

Reexamination of the application of linear free energy relationships to the azaheterocyclic systems. II. Substituent effects on the basicity of benzazines

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Received 10 June 1976

Accepted for publication 25 September 1978

The pK_a values of all quinolines, isoquinolines, quinazolines, quinoxalines, pteridines, and acridines are submitted to correlations according to both the Hammett and two-parameter Taft equations. The substituent effects on the basicity of those systems are discussed.

Значения pK_a хинолинов, изохинолинов, хиназолинов, хиноксалинов, птеридинов и акридинов коррелированы по уравнению Гаммета и двух-параметрическому уравнению Тафта. Обсуждено влияние заместителей на основность таких систем.

Up to the present, not too much attention has been paid to the substituent effects on the basicity of benzazines. The *Perrin's* predictions of the strength of such bases achieved only a moderate success [1]. It is known that the effects of all 2-, 3-, and 4-substituents on the basicity of quinoline should be discussed in terms of σ_m and σ_p like in the pyridine system [2, 3]. Special substituent constants recently proposed for the correlating effects of substituents in the benzene ring as regards the basicity of the system [4—6] have been replaced by σ_m for all 5- and 7-substituents in quinoline as well as 2-, 5-, and 8-substituents in isoquinoline and by σ_p for the 6- and 7-substituents in both quinoline and isoquinoline [7]. This is sometimes contrary to the predictions based on the mesomeric structures. No reasonable set of σ has been found for correlating effects of 8-substituents in quinoline. The same kind of correlations in the series of cinnolines was unsuccessful [8], and the effect of

Table 1. pK_{a, H_2O}^{20} of various benzazines and their derivatives ^a

Compound	pK_a	Compound	pK_a	Compound	pK_a	Compound	pK_a
Quinoline	4.94	Quinoline (contd)		Quinazoline (contd)		9-Aminoacridine (contd)	
2-Me	5.90	8-Br	3.13 ^e	6-OMe	2.85*	2-Ph	9.4
2-OMe	3.20	8-NO ₂	2.59	6-NH ₂	3.29	2-OMe	9.2
2-SMe	3.75	Isoquinoline	5.40	6-NO ₂	4.18	2-Cl	8.5
2-NH ₂	7.97	1-OMe	3.05	7-Me	3.17	2-CONH ₂	8.4
2-COOMe	1.77 ^b	1-SMe	3.93	7-Cl	3.29	2-COOMe	8.2
3-Me	5.21	1-NH ₂	7.66	7-OMe	2.89	2-CN	7.7
3-OMe	4.88	4-NH ₂	6.28	7-NH ₂	4.60*	2-NO ₂	7.5
3-SMe	3.91	4-Br	3.38	7-NO ₂	4.05	3-NH ₂	11.1
3-NH ₂	4.95*	4-NO ₂	1.35	8-Me	3.20	3-Me	9.8
3-F	2.48 ^c	5-NH ₂	5.59	8-Cl	3.30	3-Cl	9.2
3-Cl	2.48 ^c	5-NO ₂	3.53	8-OMe	5.51	3-OMe	9.7*
3-Br	2.72 ^d	6-NH ₂	7.17	8-NH ₂	2.81	3-NO ₂	7.5
3-NO ₂	1.04 ^d	6-NO ₂	3.47	8-NO ₂	4.00	4-Me	9.8
4-Me	5.68	7-NH ₂	6.20	Acridine	5.60	4-NH ₂	9.0*
4-OMe	6.57	7-NO ₂	3.61	2,7-di-NH ₂	6.18	4,5-di-Me	9.0*
4-SMe	5.81	8-NH ₂	6.06	2-NH ₂	5.88	4-Et	9.8
4-NH ₂	9.17	8-NO ₂	3.59	2-Me	5.79	4-OMe	9.5
4-Cl	3.72 ^e	Cinnoline	2.42	2-OH	5.62	4-Cl	8.0
5-Me	4.68	4-OMe	3.21	2-OMe	5.52	4-NO ₂	7.5
5-SMe	4.50	4-SMe	3.13	3,6-di-NMe ₂	10.45	4-Ph	8.9
5-NH ₂	5.46	4-NH ₂	6.84	3,6-di-NH ₂	9.65	Pteridine	4.12
5-Cl	3.65 ^e	Quinoxaline	0.56	3-NMe ₂	8.20*	2-NMe ₂	3.03
5-Br	3.62 ^e	2-Me	0.95	3-NH ₂	8.04	2-SMe	2.22
5-CF ₃	3.15	2-OMe	0.29	3-NH ₂ -6-Cl	7.26	2-NHMe	3.62
5-NO ₂	2.69	2-SMe	0.27	4-NH ₂	4.40	2-NHBu	3.94 ^f
6-Me	5.22	2-NH ₂	3.96	4-NHAc	4.40	2-NH ₂	4.29
6-OMe	5.06	2-NHMe	4.13	4,5-di-Me	4.56	2-OMe	2.13
6-SMe	4.75	Quinazoline	3.51	4-OMe	5.31	2-Me	4.87
6-NH ₂	5.63	2-Me	4.52	4-Me	5.65	4-NMe ₂	4.33

