Table III. ^{1}H NMR Chemical Shifts (ppm) for Three Characteristic Protons from (*R*)-(+)-MTPA Derivatives [RCH(O-MTPA)COOCH$_3$] of 2-Hydroxy Acids

acids	AC[a]	CH_3OOC	CH_3O	CH_3CH_2
$CH_3CH_2CH(OH)COOH$	*R*	3.77	3.63	0.87
	S	3.73	3.55	0.99
$CH_3CH_2CH_2CH(OH)COOH$	*R*	3.77	3.63	0.84
	S	3.73	3.55	0.92
$(CH_2)_2CHCH(OH)COOH$	*S*	3.75	3.57	
$C_6H_5CH_2CH(OH)COOH$	*R*	3.75	3.54	
	S	3.75	3.31	

[a] AC, absolute configuration.

(d, J = 7 Hz, 1 H), 1.17 (m, 1 H), 0.57 and 0.46 (md, 4 H); ^{13}C NMR (CD_3COCD_3) δ 175.8, 72.6, 15.3, 2.0, 1.9; MS, m/e 117.054 78 (calcd for $C_5H_5O_3$, 117.055 16).

(*S*)-3-Phenyllactic Acid (28). Run 5. The synthesis of **28** was performed on a 15-mmol scale using the procedure for run 2. The starting materials comprised 15 mmol of phenylpyruvic acid, 19 mmol of sodium formate, 0.1 mmol of NAD, 1.5 mmol of Tris, and 0.3 mmol of mercaptoethanol. The reaction was stopped when 13.3 mL of 1.14 N HCl had been added (8 days). The products obtained as white solids weighed 2.43 g (14.6 mmol, 96%): mp 124-125 °C (lit.[34] mp 124-125 °C); ^{1}H NMR ($CDCl_3$) δ 7.26 (m, 5 H), 5.23 (br s, 2 OH), 4.4 (dd, 1 H), 3.18 (dd, 1 H), 2.97 (dd, 1 H); MS, m/e 167.071 37 (calcd for $C_9H_{10}O_3$, 167.0781).

(*R*)-(+)-MTPA Derivatives of 2-Hydroxy Acids. The MTPA derivatives were synthesized as described elsewhere.[30] The 2-hydroxy acids were methylated with diazomethane in ether to the corresponding methyl esters, which were treated with (*S*)-(+)-MTPA-Cl in CCl_4-benzene in the presence of 3-(dimethylamino)propylamine to obtain the corresponding MTPA derivatives. ^{1}H NMR chemical shifts for some characteristic protons are summarized in Table III.

Determination of Enantiomeric Excess by ^{1}H NMR Spectroscopy. (*S*)-2-Hydroxy Acids. For calibration, five samples were prepared by mixing 0.5 mL of $CDCl_3$ and 15 μL of one of the following: (1) the MTPA derivative of **25**; (2) the MTPA derivative of racemic **25**; (3) **1**, with 1% of **2**; (4) **1**, with 2% of **2**; (5) **1**, with 33% of **2**. The minor enantiomer could be detected at 0.5% of the major enantiomer. The enantiomeric excess was determined on the basis of the difference in chemical shift for methoxy protons.

(*S*)-1-Butene Oxide. For calibration, five samples were prepared by mixing 60 μL of Eu(hfc)$_3$ (100 mg/mL $CDCl_3$), 0.5 ml of $CDCl_3$, and 10 μL of one of the following: (1) **32** only; (2) racemic **32** only; (3) **1**, with 2% of **2**; (3) **1**, with 4% of **2**; (4) **1**, with 6% of **2**. One percent of the minor enantiomer could be detected.

(*S*)-1-Butene Oxide (32). An oven-dried 300-mL three-necked round-bottomed flask fitted with a silicon stopper, magnetic stirring bar, dropping funnel, and reflux condenser was cooled to room temperature under nitrogen. Compound **25** (15 g, 144 mmol), from run 2, was dissolved in dry THF (80 mL) and transferred into the flask with a long cannula under nitrogen. The flask then was cooled to 0 °C in an ice-ethanol bath. The borane solution in THF (1 M, 260 mL) was placed in the dropping funnel and added dropwise over 2 h. The mixture was allowed to stir under nitrogen at room temperature for 20 h. A water-THF mixture (1:1, 60 mL) was slowly added to hydrolyze the unreacted hydrides. The heterogeneous mixture was stirred until no more gas evolution occurred and poured into cold, saturated, aqueous Na_2CO_3 solution (100 mL). The organic layer was separated and the aqueous layer extracted 4 times with 100-mL portions of THF. The combined organic phase was dried over anhydrous $MgSO_4$ and evaporated. The residue was distilled at reduced pressure (9 Torr) to obtain diol **29** (11.7 g, 91%): bp 94-96 °C [lit.[35] bp 90-95 °C (6 Torr)]; $[\alpha]^{23}_D$ -15.35° (c 2.6, EtOH)[lit.[35] $[\alpha]^{22}_D$ -12.87° (c 2.6, EtOH)]; IR (neat) ν_{max} 3330 (s), 2960 (s), 2920 (s), 2870 (s), 1460 (s), 1120 (s), 1050 (s), 980 (s), 910 (m), 855 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.61 (m, 2 H), 3.41 (m, 1 H), 2.74 (br s, 2 OH), 1.44 (m, 2 H), 0.93 (t, J = 7.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 73.4, 65.8, 26.0, 9.7.

