

NMR Quantification of Halogen-Bonding Ability To Evaluate Catalyst Activity

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H alogen bonding (X-bonding) is a noncovalent interaction between an electrophilic halogen atom and a Lewis base.¹ Owing to the high directionality, hydrophobicity, and tunability, X-bonding has been utilized in crystal engineering and material science to control molecular assembly.^{2,3} More recently, X-bonding has been applied to molecular recognition⁴ and catalysis⁵ in solution phase.⁶ In general, X-bonding of organic scaffolds is a relatively weak interaction with a low association affinity to Lewis bases.⁷ The investigation of X-bonding on organic scaffolds relies on high sensitivity techniques such as IR,⁸ Raman,⁹ UV–vis,¹⁰ and NMR^{11–13} spectroscopies.

Due to the versatility and ability to provide detailed structural information, solution NMR spectroscopy has been the most common technique for analyzing X-bonding for organic scaffolds (Figure 1).¹¹ With ¹H and ¹⁹F NMR, chemical shifts provide insight regarding X-bonding at least two bonds away from the interaction site to the reporter nucleus, albeit often with low magnitudes of the detectable signal (Figure 1A).^{5f,11b,c} Examples of ¹³C NMR spectroscopy have been successfully used to detect the formation of Xbonding in solution, yet the intrinsic low abundance limits the sensitivity, decreasing the applicability to quantify X-bonding (Figure 1B).^{5j,12} Several examples of quantification of Xbonding using ¹⁵N NMR spectroscopy have been reported;¹³ however, even though the reporter nitrogen is directly interacting with the halogen atom, the author reported that the evaluation of weak X-bonding interactions is not sufficiently accurate (Figure 1C).



Figure 1. Quantification of noncovalent interactions using NMR spectroscopy.

³¹P NMR spectroscopy has been successfully applied to quantify noncovalent interactions upon binding to triethyl-

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phosphine oxide (TEPO) as a Lewis basic probe.^{14–16} First reported by Gutmann and Beckett to measure Lewis acidic solvents,¹⁴ we and others have since adapted this method to quantify the H-bonding ability and Lewis acidity of various catalysts.^{15,16} Previous work in our group has successfully demonstrated the proportional relationship of H-bonding ability and catalytic activity for a variety of H-bonding donors using ³¹P NMR spectroscopy (Figure 1D).¹⁶ Compared to the extensive application for H-bonding, the investigation of Xbonding ability for organocatalysts is limited.^{5j,17} Here, we report using the ³¹P NMR spectroscopy method to systematically quantify X-bonding ability and correlate the catalytic ability for XBD organocatalysts (Figure 1E). This work examines representative XBD compounds including neutral (1-4), cationic benzimidazolium- (5), $5^{5e,f}$ imidazolium- (6-7), $5^{5e,f,i}$ and bis(imidazolium)-based $5^{5e,g}$ (8-9) structures (Figure 2).



Method Validation. To validate ³¹P NMR spectroscopy as a method to quantify X-bonding ability, factors such as the XBD–TEPO equilibrium, solvent interferences, and the competition of other noncovalent interactions from impurities were carefully examined.¹⁸ Downfield ³¹P NMR shifts ($\Delta\delta$) are observed upon TEPO binding to XBDs (Figure 3A).¹⁹ Stronger X-bonding ability is expected to correlate to larger $\Delta\delta$ (³¹P) values. To assess the XBD–TEPO binding equilibrium,²⁰ titration experiments of XBD (relative to TEPO) were investigated (Figure 3B). For imidazolium- (6•OTf) and bis(imidazolium)-based triflate (8c•OTf) XBDs, saturation occurs at approximately 10 and 15 equiv, respectively. With the weakly coordinating counteranion, 7e•BAr^F and 8c•BAr^F XBDs



Figure 3. (A) Example ³¹P NMR spectra for the downfield ³¹P NMR shifts upon TEPO binding to XBD (in CD_2Cl_2). (B) Titration experiments comparing XBDs. Calculation of binding constant: **8c**·**BAr**^F, $K_a = 186 \pm 4 \text{ M}^{-1}$ (see Supporting Information).²¹

Equivalents of XBDs

possess enhanced binding ability²¹ and saturation was observed for each at \sim 5 equiv.

