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Electron-Withdrawing Trifluoromethyl Groups in Combination with Hydrogen Bonds in Polyols: Brønsted Acids, Hydrogen-Bond Catalysts, and Anion Receptors

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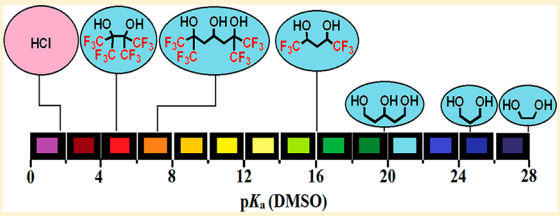
Supporting Information

ABSTRACT: Electron-withdrawing trifluoromethyl groups were characterized in combination with hydrogen-bond interactions in three polyols (i.e., $CF_3CH(OH)CH_2CH(OH)CF_3$, **1**; $(CF_3)_2C(OH)C(OH)(CF_3)_2$, **2**; $((CF_3)_2C(OH)CH_2)_2CHOH$, **3**) by p$K_a$ measurements in DMSO and H_2O, negative ion photoelectron spectroscopy and binding constant determinations with Cl^-. Their catalytic behavior in several reactions were also examined and compared to a Brønsted acid (HOAc) and a commonly employed thiourea ($(3,5\text{-}(CF_3)_2C_6H_3NH)_2CS$). The combination of inductive stabilization and hydrogen bonds was found to afford potent acids which are effective catalysts. It also appears that hydrogen bonds can transmit the inductive effect over distance even in an aqueous environment, and this has far reaching implications.



INTRODUCTION

In recent years the development and application of Brønsted acids has emerged as a fast growing branch of chemistry.[1] These compounds can be broadly classified into two categories: those with one acidic site, such as BINOL-derived phosphoric acids,[2] bis(sulfonyl)imides,[3] *N*-triflyl phosphoric amides,[4] and carboranes,[5] and those with two acidic hydrogens, such as thioureas,[6] biphenols,[7] and TADDOL derivatives.[8] These compounds are often employed as catalysts but sometimes require large loadings and are corrosive, harmful to plants and animals, and sensitive to heat.[9] We recently introduced a promising new variant that makes use of multiple hydrogen bonds to stabilize a charged center and enhance the acidity.[10] For example, 1,3,5-pentanetriol ($HOCH_2CH_2CH(OH)CH_2CH_2OH$), a simple aliphatic alcohol with three hydroxyl groups, was found to be more acidic than 2,2,2-trifluoroethanol (TFE) in DMSO and almost as acidic as phenol (i.e., the pK_a's of TFE, 1,3,5-pentanetriol, and PhOH are 23.4, 19.7, and 18.0, respectively). That is, the formation of two hydrogen bonds to the alkoxide center in the conjugate base of the triol leads to a 10.6 pK_a acidification relative to isopropanol. A larger hydrogen-bonding network in a heptaol ($(HOCH_2CH_2CH(OH)CH_2CH_2)_3COH$) was found to result in a compound that is more acidic than acetic acid (pK_a = 11.4 vs 12.3) and 21 orders of magnitude stronger than *tert*-butanol.[11] Electron-withdrawing groups can be incorporated into polyols of these sorts and should lead to even stronger Brønsted acids. To explore this possibility, three trifluoromethyl-containing polyols (**1**−**3**, Figure 1) were characterized by a number of means including aqueous and DMSO pK_a determinations, chloride anion binding association constants in acetonitrile, and gas-phase adiabatic electron detachment energies (ADEs) of their conjugate bases. The catalytic abilities of these compounds were also explored in a Friedel−Crafts alkylation and an aminolysis of an epoxide. These experimental results were supplemented with detailed computations as well.

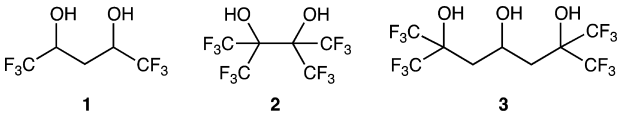


Figure 1. Trifluoromethyl group containing polyols.

