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Linear Free Energy Relations and the Hammett Equation for Substituted Pyridine 1-Oxides (1)

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It is recommended that a self-consistent set of sigma constants be used to obtain linear free energy relations with pyridine 1-oxides rather than using adjusted benzoic acid sigma constants. These recommended constants are derived from the literature values of the acid dissociated constants of the protonated substituted pyridine 1-oxides. A survey and discussion of linear free energy relations using these new constants (σ_{PyNO}) is given. Comparisons of correlations using adjusted benzoic acid sigma constants and (σ_{PyNO}) are presented.

Since the development of the Hammett equation and the benzoic acid sigma constants, studies have shown the existence of linear free energy relationships which have required different sets of sigma constants. Roberts and Moreland (4) found a relation for 4-substituted bicyclo-[2.2.2]octane-1-carboxylic acid where there is no conjugation in the ring system and they calculated sigmas for this system. Also, Jaffe (5) found relationships for substituted phenols and anilines where conjugation with the aromatic ring proceeds directly to the reaction site and new constants were calculated for these two systems.

A novel attack to the problem of linear free energy relations with pyridine 1-oxide systems was first suggested by Jaffe (6) and subsequently by Katritsky and Swinbourne (7). A substituent constant was assigned to the heteroatom "substituent" (N) and correlations were made by an additive procedure. Shindo (8) extended this idea to substituted pyrazine *N*-oxides by assigning σ values to the ring nitrogen and to the N-O group for the mono and dioxides. Hence adjusted benzoic acid sigma constants alone are not sufficient for aromatic amine oxides, but in some cases additive relations or some type of adjusting procedure, which takes into account the additional resonance forms made available by an introduction of a nitrogen atom into the aromatic ring system must be utilized. This type of procedure is fundamentally sound although inconvenient, but does call to attention that the pyridine 1-oxide system and benzoic acid systems behave differently. Since linear free energy correlations with pyridine 1-oxides are becoming so wide-spread, it is necessary to develop and use a consistent set of constants.

Some of the correlations using adjusted benzoic acid

sigma constants to correlate different physical properties of various systems containing substituted pyridine 1-oxides are: (9-21)

1. F^{19} chemical shifts in the system $\text{TiF}_4 \cdot \text{CH}_3\text{C}(\text{O})\text{N}(\text{CH}_3)_2 \cdot 4\text{-Z-PyNO}$ (9).
2. The electronic spectrum of VOL_2X_2 where L is a 4-substituted pyridine 1-oxide (10).
3. The O-H stretching frequency $\bar{\nu}_{\text{OH}}$ in the reaction of phenol with 4-substituted pyridine 1-oxides (11).
4. The electronic and infrared spectra of nickel(II)

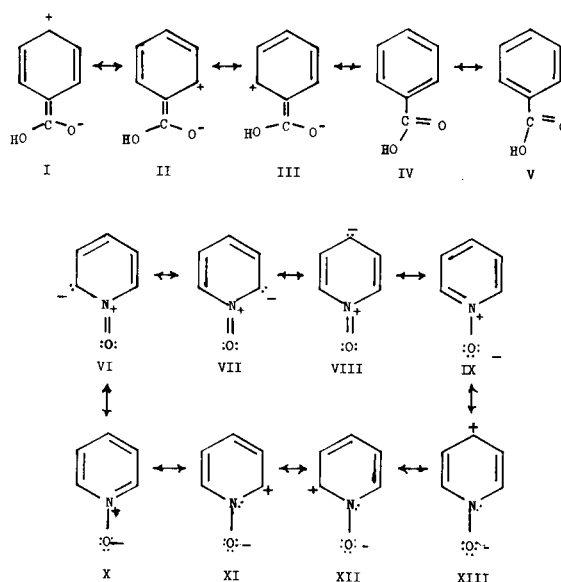


Figure 1. Canonical forms for benzoic acid and pyridine 1-oxide.

