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Characterization of Brønsted Acid–Base Complexes by ^{19}F DOSY

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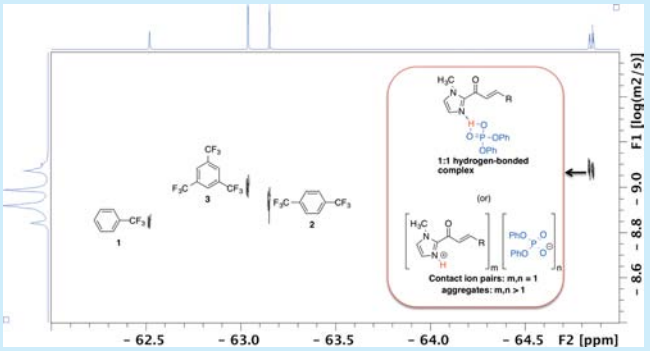
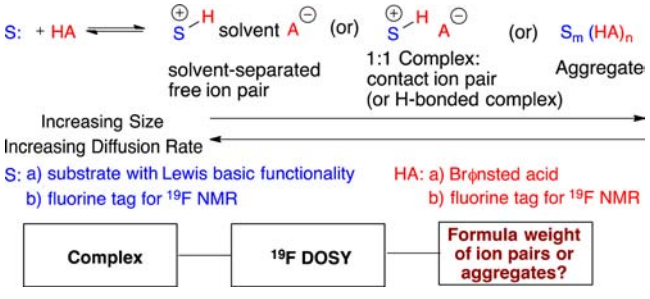
Supporting Information

ABSTRACT: A ^{19}F DOSY protocol for the determination of formula weights for acid–base complexes in solution has been developed. ^{19}F internal standards were chosen and were used to evaluate the formula weights of complexes in solution using simple diffusion coefficient (D)–formula weight (FW) analysis. This method has potential applications in characterization of reactive intermediates in catalytic asymmetric reactions.



A chiral templates play influential roles in stereoselective organic transformations.[1] We have demonstrated that the judicious choice of template in conjunction with chiral catalyst (Lewis or Brønsted acid) can affect both reactivity and stereoselectivity.[2] Chiral Brønsted acids, particularly phosphoric acids, have emerged as powerful asymmetric catalysts in a plethora of organic transformations,[3] activating substrates via hydrogen bonding or by complete protonation[4] (Scheme 1).

Scheme 1. Reaction Scheme for ^{19}F DOSY Experiments



For effective enantioselectivity, proximity between the reactive site and the catalyst chirality is crucial.[5] If an ion pair is solvent-separated, for example, high enantioselectivity is unlikely. In the context of understanding and developing asymmetric Brønsted acid catalysis, we became interested in studying Brønsted acid–base interactions in solution.

Diffusion ordered NMR spectroscopy (DOSY) has emerged as an effective tool for studying non-covalent interactions in solution. Since diffusion depends on size, coordination reduces diffusion rates. The pulse field gradient spin-echo diffusion method introduced by Stejskal and Tanner[6] has been used extensively to study ion pairing, aggregation, hydrogen bonding, π–π stacking in supramolecular systems,[7] and transition metal catalysis.[8] Diffusion constants (D) can be used to determine formula weights (FW) using the relationship log $D \propto$ log FW. Williard[9] and others[10] have used DOSY to determine formula weights of polymers and solution structures of organometallic complexes. While ^{1}H DOSY has been used most extensively, peak overlap is problematic. Thus, several heteronuclear (^{13}C, ^{31}P, ^{6}Li, etc.) DOSY methods have been developed.[11]

We envisaged that applying DOSY to complexes between basic substrates and Brønsted acids would help in the understanding of ion pairing and aggregation (Scheme 1). Solvent-separated ion pairs should show different diffusion profiles from contact ion pairs. Likewise, aggregates should be distinguishable from 1:1 complexes. Unfortunately our initial attempts using ^{1}H DOSY were somewhat discouraging due to signal overlap.

We reasoned that ^{19}F DOSY might be a very practical alternative, due to its well-resolved signals and high sensitivity, which facilitate peak picking and curve-fitting analysis. Conceptually the ^{19}F can be present in the acid, the substrate, or both (Scheme 1). Brønsted acid catalysts such as chiral *N*-triflylphosphoramides and chiral thioureas contain fluorine atoms, as do several Lewis acid counterions such as BF_4^-, $CF_3SO_3^-$, $(CF_3SO_2)_2N^-$, PF_6^-, and SbF_6^-. Many of the substrates that we use in catalytic reactions also contain fluorines (see **7a**, Scheme 2). Dual labeling should also be possible, in which both substrate and acid are fluorinated; if complexation occurs, then fluorine signals associated with both substrate and acid should show the same diffusion rates. In this letter we disclose the development and effectiveness of ^{19}F DOSY for successful formula weight determination in simple acid base complexes.