EXPERIMENTAL SECTION

General. All glassware, needles, syringes, and NMR tubes were dried overnight in ovens at 110 °C and subsequently stored in a desiccator containing rubber septa and charged with phosphorus pentoxide. DMSO and DMSO-d_6 were dried under vacuum (1.5 Torr) over CaH_2 at reflux for several hours and then were distilled under these conditions. The resulting solvents were stored in dark vials over 3 Å molecular sieves that had been activated in a furnace at 320 °C for 1 day and then kept under an argon atmosphere for up to a few days. Pentane was dried and distilled over P_2O_5 and then used three times in succession to rinse mineral oil away from a 30% suspension of potassium hydride as part of the process for making the potassium salt of dimsyl anion (i.e., CH_3SOCH_2K). Fresh solutions of dimsyl

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potassium were prepared daily by reacting KH with DMSO or DMSO-d_6 at room temperature over a 30 min period. All of the dry solvents were routinely degassed immediately before use by bubbling dry argon through them for ~20 min. Chloroform-d was dried by storing it over activated 4 Å molecular sieves, diol **2** was used as supplied (Matrix Scientific), and triol **3** was prepared as previously described[12] but was purified by vacuum sublimation at 15 Torr and 70 °C rather than by recrystallization. NMR spectra were recorded on Varian VI-300 and VI-500 spectrometers at 295 K, and the chemical shifts are given in parts per million (δ) relative to the residual solvent peak. Mass spectra were obtained with a Bruker BioTof II electrospray ionization time-of-flight mass spectrometer using polyethylene glycol 200 as an internal standard.

meso-2-Phenyl-4,6-bis(trifluoromethyl)-1,3-dioxane. In a 500 mL round-bottomed flask, 4.0 g (19 mmol) of a 40: 60 mixture of *meso*- and *dl*-1,1,1,5,5,5-hexafluoropentane-2,4-diol,[13] 2.9 mL (3.0 g, 19 mmol) of benzaldehyde dimethylacetal, and 15 mg of *para*-toluenesulfonic acid were dissolved in 200 mL of dry methylene chloride freshly distilled from CaH_2. After magnetically stirring this solution at room temperature for 7 days, it was vigorously extracted with water (5 × 50 mL). The aqueous layers were combined and set aside for later use because they contain the racemic 1,1,1,5,5,5-hexafluoropentane-2,4-diol. The organic layer was dried over $MgSO_4$ and concentrated with a rotary evaporator at water aspirator pressure to afford the crude ketal. It was then dissolved in ethanol, brought to a boil, and water was added until the solution turned cloudy. Upon slowly allowing the mixture to cool to room temperature, white needle-like crystals of *meso*-2-phenyl-4,6-bis(trifluoromethyl)-1,3-dioxane formed. They were filtered away from the mother liquor to yield 2.1 g (37% from the starting diol mixture and 92% when accounting for the diastereomeric ratio) of the title compound.[13a] ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.85 (2H, m), δ 4.42 (2H, m), δ 5.69 (1H, s), δ 7.20−7.45 (5H, m). ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.6, δ 73.4 (q, J = 33.2 Hz), 101.3, 126.3, 128.5, 129.9, 130.0 (q, J = 280 Hz), 136.2. ^{19}F NMR (282 MHz, DMSO-d_6) δ −80.3 (d, J = 5.9 Hz). HRMS-ESI: calcd for $C_{12}H_{11}F_6O_2^+$ $(M + H)^+$, 301.0658; found, 301.0665.

dl-1,1,1,5,5,5-Hexafluoropentane-2,4-diol. The combined aqueous material set aside earlier was vigorously extracted with diethyl ether (3 × 50 mL) and dried over $MgSO_4$. Removal of the ether at water aspirator pressure with a rotary evaporator gave an enriched diastereomeric mixture of *dl*-1,1,1,5,5,5-hexafluoropentane-2,4-diol (~95:5 of the desired *dl* isomer to the undesired *meso* compound).[13a] Further enrichment of the *dl* diastereomer was done by reketalizing the mixture as described above to afford 1.7 g of *dl*-1,1,1,5,5,5-hexafluoropentane-2,4-diol as a white solid in >99: 1 diastereomeric purity. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.65 (2H, m), 4.1 (2H, m), 6.49 (2H, d, J = 6.9, OH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.0 (s, CH_2), 66.7 (q, J = 32.9 Hz, $CHCF_3$), 125.6 (q, J = 280 Hz, CF_3). ^{19}F NMR (282 MHz, DMSO) δ −78.6 (d, J = 5.6 Hz). HRMS-ESI: calcd for $C_5H_5F_6O_2^-$ $(M - H)^-$, 211.0199; found, 211.0201.