Table 1 (Continued)

Compound	pK _a	Compound	pK _a	Compound	pK _a	Compound	pK _a
6-Br	3.91 ^c	2-NH ₂	4.82	4,5-di-NH ₂	4.12*	4-NHMe	3.70
6-COO ⁻	4.82	2-OMe	1.31	4,5-di-Me	4.56*	4-COOEt	3.62*
6-COOMe	3.80 ^c	2-SMe	1.60	4-NH ₂ -5-Me	3.95	4-NH ₂	3.56
6-NO ₂	2.76	4-Me	2.52	9-NMe ₂	9.13	4-SMe	2.59
7-Me	5.05	4-Cl	-1.60	9-NHNH ₂	7.15	4-Me	2.94
7-NH ₂	6.65	4-OMe	3.13	9-Me	5.89	4-OMe	1.04
7-F	3.85 ^c	4-SMe	3.01	9-COOMe	3.45	6-NMe ₂	4.31
7-Br	3.87 ^c	4-NH ₂	5.73	9-Aminoacridine	9.6	6-Cl	3.72
7-CF ₃	3.20	5-Me	3.63	1-NH ₂	10.6	6-OMe	3.60
7-NO ₂	2.44	5-Cl	3.75	1-OMe	9.8	6-NH ₂	4.15
8-Me	5.05	5-OMe	3.41	1-Me	9.7	7-NMe ₂	2.53
8-SMe	3.50	5-NH ₂	3.57	1-Cl	8.1	7-SMe	2.49
8-NH ₂	3.99	5-NO ₂	3.75	1-NO ₂	7.3	7-NHMe	2.56 ^h
8-F	3.37 ^c	6-Me	3.41	2-NH ₂	10.0	7-NH ₂	2.96
8-Cl	3.12 ^c	6-Cl	3.55	2-Me	9.6	7-OMe	1.64
						7-Me	3.49
						7-Cl	3.26 ⁱ

a) If not denoted, the pK_a data for all quinolines, isoquinolines, cinnolines, quinoxalines, and quinazolines are taken from [11] and for acridines from [12]. The inaccuracy of the pK_a²⁰ values is within the range ± 0,005 unit. The values earmarked with (*) are omitted due to strong deviation of the points from the correlation. For 9-aminoacridines pK_a³⁷ are given.

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Table 2. ρK_n^{20} — σ substituent constants correlation in the series of fused six-membered systems

