O-Alkylation of *N*-Phenylhydroxylamine in Dimethyl Sulfoxide with Methylarenesulfonates

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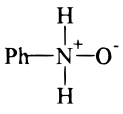
The methylation of *N*-phenylhydroxylamine (NPHA) with methylarenesulfonates in DMSO gives alkylation of the O atom in contrast to methylation in methanol where N alkylation occurs. The Hammett ρ values indicate that alkylations with N-methylanilines and NPHAs both involve the N atom. The NPHAs show "nominal α-effects" but involve comparison of N atoms with O atoms. The reactivity of the principle component, the zwitterion I, is examined with leaving group studies and comparison with benzyl alkoxide reactivity.

N-Phenylhydroxylamine (NPHA) exists largely as the zwitterion, **1**, in DMSO.[1] The evidence for this statement consists of the finding that ρ values for the basicity of NPHA change from −5.69 to −1.20 when the solvent is changed from methanol to DMSO. The corresonding change in the ρ value for the sterically similar *N*-methylanilines is −4.70 to −4.83.[1] Observation of the prototropic shift in the spectroscopy of the NPHA molecules is also reported.[1] Alkylation studies also show that the O atom is alkylated instead of the N atom, as is the case in methanol.[2] This functionality has not been previously investigated, so this paper reports the initial studies on its reactivity.



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Experimental Section

When 504 mg (4.62 mmol) of freshly prepared *N*-phenylhydroxylamine was treated with 5.13 mmol of methyl 4-nitrobenzenesulfonate (4-nosylate) in 75 mL of pure DMSO overnight a pale yellow mixture was obtained. This solution was added to 1 M cold hydrochloric acid and extracted three times with dichloromethane to remove most of the DMSO. Neutralization with sodium bicarbonate solution and 3-fold extraction with dichloromethane gave, after drying and solvent removal, a 34% yield of *O*-methyl *N*-phenylhydroxylamine, having a CH_3O signal in DMSO-d_6 at 3.78 ppm and IR bands suitable for OCH_3 at 2820−2810 cm^{-1} [3] and an OCH_3 stretch at 1150 cm^{-1} as well as NO at 1260 cm^{-1} (twinned with N−C for aromatic amine at 1240 cm^{-1}). Additionally, the ^1H NMR spectrum was extremely simple when the reaction was done in DMSO-d_6, showing only the OMe signal, with no trace of rearranged products associated with methylation of N in methanol-d_6.

The reactivity of substituted NPHA and *N*-methylanilines vs. substituted methylarenesulfonates in DMSO-d_6, reaction 1, was measured by our published kinetic method on a Varian XL200 NMR.[2,4]

Table 1. Summary of Rate Data for Methylation of Substituted *N*-methyanilines and Substituted *N*-Phenylhydroxylamines with Methylarenesulfonates in DMSO-d_6 at 29.5 °C

G_1	G_2	X	$k \times 10^5$(SD)	pK_{lg}^{Me}
		Me		
4-Me	4-MeO		9.95(0.05)	0.68
4-MeO	4-MeO		13.4(0.08)	
H	4-MeO		2.2(0.08)	
3-Cl	4-MeO		0.66(0.01)	
4-Cl	4-MeO		1.25(0.1)	
4-Cl	4-Br		9.1(0.3)	−0.74
4-Cl	4-NO_2		40.1 (0.0)	−2.36
4-Cl	H		3.5(0.5)	0.00
4-Cl	4-Me		1.7(0.2)	0.46
4-Cl	3-NO_2		9.1(0.4)	−2.15
4-Cl	4-Me, 3-NO_2		25.7(0.3)	−1.75
		OH		
H	4-MeO		6.2(0.1)	
H	4-Me		10.0(0.1)	
H	H		15.6(0.3)	
H	4-Br		38.3(0.4)	
H	4-F		32.5(0.3)	−0.33
4-Br	4-MeO		4.12(0.5)	
4-Me	4-MeO		17.6(0.5)	
4-NO_2	4-MeO		0.33(0.1)	

$$G_1ArNHX + CH_3O_3SArG_2 \xrightarrow{DMSO\text{-}d_6} G_1ArN^+HMe_2\ (a) \text{ or } G_1ArNH_2{}^+OCH_3\ (b) + {}^-O_3SArG_2 \quad (1)$$

Table 1 summarizes the results. A Hammett plot of log k_{nuc} for methylation with methylarenesulfonate ester in DMSO, Figure 1, shows a ρ value of −1.70. The corresponding plot for *N*-methylanilines, also in Figure 1, shows $\rho = -2.10$ for this "normal" nucleophile. Figure 2 shows β_{lg}^{Me} determinations[5] for both nucleophiles in DMSO-d_6.

