Correlation of the Acid Dissociation Constants of Some Multisubstituted Diphenyl- and Phenylpyridylamines

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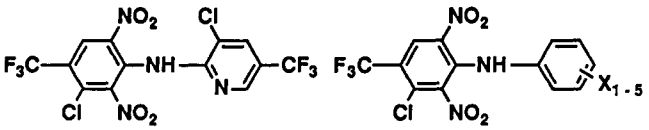
Received July 23, 1990

The acid dissociation constants of a number of diphenyl- and phenylpyridylamines bearing multiple electron-withdrawing substituents were measured in 1:1 ethanol/water. The ionization constants were correlated quantitatively by application of Hammett–Taft-type equations and regression analysis. The effects that were exerted by substituents that were crowded near each other in the vicinity of the NH bridge of these compounds could be readily separated into electronic and steric components. The effects included those that were specific to the proximity of the substituent to the NH bridge and those that influenced the behavior of the aza functional group of the pyridinyl compounds electronically.

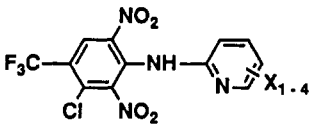
Introduction

3-Chloro-*N*-[3-chloro-2,6-dinitro-4-(trifluoromethyl)-phenyl]-5-(trifluoromethyl)-2-pyridinamine, fluazinam, is an agricultural fungicide.[1] We reported earlier[2] that

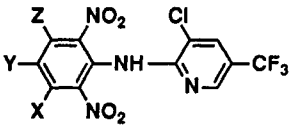


Fluazinam

(I)



(II)



(III)

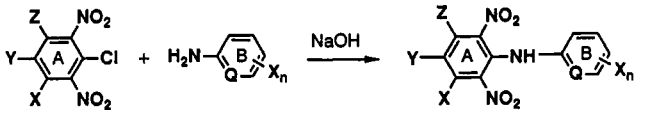
fluazinam displays an extremely potent uncoupling activity on the oxidative phosphorylation of bioenergy-transducing membranes like that of rat liver mitochondria. Because it is a weak acid, fluazinam acts as a protonophore across the mitochondrial membrane to discharge a transmembrane proton gradient. The degree to which the acid ionizes within the membrane phase is one of the most important factors that governs the acid's protonophoric activity.[3] Because the degree to which such weakly acidic uncouplers ionize should be related to their protonophoric activity,[4] we sought to correlate the acidities of fluazinam and a number of its analogues (set I, II, III) by the application of Hammett–Taft-type equations and correlation analysis.[5]

The compounds that were studied bore many and various substituents. We hoped that the correlations would show not only to what extent the effects of multiple substituents can be disentangled from each other but also how applicable was our recently developed procedure for separating the overlapping electronic and steric proximity effects of ortho substituents.[6] This study reports the results of an analysis of the structure–acidity relationships in these three series of compounds. Also, valuable information about the stereoelectronic characteristics of the compounds is provided.

Materials and Methods

Compounds and Chemicals. The solvents and the chemicals used to prepare the buffer solutions were of reagent grade (Wako Pure Chemical Industries).

Scheme I



Q = CH, n = 1-5; or Q = N, n = 1-4

The desired compounds were prepared by the condensation of a substituted chlorobenzene with an aromatic amine in the presence of anhydrous NaOH[7] in an aprotic solvent like DMF, DMSO, or THF (Scheme I). 2,4-Dichloro-3,5-dinitrobenzotrifluoride (A: X = Cl, Y = CF_3 and Z = H) was used for the preparation of the series I and II compounds. This precursor was prepared by nitration of commercially available 2,4-dichlorobenzotrifluoride with HNO_3/H_2SO_4.[8] 2-Amino-3-chloro-5-(trifluoromethyl)pyridine (B: Q = N, X_n = 3-Cl-5-CF_3), which was used for the preparation of series III compounds, was synthesized by the method reported.[9]

Preparation of the Anilines Used To Prepare Series I Compounds. The substituted aniline precursors of compounds **1–9**, **11–14**, and **19** were of reagent grade (Aldrich). Those of compounds **15–17** were prepared by bromination[10] of commercially available *m*- and *p*-(trifluoromethyl)anilines. 2,4-Dichloro-5-(trifluoromethyl)aniline (the precursor of compound **10**) was prepared by Na_2S reduction of 2,4-dichloro-5-nitrobenzotrifluoride, which was prepared by nitration of 2,4-dichlorobenzotrifluoride. 2,4-Dichloro-6-(trifluoromethyl)aniline and 2,4,6-trichloro-3,5-bis(trifluoromethyl)aniline (the precursors of compounds **20** and **23**, respectively) were prepared by chlorination[10] of the corresponding commercially available anilines. 6-Bromo-2-chloro-4-(trifluoromethyl)aniline (the precursor of compound **18**) was synthesized by successive chlorination and bromination of 4-(trifluoromethyl)aniline. 2,6-Dichloro-4-nitroaniline (the precursor of compound **21**) was prepared by nitration of 2,6-dichloroaniline.

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2,4,6-Trichloro-3-methylaniline (the precursor of compound 22) was prepared by chlorination of 3-methylaniline.

Preparation of the Aminopyridines Used To Prepare Series II Compounds. The 2-aminopyridine precursors of compounds 24–28 and 42–45 were prepared by procedures previously reported.[9] The precursors of compounds 29–31 and 46 were obtained by the bromination of the appropriate aminopyridines. The latter were synthesized by a literature method.[9] The precursors of compounds 32–38, 41, and 47 were prepared, in a similar manner, by the chlorination of the corresponding substituted aminopyridines.[9] 6-Amino-5-chloro-2-(dimethylamino)-3-(trifluoromethyl)pyridine and 6-amino-5-chloro-2-(methylamino)-3-(trifluoromethyl)pyridine (the precursors of compounds 39 and 40, respectively) were derived from 2-amino-3,6-dichloro-5-(trifluoromethyl)pyridine by amination with Me_2NH and $MeNH_2$, respectively.

Preparation of the Substituted Chlorobenzenes Used To Prepare Series III Compounds. The substituted chlorobenzene precursors of compounds 48–50, 53, 58, and 59 were prepared by the nitration of the corresponding commercially available substituted benzenes. Methyl 2,4-dichloro-3,5-dinitrophenyl sulfone (the precursor of compound 51) was prepared by the nitration of methyl 2,4-dichlorophenyl sulfone, which was prepared by the oxidation of methyl 2,4-dichlorophenyl sulfide with H_2O_2. *N,N*-Diethyl-2,4-dichloro-3,5-dinitrobenzenesulfonamide (the precursor of compound 52) was obtained from the reaction of 2,4-dichloro-3,5-dinitrobenzenesulfonyl chloride and Et_2NH. Ethyl 4-chloro-3,5-dinitrobenzoate (the precursor of compound 57) was prepared by the esterification of 4-chloro-3,5-dinitrobenzoic acid, which was obtained by the nitration of 4-chlorobenzoic acid. Compounds 54–56 were synthesized by treating compound 50 with *i*-BuOH, EtOH, and *n*-PrOH, respectively, in the presence of anhydrous NaOH.[7]

All compounds were characterized by ^1H NMR (JEOL FX-90) and elemental analysis.