Reaction series ^a	ρ	ρ_I	ρ_R	ρ_I/ρ_R	$\frac{\rho_I}{\rho_I + \rho_R} 100$	Intercept			Notes
2- (+M) Quinolines	-11.61 ± 1.10	—	—	—	—	5.15 ± 0.18	0.416	0.982	6 vs. σ_m
	-4.99 ± 0.78	—	—	—	—	4.35 ± 0.27	0.666	0.955	6 vs. σ_p
	—	-11.56 ± 1.48	-4.34 ± 0.62	2.66	72.7	5.15 ± 0.32	0.502	0.981	6
3- (+M) Quinolines	-6.15 ± 0.48	—	—	—	—	4.83 ± 0.13	0.213	0.988	6 vs. σ_m
	-5.55 ± 0.39	—	—	—	—	4.75 ± 0.14	0.251	0.988	7 vs. σ_m , including NO_2
	—	-5.20 ± 0.22	-0.94 ± 0.22	5.05	84.6	4.93 ± 0.10	0.151	0.997	7
4- (+M) Quinolines	-6.18 ± 0.34	—	—	—	—	4.94 ± 0.12	0.226	0.995	5 vs. σ_p , without SCH_3
	—	-6.87 ± 0.31	-6.30 ± 0.20	1.09	—	4.90 ± 0.09	0.126	0.999	5 without SCH_3
	—	-6.60 ± 0.74	-6.19 ± 0.49	1.07	51.6	4.98 ± 0.22	0.314	0.991	6 with SCH_3
5- (+M) Quinolines	-2.07 ± 0.23	—	—	—	—	4.21 ± 0.08	0.168	0.982	5 vs. σ_p
	-2.98 ± 0.45	—	—	—	—	4.79 ± 0.12	0.228	0.967	5 vs. σ_m
5- (M) Quinolines	-2.00 ± 0.11	—	—	—	—	4.23 ± 0.05	0.133	0.992	7 vs. σ_p
	-3.09 ± 0.32	—	—	—	—	4.76 ± 0.12	0.239	0.974	7 vs. σ_m
	—	-2.29 ± 0.40	-1.54 ± 0.27	1.49	69.0	4.42 ± 0.16	0.232	0.980	7
6- (+M) Quinolines	-3.22 ± 0.42	—	—	—	—	5.10 ± 0.08	0.203	0.954	8 vs. σ_m
	-1.69 ± 0.31	—	—	—	—	4.70 ± 0.10	0.274	0.914	8 vs. σ_p
6- (M) Quinolines	-3.28 ± 0.25	—	—	—	—	5.11 ± 0.08	0.188	0.980	9 vs. σ_m
	—	-2.66 ± 0.19	-1.48 ± 0.12	1.80	64.2	4.91 ± 0.07	0.129	0.992	9
7- (+M) Quinolines	-4.56 ± 0.97	—	—	—	—	5.39 ± 0.51	0.544	0.938	5 vs. σ_m
	-2.92 ± 0.16	—	—	—	—	4.63 ± 0.07	0.149	0.995	5 vs. σ_p
7- (M) Quinolines	-2.88 ± 0.12	—	—	—	—	4.64 ± 0.06	0.133	0.997	6 vs. σ_p
	—	-2.93 ± 0.63	-2.45 ± 0.43	1.20	54.4	4.75 ± 0.31	0.366	0.982	6
8- (M) Quinolines	-1.59 ± 0.13	—	—	—	—	3.76 ± 0.05	0.082	0.987	6 vs. σ_m , without H and Me
	-0.99 ± 0.05	—	—	—	—	3.38 ± 0.02	0.055	0.994	6 vs. σ_p , without H and Me
	—	-1.23 ± 0.29	-0.68 ± 0.16	1.81	—	3.59 ± 0.19	0.080	0.991	6 without H and Me
—	-3.09 ± 0.34	-2.20 ± 0.28	1.40	56.5	4.82 ± 0.17	0.252	0.971	8 with H and Me	

Table 2 (Continued)

