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SOLVENT DEPENDENT DIFFERENCE IN pK_{HB^+} BEHAVIOUR IN *N*-METHYLANILINE AND *N*-PHENYLHYDROXYLAMINE

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The pK_{BH^+} values of the conjugate acids of *N*-phenylhydroxylamines change drastically when the pK_{BH^+} values are determined in dimethyl sulfoxide (DMSO) rather than methanol. The Hammett ρ values change from −5·69 to −1·20 on going from methanol to DMSO for protonated *N*-phenylhydroxylamines, in contrast to a shift of −4·70 to −4·83 for protonated *N*-methylanilines in the same two solvents. This large change in susceptibility indicates that the species from which the proton departs is not the same for protonated *N*-phenylhydroxylamines in the two solvents. Experimental and computational evidence supports ionization of the H^+ from the O atom for the protonated *N*-phenylhydroxylamines in DMSO.

INTRODUCTION

Equilibrium acidities are valuable for assessing electronic and steric effects due to structural variations in organic acids.[1] The quantitative expressions of acidities are pK_{HB^+} values for amines and amine-like compounds. These values are solvent dependent, reflecting the ability of the solvent to solvate the proton, the conjugate base and the undissociated acid in equation (1), the formal definition of acid dissociation for such compounds.

$$RNH_2X^+ \rightleftharpoons NHXR + H^+ \qquad (1)$$

pK_{HB^+} values also serve as indicators of reactivity when used to relate rate constants to the acidities of nucleophiles in Brønsted plots.[2] Such use has modeled transition state behavior in important questions related to methyl group transfer.[3] A recent example uses the change of pK_{HB^+} for an α-nucleophile as a function of water–dimethyl sulfoxide (DMSO) mole percentage to construct Brønsted plots[4,5] for modeling transition states. Such a usage depends on regular behavior of acidity in the solvent mixture, which we show in this paper is not true of *N*-phenylhydroxylamines in methanol–DMSO mixtures.

The purpose of this paper is to report on and discuss the non-regular behavior of the α-nucleophiles *N*-phenylhydroxylamines, **1**, in going from pure methanol to pure DMSO compared with the regular behavior of *N*-methylanilines. The finding is validated by theoretical and experimental methods.

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EXPERIMENTAL AND RESULTS

Most of the pK_{HB^+} values for the *N*-methylanilines and *N*-phenylhydroxylamines were determined in DMSO by the glass electrode method,[6] as modified by Beniot *et al.*[7] In their research they found that end-points were not sharp so they determined the H^+ concentration by measurements of voltages of mixtures containing weighed amount of the salts and the free bases. In our method we took note of these experimental difficulties, and applied an equivalent method wherein the voltage was determined in DMSO and DMSO–methanol mixtures when exactly 0·5 equiv. of the standard solution of trifluoromethanesulfonic acid (TflH) had been added to a carefully weighed amount of the amine or *N*-phenylhydroxylamine. The contents of an Aldrich Ag/AgCl combination pH electrode (No. Z11316-6) were replaced with a solution of 0·01 M Me_4NBF_4 in DMSO from a freshly opened bottle. The electrode was then soaked for 24–48 h in a solution of 0·01 M Me_4NBF_4 in dry DMSO. The calibration of the electrode was accomplished through serial dilution of a standard solution of TflH in DMSO. This calibration gave a slope of 63·3 ± 0·2 mV between $[H^+] = 1·0$ and 10^{-6} M (intercept = 527·4 ± 0·1 mV, $r = 0·9995$), in excellent agreement with Benoit *et al.*[7]

The pK_{HB^+} values in DMSO were determined with the calibrated electrode by adding 0·5 equiv. of TflH in DMSO at 25·0 ± 0·1 °C to weighed samples of the free bases that were freshly prepared in each case of *N*-phenylhydroxylamines. These species were recovered in quantitative or nearly quantitative yield from the reaction mixtures by partitioning the solutions between 6 M hydrochloric acid and methylene chloride to remove the

DMSO, then neutralizing the aqueous acid solution with sodium hydrogencarbonate and extracting with dichloromethane. Temperature control was effected using a water-jacketed cell and a circulating thermostated water-bath. The voltage was read from a standard Jenco Model 671P pH meter. Using the standardization curve the pH values at half neutralization were obtained.

