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Single-Centered Hydrogen-Bonded Enhanced Acidity (SHEA) Acids: A New Class of Brønsted Acids

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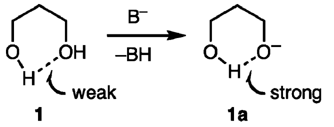
Abstract: Hydrogen bonds are the dominant motif for organizing the three-dimensional structures of biomolecules such as carbohydrates, nucleic acids, and proteins, and serve as templates for proton transfer reactions. Computations, gas-phase acidity measurements, and pK_a determinations in dimethyl sulfoxide on a series of polyols indicate that multiple hydrogen bonds to a single charged center lead to greatly enhanced acidities. A new class of Brønsted acids, consequently, is proposed.

Introduction

Acid−base reactions are ubiquitous in nature and play a critical role in a myriad of chemical transformations. Hydrogen bonds serve as templates for proton transfer reactions, and organize three-dimensional structures of O−H and N−H containing compounds. They also lead to an increase in the gas-phase deprotonation enthalpies of alcohols.[1] For example, ethylene glycol ($HOCH_2CH_2OH$) is 13.6 ± 2.6 kcal mol^{-1} (10 ± 2 pK_a units) more acidic than ethanol (CH_3CH_2OH), and 1,3-propanediol ($HOCH_2CH_2CH_2OH$, **1**) is 17.7 ± 2.8 kcal mol^{-1} (13 ± 2 pK_a units) more acidic than 1-propanol ($CH_3CH_2CH_2OH$) based upon the deprotonation enthalpies of these compounds.[2−4] In both cases, this acidification is due to the strong intramolecular hydrogen bond that forms upon deprotonation of the diol as illustrated for **1** (eq 1).



(1)

In water and other protic solvents, this effect is unimportant,[5] but a qualitatively similar stabilization is expected in hydrophobic environments such as in an enzyme active site or a nonprotic solvent such as dimethyl sulfoxide (CH_3SOCH_3, DMSO). The pK_a's of simple diols in DMSO, however, do not appear to have been reported.[6]

The Lewis structures of alkoxides (RO^-) have 3 lone pairs of electrons on the formally charged oxygen atom, all of which potentially can be used as hydrogen bond acceptors. This could lead to considerable stabilization and the development of a new class of Brønsted acids which we will refer to as single-centered hydrogen-bonded enhanced acidity acids, or SHEA acids for short. In this work, we report computations, gas-phase acidity measurements, and pK_a determinations in DMSO on a series of polyols. These compounds are found to be remarkably acidic and ultimately may rival carboranes, the strongest Brønsted acids currently known.[7]

Experimental Section

General. Dry materials are required for accurately and reproducibly measuring acidities in DMSO. Glassware, syringes, NMR tubes, and needles were dried in ovens or flame-dried and stored in a desiccator containing phosphorus pentoxide. Solvents also were dried and degassed by bubbling dry argon through them for 20 min before use. This was carried out for DMSO and DMSO-d$_6$ by refluxing them over calcium hydride for 4 h at 60−65 °C and a pressure of 1.5 Torr. Both solvents subsequently were distilled under the same conditions. Pentane, which was used to remove the mineral oil from a 30% suspension of potassium hydride before reacting the KH with DMSO to make dimsyl potassium, was distilled from phosphorus pentoxide.

Gas-Phase Experiments. All of the gas-phase experiments were carried out with a 3 T dual-cell Fourier transform mass spectrometer (FTMS) originally obtained from Extrel and subsequently updated by Ion Spec (now Varian) with newer electronics and the Omega version 8.0.325 data system. The acidities of $(HOCH_2CH_2)_2CHOH$ (**2**) and $(HOCH_2CH_2)_3COH$ (**3**) initially were bracketed with standard reference acids in both directions, and equilibrium constants were subsequently obtained either by measuring the forward and reverse proton transfer rate constants or directly establishing the equilibrium. In the former case, the conjugate bases of phenol, 3-chloropropionic acid, and 2,2-dimethylpropionic acid