To assess that TEPO binding can probe X-bonding ability, the $\Delta\delta(^{31}P)$ values for XBDs with different electrophilic halogen atoms were measured (Figure 2, Sa-5b•OTf, 7e-7g• OTf, 8c-8d•OTf). The more electrophilic halogen atom (I > Br > Cl) should correlate with larger $\Delta\delta(^{31}P)$ values. Indeed, switching from iodo to bromo and chloro (in 7e-7g•OTf) significantly decreased $\Delta\delta(^{31}P)$ values (Table 1), matching a decrease in polarizability of the halogen substituents and hence the X-bonding ability.

To validate ³¹P NMR spectroscopy and the ability of TEPO binding to quantify electronic effects for X-bonding, a Hammett plot was created for a series of 2-iodoimidazolium triflate salts (7a-7e•OTf) with electronically varied substituents on the conjugated benzene ring (Table 1, Figure 4). A linear relationship ($R^2 = 0.988$) was observed, indicating that $\Delta\delta(^{31}P)$ values can accurately quantify the electronic changes affecting X-bonding ability.

Results and Discussion. To build a scale to quantify the Xbonding ability of organocatalysts, $\Delta\delta(^{31}P)$ values were measured for a variety of XBD compounds (Table 1). TEPO binding with most neutral XBDs (e.g., 1-2, 4) results in very low $\Delta\delta$ ⁽³¹P) values, indicating low X-bonding ability; however, the X-bonding ability was notably increased with a high electronegative atom attached to the halogen atom (e.g., 3a). Without the cationic charge on the XBD core, the $\Delta\delta(^{31}P)$ values are <1.0 ppm and interactions are too weak to observe trends, highlighting the importance of the cationic charge for increasing the X-bonding ability (e.g., 4a-4d). The larger $\Delta\delta(^{31}\text{P})$ value of cationic benzimidazolium-based XBD (5a· **OTf**, $\Delta \delta(^{31}P) = 4.94$ ppm) compared to cationic imidazoliumbased XBD (6•OTf, $\Delta \delta$ ⁽³¹P) = 4.03 ppm) suggested higher Xbonding ability. This is attributed to the extended aromaticity of the benzimidazolium core.²² By increasing the electron deficiency of the benzimidazolium core (5d·OTf), the largest

Table 1. Measured ³¹P NMR Shifts and k_{obs} for XBDs in CD₂Cl₂

XBD ^a	$\Delta\delta(^{31}P)$ (ppm) Trial 1 ^b	$\Delta\delta(^{31}\text{P}) \ (\text{ppm}) \ \text{Trial } 2^b$	$\begin{array}{c} \Delta \delta(^{31} P) \\ (ppm) \\ Trial 3^{b} \end{array}$	$egin{array}{l} \operatorname{Avg}\ \Delta\delta(^{31}\mathrm{P})\ (\mathrm{ppm})^c \end{array}$	$k_{ m obs} \times 10^{-4}$ $ m min^{-1}$
1	0.20	0.22	0.22	0.21	NR ^d
2	0.12	0.14	0.13	0.13	_
3a	10.01	9.99	9.97	9.99	_e
3b	1.42	1.36	1.44	1.41	_e
3c	1.34	1.41	1.38	1.38	_
4a	0.05	0.01	0.05	0.04	_
4b	0.84	0.82	0.84	0.83	-
4c	0.89	0.89	0.97	0.92	-
4d	0.88	0.89	0.89	0.89	-
5a•OTf	4.94	4.94	4.93	4.94	4.57
5b•OTf	1.77	1.64	1.61	1.67	-
5c•OTf	1.24	1.26	1.25	1.25	-
5d•OTf	5.77	5.74	5.76	5.76	13.00
6·OTf	4.06	4.02	4.01	4.03	NR ^d
6•BAr ^F	5.75	5.65	5.66	5.68	5.77
6·SbF ₆	5.34	5.29	5.29	5.31	_g
6•BPh4	4.62	4.49	4.46	4.52	_g
7a•OTf	4.70	4.68	4.68	4.69	2.72
7b•OTf	4.79	4.78	4.78	4.78	4.86
7c•OTf	5.00	5.01	5.01	5.01	7.03
7d•OTf	5.12	5.10	5.11	5.11	7.16
7e•OTf	5.29	5.28	5.29	5.28	8.51
7e•BAr ^F	6.24	6.29	6.23	6.25	11.47
7f•OTf	1.43	1.44	1.39	1.42	NR ^d
7g∙OTf	1.22	1.13	1.27	1.21	NR ^d
8a•OTf ⁴	0.94	0.99	0.98	0.97	NR ^d
8b•OTf ^h	4.87	4.88	4.88	4.88	8.23
8c•OTf ^h	4.91	4.92	5.03	4.95	9.21
8c•BAr ^{Fi}	10.47	10.44	10.46	10.46	32.64
8d∙OTf ^h	2.54	2.46	2.52	2.51	NR ^d
9·OTf	4.01	3.90	3.89	3.91	8.28

