B is a basic indicator and $\text{p}K_{\text{BH}^+}$, the $\text{p}K_{\text{A}}$ of its conjugate acid (Figure 2A).¹³ Its validity relies on the fundamental assumption that the activity coefficient ratio $f_{\text{B}}/f_{\text{BH}^+}$ is the same for different bases of similar structure, meaning that each series of structurally-related basic indicators corresponds to one particular acidity function. The ionization ratio $[\text{BH}^+]/[\text{B}]$ is usually measured by spectrophotometry and the $\text{p}K_{\text{A}}$'s of the protonated indicators are determined by stepwise analysis of media of increasing acidity. Since the seminal work of Hammett in 1932,¹⁴ this approach has been largely improved. Jorgenson and Hartter¹⁵ re-evaluated the validity of the Hammett acidity scale and notably provided a consistent set of indicators which were shortly after also used by the Yates group to quantify the acidity of mineral acids down to $H_0 \approx -11$.¹⁶ In particular, these studies demonstrated the necessity of using basic indicators of similar structures and provided highly reliable values of experimental $\text{p}K_{\text{BH}^+}$ of a wide array of anilines. Later on, the Gillespie's group investigated the acidity of superacidic media¹⁷ (stronger than pure sulfuric acid, $H_0 < -12$). To this end, they employed nitrobenzene derivatives as basic indicators and could estimate the acidity of HF/Lewis acids mixtures with H_0 value as low as -21 .¹⁸ However, all these methods are essentially limited to UV-visible transparent media. For this reason, it has mostly been applied for concentrated aqueous mineral acids and only a handful of anhydrous HF solutions of metal fluorides could have been analyzed.¹⁹ As an alternative to spectrophotometric methods, NMR spectroscopy seems highly attractive (rapid analysis, compatible with any media, impartial to (colored) impurities, applicable to complex mixtures).²⁰ Levy *et al.* investigated the use of aromatic and aliphatic ketones as ^1H NMR probes.²¹ Carbonyl-derived indicators are however known to strongly deviate from ideal behavior (mainly through strong hydrogen-bonding effect) and do not obey the Hammett scale.²² Later on, the group of Sommer studied the protonation of *p*-methoxybenzhydryl cations by ^1H and ^{13}C NMR to explore the limit of superacidity.²³ Although this study provided useful complementary information about the reactivity of strong superacids such as HF/SbF₅, the nature of the indicators is again very different from Hammett bases and the sensitivity remains very low ($\Delta\delta^1\text{H} < 0.5$ ppm, $\Delta\delta^{13}\text{C} < 5$ ppm). This sensitivity issue was partially solved by Fărcașiu through the use of an α,β -unsaturated ketone (mesityl oxide) as NMR probe by exploiting the difference of ^{13}C chemical shifts between the two ethylenic carbon atoms as variable.²⁴ The variation of $\Delta\delta^{13}\text{C}$ increases about few tens of ppm upon protonation, allowing more precise measurements, but this method still suffers from several drawbacks: the relatively high concentration of basic indicators needed to perform ^{13}C NMR analysis necessarily impact the acidity of the medium; caution

must be taken when interpreting the results as mesityl oxide is not a true Hammett base and can be subject to strong hydrogen-bonding effect.²⁰ As shown by this brief survey, the measurement of Hammett acidity function is yet far from trivial and new approaches are necessary to tackle the current limitations of spectrophotometric and NMR methods.

Here, we report a new method for the determination of the Hammett acidity of HF/base reagents by ^{19}F NMR spectroscopy. In order to anchor our method on the original Hammett acidity function and avoid the development of a new function which would not have any significance on the Hammett scale, we anticipated that *N*-trifluoromethylanilines would be ideal candidates as highly sensitive indicators (Figure 2B).