A three-necked, 100-mL, round-bottomed flask fitted with a magnetic stirring bar, dropping funnel, and reflux condenser was charged with the diol **29** (11.5 g, 128 mmol). The flask was cooled to -15 °C in an ice-ethanol bath. A solution of 30% HBr-AcOH (97 mL, 345 mmol) was added from the dropping funnel at -15 °C over 30 min. The yellow homogeneous mixture was stirred at -15 °C for 1 h and then at room temperature for 1.5 h. The solution was poured into ice-water (200 mL) and neutralized immediately with solid Na_2CO_3 (92 g). A yellow oil separated to the bottom. The heterogeneous mixture was extracted once with a 200-mL portion and twice with 100-mL portions of ether. The combined ethereal phase was washed twice with aqueous $NaHCO_3$ solution and once with brine, dried over anhydrous $MgSO_4$, and evaporated. The yellow, oily residue was distilled at reduced pressure (9 Torr) to obtain colorless product **31** (22.3 g, 116 mmol, 91%). [The ^{1}H NMR spectrum indicated that the product contained 7% 1-acetoxy-2-bromobutane (**30**)]: bp 68-70 °C [lit.[35] bp 85-86 °C (25 Torr)]; $[\alpha]^{23}_D$ -23.16° (c 4.14, ether) [lit.[35] $[\alpha]^{23}_D$ -21.2° (c 3.54, ether)]; IR (neat) ν_{max} 2970 (s), 2920 (m), 2880 (m), 1740 (s), 1460 (m), 1430 (m), 1370 (s), 1230 (s), 1170 (m), 1020 (s), 960 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.91 (q, J = 5.9 Hz, 1 H), 3.45 (ddd, 2 H), 2.07 (s, 3 H), 1.69 (m, 2 H), 0.90 (t, J = 7.45 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.3, 73.5, 33.5, 25.5, 20.8, 9.2.

To a three-necked, 250-mL, round-bottomed flask equipped with a magnetic sitrring bar, pressure-equalizing dropping funnel, and 10-cm Vigreux column connected to an efficiently cooled condenser and receiver was added compound **31** (22.1 g, 115 mmol) in dry 1-pentanol (20 mL) followed by the slow addition of potassium pentylate (1.18 N, 97.1 mL, 115 mmol) from the dropping funnel with stirring at room temperature over 30 min. A white precipitate of potassium bromide formed. After the addition was complete, the flask was warmed in an oil bath at ca. 140-150 °C to attain distillation. Colorless fractions in the range of 59-62 °C were collected to give **32** (5.86 g, 81.2 mmol, 71%) (to distill off only the desired product and ensure >90% yield, the Vigreux column should be cooled frequently with a hair dryer during distillation): bp 59-62 °C (lit.[35] bp 62-63 °C); $[\alpha]^{23}_D$ -11.2° (c 4.9, dioxane) [lit.[36] $[\alpha]^{16}_D$ -12.25° (c 6, dioxane)]; ^{1}H NMR ($CDCl_3$) δ 2.87 (m, 1 H), 2.72 (dd, 1 H), 2.45 (dd, 1 H), 1.53 (dq, 2 H), 0.98 (t, J = 7.50 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 53.10, 46.4, 25.3, 9.41.

(35) Mori, K.; Sasaki, M.; Tamada, S.; Sugaro, T.; Masuda, S. *Tetrahedron* **1979**, *35*, 1601.

(36) Schmidt, U.; Talbiersky, J.; Bartkowiak, F.; Wild, J. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 198.

Acidities of Anilines in Dimethyl Sulfoxide Solution

Frederick G. Bordwell* and Donald J. Algrim

Contribution from the Department of Chemistry, Northwestern University, Evanston, Illinois 60208. *Received June 22, 1987*

Abstract: The equilibrium acidities of aniline and 26 of its derivatives have been measured in Me_2SO solution by an overlapping indicator method. The pK_a's cover a range of 14.8 units, from 2,4-dinitroaniline (pK_a = 15.9) to aniline (pK_a = 30.7). A comparison with values obtained by the H_- method for anilines, and also for fluorene carbon acids, is made and discussed. The pK_a values for anilines in Me_2SO are about 10 units higher than the ion pair pK_a's reported in liquid ammonia due in part to the superior ability of NH_3 to solvate the proton. A Hammett plot for 5 meta points and hydrogen gave ρ = 5.67. Points for 4-PhS, 4-CF_3, 4-$MeSO_2$, 4-$PhSO_2$, 4-MeCO, 4-PhCO, 4-CN, 4-F_3CSO_2, and 4-NO_2 deviated significantly from this line. The deviations are the result in part of enhanced solvation of the substituents resulting from direct conjugation with the anilide ion. These substituent solvation assisted (SSAR) effects contribute significantly to the need for σ^- constants in Hammett correlations. A pK_a = 56 in Me_2SO is estimated for CH_4 by extrapolation; similar extrapolations place the pK_a of $PhCH_3$ at 43 and that of NH_3 at 41.

The first acidity measurement of aniline appears to be that of McEwen using a method developed by Conant and Wheland. He assigned an ion pair pK_a of 27 to aniline in benzene, relative to MeOH in benzene, which was arbitrarily given an ion pair pK_a

0002-7863/88/1510-2964$01.50/0

of 16.[1] The acidities of a number of substituted anilines, the least acidic of which was 3-chloroaniline, were later measured by the H_- method, with H_2O–Me_2SO mixtures.[2] The acidities of aniline and nine of its derivatives have been measured in liquid ammonia at −31 °C, relative to 2,5-dichloroaniline, by NMR integration of acid–base pairs.[3] A few acidity values for anilines have also been determined by calorimetric[4] and electrochemical[5] methods. In the present paper we report pK_a values for aniline and 26 of its derivatives in Me_2SO measured by an overlapping indicator method.[6]

Results

A summary of the measurements that we have carried out is given in Table I.

