Reexamination of the application of linear free energy relationships to the azaheterocyclic systems. I. Substituent effects on the basicity of monocyclic azines*

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Extensive sets of pK_a's for pyridines, pyrimidines, pyridazines, and pyrazines are submitted to correlations according to both the Hammett and two-parameter Taft equations. Limitations of the correlation analysis of those systems are presented.

Обширный набор значений pK_a для пиридинов, пиримидинов, пиридазинов и пиразинов подвергнут корреляциям по уравнению Гаммета и двухпараметрическому уравнению Тафта. Приводятся ограничения в использовании корреляционного анализа таких систем.

Based on many recent reports [1] a general conclusion may be drawn that the Hammett equation can be successfully applied for correlating reactivity and physicochemical data for azaheterocyclic series *vs.* substituent effects. However, more careful inspection of the results of such correlations points to the Hammett equation to be a rather unprecise method in predicting properties of azines.

Because of importance of azaheterocyclic compounds in many fields of the application the correlative approach to this class of compounds should be reexamined and refined if possible. We have reexamined the pK_a—σ relationships using extended set of pK_a^{20} values for substituted pyridines, pyridazines, pyrimidines, and pyrazines (Table 1) and σ constants reported by *Jaffé* [4] as well as σ_I and σ_R constants reported by *Exner* [5].

The correlations are carried out by eqns (*1*) and (*2*)

$$pK_a = \sigma\,\varrho + \text{const} \qquad (1)$$

$$pK_a = \sigma_I\,\varrho_I + \sigma_R\,\varrho_R + \text{const} \qquad (2)$$

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Table 1

pK_{a,H_2O}^{293} of pyridine, pyridazine, pyrimidine, and pyrazine as well as their derivatives[a,m]

Compound	pK_a	Compound	pK_a	Compound	pK_a
Pyridine	5.23	Pyridine contd		Pyridine contd	
2-Me[1x]	6.03[f]	3-Ph	4.80	4-OMe	6.62
2-Et[1x]	6.03	3-SMe	4.45	4-NH_2	9.17
2-iso-Pr[1x]	5.86	3-OMe	4.48	4-NHAc[3x]	5.87[b]
2-*tert*-Bu[1x,2x]	5.76	3-NH_2	5.98	4-NHBz[3x]	5.32[b]
2,6-di-Me[1x]	6.80	3-NHAc	4.46[b]	4-NHMe	9.66[d]
2-Ph	4.48	3-NHBz	3.80[b]	4-NMe_2	9.71[d]
2-SMe	3.62	3-COO^{-}[1x]	4.80	4-COO^{-}[1x]	4.95
2-OMe	3.28	3-F[1x]	3.00	4-Cl	3.88
2-NH_2	6.86	3-Cl[1x]	2.85	4-Br	3.82
2-NHAc[3x]	4.09[b]	3-Br	2.91	4-I	4.06
2-NHBz[3x]	3.33[b]	3-I[1x]	3.28	4-Bz[1x]	3.38[c]
2-F[1x,4x]	−0.45	3-Bz[1x,2x]	3.21[c]	4-CN	1.90
2-Cl[1x]	0.76	3-CN	1.36	4-$CONH_2$	3.61
2-Br[1x]	0.91	3-$CONH_2$	3.40	4-COOMe	3.13
2-I[1x]	1.83	3-COOMe	3.26	4-COMe[1x]	3.56[c]
2-CN[4x]	−0.26	3-COMe[1x]	3.22	4-NO_2	1.61
2-$CONH_2$	2.10	3-NO_2[1x]	0.83	Pyrazine[1x]	0.65
2-COOMe	2.21	4-Me[1x]	6.08	2-SMe	0.55
2-NO_2	−2.58[e]	4-Et[1x]	6.08	2-Me[1x]	1.48
3-Me	5.79	4-iso-Pr[1x]	6.08	2-NH_2	3.14
3-Et	5.80	4-*tert*-Bu	6.03	2-NHMe[1x]	3.46
3-iso-Pr[1x]	5.78	4-Ph	5.55	2-NMe_2[1x]	3.37
3-*tert*-Bu	5.88	4-CH_2Ph[1x]	5.65	2-OMe	0.75
3,5-di-Me	6.23	4-SMe	5.97	2,5-di-Me[1x]	1.88
Pyrazine		Pyrimidine		Pyrimidine	
2,6-di-Me[1x]	1.93	4-NHMe[1x]	6.16	4-NH_2-5-Br	3.97[h]
2,3,5,6-tetra-Me[1x]	3.59	4-NMe_2	6.35	4-NH_2-5-$CONH_2$	4.45
Pyridazine	2.33	2,4-di-NH_2	7.26	4-NH_2-5-NO_2[2x]	1.98
4-Me	2.92	2-NH_2-4-Me	4.15	2-NHMe-5-CN	0.76
4-OMe	3.70	2-NH_2-4-NMe_2	7.96	2-NHMe-5-Cl	2.04
4-NH_2	6.69	2-NHMe-4-NH_2[1x]	7.60	2-NH_2-5-NO_2	0.35
4-SMe[2x]	3.26	2-NHMe-4-Cl	2.63	2-OMe-5-Br	−0.77
3,6-di-OMe	1.61	2-Cl-4-NHMe	2.83	2-NH_2-5-Br	1.95
3-SMe	2.26	2-OMe-4-NH_2	5.30	4-SMe-6-Me	3.25
3-OMe	2.52	4-OMe-6-Me	3.65	4,6-di-NH_2	6.01
3-NH_2	5.19	2-NH_2-4-OMe	5.53	4-NH_2-6-Cl	2.10
3-NH_2-6-Me	5.32	2-NH_2-4-SMe	4.75	4-NH_2−6-OMe	4.02
Pyrimidine	1.31	2-NMe_2-4-NH_2	7.64	4-NH_2-6-Me	6.25
2-Me	2.30[f]	2-NMe_2-4-OMe	5.87	4-NHMe-6-NH_2	6.32[i]
2-SMe	0.59	2-NMe_2-4-SMe	2.02	4-NHMe-6-OMe	4.23

