1994

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Recommended Citation

Persons, Cecil C.; Shaikh, Ali U.; Shiflett, Julie; and Setliff, Frank L. (1994) "Hammett Correlations of Half-Wave Reduction Potentials in a Series of N-(Aryl substituted)-Dichloronicotinamides," *Journal of the Arkansas Academy of Science*: Vol. 48 , Article 27.
Available at: http://scholarworks.uark.edu/jaas/vol48/iss1/27

Hammett Correlations of Half-Wave Reduction Potentials in a Series of N-(Aryl substituted)-Dichloronicotinamides

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Abstract

Excellent correlations of Hammett substituent constants (σ_R) of a series of N-(R-substituted aryl) -2,6-, 2,5-, and 5,6-dichloronicotinamides with polarographic half-wave potentials were observed. Although the correlations demonstrate that all three series of amides experience comparable sensitivity to the R groups at the carbonyl reduction site, the relative ease of reduction varies according to the chlorine substitution pattern on the pyridine ring. These differences are suggested to be due to combinations of mesomeric, inductive, and field effects which operate differently in the three systems. Correlation analysis also revealed that Hammett heteroatomic replacement constants previously determined by NMR studies are valid in the present polarographic studies.

Introduction

In connection with our interest in the preparation of dihalonicotinic acids and their derivatives as potential agricultural agents (Setliff and Soman, 1992), we recently reported the excellent correlation of Hammett substituent constants (σ_R) with the amide proton chemical shift in several series of N- (R- substituted aryl) -dihalonicotinamides (Setliff et al., 1992). From the correlation equations obtained therefrom, we were subsequently able to determine Hammett pyridyl 3-aza and 4-aza replacement constants by measuring the amide proton chemical shifts of several N- (pyridyl substituted) -dihalonicotinamides (Setliff et al., 1993). This paper describes an extension of the study of structural and electronic effects in these systems by the use of polarography. The objectives of this research are as follows: 1) to investigate the electronic effects of R groups upon the half-wave reduction potentials in three series of N-(R-substituted-aryl)-dichloronicotinamides, and to determine if Hammett correlations exist, 2) if such correlations exist, to test the validity of the aza replacement constants previously determined by the NMR studies, and 3) To determine the relative reduction ease of the three systems as dictated by the substitution pattern of the chlorine atoms on the pyridine ring.

Materials and Methods

The preparation of the amides has been described previously (Setliff and Soman, 1992). Samples used had been recrystallized several times and had sharp melting points.

Polarographic reductions were conducted in anhydrous dimethylsulfoxide (DMSO) containing 0.01 M tetrabutylammmonium perchlorate (TBAP) as supporting electrolyte. A three-electrode polarographic analyzer, Model PAR 174 A (Princeton Applied Research Corporation, Princeton, NJ) with a dropping mercury electrode, and a drop-timer was used in conjunction with an X-Y recorder, Model 2200 (Houston Instruments, Austin, TX). The reference electrode was a specially prepared low-porosity calomel electrode (Fisher Scientific, Pittsburgh, PA) filled with a 0.40 M solution of tetraethylammonium chloride in order to adjust the potential to 0.00 volt vs. the saturated calomel electrode (SCE). The counter electrode was a platinum wire.

Exactly 10.00 mL of the TBAP/DMSO solution was poured into the electrochemical cell and was purged with dry nitrogen for about 30 min to remove dissolved oxygen. The nitrogen flow was then diverted above the solution, and the potential of the dropping mercury electrode was scanned between 0.00 volt and -2.5 volt vs. the SCE at a rate of 5 mV/sec to obtain the d. c. background polarogram. Approximately 1 - 2 mg of the test compound was then added, the solution purged again with nitrogen for 5 min to assure complete dissolution, and the potential was scanned as above. Polarograms of all samples were obtained using this procedure.

The half-wave potentials and the number of electrons involved in the reduction were determined from the direct current polarograms using the relationship:

$$E = E_{1/2} + (0.0591/n)\log[(i_d - i)/i] \text{ volts at } 25°C$$

where $E_{1/2}$ is the half-wave potential, n the number of electrons, and i_d the diffusion current. E and i are the corresponding values of the potential and current at any

stage in the rising portion of the curve. $E_{1/2}$ and n were calculated by a least squares analysis of data using the above equation.

