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Hydrogen-Bond Networks: Strengths of Different Types of Hydrogen Bonds and An Alternative to the Low Barrier Hydrogen-Bond Proposal

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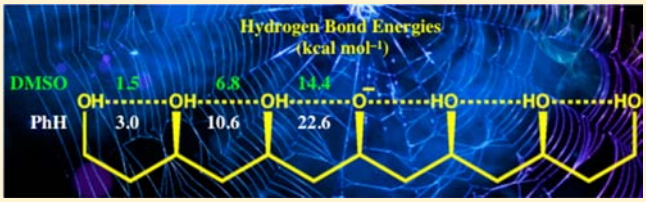
Supporting Information

ABSTRACT: We report quantifying the strengths of different types of hydrogen bonds in hydrogen-bond networks (HBNs) via measurement of the adiabatic electron detachment energy of the conjugate base of a small covalent polyol model compound (i.e., $(HOCH_2CH_2CH(OH)CH_2)_2CHOH$) in the gas phase and the pK_a of the corresponding acid in DMSO. The latter result reveals that the hydrogen bonds to the charged center and those that are one solvation shell further away (i.e., primary and secondary) provide 5.3 and 2.5 pK_a units of stabilization per hydrogen bond in DMSO. Computations indicate that these energies increase to 8.4 and 3.9 pK_a units in benzene and that the total stabilizations are 16 (DMSO) and 25 (benzene) pK_a units. Calculations on a larger linear heptaol (i.e., $(HOCH_2CH_2CH(OH)CH_2CH(OH)CH_2)_2CHOH$) reveal that the terminal hydroxyl groups each contribute 0.6 pK_a units of stabilization in DMSO and 1.1 pK_a units in benzene. All of these results taken together indicate that the presence of a charged center can provide a powerful energetic driving force for enzyme catalysis and conformational changes such as in protein folding due to multiple hydrogen bonds in a HBN.



INTRODUCTION

Hydrogen bonds can be used in synergy to provide catalytic power and enhance Brønsted acidities. For example, Shan and Herschlag reported that 2,6-dihydroxybenzoic acid is 10.9 kcal mol^{-1} (8.0 pK_a units) more acidic than benzoic acid in DMSO due to the presence of two hydrogen bonds in the conjugate base between the hydroxyl groups and the carboxylate anion.[1−3] We recently noted that an even larger acidification of 22 kcal mol^{-1} (16.1 pK_a units) in DMSO can be achieved by three hydrogen bonds to the tertiary alkoxide center in deprotonated 3-(2-hydroxyethyl)-1,3,5-pentanetriol $[(HOCH_2CH_2)_3COH$, **T4**$]$.[4] In a similar way, enzyme active sites make use of hydrogen bonds to stabilize transition-state structures by delocalizing negatively charged centers.[5−8] Extended networks of hydrogen bonds are employed, but many of the interactions are between noncharged groups. Triose phosphate isomerase (TPI) has such an arrangement (Figure 1),[9] but a single exceptionally strong low barrier hydrogen bond (LBHB) was proposed to account for the catalytic rate enhancement; this LBHB was originally proposed to be between His-95 and the enediolate, but subsequently it was suggested that Glu-165 is the residue involved in the LBHB.[10,11] LBHBs have been invoked in many additional processes (e.g., photoactive yellow protein, chymotrypsin, serine protease, and citrate synthase),[12−14] but this explanation is controversial.[15−17]

