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Hammett Correlations of the Sulfonamide Proton Chemical Shift in a Series of N-(substituted aryl)-p-Toluenesulfonamides

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We have shown previously that excellent correlations of amide proton chemical shifts with standard Hammett substituent constants (σ) are obtained in several N-(4-substituted aryl) carboxamide systems (Setliff et al., 1992; Setliff et al., 1995). In this regard we were curious as to whether similar correlations would exist in sulfonamide systems. Thus, we prepared a series of N-(4substituted phenyl)-p-toluenesulfonamides and plotted the sulfonamide proton chemical shift (δ_{NH}), as determined in dimethyl sulfoxide (DMSO), vs the standard Hammett substituent constant (σ_G) (Exner, 1988) for the substituent G in the 4-position. As in the aforementioned carboxamide series, this note also reports the results of an additivity study using two phenyl substituents. In addition, the validity of the heterocyclic nitrogen 3-aza and 4-aza replacement constants determined previously (Setliff et al., 1993) was tested.

The N-aryl-p-toluenesulfonamides were prepared from the appropriate arylamine and p-toluenesulfonyl chloride as shown in Fig. 1. The general procedure employed was as follows: The arylamine (0.50 g), dry pyridine (2.5-3.0 mL) and 1.1 molar equivalent of p-toluenesulfonyl chloride were combined and heated under reflux . For compounds where G = $(CH_3)_2N$, CH_3O, and CH_3, the reflux time was 15 minutes. For all other compounds the reflux time was extended to 45 minutes, except for G = NO_2 which required one hour.

Upon completion of reflux, the reaction mixture was cooled to room temperature and poured into cold water (300 mL). After the water was decanted, the residual oil was taken up in ethanol (200 mL) and water was slowly added in 50 mL portions until the precipitation of the sulfonamide was complete. The crude product was collected by suction filtration, washed on the filter with cold water, and recrystallized from aqueous ethanol. Yield and melting point data are reported in Table 1.
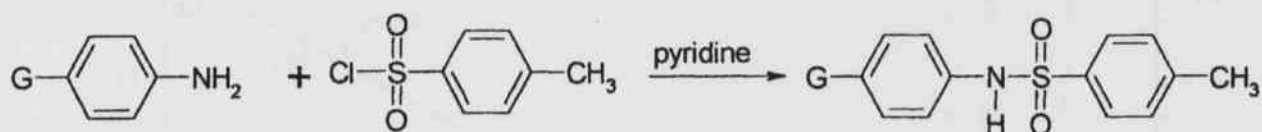

Fig. 1. Preparation of the p-toluenesulfonamides.

Table 1. Experimental data for the p-toluenesulfonamides.

G	mpt. (°C)	lit. mpt. (°C)	% Yield	δ_{NH} (ppm)	σ_G
$(CH_3)_2N$	124-125	----	59.3	9.58	-0.63
OCH_3	113-114	114	81.7	9.85	-0.28
CH_3	118-119	118	93.5	10.05	-0.14
H	101.5	103	79.0	10.24	0
F	79-80	----	80.2	10.18	0.06
4-Br-3-Me	144-145	----	64.4	10.37	0.16
Br	101	101	93.2	10.38	0.22
3-aza	171-172	----	91.0	10.52	0.26
$COCH_3$	202-205	203	85.0	10.81	0.47
CF_3	139-140	----	28.8	10.84	0.53
CN	180-181	----	83.8	11.00	0.71
NO_2	180	191	68.3	11.24	0.81
4-aza	190	----	53.1	12.20	1.71

Most of the sulfonamides' melting points were available in readily accessible tables (Rappoport, 1967), and our obtained values agreed well with those listed. The low melting point of the 4-nitrophenyl derivative was attributed to a trace quantity of residual 4-nitroaniline, as revealed in the proton NMR spectrum. Structures of all sulfonamides were verified by their infrared and ^{1}H NMR spectra as well as C,H,N elemental analyses (Quantitatative Technologies Inc., Whitehouse, NJ). The Infrared spectra were obtained (KBr disks) on a Nicolet 500 Magna FTIR instrument. The N-H stretch of the sulfonamide group was present in all compounds in the range v 3190-3390 cm^{-1}. The symmetrical and unsymmetrical stretch frequencies of the O=S=O group (v 1140-1160 and 1300-1350 cm^{-1}) respectively, were visible in all of the spectra..

