

# Charge-Enhanced Acidity and Catalyst Activation

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## S Supporting Information

**ABSTRACT:** Acidities are commonly measured in polar solvents but catalytic reactions are typically carried out in nonpolar media. IR spectra of a series of phenols in CCl<sub>4</sub> and 1% CD<sub>3</sub>CN/CCl<sub>4</sub> provide relative acidities. Non-protonated charged substituents with an appropriate counterion are found to enhance their Brønsted acidities and improve catalyst performance by orders of magnitude.

Acid–base reactions are among the most common and fundamental transformations in all of chemistry. As a result, the development of new Brønsted acids and bases are of general interest and have been the subject of extensive research efforts.<sup>1–5</sup> The strengths of these reagents are most commonly measured in water and/or dimethyl sulfoxide (DMSO), both of which are very polar solvents with high dielectric constants.<sup>6</sup> Substituent effects are also routinely studied in polar media, whereas most organic transformations are carried out in less polar solvents.<sup>7,8</sup> Structure–reactivity insights from pK<sub>a</sub> and substituent effect data, consequently, can be misleading. In this work, IR spectroscopy is used to obtain relative acidities of a series of *m*- and *p*-substituted phenols in a nonpolar solvent, and these results are better fit by gas-phase acidities than the corresponding DMSO pK<sub>a</sub> values. This observation led us to examine charged substituents in nonpolar solvents, and enhanced acidity and catalytic performance is reported.

In a clever study, Reed et al. showed that IR spectroscopy can be used to provide relative acidities of the strongest Brønsted acids known to date.<sup>9</sup> This was accomplished by comparing the N–H stretching frequencies of a series of trioctylammonium salts of deprotonated carboranes. It was found that the weaker the interaction of the base, the higher the frequency for this band. Inspired by this work and related studies,<sup>10,11</sup> we obtained the IR spectra of 20 *m*- and *p*-substituted phenols in carbon tetrachloride in the presence and absence of acetonitrile-*d*<sub>3</sub> (Table 1).<sup>12–17</sup> Dilute solutions (5 mM) of the phenols in the latter case gave rise to a sharp band for the “free” O–H stretch around 3600 cm<sup>−1</sup> (Figure 1, solid line). Addition of a small amount of CD<sub>3</sub>CN (1% v/v) led to a large 150–220 cm<sup>−1</sup> frequency reduction (i.e., a red shift) and a broadening of the band due to the formation of an ArOH...NCCD<sub>3</sub> hydrogen bond (Figure 1, dotted line).<sup>18,19</sup>

A plot of the experimental pK<sub>a</sub> values in DMSO versus the observed frequency shifts for both the meta and para isomers is reasonably well fit by a single line in which the *p*-nitro and *p*-acetyl derivatives are omitted from the least-squares analysis to improve the correlation coefficient from 0.89 to 0.94 (Figure 2).<sup>20</sup> A similar correlation between the gas-phase acidities (ΔG<sup>o</sup><sub>acid</sub>) of the phenols and the change in their O–H

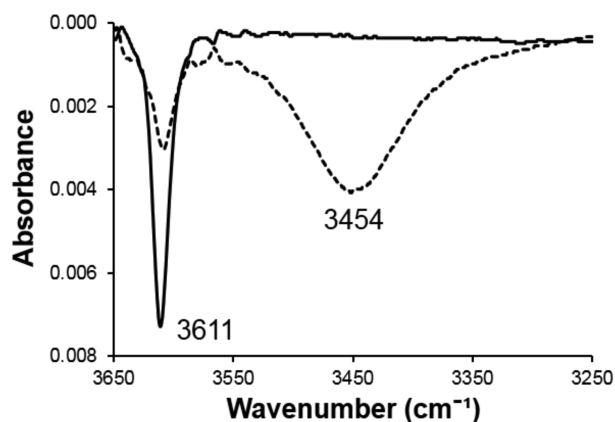
**Table 1. Hydroxyl Stretching Frequencies for Substituted Phenols in CCl<sub>4</sub> along with Their DMSO pK<sub>a</sub> and Gas-Phase Acidity Values**