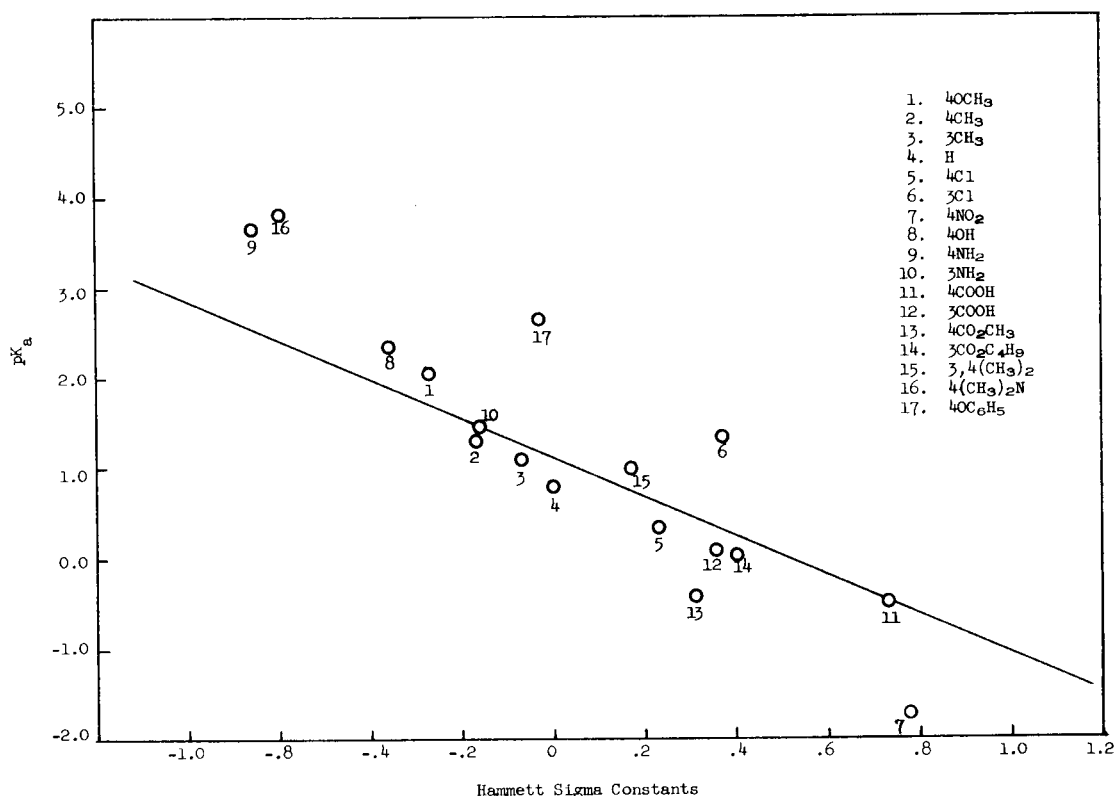


Figure 2. Plot of pK_a 's of the conjugate acids of some 3- and 4-substituted pyridine 1-oxides versus benzoic acid sigmas to determine ρ (16).

complexes with 4-substituted pyridine 1-oxides (11).

5. The N-O stretching frequency $\bar{\nu}_{N-O}$ and proton chemical shifts for the free 3- and 4-substituted pyridine 1-oxides and their uranyl chloride complexes (12).

6. The infrared frequency of the carbon-carbon double bond of 1-(4-Z-PyNO)-3-ethylene-2,4-dichloroplatinum(II) complexes (13, 19).

7. The half-wave potentials ($E_{1/2}$) of 3- and 4-substituted pyridine 1-oxides (14).

8. The basicity of 3- and 4-substituted pyridine 1-oxides (16).

9. The temperature dependence of the magnetic susceptibility of the 1:1 complex of 4-substituted pyridine 1-oxides with copper(II) chloride and bromide (15).

10. The N-O stretching frequency, $\bar{\nu}_{N-O}$, for many substituted pyridine 1-oxides (7, 17, 22-29). (See reference 17 for a complete discussion.)

