Substituent and Solvent Effects: Examining Acidity via Infrared Spectroscopy

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ABSTRACT

There is a large collection of substituent constant data measured in polar protic and polar aprotic solvents, but a lack of information on substituent effects in nonpolar aprotic solvents. In this study, substituent effects on the acidities of phenol derivatives were examined in CCl_4 using infrared (IR) spectroscopy. The IR peak of the free phenolic -OH appears at approximately 3600 cm^{-1} which is red shifted in the presence of a hydrogen bond acceptor. The magnitude of the splitting between the free and the hydrogen-bonded -OH peak is related to the acidity of the protic hydrogen. Deuterated acetonitrile was used as the hydrogen-bond acceptor to probe the relative acidities of 21 phenol derivatives in CCl_4. While most phenol derivatives exhibited similar acidity trends in CCl_4 as in DMSO and the gas phase, several demonstrated a reduction in acidity which indicates a solvent dependence on substituent effects. This study offers a facile method to examine substituent effects on the acidity of alcohols and has identified several solvent-dependent substituent effects.

INTRODUCTION

With his studies on the relative rates of ionization of substituted benzoic acid species in the early 1900s, Louis Plack Hammett, carried out one of the first systematic and quantitative studies on substituent effects. Hammett's work would eventually usher in the field of physical organic chemistry and substituent effect studies.[1] Substituent effect studies examine changes in the properties of a chemical species which result from variation in a discrete moiety present on the otherwise unchanged molecular backbone. Chemical substituents have the capacity to affect reactivity, acidity, reaction rates, regioselectivity, and a variety of other properties through their relative inductive (electron-withdrawing vs. electron-donating) effects, resonance effects, field effects, and relative distance from the reactive center.[2] Now a standard topic of study in organic chemistry courses, even a qualitative understanding of substituent effects provides insight into reaction mechanisms and prediction of major reaction products, such as in electrophilic aromatic substitution reactions.

Over the last century, the pool of substituent effect data and research has grown tremendously. Despite the seeming maturity of this field, however, there exists a significant collection of substituent effect data measured in polar protic and, to a lesser extent, polar aprotic solvents, but a dearth of information on substituent effects in nonpolar aprotic solvents. Substituents are known to display solvent dependence between polar protic and polar aprotic solvents, and such dependence will presumably appear in nonpolar aprotic media.[3-5] This consideration, coupled with deficiencies in the data, inhibits accurate understanding of the relationships between substituents and reactivity in nonpolar aprotic solvents. Remedying this surprising paucity could prove to have significant and practical applications in a variety of fields. Substituent effect studies conducted particularly on Brønsted acidity in a variety of solvents

would likely expedite progress in the development of hydrogen-bond catalysts,[6] anion receptors,[7-8] and novel Brønsted acids.[9] Within these fields, many chemical species and reactions have been developed in nonpolar aprotic solvents and share a common quality: enhancing Brønsted acidity likewise improves functionality. These fields are still growing, and it is difficult to accurately predict how structural changes are related to reactivity or stability. A stronger understanding of how substituents affect the Brønsted acidity of organic species in nonpolar aprotic solvent could facilitate more rational and systematic progress in the future.

Infrared (IR) spectroscopy has previously been demonstrated as a facile and reliable technique to measure relative acidities for both weak and strong Brønsted acids.[10-11] The relationship between IR spectroscopy and acidity hinges on IR spectroscopy's characteristic manifestation of the hydrogen bond.[12] In their studies on the strengths of novel carborane superacids, Reed et al. exploited this property by comparing the varying N—H stretching frequencies for the H—bonded contact ion pairs between trioctylammonium salts (R_3NH^+) of deprotonated carboranes (A^-) as in **I**.[10]

$$R_3N^+—H•••A^-$$

I

Strongly basic deprotonated carboranes are strong hydrogen-bond acceptors, and will significantly weaken the N—H bond, resulting in a lower stretching frequency for the H-bonded N—H bond than a free N—H bond. Weakly basic carborane anions minimally distort the N—H bond in an H-bond interaction, resulting in an N—H stretching frequency nearer the absorbing frequency of the N—H bond in free trioctylammonium. By this method, a large redshift in the N—H frequency indicates a strongly basic carborane anion (i.e. a weakly acidic carborane), while a smaller shift indicates a weakly basic carborane anion (i.e. a strongly acidic carborane).