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were generated by electron ionization of the neutral acids and the resulting $(M - 1)^-$ ions were transferred to the second cell, cooled with a pulse of argon up to pressures of $\sim 10^{-5}$ Torr, and isolated using a SWIFT excitation.[8] The subsequent reaction with a constant pressure of **2** or **3** was monitored as a function of time in order to obtain the forward (k_1) rate constant. The reverse process was monitored in a similar manner except that the alkoxides were generated by electron ionization of **2** and **3**, and they were reacted either with C_6H_5OH, $ClCH_2CH_2CO_2H$, or $(CH_3)_3CCO_2H$. To directly measure the equilibrium constant, phenoxide (*m/z* 93) was transferred to the second cell where a constant pressure of both phenol and **2** was maintained. The $C_6H_5O^-$ ion was cooled with a pulse of argon and isolated, and the ion signals were monitored over time. Equilibrium was achieved when the **2a**/$C_6H_5O^-$ ratio became constant and the equilibrium constant was measured at 3 different neutral pressures.

3-(2-Hydroxyethyl)-1,3,5-Pentanetriol (3). A solution of 2.50 g (16.45 mmol) of 4-allylhepta-1,6-dien-4-ol (Alfa Aesar) in 140 mL of anhydrous methanol was cooled to −78 °C and ozone was bubbled through it for 45 min until a blue color persisted. The excess ozone was purged from the system over 20 min by passing nitrogen through the reaction mixture and then the solution was mechanically stirred and 7.5 g (197.4 mmol) of sodium borohydride was added. Stirring was continued for 12 h during which time the solution was allowed to warm to 0 °C as the dry ice-acetone bath slowly thawed. Acidification of the reaction mixture was carried out by slowly adding concentrated HCl until the solution had a pH of ∼4−5 and a white precipitate formed. Filtration afforded a methanol solution which was concentrated at aspirator pressure with a rotary evaporator. The residue was dissolved in 150 mL of methanol and reconcentrated. This step was repeated two additional times to facilitate the removal of boron-containing compounds as volatile byproducts. The remaining residue was dissolved in a small amount of methanol and loaded on a silica column. Flash chromatography with gradient elution proceeding from neat ethyl acetate to 10:1, 5:1, and 1:1 ethyl acetate/methanol mixtures afforded 1.52 g (56%) of 3-(2-hydroxyethyl)-1,3,5-pentanetriol. ^{1}H NMR (300 MHz, CD_3OD) δ 1.76 (6H, t, $J = 6.9$ Hz), 3.72 (6H, t, $J = 6.9$ Hz). ^{13}C NMR (75 MHz, CD_3OD) δ 42.4, 59.2, 74.4. HRMS-EI: calcd for $C_7H_{15}O_4$ $(M\text{-}H)^-$ 163.0976, found 163.0961.

p*K*$_a$ Determinations. A series of three NMR tubes outfitted with small septa, so that all manipulations could be carried out under a stream of dry argon, were used for carrying out the acidity determinations. Each NMR tube was filled with 25 μL of a 0.1 M DMSO solution containing the selected indicator and enough DMSO-d_6 to increase the total volume to 1 mL. Freshly prepared dimsyl potassium (0.5 equivalents, ∼0.5−0.75 M) then was added to each solution, and the mixture was efficiently shaken before recording the ^{1}H NMR spectrum to determine the initial concentration of the indicator (IndH) and indicator anion (Ind^-). DMSO solutions (0.1 M) containing 0.25, 0.50, and 0.75 equiv of 1,3-propanediol, **2**, or **3** were then promptly added to the three NMR tubes and the ^{1}H NMR spectra were rerecorded to obtain the new IndH: Ind^- ratio and resulting equilibrium constant. Concentrations between 1−5 mM were employed in this work, and over this range it was found that ion pairing did not affect the pK_a determinations by diluting the equilibrium mixtures twice for each alcohol.

Computations. Monte Carlo and systematic conformational searches as implemented in Spartan 04 and 08 were carried out using MMFF and Sybyl force fields as well as AM1 and PM3 semiempirical calculations.[9] The lowest energy structures that resulted (those within 3−5 kcal mol^{-1} of the most favorable conformer) were then optimized using the Becke three-parameter hybrid exchange and Lee−Yang−Parr correlation density functional (B3LYP)[10] and Dunning's augmented correlation-consistent double-ζ basis set (aug-cc-pVDZ)[11] using Gaussian 03.[12] In this way, an extensive number of conformations were examined for **2**, **3**, $(HOCH_2CH_2CH(OH)CH_2)_3COH$ (**4**), and $(HOCF_2CF_2CF(OH)CF_2)_3COH$ (**4F**) but only the most favorable species from the Monte Carlo calculations were reoptimized for $(HOCF_2CF_2)_2CFOH$ (**2F**) and $(HOCF_2CF_2)_3COH$ (**3F**). Vibrational frequencies also were computed for the most favorable species, except for **3F**, and the unscaled values were used to obtain the zero-point energies and thermal corrections to 298 K. In a few instances, G3B3 and single point energy calculations with the aug-cc-pVTZ, aug-cc-pVQZ, and aug-cc-pV5Z basis sets were carried out as well.[13,14] A summary of the geometries and energies of the most favorable structures located in this work are provided in the Supporting Information.

