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Although direct insulin administration is the primary strategy for the management of diabetes, certain agents have been found to stimulate the production of insulin in the pancreas and, therefore, offer an alternative management option. Notable among these hypoglycemic agents are the sulfonylureas 1-tosyl-3-butylurea (tolbutamide) and 1-tosyl-3-(N-piperidyl)urea (Gilman, 1985). Aryl sulfonyl ureas have also received attention as potential anticancer agents. Howbert and coworkers prepared and studied 143 such compounds, several of which were 1-tosyl-3-(substituted phenyl)ureas (Howbert et al., 1990). The 1-tosyl-4-chlorophenyl derivative was found to have antitumor activity. A closely related compound, 1-(5-indanesulfonyl)-3-(4-chlorophenyl)urea, proved sufficiently active to warrant large scale production for clinical trials by Eli Lilly Co. and was assigned the generic name sulofenur.

Because of the medicinal importance of tosylureas and our previous studies of aryl substituent effects on the amide linkage of benzamides (Setliff et al., 1995), nicotinamides (Setliff et al., 1992) and p-toluenesulfonamides (Setliff and Spradlin, 2000), we undertook the present investigation of the 1-tosyl-3-(4-substituted phenyl)urea system. As in our previous work, we prepared a series of compounds with a variety of substituents (G) in the 4-phenyl position, obtained their ^{1}H NMR spectra in DMSO, and attempted to correlate the amide proton chemical shifts with the standard Hammett substituent constants (σ_G) (Exner, 1988). Unlike previous amide systems investigated, the present tosylarylurea system has two amide protons to be monitored, namely the anilide proton (on the nitrogen bonded to the benzene ring) and the sulfonamide proton (between the sulfonyl and carbonyl groups).

The series of 1-tosyl-3-(substituted phenyl)ureas (Table 1) were synthesized by the reaction of tosyl isocyanate (Aldrich) with the appropriate substituted aniline in dry chloroform (Fig. 1).
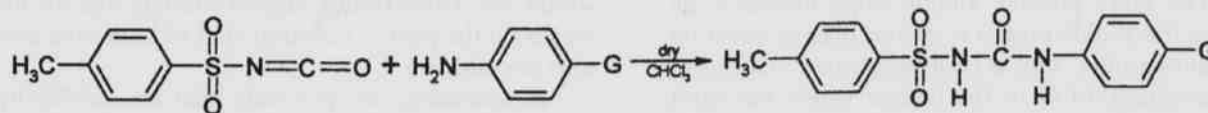
Table 1. Experimental data for the 1-tosyl-3 -(4-substituted phenyl)ureas

Cpd. #	G	% Yield	M.P. (°C)
1	H	81.4	170.5-171.5
2	CH_3	99.2	152-153
3	F	Quant.	172-173
4	OCH_3	71.9	157-158
5	Cl	90.3	176-176.5
6	CF_3	72.4	189-190
7	$COCH_3$	82.2	182-182.5
8	CN	87.8	196-197
9	NO_2	91.1	245-247 d.
10	4-Br-3-CH_3	86.0	185-186
11	3-Cl-4-OCH_3	Quant.	174-175

The experimental preparation of the ureas was carried out as follows: All substituted anilines were distilled or recrystallized prior to use. The mass of the 4-substituted aniline needed to react exactly with 0.40mL (0.516 g) of the isocyanate was calculated for each reaction. This quantity of amine was dissolved in dry chloroform (2.0 mL)(8.0 mL required for 4-nitroaniline), and 0.40 mL tosyl isocyanate was then added quickly by syringe. In most cases an exothermic reaction occurred, and a solid began to form in a matter of seconds. The resulting suspension was stirred under gentle reflux for 15 min. When instantaneous precipitation did not occur, the clear solution was heated under reflux for one hour and then cooled or evaporated to isolate the product. The crude tosylureas were washed on the vacuum filter with cold chloroform and then recrystallized from ethanol-water (the 4-nitro derivative required benzene). Experimental data are summarized in Table 1. All compounds have been prepared previously (Howbert et al. 1990) by a slightly different procedure, some in lower yield.

Fig. 1. Preparation of the 1-tosyl-3 -(4-substituted phenyl)ureas

Melting points of our compounds were in good agreement with those reported by Howbert's group. Our compounds were further characterized by IR and ^{1}H NMR analysis. The infrared spectra of all compounds (KBr disks; Nicolet Magna FT-IR spectrophotometer) exhibited the expected absorbtions for the anilide and sulfonamide NH stretch, the sulfonyl O=S=O symmetrical and unsymmetrical stretches, and the anilide carbonyl stretch. The proton spectra of all compounds (Bruker AC-F 200 MHz instrument, DMSO$_{d6}$ as solvent with TMS as internal standard) exhibited, in addition to the anilide and sulfonamide proton signals (Table 2), all other expected resonances with the expected multiplicities and integration.

