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Substituent Effects on the NH Proton Chemical Shifts of *p*-Substituted Phenylureas

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It has been recognized that the NH proton chemical shifts of substituted anilines[1,2] obey the Hammett's rule as do the side chain CH proton chemical shifts of substituted benzenes.[3] In this study the chemical shifts of the NH protons of *p*-substituted phenylureas were measured to study some correlations between the chemical shifts and vairous substituent constants, and discussions will be given about the substituent effect of *p*-substituent groups on the ureido(–$NHCONH_2$) group.

Dimethyl sulfoxide(DMSO) was chosen as solvent for the reason that DMSO dissolve the samples insoluble in most organic solvents, and also in order to eliminate complication due to the onset of proton exchange among the NH and NH_2 groups which provide an additional source of line broadening and coalescence. Under these conditions, the molecules of *p*-substituted phenylureas are isolated from each other and are hydrogen-bonded to the DMSO molecules with which they can not hydrogen exchange.[4-6]

The signals near 6.2 ppm and 3.6 ppm from the reference methyl signal of DMSO are assigned to the NH and NH_2 protons respectively and the signals near 4—5 ppm are assigned to the phenyl ring protons. In the phenylureas as well as in formamide, the ^{14}N–H spin-spin coupling is not observed because of the rapid relaxation of ^{14}N quadrupole due to the strong electric field gradients around the N nucleus caused by the CO group.[7] And the NH proton gives only a rather broadening signal due to this ^{14}N–H spin-spin interaction and the quadrupolar effect. For the NH_2 protons some difference in chemical shift would be expected between them due to the restricted rotation about the C–N bond, but only a very broadening signal is observed for the above mentioned reasons. It was observed that all the *p*-substituted phenylureas, except the NO_2 derivative, show a slight shift towards the higher field with dilution

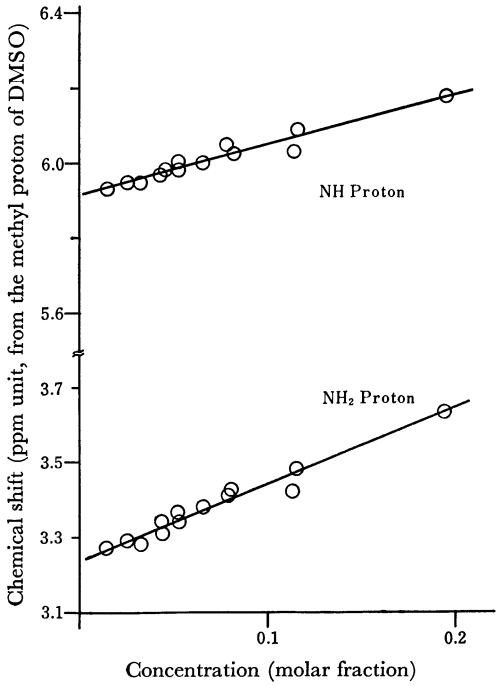

Fig. 1. Plottings of the NH and NH_2 proton chemical shift *vs.* concentration (molar fraction) of the phenylurea.

and the chemical shifts show a linear relationship with concentration (Fig. 1). The chemical shifts extrapolated to infinite dilution were obtained by the least square methods.

Now, the following factors may be considered, which affect on the chemical shifts of NH_2 and NH protons.

1) Hydrogen bonding and hydrogen exchange.
2) Magnetic anisotropy of the *p*-substituted phenyl group.
3) Variation of the electron density on each N atom.

As mentioned above, the phenylurea molecules in dilute solution exist in a solvated form with the DMSO molecules, and thus the intermolecular as well as intramolecular[8] hydrogen bondings could be ignored. Although detailed studies at various temperatures will be left in future, it is to be allowed from the example by Sunners *et al.*,[5] that the proton exchange is not very important at room temperature. Hence the hydrogen exchange between the NH and NH_2 groups may be assumed to be constant. As regards the factor (2), the anisotropic influence of the phenyl ring may predominantly exert

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8) Intramolecular hydrogen bonding between the NH_2 protons and the phenyl ring can be considered.