11. The N-O and Ti-O stretching frequencies of TiF_4 complexes of 4-substituted pyridine 1-oxides (18).

12. The OH stretching frequency $\bar{\nu}_{OH}$ in the reaction of methanol with a series of substituted pyridine 1-oxides (30).

13. The thermodynamic value K_{eq} for the charge

transfer complexes with iodine and substituted pyridine 1-oxides (20).

14. The shift of vanadyl oxygen stretching frequency $\Delta\bar{\nu}_{V-O}$ for 4-substituted pyridine 1-oxide adducts of bis-(2,4-pentanedionato)oxovanadium(IV) (21).

In almost every instance, these correlations yielded linear relations with adjusted sigmas (σ^+ , σ^- , σ_R or σ^*), and not with benzoic acid σ values. In some studies a mixture of σ^+ , σ , and σ^- were used on the same plot.

It is indeed unfortunate that one single set of substituent constants has not been used. Having such a set of constants would facilitate the recognition of unusual effects in systems containing pyridine 1-oxides. As it now stands, it is difficult to detect an unusual effect.

It is understandable that benzoic acid sigma constants do not fit the pyridine 1-oxide system. Since the resonance interaction can proceed to the reaction site in pyridine 1-oxide and not in benzoic acid, the two systems are considerably different. As pointed out by several workers, pyridine 1-oxide most probably exists in a resonance state in which the electron densities are enhanced in the 2-, 4- and 6-positions. Linton (31) measured and compared the dipole moments of pyridine