In the early 1990s some hydrogen bonds were found to have low H/D fractionation factors, downfield ^{1}H NMR signals of 10 ppm or more, infrared spectra with low frequencies and unusually broad O−H stretching bands, and short distances between the heteroatoms involved in the hydrogen bond (i.e., the X−Y distance in X···H···Y, where X and Y are nitrogen or oxygen centers).[18−21] Anionic RO$^-$···HOR′ hydrogen bond strengths of 20−25 kcal mol^{-1} are common in the gas phase, and the dissociation energy of F$^-$···HF into F$^-$ and HF is 45.8 ± 1.6 kcal mol^{-1}.[22] This led Gerlt and Gassman to propose that LBHBs can provide 15−20 kcal mol^{-1} of stabilization in enzyme-catalyzed reactions.[10] This remarkable hypothesis posited that hydrogen bonds in biological processes can be far stronger than was previously considered possible. As a result, it has received considerable attention. No hydrogen bonds, however, have been measured to be so strong in solution. The largest value to date is 7.5 kcal mol^{-1} for monodeprotonated phthallic acid (i.e., 1,2-$C_6H_4(CO_2H)CO_2^-$) in acetonitrile.[23,24] This critique of the LBHB proposal maybe a "red herring", however, because computations indicate that stronger hydrogen bonds can be formed in less polar media.[25,26]

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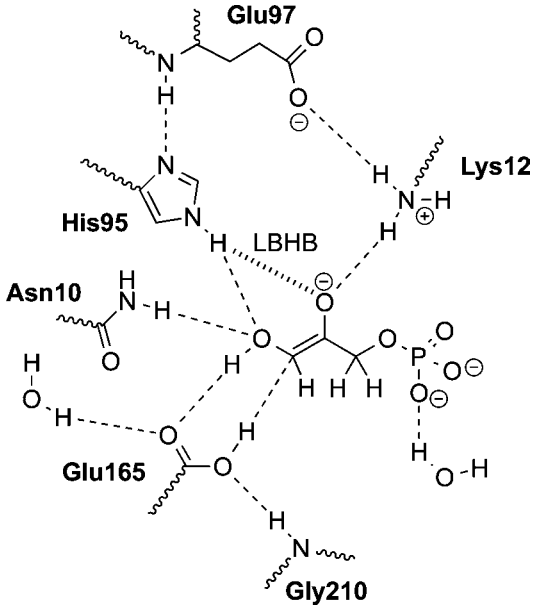


Figure 1. Hydrogen bonds in the active site of triose phosphate isomerase bound to an endiolate intermediate as indicated by computations.[9] The proposed LBHB is labeled.[10]

We have put forth a hydrogen-bonding network (HBN) alternative to the LBHB proposal that suggests that a network of multiple hydrogen-bond interactions can easily provide the required energy for enzyme-catalyzed transformations.[4,27] Primary (1°) hydrogen bonds, which we define as those between a charged center and a donor or acceptor group, typically are the strongest ones. Secondary (2°) and tertiary (3°) hydrogen bonds, which involve noncharged groups (Figure 2), are common, and their total energetic contributions

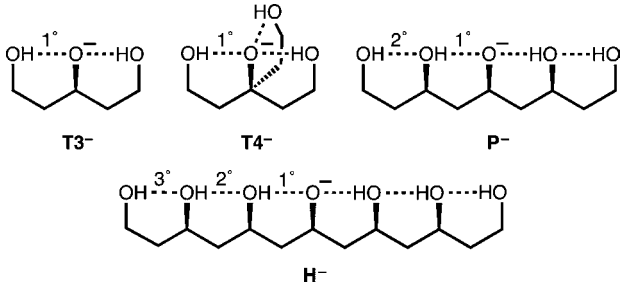


Figure 2. Most favorable hydrogen-bonding arrangements for the conjugate bases of several polyols and their different kinds of hydrogen bonds.

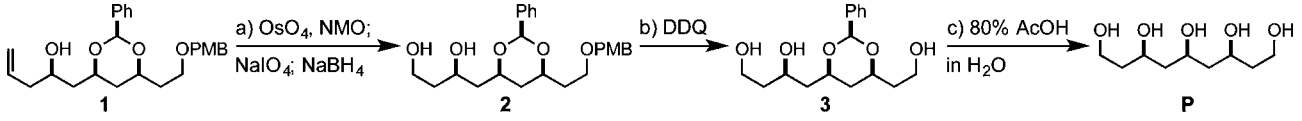
may be quite significant. To assess this hypothesis, a small covalently bound model compound was investigated by negative ion photoelectron spectroscopy in the gas phase and pK_a measurements in DMSO. This experimental work was supplemented with extensive computations to probe the energetic consequences of different types of hydrogen bonds in different environments. Large stabilizations (>15 kcal mol^{-1}) were found for two 2° hydrogen bonds between noncharged donor and acceptor groups, which can be energetically more important than an O$^-$···H−O interaction, and their importance is enhanced with a decrease in the polarity of the environment.