Absorbance and pH Measurements. The acid ionization constants were determined spectrophotometrically with a Shimadzu UV-3000 spectrophotometer. The measurements were made on solutions in 1:1 (v/v) ethanol/water because most of the acids displayed low water solubility. The pH of the buffered solutions was measured with a Radiometer Model PHM 26 pH meter immediately after the absorbance measurements was made. All the pH and absorbance measurements were made at 25 ± 0.5 °C. The pH readings were not corrected for the effect of the ethanol in the buffered solutions on the apparent ionization constant.[11] According to Albert and Serjeant,[12] comparisons between, or anlysis of, the "apparent" ionization constants of a series of compounds that were determined in a mixed solvent are valid if the compounds are closely related chemically and the amount of the organic solvent present is constant. From the values of the absorbance, A, determined at a given wavelength under various pH conditions, log K_A was calculated by use of eq 1

$$\log K_A = -\mathrm{pH} + \log [[A_{(RH)} - A]/[A - A_{(R^-)}]] + \log r \quad (1)$$

in which $A_{(RH)}$ and $A_{(R^-)}$ are the absorbances of the unionized acid and its anion, respectively, at a given wavelength, and log r is a small correction factor (0.02–0.04) for the activity coefficient of the buffer.[13] The log K_A values were calculated from absorbances measured at 3 different pH conditions and were averaged. For each compound, the series of absorbance measurements were made at least twice with different pH variations. The standard deviation from the mean value of log K_A was ±0.03.

Infrared spectra of 0.02–0.04 M solutions in spectroscopic grade CCl_4 contained in a 0.1-mm NaCl cell were recorded at 25 ± 0.5 °C with a Shimadzu IR 435 spectrophotometer. The probable error in determining the wave number of an absorption band was ±0.50 cm^{-1}.

Molecular Orbital Calculations. Molecular orbital (MO) calculations were made with the AMPAC program (QCPE No. 523) with AM1 parameterization.[14] The program was run on a FACOM M-783 computer. As a model compound, 3-chloro-2,6-dinitro-4-(trifluoromethyl)aniline was chosen. Its atomic coordinates were established by ANCHOR, a program for molecular modeling.[15] The atomic coordinates of the model compound corresponded to the structure in which the plane of the amino group and those of the two nitro groups were coplanar with the phenyl ring and in which the axis of one of the C–F bonds of the trifluoromethyl substituent was parallel to the plane of the phenyl ring, with the fluorine atom pointing away from the chlorine atom. As a starting point, the structure in which the plane of the 2-nitro group sandwiched between the amino and chloro substituents was perpendicular to the plane of the phenyl ring was chosen. Then, the plane of the 6-nitro group was rotated in steps of 30°. At the same time, the planes of the amino and 2-nitro groups were rotated in step of 30°. With the position of the 4-trifluoromethyl group fixed, the total energy of the molecule was calculated for each conformation. Once the coordinates of the amino group and the two nitro groups of the "minimum" energy conformer were fixed, the 4-trifluoromethyl group was rotated in steps of 30°. The initial geometry of each of the diphenyl- and phenylpyridylamines was then built by replacing one of the amino hydrogen atoms of the optimized structure of 3-chloro-2,6-dinitro-4-(trifluoromethyl)-aniline with the appropriate aryl group. Then, the geometry was optimized by varying the dihedral angle between the planes of the two aromatic rings in steps of 30°. The "minimum" energy conformation was fully optimized with the precise option. In each calculation, all bond lengths, bond angles, and the dihedral angle between the two rings were allowed to vary while the energy was minimized.

Procedure for the Analysis of Substituent Effects. The electronic effects that the substituents exerted on the ionization of the NH group were reflected by the sum of their Hammett-type σ constants. The σ constant[16] that was used depended upon the location of the substituent relative to the NH side chain and also upon the substitution pattern. For meta substituents, σ^0 was invariably used. To assess the significance of the conjugative effect of an electron-withdrawing para substituent, the performance of σ^- was compared with that of σ^0. For an ortho substituent, σ^0 (but not σ^-) of the same substituent in a para position was used to reflect the substituent's "ordinary" electronic effect.[6] The conjugative effect of an ortho substituent was not considered. For the "proximity" electronic effect of an ortho substituent not accounted for by σ^0 (that is, σ^0_p, where p is para), the Charton inductive parameter, σ_I, was used.[17] The Taft–Kutter–Hansch (TKH) E_s steric parameter was used to reflect the steric effect of an ortho substituent.[18] The TKH E_s is a combination of the original Taft E_s for alkyl groups[19] and a similar E_s developed by Kutter and Hansch reflecting the effects of nonalkyl substituents.[18] If it was necessary, additional σ_I and E_s terms were introduced to differentiate the ortho effects for series I compounds. This procedure for analyzing the effects of ortho substituents had been shown to be valid for a number of sets of reactivity and equilibrium data.[6,20] For the compounds of series II, the effects that substituents exerted on the behavior of the aza functional group of the pyridine ring were reflected by the sum of the σ^+ constants of the substituents, irrespective of the locations of the substituents relative to the aza-N and the substitution pattern. The σ^+ constant applies in cases where an electron-donating group interacts with an electron-deficient reaction center.[21] The σ^+ constant of an ortho substituent was assumed to be the same as that of the same substituent in a para position.[6] For the compounds of series III, the steric effects of both the meta and para substituents were shown to be relayed to the ortho nitro group through the meta

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Table I. Observed and Calculated log K_A Values and Substituent Parameters of Series I Compounds[a]

no.	compd	−log K_A obsd	−log K_A calcd[b]	−log K_A dev	σ^0_o	σ^0_m	σ^0_p	σ^-_p	$\sum(\sigma^0_{o,m},\sigma^-_p)$	$\sum\sigma_I^\circ$	$-E_s(L)^\circ$	$-E_s(S)^\circ$
1	3-CF_3	10.01	9.84	−0.18	0	0.46	0	0	0.46	0	0	0
2	4-Cl-3-CF_3	9.12	9.12	0	0	0.46	0.24	0.24	0.70	0	0	0
3	3,5-$(CF_3)_2$	8.35	8.46	0.11	0	0.92	0	0	0.92	0	0	0
4	4-Br	10.26	10.43	0.17	0	0	0.26	0.26	0.26	0	0	0
5	4-Cl	10.29	10.49	0.20	0	0	0.24	0.24	0.24	0	0	0
6	4-CF_3	9.49	9.23	−0.22	0	0	0.53	0.65	0.65	0	0	0
7	4-OCF_3	10.50	10.42	−0.04	0	0	0.25	0.25	0.25	0	0	0
8	2-Br	9.92	10.02	0.10	0.26	0	0	0	0.26	0.45	1.16	0
9	2-Cl-5-CF_3	8.70	8.72	0.02	0.24	0.46	0	0	0.70	0.47	0.97	0
10	2,4-Cl_2-5-CF_3	7.91	8.02	0.10	0.24	0.46	0.24	0.24	0.94	0.47	0.97	0
11	2-Cl-4-CF_3	8.24	8.16	−0.08	0.24	0	0.53	0.65	0.89	0.47	0.97	0
12	2,4-F_2	9.78	9.85	0.07	0.17	0	0.17	0.17	0.34	0.52	0.46	0
13	2-CF_3	9.33	9.05	−0.28	0.53	0	0	0	0.53	0.41	2.40	0
14	4-Cl-2-CF_3	8.33	8.33	0	0.53	0	0.24	0.24	0.77	0.41	2.40	0
15	2,4,6-Br_3-3-CF_3	6.59	6.32	−0.27	0.52	0.46	0.26	0.26	1.24	0.90	1.16	1.16
16	2,6-Br_2-4-CF_3	6.52	6.53	0.01	0.52	0	0.53	0.65	1.17	0.90	1.16	1.16
17	2-Br-4-Cl-6-CF_3	6.69	6.78	0.09	0.79	0	0.24	0.24	1.03	0.86	2.40	1.16
18	2-Br-6-Cl-4-CF_3	6.64	6.66	0.02	0.50	0	0.53	0.65	1.15	0.92	1.16	0.97
19	2,4,6-Cl_3	8.02	7.97	−0.05	0.48	0	0.24	0.24	0.72	0.94	0.97	0.97
20	2,4-Cl_2-6-CF_3	6.64	6.91	0.27	0.77	0	0.24	0.24	1.01	0.88	2.40	0.97
21	2,6-Cl_2-4-NO_2	4.84	4.98	0.14	0.48	0	0.82	1.24	1.72	0.90	0.97	0.97
22	2,4,6-Cl_3-3-CH_3	8.27	8.15	−0.13	0.48	−0.06	0.24	0.24	0.66	0.90	0.97	0.97
23	2,4,6-Cl_3-3,5-$(CF_3)_2$	5.26	5.22	−0.04	0.48	0.92	0.24	0.24	1.64	0.86	0.97	0.97