Samples were prepared for ^{1}H NMR spectroscopy (Bruker ACF-200 MHz instrument) at a concentration of 20mg/mL of deuterated DMSO containing 0.1% tetramethylsilane. The sulfonamide proton resonance in all compounds was clearly visible as the farthest downfield signal in the range δ 9.5-12.2 ppm (Table 1). The aromatic ring protons appeared in the expected range with the proper integration and exhibited the expected splitting patterns. Methyl, methoxy, and acetyl proton resonances appeared as sharp singlets at their normal ppm values.

Excellent linear correlation of δ_{NH} with the Hammett substituent constant σ_G (correlation coefficient 0.98) was obtained (Fig.2), and the linear relationship is expressed in slope intercept form by the equation below. The positive slope

$$\delta_{NH} = 1.16\ \sigma_G + 10.22$$

indicates the sensitivity of the sulfonamide proton to elec-

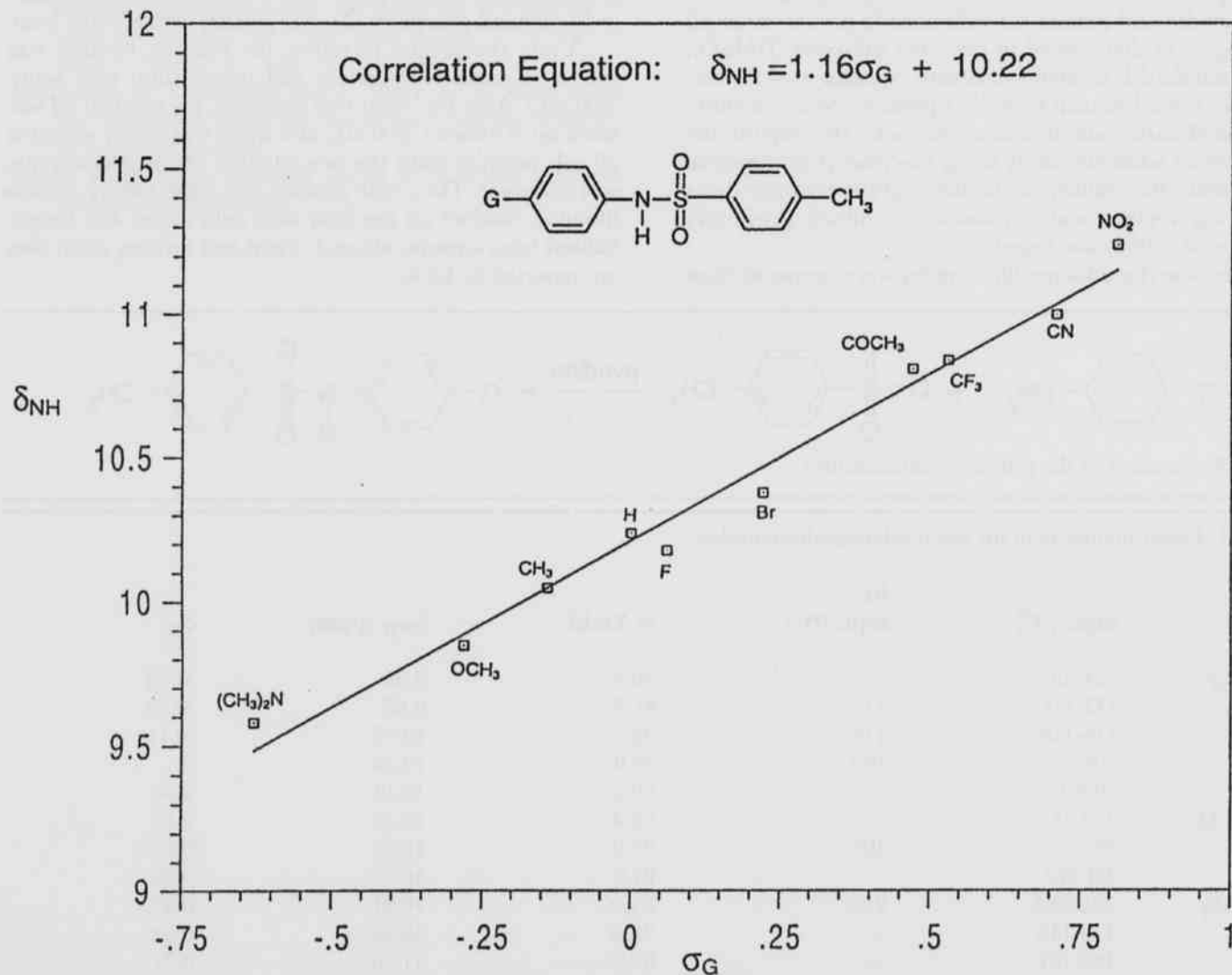Fig. 2.   Correlation of the sulfonamide proton chemical shift with the Hammett substituent constant.