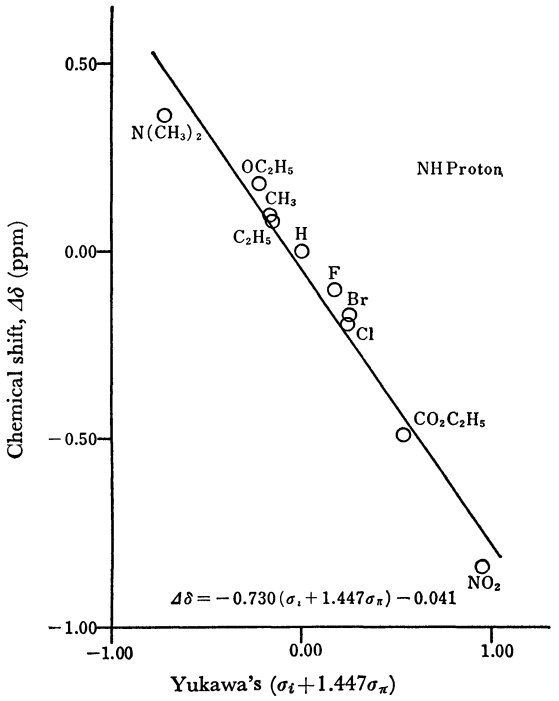

Fig. 2. Correlation of the NH proton chemical shifts and Yukawa's $(\sigma_i+\gamma\sigma_\pi)$ constant.

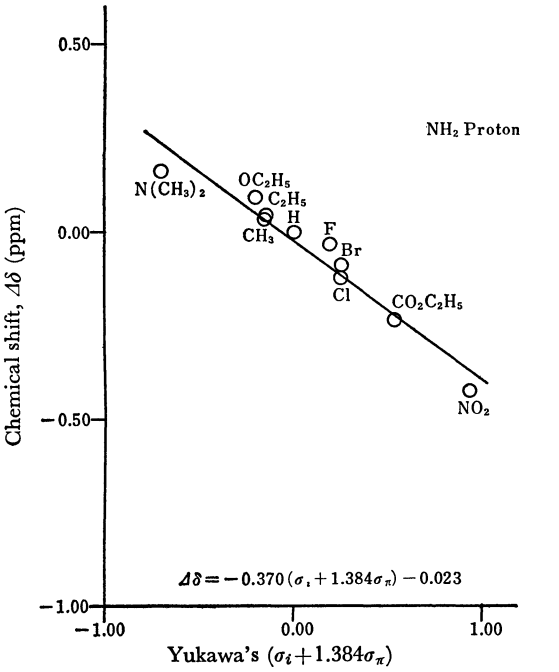

Fig. 3. Correlation of the NH_2 proton chemical shifts and Yukawa's $(\sigma_i+\gamma\sigma_\pi)$ constant.

on the chemical shifts, but the *p*-substituent may be almost ignored sterically and then the anisotropic effect may be considered to be constant. Consequently, only the factor (3), that is, the variation of shielding around the protons by the change of the electron densities on the N atoms is to be considered.

Then, studies were made as to the correlations between the difference of chemical shifts from the standard sample (phenylurea) and the various substituent constants. A fairly good linearity was obtained with Hammett's σ_p values[9] as well as with Taft's $(\sigma_I+2\sigma_R^0)$ values,[10] and the best result with Yukawa's $(\sigma_i+\gamma\sigma_\pi)$ values,[11] but not with other substituent constants. In Figs. 2 and 3 are shown the plottings against Yukawa's $(\sigma_i+\gamma\sigma_\pi)$ values except the I group since the substituent constant can not be estimated. Both the NH and NH_2 protons give a good linear relationship with Yukawa's values, namely, $\Delta\delta=-0.730(\sigma_i+1.447\sigma_\pi)-0.041$ for the NH proton and $\Delta\delta=-0.370(\sigma_i+1.384\sigma_\pi)-0.023$ for the NH_2 proton.

It is, therefore, concluded that the variation of the electron density on the N atom due to the electronic effect of *p*-substituent group determine the NH proton chemical shift. Furthermore, from the fact that the chemical shifts of the NH_2 protons as do the chemical shifts of the NH protons also in accordance with the Hammett's rule, it is confirmed that the N atom of NH_2 group is capable of conjugation with the phenyl ring system through the π-electrons of the CO group.

The ratio of the line slopes(ρ) of the NH proton to that of the NH_2 proton is about 2, that is, the NH proton shows twice as much σ-dependance as the NH_2 proton, and it appears that the H atom of the NH group directly bonded to the phenyl ring ought to be rather more sensitive to the *p*-substituent effect than do the NH_2 protons.

Experimental

Preparation of Samples. The *p*-substituted phenylureas (R-C$_6$H$_4$-NHCONH$_2$) were prepared by the reaction of sodium cyanate with the corresponding anilines in aqueous acetic acid solutions[12] and were purified by recrystallization. The identity and purity was confirmed by the mp determination and also by the IR spectra in a KBr disk.

Measurements. The PMR spectra were measured with a Varian A-60 Spectrometer at 30°C. The spectra were referred to the methyl signal of DMSO, and the chemical shifts were taken in ppm units lower field side from the reference. They were checked and corrected with the water signal of the external standard (in capillary) as a secondary reference. The position of each signal was measured using it's signal peak. A commercial guaranteed reagent was used as solvent (DMSO) and was treated with a molecular sieve before use in order to remove the contaminating water.

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