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The internal standards and the analytes chosen for the initial ^{19}F DOSY experiments are shown in Figure 1. They are as

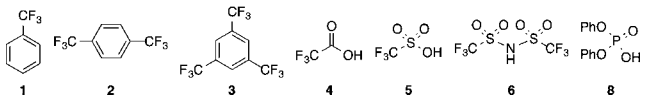


Figure 1. Internal standards and analytes chosen for initial ^{19}F DOSY studies.

follows: benzotrifluoride **1** (146 g mol^{-1}), 1,4-bis(trifluoromethyl)benzene **2** (214 g mol^{-1}), and 1,3,5-tris(trifluoromethyl)benzene **3** (282 g mol^{-1}). Trifluoroacetic acid **4** (114 g mol^{-1}) was used as the test Brønsted acid to check the validity of formula weight analysis by ^{19}F DOSY. Benzene-d_6 was used as the solvent. The standard Bruker pulse sequence (ledbpgp2s) incorporating longitudinal eddy current delay was used for ^{19}F DOSY experiments.[12]

The resulting DOSY spectrum is shown in Figure 2 and is consistent with what is expected: the diffusion coefficient

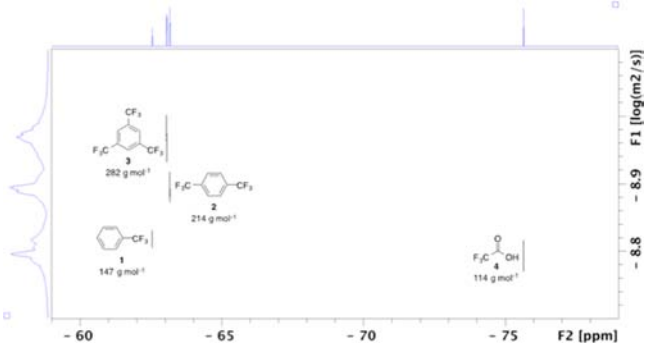


Figure 2. ^{19}F DOSY spectrum of a mixture of internal standards **1**–**3** and trifluoroacetic acid **4** in C_6D_6.

decreases in the order **4** > **1** > **2** > **3**. Of the three internal standards, the smallest one diffuses fastest and the heaviest diffuses slowest, and the smaller CF_3CO_2H diffuses fastest of all.[13] The D value for a particular species was obtained using curve fitting of signal attenuation data for the corresponding resonance in the DOSY experiment (Figure 3).

To check the validity of the formula weight (FW) analysis by diffusion experiments, we performed a linear regression analysis of log D versus log FW for the mixture of compounds **1**–**4**. The graph shows a very good correlation of the internal references selected and the predicted formula weight of **4** from DOSY

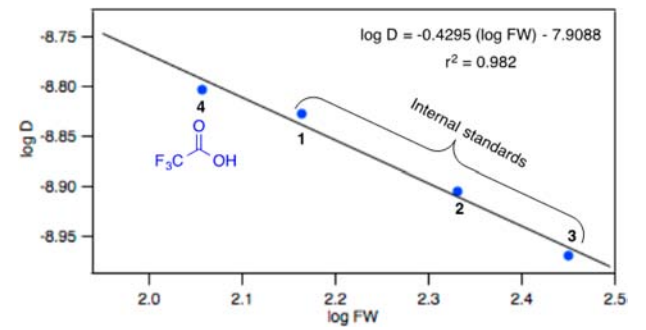


Figure 3. log D versus log FW analysis of ^{19}F DOSY of a mixture of **1**–**4** in benzene-d_6.

studies with a very high r^2 value of 0.982. The formula weight of **4** from the diffusion studies is calculated to be 120 g mol^{-1} as compared to the actual formula weight of 114 g mol^{-1} (Table 1) with only about 5% error.

Table 1. D-FW Analysis of ^{19}F DOSY Spectrum of Compounds 1–4 in C_6D_6

compd	FW (g mol^{-1})	D (m^2 s^{-1})	FW$_{DOSY}$ (g mol^{-1})[a]	error %
1	146	1.489×10^{-9}	137	6.2
2	214	1.265×10^{-9}	201	6.1
3	282	1.071×10^{-9}	295	4.6
4	114	1.595×10^{-9}	120	5.1

[a]log D = −0.4295(log FW) − 7.9088.