EXPERIMENTAL SECTION

General. ^{1}H and ^{13}C NMR spectra were recorded on Varian 400 and 500 MHz spectrometers, and the ^{1}H chemical shifts are reported relative to internal tetramethylsilane (0.00 ppm) or residual proton signals in the deuterated solvents (i.e., 7.26 ppm for $CDCl_3$ and 3.30 ppm for CD_3OD). For the ^{13}C data, CD_3OD and $CDCl_3$ at 49.05 and 77.2 ppm, respectively, were used as the reference signals. Infrared (IR) spectra were obtained with a Nicolet iS5 FT-IR spectrometer. Mass spectra were recorded with a Bruker BioTof II electrospray ionization time-of-flight mass spectrometer, and optical rotations were measured with a Jasco P-2000 digital polarimeter.

Flash column chromatography was performed on 60−200 or 230−400 mesh silica gel. Analytical thin-layer chromatography was performed with precoated glass-backed plates and visualized by quenching of fluorescence or by charring after treatment with *p*-anisaldehyde or potassium permanganate stain. Commercial reagents were used without purification unless otherwise noted, and the synthetic route for the preparation of pentaol **P** is provided in Figure 3.

*(R)-4-((2S,4R,6S)-6-(2-((4-Methoxybenzyl)oxy)ethyl)-2-phenyl-1,3-dioxan-4-yl)butane-1,3-diol (**2**).* To a stirred solution of **1**[28] (1.19 g, 2.89 mmol) in tetrahydrofuran (10 mL) at 0 °C was added osmium tetroxide (18.3 mg, 72.1 μmol), followed by *N*-methylmorpholine *N*-oxide (4.8 mol L^{-1}, 3.0 mL, 14.5 mmol) in water. The resulting mixture was warmed to room temperature and stirred for 3 h. The mixture was cooled to 0 °C, and $NaIO_4$ (3.09 g, 14.5 mmol) was added in one portion. After 1 h, $NaBH_4$ (2.19 g, 57.8 mmol) was added slowly at 0 °C. After an additional 5 min, the reaction was quenched by adding water (10 mL). The mixture was filtered through Celite, and the filtrate was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (60 to 100% EtOAc in hexanes) on silica gel (40 mL) to afford **2** (0.823 g, 69%) as a colorless oil. R_f = 0.20 (80% EtOAc in hexanes); $[\alpha]_D^{20}$ = −18.4 (CH_2Cl_2, *c* = 1.85). IR (neat) 3387, 2941, 2917, 2863, 1611, 1512, 1453, 1342, 1245, 1174, 1099, 1027 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42−7.40 (m, 2H), 7.37−7.33 (m, 3H), 7.25 (d, *J* = 8.5 Hz, 2H), 5.86 (d, *J* = 8.5 Hz, 2H), 5.55 (s, 1H), 4.46 (d, *J* = 11.5 Hz, 1H), 4.43 (d, *J* = 11.5 Hz, 1H), 4.19 (dddd, *J* = 9.5, 7.0, 4.5, 2.5 Hz, 1H), 4.13 (dddd, *J* = 11.0, 11.0, 3.0, 3.0 Hz, 1H), 4.05 (dddd, *J* = 11.0, 8.0, 4.5, 2.5 Hz, 1H), 3.85−3.80 (m, 2H), 3.78 (s, 3H), 3.65 (ddd, *J* = 9.5, 8.0, 5.0 Hz, 1H), 3.67 (br, 1H), 3.55 (ddd, *J* = 9.5, 5.5, 5.5 Hz, 1H), 2.72 (br s, 1H), 1.95−1.79 (m, 3H), 1.75−1.69 (m, 2H), 1.65 (ddd, *J* = 14.5, 2.5, 2.5 Hz, 1H), 1.60 (ddd, *J* = 13.0, 2.5, 2.5 Hz, 1H), 1.50 (ddd, *J* = 13.0, 11.0, 11.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 138.3, 130.6, 129.5, 129.0, 128.4, 126.1, 113.9, 100.8, 77.6, 74.0, 72.8, 71.6, 65.6, 61.4, 55.4, 42.9, 38.8, 37.2, 36.1. HRMS (ESI): calcd for $C_{24}H_{32}O_6Na$ [M + Na]$^+$ 439.2091, found 439.2094.