cmpd (XC <sub>6</sub> H <sub>4</sub> OH) X =	ν (cm <sup>−1</sup> )			pK <sub>a</sub> (DMSO)	ΔG <sup>o</sup> <sub>acid</sub> <sup>a</sup> (kcal mol <sup>−1</sup> )
	CCl <sub>4</sub>	1% ACN <sup>b</sup>	Δν (cm <sup>−1</sup> )		
<i>m</i> -(CH <sub>3</sub> ) <sub>2</sub> N	3616	3464	152	19.1	343.5 ± 2.0
<i>m</i> -H	3611	3454	157	18.0	341.5 ± 1.0 <sup>c</sup>
<i>m</i> -CH <sub>3</sub>	3611	3448	163	18.2	341.3 ± 1.4 <sup>c</sup>
<i>m</i> -CH <sub>3</sub> O	3611	3446	165	18.2	341.5 ± 2.0
<i>m</i> -F	3608	3423	185	15.8	337.2 ± 2.0
<i>m</i> -CF <sub>3</sub>	3605	3415	190	15.6	332.4 ± 2.0
<i>m</i> -Cl	3606	3415	191	15.8	335.3 ± 2.0
<i>m</i> -NO <sub>2</sub>	3599	3387	212	14.4	327.6 ± 2.0
<i>m</i> -CN	3606	3388	218	14.8	329.0 ± 2.0
<i>p</i> -(CH <sub>3</sub> ) <sub>2</sub> N	3616	3468	148	19.8	344.4 ± 2.0
<i>p</i> -CH <sub>3</sub> O	3616	3463	153	19.1	343.9 ± 2.0
<i>p</i> -CH <sub>3</sub>	3613	3453	160	18.9	343.8 ± 2.0
<i>p</i> -F	3608	3442	166	18.0	340.4 ± 2.0
<i>p</i> -Cl	3607	3435	172	16.7	336.5 ± 2.0
<i>p</i> -Br	3607	3415	192	16.4	
<i>p</i> -CH <sub>3</sub> CO	3599	3407	192	14.0	328.6 ± 2.0
<i>p</i> -CF <sub>3</sub>	3602	3406	196	15.3	330.1 ± 2.0
<i>p</i> -CH <sub>3</sub> SO <sub>2</sub>	3600	3390	210	13.6	324.2 ± 2.0
<i>p</i> -CN	3597	3380	217	13.2	325.5 ± 2.0
<i>p</i> -NO <sub>2</sub>	3594	3373	221	10.8	320.9 ± 2.0
<b>1</b> <sup>d</sup>	3041	3043	−2	12.5 ± 1.0 <sup>e</sup>	261.4 <sup>f</sup>
<b>2</b> <sup>g</sup>	3576	3247	329	12.5 ± 1.0 <sup>e</sup>	261.4 <sup>f</sup>
<b>3</b> <sup>h</sup>	3566	3196	370	12.4 ± 1.1 <sup>e</sup>	231.1 <sup>i</sup>

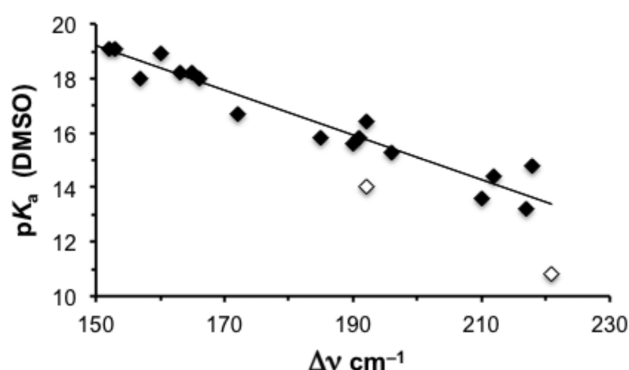
<sup>a</sup>Equilibrium determinations from ref 16 unless otherwise noted; some values are the average of two similar results. <sup>b</sup>1% ACN = 1% CD<sub>3</sub>CN/99% CCl<sub>4</sub>. <sup>c</sup>Measured by threshold collision-induced dissociation (ref 17). <sup>d</sup>**1** = *p*-HOC<sub>6</sub>H<sub>4</sub>N(*n*-C<sub>8</sub>H<sub>17</sub>)<sub>2</sub>CH<sub>3</sub><sup>+</sup> I<sup>−</sup>. <sup>e</sup>Measured by bracketing using two colored indicators. <sup>f</sup>B3LYP/6-31+G(d,p) computations on *p*-HOC<sub>6</sub>H<sub>4</sub>N(*n*-C<sub>8</sub>H<sub>17</sub>)<sub>2</sub>CH<sub>3</sub><sup>+</sup>. <sup>g</sup>**2** = *p*-HOC<sub>6</sub>H<sub>4</sub>N(*n*-C<sub>8</sub>H<sub>17</sub>)<sub>2</sub>CH<sub>3</sub><sup>+</sup> BAr<sup>F</sup><sub>4</sub><sup>−</sup> where Ar<sup>F</sup> stands for tetrakis(3,5-bis(trifluoromethyl)phenyl)-borate. <sup>h</sup>**3** = 3-hydroxy-*N*-octylpyridinium BAr<sup>F</sup><sub>4</sub><sup>−</sup>. <sup>i</sup>This calculated value is for 3-methylpyridinium phenol.