Analogous formula weight analysis by ^{19}F DOSY evaluated the formula weight of triflic acid **5** to be 154 g mol^{-1} and that of bis(trifluoromethane)sulfonimide **6** to be 287 g mol^{-1}. The DOSY-estimated formula weights are within 10% of the actual formula weights (Table 2).

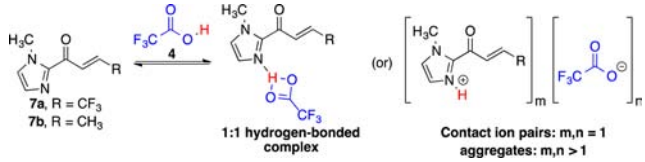
Table 2. ^{19}F DOSY-Estimated Formula Weights of Other Fluorinated Brønsted Acids

analyte	FW$_{Actual}$ (g mol^{-1})	FW$_{DOSY}$ (g mol^{-1})[a]	error %
4	114	120	5.1
5	150	155	3.3
6	281	287	2.1

[a]Calculated from the plot of log D vs log FW (see Supporting Information).

Having confirmed the feasibility of using ^{19}F DOSY for formula weight determination, we next applied these experiments to Brønsted acid–basic substrate complexes. Determining the formula weight of these complexes can give useful insights into the stoichiometry of complexes involved in catalytic reactions. Acylimidazoles (**7**) have been used extensively in asymmetric transformations.[14] We applied our ^{19}F DOSY method to determine the formula weights of the complexes formed between Brønsted acids and acylimidazoles **7** (Scheme 2). Fluorine-labeled substrate **7a** is amenable to ^{19}F

Scheme 2. Interaction between Trifluoroacetic Acid (Brønsted Acid) and Acylimidazole Substrates



DOSY using unlabeled phosphoric acids. Alternatively, double-labeling studies using **7a** in combination with fluorinated acids **4**–**6** are also possible. Substrate **7b** is itself not labeled, but can be studied with the fluorinated acids.

^{19}F DOSY was conducted on a solution containing internal standards **1**–**3**, trifluoroacetic acid **4**, and fluorinated substrate **7a**. A remarkable difference is seen in the DOSY spectrum (Figure 4). In the absence of a nitrogenated substrate, acid **4** had been faster moving than any of the three internal standards **1**–**3** (Figures 2 and 3). But in the presence of acylimidazole **7a**, trifluoroacetic acid **4** now moves slower than all three internal

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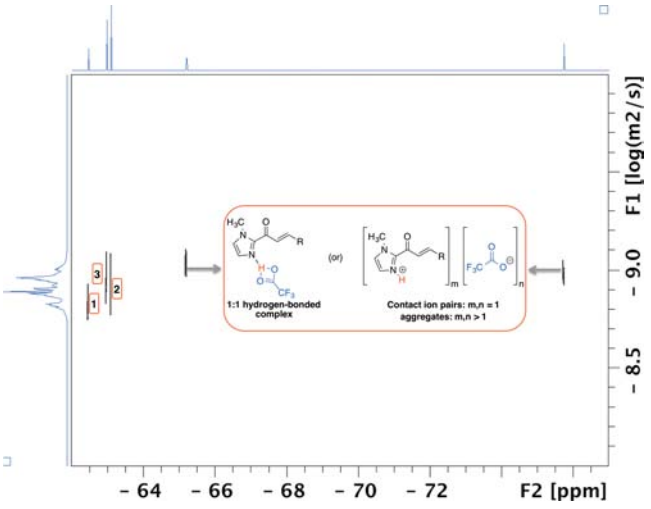

Figure 4. ^{19}F DOSY spectrum of compounds **1**−**4** and acylimidazole **7a** in C_6D_6.

standards, indicating complexation and a significant formula weight increase. Further, the labeled substrate **7a** and acid **4** move with equivalent diffusion coefficients, again indicating that they are complexed to each other. In the presence of acid **4** there is also a considerable change in the ^{19}F chemical shift of **7a** (δ^{19}F ≈ 64.9 ppm in absence of acid, δ^{19}F ≈ 65.4 ppm in the presence of acid), again indicating complexation.