Except where noted, all values were determined with a minimum of two indicators, using the previously published method,[6] and are an average of the numbers indicated. The reproducibility of the values with two indicators, under conditions where the ratio of anilide ion and aniline is varied, indicates the absence of homo-hydrogen bonding, which is strong in phenols.[7] The measurement of *p*-trifluoromethylaniline was complicated by decomposition of the anion, which we attribute to elimination of fluoride ion, as occurs with *p*-trifluoromethylphenoxide ion.[8] The pK_a was calculated from the absorbances extrapolated to the time of addition of the aniline. The value obtained was found to be independent of the concentration of indicator acid, indicator base, or the pK_a of the indicator. Measurements with *m*-nitroaniline were complicated by side reactions. Addition of *m*-$NO_2C_6H_4NH_2$ to a solution of CH_3SOCH_2K in Me_2SO produced a blue color, which darkened within 1 min. Addition of *m*-$NO_2C_6H_4NH_2$ to a solution of CH_3SOCH_2K that had been quenched with Ph_3CH caused the red color to turn to yellow and then rapidly to brown. Side reactions also aborted attempted pK_a measurements with 2,4-dinitrodiphenylamine and 2,4-dinitrotoluene.

The pK_a values for diphenylamine and 2,4-dichloro- and 3-chloroanilines in Table I are 1.35, 1.0, and 1.8 units higher than those reported in Me_2SO earlier.[5] This discrepancy can be attributed to slow electrode response with the potentiometric method, which makes it unreliable above about pK_a 14. This is at least partly responsible also for the low pK_a values for four anilines and for phenylacetylene in a report from another laboratory,[9] which we have discussed at some length earlier.[10] The pK_a value obtained by the calorimetric method[4] for 4-cyanoaniline is 0.3 unit higher than that in Table I, but those for 4-chloro-2-nitroaniline and diphenylamine are lower by 0.9 and 2.3 units, respectively.

Discussion

Equilibrium Acidities in H_2O/EtOH or H_2O/Me_2SO (H_- Method) and in Pure Me_2SO. The pK_a's obtained by the H_- method vary somewhat with the medium. For example, the acidity of 9-phenylfluorene (9-PhFlH) is 18.59 in EtOH/Me_2SO, 18.49 in H_2O/sulfolane, and 18.38 in H_2O/Me_2SO.[2] By comparing the pK_a's in H_2O/Me_2SO or EtOH/Me_2SO with those in Me_2SO (Table II), we can learn something about the difference in solvating abilities of hydrogen bond donor solvents (H_2O or EtOH),

Table I. Equilibrium Acidities of Anilines in Me_2SO at 25 °C

aniline	indicator or standard acid[a]	(p*K*)	runs[b]	p*K*[c]	selected p*K*[d]
3-Me	TH	(30.6)	1	30.97 ± 0.000	31.0
	DDH	(29.4)	2	31.05 ± 0.010	
H	TH	(30.6)	2	30.55 ± 0.023	30.7
	DDH	(29.4)	4	30.70 ± 0.020	
3-MeO	TH	(30.6)	2	30.38 ± 0.012	30.5
	DDH	(39.4)	4	30.55 ± 0.054	
3-Cl	TXH	(28.3)	2	28.53 ± 0.005	28.5
	PXH	(27.9)	2	28.54 ± 0.001	
3-CF_3	PXH	(27.9)	2	28.24 ± 0.004	28.2
3-Br	DDH	(29.4)	2	28.43 ± 0.010	28.4
	PXH	(27.9)	2	28.40 ± 0.008	
3-CN	PXH	(27.9)	2	27.47 ± 0.001	27.5
	MCPXH	(26.6)	2	27.53 ± 0.112	
4-$MeSO_2$	TPH	(25.6)	2	25.61 ± 0.001	25.6
	TBFH	(24.3_5)	2	25.54 ± 0.019	
4-CN	TPH	(25.6)	2	25.28 ± 0.012	25.3
	TBFH	(24.3_5)	2	25.24 ± 0.012	
4-$PhSO_2$	TPH	(25.6)	3	24.92 ± 0.002	24.9
4-PhCO	T1200	(25.3_3)	3	24.45 ± 0.007	24.4
	T3200	(23.4_3)	3	24.34 ± 0.027	
4-NO_2	$J2M_F$	(19.95)	3	20.90 ± 0.024	20.9
	J2M2	(19.51)	1	20.93	
	T22M1	(21.75)	4	21.01 ± 0.021	
	T22M3	(21.44)	2	20.96 ± 0.18	
	T22M4	(20.99)	3	20.93 ± 0.025	
	T31S3	(20.35)	2	20.77 ± 0.070	
2-F	DDH	(29.4)	2	28.73 ± 0.005	28.7
	PXH	(27.9)	1	28.64 ± 0.000	
	MClPXH	(26.6)	2	28.76 ± 0.008	
4-F	TH	(30.6)	1	30.67 ± 0.000	30.7
	DDH	(29.4)	2	30.68 ± 0.015	
2,4-$(F)_2$	PXH	(27.9)	3	28.61 ± 0.017	28.6
2-Cl	DDH	(29.4)	1	27.62 ± 0.000	27.6
	PXH	(27.9)	2	27.64 ± 0.000	
	MCPXH	(26.6)	1	27.57 ± 0.000	
4-PhS	DDH	(29.4)	2	28.21 ± 0.004	28.2
	TXH	(28.3)	2	28.21 ± 0.020	
4-MeCO	TPH	(25.6)	2	25.35 ± 0.003	25.3_5
	3MEOFH	(23.97)	2	25.34 ± 0.007	
4-CF_3SO_2	FH	(22.6)	2	21.82 ± 0.004	21.8
	F2	(21.37)	2	21.72 ± 0.000	
4-Cl	DDH	(29.4)	2	29.40 ± 0.012	29.4
	PXH	(27.9)	2	29.36 ± 0.007	
4-CF_3	PXH	(27.9)	4	27.07 ± 0.023	27.0[e]
	MCPXH	(29.6)	4	26.93 ± 0.058	
4-Br	DDH	(29.4)	1	29.20 ± 0.019	29.1
	TXH	(28.3)	2	28.97 ± 0.024	
	PXH	(27.9)	2	29.10 ± 0.015	
N-Ph	TPH	(25.6)	2	24.96 ± 0.001	24.9_5
	T1200	(25.33)	1	24.95 ± 0.000	
	TBFH	(24.35)	2	24.94 ± 0.004	
2,4-$(NO_2)_2$	PSFH	(15.4)	3	15.89 ± 0.045	15.9
4-NO_2-2,5-$(Cl)_2$	P31S2	(18.95)	2	17.47 ± 0.015	17.4
	J3310	(17.5)	2	17.37 ± 0.001	
	ISFH	(16.9)	2	17.21 ± 0.023	
2,6-$(Cl)_2$	TPH	(25.6)	2	24.86 ± 0.035	24.8
	TBFH	(24.35)	2	24.78 ± 0.004	
2,4-$(Cl)_2$	MCPXH	(26.6)	1	26.18 ± 0.000	26.3
	TPH	(25.6)	3	26.30 ± 0.012	

