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Preorganized Hydrogen Bond Donor Catalysts: Acidities and Reactivities

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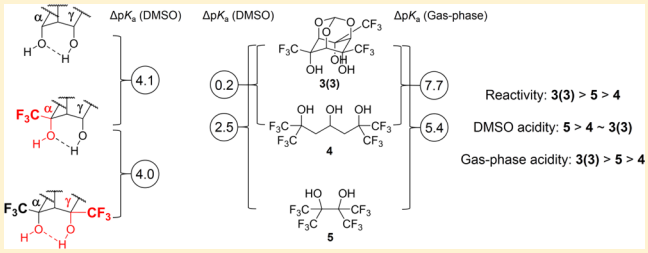
Supporting Information

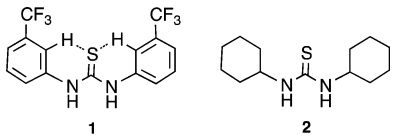
ABSTRACT: Measured DMSO pK_a values for a series of rigid tricyclic adamantane-like triols containing 0−3 trifluoromethyl groups (i.e., **3(0)**−**3(3)**) are reported. The three compounds with CF_3 substituents are similar or more acidic than acetic acid (pK_a = 13.5 (**3(1)**), 9.5 (**3(2)**), 7.3 (**3(3)**) vs 12.6 (HOAc)), and the resulting hydrogen bond network enables a remote γ-trifluoromethyl group to enhance the acidity as well as one located at the α-position. Catalytic abilities of **3(0)**−**3(3)** were also examined. In a nonpolar environment a rate enhancement of up to 100-fold over flexible acyclic analogs was observed presumably due to an entropic advantage of the locked-in structure. Gas-phase acidities are found to correlate with the catalytic activity better than DMSO pK_a values and appear to be a better measure of acidities in low dielectric constant media. These trends are reduced or reversed in polar solvents highlighting the importance of the reaction environment.



INTRODUCTION

Enzymes employ multiple stabilizing interactions such as inductive effects and hydrogen bond networks (HBNs) to control their structures and catalyze a wide variety of biochemical transformations.[1−7] For example, an array of hydrogen bonds has been implicated in playing a key role in the catalytic activity of ketosterioid isomerase by enhancing the acidity of the active site tyrosine residue from a pK_a value of 10.5 to 6.3.[2] Drawing inspiration from observations such as this, considerable effort has been expended mimicking enzyme behavior to develop more reactive and selective metal-free small molecule catalysts.[8−14] Thioureas play a particularly important role in this regard.[15−24]

Preorganization is well-known to play a critical role in enzyme catalysis but generally has not been exploited in the design of hydrogen bond catalysts.[1,25,26] Schreiner has proposed that weak C−H···S hydrogen bonds in bis(3-trifluoromethylphenyl)thiourea (**1**) and related species with strong electron-withdrawing groups (EWG) have enhanced populations of the reactive *Z,Z* conformers compared to dicyclohexylthiourea (**2**) and other derivatives that lack such substituents.[17] While the thioureas with EWG are found to be more active catalysts, this may be a reflection of their greater acidity rather than entropic effects due to preorganization. Unfortunately, suitable examples probing structural rigidity differences between compounds with the same acidity are lacking.[27,28]



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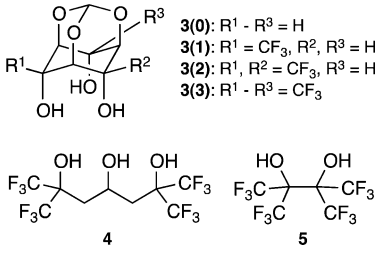
In this work the acidities of a series of adamantane-like triols **3(0)**−**3(3)**, where the parenthetical number indicates how many trifluoromethyl groups are present in the compound, were measured in DMSO. These results reveal that **3(3)** has the same acidity as **4** and is 1000-fold less acidic than **5**, but was found to be up to 2 orders of magnitude more effective as a catalyst than these flexible acyclic analogs. The effects of the CF_3 groups also revealed that highly distant dependent inductive effects can be transmitted over long distances via HBNs, and that gas-phase acidities appear to correlate with catalytic reaction rates in nonpolar media as well or better than DMSO pK_a values. In a polar environment the benefit of structural rigidity was found to be diminished and DMSO acidities provided a better guide to reactivity than those in the gas phase.