The Reed group tested the validity of this method with Brønsted acids of known acidities and found that the relative N—H stretching frequencies indeed reflected relative acidities.[10]

Drawing inspiration from the Reed group's study, we propose that a similar method may be employed to determine relative acidities of variously substituted weakly acidic alcohols. For dilute alcohol species, a sharp peak for the free O—H stretching vibration appears near 3600 cm^{-1}; in the presence of a hydrogen bond acceptor, Y, that peak is redshifted and broadened due to further stretching of the O—H bond. This hydrogen-bond interaction is depicted in **II**.

R—O—H•••Y

II

Substituents on R that enhance the acidity of the protic hydrogen should facilitate significant weakening of the O—H bond in interaction **II**, yielding a relatively large difference between the IR absorption of free and the hydrogen-bonded O—H peaks in the IR spectrum. Substituents that detract from or do not have significant effects on the acidity of the proton will produce a smaller splitting between the peaks. From this splitting, a $\Delta\nu_{OH}$ (cm^{-1}) value may be assigned, yielding a relative scale of the alcohols' acidities where a large $\Delta\nu_{OH}$ indicates a strong Brønsted acid and a small $\Delta\nu_{OH}$ indicates a weak Brønsted acid.

In this study, we investigate the relative acidities of phenol and its mono *m*- and *p*-derivatives in nonpolar aprotic solvent. Phenol derivatives were selected for this study for a variety of reasons, including (i) their common structure, (ii) their range of acidities, and (iii) their commercial availability. The *o*-phenol derivatives were neglected so as to reduce the effect of steric interactions on the observed acidity. Deuterated acetonitrile ($ACN\text{-}D_3$) and CCl_4 were selected as the hydrogen-bond acceptor and solvent, respectively, as neither strongly absorbs IR radiation between 3000 cm^{-1} and 3800 cm^{-1}.

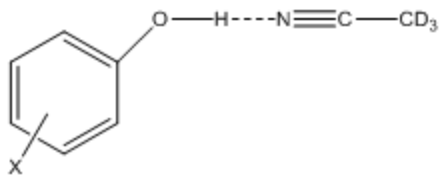

Figure 1. Proposed hydrogen bond interaction between X-substituted phenol and deuterated acetonitrile.

Herein we report the magnitudes of the free and H-bonded IR peak splitting for 21 phenol derivatives to yield the phenol derivatives' relative acidities in CCl_4 and to identify possible substituent effect solvent dependence.

EXPERIMENTAL

Septa caps, the IR solution cells, and microsyringes were stored in a desiccator containing phosphorus pentoxide with a constant flow of N_2. Remaining glassware was oven-dried. Deuterated acetonitrile (CD_3CN) was dried over 3Å activated molecular sieves. Anhydrous CCl_4 solvent was stored under argon without further treatment. Remaining reagents were used as received.

Solution Preparation

Stock phenol derivative solutions were prepared daily by transferring the phenol derivative to a dried, sealed vial and dissolving in CCl_4 to give a 10 mM stock solution. Stock CD_3CN solutions were also prepared daily by dissolving CD_3CN in CCl_4 in a dry, sealed vial to give a 2% (v/v) stock solution. Stock solutions were further diluted with CCl_4 to give solutions of 5 mM phenol derivative, 1% (v/v) CD_3CN, and 5 mM phenol derivative in 1% (v/v) CD_3CN. Phenol derivatives with partial solubility in CCl_4 (4-CN, 4-NO_2, 3-CN, 3-$N(CH_3)_2$, 4-$COCH_3$,

and 4-SO_2CH3) were prepared as above, though the concentration of the phenol derivative was approximated to be less than 5 mM.