[a] Indicator or standard acid abbreviations: TH, triphenylmethane; DDH, diphenyldiphenylmethane; THX, thioxanthene; PXH, 9-phenylxanthene; MCPXH, 9-*m*-chloro-9-phenylxanthene; TPH, 1,1,3-triphenylpropene; TBFH, 9-*tert*-butylfluorene; T1200, benzyl methyl sulfone; T3200, benzyl phenyl sulfone; J2MF, *m*-fluorophenylacetonitrile; J2M2, *m*-chloroacetonitrile; T22M1, *m*-fluorobenzyl sulfone; T22M3, *m*-chlorobenzyl sulfone; T22M4, *m*-(trifluoromethyl)benzyl sulfone; T3153, phenyl thiomethylphenyl sulfone; 3MEOFH, 3-methoxyfluorene; FH, fluorene; F2, 9-benzylfluorene; PSFH, 9-phenylthiofluorene; P31S2, α-phenylthioacetophenone; J3310, diphenylacetonitrile; ISFH, 9-isopropylthiofluorene. [b] Runs were three-point titrations. [c] Average p*K* value for the number of runs indicated, ± standard deviation between runs. [d] Weighted average for p*K* values for different indicators. [e] Decomposition occurred and one-point titrations were performed.

(1) McEwen, W. K. *J. Am. Chem. Soc.* **1936**, *58*, 1124–1128.
(2) Cox, R. A.; Stewart, R. J. *J. Am. Chem. Soc.* **1976**, *98*, 488–498 and references cited therein.
(3) Birkall, T.; Jolly, W. L. *J. Am. Chem. Soc.* **1966**, *88*, 5439–5543.
(4) Arnett, E. M.; Moriarty, T. C.; Small, L. E.; Rudolph, J. P.; Quirk, R. P. *J. Am. Chem. Soc.* **1973**, *95*, 1492–1496.
(5) Courtot-Coupez, J.; LeDémézet, M. *Bull. Soc. Chim. Fr.* **1969**, 1033–1040.
(6) Olmstead, W. N.; Margolin, Z.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3296–3299.
(7) Bordwell, F. G.; McCallum, R. J.; Olmstead, W. N. *J. Org. Chem.* **1984**, *49*, 1424–1427.
(8) Roberts, J. D.; Webb, R. L.; McElhill, F. A. *J. Am. Chem. Soc.* **1950**, *72*, 408–411.
(9) Christment, J.; Delpeuch, J.-J. *J. Chem. Soc., Perkin Trans. 2* **1977**, 407–412.
(10) Bordwell, F. G.; Algrim, D.; Fried, H. E. *J. Chem. Soc., Perkin Trans. 2* **1979**, 726–728.

Table II. Equilibrium Acidities of Carbon and Nitrogen Acids Determined by the H_- Method in EtOH/Me_2SO, H_2O/Me_2SO, and Pure Me_2SO

carbon acid[a]	$pK_a(Me_2SO)$[b]	$pK_a(H_-)$[c]	nitrogen acid	$pK_a(Me_2SO)$[b]	$pK_a(H_-)$[h]
9-CN-FlH	8.3	11.4[d]	$2,4\text{-}(NO_2)_2C_6H_3NH$	15.9	15.0
9-CO_2MeFlH	10.35	12.9[d]	$4\text{-}NO_2C_6H_4NHPh$	16.85	15.7
$(CN)_2CH_2$	11.05	11.1[d,e]	$2\text{-}NO_2\text{-}4\text{-}ClC_6H_3NH_2$	18.9	17.1
$(p\text{-}NO_2C_6H_4)3CH$	12.7	14.3[d]	$3\text{-}ClC_6H_4NHPh$	23.4	20.7
$(p\text{-}NO_2C_6H_4)_2CH_2$	15.1	15.85[d]	Ph_2NH	24.95	22.4
9-$(m\text{-}ClC_6H_4)$FlH	16.85	17.7[f]	$4\text{-}CNC_6H_4NH_2$	25.3	22.7
9-C_6H_5FlH	17.9	18.6[g]	4-NH_2-pyridine	26.5	22.3
2-CN-FlH	18.2	19.0[g]	$3\text{-}CNC_6H_4NH_2$	27.5	24.6
9-$(p\text{-}MeC_6H_4)$FlH	18.3	19.0[f]	2-NH_2-pyridine	27.7	23.5
9-$(p\text{-}MeOC_6H_4)$FlH	18.55	19.0[f]	$3\text{-}CF_3C_6H_4NH_2$	28.2	25.4
2-Br-FlH	20.0	20.6[g]	$3\text{-}ClC_6H_4NH_4$	28.5	25.6
9-$PhCH_2$FlH	21.4	21.2[g]	$C_6H_5NH_2$	30.6	
9-MeFlH	22.3	21.8[g]			
HFlH	22.6	22.1[g]			
2-MeO-FlH	22.75	22.4[g]			
9-t-BuFlH	24.35	23.4[g]			

[a] HFlH is used as an abbreviation for fluorene. [b] From measurements made in our laboratory; for a description of the method for measuring pK_a's in Me_2SO, see ref 6 and 7. [c] In EtOH/Me_2SO. [d] Bowden, K; Stewart, R. *Tetrahedron* **1965**, *21*, 261–266. [e] In water. [f] In Me_2SO–H_2O: Cockerill, A.; Lamper, J. E. *J. Chem. Soc. B* **1971**, 503–507. [g] Bowden, K.; Cockerill, A. *J. Chem. Soc. B* **1970**, 173–179. [h] In H_2O/Me_2SO: Dolman, D.; Stewart, R. *Can. J. Chem.* **1967**, *45*, 911–924 925–928.