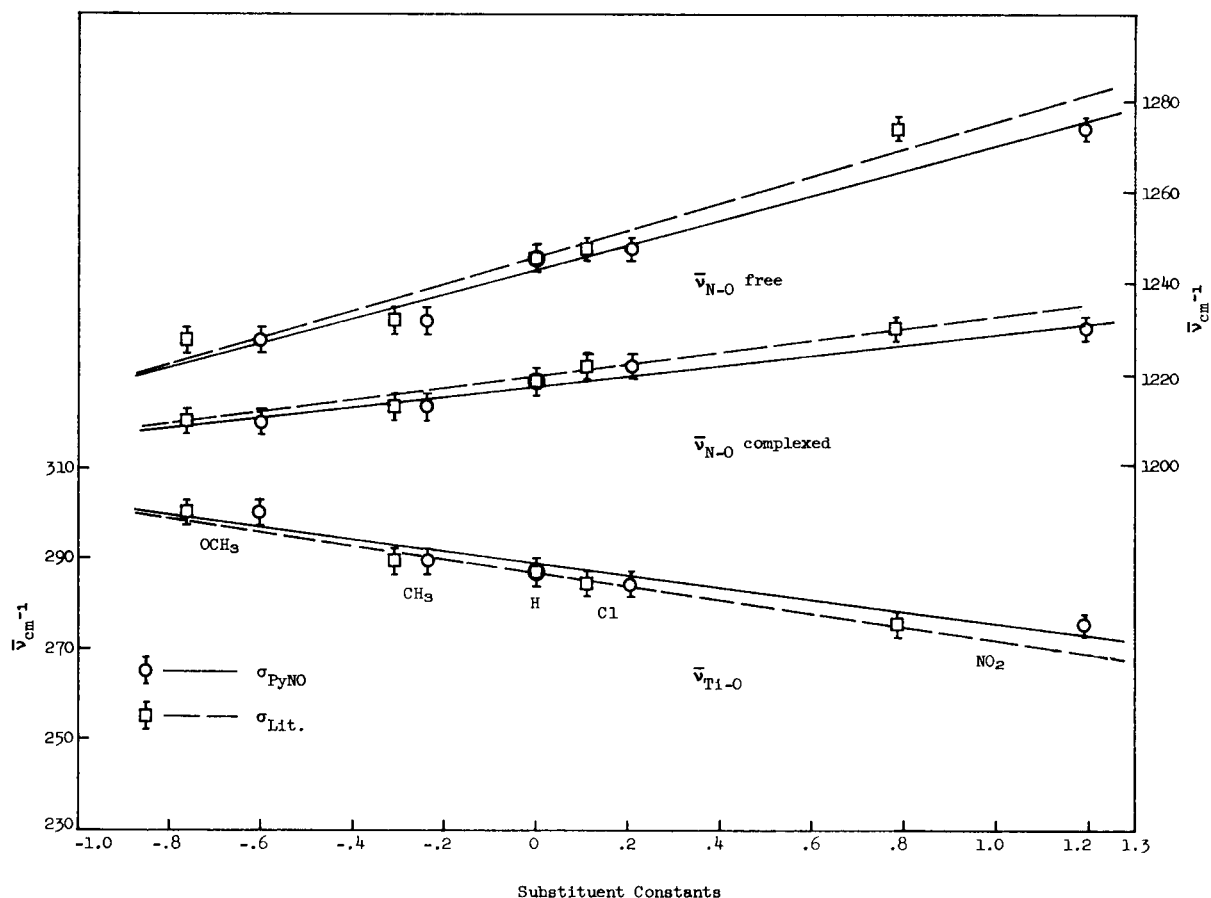


Figure 3. Comparison of plots of σ_{PyNO} and σ^+ versus $\bar{\nu}_{\text{N-O}}$ free and complexed and $\bar{\nu}_{\text{Ti-O}}$ for titanium tetrafluoride complexes of 4-substituted pyridine 1-oxides (18).

1-oxide, trimethylamine oxide and *N,N*-dimethylaniline oxide. Since the moment found for pyridine 1-oxide was considerably less than anticipated, he proposed that the final state of the molecule received contribution from structures VI-VIII (Figure 1) in which the 2- and 4-positions are electron rich. It was pointed out by Ochai (32-34) that this conclusion implied an increased susceptibility of the pyridine 1-oxide ring to substitution by electrophilic agents. The demonstrated ease of nitration mainly in the 4-position (34), in contrast to the great resistance of pyridine in this respect, substantiates this interpretation. Subsequent contributions to pyridine 1-oxide chemistry by Ochai and his collaborators (35) and by others (36-48) suggested the importance of the additional resonance structures in Figure 1. The various canonical forms pictured for pyridine 1-oxide have now been supported by charge distribution calculations (22, 49), by infrared studies showing the effect of electron release of the *N*-oxide group (23), by NMR studies (7, 50-52), and by dipole moment measurements of 4-substituted pyridine 1-oxides (53). In the dipole moment study it

was concluded that the pyridine oxide ring can create either a surfeit or a deficit of electrons at the 4-position. Considering these results and observing from Figure 1 that benzoic acid can only have a deficit of electrons on the ring system via resonance interaction, we see that groups in the 2-, 4- and 6-positions of the pyridine 1-oxide ring system would have a much greater effect on the nitrogen-oxygen bond than these same groups would have on the carbon-oxygen bond of the benzoic acid system. Hence, the mesomeric effect is more important for pyridine 1-oxide than for benzoic acid.

Hammett selected as the standard reaction for determining the benzoic acid sigma constants the ionization of substituted benzoic acids in water at 25°. He then calculated sigmas from the definition: (54)

$$\sigma \equiv \log \left(\frac{K_z}{K_o} \right)$$

In line with this, Roberts (4) used the ionization constants of 4-substituted bicyclo[2.2.2]octane-1-carboxylic acid, and Jaffe (5) used the ionization constants of phenols