^{*a*}Experiments performed at 15 mM TEPO in CD₂Cl₂ with 10 equiv of XBD unless otherwise indicated. ^{*b*} $\Delta\delta(^{31}P) = \delta(XBD \cdot TEPO \text{ complex}) - \delta(\text{free TEPO})$. ^{*c*}Standard deviation (*n* = 3) for all XBDs are <0.10 ppm. Avg $\Delta\delta(^{31}P)$ values used for correlation. ^{*d*}No reaction observed; k_{obs} assumed to be zero. ^{*c*}Not reported; observed rate is attributed to *in situ* formation of elemental halogens (e.g., I₂) rather than respective XBDs. ^{*f*}One drop of 2,6-di-*tert*-butylpyridine (DTP) was added. ^{*g*}No reaction observed with DTP added. ^{*h*}Using 15 equiv of XBD. ^{*i*}Using 5 equiv of XBD. ^{*j*}Using 3 equiv of XBD.²⁶



Figure 4. Correlation of $\Delta\delta(^{31}\text{P})$ and Hammett σ parameters for imidazolium triflates 7a-7e•OTf (Table 1).

 $\Delta\delta(^{31}\text{P})$ value among cationic XBD triflates was observed (5.76 ppm).

³¹P NMR spectroscopy was also utilized to investigate the effect of different counteranions for imidazolium **6** on X-

bonding interactions.^{5e,h} The largest $\Delta\delta(^{31}\text{P})$ value was measured for **6·BAr**^F (5.68 ppm) matching the decreased coordinating ability for the BAr^{F-} counterion and hence increased X-bonding ability. The $\Delta\delta(^{31}\text{P})$ values for **6·SbF**₆ and **6·BPh**₄ were observed to generally follow the trend for

anion-coordinating ability.^{23,24} To investigate the denticity effect based on the substituent pattern for X-bonding ability, bis(imidazolium) salts **8–9** were quantified. $\Delta\delta(^{31}\text{P})$ values were collected using 3.0 equiv of XBD (relative to TEPO) for the direct comparison between meta-substituted **8c·OTf** (2.58 ppm) and para-substituted bis(imidazolium) **9·OTf** (3.91 ppm).²⁶ The larger $\Delta\delta(^{31}\text{P})$ value of **9·OTf** suggests enhanced bidentate capability for the para-substituted bis(imidazolium); however, it was observed that meta-substituted bis(imidazolium) **8c·BAr**^F has a nearly double $\Delta\delta(^{31}\text{P})$ relative to **6·BAr**^F, suggesting bidenticity with the **BAr**^F counterion.²⁵

TEPO Signal as an Indicator for Impurities. An integral part of this quantification method is to ensure the absence of any impurities, especially trace acids formed from the counteranions. Impurities that bind with the TEPO probe effectively can broaden and shift the ³¹P NMR signal (e.g., Figure 5A vs 5B). Undesired $\Delta\delta(^{31}P)$ values from broad peaks





Figure 5. (A) Reliable and consistent $\Delta \delta({}^{3}P)$ values are determined from sharp ${}^{31}P$ NMR signals after rigorous purification (e.g., binding to **5d**•**OTf**). (B) Even when no TfOH is observed using ${}^{1}H$ and ${}^{19}F$ NMR, a broader peak is observed using ${}^{31}P$ NMR (after extraction and the first silica column).²⁷

would not accurately reflect the X-bonding ability (i.e., Figure 5B). To remove acid (and other) impurities, a purification procedure was performed for XBDs and the ³¹P NMR signals were compared before and after purification.²⁷ A sharp peak and reliable $\Delta\delta$ (³¹P) values were consistently acquired when purified XBDs were used in binding experiments (Figure 5A). Even in cases when ¹H and ¹⁹F NMR did not detect impurities, the ³¹P NMR signal was shown to be more sensitive. Therefore, it is noteworthy that ³¹P NMR and the TEPO signal can serve as a sensitive indicator for trace amounts of impurities that may not be detectable using ¹H and ¹⁹F NMR (see Supporting Information, Section VIb).