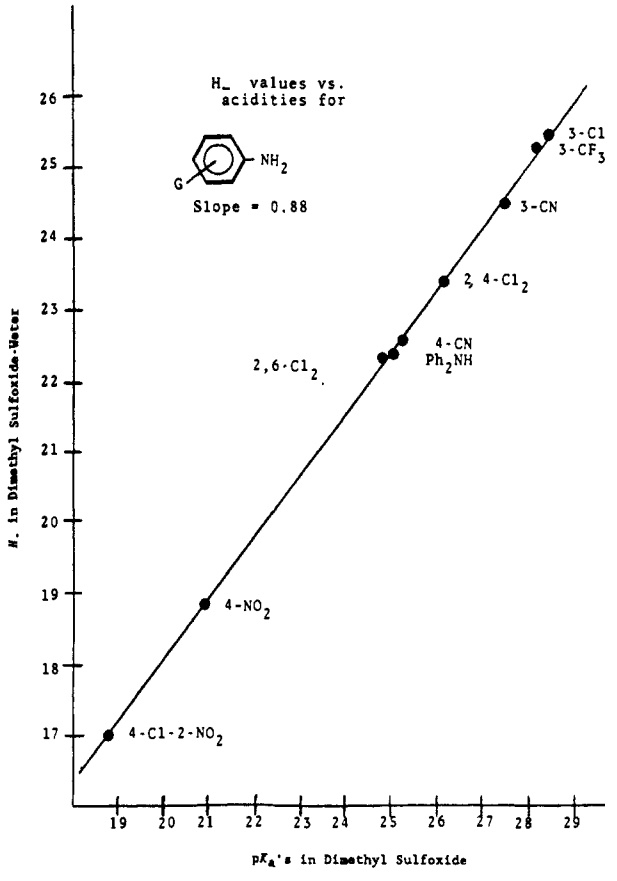

Figure 1. Plot of H_- acidities of anilines in water–dimethyl sulfoxide mixtures versus equilibrium acidities in dimethyl sulfoxide.

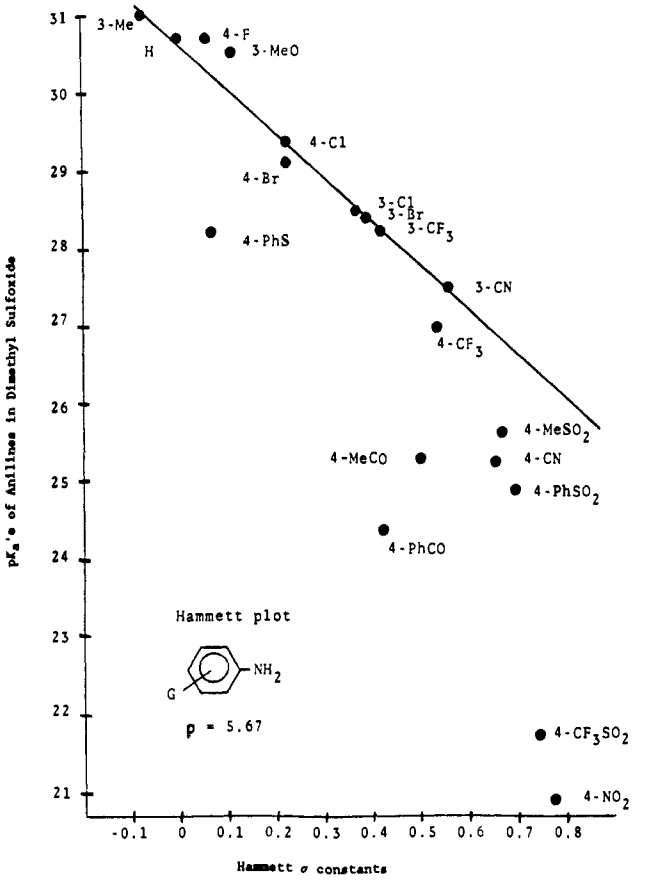

Figure 2. Hammett plot for equilibrium acidities of anilines in dimethyl sulfoxide solution.

a non-hydrogen bond donor solvent (Me_2SO), and mixtures thereof for delocalized carbanions and nitranions.

Examination of Table II shows that most of the weaker carbon acids have pK_a's in EtOH/Me_2SO or H_2O/Me_2SO media that are *higher* than in Me_2SO. Evidently the large, highly delocalized carbanions are better solvated by Me_2SO than by media containing high concentrations of hydroxylic solvents. It is only in the pK_a region above 20, where the mole percentage of ethanol or water drops to less than 25%, that the two methods reach reasonable accord. In this region the ethanol or water is effectively tied up by H bonding to Me_2SO, and the Me_2SO–HOEt or Me_2SO–H_2O aggregates solvate the carbanions in a manner comparable to that in Me_2SO itself.

The pK_a's of anilines, diphenylamines, and aminopyridines determined by the H_- method in Me_2SO/H_2O are appreciably lower than those in Me_2SO, in sharp contrast to the data for carbon acids. Apparently the Me_2SO–H_2O solvent aggregates are considerably better at solvating nitranions than is pure Me_2SO. This is consistent with the negative charge in these anions being more localized and with the superior ability of nitranions to act as H bond acceptors, relative to carbanions. A plot of H_- pK_a's versus those in Me_2SO for anilines gives a good linear correlation (Figure 1, slope = 0.88; R^2 = 0.999). We conclude that H_2O–Me_2SO aggregates show relatively constant solvation behavior with varying mixed solvent concentrations toward anilide ions, but not toward carbanions. These comparisons lead us to conclude that determinations of acidities in mixed solvents can give only a rough approximation of the acidities in the individual pure solvents.