Infrared (IR) Studies

All infrared studies were carried out with a Nicolet iS5 FT-IR Spectrometer fitted with the iD1 transmission accessory. Measurements were obtained for 5 mM phenol derivative and for 5 mM phenol derivative in 1% (v/v) CD_3CN; the CCl_4 and 1% (v/v) CD_3CN in CCl_4. Background spectra were subtracted from the acquired phenol derivative spectra, respectively. All measurements were carried out at room temperature using a 0.1 mm fixed path length liquid transmission cell with NaCl windows. Between measurements, N_2 was passed through the cell chamber in order to dry the cell and prevent condensation.

Figure 2. IR liquid transmission cell with a 0.1 mm fixed path length and NaCl salt plate windows. The fixed cell path length facilitated study of reproducible, dilute samples.

RESULTS

Dilute solutions of the phenol derivatives in the absence of CD_3CN resulted in a sharp band in the IR spectra near 3600 cm^{-1}, arising from the "free" O—H vibration. After introducing the CD_3CN, this sharp peak is broadened and red-shifted by approximately 150-220 cm^{-1}, which arises from the formation of an ArOH•••$NCCD_3$ hydrogen bond. The IR spectra for phenol are

provided in Figure 3, where the dashed line indicates the "free" phenol and the solid line is the phenol in 1% CD_3CN/CCl_4.

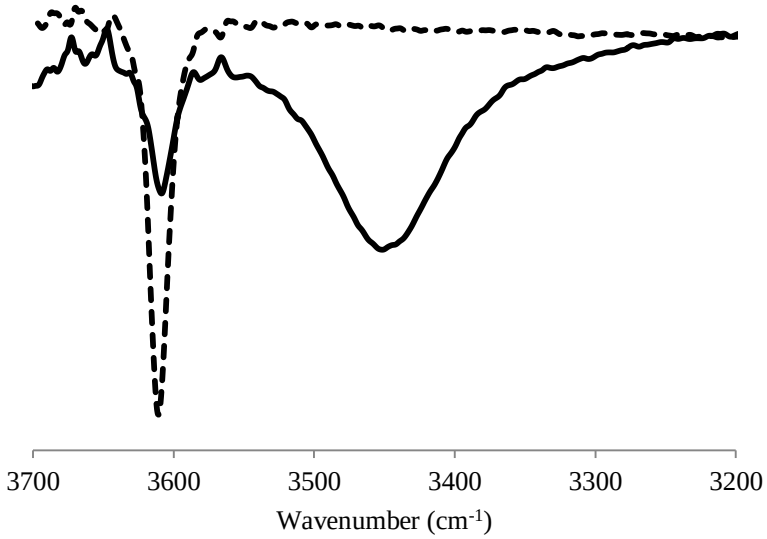

Figure 3. IR spectra of phenol in CCl_4 (dashed line) and in 1% CD_3CN/CCl_4 (solid line).

The absorption frequencies and $\Delta\nu_{OH}$ values for the 21 phenol derivatives studied are provided in Table 1.

Table 1. O—H stretching frequencies in cm^{-1} of phenol derivatives in CCl_4 with 1% (v/v) CD_3CN. The difference between the "free" and H-bonded hydroxyl IR absorbing frequencies is given as $\Delta\nu_{OH}$ in wavenumbers (cm^{-1})

XC_6H_5OH	v (cm^{-1})		$\Delta\nu_{OH}$ (cm^{-1})
X=	CCl4	1% CD3CN	
p–H	3611	3446	157
p–Br	3607	3415	192
p–CN	3597	3380	217
p–NO2	3594	3373	221
p–OOCH3	3610	3346	164
p–OCH3	3616	3468	153
p–F	3608	3442	166
p–CF3	3602	3406	196
p–Cl	3607	3435	172
p–CH3	3613	3463	160
p–N(CH3)2	3616	3468	148
p–COCH3	3599	3407	192
p–CH3SO2	3600	3390	210
m–CN	3606	3388	218
m–NO2	3599	3387	212
m–N(CH3)2	3616	3464	152
m–F	3608	3423	185
m–CH3	3611	3448	163
m–Cl	3606	3415	191
m–OCH3	3611	3446	165
m–CF3	3605	3415	190