Entropies were computed using standard statistical formulas and are provided in the output of vibrational frequency jobs by Gaussian 03. The resulting values for the neutral compounds examined in this study are too small and were corrected by taking into account the entropies of different conformations ($S = \Sigma_i x_i S_i$, where x_i is the mole fraction for each conformer derived from the Boltzmann distribution), the effect of hindered rotations (S_{hind}), and the entropy of mixing (S_{mix}). Corrections for hindered rotations were computed using models developed by Truhlar[15] and Pitzer[16] as implemented by Schlegel[17] in Gaussian 03 using the keyword freq = hindrot. Entropies of mixing ($S_{\text{mix}} = -R\ \Sigma_i x_i \ln x_i$) were determined by averaging the results of MMFF and Sybyl molecular mechanics conformational searches using the systematic algorithm in Spartan; similar results were obtained using the conformations derived from semiempirical (AM1 and PM3) calculations.[9] A simpler method for computing entropies based upon a report by Gutherie[18] also was carried out. This was done by ignoring the effect of hindered rotations and using a $R\ln 3^n$ term for the entropy of mixing, where $n = 2$ $(CH_3CH_2CH_2OH)$, 4 $(HOCH_2CH_2CH_2OH)$, 7 $((HOCH_2CH_2)_2CHOH)$, and 10 $((HOCH_2CH_2)_3COH)$, and corresponds to the number of rotatable bonds that do not necessarily lead to indistinguishable structures. This procedure was tested on 128 organic compounds with up to 10 carbon atoms by Guthrie and the reported standard deviation is 1.3 cal mol^{-1} K^{-1}. This agreement with experiment is due, at least in part, to an overestimate of the entropy of mixing which is compensated for by neglecting the effect of hindered rotations. The former contribution is significantly (25−50%) more important than the latter one for the acids studied in this work, so it is not surprising that both methods for computing the total entropy are in good accord with each other. They also both reproduce the experimental entropy of 1-propanol (77.6 ($S + S_{\text{hind}} + S_{\text{mix}}$) and 76.6 (Guthrie) vs 77.1 cal mol^{-1} K^{-1} (expt))[1] and a previous computation of the entropy of 1,3-propanediol (84.8 ($S + S_{\text{hind}} + S_{\text{mix}}$) and 85.4 (Guthrie) vs 85.7 cal mol^{-1} K^{-1} (literature)[19]). Consequently, only the results from the simpler procedure are given in the text, but both values are provided in the Supporting Information. Corrections for hindered rotations and the entropy of mixing were not carried out for the conjugate bases, with the exception of 1-propoxide ($CH_3CH_2CH_2O^-$), because the

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Table 1. Computed B3LYP/aug-cc-pVDZ Acidities of a Series of Alcohols at 298 K

cmpd (ROH)	ΔH°_{acid}(ROH)[a] calcd	expt	ΔG°_{acid}(ROH)[a] calcd	expt
$CH_3CH_2CH_2OH$	374.4	375.7 ± 1.3[b,c]	367.9	369.1 ± 1.4[b,c]
$HOCH_2CH_2CH_2OH$ (**1**)	358.3	358.0 ± 2.5[c]	354.3	355.8 ± 2.0[c]
$(HOCH_2CH_2)_2CHOH$ (**2**)	344.2 [346.0] (346.2)[d,e]	344.3 ± 1.9[f]	342.3	342.4 ± 1.2[f]
$(HOCH_2CH_2)_3COH$ (**3**)	333.7 [335.1] (334.8)[d,g]	333.0 ± 2.3[f]	335.1	334.4 ± 1.7[f]
$(HOCH_2CH_2CH(OH)CH_2)_3COH$ (**4**)	318.9		326.0	
$(HOCF_2CF_2)_2CFOH$ (**2F**)	289.0		286.9	
$(HOCF_2CF_2)_3COH$ (**3F**)	279.7[h]		281.1[i]	
$(HOCF_2CF_2CF(OH)CF_2)_3COH$ (**4F**)	260.9		267.6	