Medium Effects on Aniline Acidities. Acidities are medium

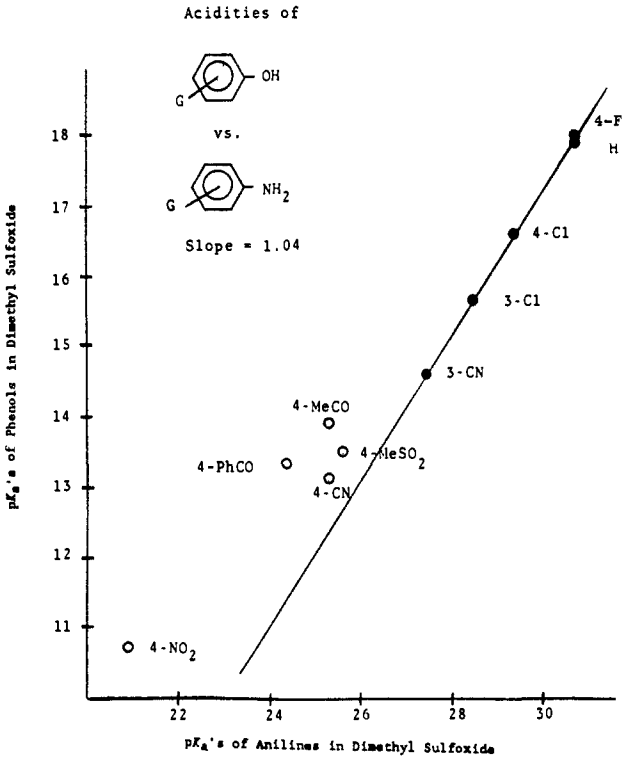

Figure 3. Plot of equilibrium acidities of phenols versus anilines in dimethyl sulfoxide solution.

dependent, the position of the equilibrium (eq 1) being dependent on the ability of the solvent, S, to solvate the acid, HA, the proton, and the anion, A^-. For anilines, this may be illustrated by comparing the acidities in Me_2SO and in liquid ammonia.

$$S + (HA)_S \rightleftarrows (H^+)_S + (A^-)_S \quad (1)$$

Measurements of the acidities of anilines in liquid ammonia have been made by Birkall and Jolly,[3] and more recently by Takemoto and Lagowski.[11] Lagowski placed the values on an absolute scale by a comparison of the acidity of $(p\text{-}CH_3C_6H_4)_2CH_2$ with that of $p\text{-}Me_2NC_6H_4NH_2$.[11] The pK_a of the carbon acid was determined potentiometrically in liquid ammonia and was related to the acidity of $p\text{-}Me_2NC_6H_4NH_2$ calculated from a Hammett plot ($\rho = 5.5$). These are ion pair acidities since the anilide ions exist as aggregates with the counterion in liquid ammonia.[11] The ion pair pK_a of aniline in liquid ammonia is 21.1 versus a pK_a of 30.7 in Me_2SO where free ions are formed on dissociation. The apparent higher acidity of aniline in liquid ammonia is due to a combination of ion pairing and the superior ability of ammonia to solvate the proton.

Correlations of Acidities and Substituent Effects. A plot of the pK_a values for anilines versus Hammett σ constants is shown in Figure 2. A good line can be drawn through the 5 meta points, 3-Me, 3-Cl, 3-Br, 3-CF_3, 3-CN, including 4-Cl, and H. The deviation of the 3-MeO point was expected because similar deviations have been observed for acidities of acetophenones,[12] arylacetonitriles,[13] and arylmethyl phenyl sulfones in Me_2SO solution.[14] A $\sigma = 0.02$ in Me_2SO has been suggested for use in Me_2SO,[12] and this would put the present point on the line.[15] The small deviations observed for 4-F and 4-Br are of the order expected for scatter in Hammett plots. The σ_p^- values needed to make the points for the other 4-substituents fit the meta line are the following: PhS (.44), CF_3 (0.65), $MeSO_2$ (0.90), MeCO (0.94), CN (0.95), $PhSO_2$ (1.02), PhCO (1.11), F_3CSO_2 (1.57),

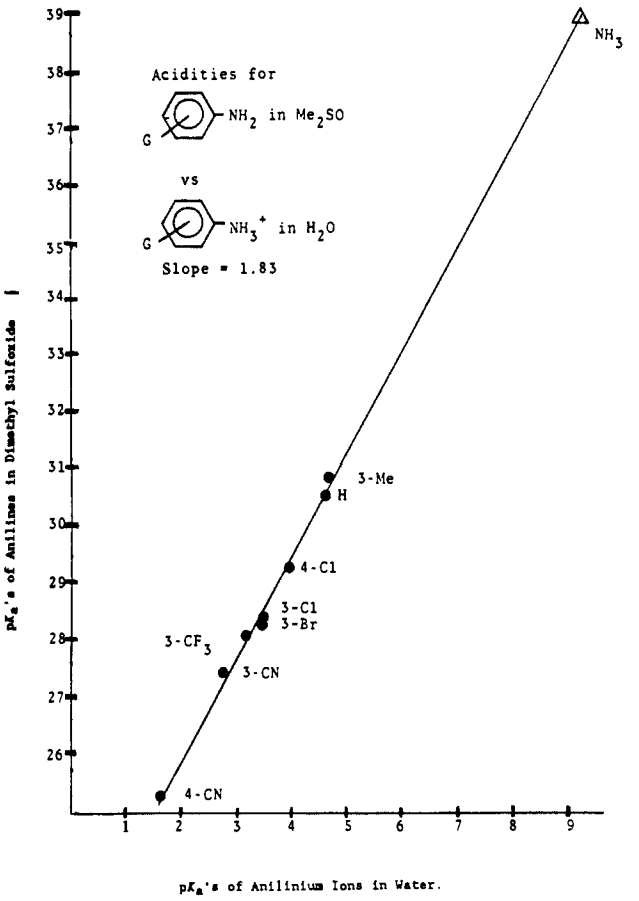

Figure 4. Acidities of anilines in dimethyl sulfoxide plotted against acidities of anilinium ions in water.