Reaction series ^a	ρ	ρ_I	ρ_R	ρ_I/ρ_R	$\frac{\rho_I}{\rho_I + \rho_R} 100$	Intercept				Notes
1- (M) Isoquinolines	-13.92 ± 2.69	—	—	—	—	5.34 ± 0.33	0.646	0.965	4	vs. σ_m
	—	-14.43 ± 3.81	-4.89 ± 1.68	2.95	74.7	5.64 ± 0.83	0.866	0.968	4	
3- (M) Isoquinolines	-5.60 ± 0.19	—	—	—	—	5.42 ± 0.08	0.129	0.999	4	vs. σ_m
	—	-5.12 ± 0.13	-1.97 ± 0.09	2.60	72.7	5.41 ± 0.07	0.068	0.999	4	
5- and 6- (M) Isoquinolines	-2.55 ± 0.12	—	—	—	—	5.37 ± 0.06	0.140	0.997	5	5 vs. σ_m , 6 vs. σ_p
	—	-1.98 ± 1.42	-1.77 ± 0.88	—	—	5.34 ± 0.70	0.705	0.947	5	
7- and 8- (M) Isoquinolines	-2.83 ± 0.16	—	—	—	—	5.59 ± 0.07	0.143	0.995	5	vs. σ_m
	—	-2.10 ± 0.14	-1.27 ± 0.08	1.65	62.3	5.40 ± 0.07	0.071	0.999	5	
2- (+M) Acridines	-1.57 ± 0.13	—	—	—	—	5.65 ± 0.02	0.045	0.986	6	vs. σ_m
	—	-1.41 ± 0.17	-0.59 ± 0.05	2.39	70.5	5.63 ± 0.03	0.041	0.993	6	
3- (+M) Acridines	-2.84 ± 0.15	—	—	—	—	6.08 ± 0.15	0.134	0.996	5	vs. σ_p
	—	-3.51 ± 0.19	-2.76 ± 0.15	1.27	55.0	6.28 ± 0.19	0.131	0.997	5	
4- (+M) Acridines	+4.65 ± 1.53	—	—	—	—	5.26 ± 0.22	0.455	0.806	7	vs. σ_m
	+1.35 ± 0.67	—	—	—	—	5.30 ± 0.31	0.545	0.672	7	vs. σ_p
	—	+0.08 ± 2.04	+0.88 ± 0.55	—	—	5.18 ± 0.31	0.547	0.757	7	
9- (+M) Acridines	-4.70 ± 0.36	—	—	—	—	5.47 ± 0.16	0.306	0.994	5	vs. σ_p
	—	-4.52 ± 0.98	-4.76 ± 0.28	0.95	48.7	5.43 ± 0.15	0.228	0.998	5	
1 (+M) 9-Amino- acridines ^c	-2.43 ± 0.32	—	—	—	—	9.15 ± 0.14	0.352	0.967	6	vs. σ_p
	-3.64 ± 0.49	—	—	—	—	9.77 ± 0.17	0.355	0.966	6	vs. σ_m
	—	2.92 ± 0.58	-1.66 ± 0.40	1.75	63.8	9.54 ± 0.26	0.380	0.971	6	
2- (+M) 9-Amino- acridines ^c	-2.71 ± 0.21	—	—	—	—	9.50 ± 0.03	0.085	0.989	6	vs. σ_m
2- (-M) 9-Amino- acridines ^c	-1.96 ± 0.27	—	—	—	—	8.89 ± 0.13	0.093	0.990	3	vs. σ_m

Table 2 (Continued)

Reaction series ^a	ϱ	ϱ_I	ϱ_R	ϱ_I/ϱ_R	$\frac{\varrho_I}{\varrho_I + \varrho_R} 100$	Intercept	Notes
2- (M) 9-Amino-acridines ^c	-2.95 ± 0.24	—	—	—	—	9.45 ± 0.07 0.184 0.978	9
	—	-2.58 ± 0.34	-1.18 ± 0.22	2.18	68.6	9.38 ± 0.13 0.232 0.969	9
3- (+M) 9-Amino-acridines ^c	-2.16 ± 0.22	—	—	—	—	9.60 ± 0.08 0.144 0.990	4 vs. σ_p
	-2.44 ± 0.17	—	—	—	—	9.52 ± 0.08 0.178 0.993	5 vs. σ_p , with NO_2
	—	-2.17 ± 0.10	-2.20 ± 0.08	0.99	49.6	9.56 ± 0.13 0.063 0.999	5
4- (+M) 9-Amino-acridines ^c	-2.97 ± 0.59	—	—	—	—	9.46 ± 0.20 0.403 0.929	6 vs. σ_m
	-2.34 ± 0.43	—	—	—	—	9.10 ± 0.16 0.374 0.939	6 vs. σ_p
	—	-2.66 ± 0.60	-1.07 ± 0.58	2.48	—	9.42 ± 0.26 0.422 0.942	6
4- (+M) Cinnolines	-6.01 ± 5.95	—	—	—	—	2.51 0.823 0.941	4 vs. σ_p
	-10.71 ± 0.70	—	—	—	—	2.49 ± 0.15 0.225 0.996	4 vs. $(\sigma_p + \sigma_m)/2$
	—	-9.06 ± 3.91	-6.48 ± 1.73	1.81	58.3	2.67 ± 0.85 0.889 0.966	4
2- (+M) Quinoxalines	-12.00 ± 3.06	—	—	—	—	1.39 ± 0.39 0.934 0.891	6
	—	-9.63 ± 1.69	-5.83 ± 0.71	1.65	62.2	$.38 \pm 0.34$ 0.485 0.979	6
2- (+M) Quinazolines	-12.38 ± 1.90	—	—	—	—	3.22 ± 0.22 0.483 0.966	5
	—	2.50 ± 0.78	-3.78 ± 0.39	3.30	76.7	3.59 ± 0.14 0.200 0.996	5
4- (M) Quinazolines	-7.61 ± 1.67	—	—	—	—	1.16 ± 0.57 1.080 0.935	5 vs. σ_p
	-11.26 ± 2.96	—	—	—	—	3.47 ± 0.55 1.245 0.885	5 vs. σ_m
	-9.83 ± 1.85	—	—	—	—	2.14 ± 0.40 0.941 0.936	6 vs. $(\sigma_p + \sigma_m)/2$
	—	-10.78 ± 02.91	-6.08 ± 1.92	—	—	2.64 ± 0.86 1.229 0.917	6
5- (M) Quinazolines	0.18 ± 0.10	—	—	—	—	3.61 ± 0.05 0.114 0.658	6 vs. σ_p
	0.26 ± 0.16	—	—	—	—	3.56 ± 0.05 0.116 0.638	6 vs. σ_m
	0.22 ± 0.06	—	—	—	—	3.61 ± 0.03 0.074 0.870	6 vs. $(\sigma_p + \sigma_m)/2$
	—	0.20 ± 0.20	0.14 ± 0.14	—	—	3.59 ± 0.09 0.130 0.668	6