[a] All parameters were from refs 6, 16, and 17. [b] Calculated by use of eq 6.

Table II. Correlation Equations for Various Subsets of Series I Compounds[a]

$$\log K_A = \rho\sum\sigma^{\#} + \rho_I\sum\sigma_I^\circ + \delta^L E_s(L)^\circ + \delta^S E_s(S)^\circ + \text{const}$$

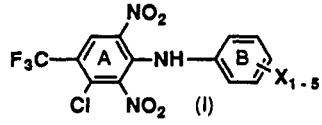
set	compds included	ρ	ρ_I	δ^L	δ^S	const	n^b	r^b	s^b	F^b	eq no.
I-1	meta and para substitutions (1–7)	2.836 (0.690)				−11.127 (0.383)	7	0.978	0.176	111.5	2
I-2	monoortho substitutions (8–14)	2.977 (0.454)				−10.771 (0.308)	7	0.991	0.114	284.2	3
I-3	I-1 + I-2 (1–14)	2.920 (0.351)	0.932 (0.390)			−11.165 (0.214)	14	0.988	0.148	219.5	4
I-3	I-1 + I-2 (1–14)	2.956 (0.457)		−0.211 (0.146)		−11.113 (0.286)	14	0.977	0.199	117.6	5
I-4	I-3 + diortho compds (1–23)	2.986 (0.249)	0.527 (0.474)	−0.152 (0.118)	−0.464 (0.311)	−11.208 (0.178)	23	0.996	0.162	557.6	6[c]

[a] The figures in parenthesea are the 95% confidence intervals. [b] Key: n, number of compounds; r, correlation coefficient; s, standard deviation; F, the value of the ratio between the regression and residual variances. [c] The standard deviation values cross-validated by the leave-one-out procedure for ρ, ρ_I, δ^L, δ_S, and constant were 0.023, 0.045, 0.018, 0.031, and 0.019, respectively, for 23 equations. The mean values of these coefficients and that of the constant coincided with those in eq 6. The average of differences between observed log K_A and that predicted by leave-one-out correlation equations was −0.003 with a standard deviation of 0.190.

substituent, thereby affecting the nitro group's stereoelectronic properties. When this "buttressing" steric effect was enough to "twist" the plane of the nitro group, the net steric effect exerted by the ortho nitro group was reflected by the TKH E_s value for the group's half-thickness.[18] The sets of electronic parameters used in the correlation equations were designated by the symbol $\sigma^{\#}$ and were defined for individual cases. The results of the correlations are reported only when each of the parameters was found to be significant (above the 95% level by the F-test).

Results of the Correlation Analyses

(1) Ionization Constants of the *N*-[3-Chloro-2,6-dinitro-4-(trifluoromethyl)phenyl]anilines (Series I).



(I)

These compounds, which, like fluazinam, possess a tetrasubstituted anilino moiety (the A ring), also possess a substituted phenyl group (the B ring) instead of a pyridine ring. Both the experimentally determined and the calculated log K_A values are listed in Table I, along with the relevant parameters used in the calculations. The correlations of various subsets of compounds are shown in Table II.

For the subset I-1 compounds, which lack ortho substituents, eq 2 was formulated. Therein, $\sum\sigma^{\#}$ was the sum of σ^0_m and σ^-_p, the appropriate constants for the meta and para substituents, respectively. In this subset, there is only one substituent, 4-trifluoromethyl, for which σ^0 and σ^- differ, but not by very much. Therefore, an almost identical correlation equation, which incorporated $\sum\sigma^0$, was formulated (not shown). For the subset I-2 compounds, in which only one of the ortho positions was occupied by a substituent, eq 3 was formulated. Again, the 4-trifluoromethyl substituent was only one for which σ^0 and σ^- differed. However, the results obtained from eq 3, in which $\sum\sigma^{\#}$ was the sum of σ^0_o, σ^0_m, and σ^-_p, were better than those obtained by using $\sum\sigma^0$ (not shown). Because the ortho substituent could only be either a halogen atom or a trifluoromethyl group, the contributions from the proximity effect components of σ_I and E_s of the ortho substituents were not significant. Those contributions

Table III. Observed and Calculated log K_A Values and Substituent Parameters of Series II Compounds[a]

no.	compd	-log K_A obsd	-log K_A calcd[b]	dev	σ^0_o	σ^0_m	σ^-_p	$\sum(\sigma^0_{o,m},\sigma^-_p)$	$\sum\sigma^+/N$	σ_I°	$-E_s^\circ$
24	6-Cl-5-CF_3	7.65	7.45	-0.20	0	0.37	0.65	1.02	0.63	0	0
25	5-Br	9.10	9.18	0.08	0	0	0.26	0.26	0.41	0	0
26	5-Cl	9.05	9.23	0.18	0	0	0.24	0.24	0.40	0	0
27	5-NO_2	6.91	6.96	0.05	0	0	1.24	1.24	0.67	0	0
28	5-CF_3	8.48	8.29	-0.19	0	0	0.65	0.65	0.52	0	0
29	3-Br-5-Cl	7.78	7.90	0.12	0.26	0	0.24	0.50	0.81	0.45	1.16
30	3-Br-5-CF_3	7.07	6.96	-0.11	0.26	0	0.65	0.91	0.93	0.45	1.16
31	3-Br-6-Cl-5-CF_3	6.19	6.12	-0.07	0.26	0	0.65	1.28	1.04	0.45	1.16
32	3-Cl-5-Br	7.96	7.98	0.02	0.24	0	0.26	0.50	0.81	0.47	0.97
33	3,5-Cl_2-4-CH_3	8.25	8.39	0.14	0.24	-0.06	0.24	0.42	0.49	0.47	0.97
34	3,5-Cl_2-4,6-Me_2	8.79	8.74	-0.05	0.24	-0.12	0.24	0.36	0.18	0.47	0.97
35	3,5,6-Cl_3-4-CF_3	5.77	5.77	0	0.24	0.83	0.24	1.31	1.52	0.47	0.97
36	3,5-Cl_2-6-CH_3	8.33	8.39	-0.06	0.24	-0.06	0.24	0.42	0.49	0.47	0.97
37	3-Cl-5-CF_3	7.11	7.09	-0.02	0.24	0	0.65	0.89	0.92	0.47	0.97
38	3,6-Cl_2-5-CF_3	6.15	6.25	0.10	0.24	0.37	0.65	1.26	1.03	0.47	0.97
39	6-NMe_2-3-Cl-5-CF_3	8.58	8.59	0.01	0.24	-0.10	0.65	0.79	-0.78	0.47	0.97
40	6-NHMe-3-Cl-5-CF_3	8.51	8.59	0.08	0.24	-0.10[c]	0.65	0.79	-0.78	0.47	0.97
41	3-CH_3	9.95	9.80	-0.15	-0.12	0	0	-0.12	-0.06	-0.01	1.24
42	6-Cl-3-NO_2[d]	7.07	6.56	-0.51	0.82	0.37	0	1.19	0.78	0.67	1.01
43	3-NO_2[d]	8.18	7.41	-0.77	0.82	0	0	0.82	0.67	0.67	1.01
44	3-NO_2-5-CF_3[d]	6.25	5.67	-0.58	0.82	0	0.65	1.47	1.19	0.67	1.01
45	3-CF_3	7.73	7.54	-0.19	0.53	0	0	0.53	0.52	0.41	2.40
46	5-Br-6-Cl-3-CF_3	5.73	5.85	0.12	0.53	0.37	0.26	1.16	1.04	0.41	2.40
47	6-Cl-3-CF_3	6.66	6.70	0.04	0.53	0.37	0	0.90	0.63	0.41	2.40