and NO_2 (1.90). σ^- values of 0.13 and 0.18, based on reactivities, have been reported for 4-PhS.[16] A σ^- value of 0.40 has been obtained for equilibrium acidities of $ArCH_2CN$ in Me_2SO.[13] The σ^- values for 4-CF_3, 4-$MeSO_2$, 4-CN, and 4-$PhSO_2$ are within 0.1 unit of those reported,[17] but those for 4-MeCO, 4-PhCO, 4-F_3CSO_2, and 4-NO_2 are larger by more than 0.1 unit (0.21 for 4-F_3CSO_2 and 0.67 for 4-NO_2).

Hammett recognized as early as 1940 that the enhanced σ constants needed for 4-NO_2, and related phenols, were associated with direct conjugation of the anion with the 4-substituent. It was not until 41 years later, however, that a correlation of gas-phase acidities of phenols with those in water revealed that these σ^- constants are required in part because of enhanced solvation of the substituents.[18a] Similar correlations have shown that these substituent solvation assisted resonance (SSAR) effects for phenoxide ions are larger in Me_2SO than in water,[18b] and that they are also present in similarly constituted N–H and C–H acids.[19] Furthermore, SSAR effects have been shown to cause similar deviations in Hammett or Brønsted plots for rates of reactions of anions of this type with electrophiles.[20] These kinetic SSAR effects are caused by the necessity to desolvate the 4-substituent during the reaction.

A plot of pK_a values of phenols versus anilines (Figure 3) shows that SSAR effects are larger in anilines than in phenols, presumably because of weaker solvation at nitrogen of the anilide

(11) Lagowski, J. J. *Pure Appl. Chem.* **1971**, *25*, 429–456.
(12) Bordwell, F. G.; Cornforth, F. J. *J. Org. Chem.* **1978**, *43*, 1763–1768.
(13) Bares, J. E. Ph.D. Dissertation, Northwestern University, 1979.
(14) Branca, J. C. Ph.D. Dissertation, Northwestern University, 1979.
(15) The larger σ constant in water ($\sigma_{m\text{-MeO}} = 0.12$) is probably due to H-bond donor solvation of the *m*-MeO group in the *m*-$MeOC_6H_4CO_2^-$ ion.
(16) Exner, O. *Correlation Analysis in Chemistry*; Chapman, N. B., Shorter, J., Eds.; Plenum: New York, 1978; Chapter 10, p 472.
(17) Sigma and σ_p^- values were taken from the following: Hine, J. *Structural Effects on Equilibrium in Organic Chemistry*; Wiley-Interscience: New York, 1975; Chapter 3.
(18) (a) Fujio, M.; McIver, R. T., Jr.; Taft, R. W. *J. Am. Chem. Soc.* **1981**, *103*, 4017–4019. (b) Mishima, M.; McIver, R. R., Jr.; Taft, R. W.; Bordwell, F. G.; Olmstead, W. N. *J. Am. Chem. Soc.* **1984**, *106*, 2717–2718.
(19) Bordwell, F. G.; Taft, R. W., unpublished results.
(20) Cripe, T. A., Ph.D. Dissertation, Northwestern University, 1985. Bordwell, F. G.; Branca, J. C.; Cripe, T. A. *Isr. J. Chem.* **1985**, *26*, 357–366.

ion than at oxygen of the phenoxide ion and a consequent greater solvation of the substituent. It is noteworthy that the slope of this plot is close to unity, indicating that the ρ values for phenols and anilines are essentially identical despite a difference of 12.7 pK units, corresponding to 17.4 kcal/mol, in the basicities of $PhNH^-$ and PhO^- ions in Me_2SO.

Extrapolations with Aniline Acidities. A plot of the pK_a's of toluene bearing 4-NO_2, 4-F_3CSO_2, 4-$PhCO_2$, 4-$PhSO_2$, and 4-CN groups versus the pK_a's of like-substituted anilines is roughly linear and was used to obtain an extrapolated pK_a of 42 for toluene.[21] This correlation is suspect since we now recognize that it requires SSAR effects for toluenes and anilines to be comparable. Nevertheless, a pK_a for toluene in Me_2SO near 42 has been supported by other extrapolations. The CN function is best suited for extrapolations because it is a powerful electron-withdrawing group with minimal steric demands. Acidities in the gas phase for CH_4, CH_3CN, and $CH_2(CN)_2$ are 409, 364, and 330 kcal/mol, respectively.[22] Introduction of one CN group into methane thus causes an acidity increase of about 33 pK_a units and introduction of the second a 25 unit further increase. The 25% smaller second increment, which can be attributed to a saturation effect, is likely to be attenuated in solution. Starting with the 20.5 pK_a unit (per *hydrogen*) difference in acidity between $CH_2(CN)_2$ (pK_a = 11.0) and CH_3CN (pK_a = 31.5 on a per hydrogen basis) and assuming a 20% saturation effect gives a pK_a of 56 for methane: $CH_2(CN)_2$ (11.0) $\xrightarrow{20.5}$ CH_3CN (31.5) $\xrightarrow{24.6}$ CH_4 (56.2). A similar extrapolation gives a pK_a of 43 for toluene: $PhCH(CN)_2$ (4.2) $\xrightarrow{18}$ $PhCH_2CN$ (22.2) $\xrightarrow{21.6}$ $PhCH_3$ (43.8 on a per hydrogen basis; assigned pK_a = 43).