Table 1 (Continued)

Compound	pK_a	Compound	pK_a	Compound	pK_a
2-OMe	1.05	2-NHMe-4-OMe	5.74	4-NHMe-6-Cl	4.24
2-OEt	1.27	2-OMe-4-NMe_2	6.17	4,6-di-NHMe	6.39
2-NH_2	3.54	4-NH_2-6-OMe	4.29	2-OMe-4-Me^{1x}	2.20
2-$NHMe^{1x}$	3.86	2-SMe-4-NH_2	4.91	4-NH_2-6-SMe	3.94
2-NHEt	4.03	2-SMe-4-Me^{1x}	2.00	4-NMe_2-6-NHMe	6.32
2-NMe_2	3.96	2-Me-4-$NH_2{}^{1x}$	6.60	4-NMe_2-6-Cl	2.42
2-COOMe	−0.68	2-Me-4-NMe_2^{1x}	7.57[g]	4,6-di-NMe_2	6.36
4-Me	1.98	2-Me-4-OMe^{1x}	4.02[g]	4-NMe_2-6-SMe	4.57
4-SMe^{2x}	2.48	2-Me-4-OPh^{2x}	3.02[g]	4,6-di-Me	2.70
4-OMe	2.50	4,5-di-NH_2	6.03	4,6-di-OMe	1.49
4-NH_2	5.71	4-Me-5-NH_2	3.15	4-OMe-6-Me	3.65
4-$NHAc^{3x}$	2.71	4,5-di-NHMe	6.03	2,4-di-NH_2-5-OPh	6.26