4 **5**

RESULT AND DISCUSSION

Inductive effects are commonly exploited in designing more efficient catalysts and host compounds in molecular recog-

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nition.[12,17,29−31] Their impact, however, falls off rapidly with distance. For example, by substituting a trifluoromethyl group for an α-hydrogen in methanol the aqueous and DMSO acidities are enhanced by 3.1 and 5.5 pK_a units, respectively, whereas CF_3 incorporation at the γ-position of 1-propanol lowers the pK_a values by only 0.7 (H_2O) and 1.2 (DMSO).[32,33] In contrast, a long-range inductive effect was recently proposed in the gas phase for triols **3(0)**−**3(3)** due to their HBNs.[34] To assess this situation in condensed media, their pK_a's were measured in DMSO.

Equilibrium acidities of **3(0)**, **3(2)**, and **3(3)** were determined as illustrated in eq 1 by ^{1}H NMR spectroscopy (Table 1).[35] Preliminary colorimetric titrations were also carried out for triol **3(1)**, and these experiments indicate that it is more acidic than 9-(phenylthio)fluorene (pK_a = 15.4) and less acidic than 9-(phenylsulfonyl)fluorene (pK_a = 11.5).[36,37] These bracketing results suggest that 13.0 < pK_a(**3(1)**) < 14.0, and so pK_a(**3(1)**) = 13.5 ± 0.5 was assigned. These measured acidities span a 10 pK_a unit range from 7.3 to 17.6 which indicates that these triols are up to 10^3- and 10^5-fold more acidic than perfluoro-*tert*-butanol (pK_a = 10.7) and acetic acid (pK_a = 12.6), respectively.[33] Even the least acidic of these four compounds (i.e., **3(0)**) is ∼13 orders of magnitude more acidic than an ordinary aliphatic alcohol such as 2-propanol (pK_a = 30.3) due to the HBN and inductive effect of the three oxygen atoms incorporated into the ring skeleton. It is also a stronger acid than 1,3,5-pentanetriol by 2.1 pK_a units and similar in acidity to phenol (pK_a = 18.0).[36]

Table 1. Experimental and Computed DMSO Acidities[a]

	pK_a		
compd	exptl	B3LYP[b]	M06-2X[c]
3(0)	17.6 ± 0.4	18.3	18.0
3(1)	13.5 ± 0.5	11.5	11.4
3(2)	9.5 ± 0.3	9.1	8.6
3(3)	7.3 ± 0.3	6.2	6.4
4	7.1 ± 0.3	10.4	8.0
5	4.8 ± 0.1	3.5	5.4
$(CF_3)_3COH$	10.7	10.9	12.3
avg error		1.3	1.1

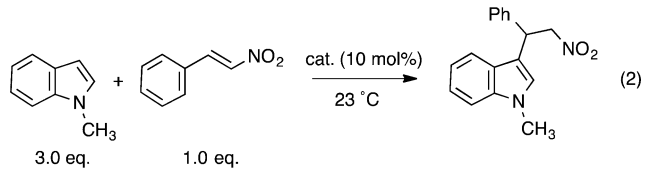
[a]Relative acidities were computed and the experimental pK_a of 1,1,1,3,3,3-hexafluoro-2-propanol (17.9; see ref 32b) was used to obtain the indicated values. [b]B3LYP = B3LYP/6-311+G(d,p). [c]M06-2X = M06-2X/maug-cc-pVT(+d)Z.

$$\mathrm{AH} + \mathrm{Ind}^- \overset{K}{\rightleftharpoons} \mathrm{A}^- + \mathrm{IndH}$$
$$\mathrm{p}K_a(\mathrm{AH}) = \mathrm{p}K_a(\mathrm{IndH}) - \log K \quad (1)$$