Table 2. Proton chemical shift data and Hammett substituent constants

Cpd. #	Sulfonamide δ_{NH} (ppm)	Anilide δ_{NH} (ppm)	σ_G
1	10.65	8.82	0
2	10.67	8.71	-0.14
3	10.75	8.89	0.06
4	10.59	8.65	-0.28
5	10.79	9.00	0.22
6	11.01	9.28	0.53
7	11.05	9.24	0.47
8	11.10	9.37	0.71
9	11.15	9.56	0.81
10	10.78	8.89	0.16*
11	10.73	8.83	10.10*

*additive value

As shown in Fig. 2, good linear correlation of the amide chemical shifts (δ_{NH}) with the standard Hammett substituent constants (σ_G) was obtained. The correlation equations with their correlation coefficients are

anilide proton $\qquad \delta_{NH} = 0.82\ \sigma_G + 8.84 \quad r^2 = 0.99$
sulfonamide proton $\quad \delta_{NH} = 0.55\ \sigma_G + 10.72 \quad r^2 = 0.96$

The better correlation of the anilide shifts can be ascribed to the fact that this proton is closer to the G substituent, and electronic effects can act more proportionately.

Analysis of the two equations provides additional information. The positive slopes (Hammett ρ value) indicate that the chemical shifts are sensitive to electron withdrawing groups (σ standard values > 0). As G becomes more electron withdrawing the acidity of the amide proton increases, permitting more efficient hydrogen bonding of the hydrogen with DMSO solvent, thus resulting in a farther downfield shift. The more positive anilide slope indicates the effect of G on the anilide proton is greater than its effect on the sulfonamide proton. This is easily explained in terms of the closer proximity of G to the former where the short range inductive and resonance effects can operate more efficiently. The magnitude of the Y intercept is a reflection of
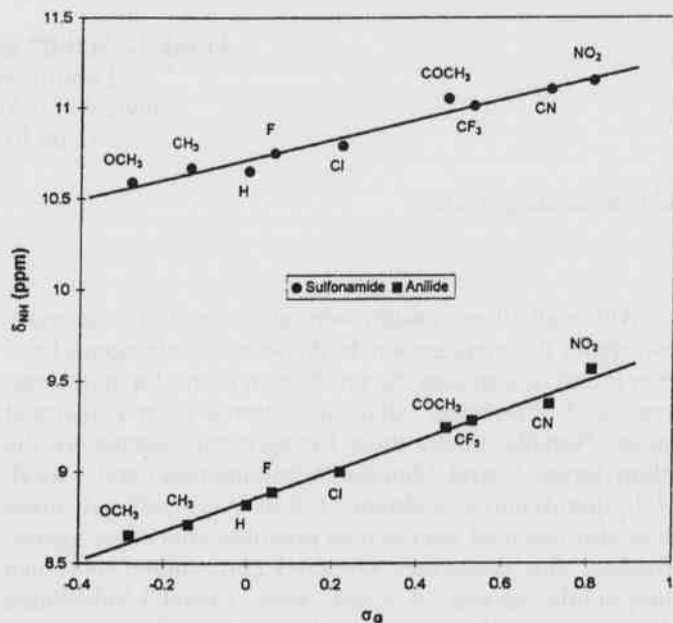

Fig. 2. Correlation of amide proton chemical shifts with Hammett substituent constants

the relative acidity of the two protons. Therefore, the sulfonamide proton (intercept 10.72) is demonstrated to be more acidic than the anilide proton (intercept 8.84). This is predictable in view of the former being situated between the sulfonyl and carbonyl groups.

In order to test for additivity of the electronic effects of two susbstituents upon the chemical shifts, we prepared two 1-tosyl-3-(3,4-diubstituted aryl)ureas, namely the 4-bromo-3-methyl derivative (cpd 10, Table 2) and the 3-chloro-4-methoxy compound (cpd 11, Table 2). For compound 10, the numerical sum of the σ values for 4-bromo (0.22) and 3-methyl (-0.06) when substituted into the respective correlation equations predicts a δ_{NH} value of 8.97 ppm for the anilide proton and 10.80 ppm for the sulfonamide proton. The experimental values obtained were 8.89 and 10.78 ppm, both within 1% of the calculated values. Similarly, for compound 11, the numerical sum of the σ values for 4-methoxy (-0.28) and 3-chloro (0.37), when inserted into the equations, yielded a predicted chemical shift of 8.91 ppm for the anilide proton and 10.77 ppm for the sulfonamide proton. The respective experimental values were 8.83 and 10.73 ppm. Again, calculated and observed values were within 1%. These results suggest strongly that the electronic effects on the proton chemical shift of both urea amide protons are additive.

In summary, we conclude that the acidity/hydrogen bonding ability of both urea protons can be controlled by the nature of the substituent in the 4-position in accordance

with Hammett theory, and that the effects of substituents in the 3-and 4-position operate in an additive fashion. Although all data were obtained in DMSO solvent, extrapolation of these data to aqueous systems could prove useful in prediction of hypoglycemic activity and/or development of synthetic strategies for the preparation of sulfonyl ureas as further candidates for antitumor therapy.

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