[a] All values are in kcal mol^{-1}. [b] See ref 1. [c] See ref 4. [d] The value in brackets is for the B3LYP/aug-cc-pV5Z//B3LYP/aug-cc-pVDZ acidity and corresponds to the infinite basis set limit. [e] The parenthetical value is for the G3B3 acidity which is based upon the Gaussian-3 model developed by Pople et al. This theoretical approach strives for chemical accuracy (±2 kcal mol^{-1}) and has proven to be very successful. For further details, see refs 13 and 14. [f] This work. [g] The value in brackets is for the B3LYP/aug-cc-pVQZ//B3LYP/aug-cc-pVDZ acidity and is 0.1 kcal mol^{-1} more acidic than the result extrapolated to the infinite basis set limit. [h] The zero-point energy and the thermal energy correction to the enthalpy for **2F** were used in this case, but the value changes by only ± 0.6 if **3** or **4F** is used. [i] ΔS°_{acid} (**3**) was used in this instance.

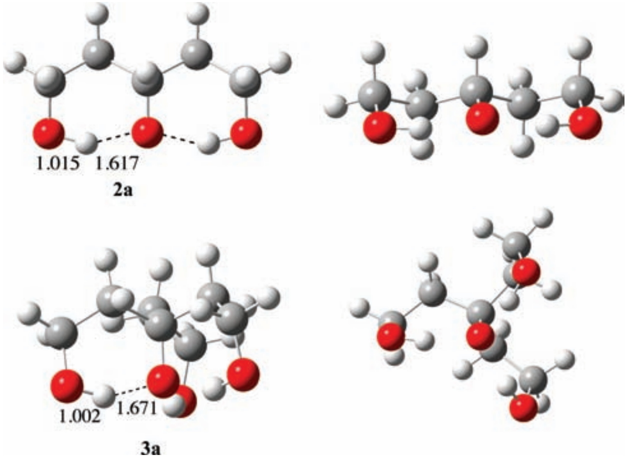

Figure 1. B3LYP/aug-cc-pVDZ geometries of the most stable structures of the conjugate bases of $(HOCH_2CH_2)_2CHOH$ (top row, 2 views) and $(HOCH_2CH_2)_3COH$ (bottom row, 2 views).

intramolecular hydrogen bonds lead to larger rotational barriers and far fewer contributing conformations.

Results/Discussion

Density functional theory calculations employing the B3LYP functional and a suitable basis set such as Dunning's augmented correlation-consistent double-ζ basis set (aug-cc-pVDZ) typically reproduce gas-phase deprotonation enthalpies (ΔH°_{acid}) to within 2−3 kcal mol^{-1}.[10,11,20] Therefore, it is not surprising that this approach well-reproduces the experimental acidities of 1-propanol and 1,3-propanediol (Table 1). The acidities of 1,3,5-pentanetriol [$(HOCH_2CH_2)_2CHOH$, **2**] and 3-(2-hydroxyethyl)-1,3,5-pentanetriol [$(HOCH_2CH_2)_3COH$, **3**], a tetraol, subsequently were computed. As anticipated, the most stable structures for the alkoxides have two and three intramolecular hydrogen bonds, respectively (Figure 1). The predicted gas-phase deprotonation enthalpies for **2** and **3** are 344.2 and 333.7 kcal mol^{-1}, respectively; these energies correspond to the heterolytic RO−H bond dissociation energies, so the smaller the number the more acidic the compound. These results correspond to a remarkable 30.2 kcal mol^{-1} (22 pK_a units) and 41.0 kcal mol^{-1} (30 pK_a units) acidification of **2** and **3** relative to 1-propanol, and suggest that these polyols are as acidic as formic acid ($\Delta H^\circ_{acid}(HCO_2H)$ = 346.2 ± 1.2 kcal mol^{-1})[21] and hydrochloric acid ($\Delta H^\circ_{acid}(HCl)$ = 333.383 ± 0.002 kcal mol^{-1}),[1] respectively. This is noteworthy given that **2** and **3** are saturated compounds and do not contain electron withdrawing substituents beyond the hydroxyl groups.