Substitution of one of the equatorial hydrogens in **3(0)** at a hydroxyl bearing carbon by a trifluoromethyl group increases the acidity of the resulting triol (i.e., **3(1)**) by 4.1 pK_a units. Subsequent additions of a second and third CF_3 substituent result in additional pK_a enhancements of 4.0 and 2.2. The effect of the first CF_3 group is not surprising since it presumably is attached to the carbon bearing the hydroxyl substituent that is ionized upon deprotonation (i.e., the α-carbon) and exerts a strong stabilizing inductive effect. In contrast, the second CF_3 group is separated from the formally charged site by three intervening carbons and is located at the γ carbon, so only a small inductive stabilization of ∼1.2 pK_a units would be expected in the absence of the HBN.[33] The large and additive nature of the second trifluoromethyl substituent can be viewed as a long-range inductive effect transmitted by the HBN. Equivalently, this effect can be ascribed to an enhanced hydrogen bond due to the presence of the added electron-withdrawing group. The effect of the remote substituent due to the HBN, consequently, is reminiscent of π-conjugation in that the consequence of an electron-withdrawing group is transmitted over a long distance. As for the third CF_3 substituent, it is less effective than the other two as one would expect for an increasingly stabilized and delocalized anion.

Computations of the DMSO acidities of **3(0)**−**3(3)** and related compounds were carried out using a polarized continuum model (Table 1). Both the B3LYP/6-311+G(d,p)[38,39] and M06-2X/maug-cc-pVT(+d)Z[40−43] results are in excellent accord with experiment in that the maximum errors are 3.3 (B3LYP) and 2.1 (M06-2X) pK_a units and the average unsigned errors are 1.3 and 1.1 pK_a units, respectively. If one uses perfluoro-*tert*-butanol instead of 1,1,1,3,3,3-hexafluoro-2-propanol as the reference acid, then there is little change in the results and the average errors are 1.3 (B3LYP) and 1.6 (M06-2X) pK_a units. For some unknown reason, however, when 2,2,2-trifluoroethanol is employed as the reference compound the average deviation from experiment increases to 4.1 pK_a units for both computational methods.

Triols **3(0)**−**3(3)** can serve as Brønsted acid and hydrogen bond catalysts. Their rigid structures should provide an entropic advantage over acyclic analogs and may enhance their catalytic abilities in an analogous manner to the preorganization of enzymes in biological systems. To assess this possibility, the Friedel−Crafts reaction between β-nitrostyrene and *N*-methylindole was investigated (eq 2). Triol **4**



(2)

and diol **5** were selected for comparison purposes because the former alcohol is as acidic as **3(3)** and the latter is even stronger.[29] In the presence of **3(3)** the reaction was almost complete in 16 h when carried out in toluene-d_8 at room temperature, and the second order half-life is 2.8 h (Table 2). Both **4** and **5** are much less efficient catalysts, and their transformations take place ∼100 and 10 times more slowly. No reaction was observed in the absence of a catalyst after 15 days, and consequently these results indicate that the DMSO acidities of these catalysts do not correlate with the reaction rates. In many respects this should not be surprising, as DMSO

Table 2. Kinetic Results for the Acid-Catalyzed Friedel−Crafts Reaction of *N*-Methylindole and β-Nitrostyrene

entry	cat.	solvent	t (h)	conv.[a]	$t_{1/2}$ (h)
1	no cat.	$C_6D_5CD_3$	360	no rxn	
2	**3(3)**	$C_6D_5CD_3$	16.3	96	2.8
3	**4**	$C_6D_5CD_3$	504	75	230
4	**5**	$C_6D_5CD_3$	96	95	22
5	**3(2)**	$C_6D_5CD_3$/1% CD_3CN	192	75	88
6	**3(3)**	$C_6D_5CD_3$/1% CD_3CN	49	94	10
7	**6**	$C_6D_5CD_3$/1% CD_3CN	168	62	110

[a]conv. = conversion (%).