Compound	pK_a	Compound	pK_a
Pyrimidine		Pyrimidine	
2,4-di-NH_2-5-Ph	6.90	2,4-di-NH_2-6-OMe	5.48
2,4-di-NH_2-5-Bz	7.27	2,4-di-NH_2-6-COOMe	5.32
2,4-di-NH_2-5-$CONH_2$	6.03	2,4-di-NH_2-6-OPh	4.80
2,4-di-NH_2-5-Br	5.60[j]	2,4,6-tri-NH_2	6.72
2-Me-4-NH_2-5-$CONH_2^{1x}$	5.04[k]	2,4-di-NH_2-6-Cl	3.60
2-Me-4-NH_2-5-$COOEt^{1x}$	4.57[k]	2-NHMe-4-NH_2-6-Cl	3.81
2-Me-4-NH_2-5-CHO^{1x}	4.50[k]	2,4-di-NH_2-6-Me	7.63
2-Me-4-NH_2-5-CN^{1x}	3.55[k]	2,4-di-NH_2-6-Ph	6.70
2-Me-4-NMe_2-5-$CONH_2^{1x}$	5.99[k]	2,4-di-NH_2-6-SMe	5.46
2-Me-4-NMe_2-5-$COOEt^{1x}$	5.60[k]	2,4-di-NH_2-6-$CONH_2$	4.90
2-Me-4-NMe_2-5-CN^{1x}	4.41[k]	2,4-di-NH_2-6-SO_3^{-2x}	4.96
2-Me-4-NHAc-5-$COOEt^{1x}$	1.45[k]	2-NH_2-4,6-di-Me	4.85
2-Me-4-OEt-5-$COOEt^{1x}$	2.73[k]	2-NHMe-4-OMe-6-Me	6.20
2-Me-4,5-di-OMe^{1x}	4.15[k]		

1*x*) The value recalculated according to *Perrin* [2] from pK_a measured at 298 K.

2*x*) The value omitted in the correlations due to deviating for not well understood reasons.

3*x*) The value omitted due to possible tautomerism.

a) If not denoted pK_a are taken from [3].

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m) The inaccuracy of pK_a before recalculating is ±0.005 unit.

assuming that the effects of the substituents in the positions vicinal to the basic centre are best correlated against σ_m [6], both the positions 3 and 5 in respect to the basic centre are of the *meta* type and the position 4 is of the *para* type.

Recently, *Johnson* [7] has carried out the analysis of the substituent effects on pK_a of 4-substituted pyridines employing the two-parameter equation with σ_I and σ_R^+. The set of Exner constants is more precise because σ_I and σ_R are selfconsistent, moreover, it is more abundant and gives more reasonable picture of the resonance and inductive composition of the operating effects.

Results of the correlations (Table 2) show that the commonly accepted $\sigma\,\varrho$ treatment of the substituent effects on the azaatom independently of their M and I character [1] and combination of pK_a of 3- and 4-substituted derivatives in one reaction series [8, 9] is incorrect.

The correlation series within the given system should be built separately for +M and −M substituents and the compounds bearing the substituents of the same resonance type in different positions of the ring should be grouped in separate series due to varying ϱ and inductive-mesomeric composition of the effect.

pK_a of azines are most sensitive to the 2-substituent effects followed by the effects of 3- and 4-substituents, respectively. The interactions between azaatom and 2-substituent are in over 70% of the inductive character. The ϱ_I/ϱ_R ratios for all 2- and 3-substituted azines are closely the same followed by such a ratio for 4-substituted systems. The composition of the effects of 4- (+M) substituents is significantly enriched in the resonance interactions whereas 4- (−M) substituents interact with the azaatom mainly, inductively. The unusually negative ϱ's are also found for all the series with the substituent in the position vicinal to one of the azaatoms in the diazine systems under consideration. It is also characteristic that the correlations in the series of diazines are either only roughly or not at all followed by the points for unsubstituted compounds. All these facts may be due to sharing first proton between both the azaatoms. Just the substituents in other positions than those vicinal to the azaatom play an essential role in distinguishing between both the azaatoms in the protonation site.

