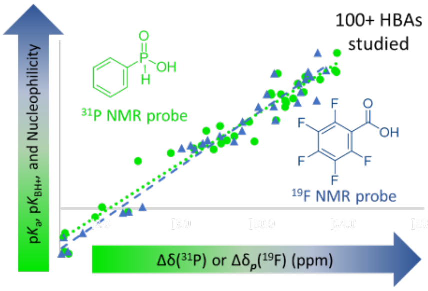
NMR Quantification of Hydrogen-bond Accepting Ability for Organic Molecules

Mira Milic, Karina Targos, Magda Tellez Chavez, Madison A. M. Thompson, Julia J. Jennings, Annaliese K. Franz*

Department of Chemistry, University of California, One Shields Avenue, Davis, California 95616, United States

ABSTRACT: The hydrogen-bond accepting abilities for more than 100 organic molecules were quantified using ^{19}F and ^{31}P NMR spectroscopy with pentafluorobenzoic acid (PFBA) and phenylphosphinic acid (PPA) as commercially available, inexpensive probes. Analysis of pyridines and anilines with a variety of steric and electronic modifications demonstrated that changes in NMR shifts can predict the secondary effects that contribute to H-bond accepting ability, establishing the ability of both PFBA and PPA binding to predict electronic trends. The H-bond accepting abilities of various metal-chelating ligands and organocatalysts were also quantified. The measured $\Delta\delta(^{31}P)$ and $\Delta\delta_p(^{19}F)$ values correlated strongly with Hammett parameters, pK_a of the protonated HBA, and proton-transfer basicity (pK_{BH+}).



Key Words: *H-bonding, H-bond acceptor, noncovalent interactions, proton transfer, heterocycle, Lewis base, organocatalysis, ^{19}F NMR spectroscopy, ^{31}P NMR spectroscopy, NMR probe*

Enhanced knowledge of hydrogen-bonding interactions can provide a deeper understanding of self-assembly and molecular recognition, with applications from medicinal and materials chemistry to catalyst design.[1] Methods to quantify H-bonding include equilibrium constants, such as pK_a and log K^H_A values,[2] and more accurate, yet highly complex, computational studies and quantum mechanical calculations.[3–8] Taft and coworkers reported the earliest example using NMR spectroscopy to quantify shielding effects on H-bonded complexes of Lewis bases (LB) to 4-fluorophenol (4-FP) as a reference acid (Figure 1A).[9] This study demonstrated that ^{19}F NMR shifts (Δδ) correlate with logarithms of the formation constants (K_f) of the LB + 4-FP complexes and that potential energy change in the formation of the LB$^+$/4-FP complexes is proportional to their standard free energy change. First reported by Gutmann in 1975, ^{31}P NMR spectroscopy has been subsequently used to quantify Lewis acidity,[10–12] H-bond donating ability (Figure 1B),[13–15] and halogen-bond donating ability.[16]

While ^{31}P NMR spectroscopy has been utilized to quantify H-bond donating ability, there is currently no simple, validated NMR method to quantify and characterize H-bond *accepting* ability apart from Taft's early precedent that correlated $\Delta\delta(^{19}F)$ for NMR shielding effects with formation constants and energy changes. Herein we report the use of both ^{19}F and ^{31}P NMR spectroscopy as a means of quantifying H-bond accepting ability for a wide variety of heterocycles and functional groups relevant to catalysis and medicinal chemistry, including pyridines, quinolines, imidazoles, amides, and chelating oxazoline ligands (Figure 1C). We selected commercially available fluorine and phosphorus-containing probe compounds as these highly sensitive heteronuclear atoms allow for rapid and easy analysis using ^{19}F and ^{31}P NMR spectroscopy. ^{19}F and ^{31}P are the only natural isotopes of fluorine and phosphorus and are both 100% naturally abundant.[17,18] The $\Delta\delta(^{19}F)$ and $\Delta\delta(^{31}P)$ NMR values upon binding to acidic probes demonstrates the ability to quantify trends in electronic and steric effects that influence H-bond accepting ability.

Probe Selection and Method Development It was critical to identify appropriate probes and develop a method to quantify H-bond acceptors (HBAs) with a range of weak to strong H-bonding capacities. Factors contributing to selection of an NMR probe included commercial availability, cost, safe handling, solubility in CH_2Cl_2, sufficiently strong complexation to detect interactions and correlation of ^{19}F or ^{31}P NMR data with the extent of interaction. For ^{31}P NMR spectroscopy, phenylphosphinic acid (PPA, pK_a = 1.83[19]) was selected as a probe (Figure 2A).[20–22] For ^{19}F NMR spectroscopy, pentafluorobenzoic acid (PFBA, pK_a = 1.47[23]) was selected as a probe (Figure 2B) and also compared with 4-fluorophenol (4-FP, pK_a = 9.89[24]), inspired by Taft.[9] NMR measurements are conducted in CH_2Cl_2 due to superior solubility properties for a broad range of organic molecules of interest,[25] with 27% (v/v) CD_2Cl_2 used for NMR locking/shimming.

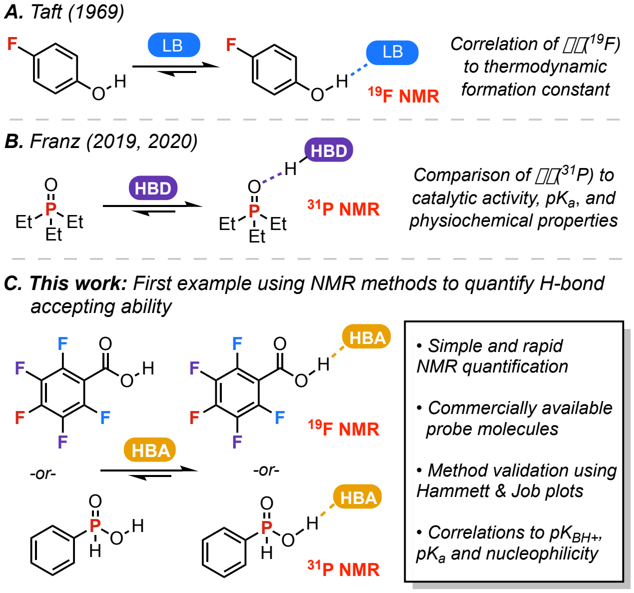


Figure 1. NMR quantification of H-bonding ability.

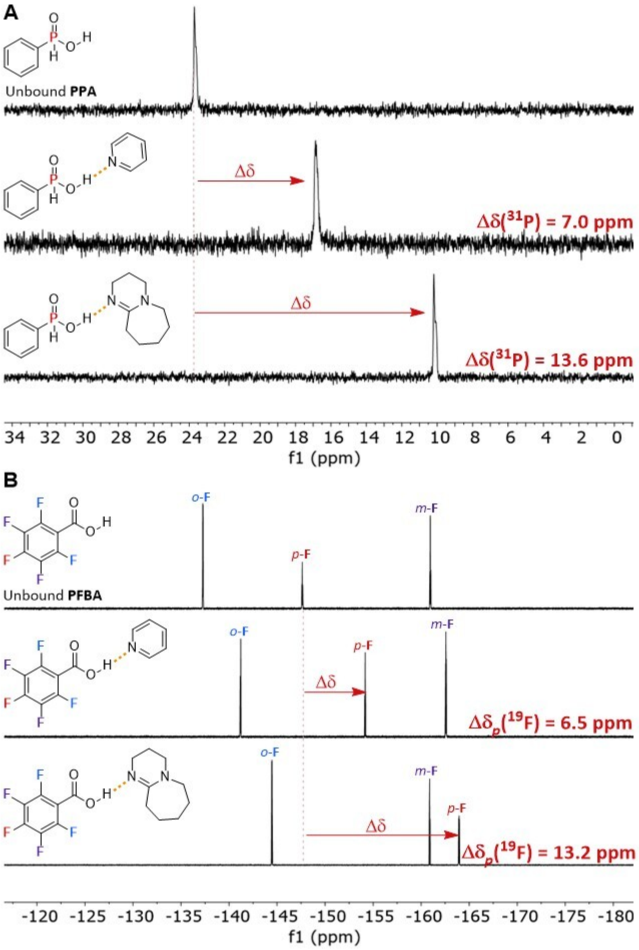


Figure 2. (A) Example of ^{31}P NMR spectrum of PPA and shifts observed upon binding to pyridine and DBU (using 3.0 equiv of HBA, in CD_2Cl_2). (B) Example of ^{19}F NMR spectrum of PFBA and shifts observed upon binding to pyridine and DBU (using 5.0 equiv of HBA, in CD_2Cl_2).