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is a very polar solvent with a high dielectric constant whereas toluene is nonpolar and has a small dielectric constant (i.e., 47.2 vs 2.4, respectively).[44] Computed B3LYP/6-311+G(d,p) and M06-2X/maug-cc-pVT(+d)Z gas-phase acidities (Table 3), however, are in keeping with the observed reactivity order. This finding is consistent with our previous report showing that the acidities of a series of substituted phenols in a nonpolar solvent (CCl_4) are better correlated with their gas-phase acidities than their DMSO pK_a values.[45]

Table 3. Computed B3LYP/6-311+G(d,p) and M06-2X/maug-cc-pVT(+d)Z Gas-Phase Acidities

	ΔG°_{acid}	
compd	B3LYP	M06-2X
3(0)	327.6	326.9
3(1)	314.9	313.7
3(2)	307.8	306.4
3(3)	301.5	300.3
4	309.6	310.8
5	302.8	307.6

Solubility is an issue for **3(0)**–**3(2)**, as these compounds have fewer trifluoromethyl groups than **3(3)** and do not dissolve in toluene-d_8. To explore these species, a small amount of acetonitrile-d_3 (1% v/v) was added as a cosolvent. This enabled **3(2)** and Schreiner's thiourea ((3,5-$(CF_3)_2C_6H_3NH)_2CS$, **6**)[15] to be examined, but since CD_3CN is a hydrogen bond acceptor its presence was expected to slow down the reaction. This was observed for **3(3)** in that the presence of CD_3CN was found to retard the transformation by a factor of ~4 (entries 2 and 6, Table 2). Nevertheless, both **3(2)** and **3(3)** were found to be more effective catalysts than **6** despite the thiourea being more acidic than **3(2)** in DMSO (i.e., pK_a = 8.5 (**6**) and 9.5 (**3(2)**)).[30]

All four triols **3(0)**–**3(3)** catalyze the aminolysis of styrene oxide with aniline at 60 °C under solvent-free conditions (eq 3 and Table 4). Interestingly, the reactivity and selectivity orders follow the DMSO and not the gas-phase acidities. That is, in general the lower the pK_a value of the catalyst, the faster the reaction and the greater the selectivity for the addition product at the more hindered position (i.e., **7**). This presumably is due in large part to the buildup of positive charge at the more substituted carbon with increasing catalyst acidity and leads to more selective nucleophilic addition by aniline. As for the comparison of the two catalysts with the same pK_a's, rigid triol **3(3)** reacts ~1.5 times faster than its flexible variant **4**. This difference is much less than that for the Friedel–Crafts reaction and may be a reflection of the reaction medium polarity. That is, the presumed entropic benefit of a preorganized or rigid catalyst versus a flexible analog is enhanced in a nonpolar environment.

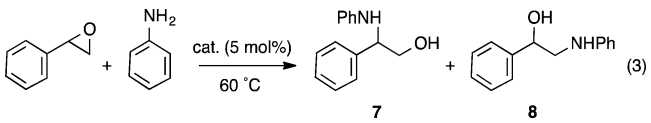

Table 4. Acid-Catalyzed Aminolysis of Styrene Oxide with Aniline

					pdt ratio (%)	
entry	cat.	time (h)	conv.[a]	k_{rel}	**7**	**8**
1	no cat.	3.5	4.0	1.0	35	65
2	**3(0)**	3.5	11	3.0	54	46
3	**3(1)**	3.5	58	33	75	25
4	**3(2)**	3.5	90	220	84	16
5	**3(3)**	1.0	96	580	91	9
6	**4**	0.5	69	370	81	19
7	**5**	0.25	68	710	88	12

[a]conv. = conversion (%).

