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Determination of Hammett Pyridine 3-Aza and 4-Aza Replacement Constants by ^{1}H NMR Studies of Amide Systems

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Abstract

Values for Hammett pyridine 3-aza and 4-aza replacement constants were obtained by correlation of the amide proton chemical shifts (in DMSO) of some N-(3-pyridyl)-and N-(4-pyridyl)-dichloronicotinamides, benzamides and acetamides with those of their N-(substituted phenyl) amide analogs using standard Hammett σ values.

Introduction

The concept of the role of the heteroatom as a "substituent" in the Hammett context has been the subject of much scrutiny (Exner, 1988). A primary consideration is that standard Hammett σ values are ultimately related to benzoic acid ionization data, and the absence of a heteroatom in benzoic acid provides sufficient variation in structure to render poor correlation. Indeed, one finds a large number of different values listed for a given heteroatomic "substituent" constant. These values, also known as σ replacement constant, vary in magnitude primarily because of the different methods employed to determine them, as well as secondary effects which may be attributed to the heteroatom. Consequently, numerous values have been reported for the pyridine 3-aza replacement constant ranging from 0.1 to 1.3, and reported 4-aza values span the range 0.6 to 1.6 (Charton, 1978). In this study we report values for the pyridine 3-aza and 4-aza replacement constants as determined from correlation of amide proton chemical shift data of N-pyridylamides with those of their N-substituted phenyl counterparts using standard Hammett σ values. Four different amide systems were studied.

Materials and Methods

Melting points were determined on a Mel-Temp II apparatus and are uncorrected. Elemental analyses were performed by Desert Analytics Organic Microanalysis Inc., Tucson, Arizona. Infrared spectra were obtained using a Perkin-Elmer model 1430 spectrophotometer equipped with a model 7300 data station, and samples were prepared as KBr disks. ^{1}H nmr spectra were determined on a Bruker AC-F 200 MHz superconducting FT spectrometer with deuterated DMSO as solvent and tetramethylsilane as the internal standard. Sample concentrations were approximately 0.1M. The known N-pyridylbenzamides **1c** and **2c** were prepared by the reaction of benzoyl chloride with 3-aminopyridine and 4-aminopyridine, and N-pyridylacetamides **1d** and **2d** were prepared by acetylation of 3- and 4-aminopyridine with acetic anhydride. N-(6-chloro-5-methyl-3-pyridyl) benzamide (**1g**) and N-(6-chloro-5-methyl-3-pyridyl) acetamide (**1h**) were synthesized as previously reported from our laboratory (Setliff, 1985). 2,6-Dichloronicotinic acid was obtained from Aldrich Chemical Co., Milwaukee, WI, and 5,6-dichloronicotinic acid was prepared as we have described previously (Setliff and Lane, 1976).

The following general procedure was employed for the preparation of new compounds **1a, 1b, 1e, 1f, 2a,** and **2b:** The appropriate dichloronicotinic acid (0.50g, 2.6 mmol) and thionyl chloride (3.0 ml) were combined and heated under reflux for 30 min. The resulting yellow transparent solution was subjected to vacuum evaporation to remove the excess thionyl chloride leaving the nicotinyl chloride as a viscous yellow oil. The oil was dissolved in dry ether (2 ml), and this solution was added slowly to a stirred solution of the appropriate aminopyridine (2.6 mmol) in dry pyridine (1.0 ml). This mixture was magnetically stirred under gentle reflux for 15 min, cooled, poured into ice water (100 ml), and the resulting suspension was vigorously stirred for 30 min. The crude amide was collected by filtration and recrystallized from either aqueous ethanol or water. Specific data for each compound are presented below.

N-(3-pyridyl)-2,6,-dichloronicotinamide(1a). This compound was obtained in 46% yield as light yellow crystals from aqueous ethanol. mp 126-127°C; ir: ν NH 3406 ν CO 1664 cm^{-1}; ^{1}H nmr: δ 10.96 (s, 1H), 8.83 (bs, 1H), 8.74 (d, J = 2Hz, 1H), 8.50 (d, J = 2Hz, 1H), 8.37 (d, J = 8Hz, 1H), 8.14 (d, J = 8Hz, 1H), 7.44 (m, 1H). *Anal.* Calcd for $C_{11}H_7N_3OCl_2$: C, 49.25; H, 2.61; N, 15.67. Found: C, 49.06; H, 2.66; N, 15.44.