Three HBA compounds representing varying basicity (based on pK_a value of the protonated heteroatom in water) were selected for preliminary titration studies: triethylamine (TEA) (pK_a of conjugate acid = 10.65[26]), quinoline (pK_a of conjugate acid = 4.92[27]), and cyclohexanone (pK_a of conjugate acid = −6.8[28]). To determine the equivalents of HBA necessary to reach the saturation point (as indicated by the maximum upfield shift) with each probe, a range from one to 10 equivalents of each HBA (relative to the probe) was titrated, while maintaining a constant probe concentration. Saturation was indicated upon plateau of the $Δδ(^{19}F)$ and $Δδ(^{31}P)$ values, and all HBAs tested with PFBA were studied at 5.0 equivalents, and all HBAs studied with PPA were studied at 3.0 equivalents to maintain consistency (see Supporting Information).[29–31] All binding studies with PPA and PFBA were performed at 0.05 M and 0.083 M in CD_2Cl_2, respectively.

Both PPA and PFBA were demonstrated to be effective probes, displaying similar large ranges of Δδ values (up to 14 ppm) and requiring similar equivalents of HBA for saturation. It is notable that there is only one NMR signal to use for $Δδ(^{31}P)$ values with PPA. For PFBA, the values for the *para* signal, $Δδ_p(^{19}F)$, are utilized for all Δδ measurements because the *para* position is more strongly sensitive to electronic effects compared to the *meta* position and less influenced by potential steric effects compared to the *ortho* position. PPA exhibits a greater sensitivity to steric effects due to more three-dimensional, tetrahedral sp^3 nature of the phosphorus in the phosphinic acid moiety (versus the planar sp^2 carboxylic acid moiety of PFBA), which may account for some variations in Δδ values between the two probes. One notable limitation is that PFBA is not an effective probe with primary amines because the lower pK_a of PFBA relative to PPA makes it readily undergo acid/base proton exchange to form insoluble salts (PPA does not have this limitation). It was noted that PPA can self-associate at concentrations greater than 0.01 M (see Supporting Information), which may influence $Δδ(^{31}P)$ values for weaker HBAs.[32] Using 4-fluorophenol (4-FP) required 7.0 or more equivalents of HBA for saturation and also afforded a smaller range of Δδ values compared to PPA and PFBA; therefore, 4-FP was not investigated further (see Supporting Information).

Hammett plots validate the use of PFBA and PPA as probes to quantify the effects of different electronic substituents on H-bond accepting ability using ^{19}F and ^{31}P NMR spectroscopy (Figure 3). A Hammett plot of *meta*- and *para*-substituted pyridines was established by plotting $Δδ(^{31}P)$ and $Δδ_p(^{19}F)$ values versus $σ$ parameters.[33] For PPA, a Hammett plot was also established using *para*-anilines. For both HBA classes studied, $Δδ(^{31}P)$ and $Δδ_p(^{19}F)$ values exhibit highly linear relationships with Hammett values, with all $R^2 \geq 0.95$.

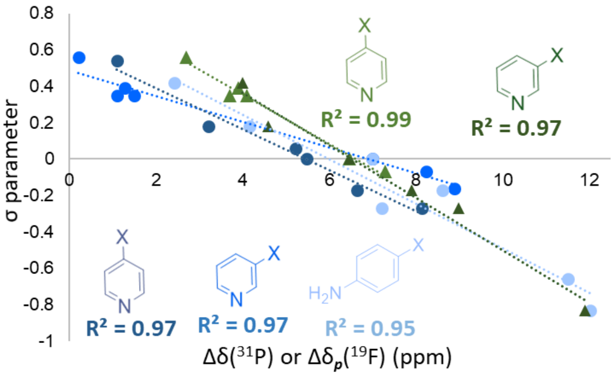


Figure 3. Correlation of $σ$ parameters[34] for *meta*-pyridines (**2a−f**) and *para*-pyridines (**1b−g**), and *para*-anilines (**34a−e**) at 0.05 M in CD_2Cl_2 with PPA (blue), and *meta*-pyridines (**2a−f**) and *para*-pyridines (**1b−g**) at 0.083 M in CD_2Cl_2 with PFBA (green) in CD_2Cl_2, with $Δδ(^{31}P)$ or $Δδ_p(^{19}F)$ values.

Discussion of HBA Classes We utilized ^{19}F and ^{31}P NMR spectroscopy to quantify H-bond accepting ability for more than 100 HBAs containing diverse heterocycles and functional groups, with various steric and electronic modifications to quantify trends within HBA classes (Figure 4).

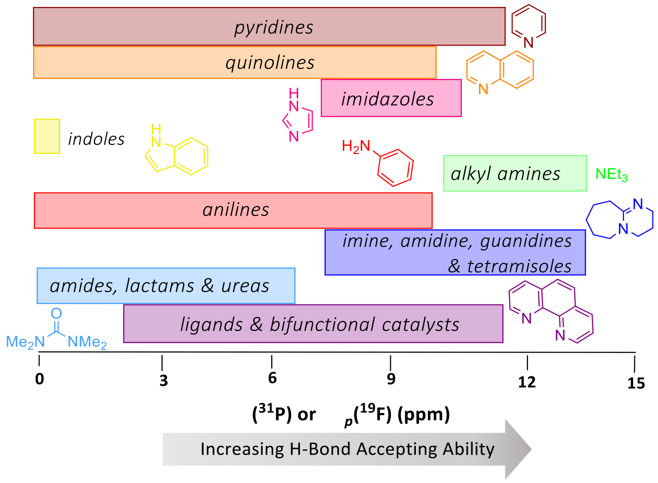


Figure 4. Scale comparing ranges of Δδ values for classes of HBAs.

Pyridines. Pyridine moieties are ubiquitous, prevalent in pharmaceuticals, agrochemicals, and ligands for metal complexes. Pyridine rings appear in approximately 25% of drugs containing heteroaromatic rings,[35] and pyridine scaffolds are frequently utilized as isosteres for amines, amides, benzene rings, and other nitrogen-containing heterocycles. Pyridines **1–7** are strong HBAs, affording a wide range of $\Delta\delta(^{31}P)$ and $\Delta\delta_p(^{19}F)$ values with $\Delta\delta(^{31}P)$ up to 12.0 ppm and $\Delta\delta_p(^{19}F)$ up to 11.9 ppm (Figure 5, Table 1). Unsubstituted pyridine **1a** displayed a $\Delta\delta(^{31}P)$ value of 7.0 ppm, and a $\Delta\delta_p(^{19}F)$ value of 6.5 ppm.

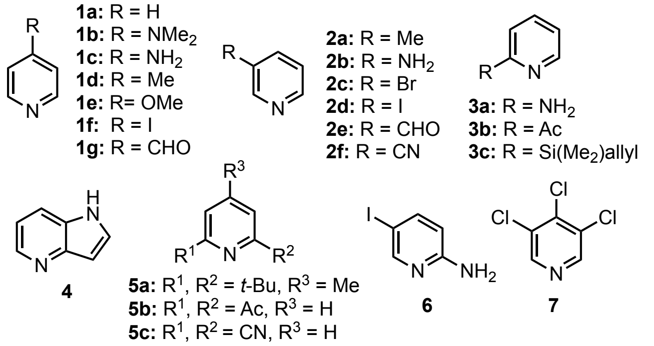


Figure 5. Pyridines studied.

Table 1. $\Delta\delta(^{31}P)$ and $\Delta\delta_p(^{19}F)$ data for pyridines binding to PPA and PFBA in CD_2Cl_2.

#	compound	^{31}P NMR ($\Delta\delta$, ppm)[a]	^{19}F NMR ($\Delta\delta_p$, ppm)[b]
1a	pyridine	7.0	6.5
1b	DMAP	12.0	11.9
1c	4-aminopyridine	11.5	--
1d	4-methylpyridine	8.7	7.9
1e	4-methoxypyridine	7.2	9.0
1f	4-iodopyridine	4.2	4.6
1g	4-pyridinecarboxaldehyde	2.4	4.0
2a	3-methylpyridine	8.2	7.3
2b	3-aminopyridine	8.9	--
2c	3-bromopyridine	1.3	3.9
2d	3-iodopyridine	1.1	4.1
2e	3-pyridinecarboxaldehyde	1.5	3.7
2f	3-cyanopyridine	0.2	2.7
3a	2-aminopyridine	7.9	--
3b	2-acetylpyridine	0.4	2.2
3c	2-(allyldimethylsilyl)pyridine	--	9.8
4	7-azaindole	5.2	7.5
5a	2,6-di-*tert*-butyl-4-methylpyridine	3.3	7.3
5b	2,6-diacetylpyridine	0.2	0.8
5c	2,6-pyridinedicarbonitrile	0.1	--
6	2-amino-5-iodopyridine	6.7	8.2
7	3,4,5-trichloropyridine	0.8	1.7

[a] 3.0 equiv of HBA in CD_2Cl_2 (0.05 M); $\Delta\delta(^{31}P)$ compared to PPA external standard, values reported as average of three replicates with average standard deviation ± 0.11 ppm;[36] [b] 5.0 equiv of HBA in CD_2Cl_2 (0.083 M); $\Delta\delta_p(^{19}F)$ compared to PFBA external standard, values reported as an average of 1.6 replicates with average standard deviation ± 0.06 ppm.[36] See Supporting Information for all standard deviations and errors.