A The Hammett acidity scale



B Acidity evaluation of HF/base reagents (*this work*)

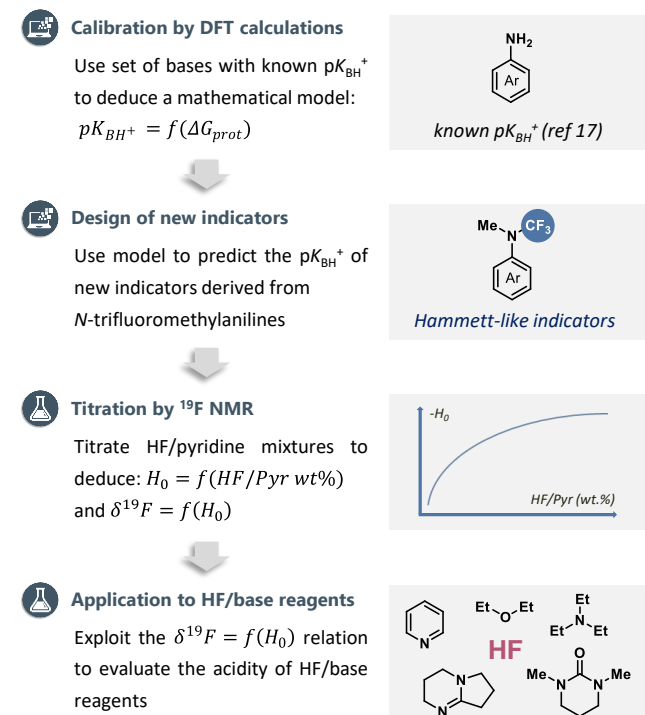


Figure 2. Toward a new approach for determining the Hammett acidity function of HF/base reagents. **A:** common definition of strong acids and superacids on the Hammett scale (ref 17). **B:** schematic representation of the workflow for determining the Hammett acidity of HF/base reagents (*this work*).

A question nevertheless remained: how can one evaluate the basicity of these indicators? Formally, one could expect to evaluate $\text{p}K_{\text{BH}^+}$ in any medium by the means of simple

DFT calculations, using Born-Haber cycles to map calculated energies in the presence and absence of solvent.²⁵ It is nevertheless known that such an approach suffers from quite large errors and fails at yielding a satisfactory reproduction of pK_{BH^+} over a large range of acidities. Several reasons account for these deficiencies, among which we may identify two significant limitations: description of the solvent is not always simple, especially when dealing with polar and protic media, thus simplifications are often made and partly account for the deviations. Second, the free energy of solvation of the proton is extremely difficult to compute.²⁶ To remedy this issue, some authors proposed to use refined thermodynamic cycles to cancel out errors as much as possible.²⁷ An alternative approach was recently proposed by Krossing and Leito through the construction of a *unified acidity scale* which allows direct connections to the aqueous pH scale, provided that single ion solvation energies are available for the chosen medium.²⁸ Unfortunately, these are not always accessible. In this work, we followed a different approach, exploiting the very concept at the core of Hammett's scale: similar indicators will present similar solvation behavior in similar media. We may thus expect to relate their computed relative Gibbs' free energies of protonation to their relative acidities: $pK_{\text{BH}^+} = \alpha \Delta G_{\text{prot}} + \beta$. The constants in the previous expression could then be determined by a fitting on experimental values for a set of indicators (here Hammett bases), affording in the end a simple yet robust semi-empirical model for the evaluation of pK_{BH^+} of structurally-related unknown indicators.

RESULTS AND DISCUSSION

To validate this approach, a first set of Hammett bases of known pK_{BH^+} was first considered.^{13,15} We studied the correlation between the experimental pK_{BH^+} and the computed Gibbs' free energies of protonation at the $\omega\text{B97xD}/6\text{-311++G(d,p)}/\omega\text{B97xD}/6\text{-31+G(d,p)}+\text{PCM}$ level of theory, after a full conformational analysis in both acid and basic forms (see SI for the full details of the computational methodology). A very satisfactory correlation could be delineated (Figure 3), pK_{BH^+} being here reproduced with an uncertainty of 0.3 units. A deeper analysis reveals that the most marked deviations from linearity are due to anilines bearing substituents in *ortho* position (see SI). In such a case, weak intramolecular H-bonding interactions could be expected in the protonated form, which may likely be misrepresented in our computational model.