Several authors have discussed the pK_a—σ correlations for polysubstituted pyrimidines [10—12]. We have recalculated these data (see Table 2). It is evident that the substituent effects are not precisely additive. This is illustrated by the previous discussion of *Johnson* and *Schofield* [13]. The effects of the methoxy group are particularly untypical when it is joined in the position capable of

Table 2

pK_a^{20}—σ correlations in the series of monocyclic azines[a]

Reaction series	ϱ	ϱ_I	ϱ_R	ϱ_I/ϱ_R	$\frac{\varrho_I}{\varrho_I+\varrho_R}100$	Intercept	s^b	r^c	n^d	Notes
2- (+M) Pyridines	−11.44±0.55	—	—	—		5.12±0.23	0.314	0.991	11	*vs.* σ_m
	—	−11.07±0.35	−3.89±0.30	2.85	74.0	5.14±0.12	0.212	0.996	11	
2- (−M) Pyridines	−11.40±1.07	—	—	—		5.54±0.14	0.361	0.996	3	*vs.* σ_m
2- (+M) and (−M) Pyridines	—	−10.39±0.28	−3.28±0.24	3.16	76.0	5.23±0.15	0.258	0.996	14	
3- (+M) Pyridines	− 6.19±0.21	—	—	—		5.28±0.17	0.160	0.991	17	
	—	− 5.82±0.14	−1.98±0.14	2.94	74.6	5.28±0.18	0.258	0.996	17	
3- (−M) Pyridines	− 5.61±0.34	—	—	—		4.98±0.22	0.148	0.994	5	
	—	− 4.99±0.10	−1.83±0.11	2.99	73.2	4.78±0.04	0.047	1.000	5	
3- (+M) and (−M) Pyridines	− 6.14±0.14	—	—	—		5.26±0.11	0.160	0.995	22	
	—	− 5.76±0.12	−2.10±0.11	2.75	73.4	5.21±0.09	0.136	0.996	22	
4- (+M) Pyridines	− 5.69±0.20	—	—	—		5.32±0.24	0.257	0.991	16	
	—	− 6.97±0.57	−5.92±0.37	1.18	54.0	5.21±0.48	0.416	0.978	16	
4- (−M) Pyridines	− 4.32±1.37	—	—	—		5.04±1.01	0.525	0.876	5	
	—	− 3.79±0.46	−1.27±0.52	2.99	74.9	4.55±0.39	0.226	0.986	5	
4- (+M) and (−M) Pyridines	− 5.31±0.19	—	—	—		5.42±0.41	0.345	0.989	21	
	—	− 5.57±0.55	−4.85±0.39	1.15	53.4	5.42±0.88	0.616	0.965	21	
3- and 4- (+M) Pyridines	− 5.87±0.13	—	—	—		5.27±0.12	0.214	0.992	33	
	—	− 7.05±0.67	−5.03±0.53	1.41		5.09±1.12	0.739	0.907	33	

Table 2 (Continued)

Reaction series	ϱ	ϱ_I	ϱ_R	ϱ_I/ϱ_R	$\frac{\varrho_I}{\varrho_I+\varrho_R}100$	Intercept	s^b	r^c	n^d	Notes
3- and 4- (−M) Pyridines	−4.69±0.27	—	—	—		5.01±0.42	0.433	0.974	10	
	—	−4.39±0.42	−1.55±0.47	2.84		4.67±0.33	0.288	0.970	10	
3- and 4- (M) Pyridines	—	−5.83±0.46	−3.94±0.37	1.48		5.28±0.74	0.755	0.927	43	(+M) and (−M)
3- (+M) Pyridazines	−8.58±0.48	—	—	—		3.55±0.09	0.195	0.995	5	*vs.* σ_m
	—	−8.47±0.69	−3.24±0.48	2.61	72.4	3.52±0.35	0.280	0.994	5	
4- (+M) Pyridazines	−6.85±0.67	—	—	—		2.03±0.25	0.326	0.991	4	*vs.* σ_p
	—	−8.61±1.46	−6.98±0.66	1.23	52.0	2.14±0.22	0.295	0.996	4	
2- (+M) Pyrazines	−12.01±2.02	—	—	—		0.68±0.34	0.451	0.924	8	except OMe and SMe
	—	−7.01±0.41	−4.16±0.22	1.68	62.7	0.69±0.10	0.181	0.991	10	
2- (+M) Pyrimidines	−8.98±0.57	—	—	—		1.93±0.10	0.309	0.986	9	*vs.* σ_m
	—	−7.74±0.64	−3.75±0.21	2.08	67.5	1.58±0.15	0.231	0.993	8	
4- (+M) Pyrimidines	−7.10±0.38	—	—	—		0.95±0.20	0.272	0.994	6	*vs.* σ_p
	—	−9.50±0.66	−7.20±0.24	1.32	56.7	1.12±0.12	0.163	0.999	6	
2,4-di (+M) Pyrimidines	−6.76±0.15	—	—	—		1.77±0.09	0.156	0.997	14	without OMe, SMe, NO_2
	−8.82±0.46	—	—	—		4.75±0.09	0.334	0.979	18	with OMe, SMe, NO_2
4,5- and 2,5-di (M) Pyrimidines	−4.12±0.10	—	—	—		2.80±0.05	0.129	0.998	7	
	−3.94±0.09	—	—	—		2.87±0.04	0.081	0.999	5	without 5-CN and 5-NO_2