[a] All parameters were taken from refs 6, 16, and 17. [b] Calculated by use of eq 8. [c] The value of NMe_2 is used. [d] Not included in eq 8.

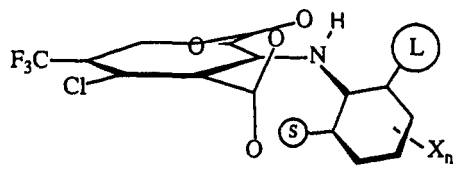


Figure 1. Model of the conformation assumed by series I compounds (L and S stand for the larger and smaller ortho substituents, respectively).

were probably included in the intercept of eq 3. The intercept was slightly, but significantly, more positive (-10.77) than those of eqs 2 and 4–6, for which the value of the intercept was very stable at -11.15 ± 0.05.

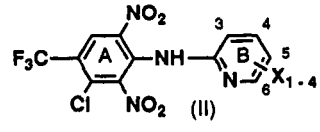
For the compounds of subset I-3 (a combination of subsets I-1 and I-2), eqs 4 and 5 were formulated. The quality of eq 4 was better than that of eq 5. However, because the colinearity of E_s and σ_I for this set of compounds was rather high (r = 0.73), it would not be relevant to disregard the steric effect of ortho substituents. Despite the uneven quality of the equations, the significant contribution that proximity effects made was first suggested therein. The ortho substituent of the compounds of subset I-2 compounds was assumed to be located on the outer edge molecular "bend", so that the substituent's steric interaction with the two ortho nitro groups of the A ring was minimized (Figure 1). Because the substituent at the other ortho position of the B ring was always a hydrogen atom in this subset, the steric effect of the ortho substituents was expressed in eq 5 by the term $\delta^L E_s(L)$, in which L denotes the larger (bulkier) of the two ortho substituents.

For the compounds of subset I-4, which includes 2,6-disubstituted compounds, the different steric effects of the smaller and larger ortho substituents were clearly indicated in eq 6. The smaller (less bulky) ortho substituents, which are forced "inside" the molecular bend, were assumed to interact sterically with the A ring substituents to a greater extent than did the larger (bulkier) ones. This interaction was reflected by the more negative value of coefficient δ^S of the $E_s(S)$ term, in which S denotes the smaller (less bulky) substituent. The use of $\sum\sigma^0$, instead of $\sum\sigma^\#$, in eq 6 produced the quality of the correlation (r = 0.981, s = 0.337, not shown).

That the values of ρ and the intercepts of the equations listed in Table II were, except in the case of eq 3, very stable was taken to indicate that the overlapping stereoelectronic effects of the B-ring substituents could be separated into discrete components almost completely. The first of these was the ordinary electronic effect, which was represented by the sum of σ^0_o, σ^0_m, and σ^-_p. The second was the proximity electronic effect of the ortho substituents, which was expressed in terms of $\sum\sigma_I$. However, it is unclear whether the effect works inductively or through a field. The greater the total ordinary and proximity electron-withdrawing effects of the B-ring substituents were, the higher the ionization constant was. The significant contribution by σ^-_p but not by σ^0_p suggested that the conjugation of the electron-rich center with an electron-withdrawing para substituent like a nitro group, which required coplanarity of the plane of the N–H bond with the B ring, was possible.

The negative signs of the $E_s(L)$ and $E_s(S)$ terms indicated that the bulkier the ortho substituent was, the greater was the degree of ionization. A similar substituent effect was observed in the ionization of the ortho-substituted benzoic acids.[6] Here also, the bulkier the ortho substituent was, the higher the ionization constant was. Thus, the relatively high acidity displayed by some series I compounds could be the result of a relief of steric congestion by ionization. In the unionized form, the environment of the somewhat distorted tetrahedral nitrogen atom would be crowded. In the anion, the environment would be less crowded, especially if the contribution to the structure of the anion of a canonical form which incorporates a trigonal nitrogen atom was enhanced by delocalization of the negative charge, especially by conjugation of the nitrogen atom with a para substituent.

(2) Ionization Constants of the *N*-[3-Chloro-2,6-dinitro-4-(trifluoromethyl)phenyl]-2-pyridylamines (Series II). The series II compounds, of which fluazinam



(II)

Table IV. Development of a Correlation Equation for Series II Compounds[a]

$$\log K_A = \rho\sum\sigma^{\#} + \rho^{+}\sum(\sigma^{+}/\mathrm{N}) + \delta E_s^{\circ} + \text{const}$$

parameters used	ρ	ρ^{+}	δ	const	n	r	s	F	eq no.
$\sum\sigma^{\#}$, E_s°	2.546		−0.449	−10.000	21	0.943	0.411	72.5	7
	(0.486)		(0.262)	(0.455)					
$\sum\sigma^{\#}$, $\sum(\sigma^{+}/\mathrm{N})$, E_s°	2.059	0.761	−0.414	−10.024	21	0.995	0.124	595.7	8[b]
	(0.165)	(0.119)	(0.079)	(0.137)					

[a] For n, r, s, and F, see Table II. [b] The standard deviation values cross-validated by the leave-one-out procedure for ρ, ρ^{+}, δ, and constant were 0.020, 0.010, 0.012, and 0.019, respectively, for 21 equations. The mean values of these coefficients and that of the constant coincided with those in eq 8. The average of differences between observed log K_A and that predicted by leave-one-out correlation equations was 0.000 with a standard deviation of 0.137.

(37) is one, were next investigated. The log K_A values are listed in Table III along with the parameters used in the calculations. Because these compounds and those of series I share common features (but not the aza functional group of the B ring), the log K_A values were first calculated using sets of parameters that were similar to those used for the series I compounds. The aza functional group of the B ring was present in all the compounds, so it was not necessary to incorporate σ^0(—N=) in $\sum\sigma^{\#}$. Also, the E_s(—N=) term was not used. Because most of the compounds were either "ortho" monosubstituted (the position 3 in formula II) or multisubstituted, correlations were made for all the members of the series, except compounds 42–44 (which each possess a 3-nitro substituent).