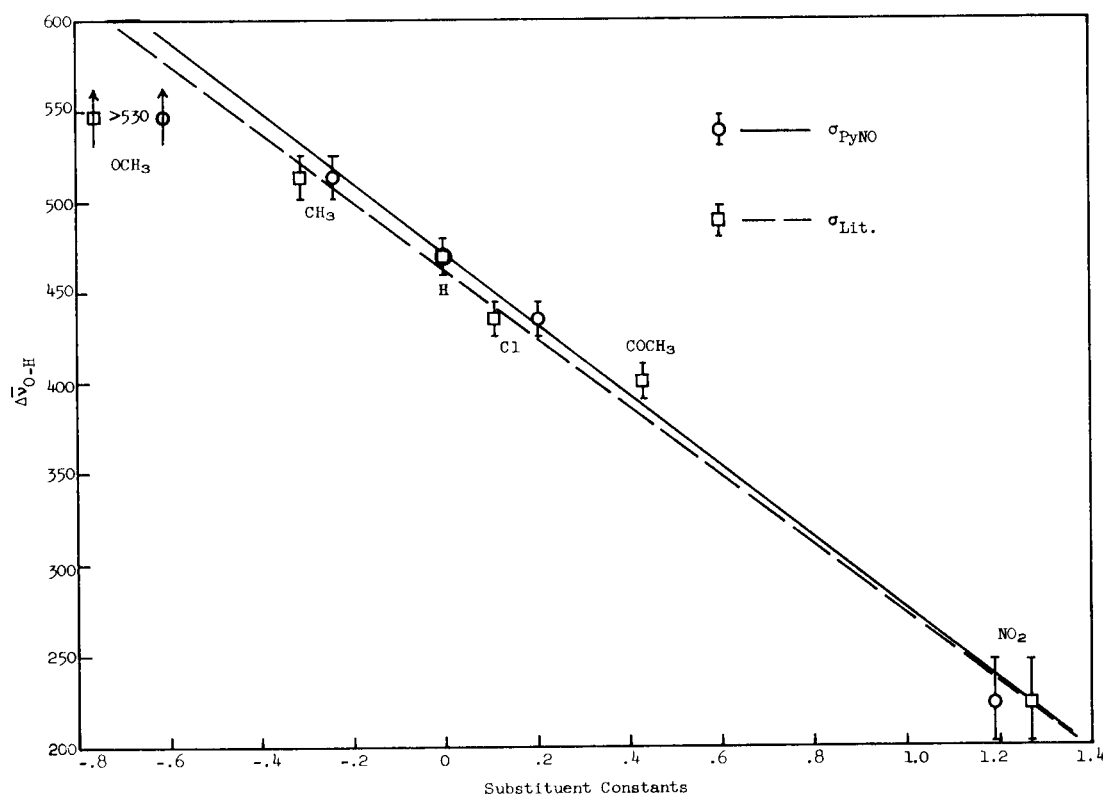
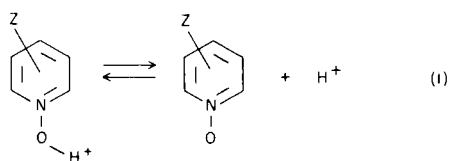


Figure 4. Comparison of plots of σ_{PyNO} and σ (σ^+ and σ^-) versus $\bar{\nu}_{\text{OH}}$ for phenol-4Z-pyridine 1-oxide adducts (11). σ^+ values were used for (CH_3O , CH_3 , Cl , and H) and σ^- values for (NO_2).

and anilines to calculate their sigma constants. We propose that this be done with pyridine 1-oxide, *i.e.*, the ionization constants of the reaction be used to calculate the sigmas



which we will call σ_{PyNO} .

Before sigma values can be determined, a value for rho (ρ) must be selected. We use the value 2.09 for two reasons: First, this value has already been determined (16) by fitting the best straight line to a plot of benzoic acid sigma constants versus pK_a ; and second, using this value for rho the calculated sigmas (σ_{PyNO}) do not differ greatly from those already used. It can be seen in Figure 2 that benzene sigma constants do not correlate very well with pK_a 's for protonated pyridine 1-oxides. In fact, Jaffe and Doak (16) used σ , σ^+ , and σ^- to determine rho.

Figure 2 is plotted with σ only. The reasons for choosing the line with slope of 2.09 are those mentioned. If rho had not been previously determined another line would have been chosen. Substituting the value of rho in the equation,

$$\sigma_{\text{PyNO}} = \frac{\Delta pK_a}{\rho}$$

the pyridine 1-oxide substituent constants, σ_{PyNO} , were computed, where $\Delta pK_a = pK_{a0} - pK_{az}$ and the subscript o indicates the unsubstituted and z the substituted substrate. The sigmas thus determined are presented for comparison in Table I along with the corresponding benzoic acid sigmas.