pK_a Determinations. Aqueous acidities were measured by potentiometric titrations using a stock solution of NaOH (0.01 M) as the titrant after calibrating the pH meter with standard buffer solutions. DMSO pK_a's were measured by the overlapping indicator method at 20−25 °C by UV and ^{1}H NMR spectroscopy as previously described.[11,14] Multiple measurements were performed for each compound using two of the following indicators as long as they were within 2 pK_a units of the polyol being measured: 4-chloro-2,6-dinitrophenol (pK_a = 3.3), 2,4-dinitrophenol (pK_a = 5.1, Sigma Aldrich), 9-fluorenetriphenylphosphonium bromide (pK_a = 6.6), and 9-thiophenylfluorene (pK_a = 15.1).[15,16] Ion-pairing and self-association of the acids were minimized by working at low concentrations (10^{-5}−10^{-3} M).

Binding Measurements. Diols **1** and **2** were mixed with CD_3CN, and the resulting 2.5 mM solutions were placed in NMR tubes. Carefully measured volumes of 100 mM tetrabutylammonium chloride in CD_3CN were sequentially added, and these titrations were monitored by recording an ^{1}H NMR spectrum at each point. The downfield chemical shifts of the OH signals were followed and nonlinear 1:1 fits of the binding isotherms were carried out using the solver add-on program for Excel to obtain the association equilibrium constants. Representative data and graphical fits of the results are provided in Tables S1 and S2 and Figures S1 and S2.

Aminolysis of Styrene Oxide. A solution of 0.093 g (1.0 mmol) aniline, 0.12 g (1.0 mmol) styrene oxide, and 5 mol % catalyst (0.05 mmol) in a 3 dram vial was stirred under argon at 60 °C for the indicated times. Reaction progress was monitored by TLC (6:1 hexanes/ethyl acetate) on 250 mm 60 F-254 silica gel plates, and upon completion, 1 mL of $CDCl_3$ was added to the vial. The resulting mixture was placed in an NMR tube to obtain the ^{1}H NMR spectrum.

Friedel−Crafts Reactions. β-Nitrostyrene (0.0074 g, 0.050 mmol), *N*-methylindole (0.020 g, 0.15 mmol), and 10 mol % of the catalyst (0.005 mmol) were dissolved in 0.6 mL of $CDCl_3$, and the ^{1}H NMR spectra of the reaction mixtures were recorded after 24 h.

Computations. Conformational searches were carried out using the MMFF force field and AM1 semiempirical calculations with Spartan 08.[17] Single-point B3LYP/6-311+G(d,p)[18] and M06-2X/maug-cc-pVT(+d)Z[19,20] energy computations were carried out on all of the resulting structures that were found to be within 3−5 kcal mol^{-1} of the most favorable species using Gaussian 09.[21] Full optimizations and vibrational frequency calculations were subsequently carried out using the same two DFT methods and basis sets on the most stable conformers of the acids and their conjugate bases.

The conductor-like polarizable continuum model[22] was used to predict pK_a values in DMSO using both computational approaches noted above. In this work, liquid-phase geometry optimizations and harmonic frequencies were computed in addition to single-point energies on the gas-phase structures. Relative pK_a values to TFE were obtained and converted to absolute values since pK_a(TFE) = 23.5 has been measured.[16]

Photoelectron Spectroscopy. Low-temperature photoelectron spectra were recorded with a home-built variable-temperature photoelectron spectrometer that has been previously described.[23] The conjugate bases of 1 and 2 were readily generated by electrospray ionization from ~10^{-3} M methanol−water solutions and were trapped and cooled to 20 K over a period of 20−100 ms by blocking incoming anions for the final 20 ms of a 100 ms acquisition. These ions were then extracted into a time-of-flight mass spectrometer at a repetition rate of 10 Hz. Photoirradiation of the mass selected anions with an excimer laser at 193 nm (6.424 eV) operating at 20 Hz was carried out to enable shot-to-shot background subtraction for all of the reported spectra. Photoelectrons were collected at ~100% efficiency and analyzed with a 5.2 m long electron flight tube. This provided spectra with a resolution (ΔE/kinetic energy) of ~2% or 30 meV at 5 eV binding energy.