The acidities of 4-nitro-*N*-methylaniline and 4-nitro-*N*-phenylhydroxylamine were special cases where the acidity was outside the limits (0·6 pH) of calibration for our electrode. 4-Nitro-*N*-methylaniline was determined by ^{1}H NMR chemical shifts as reported for 2,6-lutidine.[8] The essence of this method is that the chemical shift in the $A'_2B'_2$ spectrum of the aromatic protons is a function of the pH of the solution. The position of these signals depends on the [free base]/[acid form] ratio due to exchange of the protons between the two forms at the N atom. All that is necessary is to find the δ value where full protonation is present, then where there is no protonation present (pure DMSO). The position of these signals along this defined $\Delta\delta$ scale determines the ratio of free base to acid form. This method gave pK_{HB^+} of -0.99 ± 0.09 for 4-nitro-*N*-methylaniline. This point is plotted against σ in the Hammett plot (Figure 1).

The acidity of the conjugate acid of 4-nitro-*N*-phenylhydroxylamine was determined spectroscopically by the following method. The absorptions of free base and protonated forms of 4-nitro-*N*-phenylhydroxylamine were determined using a Beckman DU70 spectrophotometer at 25 °C. Various pH solutions of the compound in DMSO were measured and the concentrations of the free base and the protonated form were determined. The pK_{HB^+} was determined by plotting the term log([free base]/[acid form]) vs pH. Where the log term became zero, the pK_{HB^+} equals the pH on the plot.

Table 1. pK_{HB^+} values for GC_6H_4NHX in DMSO and MeOH at 25 °C

		pK_{HB^+}	
G	X	DMSO[a]	MeOH
H	Me	2·63	5·79
4-Me	Me	3·79	6·43
4-MeO	Me	4·22	–
3-Cl	Me	1·48	3·75
4-Cl	Me	1·77	–
4-NO_2	Me	−0·99	−0·018
H	OH	2·17	5·05
4-Me	OH	2·48	6·59
4-MeO	OH	2·54	6·88
4-Br	OH	1·80	–
4-NO_2	OH	1·32	0·96
4-CF_3	OH	1·35	2·08

[a] Average deviation ±0·14 units.

This method gave a pK_{HB^+} value of 1·32, that plotted vs σ rather than σ^-.

The pK_{HB^+} data are collected in Table 1 and plotted in Figures 1 and 2 for methanol and DMSO, respectively. The pK_{HB^+} values of these compounds in methanol have all been reported.[3b] The compounds were prepared by the known route[3d] by reducing an aromatic nitro compound with zinc dust and ammonium chloride.

The computations for the gas-phase proton affinities (*PA*) were performed by MOPAC 6.0, mounted on a UNIX based coprocessor board (AEON Technologies) on a 286 IBM clone using an AM1 Hamiltonian, or using Hyperchem.[9] The main problem with semi-empirical methods is that they have trouble treating the pyramidalization of the N atom.[10] The problem is not