These calculated sigma constants, σ_{PyNO} , correlate with the existing experimental data as demonstrated in Figures 3-6. Figure 3 is a comparison of a plot (18) using σ^+ with a plot using σ_{PyNO} . There is a great deal of controversy over the exact assignment of the N-O stretching frequency, $\bar{\nu}_{\text{N-O}}$, in pyridine 1-oxides, since this frequency is very solvent dependent. However if the same solvent is used for all members of the series and they are run under similar conditions, good correlations do result. (See reference 17 for a complete discussion.) Figure 4 is a

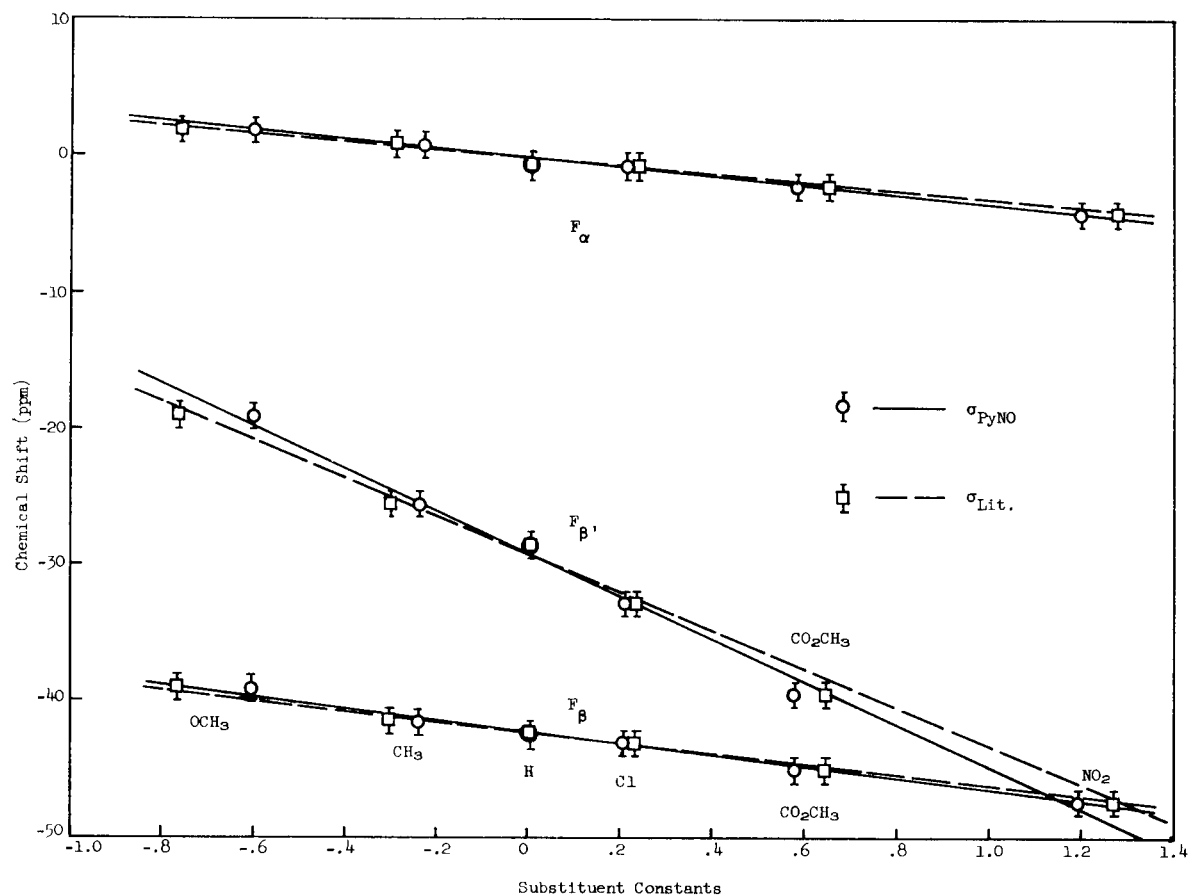


Figure 5. Comparison of plots of σ_{PyNO} and σ (σ^+ , σ and σ^-) versus F^{19} chemical shifts of titanium tetrafluoride-4Z-pyridine 1-oxide complexes (9). σ^+ values were used for (CH_3O and CH_3), σ values for (H and Cl), and σ^- values for (NO_2).