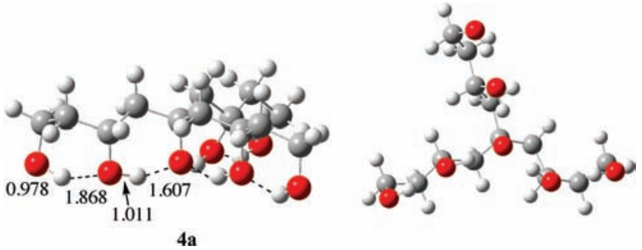

Figure 2. Two views for the B3LYP/aug-cc-pVDZ optimized geometry of the conjugate base of $(HOCH_2CH_2CH(OH)CH_2)_3COH$. Only one set of OH and hydrogen bond lengths are given for clarity but they are similar to the corresponding values for the two other side chains.

In **3a**, all three OH substituents interact with the alkoxide center via hydrogen bonds. The three donor sites (i.e., the electron pairs) on the negatively charged oxygen atom center, consequently, are exploited. This bonding arrangement can be viewed as providing the first solvation shell for the ion, but a second shell might be incorporated by substituting additional hydroxyl groups into the molecule which can interact with the electron rich oxygen atoms of the first solvation shell. 5-(2,4-Dihydroxy-1-butyl)-1,3,5,7,9-nonanepentanol [$(HOCH_2CH_2CH(OH)CH_2)_3COH$, **4**], a heptaol, was examined in this regard, and as anticipated a structure with 6 hydrogen bonds was located as the lowest energy conformer for the conjugate base (**4a**, Figure 2). The resulting acidity for **4** is 318.9 kcal mol^{-1}, which corresponds to a remarkable 55.5 kcal mol^{-1} (41 pK_a units) enhancement relative to 1-propanol. This prediction also indicates that **4** should be more acidic than nitric acid ($\Delta H^\circ_{acid}(HNO_3)$ = 324.5 ± 0.2 kcal mol^{-1})[1] and almost as potent as hydroiodic acid ($\Delta H^\circ_{acid}(HI)$ = 314.33 ± 0.03 kcal mol^{-1}),[3] which was the strongest gas-phase acid known for many years. This is remarkable for a saturated compound containing only C, H, and O atoms.

An additional strategy for increasing the acidity of SHEA acids is to further delocalize the charge by incorporating electron withdrawing substituents into the molecule. Perfluorinated polyols corresponding to **2**−**4** were examined to assess this

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effect (Table 1) even though these compounds are unlikely to be very stable.[22] All three compounds (**2F**−**4F**) are predicted to be more acidic than sulfuric acid and bis(nonafluorobutane)sulfonylimide ($\Delta H°_{\mathrm{acid}}(\mathrm{H_2SO_4}) = 306.3 \pm 3.1$ and $\Delta H°_{\mathrm{acid}}(\mathrm{HN(SO_2C_4F_9)_2}) = 291.1 \pm 2.2$ kcal mol^{-1})[23,24] even though the latter species currently is the strongest gas-phase acid measured to date.[25] Consequently, it appears that intramolecular hydrogen bonds can be used in conjunction with inductive effects to design extremely strong acids in the gas phase. Similar trends are anticipated in nonprotic solvents, but solvation will undoubtedly reduce the magnitude of the acidity enhancements. It remains to be established how far one can push the acidity of SHEA acids, but they represent a new class of acid which is apt to be synthetically useful, noncorrosive, and environmentally friendly.

To begin testing the above predictions, triol **2** and tetraol **3** were prepared. The latter compound has not previously been reported, but was generated in a one pot procedure involving the ozonolysis of 4-allyl-1,6-hepta-1,6-dien-4-ol ($\mathrm{HOC(CH_2CH{=}CH_2)_3}$) and the reduction of the resulting ozonide with sodium borohydride ($\mathrm{NaBH_4}$) in an analogous manner to Wender's synthesis of the triol.[26] The gas-phase acidity of **2** was subsequently determined by measuring the forward (k_1) and reverse rate (k_{-1}) constants for the reaction with phenol (eq 2) to obtain the