Correlation of $\Delta\delta(^{31}\mathbf{P})$ **and** ΔG^{\ddagger} **.** The ability to correlate $^{31}\mathbf{P}$ NMR data with thermodynamic properties was envisioned by using activation free energy ΔG^{\ddagger} values for reactions catalyzed by XBDs. Measured $\Delta\delta(^{31}\mathbf{P})$ values were compared

to previously calculated ΔG^{\ddagger} values²⁸ for a Friedel–Crafts addition of indole **10** to *trans*-crotonophenone **11** catalyzed by XBD organocatalysts in benzene (eq 1). The direct



comparison between $\Delta\delta(^{31}\text{P})$ and calculated ΔG^{\ddagger} values affords a good correlation ($R^2 = 0.775$). Considering the logarithm form of the Arrhenius equation, log $\Delta\delta(^{31}\text{P})$ values were also examined and show a stronger correlation with ΔG^{\ddagger} ($R^2 = 0.899$) (Figure 6). The strong correlation between log



Figure 6. Correlation $(R^2 = 0.899)$ of calculated ΔG^{\ddagger} values (in benzene)²⁸ for the Friedel–Crafts reaction of indole **10** to *trans*-crotonophenone **11** with log $\Delta \delta({}^{31}\text{P})$ values (in CD₂Cl₂).

 $\Delta\delta(^{31}\text{P})$ and calculated ΔG^{\ddagger} values demonstrates the capability of correlating ^{31}P NMR shifts with thermodynamic properties. The data also suggest that TEPO is a suitable isostere for carbonyl activation-type reactions.

Correlation of $\Delta\delta(^{31}P)$ and Catalytic Activity. The measured $\Delta \delta(^{31}P)$ values for XBDs were correlated to catalytic activity for a Friedel–Crafts indole addition (eq 1 and Figure 7A).^{28–30} In order to evaluate using ³¹P NMR spectroscopy to predict catalytic activity, the observed rates (k_{obs}) of the Friedel-Crafts addition reaction in CD₂Cl₂ were monitored using ¹H NMR spectroscopy (Table 1; see details in Supporting Information).³¹ Based on the observed correlation, when $\Delta\delta(^{31}\text{P})$ is less than 4.03 ppm, the X-bonding interaction is too weak to promote the indole addition (Table 1). The XBD with highest catalytic activity, bisimidazolium BAr^F salt (8c·BAr^F), was successfully predicted by the largest $\Delta\delta$ (³¹P) value (10.46 ppm). Moreover, a linear relationship was observed for Hammett σ parameters to the rate constants $k_{\rm obs}$ for para-substituted phenyl-imidazolium triflate XBDs (Table 1, 7a-7e•OTf) (Figure 7B). While the overall correlation for XBDs studied was lower ($R^2 = 0.765$), a high correlation is observed between $\Delta \delta(^{31}P)$ values and k_{obs} within the subclass of monodentate triflate XBDs ($R^2 = 0.922$) (Figure 7A). This correlation supports that TEPO binding and $\Delta\delta(^{31}\text{P})$ values can be a predictor of catalytic activity for



Figure 7. (A) Relationship between $\Delta\delta(^{31}\text{P})$ and k_{obs} (Table 1) for the Friedel–Crafts addition reaction of indole 10 to *trans*crotonophenone 11 in CD₂Cl₂ (solid triangle: subset of monodentate triflate XBDs; dot-filled triangle: subset of BAr^F XBDs; open triangle: all other XBDs). (B) Correlation of Hammett σ parameters and k_{obs} .

carbonyl activation-type reactions within structural classes of XBDs.