An extrapolation from the pK_a of cyanamide to that of NH_3 with use of the same CN increment as that from CH_3CN to CH_4 gives a pK_a of 41.8 for NH_3: H_2NCN (16.95) $\xrightarrow{24.6}$ 41.8. A plot of the pK_a's of anilines in Me_2SO versus the pK_a's of anilinium ions in water is linear with a slope of 1.8 (Figure 4). Extrapolation to the pK_a of NH_3 from that of NH_4^+ ion in water (9.27) gives a pK_a about 39.5 for NH_3 in Me_2SO. This extrapolation assumes that this point will fall on the line, i.e., that the ratio of α-phenyl effects will be proportional to the ratio of ρ values. This is not unreasonable since both the α-Ph effect and ρ reflect the sensitivity of the equilibrium toward substituent effects, as shown by the linear plot for α-phenyl effects versus ρ for the families $PhCH_2NO_2$, $PhCH_2COCH_3$, $PhCH(CN)_2$, PhOH, $PhCH_2CN$, and $PhCH_2Ph$ (slope = 2.4).[23] The average of this and another extrapolation leads to an estimate of 41 ± 1 for the pK_a of ammonia in Me_2SO.

Experimental Section

Materials. The anilines were for the most part commercial samples. The purity (and identity) of each sample was confirmed by spectral analyses (NMR, IR), by chromatography (VPC, TLC), and by the appropriate physical constants (bp, mp). NMR spectra were recorded on a Hitachi Perkin-Elmer R20-B spectrometer and IR were recorded on a Beckman IR-5. The purity of liquid samples was assessed on an analytical Hewlett-Packard F and M Model 5752A gas chromatograph equipped with a thermoconductivity detector. These analyses were performed with a 0.25 in. × 10 ft aluminum column packed with 3% or 5% Carbowax 20 M on acid-washed Chromasorb W. The analyses by TLC were performed with Eastman Chromagram sheets, No. 13181, silver-gel with fluorescent indicator. Purified samples of 4-fluoro- and 2,4-difluoroanilines were gifts from N. H. Andersen.

Acknowledgment. This research was sponsored by the National Science Foundation.

(21) Bordwell, F. G.; Algrim, D. J.; Vanier, N. R. *J. Org. Chem.* **1977**, *42*, 1817-1819.
(22) Bartmess, J. E.; McIver, R. T. *Gas Phase Ion Chemistry*; Bowers, M. T., Ed.; Academic: New York, 1979; Vol. 2, Chapter 11.
(23) Bordwell, F. G.; Algrim, D. J.; Bares, J. E.; Branca, J. C. *J. Org. Chem.* **1978**, *43*, 5024-5026.

Communications to the Editor

Free-Radical Reduction Reactions of Chiral Dihydronicotinamides. Enantioselective Hydrogen Atom Transfer and Electron-Transfer Processes during the Reduction of Ketones

Dennis D. Tanner* and Abdelmajid Kharrat[1]

Department of Chemistry, The University of Alberta Edmonton, Alberta, T6G 2G2 Canada

Received December 23, 1987

We wish to report that the enantioselective reductions of α,α,α-trifluoroacetophenone (TFA) by enantiomerically enriched DHNA **1** and **2** involve the enantioselective transfer of a hydrogen atom. Furthermore, the reduction of *d,l*-fenchone by **2** demonstrate enantioselective transfer of a single electron from the 4-hydropyridyl radical.

The reduction of TFA by five dihydronicotinamides (DHNA's) proceeds by a free-radical chain mechanism containing initiation and propagation steps involving single electron transfer (SET).[2] The ketyl intermediate in these reductions abstracts a hydrogen atom from the DHNA and forms a 4-hydropyridyl radical, which carries the chain by subsequent electron transfer to another molecule of TFA. Hydrolysis of the pyridinium alkoxide forms the alcohol, 1-phenyl-2,2,2-trifluoroethanol.

The enantioselective reduction of ketones by chiral 1,4-dihydropyridines (DHP's) in the presence of divalent metal ions (Mg^{2+} and Zn^{2+}) has been reported.[3-6] Metal ions were added to mimic the action of metal ions contained in NADH reductase enzymes. The metal ions catalyze the reactions and presumably help control the stereochemistry of reduction by the formation of a complex between the DHP and the ketone. Little detailed mechanistic investigation has been reported, i.e., intermediates involved, for these intermolecular biomimetic reductions; however, in the case of a covalently bonded intramolecular reduction of a benzoylformyl ester a transition state model for a hydride transfer process was proposed.[6b]

Chiral DHNA's (**1**, and **2**) used by Ohno[3a] react with TFA to

(1) Postdoctoral fellow, University of Alberta, 1986-1988.
(2) Tanner, D. D.; Kharrat, A. *J. Org. Chem.* **1988**, *53*, in press.
(3) (a) Ohno, A.; Ikeguchi, M.; Kimura, T.; Oka, S. *J. Am. Chem. Soc.* **1979**, *101*, 7036. (b) Ohno, A.; Kimura, T.; Kim, S. G.; Yamamoto, H.; Oka, S. *Bioorg. Chem.* **1977**, *6*, 21. (c) Ohno, A.; Nakai, J.; Nakamura, K.; Goto, T.; Oka, S. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3486. (d) Ohno, A.; Goto, T.; Nakai, J.; Oka, S. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3478. (e) Ohno, A.; Nakai, J.; Nakamura, K.; Goto, T.; Oka, S. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3482.
(4) Inouye, Y.; Oda, J.; Baba, N. *Asymmetric Synth.* **1983**, *2*, 1.
(5) (a) Kellog, R. M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 782. (b) Talma, A. G.; Jouin, P.; DeVries, J. G.; Troostwijk, C. B.; Buning, G. H. W.; Waninge, J. K.; Visscher, J.; Kellog, R. M. *J. Am. Chem. Soc.* **1985**, *107*, 3981.
(6) (a) Meyers, A. I.; Oppenlaender, T. *J. Am. Chem. Soc.* **1986**, *108*, 1989. (b) Meyers, A. I.; Brown, J. D. *J. Am. Chem. Soc.* **1987**, *109*, 3155.

0002-7863/88/1510-2968$01.50/0