The plots of $E_{1/2}$ vs. σ_R were done using an Axum linear regression program available from Trimetrix, Inc., Seattle, WA.

Results and Discussion

The compounds studied are described in Fig. 1 and Table 1, and the half-wave reduction potentials together with the Hammett substituent constants (Exner, 1988) are shown in Table 2. Our calculations revealed a one electron reduction in each case. The excellent linear correlations of $E_{1/2}$ with σ_R in all three series are depicted in Fig. 2. Equations of the lines in slope intercept form are represented below with the correlation coefficients shown in parentheses.

Series I	$E_{1/2} = 0.176\ \sigma_R - 1.79$	$(r^2 = 0.94)$
Series II	$E_{1/2} = 0.161\ \sigma_R - 1.71$	$(r^2 = 0.96)$
Series III	$E_{1/2} = 0.164\ \sigma_R - 1.65$	$(r^2 = 0.95)$
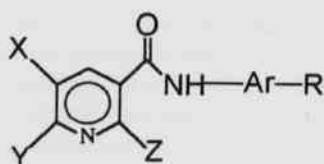
Fig. 1. The N-(Aryl Substituted)-Dichloronicotinamide series.

Table 1. Aryl Substituents for the three Dichloronicotinamide series (Fig. 1).

Cpd.	Ar–R	R-group
a.	4-Methoxyphenyl	p-Methoxy
b.	4-Methylphenyl	p-Methyl
c.	Phenyl	----------
d.	4-Fluorophenyl	p-Fluoro
e.	3-Chloro-4-methoxyphenyl	m-Chloro p-Methoxy
f.	4-Chlorophenyl	p-Chloro
g.	3-Pyridyl	3-Aza
h.	4-Chloro-5-methyl-3-pyridyl	m-Methyl 3-Aza
i.	4-Trifluoromethylphenyl	p-Trifluoromethyl
j.	4-Pyridyl	4-Aza

Table 2. Hammett Substituent Constants (σ_R) and Half-wave Potential Values ($E_{1/2}$) for the three Dichloronicotinamide Series (Fig. 1).

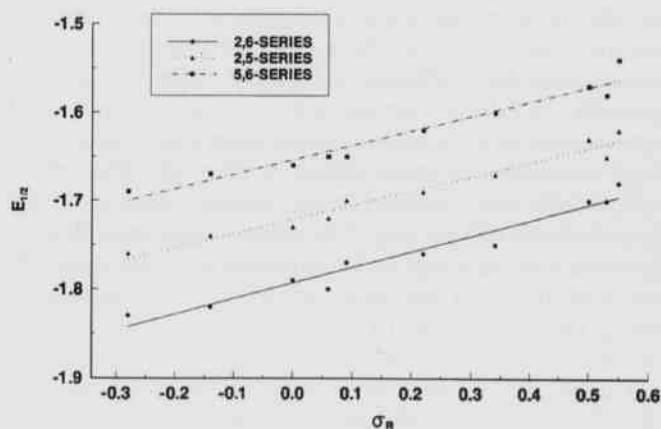| Cpd.	R	σ_R	$E_{1/2}$ I	$E_{1/2}$ II	$E_{1/2}$ III
a.	O-CH$_3$	-0.28	-1.83 V	-1.76V	-1.69 V
b.	CH$_3$	-0.14	-1.82 V	-1.74 V	-1.67 V
c.	H	0.00	-1.79 V	-1.73 V	-1.66 V
d.	F	0.06	-1.80 V	-1.72 V	-1.65 V
e.	p-O-CH$_3$ m-Cl	$\Sigma_{\sigma R}$ (additive) (0.09)	-1.77 V	-1.70 V	-1.65 V
f.	Cl	0.22	-176 V	-1.69 V	-1.62 V
g.	30aza	0.34	01.75 V	-1.67 V	-1.60 V
h.	3-aza p-Cl m-CH$_3$	$\Sigma_{\sigma R}$ (additive) (0.50)	-1.70 V	-1.63 V	-1.57 V
i.	CF$_3$	0.53	-1.70 V	-1.65 V	-1.58 V
j.	4-aza	0.55	-1.68 V	-1.62 V	-1.54 V

Fig. 2. Correlations of $E_{1/2}$ with Hammett σ_R values.