The substituted benzyl alcohols were used as received or were synthesized by sodium borohydride reduction of the

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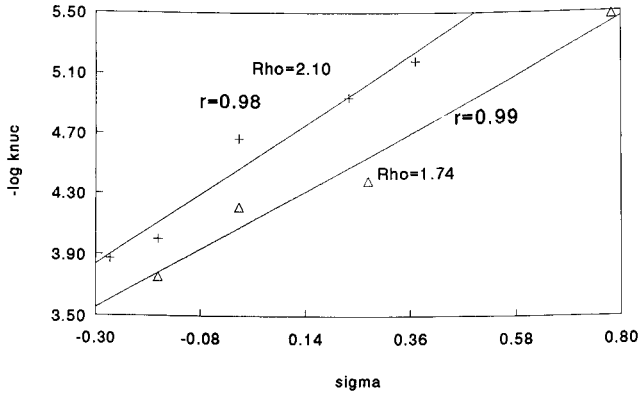


Figure 1. Hammett plot for substituted *N*-phenylhydroxylamines and *N*-methylanilines in DMSO-d_6 at 29.5 °C.

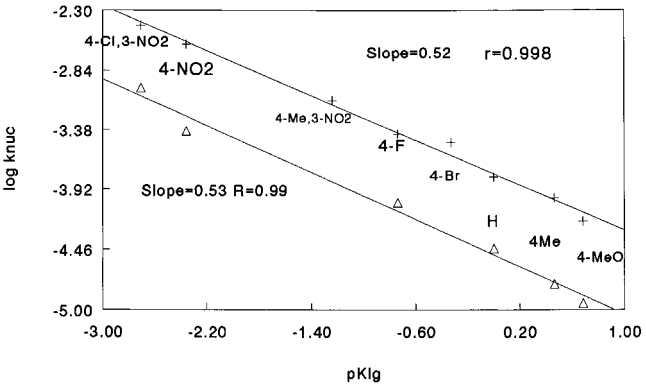
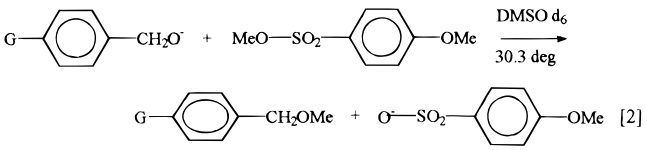


Figure 2. Determination of β_{lg}^{Me} for 3-ClNPHA (+) and *N*-methylaniline (△) in DMSO-d_6 at 29.5 °C.

Table 2. Summary of Rate Data for Methylation of Substituted Benzyl Alkoxide Anions in DMSO-d_6 at 30.3 °C, Eq 2



[2]

G	$k \times 10^2$(SD)	G	$k \times 10^2$(SD)
4-Me	5.2(0.3)	4-NO_2	2.3(0.1)
4-Cl	3.4(1.0)	4-MeO	6.2(0.5)

corresponding aldehydes in ethanol. All physical properties measured were consistent with the literature values of these compounds.

The sodium salts were generated in situ by addition of a standardized solution of deuterated dimsyl ion in DMSO-d_6 and dilution to give 0.20 molar solutions in DMSO-d_6. Kinetics of eq 2 were determined, with the internal standard being the DMSO-d_5 formed. Table 2 summarizes the data, with the Hammett plot shown in Figure 3. The ρ value for alkylation of the deprotonated alcohols of 0.41 is much smaller than for either *N*-methylaniline or NPHA.