Nevertheless, this semi-empirical approach could be considered efficient, and we then turned our attention to a new set of *N*-trifluoromethylaniline-based indicators which can be prepared in few steps from the corresponding primary anilines (Figure 4).^{29,30}

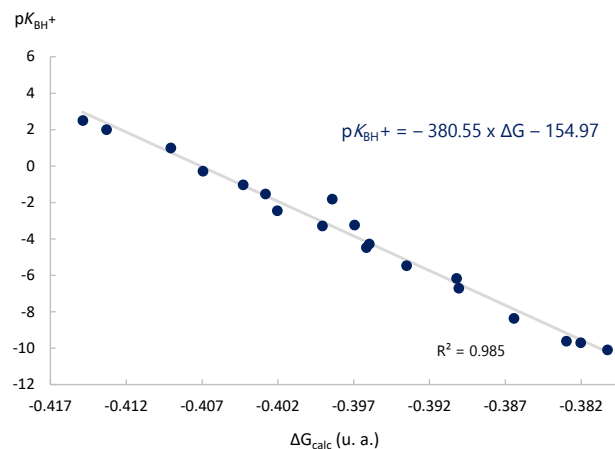


Figure 3. Plot of experimental pK_{BH^+} of true Hammett bases (primary anilines) as a function of their calculated protonation enthalpies. Computed at the $\omega\text{B97xD}/6\text{-311++G(df,2p)}/\omega\text{B97xD}/6\text{-31+G(d,p)}$ level of theory with a PCM solvation model (HF).

Because of the apparent difficulty in describing weak H-bonding interactions in *ortho* position, all considered molecules were chosen to be only *para* and/or *meta* substituted. We also limited the scope of aromatic substituents to alkyl, nitro and halogen functional groups (with the exception of methoxy group for the most basic indicators **1** and **2**) so as to not deviate too much from the structures of true Hammett bases.¹⁵ Despite this constraint, we could propose a set of indicators covering a large range of computed pK_{BH^+} from -3 to -10. Because the titration of HF/base by ^{19}F NMR spectroscopy necessitated low temperature analysis for better accuracy (*vide infra*), the pK_{BH^+} of the indicators **1-16** were also computed at 0 °C and -40 °C (see the SI for the details of the thermodynamic model used).

With this library of indicators in hand, we then turned to the experimental evaluation of acidity of HF/base reagents starting with the popular HF/pyridine mixtures. ^{19}F NMR analysis of indicators **1-16** in HF/pyridine of increasing concentration at -40 °C provided consistent sigmoid titration curves (Figure 5).³¹ Importantly, the large variation of ^{19}F chemical shifts upon protonation (8.5 ppm < $\Delta\delta^{19}\text{F}$ < 13.2 ppm) allowed accurate determination of the half-protonation points for each indicator which correspond to $pK_{\text{BH}^+} = H_0$. Analyses of representative indicators **5**, **11** and **15** were repeated three times with different batches of condensed HF in order to verify the reproducibility of the method. No significant deviation in the monitored half-protonation points ($\text{wt}\%_{0.5}$) was observed in each case (**5**: 66.4 < $\text{wt}\%_{0.5}$ < 66.7, **11**: 75.3 < $\text{wt}\%_{0.5}$ < 75.7, **15**: 83.9 < $\text{wt}\%_{0.5}$ < 84.4). The limit of the method was reached with indicator **16** for which no leveling was observed in the sigmoid curve at high acidity. ^{19}F NMR analysis of **16** in HF/SbF₅ superacid ($H_0 \approx -20$)^{19c} gave a $\delta^{19}\text{F} = 70.9$ ppm, very close to the value obtained in 100% HF ($\delta^{19}\text{F} = 70.1$ ppm, see SI).