Table 2 (Continued)

Reaction series ^a	ρ	ρ_1	ρ_R	ρ_1/ρ_R	$\frac{\rho_1}{\rho_1 + \rho_R} 100$	Intercept	Notes
6- (M) Quinazolines	0.61 ± 0.14	—	—	—	—	3.57 ± 0.07 0.147 0.929	5 vs. σ_p
	0.88 ± 0.21	—	—	—	—	3.44 ± 0.08 0.149 0.928	5 vs. σ_m
	0.74 ± 0.15	—	—	—	—	3.51 ± 0.06 0.134 0.941	5 vs. $(\sigma_p + \sigma_m)/2$
7- (M) Quinazolines	—	0.67 ± 0.19	0.48 ± 0.15	1.39	58.2	3.51 ± 0.08 0.120 0.969	5
	1.01 ± 0.18	—	—	—	—	3.21 ± 0.08 0.150 0.969	4 vs. σ_p , without H
8- (M) Quinazolines	—	0.73 ± 0.03	0.97 ± 0.03	0.075	42.9	3.28 ± 0.02 0.018 0.999	4
	0.70 ± 0.29	—	—	—	—	3.40 ± 0.09 0.220 0.867	6 vs. σ_p
	0.98 ± 0.36	—	—	—	—	3.23 ± 0.07 0.260 0.809	6 vs. σ_m
2- (+M) Pteridines	—	0.66 ± 0.38	0.60 ± 0.26	—	—	3.37 ± 0.17 0.249 0.873	6
4- (+M) Pteridines	-9.46 ± 0.68	—	—	—	—	5.03 ± 0.76 0.782 0.787	6
	—	-8.66 ± 0.87	-3.31 ± 0.28	2.61	66.8	2.15 ± 0.81 0.180 0.992	5 vs. σ_m
6- (+M) Pteridines	-1.08 ± 0.41	—	—	—	—	2.60 ± 0.19 0.194 0.994	5
	—	-1.17 ± 0.56	-0.37 ± 0.29	—	—	4.83 ± 0.23 0.194 0.833	5 vs. σ_m
7- (+M) Pteridines	—	-1.01 ± 1.51	1.06 ± 0.94	—	—	4.05 ± 0.21 0.215 0.866	5
						3.55 ± 0.65 0.667 0.627	6

a) (M) – Compounds bearing +M and –M substituents are combined in one reaction series.

b) Standard deviations.

c) Correlation coefficient.

d) Number of the experimental points.

e) pK_a^{37} values are correlated vs. σ constants.