DISCUSSION

Acidity data is not available for phenol derivatives in nonpolar aprotic solvent. From precedent established by Reed, et al., the obtained $\Delta\nu_{OH}$ values are believed to be an accurate gauge of relative acidity. In order to gauge potential solvent effects on the relative acidity of the phenol derivatives, $\Delta\nu_{OH}$ in CCl_4 values were compared to the derivatives' corresponding pK_a values in DMSO and their gas phase acidities, which are provided in Table 2.

Table 2. pK_as and gas phase acidities of the 21 substituted phenols examined in this study.[13-14]

XC_6H_5OH X=	pK_a (DMSO)	Gas Phase Acidity (kcal mol^{-1})
4-H	18	343
4-Br	16.36	-
4-CN	13.2	326.4
4-NO2	10.8	322.1
4-Acetoxy	14.1	331.3
4-Methoxy	19.1	344.2
4-F	18	340.7
4-CF3	15.3	331.1
4-Cl	16.7	337.1
4-CH3	18.9	344.1
4-N(CH3)2	19.8	345.1
4-COCH3	14	329.7
4-MeSO2	13.64	325.4
3-CN	14.8	330
3-NO2	14.4	328.6
3-N(CH3)2	19.05	344.2
3-F	15.8	337.7
3-CH3	18.2	343.4
3-Cl	15.8	335.9
3-Methoxy	18.2	341.9
3-CF3	15.6	333.4

The $\Delta\nu_{OH}$ values were plotted against corresponding pK_a (DMSO) values. Of the 21 phenol derivatives, 18 demonstrate a roughly linear relationship between their $\Delta\nu_{OH}$ values and their pK_a (DMSO) values, as shown in Figure 4. This correlation between acidities in differing solvents suggests that acidity trends amongst these 18 species do not vary between polar aprotic and non-polar aprotic solvents, i.e. there is limited solvent dependence on their acidity. The remaining three derivatives, 4-nitrophenol, 4-cyanophenol, and 4-acetoxyphenol are highlighted in Figure 4 and demonstrate negative deviations from this linearity. If the three species were to have $\Delta\nu_{OH}$ values corresponding to the trend observed for the remaining species, those $\Delta\nu_{OH}$ values would have to be significantly increased. This observation suggests that 4-nitrophenol, 4-cyanophenol, and 4-acetoxyphenol are relatively less acidic in CCl_4 than in DMSO. For example,

whereas 4-nitrophenol is approximately 4 pK_a units more acidic than 3-cyanophenol in DMSO, they manifest nearly identical $\Delta\nu_{OH}$ values in CCl_4, i.e. nearly identical acidities in CCl_4. Phenol substituted with -NO_2, -CN, and -$OOCCH_3$ in the *para* position demonstrates solvent dependence on acidity between polar aprotic and nonpolar aprotic solvents.