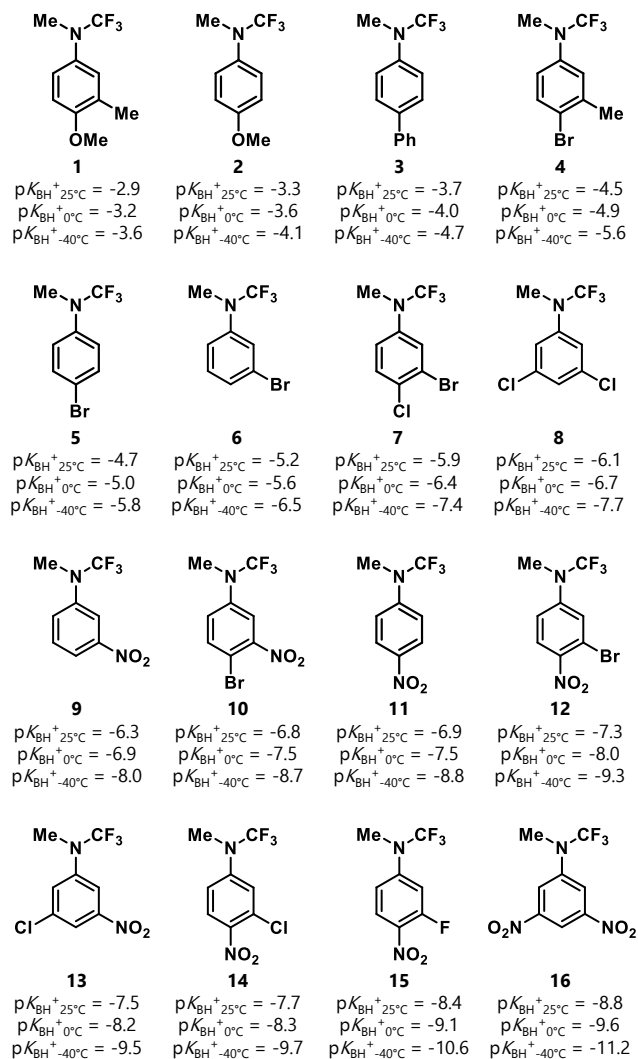


Figure 4. Library of indicators used in this study and their Boltzmann averaged calculated pK_{BH^+} (at 25, 0 and $-40^\circ C$) at the $\omega B97xD/6-311++G(df,2p)//\omega B97xD/6-31+G(d,p)$ level of theory with a PCM solvation model (HF).

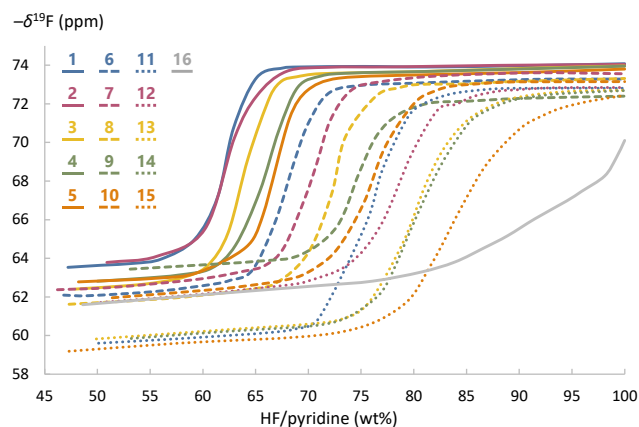


Figure 5. ^{19}F chemical shifts of indicators 1–16 as a function of the weight percentage of HF in pyridine (measured by ^{19}F NMR at $-40^\circ C$).

We could therefore assign a H_0 value (at $-40^\circ C$) of -11.2 for a 92.9 wt% solution of HF/pyridine by extrapolation (setting $\delta^{19}F = 70.9$ ppm at infinite acidity)³⁰ although this value must be treated with all due caution (noticeably, this result was not included in further data treatment for the sake of consistency).