Alcohols **3(0)**, **3(1)** and binol were examined as catalysts for the room temperature Morita–Baylis–Hillman reaction between hydrocinnamaldehyde and cyclohexanone in the presence of 2 equiv of tributylphosphine (eq 4). This transformation was essentially complete within 3.5 h when **3(0)** was employed whereas only 14% conversion was observed in double the time without the triol (Table 5). More acidic catalysts such as **3(1)** and binol, which is estimated to be ~3.9 pK_a units more acidic than **3(0)**,[46,47] were found to be less effective. This can be explained by deactivation of the catalysts by the presence of basic tributylphosphine and is not surprising since enhancing the acidity of a Brønsted acid or hydrogen bond catalyst in a chemical transformation that makes use of a base as a cocatalyst or a reagent that plays a role in the rate-determining step can have a deleterious effect on the reaction rate. As a result, **3(2)** and **3(3)** were not examined in this transformation.

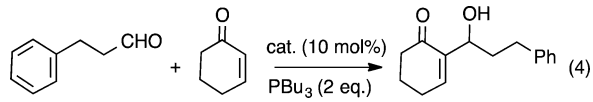

Table 5. Acid-Catalyzed Morita–Baylis–Hillman Results

entry	cat.	t (h)	conv.[a]	k_{rel}
1	no cat.	7	14	1.0
2	**3(0)**	3.5	98	9.8
3	**3(1)**	7	56	1.7
4	binol	7	98	4.9

[a]conv. = conversion (%).

CONCLUSION

Acidity measurements of the pK_a's of **3(0)**–**3(3)** were carried out in DMSO and reveal that an HBN is analogous to π-electron delocalization in that both can transmit charge-stabilizing effects over long distances. More specifically, incorporation of a CF_3 group at a hydroxyl bearing carbon in **3(0)** (i.e., the α-carbon) enhances the acidity by 4.1 pK_a units and the addition of a remote second CF_3 substituent at one of the γ-carbons leads to the same increase in acidity (i.e., 4.0 pK_a units). These rigid triols also serve as Brønsted acid and hydrogen bond catalysts in organic transformations. Their reactivity was compared to flexible analogs of similar or greater acidity, and in a nonpolar environment the locked-in triols were found to lead to rate enhancements as large as 100-fold. The relative reactivity order was also found to correlate with the catalysts gas-phase acidities (ΔG°_{acid}) and not their DMSO pK_a values. This finding taken together with a previous report showing that the acidities of substituted phenols in CCl_4 are better fit by ΔG°_{acid} than their DMSO pK_a's[47] suggests that this is a general observation. In a polar medium the observed

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benefit of a rigid versus a flexible catalyst was greatly diminished, and DMSO pK_a values are a better guide to reactivity than gas-phase acidities.

EXPERIMENTAL SECTION

General. Compounds **3(0)**−**3(3)** and **4** were synthesized as previously described.[29,34,48] Molecular sieves (3 Å) were activated at 320 °C overnight and then used to dry solvents over the course of a few days. DMSO and DMSO-d_6 were degassed by carrying out three freeze−pump−thaw cycles and stored over freshly activated molecular sieves in a drybox under a nitrogen atmosphere for up to several days before use. NMR tubes, vials, and flasks were oven-dried and kept in a drybox along with needles, syringes, and NMR caps. Pentane was dried over P_2O_5 at reflux for 1 h and subsequently distilled. Dimsyl potassium (i.e., KCH_2SOCH_3) was prepared daily under argon by reacting DMSO for 45 min with a 30% suspension of potassium hydride in mineral oil that had been washed 3 times with dry pentane. A 500 MHz NMR spectrometer was used to record ^{1}H spectra at 295 K.

Acidity Determinations. The acidities of triols **3(0)**, **3(2)**, and **3(3)** were measured in dry DMSO at 23 °C by ^{1}H NMR as previously described.[36] Multiple measurements were performed for each compound using one of the following indicators: 1,2,2-triphenylethanone (pK_a = 18.8), 9-carbomethoxyfluorene (pK_a = 10.3), or (9-fluorenyl)triphenylphosphonium bromide (pK_a = 6.6).[37] Alcohol **3(1)** was examined by carrying out colorimetric titrations with 9-(phenylthio)fluorene (pK_a = 15.4) and 9-(phenylsulfonyl)fluorene (pK_a = 11.5) in both the forward and reverse directions.[33] Since the conjugate bases of these two indicators give colored solutions, it was possible to determine the favored direction and the relative magnitude of the equilibrium constant in both instances (i.e., ≤ 1 or ≥ 1). DMSO acidity values for additional compounds are provided in the Supporting Information.