Reagents and conditions: a) OsO_4, NMO, THF, 0 °C to rt; $NaIO_4$, 0 °C; $NaBH_4$, 0 °C, 69%. b) DDQ, CH_2Cl_2, H_2O, 0 °C, 43%. c) AcOH/H_2O (4:1), 80 °C, 22%.

Figure 3. Synthetic route for the preparation of pentaol **P**.

*(R)-4-((2S,4R,6S)-6-(2-Hydroxyethyl)-2-phenyl-1,3-dioxan-4-yl)-butane-1,3-diol (**3**).* To a stirred solution of **2** (0.660 g, 1.59 mmol) in dichloromethane (8 mL) at 0 °C was added water (0.4 mL), followed by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1.08 g, 4.75 mmol) under N_2. The resulting mixture was stirred at the same temperature for 2 h. The reaction mixture was quenched by adding saturated aqueous sodium bicarbonate (20 mL) and filtered through a pad of Celite. The filtrate was extracted with EtOAc (3 × 30 mL), and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (1 to 10% MeOH in EtOAc) on silica gel (40 mL) to afford **3** (0.203 g, 43%) as a colorless oil. R_f = 0.26 (10% MeOH in EtOAc); $[\alpha]_D^{19}$ = +1.6 (CH_2Cl_2, c = 0.64). IR (neat) 3341, 2923, 2871, 1453, 1406, 1343, 1215, 1102, 1057, 1027 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.44−7.42 (m, 2H), 7.38−7.33 (m, 3H), 5.59 (s, 1H), 4.21−4.15 (m, 2H), 4.15−4.09 (m, 1H), 3.87−3.78 (m, 4H), 3.55 (br s, 1H), 2.71 (br s, 1H), 2.10 (br s, 1H), 1.93−1.87 (m, 2H), 1.84−1.78 (m, 1H), 1.74−1.70 (m, 2H), 1.66 (ddd, J = 15.0, 3.0, 3.0 Hz, 1H), 1.63−1.56 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 129.2, 128.6, 126.1, 101.0, 77.6, 75.9, 71.5, 61.4, 60.1, 42.9, 38.8, 38.1, 37.1. HRMS (ESI): calcd for $C_{16}H_{24}O_5Na$ $[M + Na]^+$ 319.1516, found 319.1526.

*Nonane-1,3,5,7,9-pentaol (**P**).* To a flask with **2** (0.456 g, 1.54 mmol) was added a solution of acetic acid (8 mL, 80%) in water. The resulting mixture was heated to 90 °C and stirred for 1 h. The solvent was removed under reduced pressure, and the resulting residue was purified by flash chromatography (2−20% MeOH in EtOAc) on silica gel (30 mL) to afford **P** (70.0 mg, 22%) as a colorless oil. R_f = 0.44 (30% MeOH in EtOAc). IR (neat) 3342, 2955, 2925, 2854, 1734, 1647, 1508, 1457, 1260, 1107 cm^{-1}. ^1H NMR (500 MHz, CD_3OD) δ 3.98 (dddd, J = 7.5, 7.5, 5.0, 5.0 Hz, 1H), 3.93 (dddd, J = 9.0, 9.0, 4.5, 4.5 Hz, 2H), 3.69 (t, J = 6.5 Hz, 4H), 1.72 (dddd, J = 14.0, 7.0, 7.0, 4.0 Hz, 2H), 1.66−1.56 (m, 6H). ^{13}C NMR (100 MHz, CD_3OD) δ 70.2, 68.8, 60.1, 45.5, 41.0. HRMS (ESI): calcd for $C_9H_{20}O_5Na$ $[M + Na]^+$ 231.1203, found 231.1201.