$$\underset{\mathbf{2}}{(\mathrm{HOCH_2CH_2})_2\mathrm{CHOH}} + \mathrm{C_6H_5O^-} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{\mathbf{2a}}{(\mathrm{HOCH_2CH_2})_2\mathrm{CHO^-}} + \mathrm{C_6H_5OH} \qquad (2)$$

equilibrium constant, since $K = k_1/k_{-1}$. Both rate constants were determined three times to afford $k_1 = (2.0 \pm 0.2) \times 10^{-10}$ cm^3 molecule^{-1} s^{-1} and $k_{-1} = (9.7 \pm 1.6) \times 10^{-10}$ cm^3 molecule^{-1} s^{-1} where the uncertainties represent the standard deviations of the measurements. These results lead to $K = 0.206 \pm 0.040$ which also was independently determined by directly establishing the equilibrium. That is, a constant pressure of both phenol and **2** were allowed to react with **2a** and phenoxide ion, and within a few seconds the ion ratio became constant and the equilibrium was established. Three measurements at different neutral pressures afforded $K = 0.201 \pm 0.006$ which is in excellent accord with the first determination. A combined value for the equilibrium constant of 0.204 ± 0.020 leads to a gas-phase acidity difference ($\Delta G°_{\mathrm{acid}}(\mathbf{2}\text{-}\mathrm{C_6H_5OH})$) of 0.95 ± 0.60 kcal mol^{-1}, where an uncertainty for K of ± 100% was adopted for statistical purposes. Angel and Ervin have reported a precise determination for the gas-phase acidity of phenol ($\Delta G°_{\mathrm{acid}} = 341.5 \pm 1.0$ kcal mol^{-1}),[27] which enables $\Delta G°_{\mathrm{acid}}(\mathbf{2}) = 342.4 \pm 1.2$ kcal mol^{-1} to be assigned. To convert this free energy into an enthalpy ($\Delta H°_{\mathrm{acid}}$), the entropies of **2** and **2a** are needed; the value for a proton is well-known to be 26.04 cal mol^{-1} K^{-1}. These quantities were computed (109.7 and 90.1 cal mol^{-1} K^{-1}, respectively) using unscaled B3LYP/aug-cc-pVDZ vibrational frequencies and a recent approach described by Gutherie[18] to give $\Delta S°_{\mathrm{acid}} = 6.4$ cal mol^{-1} K^{-1}. A similar value ($\Delta S°_{\mathrm{acid}} = 8.7$ cal mol^{-1} K^{-1}) was obtained by accounting for the effects of hindered rotations and calculating the entropy of mixing from the Boltzmann distribution of the contributing conformations of **2**, but at considerably greater computational cost. Since the simpler method reproduces the entropies of 1-propanol and 1,3-propanediol to within 0.5 cal mol^{-1} K^{-1}, and the standard deviation for a 128 compound test set is 1.3 cal mol^{-1} K^{-1},[18] it was employed in this study. An arbitrary uncertainty of ± 5 cal mol^{-1} K^{-1} was assumed for $\Delta S°_{\mathrm{acid}}$ for statistical purposes, and leads to $\Delta H°_{\mathrm{acid}} = 344.3 \pm 1.9$ kcal mol^{-1}. This value is in excellent accord with the B3LYP/aug-cc-pVDZ prediction (344.2 kcal mol^{-1}) as well as computed B3LYP/aug-cc-pV5Z //B3LYP/aug-cc-pVDZ and G3B3 acidities of 346.0 and 346.2 kcal mol^{-1}, respectively; G3B3 energies are a variant of G3 theory and typically are accurate to within 2 kcal mol^{-1}.[13,14]

The acidity of **3** also was measured by an equilibrium determination. In this case the rate constants for the acid−base reactions with 3-chloropropionic acid and 2,2-dimethylpropionic acid were obtained as illustrated in eq 3 for the former case. Three independent measurements for

$$\underset{\mathbf{3}}{(\mathrm{HOCH_2CH_2})_3\mathrm{COH}} + \mathrm{ClCH_2CH_2CO_2^-} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{\mathbf{3a}}{(\mathrm{HOCH_2CH_2})_3\mathrm{CO^-}} + \mathrm{ClCH_2CH_2CO_2H} \qquad (3)$$