The highest $\Delta\delta(^{31}P)$ and $\Delta\delta_p(^{19}F)$ values in the pyridine class were displayed by **1b** ($\Delta\delta(^{31}P) = 12.0$ ppm, $\Delta\delta_p(^{19}F) = 11.9$ ppm) and **1c** ($\Delta\delta(^{31}P) = 11.5$ ppm). The exceptional H-bond accepting abilities of these compounds are attributed to the strong π-donating abilities of the activating dimethylamino and amino substituents that allow for enhanced H-bond accepting ability at the heterocyclic nitrogen. Methyl-substituted pyridines afford larger $\Delta\delta(^{31}P)$ and $\Delta\delta_p(^{19}F)$ values, as displayed by **1d** ($\Delta\delta(^{31}P)$ = 8.7 ppm, $\Delta\delta_p(^{19}F)$ = 7.9 ppm) and **2a** ($\Delta\delta(^{31}P)$ = 8.2 ppm, $\Delta\delta_p(^{19}F)$ = 7.3 ppm). Conversely, the presence of deactivating, electron-withdrawing substituents such as halogens, afforded smaller $\Delta\delta(^{31}P)$ and $\Delta\delta_p(^{19}F)$ values, e.g. **1f** ($\Delta\delta(^{31}P)$ = 4.2 ppm, $\Delta\delta_p(^{19}F)$ = 4.6 ppm) and **2c** ($\Delta\delta(^{31}P)$ = 1.3 ppm, $\Delta\delta_p(^{19}F)$ = 3.9 ppm). The presence of π-accepting, electron-withdrawing substituents likewise exhibited prohibitive effects on H-bond accepting ability, demonstrated by carbonyl-substituted pyridines (**1g**: $\Delta\delta(^{31}P)$ = 2.4 ppm, $\Delta\delta_p(^{19}F)$ = 4.0 ppm; **2e**: $\Delta\delta(^{31}P)$ = 1.5 ppm, $\Delta\delta_p(^{19}F)$ = 3.7), **2f** ($\Delta\delta(^{31}P)$ = 0.2 ppm, $\Delta\delta_p(^{19}F)$ = 2.7 ppm), and **3b** ($\Delta\delta(^{31}P)$ = 0.4 ppm, $\Delta\delta_p(^{19}F)$ = 2.2 ppm) substituted pyridines. The high value of **3c** ($\Delta\delta_p(^{19}F)$ = 9.8 ppm) is attributed to the inductive electron-donating effect of the $\sigma_{C\text{-}Si}$ of a silyl group.[37]

The $\Delta\delta(^{31}P)$ and $\Delta\delta_p(^{19}F)$ values of **5a** ($\Delta\delta(^{31}P)$ = 3.3 ppm, $\Delta\delta_p(^{19}F)$ = 7.3 ppm) demonstrate that the bulky, sterically-demanding *tert*-butyl groups do not completely inhibit H-bonding interactions with the PPA or PFBA probes as a shift is still observed. This supports that PPA is more sensitive to steric effects compared to PFBA, as the magnitude of the $\Delta\delta(^{31}P)$ value is significantly reduced. In the case of PFBA, it appears that the inductive electron-donating effects of the *tert*-butyl and methyl substituents balance with the steric effects to enhance $\Delta\delta_p(^{19}F)$ slightly relative to **1a** ($\Delta\delta_p(^{19}F)$ = 6.5 ppm), but still less than **1d** ($\Delta\delta_p(^{19}F)$ = 7.9 ppm).

Quinolines and isoquinolines. Quinoline moieties are found in a variety of naturally occurring alkaloids, and approximately 10% of pharmaceuticals on the market contain quinoline moieties,[35] including antimalarials such as quinine and chloroquine. The quinoline and isoquinoline HBA class (**8–12**) invoke $\Delta\delta(^{31}P)$ values up to 9.6 ppm, and $\Delta\delta_p(^{19}F)$ values up to 8.6 ppm (Figure 6, Table 2). Unsubstituted quinoline **8** ($\Delta\delta(^{31}P)$ = 7.6 ppm, $\Delta\delta_p(^{19}F)$ = 6.7 ppm), acridine **9** ($\Delta\delta(^{31}P)$ = 9.6 ppm, $\Delta\delta_p(^{19}F)$ = 8.6 ppm) and isoquinoline **10** ($\Delta\delta(^{31}P)$ = 8.0 ppm, $\Delta\delta_p(^{19}F)$ = 7.1 ppm) afford similar values to those of pyridine, albeit slightly deviating from the expected trend based on pyridine. The slightly larger $\Delta\delta(^{31}P)$ and $\Delta\delta_p(^{19}F)$ value for **8** vs. **9** and **10** is in accordance with the pK_a for protonated **8** (4.92) compared to the pK_a for **9** (5.60) and **10** (5.40) (vida infra).[27] Substituted quinolines with methoxy, chloro and cyano groups *ortho* to the heterocyclic nitrogen (**11a–c**) afforded very low $\Delta\delta(^{31}P)$ and $\Delta\delta_p(^{19}F)$ values, attributed to both the electron-withdrawing and steric effects of these substituents. Interestingly, placement of a hydroxyl group at the 8-position (**12**) did not result in as large of a decrease in $\Delta\delta(^{31}P)$ and $\Delta\delta_p(^{19}F)$ values with respect to **8** as was expected. Tetrahydroquinoline **13** ($\Delta\delta(^{31}P)$ = 6.6 ppm and $\Delta\delta_p(^{19}F)$ = 6.0 ppm) and **14** ($\Delta\delta(^{31}P)$ = 10.9 ppm, $\Delta\delta_p(^{19}F)$ = 10.2 ppm) were also compared. The largest $\Delta\delta(^{31}P)$ and $\Delta\delta_p(^{19}F)$ values was measured for **14**, attributed to sp^3-hybridization at nitrogen, and localization of the nitrogen lone pair (i.e. **14** vs **13**). These values can be compared to other alkyl amines (vida infra).

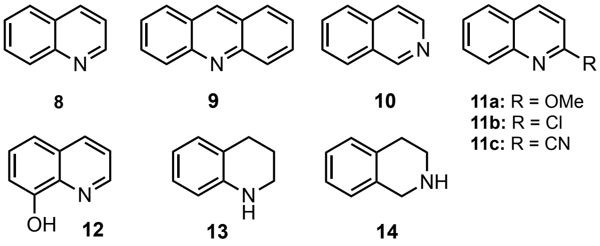


Figure 6. Quinolines and tetrahydroquinolines studied.

Table 2. $\Delta\delta(^{31}P)$ and $\Delta\delta_p(^{19}F)$ data for quinolines binding to PPA and PFBA.

#	compound	^{31}P NMR ($\Delta\delta$, ppm)[a]	^{19}F NMR ($\Delta\delta_p$, ppm)[b]
8	quinoline	7.6	6.7
9	acridine	9.6	8.6
10	isoquinoline	8.0	7.1
11a	2-methoxyquinoline	0.6	2.3
11b	2-chloroquinoline	0.1	1.1
11c	2-quinolinecarbonitrile	0.2	1.0
12	8-hydroxyquinoline	6.7	4.8
13	1,2,3,4-tetrahydroquinoline	6.6	6.0
14	1,2,3,4-tetrahydroisoquinoline	10.9	10.2

[a]3.0 equiv of HBA in CD_2Cl_2 (0.05 M); $\Delta\delta(^{31}P)$ compared to PPA external standard, values reported as average of 4.25 replicates with average standard deviation ± 0.04;[36] [b]5.0 equiv of HBA in CD_2Cl_2 (0.083 M); $\Delta\delta_p(^{19}F)$ compared to PFBA external standard, values reported as an average of 1.75 replicates with average standard deviation ± 0.09 ppm.[36] See Supporting Information for all standard deviations and errors.

Imidazoles and triazole. Imidazoles are ubiquitous scaffolds in azole-based antifungal drugs[38] and many agrochemicals.[39] Imidazoles (**15–18**) are excellent HBAs and displayed high $\Delta\delta(^{31}P)$ and $\Delta\delta_p(^{19}F)$ values: $\Delta\delta(^{31}P)$ range from 8.5 to 11.0 ppm, and $\Delta\delta_p(^{19}F)$ range from 6.9 to 9.6 ppm (Figure 7, Table 3). The large values are attributed to the π-donating effects of the adjacent aromatic nitrogen atom to the non-aromatic nitrogen atom, which can place electron density and a negative charge on the aromatic nitrogen atom. Interestingly, **16** afforded reduced $\Delta\delta(^{31}P)$ and $\Delta\delta_p(^{19}F)$ values compared to **15**; it is unknown as to why methylation decreases H-bond accepting ability with this HBA, when the opposite would be expected. The presence of an extended π-system decreases H-bond accepting ability, exemplified by **17**. As a weak acid (pK_a = 8.2),[40] **18** displayed poor H-bond accepting ability ($\Delta\delta(^{31}P)$ = 3.1 ppm, $\Delta\delta_p(^{19}F)$ = 3.0 ppm).