RESULT AND DISCUSSION

Hydrogen bonding is ubiquitous in biological systems and plays a critical role in molecular recognition and catalysis. Designing small molecules to mimic this behavior is a major challenge and the subject of much ongoing research. Brønsted acids and hydrogen bond catalysts can be exploited in this regard. We recently reported that hydrogen-bond networks can be used to delocalize a charge site and increase the acidity or basicity of a compound.[24] Proof of concept computations on perfluoropolyols, species that are apt to be stable only at cryogenic temperatures, revealed that hydrogen-bond arrays in conjunction with electron-withdrawing groups lead to very strong Brønsted acids.[11] To test this prediction, three trifluoromethyl group containing polyols were examined.

Electrospray ionization of 1,3-bis(trifluoromethyl)-1,3-propanediol (**1**) and 1,1,2,2-tetra(trifluoromethyl)-1,2-ethanediol (**2**) afforded their corresponding $(M - 1)^-$ ions, and the photoelectron spectra of these anions (**1a** and **2a**) were obtained at 20 K with an excimer laser at 193 nm (Figure 2).[25] These broad spectra are similar to those of other deprotonated polyols, and the top of the bands give the vertical electron

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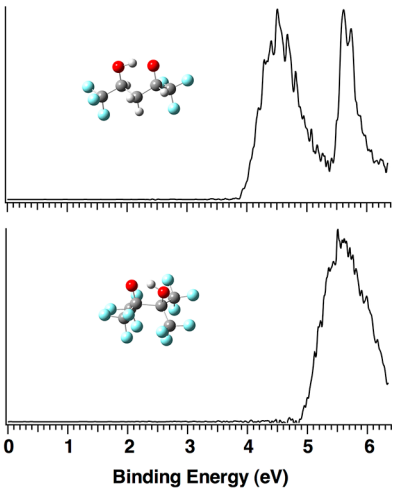

Figure 2. Low-temperature (20 K) photoelectron spectra of $CF_3CH(OH)CH_2CH(O^-)CF_3$ (**1a**, top) and $(CF_3)_2C(OH)C(O^-)(CF_3)_2$ (**2a**, bottom) at 193 nm (6.424 eV).

detachment energies (VDEs), whereas a linear extrapolation of the onset region affords the adiabatic electron detachment energies (ADEs, Table 1).[26] The resulting values are very large for alkoxide ions and correspond to enhancements relative to ethoxide and 2,2,2-trifluoroethoxide of up to 3.29 and 2.45 eV (75.9 and 56.5 kcal mol^{-1}), respectively, for **2a**.[27] This is due to the stabilization of **1a** and **2a** resulting from their strong intramolecular hydrogen bond and the presence of the electron-withdrawing trifluoromethyl substituents. The latter effect is worth 16 kcal mol^{-1} per CF_3 group and was determined by comparing the ADEs of **1a** and **2a** to estimates for the conjugate bases of 1,3-propanediol (2.59 ± 0.14 eV) and 1,2-ethanediol (2.28 ± 0.14 eV).[28] It also results in electron-binding energies that are larger than those for the conjugate bases of strong acids, such as CH_3CO_2H (3.47 ± 0.01 eV),[29] HCl (3.613577 ± 0.000044 eV),[30] HNO_3 (3.937 ± 0.014 eV),[31] and in the later case, even for H_2SO_4 (4.75 ± 0.10 eV).[32] B3LYP/aug-cc-pVDZ and M06-2X/maug-cc-pVT(+d)Z calculations are in accord with these findings, but the latter approach is more accurate. It reproduces the experimental ADEs with an average error of 0.16 eV, which is the same value that was previously reported for a different set of polyol anions.

The photoelectron spectra of **1a** and **2a** reveal that the combination of intramolecular hydrogen bonds and electron-withdrawing groups can lead to very stable anions in the gas phase. To assess the impact of this stabilization in solution, the pK_a's of **1**−**3** were measured in DMSO by ^1H NMR and UV spectroscopy (Table 2). The former values span from 4.8 to 16.0, which makes these compounds remarkably acidic alcohols.