each quantity, where the first numbers are for 3-chloropropionic acid and the following ones in brackets are for 2,2-dimethylpropionic acid, afforded $k_1 = (8.0 \pm 2.4) \times 10^{-11}$ [$(2.4 \pm 0.7) \times 10^{-11}$] cm^3 molecule^{-1} s^{-1}, $k_{-1} = (1.1 \pm 0.3) \times 10^{-10}$ [$(1.7 \pm 0.5) \times 10^{-9}$] cm^3 molecule^{-1} s^{-1}, and $K = 0.73 \pm 0.30$ [0.014 ± 0.006].[28] These results lead to $\Delta\Delta G°_{\mathrm{acid}} = 0.2 \pm 0.1$ and 2.5 ± 0.8 kcal mol^{-1}, respectively, and can be combined with $\Delta G°_{\mathrm{acid}}(\mathrm{ClCH_2CH_2CO_2H}) = 333.8 \pm 2.0$ kcal mol^{-1} and $\Delta G°_{\mathrm{acid}}((\mathrm{CH_3})_3\mathrm{CCO_2H}) = 337.6 \pm 2.0$ kcal mol^{-1},[1] to give $\Delta G°_{\mathrm{acid}}(\mathbf{3}) = 333.6 \pm 2.1$ and 335.1 ± 2.2 kcal mol^{-1}, respectively. These two independent determinations afford $\Delta G°_{\mathrm{acid}}(\mathbf{3}) = 334.4 \pm 1.7$ kcal mol^{-1}, which was combined with the computed entropies for **3** and **3a** (134.1 and 103.4 cal mol^{-1} K^{-1}, respectively) to give $\Delta H°_{\mathrm{acid}}(\mathbf{3}) = 333.0 \pm 2.3$ kcal mol^{-1}. This value is in excellent accord with the respective B3LYP/aug-cc-pVDZ, B3LYP/aug-cc-pVQZ//B3LYP/aug-cc-pVDZ, and G3B3 predictions of 333.7, 335.1, and 334.8 kcal mol^{-1}.

Our gas-phase measurements on triol **2** and tetraol **3** indicate that these compounds are similar in acidity to formic acid ($\Delta H°_{\mathrm{acid}}(\mathrm{HCO_2H}) = 346.2 \pm 1.2$ kcal mol^{-1})[21] and hydrochloric acid ($\Delta H°_{\mathrm{acid}}(\mathrm{HCl}) = 333.383 \pm 0.002$ kcal mol^{-1}),[1] respectively. This makes the tetraol the strongest acid of its type (i.e., a saturated alcohol comprised only of C, H, and O atoms) measured to date, and clearly indicates that multiple hydrogen bonds to a single charged center can dramatically enhance gas-phase acidities. Similar trends are anticipated in nonprotic solvents since intermolecular hydrogen bonds with the solvent are precluded.

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Table 2. DMSO Acidities for a Series of Alcohols

cmpd (ROH)	pK_a	ΔpK_a (PrOH - ROH)	estimated pK_a[a]
$CH_3CH_2CH_2OH$	30.0[b]	0.0	31.6 (31.9)
$HOCH_2CH_2CH_2OH$ (**1**)	25.4 ± 0.3 (5)[c,d]	4.6 [6.3][e]	
$(HOCH_2CH_2)_2CHOH$ (**2**)	19.7 ± 0.2 (6)[c,d]	10.3 [14.0][e]	
$(HOCH_2CH_2)_3COH$ (**3**)	16.1 ± 0.2 (6)[c,d]	13.9 [19.0][e]	
$(HOCH_2CH_2CH(OH)CH_2)_3COH$ (**4**)			10.5(11.7)
$(HOCF_2CF_2)_2CFOH$ (**2F**)			−0.9 (−7.2)
$(HOCF_2CF_2)_3COH$ (**3F**)			−4.8 (−10.0)
$(HOCF_2CF_2CF(OH)CF_2)_3COH$ (**4F**)			−11.6 (−16.5)

[a] These predictions were derived from the linear correlation between the measured DMSO pK_a values and the computed B3LYP deprotonation enthalpies or free energies; the latter results are given in parentheses. [b] An estimated value based on the literature pK_a's for CH_3OH (29.0), CH_3CH_2OH (29.8),[30] and $(CH_3)_2CHOH$ (30.3). [c] This work. Uncertainties are given as the standard deviation of the data while the parenthetical values indicate the number of measurements that were carried out. [d] 2-Methyl-1-phenyl-1-propanone (pK_a = 26.25), 2-phenylindene (pK_a = 19.4), and 9-thiophenylfluorene (pK_a = 15.4) were used as the reference acids for the titrations of 1,3-propanediol (**1**), **2**, and **3**, respectively. [e] Values in brackets are in kcal mol^{-1}.