frequency shifts is obtained for all of the compounds including the *p*-NO<sub>2</sub> and *p*-COCH<sub>3</sub> derivatives, but in this case, the data are best fit by separate lines for the meta and para isomers (Figure 3). These results suggest that resonance delocalization is not as effective in carbon tetrachloride as it is in dimethyl sulfoxide because this is a completely stabilizing mechanism for solvent-separated ion pairs (DMSO) but not for tight ion pairs

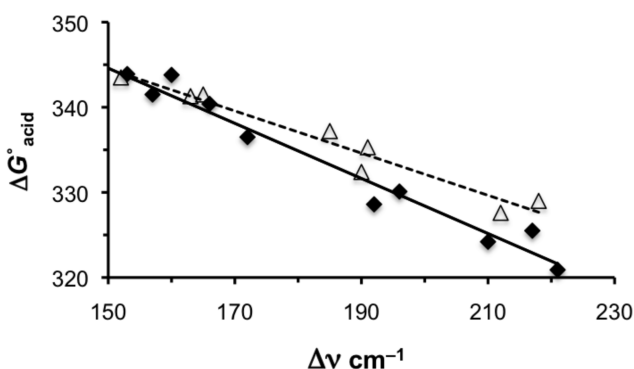
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**Figure 1.** Representative IR spectrum of phenol in  $\text{CCl}_4$  (solid line) and in 1%  $\text{CD}_3\text{CN}/\text{CCl}_4$  (dotted line).



**Figure 2.** DMSO  $\text{pK}_a$  values vs m- and p-substituted phenol O–H frequency shifts in  $\text{CCl}_4$  upon addition of  $\text{CD}_3\text{CN}$ . A linear least-squares fit of the data affords  $y(\text{pK}_a) = -0.0822(\Delta\nu) + 31.6$ ,  $r^2 = 0.936$ , where the open diamonds are for the  $p\text{-NO}_2$  and  $p\text{-COCH}_3$  derivatives, which were excluded from the analysis.



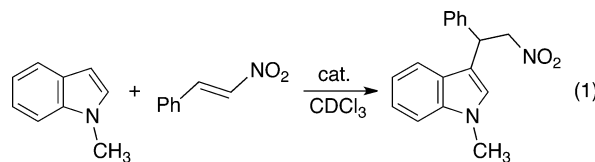
**Figure 3.** Gas phase acidities ( $\text{kcal mol}^{-1}$ ) vs O–H frequency shifts for m- (triangles) and p-substituted (diamonds) phenols. Linear least-squares analyses give  $y(\text{pK}_a) = -0.241(\Delta\nu) + 380.3$ ,  $r^2 = 0.950$  (meta) [dotted line] and  $y(\text{pK}_a) = -0.324(\Delta\nu) + 393.2$ ,  $r^2 = 0.970$  (para) [solid line].

( $\text{CCl}_4$ ). That is, in the latter case charge dispersal diminishes the electrostatic stabilizing interaction between oppositely charged ions, and this results in a delicate balance between charge delocalization and Coulombic attraction. In the gas phase, counterions are absent and charge delocalization is of paramount importance, so it is not surprising that the behavior of the para derivatives diverge from the meta isomers. It was unexpected, however, that the gas-phase acidities correlate with

those in nonpolar media better than the DMSO  $\text{pK}_a$  values. Consequently, they may be more useful in structure–reactivity relationships.

Gas-phase substituents with the largest impact are charged groups, whereas in polar media they are much less effective.<sup>21,22</sup> For example,  $p\text{-COCH}_3$ ,  $p\text{-CN}$ , and  $p\text{-NO}_2$  substituted phenols are all more acidic than the  $p\text{-N}(\text{CH}_3)_3^+$  derivative in DMSO,<sup>13</sup> but the trimethylammonium ion is predicted to be at least 45  $\text{pK}_a$  units (i.e.,  $62.7 \text{ kcal mol}^{-1}$ ) more acidic than the other species in the gas phase. This suggests that there should be an acidity reversal for these compounds in nonpolar solvents and a new strategy of enhancing Brønsted acidities and catalytic efficiencies in organic transformations.<sup>23–26</sup> To test this hypothesis,  $p$ -dioctylaminophenol was synthesized and subsequently methylated with methyl iodide; octyl groups were used to enhance the salt's solubility in carbon tetrachloride. The resulting methyl(dioctyl)ammonium ion (i.e.,  $p\text{-HOC}_6\text{H}_4\text{N}(\text{n-C}_8\text{H}_{17})_2\text{CH}_3^+ \text{I}^-$ , **1**) has a broad OH band at  $3041 \text{ cm}^{-1}$ , which indicates that there is a  $\text{OH}\cdots\text{I}^-$  hydrogen bond even though iodide is a weakly basic anion. Not surprisingly then, the IR spectrum of this salt is essentially unchanged upon addition of 1%  $\text{CD}_3\text{CN}$ . These results imply that **1** is not particularly acidic in  $\text{CCl}_4$ , and so tetrakis(3,5-bis(trifluoromethyl)phenyl)borate ( $\text{BAR}_4^{\text{F}_4^-}$ ) was used to replace the iodide counterion. The resulting phenol ( $p\text{-HOC}_6\text{H}_4\text{N}(\text{n-C}_8\text{H}_{17})_2\text{CH}_3^+ \text{BAR}_4^{\text{F}_4^-}$ , **2**) has an OH stretch at  $3576 \text{ cm}^{-1}$ , which is red-shifted down to  $3247 \text{ cm}^{-1}$  in the presence of acetonitrile- $d_3$ . This decrease of  $329 \text{ cm}^{-1}$  is 50% larger than for  $p$ -nitrophenol, the compound with the biggest shift that we previously observed, and indicates that **2** is more acidic in  $\text{CCl}_4$  than the other phenols that were examined.