Table 2 (Continued)

Reaction series	ϱ	ϱ_I	ϱ_R	ϱ_I/ϱ_R	$\frac{\varrho_I}{\varrho_I+\varrho_R}100$	Intercept	s^b	r^c	n^d	Notes
2,4-diNH_2-5 (+M) Pyrimidines	− 4.05±0.80	—	—	—		3.83±0.56	0.411	0.901	8	
2,4-diNH_2-5 (−M) Pyrimidines	− 5.55±0.78	—	—	—		2.90±0.32	0.226	0.990	3	
2,4-diNH_2-5 (M) Pyrimidines	− 4.73±0.50	—	—	—		3.32±0.32	0.380	0.952	11	
2-Me-4 (+M) -5 (+M) Pyrimidines	− 5.74±0.53	—	—	—		2.52±0.26	0.338	0.984	6	
2-Me-4 (+M) -5 (+M) Pyrimidines	− 4.95±0.53	—	—	—		3.10±0.14	0.333	0.975	9	
2-Me-4,5-bi (M) Pyrimidines	− 5.05±0.34	—	—	—		2.97±0.14	0.368	0.972	15	
2-Me-4 (+M) Pyrimidines	− 6.88±0.24	—	—	—		1.75±0.12	0.154	0.998	5	
2-OMe-4 (+M) Pyrimidines	− 6.66±0.22	—	—	—		1.85±0.09	0.136	0.999	4	
2-SMe-4 (+M) Pyrimidines	− 6.58±0.30	—	—	—		1.63±0.12	0.189	0.998	4	
2-NH_2-4 (+M) Pyrimidines	− 5.66±0.21	—	—	—		2.73±0.13	0.144	0.999	4	
2-NHMe-4 (+M) Pyrimidines	− 5.43±0.19	—	—	—		3.00±0.10	0.140	0.999	3	
2-NMe_2-4 (+M) Pyrimidines	− 5.10±0.76	—	—	—		3.29±0.40	0.394	0.978	4	
4-Me-2 (+M) Pyrimidines	− 5.38±1.37	—	—	—		2.26±0.27	0.414	0.967	3	
4-OMe-2 (+M) Pyrimidines	−16.54±1.47	—	—	—		1.78±0.59	0.254	0.998	5	
4-NH_2-2 (+M) Pyrimidines	− 7.96±1.29	—	—	—		0.91±0.94	0.453	0.940	7	
4-NMe_2-2 (+M) Pyrimidines	− 7.06±1.27	—	—	—		1.51±0.96	0.330	0.955	5	
4-NMe_2-6 (+M) Pyrimidines	− 6.96±0.29	—	—	—		0.04±0.19	0.231	0.991	13	
4-OMe-6 (+M) Pyrimidines	− 7.29±0.69	—	—	—		0.93±0.27	0.183	0.987	5	

a) Confidence intervals were calculated assuming the 95—99% confidence level (the Student test).
b) Standard deviations.
c) Correlation coefficient.
d) Number of the experimental points.

transmitting resonance effect to the azaatom (see ϱ for the series of 2-substituted 4-methoxypyrimidines in comparison with ϱ for other 2,4-disubstituted pyrimidine series).

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