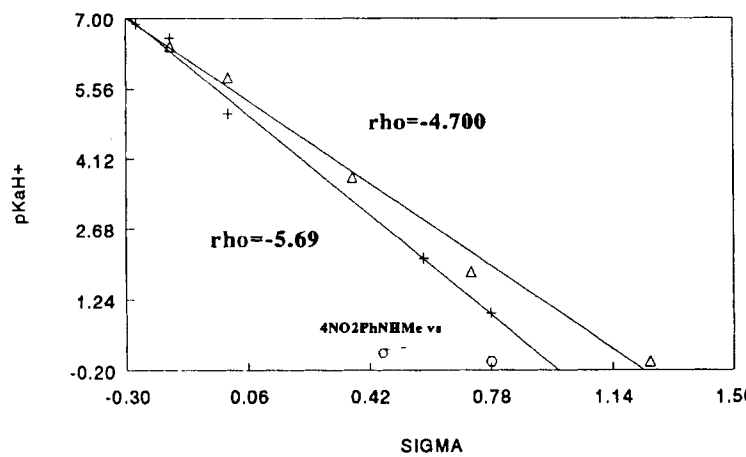


Figure 1. Hammett plots for the pK_{HB^+} values of *N*-methylanilines and *N*-phenylhydroxylamines in methanol. (+) GPhNHOH; (Δ) GPhNHMe; (O) 4-NO_2PhNHMe vs σ^-

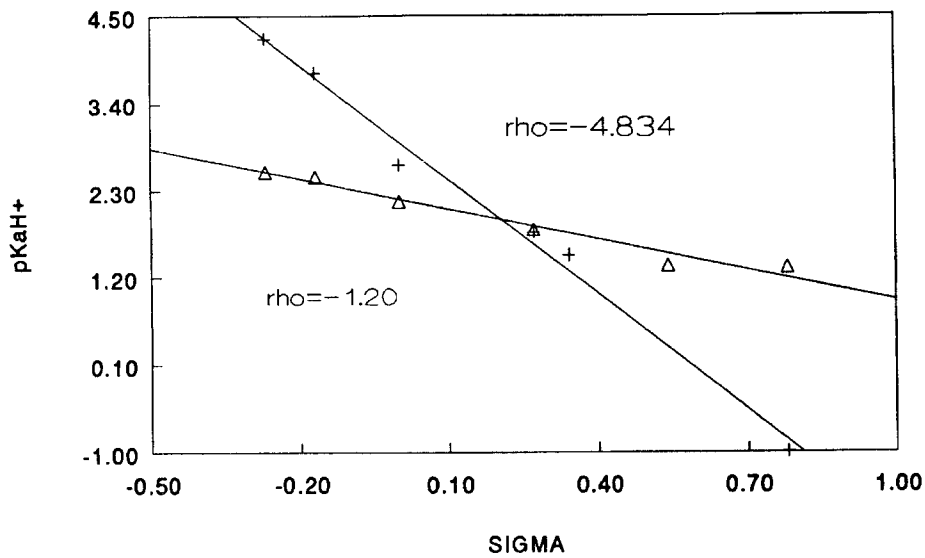


Figure 2. Hammett plots for the pK_{HB^+} values of *N*-methylanilines and *N*-phenylhydroxylamines in pure dimethyl sulfoxide. (+) GPhNHMe; (Δ) GPhNHOH

severe in amines such as methylamine, but seems to require the highest basis set with polarization functions with aromatic amines. This problem has recently been discussed with reference to aromatic amines.[11] All geometries were tested for minimization by FORCE calculations wherein no negative eigenvalues were found for diagonalization of the Hessian matrix. The *ab initio* computations on NH_2OH and NH_3O were performed using G92W (Gaussian 92 for Windows) loaded into a Gateway 2000 486DX2 66 MHz computer or with Spartan, using an SGI *Indy*, for the solvated species. The potential energy surface was optimized using the EF keyword that causesthe program to optimize geometries by following the eigenvalues of the Hessian matrix. No signal from the program that negative eigenvalues were present means that the states obtained were minima. Simulations of ^1H NMR spectra were performed using HYPER NMR, a product of Hypercube (Waterloo, Ontario, Canada). Computation of infrared spectra of compounds is a standard feature of the HyperChem 4.0 that was used in this study.

DISCUSSION

The striking feature between the two solvent systems is the behavior of the GC_6H_4NHOH molecular system. This system in pure MeOH has a more negative ρ value (−5·69) than *N*-methylaniline derivatives, but the change in this parameter in the MeOH–DMSO transfer is 474% toward more positive values. Such a large change corresponds to *ca* 4·5 powers of ten per unit σ. The change in ρ value for the C_6H_4NHMe system is a mere 2·9%.