Table 2. Calculated and Experimental pK_a Values

cmpd (ROH)	B3LYP/6-311+G(d,p)	M06-2X/maug-cc-pVT(+d)Z	expt DMSO
1	17.5	16.0	16.0 ± 0.1
2	0.6	2.3	4.8 ± 0.1
3	9.4	6.8	7.1 ± 0.3
$(CF_3)_3COH$	8.3	9.6	10.7[a]
$HOCH_2CH_2OH$[b]	24.7	24.1	28.0[c]
$HOCH_2CH_2CH_2OH$[b]	23.9	23.3	25.4 ± 0.3
$(HOCH_2CH_2)_2CHOH$[b]	20.1	18.3	19.7 ± 0.2
PhOH[b]	18.2	19.4	18.0
CH_3CO_2H[b]	13.7	12.8	12.3
HCl[a]			1.8

[a]See ref 16. [b]See ref 11. [c]This value was obtained from a linear correlation between ΔH°_{acid} and pK_a, see ref 10.

Diol **1** is the least acidic of the three but the two trifluoromethyl groups enhance its acidity by 9.4 pK_a units relative to 1,3-propanediol. As a result, it is a stronger acid than phenol by one hundred fold. Triol **3** is 8.9 orders of magnitude more acidic than **1** and 12.6 pK_a units more acidic than the unsubstituted polyol without any trifluoromethyl groups. It is also a little more than 10^5 times stronger than acetic acid even though it is a saturated compound. The most acidic compound of the series is diol **2**, which is 10^{23} times more acidic than ethylene glycol, 7.5 pK_a units stronger than acetic acid, and within 3 pK_a units of the value of HCl. These results reveal that the combination of intramolecular hydrogen-bonding and electron-withdrawing trifluoromethyl groups can lead to saturated polyols that are quite acidic in DMSO.

In protic solvents intramolecular hydrogen-bond stabilization of polyol conjugate bases is relatively unimportant because the anions are stabilized by intermolecular hydrogen bonds with the solvent. As a result, the pK_a of ethylene glycol and ethanol in water differ by only 0.5 pK_a units (i.e., 15.4 vs 15.9).[33] The acidities of **2** and **3** consequently were measured in water as this presumably provides an opportunity to probe the effects of the trifluoromethyl group in the absence of intramolecular hydrogen-bond stabilization. These compounds were found to be acidic (i.e., pK_a = 5.6 and 7.1, respectively) and are stronger acids than 1,1,1,3,3,3-hexafluoro-2-propanol (HFP, pK_a = 9.3), but neither one is as strong as acetic acid (pK_a = 4.8). The acidity of **2** is not surprising in that the four trifluoromethyl groups are on adjacent carbons and exert a strong stabilizing inductive effect. That is, there is a 10^{10} acidity enhancement of **2** relative to ethylene glycol which leads on average to a 2.5 pK_a unit effect per CF_3 group. In contrast, the four CF_3 groups in **3** are separated by three intervening carbons

Table 1. Experimental and Computed ADE and VDE in eV for Deprotonated Alcohols and Diols

cmpd (RO^-)	expt ADE	expt VDE	calcd[a] ADE	calcd[a] VDE
$CH_3CH_2O^-$	1.7120 ± 0.0040[b]		1.65 (1.58)	1.82 (1.72)
$CF_3CH_2O^-$	2.5541 ± 0.0043[b]		2.80 (2.79)	2.95 (2.88)
$CF_3CH(OH)CH_2CH(O^-)CF_3$ (**1a**)	4.00 ± 0.10	4.51 ± 0.10	3.73 (4.09)	4.31 (4.56)
$(CF_3)_2C(OH)C(O^-)(CF_3)_2$ (**2a**)	5.00 ± 0.10	5.51 ± 0.10	4.74 (4.82)	5.27 (5.37)
$((CF_3)_2C(OH)CH_2)_2CHO^-$ (**3a**)			4.45 (4.64)	5.27

[a]Computed values are at 0 K and correspond to B3LYP and M06-2X (in parentheses) energies. The aug-cc-pVDZ basis set was used for computing VDEs and ADEs with the former functional. M06-2X ADEs were computed with the larger maug-cc-pVT(+d)Z basis set. [b]See ref 27.

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so little, if any, effect was expected from one of the geminal pairs of trifluoromethyl substituents. The 2.2 pK_a unit acidity enhancement relative to HFP, however, suggests that hydrogen bonds can transmit the inductive effect over distance even in an aqueous environment. This would provide an important long-range stabilizing mechanism that may have far reaching implications in biological processes.