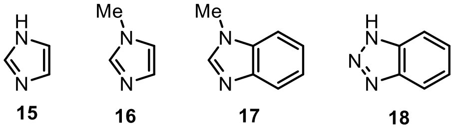


Figure 7. Imidazoles and triazole studied.

Table 3. $\Delta\delta(^{31}P)$ and $\Delta\delta_p(^{19}F)$ data for imidazoles and triazole binding to PPA and PFBA.

#	compound	^{31}P NMR ($\Delta\delta$, ppm)[a]	^{19}F NMR ($\Delta\delta_p$, ppm)[b]
15	imidazole	11.0	9.6
16	1-methylimidazole	9.4	9.0
17	1-methylbenzimidazole	8.5	6.9
18	1,2,3-benzotriazole	3.1	3.0

[a]3.0 equiv of HBA in CD_2Cl_2 (0.05 M); $\Delta\delta(^{31}P)$ compared to PPA external standard, values reported as average of 3.75 replicates with average standard deviation = 0.10 ppm;[36] [b]5.0 equiv of HBA in CD_2Cl_2 (0.083 M); $\Delta\delta_p(^{19}F)$ compared to PFBA external standard, values reported as an average of 1.75 replicates with average standard deviation = 0.06 ppm.[36] See Supporting Information for all standard deviations and errors.

Indoles. Indoles are highly biologically-active, behaving as intercellular signaling molecules[41] and privileged scaffolds in medicinal chemistry.[42] Indoles (**19–21**) are poor HBAs with negligible shifts, and $\Delta\delta(^{31}P)$ and $\Delta\delta_p(^{19}F)$ values are all less than 1.0 ppm for the indoles investigated (Figure 8, Table 4). These results were expected based on the aromaticity of the ring, rendering the lone pair electrons on the nitrogen less available to accept a proton.

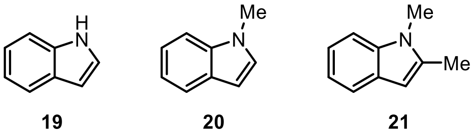


Figure 8. Indoles studied.

Table 4. $\Delta\delta(^{31}P)$ and $\Delta\delta_p(^{19}F)$ data for indoles binding to PPA and PFBA.

#	compound	^{31}P NMR ($\Delta\delta$, ppm)[a]	^{19}F NMR ($\Delta\delta_p$, ppm)[b]
19	indole	0.2	0.2
20	1-methylindole	0.5	0.6
21	1,2-dimethylindole	0.1	0.2

[a]3.0 equiv of HBA in CD_2Cl_2 (0.05 M); $\Delta\delta(^{31}P)$ compared to PPA external standard, values reported as average of 1.33 replicates with average standard deviation ± 0.01 ppm;[36] [b]5.0 equiv of HBA in CD_2Cl_2 (0.083 M); $\Delta\delta_p(^{19}F)$ compared to PFBA external standard, values reported as an average of 1.75 replicates with average standard deviation ± 0.09 ppm.[36] See Supporting Information for all standard deviations and errors; all indoles were studied with one trial run with PFBA.

Alkyl amines. Alkyl amines are among the most prevalent functionalities utilized in medicinal chemistry, with nearly 43% of drugs currently on the market containing an aliphatic amine moiety.[35] Amines such as chiral prolines, imidazolidinones, and phenylalanines have utility as catalysts for asymmetric reactions, while smaller amine organocatalysts such as morpholine, *N*-methylmorpholine, and triethylamine have been shown to catalyze achiral reactions such as Knoevenagel condensations.[43–45] Alkyl amines (**22**–**33**) are the strongest HBA class investigated with Δδ(^{31}P) values ranging from 10.4 to 14.6 ppm, and Δδ$_p$(^{19}F) values ranging from 9.8 to 12.7 ppm (Figure 9, Table 5). Among the strongest HBAs profiled in this study are tertiary amines, such as **26** (Δδ(^{31}P) = 14.6 ppm, Δδ$_p$(^{19}F) = 12.3 ppm). This class also includes **23** (Δδ(^{31}P) = 12.1 ppm, Δδ$_p$(^{19}F) = 12.4 ppm) and **22** (Δδ(^{31}P) = 11.3 ppm, Δδ$_p$(^{19}F) = 11.7 ppm), which are frequently utilized as organocatalysts for Baylis-Hillman and Michael reactions.[46–48]

The Δδ(^{31}P) values for alkyl amines generally follows the H-bond accepting ability of tertiary amines > secondary amines > primary amines.[49] The presence of longer, more branched alkyl groups increases H-bond accepting ability by inductive effects, as evidenced by **26** (Δδ(^{31}P) = 14.6 ppm, Δδ$_p$(^{19}F) = 12.3 ppm) relative to **27** (Δδ(^{31}P) = 12.8 ppm, Δδ$_p$(^{19}F) = 12.0 ppm).

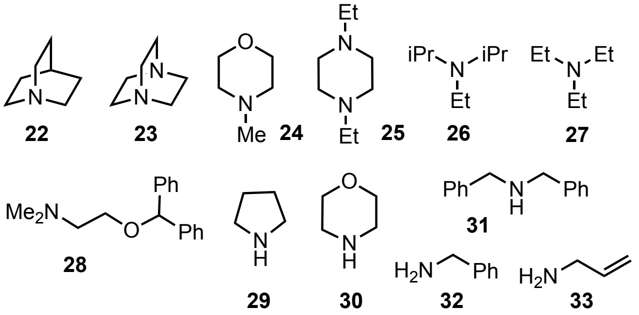


Figure 9. Alkyl amines studied.

Table 5. Δδ(^{31}P) and Δδ$_p$(^{19}F) data for alkyl amines binding to PPA and PFBA.

#	compound	^{31}P NMR (Δδ, ppm)[a]	^{19}F NMR (Δδ$_p$, ppm)[b]
22	quinuclidine	12.1	12.4
23	DABCO	11.3	11.7
24	*N*-methylmorpholine	10.7	10.6
25	1,4-diethylpiperazine	12.3	10.9
26	DIPEA	14.6	12.3
27	TEA	12.8	12.0
28	diphenhydramine	11.1	12.7
29	pyrrolidine	10.8	10.6
30	morpholine	11.1	9.8
31	dibenzylamine	12.2	10.6
32	benzylamine	10.4	--
33	allylamine	10.5	--

[a]3.0 equiv of HBA in CD_2Cl_2 (0.05 M); Δδ(^{31}P) compared to PPA external standard, values reported as average of 1.91 replicates with average standard deviation ± 0.04 ppm;[36] [b]5.0 equiv of HBA in CD_2Cl_2 (0.083 M); Δδ$_p$(^{19}F) compared to PFBA external standard, values reported as an average of 1.4 replicates with average standard deviation ± 0.1 ppm.[36] See Supporting Information for all standard deviations and errors.

Anilines. Anilines are commonly utilized in materials, as urethane precursors,[50] and synthetic azo dyes. Anilines (**34**–**39**) are generally moderate HBAs with substituent-dependent Δδ(^{31}P) values up to 11.8 ppm (Figure 10, Table 6). The largest Δδ(^{31}P) value exhibited by the mono 4-substituted anilines was displayed by **34b** (Δδ(^{31}P) = 8.1 ppm), attributed to the strongly activating π-donating effects of the methoxy substituent. Deactivating, highly electron-withdrawing substituents severely diminished H-bond accepting ability, as exemplified by **34f** (Δδ(^{31}P) = 1.1 ppm). The presence of two deactivating, highly electron-withdrawing substituents almost completely inhibited H-bond accepting ability, demonstrated by **35** (Δδ(^{31}P) = 0.2 ppm) and **36** (Δδ(^{31}P) = 0.2 ppm). The replacement of a proton with an alkyl or allyl group slightly enhanced Δδ(^{31}P) value relative to **34a**, as demonstrated by **37a** (Δδ(^{31}P) = 6.4 ppm) and **37b** (Δδ(^{31}P) = 5.9 ppm, Δδ$_p$(^{19}F = 4.0 ppm) due to inductive effects. The presence of the electropositive silicon atom increased H-bonding ability in **37c** (Δδ(^{31}P) = 11.3 ppm) relative to other substituents. For **37d**, delocalization of the nitrogen lone pair eliminated H-bond accepting ability (Δδ(^{31}P) = 0.1 ppm, Δδ$_p$(^{19}F) = 0.1 ppm). Interestingly, diamine **39** (Δδ(^{31}P) = 11.8 ppm, Δδ$_p$(^{19}F) = 11.0 ppm) displayed high Δδ values regardless of the aryl ring and steric effects of the *sec*-butyl groups, attributed to the reduced delocalization for each amine substituent into the aryl ring, making the H-bonding accepting ability match that of alkyl amines such as **31**.