At this stage, we were able to associate to a given HF/pyridine composition a computed H_0 , in a 60–90 wt% range at -40 and $0^\circ C$ (Figure 6).³² As one may note, a clear trend emerges from this study. H_0 is not a linear function of the weight percentage of HF in pyridine, but it is nevertheless a monotonous function which seems to converge towards the H_0 value of neat HF.^{19a,b} An estimated value of $H_0 \approx -15$ for pure HF was previously extrapolated from titration curves obtained with HF/KF and HF/SbF₅ solutions.^{19c} However, it has been shown that very small concentrations of basic impurities cannot be avoided in experimental conditions and even the purest HF that has been prepared displays an approximative value of $H_0 \approx -11$.^{19c} The small (millimolar) concentration of indicators used in this study should not impact the measured acidity in the 60–95 wt% HF/pyridine range but measurements at higher acidity remain therefore elusive at this stage. This also prompted us to evaluate the impact of water on the acidity of HF/pyridine mixtures. To this end, increasing amount of water was added on purpose to 70 wt% and 90 wt% HF/pyridine solutions whose acidities were measured respectively with indicators 7 and 16 (see SI). Noticeable decrease of acidity was observed only when the water concentration exceeded 2% in both cases ($\Delta H_0 \geq 0.5$). Above this concentration, partial hydrolysis of indicators occurred as indicated by the presence of signals corresponding to fluorophosgene and trifluoromethanol in the ^{19}F NMR spectra.³³

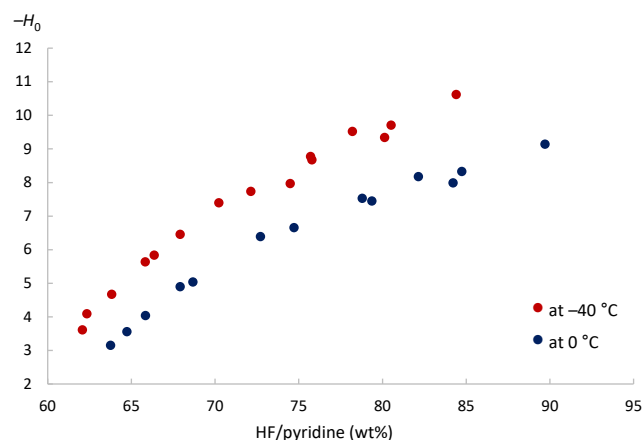


Figure 6. Plot of $-H_0$ (at 0 and $-40^\circ C$) values as a function of the weight percentage of HF in pyridine obtained with indicators 1–15.

With this method in hand, we could then evaluate the acidity of a set of HF/base reagents by relating the direct measure of $\delta^{19}F$ of adequate indicators to H_0 values (nearing the equivalence) (Figure 7).³⁰ We started this study with a commercially available solution of HF/pyridine (ca. 70 wt%, Merck) whose acidity was measured at $H_0 (0^\circ C) = -5.1$.⁴

This value compares well with the acidity of a 70 wt% HF/pyridine prepared in our lab (H_0 (0 °C) = -5.2). Interestingly, similar acidity was obtained for the Et₂O·5HF (H_0 (0 °C) = -5.3) solution developed by Olah and Prakash as convenient reagent for the hydro- and halofluorination of olefins.^{6b} The solution of HF with the non-basic hydrogen-bond acceptor DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone) reported by Hammond and Xu displays a higher acidity at H_0 (0 °C) = -6.0.^{7b} On the other hand, the complex of HF with the stronger base DBN·7HF³⁴ was logically found less acidic with H_0 (0 °C) measured at -2.7. We could however not precisely determine the H_0 value for Et₃N·5HF^{9a} as even the most basic indicator **1** remained neutral during its analysis at 0 °C. Partial protonation of indicators **1** and **3** was nevertheless observed in Et₃N·5HF at -40 °C so we could tentatively estimate a H_0 (-40 °C) close to -2. Finally, no sign of protonation was detected from the analysis of indicator **1** in Et₃N·3HF (Merck)⁵ even at low temperature, thus indicating a H_0 value higher than -2.