Discussion

Any mechanism for this reaction must account for the involvement of N atoms on both nucleophiles to nearly the same extent from the signs and magnitudes of the ρ values. The negative signs indicate that both alkylations are hindered by electron withdrawal.[9] The O atom on the NPHA is more reactive than the N atom on *N*-methylaniline. This last fact may indicate a greater steric freedom for the O atom to approach the CH_3 group of the methylarenesulfonate. Alternatively, the slightly greater value of ρ for the *N*-methylaniline series may indicate greater resonance stabilization of the lone pair on N. The enhanced reactivity of the O atom could also be due to internal base catalysis provided by the "α-effect" of the lone pair of electrons on N, but this is unlikely because data show that the principle species is **1**.

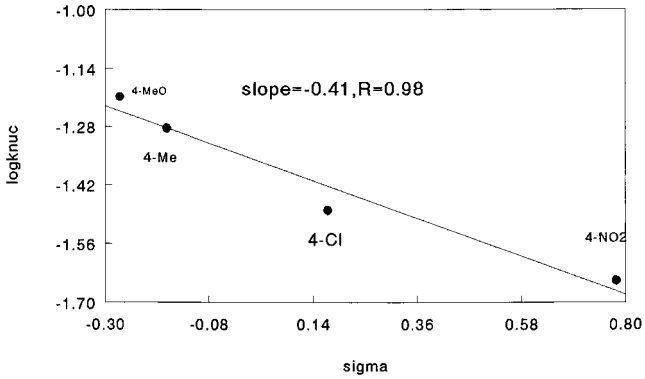


Figure 3. Hammett plot for g-BzONa in DMSO-d_6 vs $MeO_3SC_6H_4OMe$.

The nominal "α-effect" in this experiment matches N atoms on substituted *N*-methylanilines with the O atoms on substituted NPHA, "α-nucleophiles", so no real α-effect can be determined. (Although the pK_{NucH^+} values of the two nucleophiles are matched, they refer to different ionization sites from different atoms.) The mechanism must not involve OH, but the O^-, so the nucleophilicity might be expected to be more than the N atom on the normal nucleophile. The fact that the reactivity is higher than the uncharged N atom is thus not surprising.

The alkylation of the functional group $-NH_2^+O^-$ has not previously been studied, so this kind of reactivity may be normal for this group. The k_{rel} values are 2.84−4.17 (for G_1 = H, G_1 = 4-Br) compared to the *N*-methylaniline. Comparing Tables 1 and 2 shows that the benzyl alkoxide ions are much more reactive than the zwitterion, **1**. This is probably due to the expected greater basicity of the alkoxides. The two normal nucleophile series bracket the reactivity of the zwitterion, **1**, and serve to indicate the kind of reactivity to be expected of these species.

To ascertain the degree of transmission of the substituent effects to the O^- atom in **1** we compare the Hammett plots of reaction 1 with the sterically and structurally similar benzylalkoxide anions, eq 2 (Table 2). The Hammett plot shows that transmission of electronic effects through the CH_2 group (ρ = 0.41) is substantially less than through the $-NH_2^+-$ group (ρ = 1.74). The maximum ρ possible from the data, by neglecting the 4-Cl point, is 0.61, still only ca. 35% of that for the $-NH_2^+$ group ρ value.

It is possible that these ρ values indicate that the $-NH_2^+$ group transmits electronic information in solution chemistry better than the CH_2 group to the O^- center. That this cannot be the case for this apparently improved transmission of electronic information for the $-NH_2^+$ group was obtained from consideration of the results of computational chemistry. Structures for the substituted zwitterions, **1**, and substituted benzyl alkoxides were optimized with the AM1 Hamiltonian (HyperChem). The