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tron withdrawing groups as was the case in the previous carboxamide studies. It is noteworthy that the sulfonamide slope of 1.16 is larger than any of the carboxamide slopes which were of the order 0.57 - 0.70 (Setliff et al., 1993). A direct comparison of the p-toluenesulfonamide and benzamide correlations (Setliff et al., 1995) are shown in Fig. 3. The difference in slope is likely due to the greater acidity of the sulfonamide protons owing to the adjacent sulfonyl group. Enhanced acidity in turn results in more efficient hydrogen bonding to the DMSO solvent, thus causing greater deshielding of the amide proton signal. The substituents exert proportional effects in the two systems as noted in Fig. 3.

As we had done in our earlier studies on the various carboxamide systems, we checked for additivity of the effects of two substituents on the N-phenyl ring. Thus, we prepared N-(4-bromo-3methylphenyl)-p-toluenesulfonamide and observed the δ_{NH} at 10.37 ppm (Table 1). When the algebraic sum of $\sigma_{4-bromo}$ (0.22) and $\sigma_{3-methyl}$ (-0.6) is substituted for σ_G in the correlation equation, the calculated value for δ_{NH} is 10.40 ppm. This small deviation (0.03 %) from the exper-

imental value suggests that the bromo and methyl substituents do exert a predictable additive effect on the chemical shift of the sulfonamide proton.