Liquid-phase DMSO pK_a values were calculated for $(CF_3)_3COH$ and **1**–**3**. This was accomplished by computing their gas-phase acidities ($\Delta G°_{acid}$) and that of TFE (Table 3)

Table 3. Calculated and Experimental Gas-Phase Acidities ($\Delta G°_{acid}$, in kcal mol^{-1})

cmpd (ROH)	B3LYP/6-311+G(d,p)	M06-2X/maug-cc-pVT(+d)Z	expt
CF_3CH_2OH	351.4	354.0	354.1 ± 2.0[a]
$(CF_3)_3COH$	321.0	325.6	324.0 ± 2.0[a]
1	330.1	330.6	
2	302.8	307.6	
3	309.6	310.8	

[a]See ref 27.

and then calculating the solvation energies of the acids and their conjugate bases with a polarized continuum model. B3LYP/6-311+G(d,p) and M06-2X/maug-cc-pVT(+d)Z energies were used for this purpose, and absolute pK_a's were derived from the relative values to TFE and its experimentally measured acidity of 23.5. Both methods do well but the average unsigned errors for the gas-phase acidities (2.9 (B3LYP) and 0.9 (M06-2X) kcal mol^{-1}) and the DMSO pK_a's (2.6 (B3LYP) and 1.0 (M06-2X)) are noticeably smaller for the M06-2X density functional. The largest deviations from experiment (3.0 kcal mol^{-1} and 4.2 pK_a units (B3LYP) vs 1.6 kcal mol^{-1} and 2.5 pK_a units (M06-2X)) are also better for the meta hybrid generalized gradient approximation Minnesota 06 functional. Both methods are least accurate for **2**, and this may be a reflection of the four CF_3 groups being in close proximity to each other.

Triol **3** has two ionization sites, and our experiments do not indicate which one is more acidic. B3LYP/6-311+G(d,p) computations were carried out to address this issue. In the gas-phase deprotonation of the internal hydroxyl group is energetically preferred over a terminal one, but only by 0.84 kcal mol^{-1}. This can be attributed to the formation of two direct hydrogen bonds to the charged center in the former case as opposed to one, along with a secondary hydrogen bond, in the latter instance (Figure 3). The same stability order is found

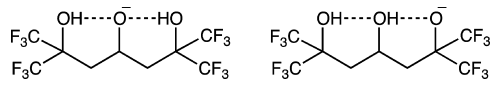
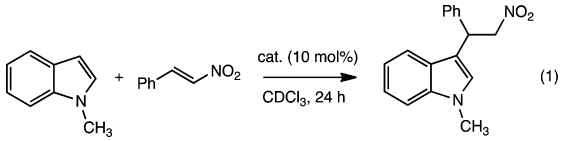


Figure 3. Isomeric conjugate bases of triol **3**.

in DMSO, but solvation reduces the predicted energy difference to 0.36 kcal mol^{-1}. As a result, the relative stabilities were also computed in water since it has a higher dielectric constant than that for DMSO (i.e., ε = 78.4 vs 46.8, respectively).[21] In this case there is a reversal, and now the terminal alkoxide anion is found to be more stable than the internal one by 0.81 kcal mol^{-1}. These results indicate that both the inductive effect and hydrogen-bond stabilization are sensitive to the medium, and as a result, the preferred ionization site can vary with the dielectric constant of the solvent. The energy differences here, however, are quite small, and the most stable structure may vary with the computational approach; M06-2X/maug-cc-pVT(+d)Z calculations predict that the internal alkoxide anion is more stable in all three cases but that the energy differences are 0.55 (gas phase), 0.71 (DMSO), and only 0.06 kcal mol^{-1} in water.