The results are shown in Table IV. The independent variables $\sum\sigma^{\#}$ (the sum of $\sigma^0_{o,m}$ and σ^{-}_p) and E_s° were used to formulate eq 7. The introduction of the σ_I° term was shown to be unnecessary, probably because colinearity of σ_I° and E_s° was fairly high (r = 0.61) for this set of compounds. The quality of the correlation was much poorer than that produced by the use of eq 6. This result suggested that some factor had been overlooked. This factor may have been the effect that substituents exerted on the delocalization of the lone-pair electrons of the aza nitrogen atom. When the sum of the σ^{+} constants of the B ring substituents (σ^{+}_m for the 3- and 5-substituents, and σ^{+}_p for the 4- and 6-substituents) was introduced as an additional parameter term, the quality of the correlation was much improved (eq 8). The σ^{+} constant applies in cases in which an electron-donating group interacts with an electron-deficient reaction center, which, in this case, was the aza nitrogen atom. It works as a "sink" for electrons migrating from the electron-donating substituents. The effect was particularly pronounced when the substituents were capable of conjugation. Thus, the electron-donating effect of a 6-substituent like NMe_2 (compound **39**) or NHMe (compound **40**) was much greater than that predicted by σ or σ^0. It was not necessary to use σ^0 to reflect the effect of such substituents. The aza functional group did not exert a significant steric effect, so the degree of twisting of the 6-substituents, which are capable of conjugation, was not great. The effect of electron donation to the aza nitrogen atom could be relayed to the NH group to retard its ionization. The assignment of a positive sign to the $\sum\sigma^{+}/\mathrm{N}$ term to compensate for this effect was thus understandable.

It was assumed that, in the anion of a series II compound, the negative charge formally located on the bridge nitrogen atom could be delocalized most effectively into the aza functional group of the pyridine ring. Equation 8 reflected the beliefs that the formation of such an ambident anion was controlled by the effect of substituents on the two ambident nitrogen positions and that the effects were additive. The magnitude of the coefficient ρ in eq 8 was considerably lower than that of ρ in eq 6 (2.06 vs 2.99). However, in eq 8, the sum of ρ and ρ^{+}/N equaled

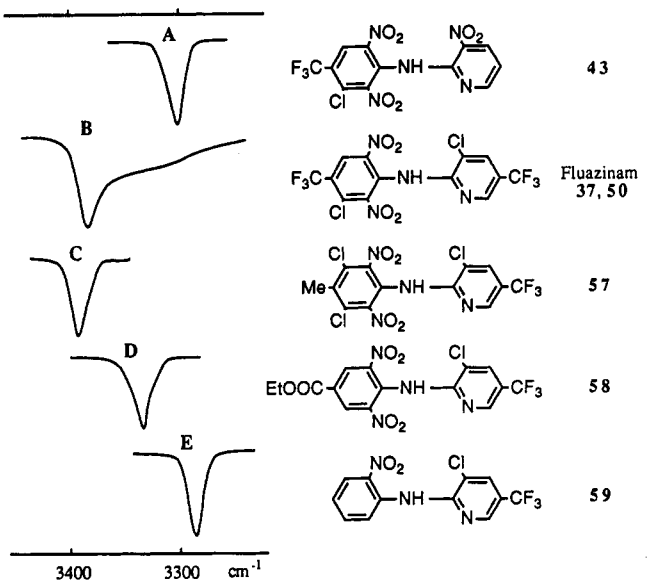


Figure 2. NH stretching absorption band in the IR spectra of fluazinam and related compounds (0.04 M in CCl_4; the shape of the absorption band and its position did not change over the concentration range 0.02–0.1 M).

2.82, which was close to 2.99. This indicated that the two effects were, in fact, additive. In qualitative terms, the lower value of ρ in eq 8 could be the result of overestimating the electronic effects of the B ring substituents. Because they were counteracted by the strong electron-withdrawing effect of the aza functional group, the net electron-withdrawing effect of the B-ring substituents would be smaller than that reflected by $\sum\sigma^{\#}$, hence the lower ρ value in eq 8. The smaller contribution of the $\rho\sum\sigma^{\#}$ term was compensated for by the $\rho^{+}\sum(\sigma^{+}/\mathrm{N})$ term, which reflected the effect of substituents in overcoming the electron-withdrawing effect of the aza nitrogen atom.

In eq 8, the coefficient δ of the E_s term, which reflected the steric effect of the 3-ortho substituents, was more negative (−0.41) than that (−0.15) of the E_s(L) term that was found in eq 6 for the series I compounds. Because, in the series II compounds, the aza nitrogen atom is inside the molecular bend, δ in eq 8 corresponded to δ^{L} in eq 6. The proximity electronic effect of the 3-ortho substituents, expressed in terms of σ_I, would be reflected to a certain extent by this term because the two were colinear.

The experimentally determined values of log K_A of the three 3-nitro derivatives 42–44 were much lower than those calculated by eq 8. That 42–44 were weaker acids than predicted was probably the result of the formation of an intramolecular hydrogen bond between the NH group and the nitro group, which stabilized the unionized forms to some extent. In the IR spectrum of compound **43**, the NH stretching band appeared at 3300 cm^{-1} (Figure 2A). In the absence of hydrogen bonding, the NH stretching band generally appears at ca. 3400 cm^{-1}.[22] For example, in the

Table V. Observed and Calculated log K_A Values and Substituent Parameters for Series III Compounds[a]

no.	compd	−log K_A obsd	−log K_A calcd[b]	dev	σ^0_m	σ^0_p	$\sum\sigma^0_{o,m,p}$	$\sum\sigma^{\#c}$	$-\sum E_s^o$	$-E_s^m$	$-E_s^p$	$E_s^m \cdot E_s^p$
48	3-Br-4-CF_3	7.26	7.28	0.02	0.39	0.53	2.56	2.41	3.53	1.16	2.40	2.78
49	3-Cl-4-CH_3	10.58	10.70	0.12	0.37	−0.12	1.89	1.74	3.53	0.97	1.24	1.20
50	3-Cl-4-CF_3	7.11	7.23	0.12	0.37	0.53	2.54	2.39	3.53	0.97	2.40	2.33
51	3-Cl-4-SO_2Me	6.16	6.13	−0.03	0.37	0.73	2.74	2.59	3.53	0.97	2.65[d]	2.57
52	3-Cl-4-SO_2NEt_2	7.57	7.60	0.03	0.37	0.63[e]	2.64	2.49	3.53	0.97	5.25[d]	5.09
53	3-I-4-CF_3	7.72	7.71	−0.01	0.35	0.53	2.52	2.37	3.53	1.40	2.40	3.36
54	3-O-*i*-Bu-4-CF_3	8.53	8.48	−0.05	0.10	0.53	2.27	2.12	3.53	0.55	2.40	1.32
55	3-OEt-4-CF_3	8.53	8.48	−0.05	0.10	0.53	2.27	2.12	3.53	0.55	2.40	1.32
56	3-O-*n*-Pr-4-CF_3	8.48	8.48	0	0.10	0.53	2.27	2.12	3.53	0.55	2.40	1.32
57	3,5-Cl_2-4-CH_3	9.94	9.81	−0.13	0.74	−0.12	2.26	1.94	2.02	1.96	1.24	2.41
58	4-COOEt[f]	9.30	8.26	1.04	0	0.44	2.08	2.08	5.04	0	4.16[d]	0

[a] All the parameters were taken from refs 6, 16, and 17 unless otherwise indicated. [b] Calculated by use of eq 14. [c] σ^0 for meta and para substituents. For 2,6-$(NO_2)_2$, $\sum\sigma_I$ for compound **57**, $\sum\sigma^0$ for compound **58**, and $\sigma_I + \sigma^0$ for the remaining compounds. [d] Estimated from the linear relationship between E_s and B_5 for H, F, Cl, Br, and I groups, The B_5 values were obtained by STERIMOL calculations (ref 23). [e] The value for SO_2NMe_2 is used. [f] Not included in eq 14.