pK_a Determination. The acidity of $(HOCH_2CH_2CH(OH)CH_2)_2CHOH$ (**P**) was measured in dry DMSO at room temperature (22 °C) by ^1H NMR spectroscopy as previously described.[4] Potasium was used as the counterion (i.e., KH was used to generate dimsyl anion), 1-acetylindolin-2-one (pK_a = 13.5)[29] was used as the reference indicator, and five independent determinations were carried out to obtain the pK_a of the pentaol. In all of these experiments a low concentration of the polyol was used (i.e., 1 mM) to minimize ion pairing and self-association of the acid.

Photoelectron Spectroscopy. A low-temperature photoelectron spectrum of the conjugate base of $(HOCH_2CH_2CH(OH)CH_2)_2CHO^-$ ($\mathbf{P}^-$) was recorded at 20 K with a photoelectron spectrometer that has been previously described.[30] The conjugate base of the pentaol was generated by electrospray ionization from an ~10^{-3} M methanol−water solution, and the mass selected ion was photoirradiated with a F_2 excimer laser at 157 nm (7.867 eV) operating at 20 Hz to enable shot-to-shot background subtraction. Photoelectrons were collected with nearly perfect efficiency and analyzed with a 5.2 m long electron flight tube. This provided spectra with a resolution (ΔE/kinetic energy) of ~2% or 50 meV at 5 eV binding energy.

Computations. Monte Carlo and systematic conformational searches were carried out with Spartan 08 using the MMFF force field.[31] B3LYP/6-311+G(d,p)[32,33] and M06-2X/maug-cc-pVT(+d)Z[34−37] single point energy calculations were subsequently carried out with Gaussian 09[38] on all of the structures that were found within 7 kcal mol^{-1} of the most stable one. Full geometry optimizations and frequency calculations were then carried out on all of the species within 5 kcal mol^{-1} of the most favorable conformer using both density functional theory approaches. For computing the vertical and adiabatic detachment energies (i.e., VDEs and ADEs, respectively), both the anions and radicals were reoptimized with the B3LYP functional and the aug-cc-pVDZ basis set, and M06-2X/maug-cc-pVT(+d)Z single point energies were obtained too. The resulting ADEs are reported at 0 K.

Liquid-phase pK_a values in various solvents were computed relative to methanol at 298 K using the conductor-like polarized continuum model (CPCM).[39,40] Single point energies were obtained with the B3LYP/6-311+G(d,p) and M06-2X/maug-cc-pVT(+d)Z methods on their optimized gas-phase structures. The "iterative", "maxExtIt=1000", "mxIter=1000", and "QConv=VeryTight" keywords were employed to solve the PCM electrostatic problem and to compute the polarization charges to a convergence threshold of 10^{-12} within 1000 steps. For DMSO, 70 surface elements (tesserae) and an area of 0.2 Å for each sphere were used, whereas the default parameters were employed for the other solvents. All of the relative pK_a values in each solvent were adjusted to the DMSO scale by setting the pK_a of methanol to 29.0.

RESULTS AND DISCUSSION

To probe the energetic consequences of 1° and 2° hydrogen bonds, the all *syn*-pentaol $[(HOCH_2CH_2CH(OH)CH_2)_2CHOH$, **P**] was synthesized by a three step route starting from a previously reported precursor (Figure 3).[28] Electrospray ionization of the pentaol from an aqueous methanolic solution afforded the $(M - 1)^-$ ion ($\mathbf{P}^-$), and its photoelectron spectrum was recorded at 20 K using a F_2 excimer laser producing 157 nm (7.867 eV) photons (Figure 4). The spectrum is qualitatively similar to the previously