N-(3-pyridyl)-5,6-dichloronicotinamide(1b). This compound was obtained in 52% yield as white fluffy needles from aqueous ethanol. mp 188-189°C; ir: ν NH 3237, ν CO 1677 cm^{-1}; ^1H nmr: δ 10.76 (s, 1H), 8.91 (d, J = 2Hz, 1H), 8.89 (bs, 1H), 8.65 (d, J = 2Hz, 1H), 8.36 (bs 1H), 8.20 (d, 1H), 7.44 (m, 1H). *Anal.* Calcd for $C_{11}H_7N_3OCl_2$: C, 49.25; H, 2.61; N, 15.67. Found: C, 48.88; H, 2.72; N, 15.52.

N-(6-chloro-5-methyl-3-pyridyl)-2,6-dichloronicotinamide(1e). This compound was obtained in 73% yield as tan needles from aqueous ethanol. mp 215-216°C; ir: ν NH 3276, ν CO 1644 cm^{-1}; ^1H nmr: δ 11.02 (s, 1H), 8.51 (s, 1H), 8.23 (d, J = 8Hz, 1H), 8.12 (s, 1H), 7.78 (d, J = 8Hz, 1H), 2.36 (s, 3H). *Anal.* Calcd for $C^{12}H_8N_3OCl_3$: C, 45.50; H, 2.53; N, 13.27. Found: C, 45.68; H, 2.58; N, 13.12.

N-(6-chloro-5-methyl-3-pyridyl)-5,6-dichloronicotinamide(1f). This compound was obtained in 73% yield as tan needles from aqueous ethanol. mp 217-218°C; ir: ν NH 3277, ν CO, 1649 cm^{-1}; ^1H nmr: δ 10.79 (s, 1H), 8.89 (d, J = 2Hz, 1H), 8.62 (d, J = 2Hz, 1H), 8.59 (d, J = 2 Hz, 1H), 8.15 (d, J = 2Hz, 1H), 2.35 (s, 3H). *Anal.* Calcd for $C_{12}H_8N_3OCl_3$: C, 45.50; H, 2.53; N, 13.27. Found: C, 45.34; H, 2.54; N, 13.21.

N-(4-pyridyl)-2,6-dichloronicotinamide(2a). This compound was obtained in 86% yield as yellow fluffy needles from water. mp 150-151°C; ir: ν NH 3469, ν CO 1678 cm^{-1}; ^1H nmr: δ 11.09 (s, 1H), 8.52 (bs, 2H), 8.26 (d, J = 8Hz, 1H), 7.79 (d, J = 8Hz, 1H) 7.65 (bs, 2H). *Anal.* Calcd for $C_{11}H_7N_3OCl_2$: C, 49.25; H, 2.61; N, 15.67. Found: C, 49.07; H 2.59: N, 15.76.

N-(4-pyridyl)-5,6-dichloronicotinamide(2b). This compound was obtained as white fluffy needles from water. mp 195-196°C (with sublimation); ir: ν NH 3507, ν CO 1677 cm^{-1}; ^1H nmr: δ 10.87 (s, 1H), 8.90 (d, J = 2Hz, 1H), 8.63 (d, J = 2Hz, 1H), 8.53 (bs, 2H), 7.76 (bs, 2H). *Anal.* Calcd for $C_{11}H_7N_3OCl_2$: C, 49.25; H, 2.61; N, 15.67; Found: C, 49.23; H, 2.60; N, 15.50.