A similar change in ρ value occurs in carboxylic acids when the point of the ionizing species is separated further from the substituent by an insulating CH_2 group.[12] Similar results occur in a series of benzohydroxamic acids ($\rho \approx 1{\cdot}0$,[13] but $\rho \approx 0{\cdot}6$ for the *N*-methylbenzohydroxamic acids[14]). This change in ρ value therefore perhaps indicates a change in the site of ionization from the imine NH to the OH.

These literature data indicate that the probable cause of the large change in ρ for the $GC_6H_4N_2HOH^+$ system is ionization of the OH rather than the NH in pure DMSO:

$$\underset{\mathbf{1}}{GC_6H_2NH^+\text{–}OH{=}S(CH_3)_2} \rightleftharpoons \underset{\mathbf{2}}{GC_6H_4NH^+_2\text{–}O^-{+}(CH_3)_2S^+{=}OH} \quad (2)$$

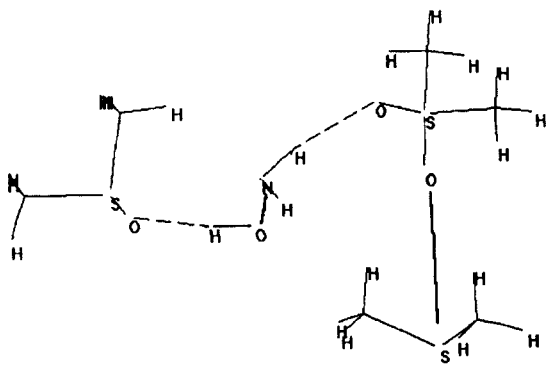
The theoretical possibility that a zwitterionic form of hydroxylamine would be more stabilized in DMSO was explored in two ways. The first study used an *ab initio* calculation at the 6–31G** level of theory for both hydroxylamine (**3**) and its zwitterion (**4**). The HF energies at this level were **3** = −130·9917 and **4** = −130·9440 hartrees mol^{-1}. This result indicate that there is a difference between the forms of free base for the hydroxylamine isomers in the gas phase of *ca* 125 kJ mol^{-1}. The second study used 3–21G level computations for various degrees of solvation by DMSO for each form of the hydroxylamine. The best method for doing these studies would be an *ab initio* series at about the same level of theory as for the study of **3** and **4**. These studies with individual solvent

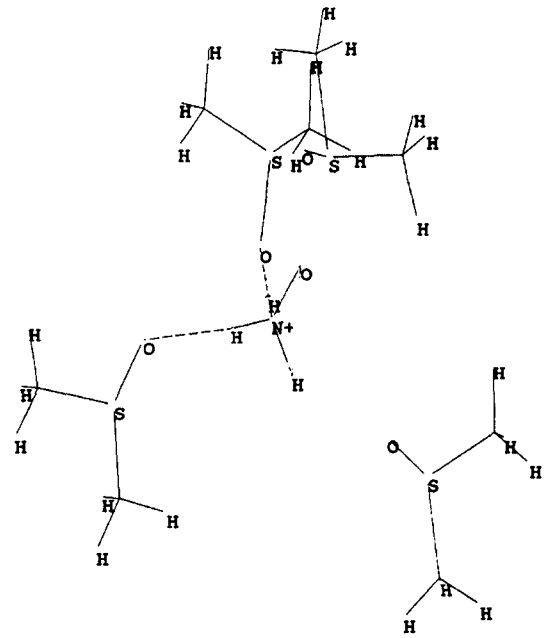
molecules would be very expensive in computer time, so the simpler level of theory was selected.

3 4

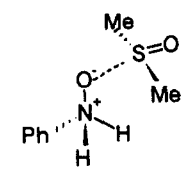
The solvated geometries involve three DMSO molecules for the NH_2OH form (**5**) and four molecules of DMSO in the zwitterion form (**6**). The 3–21G HF energies for DMSO and hydroxylamine were **5** = −1776·8889 and **6** = −2325·7239 hartrees mol^{-1}. The hydroxylamine solvated by three DMSO molecules has an optimized geometry at −0·5952 hartrees, which is −1562·6 $kJ\,mol^{-1}$ lower than for the components. The zwitterionic form, **4**, had an HF energy of −130·2153 hartrees mol^{-1} and the solvation geometry with four DMSO molecules had an energy 0·7922 hartree lower than the components, which is 2077·8 $kJ\,mol^{-1}$ lower than for the components. The trend supports the conclusion we have drawn on the basis of the change in ρ values.