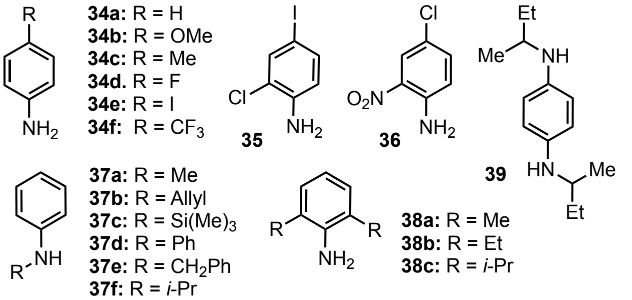


Figure 10. Anilines studied.

Table 6. Δδ(^{31}P) and Δδ$_p$(^{19}F) data for anilines binding to PPA and PFBA.

#	compound	^{31}P NMR (Δδ, ppm)[a]	^{19}F NMR (Δδ$_p$, ppm)[b,c]
34a	aniline	5.5	--
34b	4-methoxyaniline	8.1	--
34c	4-methylaniline	6.7	--
34d	4-fluoroaniline	5.2	--
34e	4-iodoaniline	3.2	--
34f	4-trifluoromethylaniline	1.1	--
35	2-chloro-4-iodo-aniline	0.2	--
36	4-chloro-2-nitroaniline	0.2	--
37a	*N*-methylaniline	6.4	--
37b	*N*-allylaniline	5.9	4.0
37c	*N*-trimethylsilaneaniline	11.3	--
37d	diphenylamine	0.1	0.1
37e	*N*-benzylideaniline	3.9	2.9
37f	*N*-isopropylaniline	7.9	8.7
38a	2,6-dimethylaniline	3.9	--
38b	2,6-diethylaniline	4.1	--
38c	2,6-diisopropylaniline	4.5	--
39	*N,N*-di-*sec*-butyl-*p*-phenylene diamine	11.8	11.0

[a]3.0 equiv of HBA in CD_2Cl_2 (0.05 M); Δδ(^{31}P) compared to PPA external standard, values reported as average of 1.4 replicates with average standard deviation ± 0.04 ppm;[36] [b]5.0 equiv of HBA in CD_2Cl_2 (0.083 M); Δδ$_p$(^{19}F) compared to PFBA external standard, values reported as an average of 1.4

replicates with average standard deviation ± 0.1 ppm.[36] See Supporting Information for all standard deviations and errors. [c]Primary anilines could only be studied with PPA due to salt formation upon PFBA addition.

The $\Delta\delta(^{31}\text{P})$ values of a variety of 2,6-disubstituted anilines (**39a–c**) were also investigated to probe steric and inductive effects. Predictably, the $\Delta\delta(^{31}\text{P})$ values for the 2,6-disubstituted anilines are smaller than that of **34a** due to steric interactions that can reduce binding. However, the trend for the $\Delta\delta(^{31}\text{P})$ values of **39a-c** is opposite to what is expected for the steric effects with the $\Delta\delta(^{31}\text{P})$ value of **39a** ($\Delta\delta(^{31}\text{P})$ = 3.9 ppm) smaller than **39b** ($\Delta\delta(^{31}\text{P})$ = 4.1 ppm), which is in turn smaller than **39c** ($\Delta\delta(^{31}\text{P})$ = 4.5 ppm). These results suggest that the inductive effects of the alkyl groups also influence binding to PPA in addition to steric effects.

Amidine, guanidines, benzotetramisoles and imine. Amidines, guanidines and benzotetramisoles are highly relevant in drug design; guanidines can be found in the popular antidiabetic drug Metformin, and the antiparasitic drug levamisole (Ergamisole) contains a tetramisole moiety, which also has utility in the kinetic resolution of racemic secondary alcohols.[51–53] The related amidine, guanidines and benzotetramisoles (**40**–**44**) studied are strong HBAs with $\Delta\delta(^{31}\text{P})$ values ranging from 9.1 to 13.7 ppm, and $\Delta\delta_p(^{19}\text{F})$ values ranging from 6.7 to 13.2 ppm (Figure 11, Table 7). The strong non-nucleophilic bases display high H-bond accepting ability, with amidines and guanidines measured as the strongest HBAs: **40** ($\Delta\delta(^{31}\text{P})$ = 13.6 ppm, $\Delta\delta_p(^{19}\text{F})$ = 13.2 ppm), **41** ($\Delta\delta(^{31}\text{P})$ = 11.5 ppm, $\Delta\delta_p(^{19}\text{F})$ = 12.0 ppm), and **42** ($\Delta\delta(^{31}\text{P})$ = 13.7 ppm, $\Delta\delta_p(^{19}\text{F})$ = 12.7 ppm). For the benzotetramisoles studied, ring size influenced H-bond accepting ability with n = 2 > n =1. When n = 1 (**43a**; $\Delta\delta(^{31}\text{P})$ = 10.1 ppm and $\Delta\delta_p(^{19}\text{F})$ = 10.2 ppm, and when n = 2 (**43b**; $\Delta\delta(^{31}\text{P})$ = 12.3 ppm and $\Delta\delta_p(^{19}\text{F})$ = 11.9 ppm). For comparison, the imine **44** displays reduced, albeit good, H-bond accepting ability ($\Delta\delta(^{31}\text{P})$ = 9.1 ppm, $\Delta\delta_p(^{19}\text{F})$ = 6.7 ppm).

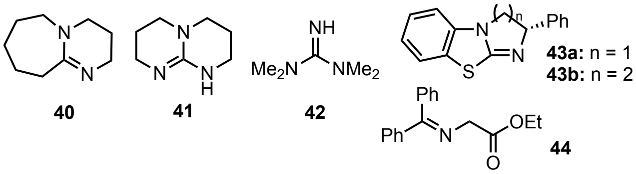


Figure 11. Amidine, guanidines, benzotetramisoles and imine studied.

Table 7. $\Delta\delta(^{31}\text{P})$ and $\Delta\delta_p(^{19}\text{F})$ data for amidine, guanidines, benzotetramisoles and imine binding to PPA and PFBA.

#	compound	^{31}P NMR ($\Delta\delta$, ppm)[a]	^{19}F NMR ($\Delta\delta_p$, ppm)[b]
40	DBU	13.6	13.2
41	TBD	11.5	12.0
42	1,1,3,3-tetramethylguanidine	13.7	12.7
43a	(*S*)-BTM	10.1	10.2
43b	(*S*)-HBTM	12.3	11.9
44	*N*-(diphenylmethylene)glycine ethyl ester	9.1	6.7

[a]3.0 equiv of HBA in CD_2Cl_2 (0.05 M); $\Delta\delta(^{31}\text{P})$ compared to PPA external standard, values reported as average of 1.66 replicates with average standard deviation ± 0.04 ppm;[36] [b]5.0 equiv of HBA in CD_2Cl_2 (0.083 M); $\Delta\delta_p(^{19}\text{F})$ compared to PFBA external standard, values reported as an average of 1.5 replicates with average standard deviation ± 0.06 ppm.[36] See Supporting Information for all standard deviations and errors.

Amides Amides such as formamides, lactams, and ureas possess diverse applications, ranging from peptide backbones to pharmaceutical agents to polymers such as nylon. Formamides, in addition to their utility as polar aprotic solvents (e.g. **45**), possess highly diverse applications, ranging from nucleophiles in Michael additions[54] to organocatalysts for the allylation of aldehydes with allyltrichlorosilane.[55] Most recently, they have aroused interest due to the central role they may play in prebiotic, or "Origin of Life" chemistry.[56,57] Lactams and sulfonamides are present in many pharmaceuticals, such as antibacterial and antimicrobial *β*-lactam and sulfa drugs.

For the class of amides (**45–55**), reduced H-bond accepting ability is observed with overall smaller $\Delta\delta(^{31}\text{P})$ and $\Delta\delta_p(^{19}\text{F})$ values ($\Delta\delta(^{31}\text{P})$ up to 3.3 ppm, and $\Delta\delta_p(^{19}\text{F})$ up to 4.1 ppm). The trend corresponds to resonance delocalization effects as well as an observation of decreased solubility of these highly polar functional groups in CD_2Cl_2 (Figure 12, Table 8). The H-bond accepting of formamides **45–48** and lactams **49–52** occurs at the carbonyl oxygen instead of at nitrogen.[58] Ureas **53–54** exhibit enhanced H-bond accepting ability compared to amides due to enhanced electron donation onto oxygen, but smaller Δδ values compared to guanidines **41–42** (vida supra). Sulfonamide **55** displayed poor H-bond accepting ability ($\Delta\delta(^{31}\text{P})$ = 0.6 ppm, $\Delta\delta_p(^{19}\text{F})$ = 1.5 ppm) attributed to the highly electron-withdrawing nature of the sulfone moiety, and reduced solubility in CD_2Cl_2.