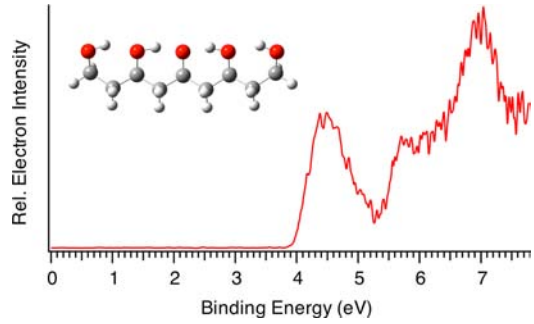


Figure 4. Low-temperature (20 K) photoelectron spectrum of pentaol $\mathbf{P}^-$ at 157 nm (7.867 eV).

reported one for the conjugate base of the related triol (i.e., $(HOCH_2CH_2)_2CHOH$, **T3**),[41] but the electron binding energy of $\mathbf{P}^-$ is much larger and additional bands at higher energies corresponding to excited states of the photoproduced radical are observed. A linear extrapolation of the onset region provides the adiabatic detachment energy (ADE), and the top of the first band gives the vertical detachment energy (VDE). These values are 4.05 and 4.45 eV, respectively, for $\mathbf{P}^-$ and are remarkable in that the ADE is larger than that for the conjugate bases of strong acids such as acetic, hydrochloric, and nitric acids (i.e., 3.470 ± 0.010, 3.613577 ± 0.000044, and 3.937 ± 0.014 eV, respectively).[42−44]

There are three different hydroxyl groups in the pentaol at C1, C3, and C5 that could be deprotonated, but as expected the central alkoxide at C5 is predicted to be the most stable conjugate base (Figure 2). Its structure has two 1° and two 2° hydrogen bonds and is predicted to be 3.3 kcal mol^{-1} more stable than the alternative C3-deprotonated 2° alkoxide at the B3LYP/aug-cc-pVDZ level; the most stable conformer of the C3 deprotonated alcohol distorts from the linear structure to form three primary hydrogen bonds to the alkoxide center and one secondary hydrogen bond between two noncharged hydroxyl groups. The computed B3LYP/aug-cc-pVDZ, M06-2X/maug-cc-pVT(+d)Z//B3LYP/aug-cc-pVDZ, and M06-2X/maug-cc-pVT(+d)Z ADEs for $\mathbf{P}^-$ are 3.69, 3.80, and 3.82 eV,

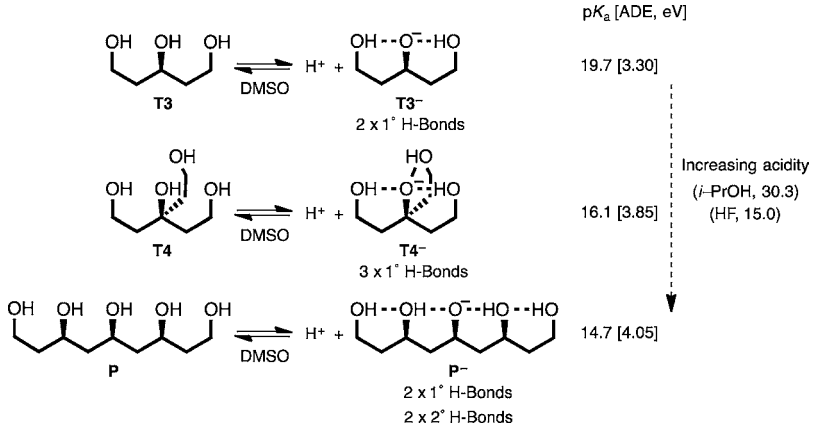


Figure 5. DMSO acidities of polyols **T3**, **T4**, **P**, and reference acids (*i*-PrOH and HF) along with select ADEs of their conjugate bases.