comparison of a plot (11) using σ^+ and σ^- with a plot using σ_{PyNO} . In Figure 4 σ^+ values were used with the strongly activating substituents (CH_3O and CH_3) and with the substituents (H and Cl) and σ^- values with the strongly deactivating substituent (NO_2). Figure 5 is a comparison of a plot (19) using σ^+ and σ^- with a plot using σ_{PyNO} . In Figure 5 σ^+ values were used with the strongly activating substituents (CH_3O and CH_3) σ values with (H and Cl) and σ^- values with the strongly deactivating substituent (NO_2). Figure 6 is a plot of σ_{PyNO} versus $\log K_{\text{eq}}$ (20). There exists no example, to our knowledge, where adjusted σ_{PyNO} values are necessary. In fact all of the available data may be satisfactorily correlated with σ_{PyNO} .

It is not inconceivable, however, that there may occur an instance where the σ_{PyNO} constants will not correlate with some piece of data. Such an example may be a system which can have an appreciable difference in π bonding for one member of the series, either directly or

via back donation to the N -oxide moiety. If this situation should arise and adjusted sigmas seem necessary, they could then be calculated.

Considering the variety of linear free energy correlations which have been made with pyridine 1-oxides, one can expect many additional correlations to be made. The reasons for the wide-spread correlations involving this system are the ready availability of a large number of substituted pyridine 1-oxides and the wide range of basicities with a concomitant minimal change in steric interaction at the reaction site. These properties are also present in other heterocyclic N -oxides, *e.g.*, acridine and quinoline N -oxides. The investigation of the chemistry of these two systems will probably demonstrate the necessity of new constants. If indeed this is the case then the new constants should be derived from pK_a 's and not be either adjusted σ_{PyNO} 's or benzene sigma constants.