Substituents on the benzene ring affect the ease of reduction in the same way in the three series as evidenced by reducibility enhancement by the more electron withdrawing substituents. The similarity of the slopes (coefficients of σ_R corresponding to a Hammett ρ value) suggests that the reduction sensitivity to these groups is approximately the same. It is noteworthy that effects of substituent groups are additive in these systems. Disubstituted N-aryl compounds Ie, IIe, and IIIe gave $E_{1/2}$ values that correlate well with the their additive σ_R's. Furthermore, the heteroatomic replacement constants for 3-aza and 4-aza as determined previously by proton NMR studies (Setliff et al., 1993) correlate extremely well (compounds Ig, IIg, and IIIg, and Ij, IIj, and IIIj), and these replacement constants are additive with the Hammett σ_R

values as exhibited by compounds Ih, IIh, and IIIh.

The relative ease of reduction of the three series (as indicated by the magnitude of the $E_{1/2}$ values in Table 2 as well as the intercept values in the three correlation equations) is III > II > I. More specifically, the 5,6 series with the lowest potentials reduce the easiest, while the 2,6 series which requires the highest potentials is the most difficult to reduce. As mentioned previously the R groups affect all three systems to the same degree, so the difference in reducibility must be attributed to the positioning of the chlorine atoms on the pyridine ring.

Although detailed mechanistic studies are unavailable on polarographic reductions of amides, aldehydes and ketones have been studied extensively (Zuman, 1967). In these systems it has been established that reduction is initiated by a one electron attack at the carbonyl carbon, and our results suggest a similar process is likely in the amides. Amides are more difficult to reduce than aldehydes or ketones due to electron enrichment at their carbonyl carbon arising from resonance of the nitrogen lone pair. This process operates in all three of our amide systems, but most effectively in the 2,6-dichloro system (series I), and least effectively in the 5,6-dichloro system (series III). In the 2,6-series, we propose that the field effect of 2-chloro helps to stabilize the previously mentioned resonance form as shown in Fig. 3A. This effect coupled with the "through conjugation" (measomeric) effect of the 6- chloro (Fig. 3B) ensures appreciable electron density at carbonyl carbon, resulting in the most difficult reducibility of the three series. (The electron withdrawing inductive effect of 2-chloro is apparently neutralized by its mesomeric effect and does not have a net effect upon the electron density at the carbonyl carbon). In the 2,5- series the stabilizing field of the 2-chloro is still operative, but the 5-chloro, being incapable of any "through conjugation", can only exert an electron withdrawing inductive effect which partially offsets the electron enriching process. The net result is a slightly more positive carbonyl carbon. Finally, in the case of the 5,6-series the stabilizing field effect of 2-chloro is absent, and the weak mesomeric effect of 6-chloro is overshadowed by the significant electron withdrawing inductive effect of 5-chloro. The net result is the most positive carbonyl carbon of the three series. Similar combinations of field, inductive, and mesomeric effects have been used to rationalize reactivities of a series of substituted phenylpropiolic acids (Roberts and Carboni, 1955).

Future work will include electrochemical mechanistic studies with the goal of isolation and characterization of reduction products. Different solvent systems will also be investigated.
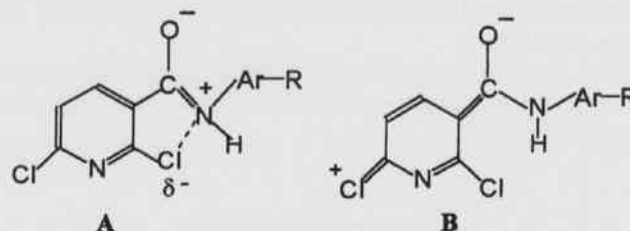

Fig. 3. Electron Enriching Processes at the Carbonyl Carbon.

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