Finally, we were curious to see if our heterocyclic replacement constant values of σ_{3-aza} and σ_{4-aza} as determined in the previously studied carboxamide systems would be valid in the sulfonamide system. Therefore, we prepared N-(3-pyridyl)-p-toluenesulfonamide (G = 3-aza in Table 1) and N-(4-pyridyl)-p-toluenesulfonamide (G = 4-aza in Table 1) and observed their respective δ_{NH} values as shown in Table 1. Substitution of these experimental values into the correlation equation and solving for σ_G yields a replacement constant value of 0.26 for σ_{3-aza}, and 1.71 for σ_{4-aza}. The positive values indicate the electron withdrawing nature of the heterocyclic nitrogen, and the magnitude of the 4_{-aza} should be greater since the electron withdrawing "through conjugation" resonance effect that establishes a formal negative charge on the ring nitrogen is operative. Although the 3-aza value is fairly close to the mean value of 0.34 determined from the various carboxamide systems (Setliff et al., 1993), the 4-aza value of 1.71 is much greater
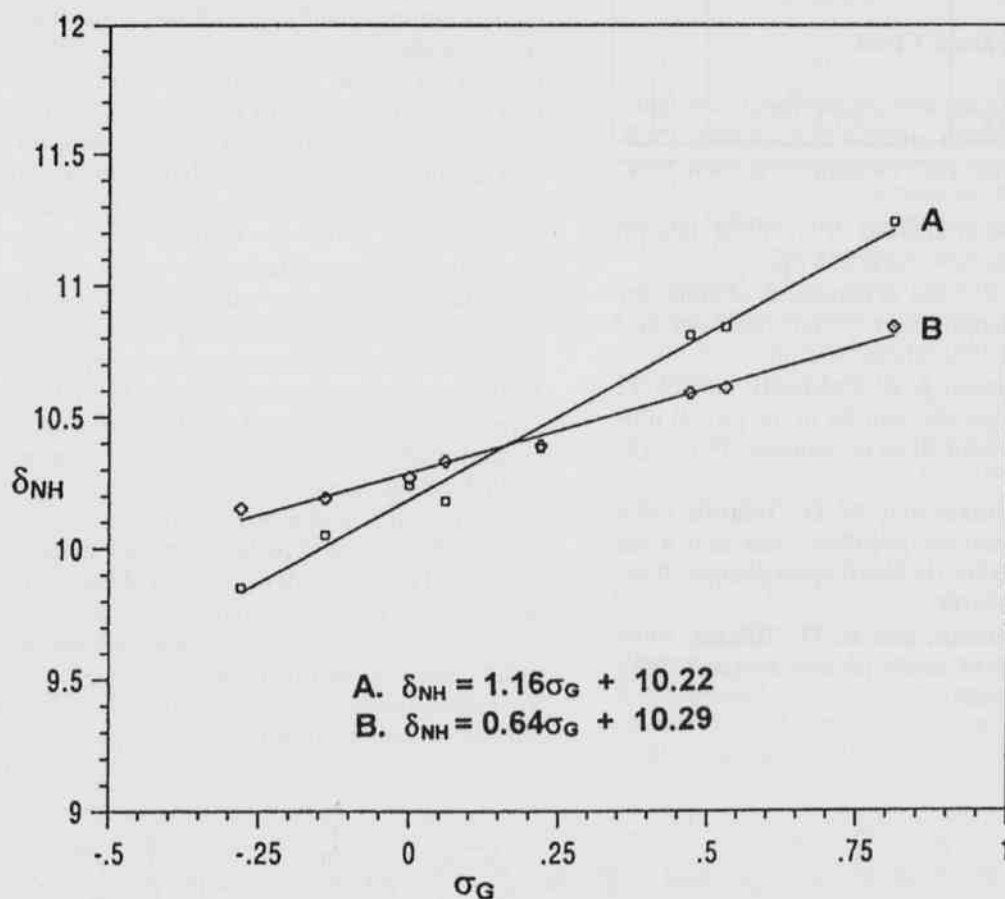

A. $\delta_{NH} = 1.16\sigma_G + 10.22$
B. $\delta_{NH} = 0.64\sigma_G + 10.29$

Fig. 3. Comparison of the p-toluenesulfonamide (A) and the benzamide (B) correlations.

than the mean carboxamide value of 0.55. This could be explained in terms of poor competitive delocalization of the sulfonamide nitrogen's lone pair with the sulfonyl oxygens owing to inefficient 2pN-3pS π overlap. This, in turn, would allow for very efficient "through conjugation" to the 4-aza nitrogen. However, in the carboxamide systems competitive delocalization of the nirogen lone pair with the the carbonyl group, which involves 2pN-2pC π overlap is more effective allowing less efficient "through conjugation" to the 4-aza nitrogen in those systems.

Although we conclude that Hammett correlations exist, and that effects of two groups are predictably additive, we can not say that the heteroatomic replacement values are interchangeable with those in carboxamide systems. Actually, the literature reports numerous values for $\sigma_{3\text{-}aza}$ and $\sigma_{4\text{-}aza}$ which vary according to the methods used to determine them (Charton, 1978). Unlike the classical Hammett substituent constants, heterocyclic atomic replacement constants are not truly constants at all.

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