Friedel−Crafts Reactions. In a capped NMR tube, 0.0075 g (0.050 mmol) of β-nitrostyrene and 10 mol % of the catalyst (0.0050 mmol) were dissolved in 0.58 mL of the solvent under argon. *N*-Methylindole (19 μL, 0.020 g, 0.15 mmol) was syringed into the NMR tube at 23 °C, and the reaction progress was monitored using the ^{1}H NMR signals at 8.04 and 5.23 ppm for the limiting reactant and the Friedel−Crafts product, respectively. A second-order kinetic expression (i.e., $\ln([N\text{-methylindole}][\beta\text{-nitrostyrene}]_o/[\beta\text{-nitrostyrene}][N\text{-methylin-dole}]_o) = k([N\text{-methylindole}]_o - [\beta\text{-nitrostyrene}]_o)t$) was used to fit the data and obtain both the rate constants and the first half-lifes for the disappearance of β-nitrostyrene.

Aminolysis of Styrene Oxide. In a 0.5 dram vial, 23 μL (0.024 g, 0.20 mmol) of styrene oxide, 18 μL (0.018 g, 0.20 mmol) of aniline, and 5 mol % (0.010 mmol) of the catalyst were mixed together at 60 °C. Reaction progress was qualitatively monitored by TLC (20/80 EtOAc/hexanes) on 250 mm 60 F-254 silica gel plates. At select times aliquots were withdrawn and dissolved in 0.60 mL of $CDCl_3$, and their ^{1}H NMR spectra were obtained. Reaction progress was determined using chemical shifts at 2.82 (styrene oxide), 4.52 and 4.95 ppm (products).

Morita−Baylis−Hillman Transformations. Cyclohexenone (48 μL, 0.048 g, 0.50 mmol), hydrocinnamaldehyde (33 μL, 0.034 g, 0.25 mmol), and 10 mol % (0.025 mmol) of the catalyst were dissolved in 0.25 mL of THF-d_8 under argon in a capped NMR tube. Tributylphosphine (130 μL, 0.11 g, 0.52 mmol) was added via syringe at room temperature, and the reaction progress was monitored as a function of time by monitoring the disappearance of the aldehyde signal at 9.73 ppm and the appearance of the product at 7.04 ppm in the ^{1}H NMR spectra.

Computations. All of the calculations carried out in this work were performed at the Minnesota Supercomputer Institute for Advanced Computational Research using Gaussian 09.[49] Full geometry optimizations and vibrational frequencies were carried out on triols **3(0)**−**3(3)** and their conjugate bases with the B3LYP density functional and the 6-31+G(d,p) basis set.[38,39] The most stable conformers located were reoptimized with the larger 6-311+G(d,p) basis set as well as with the M06-2X functional and the aug-cc-pVDZ basis set.[40−42,50] Vibrational frequencies were recomputed with the latter method, and in this case single-point energies were subsequently carried out with the maug-cc-pVT(+d)Z basis set.[43] Conductor-like polarized continuum model (CPCM)[51,52] B3LYP/6-311+G(d,p) and M06-2X/aug-cc-pVT(+d)Z single point energies were also computed to obtain free energies and relative DMSO pK_a values at 298 K. These results were converted to absolute values by using 1,1,1,3,3,3-hexafluoro-2-propanol as a reference compound and employing its experimentally measured pK_a of 17.9.[32]

ASSOCIATED CONTENT

Supporting Information

Kinetic data, estimated acidities, and computed geometries and energies are provided along with the complete citation to ref 49. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01475.

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Notes

The authors declare no competing financial interest.

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