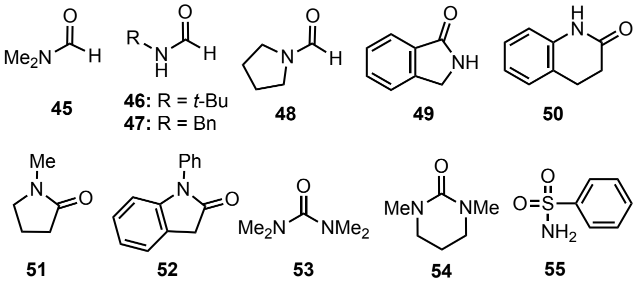


Figure 12. Amides studied.

Table 8. $\Delta\delta(^{31}\text{P})$ and $\Delta\delta_p(^{19}\text{F})$ data for amides binding to PPA and PFBA.

#	compound	^{31}P NMR ($\Delta\delta$, ppm)[a]	^{19}F NMR ($\Delta\delta_p$, ppm)[b]
45	DMF	3.3	3.4
46	*N-tert*-butylformamide	0.7	3.1
47	*N*-benzylformamide	0.5	2.8
48	1-formylpyrrolidine	1.0	3.7
49	isoindolin-1-one	0.1	1.2
50	3,4-dihydroquinoline-2-(1*H*)-one	0.5	2.3
51	1-methyl-2-pyrrolidinone	1.7	3.1
52	1-phenylindolin-2-one	0.2	1.4
53	tetramethylurea	2.1	4.1
54	DMPU	2.3	4.1
55	benzenesulfonamide	0.6	1.5

[a]3.0 equiv of HBA in CD_2Cl_2 (0.05 M); $\Delta\delta(^{31}\text{P})$ compared to PPA external standard, values reported as average of 1.54 replicates with average standard deviation ± 0.07 ppm;[36] [b]5.0 equiv of HBA in CD_2Cl_2 (0.083 M); $\Delta\delta_p(^{19}\text{F})$ compared to PFBA external standard, values reported as an average of 1.1 replicates with average standard deviation ± 0.05 ppm.[36] See Supporting Information for all standard deviations and errors.

Metal-chelating ligands and bifunctional catalysts. The H-bond accepting abilities of privileged metal-chelating ligands and catalysts containing more than one amine or heterocycle (e.g. **56–63**) were investigated (Figure 13, Table 9). TMEDA (**56**) is a classic example of a metal-chelating ligand that displays excellent H-bond accepting ability ($\Delta\delta(^{31}\text{P})$ and $\Delta\delta_p(^{19}\text{F})$ = 11.8 ppm) characteristic of aliphatic amines.

For compounds containing more than one HBA site, it was considered whether steric effects would be observed and if more equivalents of HBA would be needed for saturation of the probe. When bipyridine **57** was initially studied at 3.0 equivalents with PPA, the $\Delta\delta(^{31}\text{P})$ value was measured as 3.9 ppm. Increasing to 12 equivalents of **57**, the $\Delta\delta(^{31}\text{P})$ value increases to 6.3 ppm, which more closely matches the value observed for **1a**. In contrast to PPA, when **57** was studied with varying equivalents of PFBA, at up to 12 equivalents, the $\Delta\delta_p(^{19}\text{F})$ value remained constant at 4.9 ppm (see Supporting Information). As the two pyridine rings favor the *trans* orientation (the *trans* conformation is preferred over the *cis* by approximately 27.0 kJ/mol,[59] upon protonation, a slightly twisted *cis* form is favored[60]) this deviation may support the greater sensitivity of PPA to steric effects.

The addition of a pyridine to oxazoline (**59**) resulted in $\Delta\delta(^{31}\text{P})$ and $\Delta\delta_p(^{19}\text{F})$ values ($\Delta\delta(^{31}\text{P})$ = 7.6 ppm, $\Delta\delta_p(^{19}\text{F})$ = 5.5 ppm) with H-bonding ability more similar to **1a** rather than an oxazoline. The dimethyl group on the oxazoline site of **59** may hinder PPA and PFBA binding, and facilitate probe binding to the pyridine moiety; this may be the reason as to why the $\Delta\delta(^{31}\text{P})$ and $\Delta\delta_p(^{19}\text{F})$ values of **59** are similar to those of **1a**. The larger $\Delta\delta(^{31}\text{P})$ and $\Delta\delta_p(^{19}\text{F})$ values of **58** relative to **57** demonstrate that ring-locking increases H-bond accepting ability. Bidentate ligands generally saturated more quickly/saturated at a lower HBA:probe ratio with PFBA than with PPA, which is assumed to be due to the greater of acidity of PFBA, in addition to the fact that it is less sterically encumbered and does not self-associate like PPA. Bisoxazoline (BOX) ligands are highly versatile chiral metal-chelating ligands in asymmetric catalysis and coordination chemistry.[61–63] Bisoxazolines **60a–61** afforded large Δδ values with $\Delta\delta(^{31}\text{P})$ = 7.2 to 11.6 ppm, and $\Delta\delta_p(^{19}\text{F})$ = 9.3 to 10.2 ppm, with the largest Δδ values observed for **61** ($\Delta\delta(^{31}\text{P})$ = 11.7 ppm, $\Delta\delta_p(^{19}\text{F})$ = 10.2 ppm).

Bifunctional cinchona alkaloids **62a–b**,[64–66] structurally-related quinine and quinidine (**62c–d**), and the Hoveyda-Snapper desymmetrization agent (**63**)[67] were also studied. Bifunctional cinchona alkaloids containing both quinuclidine ($\Delta\delta(^{31}\text{P})$ and quinoline moieties exhibit large $\Delta\delta(^{31}\text{P})$ and $\Delta\delta_p(^{19}\text{F})$ values, similar to those of quinine and quinoline. The Hoveyda-Snapper catalyst (**63**; $\Delta\delta(^{31}\text{P}$ = 11.7 ppm, $\Delta\delta_p(^{19}\text{F})$ = 10.6 ppm) displays values similar to imidazole **15**, demonstrating that the H-bond accepting ability is retained despite the additional two H-bond accepting functionalities.

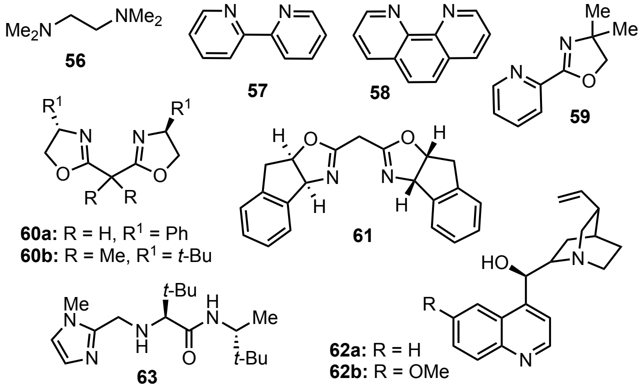


Figure 13. Bifunctional metal-chelating ligands and organocatalysts studied.

Table 9. $\Delta\delta(^{31}\text{P})$ and $\Delta\delta_p(^{19}\text{F})$ data for metal-chelating ligands and bifunctional catalysts binding to PPA and PFBA.

#	compound	^{31}P NMR (Δδ, ppm)	^{19}F NMR ($\Delta\delta_p$, ppm)[b]
56	TMEDA	11.8	11.8
57	2,2'-bipyridine	6.3[d]	4.9
58	1,10-phenanthroline	7.7	6.0
59	2-(4,4-dimethyl-4,5-dihydro-2-oxazolyl)pyridine	7.6	5.5
60a	2,2′-methylenebis[(4*S*)-4-phenyl-2-oxazoline]	10.4	10.0
60b	2,2'-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline	7.2	9.3
61	(3aS,3′aS,8aR,8′aR)-2,2′-methylenebis[3a,8a-dihydro-8H-indeno[1,2-d]oxazole]	11.7	10.2
62a	cinchonidine	9.7	--[c]
62b	quinine	9.9	9.8
63	Hoveyda-Snapper catalyst	11.7	10.6

[a]3.0 equiv of HBA in CD_2Cl_2 (0.05 M); $\Delta\delta(^{31}\text{P})$ compared to PPA external standard, values reported as average of 1.83 replicates with average standard deviation ± 0.06 ppm;[36] [b]5.0 equiv of HBA in CD_2Cl_2 (0.083 M); $\Delta\delta_p(^{19}\text{F})$ compared to PFBA external standard, values reported as an average of 1.5 replicates with average standard deviation ± 0.05 ppm.[36] See Supporting Information for all standard deviations and errors; [c]**62a-b** were insoluble in CH_2Cl_2; however, they solubilized upon addition of PPA but formed salts upon PFBA formation; [d]**57** studied at 12.0 equiv relative to PPA.