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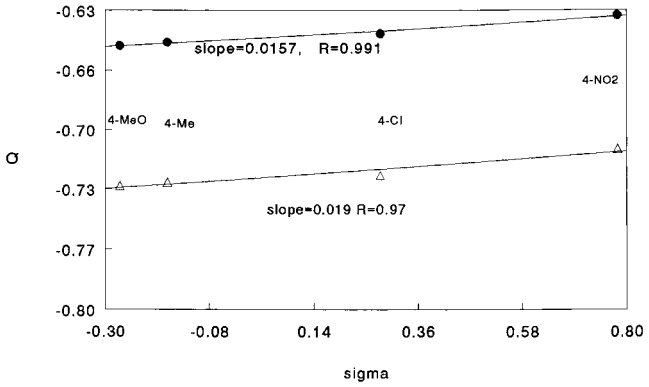
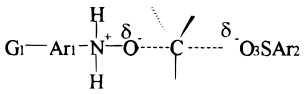


Figure 4. Hammett plot of O charge (Mulliken) for G-C_6H_4-NH_2O zwitterions (●) and for G-BzO^- anions (△).

Hammett plots for the computed charges (Mulliken charges) on the O^- atom appear in Figure 4. The ρ values (0.016 and 0.019) are small, and nearly the same, with a slight advantage for transmission of the substituent effect for the CH_2 group. If these ρ values can be accepted as indicators of gas-phase susceptibility of the O^- atoms to the substituent effects for the two species, then the larger ρ value for alkylation of NPHA must have a different explanation than transmission of electronic information through the respective groups to the O^- center.

The most probable reason for the similarity in ρ values between *N*-methylaniline and NPHA on alkylation, in spite of alkylation at sites differing in distance from the benzene ring, is that charge development around the region of the two N atoms of each species is similar. In the alkylation of *N*-methylaniline a formal positive charge develops on the N atom, although high-level ab initio computations indicate it is more likely that this charge is not entirely localized on N in either case, but also involves the H atom and the CH_3. In **1** a formal charge already exists on N but is formally neutralized by the oppositely charged O^-. This is shown in ammonia oxide, where the N atom is actually negative[9] at the 6-31* level of theory but the overall NH_3 group is positive. Also, trimethylammonium ion shows a positive charge on N at this same level of theory.[10] Formal charge on N is not fully descriptive of the situation. Both species show a major portion of positive charge on the H atoms. In either case, the positive charges develop around the NH, and the NH_2 groups are greatly increased as alkylation occurs in both cases. As the O atom becomes alkylated the negative charge on O, which should actually help stabilize the formal charge on the NH_2 portion (which are always positively charged in these species at all levels of theory) decreases, Chart 1. At the end of the reaction formal charge on NH_2 is no longer balanced by this negative charge on O^-. The process of concentrating formal positive charge next to the benzene ring is thus similar in both *N*-methylaniline and *N*-phenylhydroxylamine zwitterion. The susceptibility parameter, ρ, is thus expected to be similar in the two species, which is observed.

Chart 1



A second interpretation, suggested by a reviewer, is that the similarity of the ρ values is difficult to interpret in detail. One important factor must be the progress of bond formation between the nucleophilic atom and the methyl group at the transition state; this degree of bond formation could be similar or different in the two cases. Departure of the leaving group is, however, very nearly the same ($\beta_{lg}^{Me} = 0.53$ vs. 0.52).

The β_{lg}^{Me} values for *N*-methylaniline and 3-ClNPHA zwitterion, Figure 2, are very similar (0.53 and 0.52, respectively). This fact indicates a transition state (TS) that produces nearly the same degree of bond cleavage between the CH_3 and the arenesulfonate anion leaving group. The $-NH_2{}^+O^-$ group is thus behaving like a "normal" nucleophile from the standpoint of pushing out the leaving group. Interestingly, the β_{lg}^{Me} value for *N*-methylaniline in DMSO-d_6 is nearly the same as for methanol-d_4 (2) (0.53), whereas the value for the NPHA changes from 0.47 in methanol-d_4 (2) to DMSO-d_6, 0.52, indicating a lesser nucleophilic push for the zwitterion than for the normal NPHA. These changes are small, but similar changes are claimed to be real and significant.[5] This finding is consistent with the reported α-effect for NPHA in methanol-d_6,[2] but shows no special reactivity occurs in DMSO-d_6.

Acknowledgment. We thank the National Science Foundation for supporting this work through NSF-RUI 9214994. We also thank reviewer 2 for his remarks, which stimulated the comparison work with substituted benzyl alkoxides.

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