To assess this result further, the Friedel–Crafts reaction between  $\beta$ -nitrostyrene and  $N$ -methylindole was studied in chloroform (eq 1). This transformation was chosen because it is



an acid-catalyzed process and its rate should serve as an indicator of the phenol acidity.<sup>24,27</sup> As expected, **1** is a very poor catalyst,  $p$ -nitrophenol is about 7 times better, and **2** is 200-fold more reactive (Table 2, entries 1–3). These results are in accord with the acidity reversal of  $p$ -nitrophenol and **2** in going

**Table 2.** Kinetic Results for a Friedel–Crafts Reaction (eq 1)<sup>a</sup>

entry	catalyst	[nitrostyrene] (mM)	$t_{1/2}$ (h)	$t_{1/2}$ (rel)
1	$p\text{-HOC}_6\text{H}_4\text{NO}_2$	83	1200	1
2	<b>1</b>	83	8400	0.14
3	<b>2</b>	83	42	29
4	<b>3</b>	83	1.6	750
5	$p\text{-HOC}_6\text{H}_4\text{NO}_2$	235	640	1
6	<b>2</b>	235	37	17
7	$p\text{-HOC}_6\text{H}_4\text{NO}_2$	29	4100	1
8	<b>2</b>	29	64	64
9	<b>3</b>	29	2.1	2000

<sup>a</sup>Three equivalents of  $N$ -methylindole and a fixed amount of catalyst (8.3 mM) were used in each case.

from DMSO to  $\text{CCl}_4$ . The relative rates of this transformation, however, are expected to be concentration-dependent since the reactants are polar compounds and the relative acidity of *p*-nitrophenol and **2** is sensitive to the polarity of the medium. This hypothesis was borne out in that when the concentrations of the two reactants were tripled (entries 5 and 6),  $k_2/k_{p\text{-HOC}_6\text{H}_4\text{NO}_2}$  decreased from 29 to 17. Likewise, when the original concentrations were reduced by a factor of 3 (entries 7 and 8) the ratio increased from 29 to 64. This latter difference is even larger (i.e., 180) when the reaction is run in toluene- $d_8$ .

Additional gas-phase computations revealed that 3-hydroxy-*N*-methylpyridinium ion is 22  $\text{pK}_a$  units (30  $\text{kcal mol}^{-1}$ ) more acidic than *p*-methyl(dipentyl)ammonium phenol, so the octylammonium  $\text{BAR}_4^-$  salt of 3-hydroxypyridine (i.e., **3**) was synthesized. Its IR spectra in  $\text{CCl}_4$  and 1%  $\text{CD}_3\text{CN}/\text{CCl}_4$  have bands at 3566 and 3196  $\text{cm}^{-1}$ , respectively. This red shift of 370  $\text{cm}^{-1}$  indicates that **3** is more acidic than **2** in carbon tetrachloride as predicted by the B3LYP/6-31+G(d,p) calculations. The pyridinium ion **3** was also found to be a more active catalyst than *p*-nitrophenol and **2** by factors of up to 2000 and 30, respectively (entries 7–9).

Protonated catalysts have been successfully employed in organic transformations<sup>24,28–31</sup> but provide an additional hydrogen bond donor site that can be actively involved in the reaction. Nonprotonated ions eliminate this concern and can enhance acidities of ionizable groups in nonpolar environments. This effect undoubtedly can be reversed to increase the basicity of basic sites, and the exploitation of electrostatics is an exciting avenue for further exploration.<sup>21</sup> Studies along these lines are in progress, and even more dramatic effects may be obtained by incorporating the counterion into the reagent at a remote noninteracting location.

## ■ ASSOCIATED CONTENT

### ● Supporting Information

Experimental and computational sections including synthetic procedures, NMR spectra, and calculated structures and energies along with the complete citation to ref 18 are provided. 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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