Results and Discussion

We reported the excellent correlation of the amide proton chemical shift (δ_{NH}, ppm in DMSO) of a series of N-(substituted phenyl)-2,6-dichloronicotinamides and N-(substituted phenyl)-5,6-dichloronicotinamides with standard Hammett σ constants for the substituents on the benzene ring (Setliff et. al., 1992) The respective correlation equations are:

(1) $\delta_{NH} = 0.70\sigma + 10.71$ $(n = 8; r^2 = 0.99)$

(2) $\delta_{nh} = 0.57\sigma + 10.56$ $(n = 8; r^2 = 0.99)$

Similarly, a series of N-(substituted phenyl) benzamides afforded the excellent correlation described by equation (3), (Soman, 1992).

(3) $\delta_{NH} = 0.64\sigma + 10.29$ $(n = 8; r^2 = 0.99)$

and a prior paper which examined a number of N-(substituted phenyl) acetamides (substituted acetanilides) in DMSO (Giffney and O'Connor, 1975) reported the correlation:

(4) $\delta_{NH} = 0.73\sigma + 9.93$ $(n = 12; r^2 = 0.99)$

To obtain a value for $\sigma_{3\text{-aza}}$ we prepared N- (3 pyridyl)-2,6-dichloronicotinamide (**1a**), - 5,6-dichloronicotinamide (**1b**), - benzamide (**1c**), and - acetamide (**1d**), measured their amide proton chemical shifts in DMSO, and subsequently substituted these values into the appropriate equation. The results are summarized in Table 1, Part A, and the values obtained for the four amide systems are reasonably consistent, with a mean of 0.34. Values for $[\sigma_{4\text{-aza}}]$ were obtained in an analogous fashion by preparing the N-(4-pyridyl)- 2,6- and 5,6-dichloronicotinamides (**2a** and **2b**), - benzamide (**2c**), and - acetamide (**2d**). The results are presented in Table 1, Part C, and an average value of 0.55 was calculated from the fairly consistent results derived from the four amide systems. It is interesting, although not particularly significant, that these values agree best with those previously determined from infrared measurements. Joeckle and coworkers reported $\sigma_{3\text{-aza}}$ as 0.33 and $\sigma_{4\text{-aza}}$ as 0.62 by correlation of the intensities of the methyl C-H and amino N-H stretching modes of 3- and 4-methylpyridine and 3- and 4-aminopyridine with a series of ring substituted toluenes and anilines (Joeckle et al., 1966).

In order to determine if our $\sigma_{3\text{-aza}}$ value of 0.34 would operate predictably in concert with standard Hammett σ values in the systems studied herein, we prepared compounds **1e** through **1h** and measured the amide proton chemical shifts. Using the $\sigma_{3\text{-aza}}$ value of 0.34 together with the standard Hammett values (Exner, 1988) of 0.22 for $\sigma_{4\text{-chloro}}$ and -0.06 for $\sigma_{3\text{-methyl}}$, an additive σ value of 0.50 was obtained. When this additive value is substituted into four correlation equations, the δ_{NH} thus calculated compares favorably with the observed values in the four amide systems. The results are summarized in Table 1, Part B.

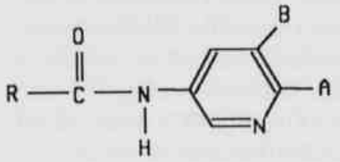
At this point it is appropriate to mention that an earlier report (Katritsky and Swinbourne, 1967), which described ^1H nmr studies of ring substituted β-phenylacrylic acids in DMSO, exhibits a good linear correlation of the α-vinylic proton chemical shift with standard Hammett σ values. From the chemical shifts of the corresponding β-(3-pyridyl)- and β-(4-pyridyl) acrylic acids, 3-aza and 4-aza replacement constants of 0.6 and 0.8 were graphically determined. No correlation equation was presented, but on analysis of these data we derived the equation shown as (5):

(5) $\delta_{\alpha}\text{-vinylic} = 0.32\sigma + 6.49 \quad (n = 8; r^2 = 0.97)$

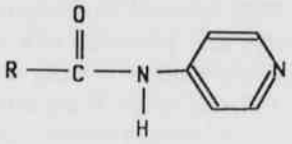
The rather small coefficient of σ indicates a comparatively weaker response of the vinylic proton to the transmission of electronic effects than the amide proton in our systems. The enhanced sensitivity in the amide systems is undoubtedly related to the large amount of hydrogen bonding of the amide proton to the DMSO solvent, which in turn renders the amido nitrogen sufficiently negative and therefore quite responsive to electronic effects. The larger aza replacement values generated from the acrylic acid data are obviously not explainable in terms of hydrogen bonding of the vinylic proton itself, but possibly could be explained in terms of secondary effects resulting from hydrogen bonding of the acid proton.