To test this hypothesis, the pK_a's of 1,3-propanediol, triol **2**, and tetraol **3** were measured using three reference acids in DMSO. The equilibria were monitored by ^{1}H NMR as described by Chu, Deng, and Cheng,[29] and at low millimolar concentrations the equilibrium constants were found to be independent of the polyol concentrations. The resulting pK_a values were found to decrease with the addition of each hydroxyl group (Table 2) and the acidities increase as anticipated based upon our gas-phase measurements and computations. 1,3-Propanediol is 4.6 pK_a units more acidic than 1-propanol, and this indicates that the conjugate base of the former acid is stabilized in DMSO by the presence of an intramolecular hydrogen bond. As a result, the diol is almost as acidic as 2,2,2-trifluoroethanol (pK_a(CF_3CH_2OH) = 23.5). Triol **2** was found to be more acidic than the diol and CF_3CH_2OH, and is closer in acidity to 1,1,1,3,3,3-hexafluoro-2-propanol (pK_a(($CF_3)_2CHOH$) = 17.9).[31] Tetraol **3** is more acidic yet, and is a stronger acid than $(CF_3)_2CHOH$, imidazole (pK_a = 18.6) and phenol (pK_a(C_6H_5OH) = 18.0). These results indicate that the effect of multiple hydrogen bonds to a single charged center is additive, and that **3** is the most acidic saturated alcohol of its kind in DMSO to be reported to date.

If one plots the experimentally determined pK_a values for the 1,3-propanediol (**1**), triol **2**, and tetraol **3** against their computed gas-phase deprotonation enthalpies (Figure 3), then a straight line results (pK_a (ROH) = 0.380 × ΔH°_{acid}(ROH) − 110.7 kcal mol^{-1}, $r^2 = 0.998$) which enables one to predict the pK_a values in DMSO for the remaining acids listed in Table 1. Similar results are obtained if one uses ΔG°_{acid} rather than ΔH°_{acid} and both sets of predictions are provided in Table 2. The derived value for 1-propanol from the linear regression is in good accord with the experimental prediction while heptaol **4** is found to be more acidic than acetic acid (pK_a(HOAc) = 12.3). All of the fluorinated derivatives are predicted to have negative pK_a values which, if true, makes them more acidic than HCl (pK_a = 1.8) and CH_3SO_3H (pK_a = 1.6). These crude estimates will need to be modified as more experimental data becomes available, particularly, for pK_a values that correspond to large extrapolations, as there is no a priori reason why the liquid-phase results and gas-phase deprotonation enthalpies or free energies should be linearly related. It is worth noting, however, that similar correlations in DMSO have been previously reported for delocalized carbanions and that the solvation energies are essentially constant in this medium.[32] In any case, the correlation between gas-phase deprotonation enthalpies and DMSO pK_a values suggests that strong liquid-phase acids can be made from polyols.

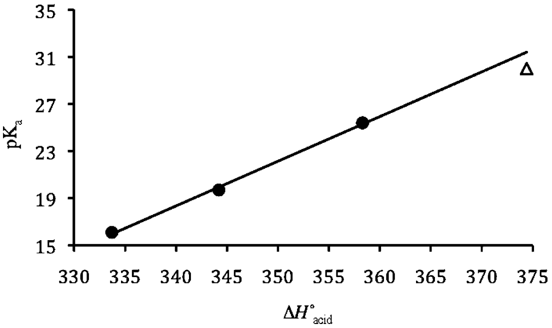

Figure 3. Measured DMSO pK_a values for 1,3-propanediol (**1**), triol **2**, and tetraol **3** versus their computed B3LYP acidities in kcal mol^{-1}; 1-propanol is given by the open triangle but was omitted from the linear fit of the data.

SHEA acids are surprisingly acidic and multiple hydrogen bonds can lead to enormous acidity enhancements both in the gas-phase as well as in a nonprotic solvent such as DMSO. Therefore, it is likely that this behavior occurs in living systems and is exploited by Nature.

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Supporting Information Available: Computed structures and energies are provided (13 pgs) and complete ref 12. This material is available free of charge via the Internet at http://pubs.acs.org.

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