The gas-phase proton affinities of the *N*-phenylhydroxylamines were also computed by the AM1 Hamiltonian in HyperChem. Although PM3 proton affinities are useful for many gas-phase acidities, the average unsigned error for nitrogen acids is smaller for AM1.[15] The Hammett plots for the *PA* are presented in Figure 3. It is evident that the effect of substituents is nearly the same no matter where ionization occurs, from NH or OH. The slopes of the lines are similar. Ionization in the gas phase from the OH bond produces energies that are much higher than for the NH ionization. One can conclude from this that specific solvation by the DMSO molecules makes the ionization site more stable by interacting in a unique way with it. Such an ion–dipole interaction is possible as in **6** with a fourth DMSO molecule, but not in **5**. Such an interaction has recently been cited as affecting the ability of the NO_2 group to stabilize negative charge in a substituent solvation-assisted resonance (SSAR) effect.[16] Such an interaction in the present case is shown in **7**.





Experimental support for the OH ionization hypothesis came from IR and NMR studies. The IR studies were performed on a Nicolet 205 FTIR instrument using freshly polished NaCl plates and a demountable cell holder. In media such as Nujol, where intermolecular hydrogen bonding should be at a maximum, the *N*-phenylhydroxylamines all showed clearly two bands in the 3300–3400 cm^{-1} region, although they overlapped. These were due to OH and NH stretching. Computed spectra, via AM1 calculations in HyperChem, also supported two bands in this region. In dilute (1%) DMSO or DMSO-d_6 solution only one band at 3300 cm^{-1} was observed. Experiments with substituted anilines always showed two bands for symmetric and asymmetric stretching in this region in DMSO or DMSO-d_6. In a single experiment, using DMSO specially dried over CaH_2, 4-methyl-*N*-phenylhydroxylamine showed two sharp bands in the 3300–3400 cm^{-1} region. When this sample was allowed to age for 20 min the two bands became one band at *ca* 3300 cm^{-1}. This experiment was very hard to repeat, but it is indicative of what may be a rearrangement of a normal form of an *N*-phenylhydroxylamine to a form similar to **7**. Further evidence for this possibility comes from the ^1H NMR study below.



7

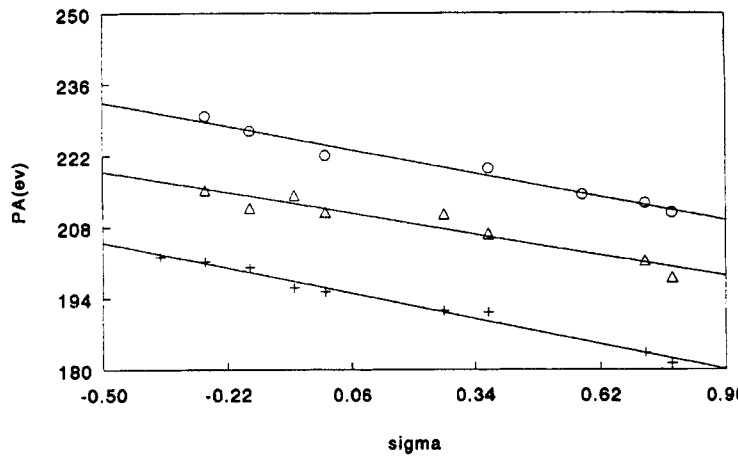


Figure 3. Hammett plots of AM1 gas-phase proton affinities. (+) PhNHOH; (Δ) PhNHMe; (O) $PhNH_2O$

An interesting point comes from the consideration of what the IR spectrum of a species such as **7** should exhibit. Normally, two bands of NH stretching, one due to symmetric and one due to asymmetric stretching modes, should be observed. In DMSO or DMSO-d_6 only one band is apparently present. Computing the IR spectrum with the AM1 Hamiltonian of HyperChem predicted only one vibrational mode for the zwitterionic species **7**. The same kinds of computations for aniline showed clearly the two expected fundamental modes of vibration of twin NH bonds. We do not have a good explanation for why the theoretical spectrum should be so, but the fact corroborates the experimental IR spectrum in DMSO.