substituents on the basicity of quinazoline, quinoxaline, pteridine, and acridine has not been yet considered in terms of any extrathermodynamic relationship. Therefore, the pK_a^{20} values of the corresponding series (Table 1) are correlated against σ as well as σ_I and σ_R according to eqns (1) and (2)

$$pK_a = \sigma \rho + \text{const} \quad (1)$$

$$pK_a = \sigma_I \rho_I + \sigma_R \rho_R + \text{const} \quad (2)$$

The results of the correlations (Table 2) allow following conclusions to be drawn. The single benzene ring in all the quinoline, isoquinoline, cinnoline, quinazoline, and quinoxaline systems changes neither the ability of heterocyclic rings to transmit the effects of the substituents to the nitrogen atom nor the inductive-mesomeric composition of the effects operating in monocyclic azines [9]. However, two benzene rings fused with the pyridine ring (the acridine system) decrease the transmissive ability of the central ring. The effectiveness of both the inductive and mesomeric effects is almost proportionally reduced. The Hammett equation is only poorly fulfilled for all three cinnoline, quinazoline, and quinoxaline systems but the results of the correlations according to eqn (2) are again satisfactory and they resemble those obtained with the corresponding monocyclic azines. Nevertheless, the cinnoline system is supposed either to share the first proton with both the nitrogen atoms or to form bicentred cation (see correlation against $(\sigma_p + \sigma_m)/2$). The correlation within the series of 4-substituted quinazolines failed perhaps for the same reason.

All the 5-, 7-, and 8-positions in the quinoline system are of the *para* type and only the pK_a values of 6-substituted quinolines may be correlated against σ_m . The mesomeric effects are transmitted to the nitrogen atom from the 7-position more effectively than from the 5-position. The slopes of the correlations within these series are about two times lower in comparison with the series having the substituents in the heterocyclic rings. They vary from one series to another to such an extent, that these series should not be combined together. The effectiveness of both the inductive and mesomeric portion of the total effects of substituents is also different as presented by both the ρ_I/ρ_R and $100 \rho_I/(\rho_I + \rho_R)$ ratios. The correlations in the series of 3-substituted quinolines including and excluding the data for the 3-nitro group point to a similar variation of the interactions depending on the +M and -M character of the substituents as it has been shown in the pyridine series [9] whereas the +M and -M character of the substituents in the benzene ring plays no important part.

The pK_a values of 5- and 6-substituted isoquinolines can be discussed in one integrated series but only in terms of the Hammett equation. This points to the essential change in the importance of both the inductive and mesomeric interactions involving the basic centre transmitted from those positions. However, both

the 7- and the 8-substituted isoquinoline series can be integrated and the correlations are not affected for that reason.

The ability of the acridine system to transmit the substituent effects through the benzene ring to the nitrogen atom resembles that found in the corresponding quinoline and isoquinoline series. The 2- and 7-positions of acridine are of the *meta* type, whereas all 1-, 3-, 6-, 8-, and 9-positions are of the *para* type. This is in agreement with the mesomeric structures bearing the positive charge on the nitrogen atom. The 4- and 5-substituents show interactions which vary in their magnitude and composition. The correlations are rather accidental and can eventually be carried out only for selected substituents. The points found for 9-aminoacridine and its derivatives do not follow the correlation valid for 9-substituted acridines. They form a separate line. That is justified owing to the amino-ketimine tautomerism [10].

Very poor correlations appear in the series of the 5- and 6-quinazoline derivatives. In this case, only a trend to the linearity with the positive slope, which is characteristic of nucleophilic substitution, is to be observed. Hence, it can reflect the significance of the 3,4-hydration accompanying the protonation [11]. The correlation found for 7-substituted quinazolines which is of mesomeric character in respect to both the nitrogen atoms is again satisfactory. The correlation is satisfactory provided the points corresponding to both the H and NH₂ groups are omitted. It seems to be an evidence for the variation of the protonation site depending on the electronic effects of substituents. The effects of 8-substituents again poorly correlate with σ . As the 8-position is mesomeric in respect to the 4-position which is hydrated, the lack of correlation seems to be comprehensible.

Recent studies carried out by *Neiman* [13] suggest that the pteridine system may be preferably protonated at the pyrazine moiety. Simultaneously, this system is supposed to undergo a 3,4-hydration following the addition of the first proton [11]. Among all four 2-, 4-, 6-, and 7-substituted pteridine series only the second one exhibits satisfactory correlations. The fact that a correlation appears only with σ_m shows that the N₁ atom cannot be a site of the protonation. Both the ρ_1 and ρ_1/ρ_R ratios are typical of the series bearing the substituents in the positions vicinal to the basic centre and they are decidedly too high for the substituents of the rings fused with a ring bearing a basic centre. Therefore, the N₃ atom may be the protonation site of pteridine.

This project has been supported by the Department of Carbochemistry of the Main Institute of Mining from the Government funds for the development of the research on the complex utilization of coal.

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