Table VI. Correlation Equations for Series III Compounds[a]

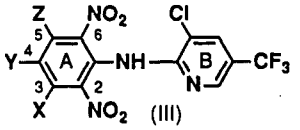
$$\log K_A = \rho\sum\sigma^b + \delta^o\sum E_s^o + \delta^m E_s^m + \delta^p E_s^p + \delta^{m,p}(E_s^m \cdot E_s^p) + \text{const}$$

set	compds included	ρ	δ^o	δ^m	δ^p	$\delta^{m,p}$	const	n	r	s	F	eq no.
III-1	48–56	3.268 $\sum\sigma^{\#c}$ (1.144)					−16.381 (2.961)	9	0.931	0.486	45.6	9
		4.647 $\sum\sigma^0$ (1.032)					−19.197 (2.502)	9	0.971	0.322	113.3	10
		5.793 $\sum\sigma^0$ (0.337)		0.721 (0.064)	0.382 (0.075)		−20.455 (0.636)	9	0.999	0.068	897.3	11
		5.791 $\sum\sigma^0$ (0.317)				−0.326 (0.064)	−21.186 (2.121)	9	0.999	0.067	1375.7	12
III-2	48–57	5.791 $\sum\sigma^0$ (0.317)	−0.700 (0.119)			−0.326 (0.064)	−23.657 (0.676)	10	0.999	0.067	1169.2	13
		5.939 $\sum\sigma^{\#d}$ (0.340)				−0.347 (0.074)	−20.614 (0.661)	10	0.998	0.086	1077.6	14[e]

[a] For n, r, s, and F, see Table II. [b] Various types of σ are used. [c] σ^- for para and σ^0 for meta and 2,6-$(NO_2)_2$. [d] σ^0 for meta and para substituents. For 2,6-$(NO_2)_2$, $\sum\sigma_I$ for compound **57** and $\sigma_I + \sigma^0$ for the remaining compounds. [e] The average and standard deviation values cross-validated by the leave-one-out procedure for ρ, $\delta^{m,p}$, and constants were 5.948 ± 0.092, −0.349 ± 0.012, and −20.632 ± 0.194, respectively. The averaged and standard deviation for differences between observed log K_A and that predicted by 10 leave-one-out correlation equations was −0.003 ± 0.119.

spectrum of diphenylamine, recorded under the same experimental conditions as that of **43**, the NH stretching band appeared at 3425 cm^{-1}. For compound **37** (fluazinam), in which intramolecular hydrogen-bonding of the NH group with the B-ring substituents is improbable, the NH stretching band was observed at 3380 cm^{-1} (Figure 2B). The free NH stretching frequency should decrease with an increase in the net electron-withdrawing effect of the B ring substituents, provided other factors remained unchanged. However, the net electron-withdrawing effect of the B-ring substituents of compounds **43**, in terms of $\sum\sigma^{\#}$ and σ_I, was little different from that of the B-ring substituents of fluazinam (**37**). Thus, the band observed at 3300 cm^{-1} in the spectrum of compound **43** could be the NH stretching band of an intramolecular hydrogen bond between the NH group and the B-ring nitro group. A shoulder at 3300 cm^{-1} in the spectrum of fluazinam was attributed to a weak hydrogen bond between the NH group and an ortho nitro group of the A ring. In Table III, the log K_A values of compounds **42–44** were calculated using the TKH E_s value (−1.01) of the 3-ortho nitro group that reflected the steric effect of the group when its plane was oriented *perpendicular* to the plane of the ring.[18] The use of the TKH E_s value (−2.52)[18] that reflected the steric effect of the group when its plane and that of the ring were *coplanar* gave much greater deviations from the experimentally determined values of log K_A.

(3) Ionization Constants of the 3-Chloro-*N*-(2,6-dinitrophenyl)-5-(trifluoromethyl)-2-pyridinamines (Series III). In the series III compounds, a variety of



(III)

substituents was present on the A ring. Fluazinam (**50**) is also a member of this series. The experimentally determined and calculated log K_A values are listed in Table V. The results of the correlations are summarized in Table VI.

First, the compounds of subset III-1, in which the A ring was substituted at the 2- and 6-positions by nitro groups and at the 3- and 4-positions by the groups X and Y, were investigated. In eq 9, $\sum\sigma^{\#}$ was the sum of σ^-_p (for each of the para substituents) and σ^0 (for the two ortho nitro substituents and each of the meta substituents). $\sum\sigma^{\#}$ was similar in form to that used in eq 6 for the series I compounds. The resulting poor quality of the correlation raised questions about the validity of using $\sum\sigma^{\#}$ and suggested that additional factors should be considered.

In these compounds, the plane of the B ring was assumed to be oriented nearly perpendicular to the plane of the A ring, which bears two ortho nitro substituents. In such a conformation, the electron-withdrawing para substituents of the B ring were capable of conjugation, as the

(22) Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*, 3rd ed.; John Wiley & Sons: New York, 1974; p 102.

formulation of eqs 6 and 8 indicated. However, conjugation of the electron-rich center with such A-ring electron-withdrawing para substituents as SO_2Me and SO_2NEt_2, for which σ^- differs from σ^0, could be difficult because steric hindrance by the two ortho nitro groups would prevent the A ring and the *N*-phenyl bond from becoming coplanar. The steric effects of the two A-ring ortho nitro groups could influence the acidity of the series III compounds to a greater degree than the steric effects of the B-ring ortho substituents influenced the acidity of the series I and II compounds. The conversion of an unionized tetrahedral nitrogen atom to an ionized trigonal nitrogen atom might relieve steric congestion and promote ionization to some extent. With these points in mind, eq 10, in which $\sum\sigma^0$ reflected the effects of the X and Y substituents, was formulated.

Although eq 10 represented a significant improvement over eq 9, its quality was still not very high. Further elaboration was necessary. Examination of the residuals indicated that the bulkier the X and Y substituents were, the greater the negative deviation of the observed log K_A from that calculated by use of eq 10 tended to be. The introduction of E_s terms to reflect the effects of both the meta and para substituents resulted in an excellent correlation, as expressed by eq 11. That the introduction of two significantly positive E_s terms was necessary could mean that the bulkiness of the para substituent amplifies the steric effect of the meta substituent. In other words, the steric effect of the para substituent is relayed through the meta substituent to the ortho nitro group and acts to lower the ionization constant. Thus, the steric effects of the meta and para substituents may reinforce each other. In fact, it was found that the cross-product, $E_s^m \cdot E_s^p$, reflected the effects almost as satisfactorily, as shown in eq 12. The amplification of the steric effect of the meta substituent is proportional to the bulkiness of the para substituents.

For a para substituent like COOEt, SO_2Me, or SO_2NEt_2, the TKH E_s value is not available. Therefore, it was estimated from the linear relationship (r = 0.999) between E_s and the STERIMOL B_5 parameter that is defined for such symmetric substituents as H, F, Cl, Br, and I. The B_5 parameter, as defined by Verloop,[23] represents the maximum width of the substituent in the direction perpendicular to the axis connecting the α-atom of the substituent to the rest of the molecule.