Molecular recognition of anions via ion channels and transporters is biologically important in stabilizing membrane potentials and controlling cell volumes and is intimately connected to a number of debilitating diseases.[34] An acidic and flexible polyol ($HOCH_2CH_2CH(OH)CH_2)_3C$-OH, pK_a = 11.4 ± 0.2) was recently reported to bind chloride in acetonitrile with an association constant of 360 M^{-1} despite being an aliphatic alcohol that can form intramolecular hydrogen bonds.[35] Diols **1** and **2** bracket the acidity of this heptaol (i.e., **1** and **2** are 5–6 pK_a units less acidic and more acidic than it), and consequently their binding constants were also measured. The less acidic diol (**1**) was found to have an association constant with chloride of 3300 M^{-1} in acetonitrile. This is nine times larger than for the more acidic heptaol, 100 fold bigger than an α-D-ribose receptor in which the C1 and C5 hydroxyl groups are protected as their methyl and trityl (Ph_3C) ethers, respectively, and 14 times larger than for the corresponding β-anomer.[36] Our association constant is also greater than for phenols, such as catechol ($1,2\text{-}(HO)_2C_6H_4$, ~3 fold) and resorcinol ($1,3\text{-}(HO)_2C_6H_4$, 23 times).[37] 1,1,2,2-Tetra(trifluoromethyl)ethylene glycol (**2**) has a binding constant with Cl^- of 6700 M^{-1}, which is the largest measured value for an aliphatic alcohol to date, but it is only about twice as large as for **1** even though their acidities differ by 11 orders of magnitude in DMSO. This clearly indicates that there is only a loose relationship between the acidity of a compound and its anion binding affinity undoubtedly because the cavity size of the receptor, steric interactions, and the solvation of the bound complex also play a role.

Our physical characterization of polyols **1**–**3** suggests that they could be good Brønsted acid catalysts, and since they are all capable of forming multiple hydrogen bonds in advance of proton transfer, they maybe more effective than other specific acid catalysts. To explore this possibility, their catalytic behavior in a Friedel–Crafts[38] reaction between β-nitrostyrene and *N*-methylindole (eq 1) was investigated. All three polyols promote



(1)

this transformation and the reaction rates, as indicated by the percent conversion, correlate with their acidities not with the number of hydroxyl groups (Table 4). That is, 10 mol % of the strongest acid (**2**) leads to a 95% conversion at room temperature in 24 h whereas it is 19% with the weakest acid (**1**). Acetic acid does not catalyze this process, however, even though it is four pK_a units more acidic than **1** in DMSO. This indicates that general acid catalysis is involved and strongly suggests that more than one hydrogen bond is involved in this transformation (i.e., the reaction proceeds via hydrogen-bond catalysis).

All three alcohols also catalyze the aminolysis of styrene oxide with aniline at 60 °C under solvent-free conditions (SFC,

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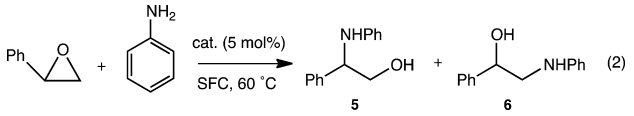
Table 4. Results for Acid-Catalyzed Transformations

	conversion (%)[a]		
catalyst	eq 1	eq 2[b]	5:6
1	19	89	73: 27
2	95	100	88: 12
3	53	100	81: 19
no catalyst	4	5	43: 57
HOAc	4	78	86: 14

[a]Determined by ^{1}H NMR. [b]Reaction time = 2.75 h except for when 2 was used, then it was 20 min.

eq 2, Table 4). The reactivity order again is in accord with the acidity of the three alcohols as is the selectivity. That is, the



most acidic acid (**2**) catalyzes the reaction most efficiently and leads to the most selective transformation. It is also a more effective catalyst in this reaction than Shreiner's thiourea ((3,5-$(CF_3)_3C_6H_3NH)_2CS$) by about an order of magnitude.[39] Acetic acid is 4 orders of magnitude more acidic than **1** in DMSO but is a slightly less efficient catalyst. This indicates that general acid catalysis is also important in this reaction.

CONCLUSION

Diols **1** and **2** and triol **3** were found to be quite acidic in DMSO and water. The conjugate bases of the most acidic and least acidic compounds (i.e., **2** and **1**, respectively) are also remarkably stable in the gas phase as indicated by their ADEs, which in the former case exceeds that of deprotonated sulfuric acid. Taken together, these results suggest that the inductive effect can be transmitted via hydrogen bonds. Diols **1** and **2** also bind chloride anion in acetonitrile with the largest binding constants reported to date for an aliphatic alcohol (i.e., K = 3300 (**1**) and 6700 (**2**) M^{-1}) and are capable of acting as Brønsted acid and hydrogen-bond catalysts (i.e., specific and general acid catalysts, respectively). As a result, hydrogen bonding in conjunction with electron-withdrawing groups is a promising avenue for developing molecular recognition hosts and Brønsted acid and hydrogen-bond catalysts.

ASSOCIATED CONTENT

Supporting Information

Computed geometries and energies are provided along with experimental data for the binding constant determinations and the complete citation to ref 21. 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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