Strong Correlation of $\Delta\delta(^{31}\text{P})$ and $\Delta\delta_p(^{19}\text{F})$ data to p$K_{\text{BH+}}$ values The $\Delta\delta(^{31}\text{P})$ and $\Delta\delta_p(^{19}\text{F})$ values to quantify HBA ability correlate highly with proton-transfer basicity (p$K_{\text{BH+}}$) measurements[68] (Figure 14) derived from the earlier studies of Scorrano[69] and Arnett.[70] Proton-transfer basicity (p$K_{\text{BH+}}$) is the aqueous proton basicity of a neutral base, described by the dissociation constant of its conjugate acid, BH^+, with respect to a reference acid. For amphoteric compounds studied, such as primary and secondary amines, p$K_{\text{BH+}}$ would describe the acid/base pair $R\text{-}NH_3^+/R\text{-}NH_2$, and not $R\text{-}NH_2/R\text{-}NH^-$, for instance. Thermodynamic p$K_{\text{BH+}}$ values, originally tabulated under the assumption that weaker bases follow the Hammett acidity principle,[71] are now considered less valid compared to pK_{BHX} values[68] and other computational methods to quantify basicity; however, the high correlation between p$K_{\text{BH+}}$ values and $\Delta\delta(^{31}\text{P})$ and $\Delta\delta_p(^{19}\text{F})$ still provides valuable insight regarding H-bonding ability. Although such high correlations are indicative of $\Delta\delta(^{31}\text{P})$ and $\Delta\delta_p(^{19}\text{F})$ values being closely coincident with proton-transfer basicity, the slight deviations from linear behavior suggest that

pK_{BH+} values may not account for steric and electronic effects that are more accurately measured upon HBA binding to PPA and PFBA.

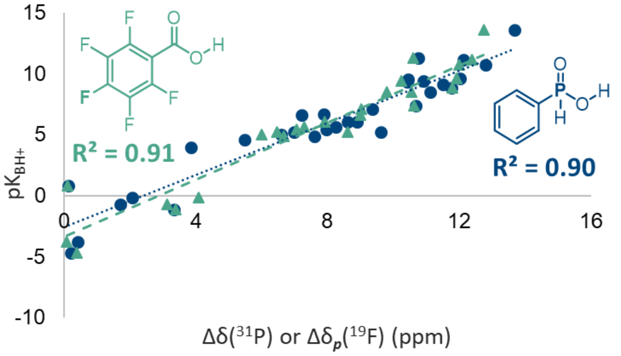


Figure 14. Correlation of Δδ(^{31}P) and $Δδ_p$(^{19}F) values (in CD_2Cl_2) with proton-transfer basicity, pK_{BH+}. For PPA and PFBA, *N* = 31 and 25, respectively.

Strong Correlation of Δδ(^{31}P) and $Δδ_p$(^{19}F) data to pK_a values for protonated HBAs When Δδ(^{31}P) and $Δδ_p$(^{19}F) values are plotted versus pK_a values (in water) of protonated HBAs, excellent correlation was afforded for both PPA (R^2 = 0.94) and PFBA (R^2 = 0.96) (Figure 15). This high correlation is attributed to the extent of acid/base proton exchange occurring since both probes are reasonably strong acids (vide supra), when the pK_a values of protonated HBAs significantly larger than the pK_a values of PPA and PFBA (Figure 15). For example, the pK_a of protonated **22** (pK_a = 11.0)[72] is significantly higher than the pK_a of PFBA (pK_a = 1.48) and PPA (pK_a = 1.83), so it can be assumed that acid/base proton exchange is occurring (Scheme 1, eq 2). However, when the pK_a values for protonated HBAs are closer to PFBA and PPA, such as protonated **8** (pK_a = 4.92)[27], it is assumed that H-bonding interactions predominate rather than acid/base proton exchange (eq 3). When protonated HBAs have pK_a values approximately equal to or less than the pK_a values of PPA and PFBA (such as with **45**) then there is expected to be minimal or no H-bonding as reflected by the low or negligible Δδ(^{31}P) and $Δδ_p$(^{19}F) values (Scheme 1, eq 4).

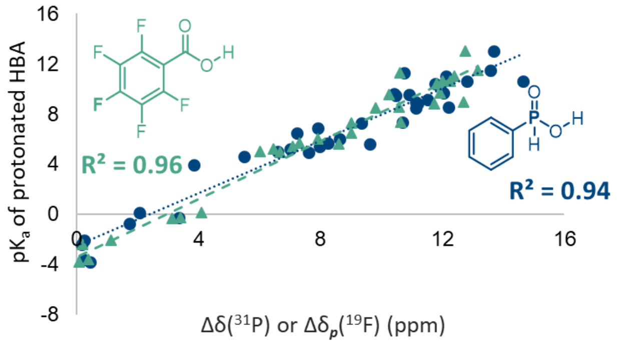
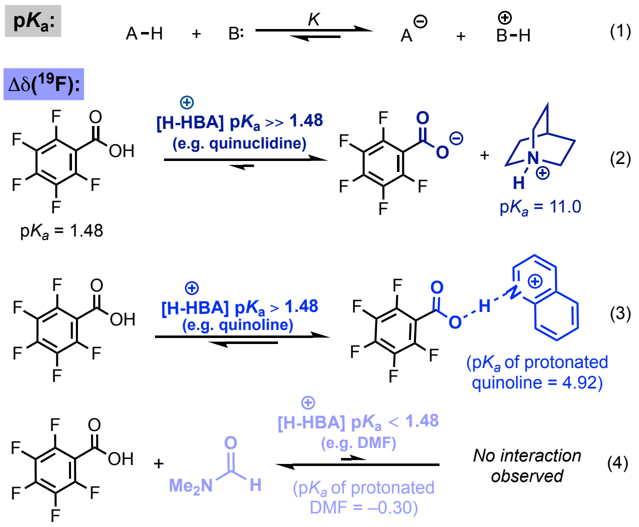


Figure 15. Correlation of Δδ(^{31}P) and $Δδ_p$(^{19}F) values (in CD_2Cl_2) with pK_a values for protonated HBAs. For PPA and PFBA, *N* = 36 and 30, respectively.



Scheme 1. Interactions based on relative difference between $Δδ_p$(^{19}F) value and pK_a value of the protonated HBA.

Good Correlation of Δδ(^{31}P) and $Δδ_p$(^{19}F) data to Mayr Nucleophilicity[73] Over the past few decades, Mayr and coworkers have compiled a reactivity scale for a variety of nucleophiles and electrophiles, most commonly in CH_2Cl_2, but also in solvents such MeCN, DMSO, and water.[74,75] Although it is understood that H-bond accepting ability is not synonymous to nucleophilicity, we were interested to compare Δδ(^{31}P) and $Δδ_p$(^{19}F) values for many of the HBAs that also have reported Mayr *N* parameters.

Initial comparisons for Δδ(^{31}P) and $Δδ_p$(^{19}F) values with Mayr nucleophilicity for only nitrogen-nucleophilic compounds (N-nucleophiles) indicated low correlations (R^2 = 0.40 with PPA, R^2 = 0.52 with PFBA, see Supporting Information); however, overall correlations improved when a broader class of HBAs including O- and C-nucleophiles were added (Figure 16). These correlations for N-, O-, and C-nucleophiles suggest that Δδ(^{31}P) and $Δδ_p$(^{19}F) values can be used to predict relative nucleophilicity.

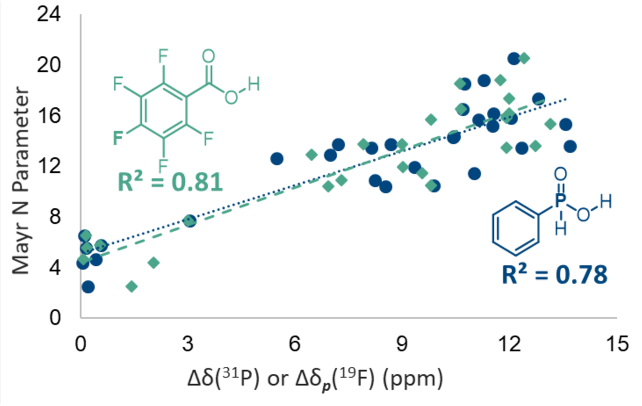


Figure 16. Plot of Δδ(^{31}P) and $Δδ_p$(^{19}F) values (in CD_2Cl_2) *vs.* Mayr Nucleophilicity (*N*) parameters for N-, O-, and C-nucleophiles. For PPA and PFBA, *N* = 31 and 26, respectively.