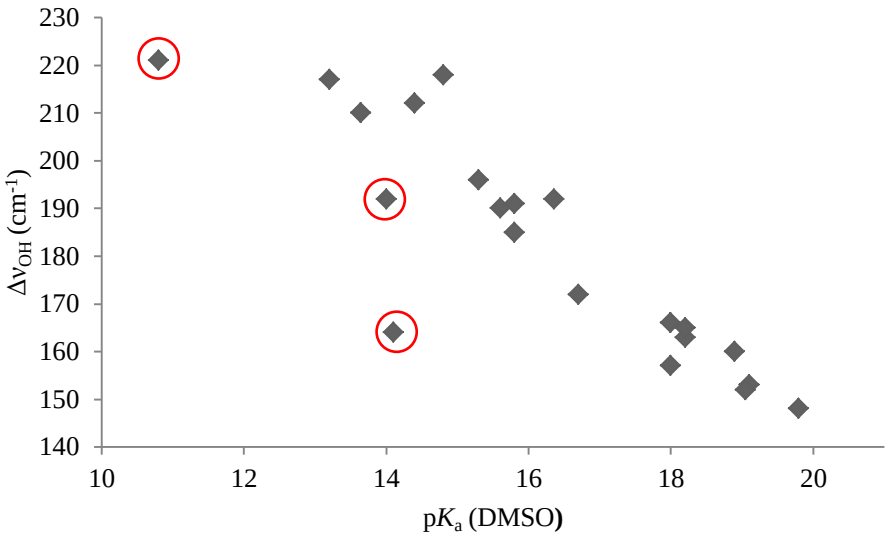

Figure 4. $\Delta\nu_{OH}$ (cm^{-1}) in CCl_4 values for the 21 phenol derivatives under study vs. the phenol derivatives' corresponding pK_a values in DMSO.[13] A roughly linear trend is observed for 18 of the 21 phenol derivatives, demonstrating the similarity in the relative acidities of the phenol derivatives in CCl_4 and in DMSO; for these derivatives solvent-dependent effects on acidity are not, therefore, observed. The three highlighted points (4-NO_2, 4-CN, 4-$OOCH_3$) reflect derivatives which deviate from this linear relationship. These three derivatives thus demonstrate solvent dependence on relative acidities, where their acidities are significantly reduced in CCl_4 as compared to their acidity in DMSO.

The $\Delta\nu_{OH}$ values were then compared to the phenol derivatives' gas phase acidities. The gas phase approximates a solvent-free environment. As shown in Figure 5, the plot of $\Delta\nu_{OH}$ vs. gas phase acidity, reveals a linear trend amongst the phenol species with a single significant deviation, 4-acetoxyphenol. Again 4-acetoxyphenol's acidity in CCl_4 appears to be reduced compared to its relative acidity in the gas phase. The relative acidities of 4-nitrophenol and 4-cyanophenol's in CCl_4, however, more strongly correlate to their gas phase acidities, as opposed to their acidities in DMSO.