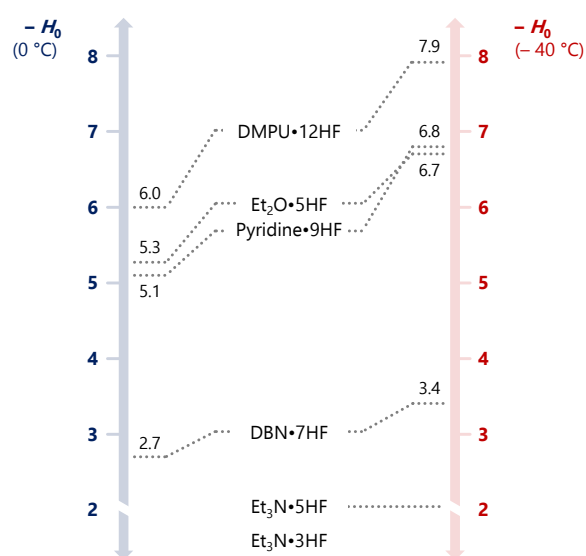


Figure 7. Hammett acidity function of common HF/base fluorinating reagents measured at 0 and -40 °C.

CONCLUSION

In summary, we have developed a new method based on ¹⁹F NMR spectroscopy to evaluate the acidity of HF/base solutions that are increasingly exploited in organic synthesis. In particular, this method allows for highly sensitive measurements and short-time analyses and the pK_{BH}^+ of the indicators are conveniently obtained by DFT calculations. Moreover, the indicators were rationally-designed to fit on the widespread Hammett scale ensuring a facile comparison of acidity strength with other strong acids. This method was applied to a set of common HF/base reagents whose acidities were still unknown despite the crucial role they play in the efficiency and selectivity of fluorination reactions. We believe that this study will pave the way for the emergence of new synthetic strategies exploiting the acidic properties of such media, and not just as fluorinating reagents. Further

applications of this method to other anhydrous strong protic acids are also expected.

ASSOCIATED CONTENT

The Supporting Information is available free of charge at <https://pubs.acs.org>.

Experimental procedures, characterization data, and NMR spectra of compounds (PDF)

Computational details and additional computational results discussed in the text (PDF)

AUTHOR INFORMATION

Corresponding Authors

Bastien Michelet – Université de Poitiers, UMR-CNRS 7285, IC2MP, 4 rue Michel Brunet, TSA 51106, 86073 Poitiers Cedex 9, France; orcid.org/0000-0002-3248-5781;

Email: bastien.michelet@univ-poitiers.fr

Frédéric Guégan – Université de Poitiers, UMR-CNRS 7285, IC2MP, 4 rue Michel Brunet, TSA 51106, 86073 Poitiers Cedex 9, France; orcid.org/0000-0002-4932-8643;

Email: frederic.guegan@univ-poitiers.fr

Sébastien Thibaudeau – Université de Poitiers, UMR-CNRS 7285, IC2MP, 4 rue Michel Brunet, TSA 51106, 86073 Poitiers Cedex 9, France; orcid.org/0000-0002-6246-5829;

Email: sebastien.thibaudeau@univ-poitiers.fr

Authors

Mélissa Longuet – Université de Poitiers, UMR-CNRS 7285, IC2MP, 4 rue Michel Brunet, TSA 51106, 86073 Poitiers Cedex 9, France

Kassandra Vitse – Université de Poitiers, UMR-CNRS 7285, IC2MP, 4 rue Michel Brunet, TSA 51106, 86073 Poitiers Cedex 9, France

Agnès Martin-Mingot – Université de Poitiers, UMR-CNRS 7285, IC2MP, 4 rue Michel Brunet, TSA 51106, 86073 Poitiers Cedex 9, France; orcid.org/0000-0002-2633-3714

Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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(32) The lower H_0 values obtained at lower temperature at a given HF/pyridine composition can be directly correlated to the

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