Table 1. Calculated pK_a Values for Triol T3 and Pentaol P in Solvents with Different Dielectric Constants[a]

		B3LYP/6-311+G(d,p)			M062X/maug-cc-pVT(+d)Z		
solvent	ε[b]	**T3**	**P**	Δ(**T3**−**P**)	**T3**	**P**	Δ(**T3**−**P**)
DMSO	46.8	16.9	14.4	2.5	17.3[19.7][c]	14.5[14.7][c]	2.8
acetone	20.5	18.5	15.9	2.6	16.9	14.0	2.9
CH_2Cl_2	8.9	17.6	14.5	3.1	16.0	12.7	3.3
THF	7.4	17.2	14.0	3.2	15.7	12.2	3.5
$CHCl_3$	4.7	16.0	12.3	3.7	14.5	10.5	4.0
benzene	2.3	12.6	7.3	5.3	11.1	5.5	5.6

[a]All of acidities were computed relative to methanol, which has an experimental pK_a of 29.0 in DMSO (ref 45). This value was also used as the anchor point in all of the other solvents (i.e., all of the relative acidities were scaled so that pK_a(CH_3OH) = 29.0 in each solvent). [b]See ref 38. [c]Experimental values are given in brackets; see ref 4 for the value for **T3**.

respectively, all of which reproduce the experimental result with accuracies that previously have been noted.[41]

The strength of the hydrogen-bond network (HBN) in $\mathbf{P}^-$ can be assessed by comparing its ADE to appropriate reference ions. For example, its ADE is 0.2 eV (4.6 kcal mol^{-1}) larger than for $(HOCH_2CH_2)_3CO^-$ ($\mathbf{T4}^-$, ADE = 3.85 eV),[41] which reveals that in this case two 1° and two 2° hydrogen bonds are more effective than three 1° hydrogen bonds. In other words, two 2° hydrogen bonds can exceed the strength of one strong ionic hydrogen bond. If one also compares $\mathbf{P}^-$ and $\mathbf{T3}^-$ (ADE = 3.30 eV),[41] the 0.75 eV (17.3 kcal mol^{-1}) difference provides a direct measure of the total cooperative effect due to the presence of the two primary hydroxyl groups in the former ion. Consequently, a 2° hydrogen bond in $\mathbf{P}^-$ enthalpically can be considered to be worth 8.6 kcal mol^{-1} in the gas phase.

To assess the energetics of 2° hydrogen bonds in condensed media, the pK_a of the pentaol was measured in DMSO relative to 1-acetylindolin-2-one (pK_a = 13.5).[29] Five independent determinations of the equilibrium constant gave pK_a (**P**) = 14.7 ± 0.1, which is a striking result since it indicates that the pentaol is more acidic than hydrofluoric acid (pK_a = 15.0, Figure 5).[45] In accord with the gas phase results based upon the ADE determinations, the pentaol is 1.4 pK_a units (1.9 kcal mol^{-1}) more acidic than $(HOCH_2CH_2)_3COH$ (**T4**, pK_a = 16.1 ± 0.2). This indicates that 2° hydrogen bonds are also important and provide a significant amount of stabilization in DMSO. By comparing the pK_a's of **P** and **T3** (19.7 ± 0.2),[4] the free energy of the 2° hydrogen bonds can be viewed to be worth 2.5 pK_a units (3.4 kcal mol^{-1}) or 40% of the enthalpic value in the gas phase, and this difference largely can be attributed to the entropy. The nominal strength of the 1° hydrogen bonds is additive in DMSO [i.e., 1/2 pK_a ($(CH_3)_2CHOH$ − **T3**) ≅ 1/3 pK_a ($(CH_3)_3COH$ − **T4**)], and they are worth 5.3 pK_a units (7.2 kcal mol^{-1}) per hydrogen bond; the pK_a's of isopropanol and *tert*-butanol are 30.3 and 32.2 in DMSO.[45] The 1° interactions consequently are worth about twice as much as the 2° ones in these compounds. A total stabilization of 15.6 pK_a units (21.1 kcal mol^{-1}) results from all four hydrogen bonds in $\mathbf{P}^-$, and this is large enough to account for the missing energy that originally led to the LBHB proposal, even though no single hydrogen bond contributes more than 7.2 kcal mol^{-1}.