Conclusions We have quantified H-bond accepting abilities for over 100 compounds, focusing on heterocycles and amines that are important for medicinal chemistry, organocatalysis and ligand design. Phenylphosphinic acid and pentafluorobenzoic acid are inexpensive, commercially available non-toxic probes that allow for rapid data acquisition using either ^{31}P or ^{19}F NMR spectroscopy. The $\Delta\delta(^{31}\mathrm{P})$ and $\Delta\delta_p(^{19}\mathrm{F})$ values measured upon HBA binding to either PPA or PFBA show strong correlation to electronic effects, proton-transfer basicity, and pK_a of the protonated HBA. Moderate correlations are also observed with Mayr nucleophilicity parameters. The rapid and simple use of ^{31}P and ^{19}F NMR measurements to compare and predict thermodynamic and reactivity properties may have future implications in the design of novel organocatalysts and medicinal compounds.

Experimental Section

General Methods and Materials. All nuclear magnetic resonance (NMR) spectra were obtained on Bruker Nanobay AVIIIHD 400 or Varian VNMRS 600 MHz spectrometers at room temperature. Chemical shifts were reported in parts per million (δ scale) and rounded to the nearest hundredth. Chemical shifts were referenced according the following standards: pentafluorobenzoic acid or 4-fluorophenol external standard in CD_2Cl_2 for ^{19}F{^{1}H} signals and phenylphosphinic acid (PPA) external standard in CD_2Cl_2 for ^{31}P{^{1}H} signals. For PPA, NMR measurements were performed with 3.0 equiv of HBA (relative to PPA) at a concentration of 0.05 M in CD_2Cl_2. For PFBA, NMR measurements were performed with 5.0 equiv of HBA (relative to PFBA) at a concentration of 0.083 M in CD_2Cl_2. External standards of PFBA and PPA were taken daily to calculate Δδ values.

For external standards of unbound PPA and PFBA, small deviation in the ranges of δ values were afforded that was attributed to magnetic drift of the instruments, human error in sample preparation (e.g. external standards were taken daily by different researchers, and slight changes in PPA and PFBA stock concentration), and any hidden impurities such as water, that may have been present. Electronic scales utilized to weigh HBAs, PPA and PFBA only provided measurements to tenth place; thus if 15.65 mg of an HBA were required, for instance, the scale would not be able to produce a measurement more accurate than 15.60 mg. For example, if 15.60 mg of the HBA was utilized for binding studies with PPA or PFBA, slightly different Δδ values would be afforded than if 15.69 mg was utilized, as the ^{31}P and ^{19}F NMR spectra are very sensitive to concentration effects. $\Delta\delta(^{31}\mathrm{P})$ NMR values reported relative to the external standards of unbound PPA (range from ~δ 23.6 ± 0.3 ppm in CD_2Cl_2) and $\Delta\delta_p(^{19}\mathrm{F})$ NMR values reported relative to the external standards of unbound PFBA (range from ~δ –147.6 ± 0.25 ppm in CD_2Cl_2).

Commercially available reagents were purchased and used without further purification unless otherwise indicated. Purity of all reagents utilized were verified via ^{1}H NMR spectroscopy prior to use. Anhydrous CH_2Cl_2 was dispensed from a solvent system that passes solvent through two columns of dry neutral alumina. Anhydrous CD_2Cl_2 was obtained from Acros Organics. Pentafluorobenzoic acid (PFBA) and 4-fluorophenol (4-FP) were obtained from Sigma Aldrich, and phenylphosphinic acid (PPA) was obtained from TCI Chemicals. All HBA compounds were obtained from Sigma Aldrich, Fischer Scientific, Oakwood Chemical, or Acros Organics. Liquid amines, such as TEA, DIPEA, and pyridine, were purified by first stirring over calcium hydride, followed by distillation at reduced pressure under nitrogen.

Procedure for ^{31}P NMR Titration Experiments with PPA

Probe concentration was held constant for titration experiments, and varying amounts of the HBA were added to give the desired equivalents of HBA. A stock solution was made with the PPA probe in CD_2Cl_2 (0.0611 M). Additional stock solutions of the HBA in CH_2Cl_2 were also made, of the appropriate concentration per varying equivalent. Into an oven-dried, argon-purged NMR tube was added 0.15 mL of the PPA probe stock solution, then 0.4 mL of the HBA stock solution, to give a volume of 0.55 mL. The decoupled ^{31}P NMR spectrum of each sample was collected at room temperature with 16 scans and compared to a PPA standard.

Procedure for ^{19}F NMR Titration Experiments with PFBA and 4-FP

Probe concentration was held constant for titration experiments, and varying amounts of the HBA were added to give the desired equivalents of HBA. A stock solution was made with the PFBA or 4-FP probe in CD_2Cl_2 (0.0611 M). Additional stock solutions of the HBA in CH_2Cl_2 were also made, of the appropriate concentration per varying equivalent. Into an oven-dried, argon-purged NMR tube was added 0.15 mL of the PFBA or 4-FP probe stock solution, then 0.4 mL of the HBA stock solution, to give a volume of 0.55 mL. The decoupled ^{19}F NMR spectrum of each sample was collected at room temperature with 16 scans and compared to an external standard of PFBA or 4-FP.

Procedure for Job Plot Analysis of HBA and PFBA and PPA

To determine the binding stoichiometry of PFBA or PPA and an HBA, Job plots were constructed with TEA and quinuclidine. A stock solution of the HBA (0.05 M) in $CDCl_3$ was made as well as a stock solution of PFBA or PPA in $CDCl_3$ (0.05 M). To oven-dried, argon-purged NMR tubes were added the necessary amounts of each stock solution to vary the mole fraction of PFBA or PPA between 0.1 and 1.0, with a final solution volume of 0.6 mL in the NMR tube. The decoupled ^{19}F or ^{31}P NMR spectrum of each sample was collected at room temperature with 16 scans and compared to an external standard of PFBA or PPA.

General Experimental Procedure for PPA Measurement

Based on the final concentration of 0.05 M for the NMR sample, the selected HBA (3.0 equiv, 0.0275 mmol) was dissolved in 0.4 mL of CH_2Cl_2 and transferred to an oven-dried, argon-purged NMR tube. Then 0.15 mL (1.0 equiv, 0.0092 mmol) of a stock solution of PPA (0.0611 M in CD_2Cl_2) was added to the NMR tube which was inverted several times to allow for mixing. The ^{31}P NMR spectrum of each sample was collected at room temperature with 16 scans and compared to an external standard of PPA to determine the change in the chemical shift resulting from interaction of PPA with the HBA. Only HBAs that were completely soluble in CH_2Cl_2 were tested to assure that the peak being measured was the bound species; compounds that were soluble in CH_2Cl_2, yet that did not instantly solubilize, were subject to agitation by a Vortex mixer.

General Experimental Procedure for PFBA Measurement

Based on the final concentration of 0.083 M for the NMR sample, the selected HBA (5.0 equiv, 0.0458 mmol) was dissolved in 0.4 mL of CH_2Cl_2 and transferred to an oven-dried, argon-purged NMR tube. Then 0.15 mL (1.0 equiv, 0.0092 mmol) of a stock solution of PFBA (0.0611 M in CD_2Cl_2) was added to the NMR tube which was inverted several times to allow for mixing. The ^{19}F NMR spectrum of each sample was collected at room temperature with 16 scans and compared to an external standard of PFBA to determine the change in the chemical shift (ppm) resulting from interaction of PFBA with the HBA. Only HBAs that were completely soluble in CH_2Cl_2 were tested to assure that the peak being measured was the bound species; compounds that were soluble in CH_2Cl_2, yet that did not instantly solubilize, were subject to agitation by a Vortex mixer.

ASSOCIATED CONTENT

Supporting Information.

The supporting information is available free of charge via the Internet at http://pubs.acs.org (PDF).

AUTHOR INFORMATION

Corresponding Author

***Tel:** 530-752-9820. **E-mail:** akfranz@ucdavis.edu

Notes

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ABBREVIATIONS

PPA, phenylphosphinic acid; PFBA, pentafluorobenzoic acid; 4-FP, 4-fluorophenol; TEA, triethylamine; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; TBD, 1,5,7-triazabicyclo[4.4.0]dec-5-ene; DMAP, 4-dimethylaminopyridine; DABCO, 1,4-diazabicyclo[2.2.2]octane; DIPEA, *N,N*-diisopropylethylamine or Hünig's base; THF, tetrahydrofuran; BOX, bis-oxazoline; TMEDA tetramethylethylenediamine; TEPO, triethylphosphine oxide; DMF, DMPU, 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1*H*)-pyrimidinone; BTM, benzotetramisole; HBTM, homobenzotetramisole.

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(30) For moderate HBAs, such as quinolines, which generally afford $\Delta\delta$(31P) and $\Delta\delta$p(19F) values in the range of 6.0-8.0 ppm, the plateau was more gradual and it was observed that 5.0 equivalents are needed.

(31) We believe that strong HBAs may undergo complete proton transfer, whereas moderate or weak HBAs exclusively engage in H-bonding interactions.

(32) When Job plots analyses were performed with PPA and PFBA, 1:1 binding stoichiometry for PFBA with HBAs was observed. However, binding stoichiometry for PPA with HBAs was 1.2:1, due to the propensity of PPA to self-associate at 0.05M.

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