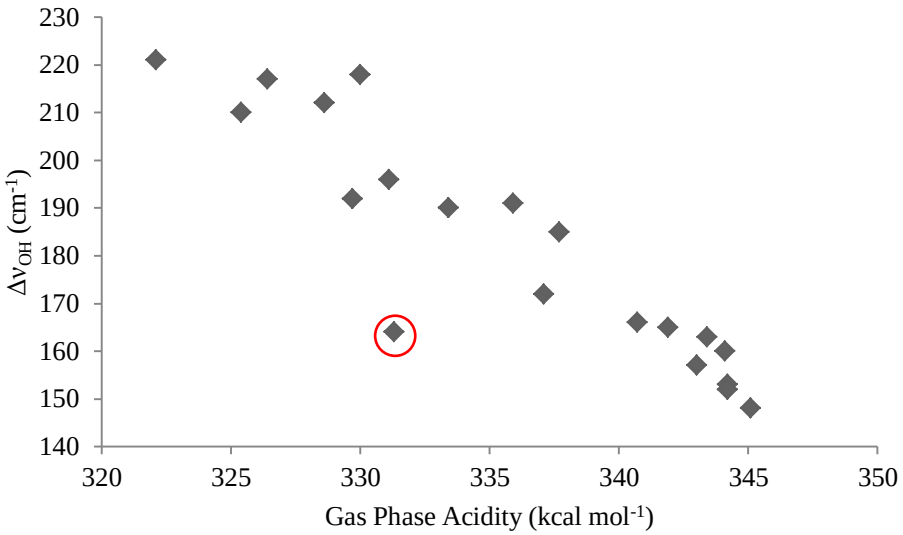

Figure 5. $\Delta\nu_{OH}$ (cm^{-1}) in CCl_4 values for 20 phenol derivatives under study vs. the phenol derivatives' corresponding acidities in the gas phase.[14] (Gas phase acidity data was unavailable for 4-bromophenol). A linear trend is observed for 19 of the 21 phenol derivatives, demonstrating the similarity in the relative acidities of the phenol derivatives in CCl_4 and in the gas phase. The acidity in the gas phase appears to correspond to acidity in CCl_4. The highlighted point (4-$OOCH_3$) deviates from this linear relationship. The acidity of 4-acetoxyphenol is reduced in CCl_4 as compared to the gas phase.

The deviations between 4-nitrophenol and 4-cyanophenol's relative acidities in CCl_4, DMSO, and the gas phase suggest that there is a solvent-solute interaction occurring in DMSO that is absent or unfavorable in the gas phase and CCl_4 which enhances these species' acidities in a polar aprotic solvent. It is valuable to consider the interactions between solvent and the fully deprotonated conjugate base of the phenol species in order to understand these observations. The conjugate bases of 4-cyanophenol and 4-nitrophenol have two favorable resonance structures. Figure 6 examines the conjugate base of 4-cyanophenol in solution with a corresponding counter-ion M^+.

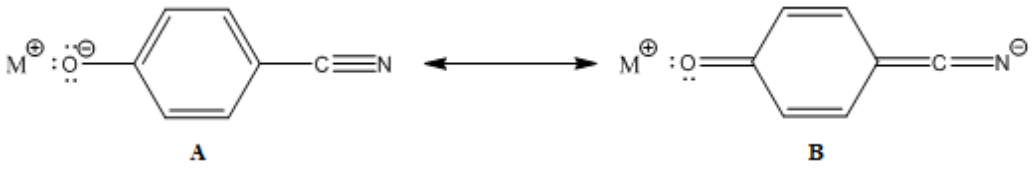

Figure 6. Resonance forms of the conjugate base of 4-cyanophenol.

In structure **A**, the counterion and phenoxide ion form a contact ion pair where the charged species are in close proximity; in **B**, the charges are separated. Contact ion pairs are readily solvated by polar solvents, and to a lesser extent nonpolar solvents. Nonpolar solvents such as CCl_4 can solvate these pairs due to the close interaction of the ions which results in a reduction in the effective charge felt by the solvent molecules. However, separated ions are rarely observed in nonpolar media due to the solvent's relative inability to solvate hard charges. Polar solvents are able to solvate both **A** and **B**.[15] In CCl_4, **B** is poorly solvated and thus becomes a less likely resonance structure. The resonance-stabilization of 4-nitrophenol and 4-cyanophenol's conjugate base is likely attenuated in CCl_4, resulting in the observed reduced acidity when compared to DMSO.

At the time of writing, the cause for 4-acetoxyphenol's reduced acidity in CCl_4 when compared to its acidity in DMSO and the gas phase is not yet understood.

CONCLUSION

The purpose of this investigation was to examine substituent effects on Brønsted acidity in nonpolar aprotic solvent. The relative acidities of 21 substituted phenols were determined by exploiting the unique manifestation of hydrogen-bond interactions in infrared spectroscopy. It was shown that substituents that facilitated resonance-stabilized conjugate bases resulted in reduced relative acidity in CCl_4 while the remaining phenol derivatives (excepting 4-acetoxyphenol) demonstrated no solvent-dependence on relative acidity. IR spectroscopy offers a straightforward approach to examine relative acidities of organic species. Similar studies in the future may examine the effects of other nonpolar aprotic solvents on acidity or probe possible solvent-dependent substituent effects in thioureas, alkyl alcohols, and carboxylic acids. Accumulation of data on the effects of solvent and substituents on Brønsted acidity has the

potential to facilitate and accelerate progress in a variety of fields, offering a fertile and productive area of ongoing research.

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