Dimethyl sulfoxide has a large dielectric constant (ε = 46.8),[38] and while it stabilizes cations more effectively than anions, the HBN in $\mathbf{P}^-$ undoubtedly is energetically more important in less polar media. In enzyme active sites the local dielectric constant varies from system to system, but values ranging from 3 to 35 are commonly cited[46−52] and are all smaller than for DMSO. Consequently, the pK_a's of **T3** and **P** were computed using the CPCM model in different solvents (Table 1). Both the B3LYP and M06-2X results are in excellent accord with the measured values in DMSO, and while the former predictions are 1.5−1.9 pK_a units larger than the latter ones in the other solvents, the differences between the two compounds are only 0.2−0.3 pK_a units. Both functionals indicate that the acidities of **T3** and **P** increase with a decrease in the dielectric constant of the solvent as anticipated. This change is 6.2 pK_a units (8.4 kcal mol^{-1}) for the triol in going from DMSO to benzene based upon the more reliable M06-2X values. Consequently, the nominal 1° hydrogen bond strength increases from 5.3 (expt) to a predicted value of 8.4 pK_a units (i.e., from 7.2 to 11.3 kcal mol^{-1}).[53] The acidity differences between **P** and **T3** indicate that the 2° hydrogen bonds also become stronger and can be viewed as going from 2.5 to 3.9

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pK_a units (i.e., from 3.4 to 5.3 kcal mol^{-1}).[54] As a result, all four hydrogen bonds in $\mathbf{P}^-$ provide a total stabilization of 24.6 pK_a units (31.9 kcal mol^{-1}) in benzene as opposed to 15.6 pK_a units (21.1 kcal mol^{-1}) in DMSO.

Given the strength of the 2° hydrogen bonds in $\mathbf{P}^-$, computations in DMSO were carried out on the all syn linear heptaol **H** to probe the effect of hydrogen bonds that are one "solvent shell" further removed from the formally charged center. The predicted pK_a for this model compound is 13.7 (B3LYP) and 13.4 (M06-2X), and the latter value is 1.1 pK_a units (1.5 kcal mol^{-1}) more acidic than **P**. In benzene the predicted pK_a is 5.1 (B3LYP) and 3.3 (M06-2X), and both values indicate that in this solvent **H** is 2.2 pK_a units (3.0 kcal mol^{-1}) more acidic than **P**. These results indicate that the 3° hydrogen bonds in **H** are worth ∼25% of the 2° ones in **P**. However, because a larger number of hydrogen bonds can be formed in each successive solvent shell, 3° interactions may make important contributions to the catalytic ability of enzymes in some instances.

CONCLUSIONS

Experimental and computational data on simple model polyhydroxyl alcohols reveal that hydrogen bonds to a charged center and those that are one solvent shell further away (i.e., 1° and 2° hydrogen bonds, respectively) both make significant energy contributions to the stability of their conjugate bases. The former interactions are stronger and provide 5.3 pK_a units of stabilization in DMSO, which increases to 8.4 pK_a units in benzene for the compounds studied herein. Secondary hydrogen bonds are weaker, but stabilizations of 2.5 (DMSO) and 3.9 (benzene) pK_a units per hydrogen bond were found for the linear pentaol **P**. Tertiary hydrogen bonds in the linear heptaol **H** are even weaker, yet they still contribute 0.6 (DMSO) and 1.1 (benzene) pK_a units per hydrogen bond. There are also opportunities for more than two 2° and 3° hydrogen bonds in the HBN around an enzyme active site. These polyol model compounds provide the requisite energy required for enzyme catalysis via a network of hydrogen bonds, none of which is unusually strong. The stabilization brought about by multiple bonds in a HBN consequently provides an alternative to the LBHB proposal. It also indicates that acid−base processes leading to formation or elimination of charged centers alters the strength of HBNs and provides a driving force for conformational changes including those involved in protein folding.

ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra along with computed geometries and energies are provided along with the complete citation to ref 38. 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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(54) This value (3.9 pK_a units) was obtained as follows: 1/2[pK_a (*i*-PrOH − **T3**)$_{expt}$ − (pK_a (**P**)$_{DMSO}$ − pK_a (**P**)$_{PhH}$)$_{calcd}$ + (pK_a (**T3**)$_{DMSO}$ − pK_a (**T3**)$_{PhH}$)$_{calcd}$].