In conclusion, it appears that the pyridine 3-aza and 4-aza values reported herein are valid for correlation studies involving the hydrogen bonded amide proton in DMSO. As in all previously reported cases, (Charton, 1978) our results also demonstrate a larger value for $[\sigma_{4\text{-aza}}]$ owing to mesomeric as well as inductive effects which are operative in the 4- position.

Table 1. Correlation Data for the N-(pyridyl)amide Systems



1



2

Cpd.	R	A	B	Obs. δ_{NH}	Correl. Eq/ No.	$\sigma_{3\text{-aza}}$[a]	Calc.[b] δ_{NH}
A.							
1a	2,3-diC1-3-pyridyl	H	H	10.96	1	0.37	---
1b	5,6-diCl-3-pyridyl	H	H	10.76	2	0.35	---
1c	phenyl	H	H	10.49	3	0.31	---
1d	methyl	H	H	10.17	4	0.34	---
B.							
1e	2,6-diCl-3-pyridyl	C1	CH_3	11.02	1	---	11.06
1f	5,6-diCl-3-pyridyl	C1	CH_3	10.80	2	---	10.84
1g	phenyl	C1	CH_3	10.55	3	---	10.61
1h	methyl	C1	CH_3	10.39	4	---	10.30
C.						$\sigma_{4\text{-aza}}$[c]	
2a	2,6-diCl-3-pyridyl	–	–	11.09	1	0.56	---
2b	5,6-diCl-3-pyridyl	–	–	10.87	2	0.56	---
2c	phenyl	–	–	10.63	3	0.53	---
2d	methyl	–	–	10.34	4	0.55	---

[a] mean value is 0.34 [b] $\sigma\text{additive} = (0.34 + \sigma_{4\text{-C1}} + \sigma_{3\text{-Me}})$ [c] mean value 0.55

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Literature Cited

Charton, M. 1978. Heteroaromatic replacement con stants. Pp. 233-236, *In* Correlation analysis in chemistry, (N.B. Chapman and J. Shorter, eds.) Plenum Press, New York 465 pp.

Exner, O. 1988. Correlation analysis of chemical data. pp. 133-135. Plenum Press, New York, 275 pp.

Giffney, C.J. and **C.J. O'Conor.** 1975. Substituent effects on the nmr spectra of substituted acetanilides and phenylureas. J. Magn. Res. 18:230-234.

Joeckle, R., E.D. Schmid, and **R. Mecke.** 1966. Untersuchungen der IR gruppenintensitaten eniger monosubstituierter pyridin und benzolderivate. Z. Naturforsch. 21A:1906-1907.

Katritsky, A.R. and **F.J. Swinbourne,** 1967. Applications of proton resonance spectroscopy to structural problems. Determination of Hammett sigma constants for heterocycles. J. Chem. Soc. 6707-6710.

Setliff, F.L. 1985. New haloacetamido and benzamidomethyl pyridines. Org. Prep. Proc. Int. 17:68-69.

Setliff, F.L., and **J.E. Lane.** 1976. Some 2,5- and 5,6- dihalo nicotinic acids and their precursors. part IV. J. Chem. Eng. Data 21:246-247.

Setliff, F.L., N.G. Soman, J.Z. Caldwell and **D.L. Rogers.** 1992. Hammett correlations in the proton nmr spectra of some N-aryldihalonicotinamides. Proc. AR. Acad. Sci. 46:72-74.

Soman, N.G. 1992. Studies on the preparation and properties of some 2,6- and 5,6- dichloronicotinic acids. Unpublished M.S. Thesis, University of Arkansas at Little Rock, 106 pp.