^{1}H NMR spectroscopy of *N*-phenylhydroxylamine corroborated the existence of **7** as a dominant species in that medium. In deuterochloroform the aromatic region of the spectrum of *N*-phenylhydroxylamine, 6·2–7·5 ppm, is similar to that of *N*-methylaniline or phenylhydrazine, although shifted downfield from that of phenylhydrazine by *ca* 0·15 ppm. The multiplets were centered at 6·8 ppm (3H) and 7·2 (2H) ppm. Two signals for each of the protons attached to the heteroatoms N and O were distinctly separated at 6·1 and 1·8 ppm. Two such signals are also present in phenylhydroxylamine in deuterochloroform. Simulation of this spectrum with HYPER NMR reproduced the shape of the aromatic signals nearly exactly. Two sets of much less intensive signals appeared at 8·2 and 7·55 ppm as broad, faint multiplets in the experimental spectrum. In DMSO-d_6 a dramatic shift occurred that placed the aromatic region signals at 8·2 ppm (2H), 7·2 ppm (1·3H), and 6·8 ppm (3·8H) with a single signal representing 2H at 3·35 ppm. Incremental addition of deuterochloroform to the DMSO-d_6 sample produced a dramatic shift of the DMSO-d_6 signals toward 8 ppm at 10% $CDCl_3$ content. At 30% $CDCl_3$ this sample slowly reverted from the signals at 10% $CDCl_3$ to a spectrum having the characteristics of the $CDCl_3$ sample plus broad signals at 7·95 and 7·4 ppm. When DMSO-d_6 was incrementally added to the $CDCl_3$ sample (5%), the set of signals at *ca* 8 ppm increased in intensity, as did the signal at 7·5 ppm. At 30% DMSO-d_6 the signal at 6·8 ppm was much diminished, but the intensity of the signal at 8·10 ppm increased. Overlapping both regions was a broad signal without much fine structure. The signals due to protons associated with the heteroatoms appeared at 4·5 ppm as a broad singlet. The conclusion from this study was that two species were present in each solvent, and they were interconverted by dilution of one solution with the other solvent. In the spectrum measured in 30% $CDCl_3$–DMSO-d_6, both species are simultaneously present.

These studies support the hypothesis that a species with a formal positive charge, such as **7**, occurs in DMSO-d_6. This conclusion was demonstrated by synthesizing *N,N*-dimethylaniline *N*-oxide and determining the ^{1}H NMR spectrum in $CDCl_3$. The synthesis was carried out with *m*-chloroperbenzoic acid in methanol.[17] The ^{1}H NMR spectrum in $CDCl_3$ showed aromatic signals at 6·8 ppm (2H), 7·3 ppm (3·4H) and 7·6 ppm (1·6H), similar to the signals of *N*-phenylhydroxylamine in DMSO-d_6. When DMSO-d_6 was added to this sample (30%), a new set of signals appeared, in addition to those already described, at 6·95 ppm. This set of observations indicates consistency with the hypothesis that **7** is a dominant species in DMSO.

CONCLUSIONS

The change in the slopes of the Hammett plots for solvent effects between methanol and DMSO are minor for the series of substituted *N*-methylanilines, but major for comparable *N*-phenylhydroxylamines. The greater

change in slope can be attributed to ionization of the H^+ from the O atom in the hydroxylamine portion in DMSO, which is not found in methanol. In methanol, the similarity of the slopes of Hammett plots indicates ionization of the H^+ from the N atoms in the two types of molecules.

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