The formula weight analysis graph is shown in Figure 5. Based on the experimentally obtained D value of 9.993×10^{-10},

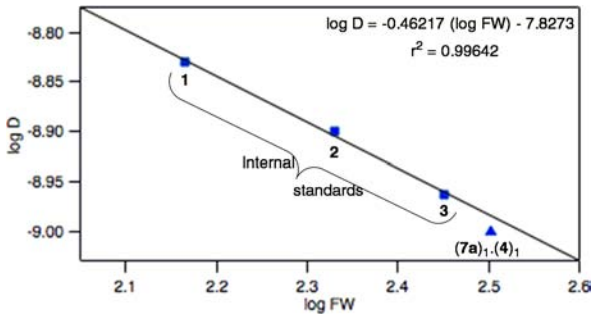

Figure 5. Analysis of ^{19}F DOSY for a mixture of **1**−**4** and **7a** in C_6D_6.

a very good correlation is obtained for the internal references (r^2 = 0.9996) and a formula weight of 343 g mol^{-1} is obtained for the complex. This 343 g mol^{-1} estimation is relatively close (7.8% error) to what would be expected for a 1:1 acid−base complex between substrate **7a** and trifluoroacetic acid **4** (actual FW = 318 g mol^{-1}). Thus, chemical shift change, change in diffusion rates, and matching diffusion rates for the substrate and acid clearly show complexation, with the actual diffusion rate suggesting 1:1 complexation.

We next performed analogous ^{19}F DOSY experiments using both labeled and unlabeled substrates **7a** and **7b** and two stronger Brønsted acids **5** and **6**. The results are shown in Table 3. Interestingly, while trifluoroacetic acid gave a 1:1 complex with **7a**, the strongly acidic bis(trifluoromethane)sulfonimide **6** gave a 2:2 complex. We were unable to determine the formula weight of the complex of **7a** with triflic acid **5** due to precipitation of the complex. Unlabeled acylimidazole **7b** formed 2:2 complexes with both triflic acid **5** and bis(trifluoromethane)sulfonimide **6**. While the interactions of **7a** with acids

Table 3. Predicted Formula Weights of Various Acylimidazole−Brønsted Acid Complexes

acid	FW_{Calcd} (g mol^{-1})	complex	FW_{DOSY} (g mol^{-1})[a]	error %
4	318	$(\mathbf{7a})_1\cdot(\mathbf{4})_1$	343	7.8
5	708	$(\mathbf{7a})_m\cdot(\mathbf{5})_n$	–[b]	–[b]
6	970	$(\mathbf{7a})_2\cdot(\mathbf{6})_2$	950	2.1
5	600	$(\mathbf{7b})_2\cdot(\mathbf{5})_2$	624	4.0
6	862	$(\mathbf{7b})_2\cdot(\mathbf{6})_2$	847	1.7
8	454	$(\mathbf{7a})_1\cdot(\mathbf{8})_1$	429	5.5

[a]Calculated from the plot of log D vs log FW (see Supporting Information). [b]The complex precipitates, and no fluorine peaks corresponding to **7a** and **5** were observed.

4 and **6** represent double-labeling experiments, the interaction of **7b** with acids **5** and **6** demonstrates the utility of the ^{19}F DOSY approach for unlabeled substrates reacting with fluorine-tagged acids. The predicted formula weights of these higher molecular weight complexes are well within the experimental error.

We also studied the complexation between fluorine-tagged acylimidazole **7a** and unlabeled phosphoric acid **8**, which is representative of the types of chiral Brønsted acids used in asymmetric reactions. When ^{19}F DOSY was conducted on a solution containing internal references (**1**−**3**) acylimidazole **7a** and phosphoric acid **8** (Table 3, last entry) a formula weight of 429 g mol^{-1} corresponding to a 1:1 complex (454 g mol^{-1}) was obtained. This result shows promise toward the characterization of complexes in chiral Brønsted acid mediated transformations.

We have developed a ^{19}F DOSY internal reference system for the successful prediction of formula weights in solution. The sharp, well-resolved signals and high sensitivity of ^{19}F NMR facilitate DOSY usage. Plots of log D versus log FW show excellent linearity, and the agreement between DOSY-calculated and actual formula weights appears excellent. Fluorine labeling can be incorporated in the substrate, the acid, or both. In benzene-d_6 solvent, substrate **7a** forms 1:1 complexes with trifluoroacetic acid **4** and phosphoric acid **8**. In contrast, 2:2 complexes are formed with the strongly acidic bis(trifluoromethane)sulfonimide **6** and acylimidazoles **7a** and **7b**. Complexes show no indication of solvent-separated ion pairs. Continuing studies will apply ^{19}F DOSY in combination with other spectroscopic techniques to help characterize the solution structures of several asymmetric catalytic systems.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures as well as complete NMR diffusion data. 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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