The experimentally determined log K_A of compound **57** (3,5-dichloro-4-methyl-substituted), a compound in which both meta positions are occupied, was significantly more negative than that calculated by the use of eq 12. For compound **57**, the amplifying effect described previously should be counted twice. The amplifying steric effects of the meta and para substituents may be such as to twist the planes of both ortho nitro substituents simultaneously. The degree to which the plane of the 6-nitro is twisted is probably almost identical with that to which the plane of the 2-nitro group is twisted. For compound **58** (4-ethoxycarbonyl-substituted), both meta positions are unoccupied. The degree to which the planes of both ortho nitro groups are twisted is thus perhaps much smaller than that to which the plane of the 2-nitro group of the 3,4-disubstituted compounds is twisted. The cross-product, $E_s^m \cdot E_s^p$, which is zero in this case, was not required to calculate the log K_A of this compound by the use of eq 12. Incidentally, eq 12 predicted log K_A rather well (Δ = 0.16). However, because the stereoelectronic situations of the two ortho nitro groups differ from those of the subset I compounds, the "successful" prediction of log K_A may only have been a fortuitous occurrence.

The possible steric effects that would be induced by twisting the planes of the two ortho nitro groups were examined. First, the plane of the ortho nitro group was assumed to be either coplanar with, or perpendicular to, the A-ring plane. The TKH E_s values for the nitro group in the latter conformation (−1.01) and in the former conformation (−2.52) were used to construct the steric parameter, $\sum E_s^\circ$, that reflected the effects of the two groups. For the X,Y-disubstituted compounds of subset 1, E_s(perpendicular) for the 2-nitro group and E_s(coplanar) for the 6-nitro group were added. For compounds **57** and **58**, E_s(perpendicular) and E_s(coplanar) were doubled, respectively. However, when $\sum E_s^\circ$ was used as an additional independent variable, log K_A of compound **58** was calculated more positive (Δ = 1.22) than that which was determined experimentally. If compound **58** was not considered, eq 13, of a quality almost equivalent to that of eq 12, was formulated by incorporating the cross-product $E_s^m \cdot E_s^p$.

The possible electronic effects that would be induced by twisting the planes of the two ortho nitro groups were next examined. To reflect the effect of a nitro group whose plane was coplanar with that of the A ring, σ^0 = 0.82 was used. To reflect the effect of a nitro group whose plane was perpendicular to that of the A ring, σ_I = 0.67 was used. In the latter case, the resonance component, σ_R, of σ^0 was considered to be insignificant and was omitted. For compounds **57** and **58**, the values of σ_I and σ^0 were doubled, respectively. For the remaining compounds, the sum, $\sigma^0 + \sigma_I$, was used. In eq 14, $\sum\sigma^\#$ is the sum of the σ constants of the two ortho nitro groups that apply to the two conformations described previously and $\sigma^0_{m,p}$. A slightly poorer correlation quality was generated by eq 14 only when compound **58** was not considered. The introduction of the $\sum E_s^\circ$ term into eq 14 did not improve the quality of the correlation.

The IR spectra shown in Figure 2 provided information that was useful for explaining the seemingly anomalous behavior of compound **58**. In the spectrum of compound **57**, a band at 3393 cm^{-1} (Figure 2C), which was close to that observed in the spectrum of fluazinam, could be assigned to the free NH stretching. The plane of each of the nitro groups of **57** is so much twisted from coplanarity with the ring plane that the resonance component of the group's electron-withdrawing effect is lost. Furthermore, the formation of an intramolecular hydrogen bond between an oxygen atom of a nitro group and the hydrogen atom of the amino group is not possible. In the spectrum of compound **58**, however, an NH stretching band was observed at a lower frequency, 3330 cm^{-1} (Figure 2D). In this case, the planes of the ortho nitro groups are not twisted to such a great degree and, consequently, intramolecular hydrogen bonding is significant. Thus, the degree of ionization of compound **58** is less than that predicted by eqs 13 and 14. The spectrum of a reference compound that lacks one ortho nitro group and in which significant steric congestion around the NH group is absent, 3-chloro-*N*-(2-nitrophenyl)-5-(trifluoromethyl)-2-pyridinamine (**59**), showed an NH stretching band at 3285 cm^{-1} (Figure 2E). That frequency was the lowest observed among the compounds described here and showed that the extent of intramolecular hydrogen bonding was as expected indeed high. The acid ionization constant of compound **59** was too low to be measured.

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From the arguments used to formulate eqs 13 and 14, it was concluded that the net steric effect of the meta and para substituents was almost definitely of the amplifying type that twists the planes of the two ortho nitro groups. The lower the intensity of the effect was, in terms of $E_s^m \cdot E_s^p$, the lower was the degree to which the planes of the two ortho nitro groups were twisted from coplanarity with the plane of the A-ring. The electron-withdrawing (σ^0) and the steric [$-E_s$ (coplanar)] effects are higher in this conformation than in the conformation in which the planes of the nitro groups are nearly perpendicular to the plane of the A ring. Consequently, ionization is enhanced.

In spite of the excellent quality of the correlations, there remain some uncertainties in eqs 13 and 14 that must be resolved by future studies. Because the two ortho substituents were both nitro groups and also because twisting the planes of the groups reduces both the steric and electronic effects of the groups, the contributions from the two effects were not separated in eqs 13 and 14. The size and sign of the $\sum E_s^o$ term in eq 13 are similar to those of $\sum E_s^o$ in eq 8. However, it is not clear if the bulkiness of an ortho substituent on the A ring influences the ionization of the NH group in a manner similar to that of an ortho substituent on the B ring. The intercept of eq 13 is more negative than those of eqs 12 and 14. In these equations, the component attributed to the ortho steric effect was assumed to be a constant that was included in the intercept. Furthermore, the $\sum E_s^o$ term in eq 13 and the modification of $\sum \sigma^0$ to $\sum \sigma^\#$ in eq 14, which address the twisting patterns of the ortho nitro groups, seem to reiterate the amplifying effect that the meta and para substituents exert on the two ortho nitro groups. This effect is already reflected in the $E_s^m \cdot E_s^p$ term. Perhaps the amplifying effect in these heavily substituted compounds is indeed greater than that expressed by cross-product term. The value of ρ in eqs 12–14 was much higher than that in eq 6, which applied to the series I compounds that possessed substituents on the phenyl ring. The value of ρ could be lower if the negative charge that would be generated upon ionization is appreciably delocalized into the distant B-ring in the form of an ambident anion. Thus, there could be other factors that affect the value of ρ. The ionization of a series of sterically congested weak acids, the 4-substituted 2,6-di-*tert*-butylphenols, ρ (calculated from log K_A values measured in 1:1 ethanol/water) was 4.62, 1.73 times higher than that calculated for the ionization of 4-substituted phenols.[24] It is believed that this relatively high value of ρ reflected the steric inhibition of solvation of the phenoxide ion by the two ortho *tert*-butyl groups.[24,25] Steric inhibition of the solvation of the anions of the series III compounds by the two "large" ortho nitro groups would be more pronounced in anions in which the negative charge is less effectively delocalized by electron-withdrawing substituents. Steric inhibition of solvation would be expected to less in analogues that lack ortho substituents. Thus, the range of possible variations in the log K_A of series III compounds would be broader than that of analogues which lack the two ortho nitro substituents, the presence of which is reflected in a higher value of ρ.