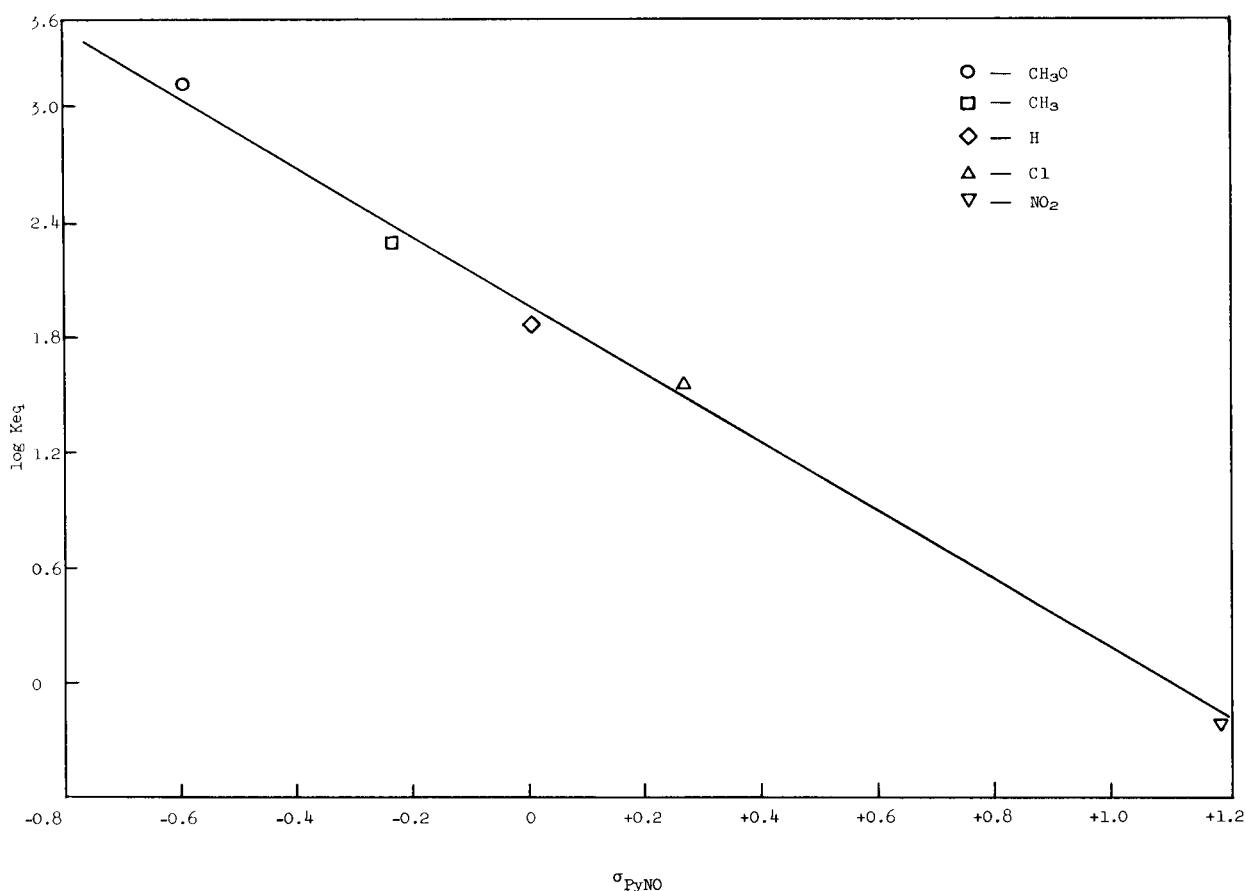


Figure 6. Plot of σ_{PyNO} versus $\log K_{\text{eq}}$ for the reaction of 4-substituted pyridine 1-oxides with iodine (20).

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TABLE I

Comparison of Benzoic Acid Constants with σ_{PyNO} Values

Substituent	pK_a Lit.	Benzoic Acid Sigmas				Calculated Sigma
		σ^- (h)	σ (h)	σ^+ (i)	σ_R (g)	
1. 4OCH ₃	2.05 (a)	—	-.268	-.764	-.51	-.603
2. 4CH ₃	1.29 (b)	—	-.170	-.306	-.11	-.240
3. 3CH ₃	1.08 (b)	—	-.069	-.065	—	-.139
4. H	.79 (b)	0	0	0	0	0
5. 4Cl	.36 (c)	—	.227	.11	-.24	.206
6. 3Cl	1.34 (f)	—	.373	.391	—	-.263
7. 4NO ₂	-1.7 (b)	1.27	.778	.777	.65 (.16)	1.19
8. 4OH	2.36 (b)	—	-.357	-.82 (k)	-.60	-.751
9. 4NH ₂	3.65 (c)	—	-.660	-1.33 (k)	-.76	-1.37
10. 3NH ₂	1.47 (b)	—	-.161	—	—	-.325
11. 4COOH	-.48 (d)	.728	.728	—	—	.608
12. 3COOH	.09 (d)	—	.355	—	—	.335
13. 4CO ₂ CH ₃	-.41 (e)	.64	.31	—	-.09	.574
14. 3CO ₂ C ₄ H ₉	.03 (b)	—	.398	—	—	.364
15. 3,4(CH ₃) ₂	1.01 (b)	—	.170	—	—	-.105
16. 4(CH ₃) ₂ N	3.88 (a)	—	-.60	-1.49 (k)	—	-1.48
17. 4OC ₆ H ₅	2.67 (a)	—	-.028	-.63 (k)	-.41 (l)	-.574
18. 4CN	-1.17 (m)	—	.63	—	—	.94

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