Comparison of $\Delta\delta(^{31}P)$ Values between Noncovalent Interactions. TEPO binding and ³¹P NMR quantification provide a common scale to compare X-bonding with other noncovalent interactions commonly used in catalysis. Xbonding is a relatively weak noncovalent interaction with $\Delta\delta(^{31}P)$ values for TEPO binding up to 10.5 ppm compared to that of H-bonding (up to 24.6 ppm)¹⁶ and Lewis acid ligand/ counterion complexes (up to 48.2 ppm).^{15c}

Conclusions. A commercially available phosphine oxide can quantify X-bonding ability using ³¹P NMR spectroscopy. Altering the structures and halogen atoms on XBD scaffolds supports that TEPO is probing X-bonding interactions. We also demonstrated that TEPO binding serves as a sensitive indicator of residual acidic impurities. We successfully correlated $\Delta\delta(^{31}P)$ values for TEPO binding with activation free energy values previously reported for a Friedel–Crafts indole addition reaction with *trans*-crotonophenone. TEPO binding also correlated with catalytic activity measured within the class of monodentate triflate XBDs. We expect that this rapid method can be applied to predict the catalytic ability of new XBDs that will enhance knowledge for X-bonding catalysis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02427.

Experimental procedures, characterization, ³¹P NMR data, NMR spectra, and kinetic analysis (PDF)

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Notes

The authors declare no competing financial interest.

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(18) To obtain valid and reproducible numbers, it is important to ensure that no residual triflic acid is present, which can lead to large $\Delta\delta(^{31}\text{P})$ values due to TfOH-TEPO binding.

(19) When different probes such as d-pyridine and tetraethyl methylenebis(phosphonate) were evaluated, no obvious changes in chemical shift were observed. Using chlorodiethylphosphine was not evaluated as a probe because it is a highly flammable liquid. TEPO was determined to be the most safe, stable, and effective phosphorous probe relative to other options.

(20) Job plots were performed and confirmed a 1:1 binding stoichiometry with TEPO for both 6.OTf and 8c.OTf (see Supporting Information, Section IV).

(21) Preliminary calculations of binding constants (K_a) based on data from titration experiments: **6**•**OTf**, $K_a = 50 \pm 4 \text{ M}^{-1}$, **8c**•**OTf**, $K_a = 15 \pm 3 \text{ M}^{-1}$, and **8c**•**BAr**^F, $K_a = 186 \pm 4 \text{ M}^{-1}$. See Supporting Information (Section III) for more details.

(22) The larger $\Delta \delta$ ⁽³¹P) value of **5a·OTf** also removes the potential for TEPO binding to be attributed to H-bonding interaction with C4 and C5 protons on the cationic imidazolium core.

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(24) For the discussion of counteranion series, see details in Supporting Information (Section VId).

(25) For bis(imidazolium) triflates, the Job plot demonstrates a 1:1 binding pattern for **8c·OTf** with TEPO and $\Delta\delta(^{31}P) = 4.95$ ppm. Furthermore, the $\Delta\delta(^{31}P)$ values of monoiodinated **8b·OTf** (4.88 ppm) and di-iodinated **8c·OTf** (4.95 ppm) are comparable, suggesting that the steric interactions of the meta-substituted bis(imidazolium) triflate do not favor bidentate X-bonding interactions with TEPO.

(26) Due to the low solubility of para-substituted bis(imidazolium) 9•OTf, $\Delta\delta(^{31}P)$ was collected using 3 equiv of XBD.

(27) For the effect of residual TfOH on $\Delta\delta(^{31}\text{P})$ values and the examination of purification procedure for XBD triflates, see details in Supporting Information, Section VIa.

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(30) Molecular iodine has been reported as a catalyst in this reaction, see: von der Heiden, D.; Bozkus, S.; Klussmann, M.; Breugst, M. Reaction Mechanism of Iodine-Catalyzed Michael Additions. J. Org. Chem. 2017, 82 (8), 4037–4043. The investigation of $\Delta\delta(^{31}P)$ values and the catalytic activity of molecular iodine was also attempted here (see Supporting Information, Section VIf). We observed varied NMR signals and believe that HI and/or higher iodine species are involved under TEPO binding conditions which led us to not include these $\Delta\delta(^{31}P)$ values in the correlation.

(31) Induction periods were observed in kinetic experiments which are attributed to the dissociation of XBD salts to produce the active forms of the catalyst during the induction period (see ref 28 and details in Section VIIIb of Supporting Information).

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