Discussion

To formulate the best quality correlation equations, several assumptions about the preferred conformations of the compounds of each series were made. MO calculations, in which the AM1 Hamiltonian was applied, were made to determine if the assumptions were reasonable. For selected compounds of series I, those in which at least one ortho position of the B ring was occupied by a substituent, the most stable conformation was determined and the relative conformational energy was calculated. For compound **13** (2-trifluoromethyl-substituted), the angle between the planes of the A and B rings was calculated to be 66°, whereas for the 2,6-disubstituted compound **20** (2,4-dichloro-6-(trifluoromethyl)-substituted), it was calculated to be 85°. The presence of two ortho substituents apparently causes the two ring planes to twist to greater extent than does the presence of only one ortho substituent. In compound **13**, the plane defined by the amino group nitrogen atom and the bridgehead carbon atoms and the plane of the B ring were nearly coplanar (interplane angle 22°). However, in compound **20**, the interplane angle was calculated to be 48°. In the corresponding anions, the interplane angles may be smaller, so that conjugation of the electron-rich center with the para substituents is not severely restricted, as was assumed in the formulation of eq 6. Furthermore, for compound **20**, the conformation in which the ortho trifluoromethyl group projects outside the molecular bend was found to be about 7.8 kcal/mol more stable than that in which the trifluoromethyl group is inside the molecular bend.

The heats of formation, ΔH, of compounds **13**, **14** (2-(trifluoromethyl)-4-chloro-substituted), and **20** were calculated. The difference between the calculated ΔHs of compounds **13** and **14** was −5.4 kcal/mol, but that between the calculated ΔHs of compounds **14** and **20** was −3.3 kcal/mol. Thus, the introduction of a chloro substituent into the ortho position of compound **14** was less destabilizing than the introduction of a chloro substituent into the para position of compound **13**, because of the preexisting greater extent of steric congestion in compound **13**.

Similar MO calculations were made for fluazinam (**37** and **50**) and compounds **57** and **58**, which represented the compounds of series II and III. The calculations showed that, in **57** (2,6-dinitro-3,5-dichloro-4-methyl-substituted), the plane of one nitro group was twisted by 63° and that the other was twisted by 56°. That is, both groups were more nearly perpendicular to the plane of the A-ring. The minimum energy conformation of compound **58** (2,6-dinitro-4-(ethoxycarbonyl)-substituted), which lacked meta substituents on the A-ring, was that in which the planes of the two nitro groups were twisted by 27° and 35°. That is, the planes of both groups were more nearly coplanar with the plane of the A ring. In fluazinam, representative of the series III compounds which lack one meta substituent, the plane of the 2-nitro group was twisted by 63°. However, the plane of the 6-nitro group was twisted by only 26°. The results of the MO calculations are believed to justify the assignment of those steric and electronic parameters for the ortho nitro groups that were used to formulate eqs 13 and 14.

For these compounds to be "weakly" acidic, and thus to permit the measurement of their ionization constants by conventional methods, it was necessary that the substituents on the aromatic rings be limited to those with electron-withdrawing properties. The presence of such substituents was also required for these compounds to display any appreciable biological uncoupling activity. Thus, one of shortcomings of this study was that the effects of electron-*donating* substituents were not fully evaluated. To compensate for this, various electron-withdrawing substituents in different substitution patterns were used. The use of complicated combinations of vicinal and 2,6-

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substituents were inevitable in these circumstances. In spite of this, the analyses described here are believed to have been quite successful in differentiating the various stereoelectronic effects exerted on the acidity by multiple substituents. No published example of Hammett-Taft-type correlation analysis has dealt with such complicated multiple substituent effects as does the present study. The use of different σ constants to reflect the effects of substituents at different locations was clearly justified. The quality of the results also validates the procedure used for the analysis of the ortho effect.[6]

Registry No. 1, 70757-08-3; 2, 70757-13-0; 3, 70757-16-3; 4, 133229-78-4; 5, 59431-90-2; 6, 70757-07-2; 7, 133229-79-5; 8, 133229-80-8; 9, 133229-81-9; 10, 133229-82-0; 11, 133229-83-1; 12, 70757-03-8; 13, 70756-87-5; 14, 133229-84-2; 15, 133229-85-3; 16, 133229-86-4; 17, 133229-87-5; 18, 133229-88-6; 19, 70756-90-0; 20, 133229-89-7; 21, 70757-02-7; 22, 133229-90-0; 23, 133229-91-1; 24, 133229-92-2; 25, 133270-12-9; 26, 79614-58-7; 27, 133229-93-3; 28, 79614-71-4; 29, 79614-70-3; 30, 79614-73-6; 31, 79614-85-0; 32, 79614-72-5; 33, 79614-64-5; 34, 79614-63-4; 35, 133229-94-4; 36, 79614-60-1; 37, 79622-59-6; 38, 79614-87-2; 39, 133229-95-5; 40, 133229-96-6; 41, 133229-97-7; 42, 133229-98-8; 43, 133229-99-9; 44, 133230-00-9; 45, 79614-88-3; 46, 79614-83-8; 47, 133230-01-0; 48, 83663-58-5; 49, 133230-02-1; 51, 133230-03-2; 52, 133230-04-3; 53, 133230-05-4; 54, 79614-96-3; 55, 79614-92-9; 56, 79614-93-0; 57, 133230-06-5; 58, 133230-07-6; 59, 133230-08-7.

Supplementary Material Available: Melting points and other analytical data for compounds 1-59 and absorption maxima and molar absorptivities for compounds 1-59 and their respective anions (5 pages). Ordering information is given on any current masthead page.

2-Amino-2-deoxyhexoses as Chiral Educts for Hydroxylated Indolizidines. Synthesis of (+)-Castanospermine and (+)-6-Epicastanospermine

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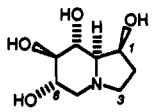
Received November 29, 1990

D-2-Amino-2-deoxyglucosaminic acid, obtained from D-glucosamine, and a D-2-amino-2-deoxymannosaminic acid derivative, obtained from D-glucono-δ-lactone, were derivatized and converted to the corresponding configurationally stable aldehydes. The *N*-(9-phenylfluoren-9-yl)-protected mannosamine derivative was readily transformed into a variety of configurationally stable α-amino ketones, thus providing convenient and versatile chiral educts. These educts may be envisaged as derivable from polyhydroxy α-amino acids. Examples of the utility of these chiral educts are provided by the efficient conversion of a D-mannosaminic acid derivative into the polyhydroxy indolizidine alkaloids (+)-castanospermine and (+)-6-epicastanospermine.

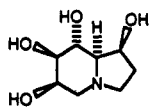
Introduction

Attaching a 9-phenylfluoren-9-yl group to the nitrogen of an α-amino acid has led to useful intermediates for the preparation of α-amino ketones and α-amino aldehydes of unusually high configurational stability.[1] We now report an extension of this methodology to 2-amino-2-deoxyhexoses as polyhydroxylated analogues of the simple amino acids, aldehydes, and ketones. We have also explored some selective transformations of these 2-aminohexoses. Our general strategy is demonstrated by the synthesis of the epimeric tetrahydroxyindolizidine alkaloids from a *N*-(9-phenylfluoren-9-yl)mannosamine derivative.

Castanospermine (1) and 6-epicastanospermine (2) are found in *Castanospermum australe*[2] and *Alexa leiopetala*,[3] respectively. Due to their biological activity, 1 and 2 have generated considerable interest. Castanospermine (1) is a potent inhibitor of several glycosidases[4] and shows anticancer,[5] antiviral,[6] and antiretroviral[7] activity. 6-Epicastanospermine (2) shows significant difference in its glycosidase inhibition activity,[8] due to the epimeric stereochemistry at C-6. In addition, recent studies have shown that selective derivatization of the hydroxyl groups of 1 can result in increased biological activity.[9]



1



2

Our objective was to develop an efficient route to an intermediate, derivable from a 2-amino-2-deoxyhexose, which could lead to the preparation of both castanospermine (1) and 6-epicastanospermine (2). To do so we planned to exploit the synthetic methodology developed for simple amino aldehydes.[1,10] The target intermediate

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