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Basicity of 4-Aminopyrimidine and 2,4-Diaminopyrimidine Derivatives

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Summary. The basic dissociation constants for a series of 30 4-aminopyrimidine and 2,4-diaminopyrimidine derivatives were determined in 2% v/v aqueous methanol by a spectrophotometric method. The determined pK_a values correlate well with *Hammet's* σ constants.

Keywords. Aminopyrimidine; *Hammett* constants; Basicity.

Basizität von 4-Aminopyrimidin- und 2,4-Diaminopyrimidinderivaten

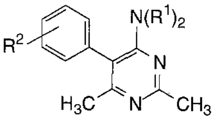
Zusammenfassung. Die basischen Dissoziationskonstanten einer Reihe von 30 4-Aminopyrimidin- and 2,4-Diaminopyrimidinderivaten wurden in 2% v/v wäßrigem Methanol durch spektroskopische Methoden bestimmt. Die ermittelten pK_a-Werte korrelieren gut mit den entsprechenden *Hammett*-Parametern σ.

Introduction

4-Amino- and 2,4-diaminopyrimidine derivatives are of importance owing to their biological activity. Particularly derivatives of 2,4-diaminopyrimidine are of great interest because of their various growth-inhibitory properties, especially anifolic activity. A lot of 4-amino- and 2,4-diaminopyrimidine derivatives has been prepared, and the basic dissociation constants for most of these compounds have been determined [1–8]. Recently, we reported on the synthesis of new 4-amino- and 2,4-diaminopyrimidine derivatives (4-amino-2,6-dimethyl-5-phenylpyrimidine, 4-dimethylamino-2,6-dimethyl-5-phenylpyrimidine, 2,4-*bis*-dimethylamino-6-methyl-5-phenyl-pyrimidine, and a series of their derivatives substituted in the benzene ring [9–11]). The synthesis of 2,4-*bis*-dimethylamino-6-methylpyrimidine and some 5-alkyl-2,4-*bis*-dimethylamino-6-methylpyrimidines has also been described [11].

We now have examined the basicity of these compounds, and we have correlated the determined pK_a values for 4-amino-6-phenyl- and 2,4-diamino-5-phenylpyrimidine derivatives with the *Hammett* constants of the substituents in the benzene ring.

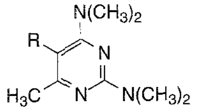
Table 1. pK_a values and ultraviolet absorption data of 4-amino-2,6-dimethyl-5-phenylpyrimidines and 4-dimethylamino-2,6-dimethyl-5-phenylpyrimidines



	R^1	R^2	m.p. (°C) or b.p. (°C/torr)	pK_a (20 °C)	Ultraviolet absorption[a]	
					Neutral species λ_{max} ($\varepsilon \times 10^{-3}$)	Monocation λ_{max} ($\varepsilon \times 10^{-3}$)
1	H	H	202–203	7.02	239(9.3) 274(7.4)	260(12.2)
2	H	3-CH_3	177–178	7.05	240(8.1) 273(7.0)	261(11.2)
3	H	3-OCH_3	200–202	6.95	241(11.8) 278(8.3)	250(12.4), 269(11.1)
4	H	3-Cl	187–189	6.78	242(8.9) 277(7.8)	260(13.9)
5	H	3-NO_2	203–205	6.57	278(12.2)	263(16.3)
6	H	4-CH_3	179–180	7.10	241(8.9), 274(7.5)	264(11.8)
7	H	4-OCH_3	152–154	7.18	224(15.6), 243(8.8) 274(8.6)	225(13.8), 268(10.5)
8	H	4-Cl	200–201	6.90	240(9.0) 274(7.6)	259(12.6)
9	H	4-Br	189–190	6.88	229(17.0) 241(10), 278(7.8)	227(16.4), 263(11.3)
10	H	4-NO_2	267–268	6.48	238(14.5) 278(16.5)	266(19.9)
11	CH_3	H	152–154 / 2.5	7.94	263(13.7)	283(13.9)
12	CH_3	3-CH_3	160–162 / 2.5	8.00	265(11.0)	277(13.5)
13	CH_3	3-OCH_3	158–160 / 1	7.75	230(23.4) 272(9.7)	236(20.6) 247(21.8) 282(12.5)
14	CH_3	3-Cl	67.5–68.5	7.60	266(10.8)	277(13.5)
15	CH_3	3-NO_2	139–140	7.38	270(16.9)	272(19.2)
16	CH_3	4-CH_3	74–76	8.10	273(12.7)	281(13.8)
17	CH_3	4-OCH_3	172–174 / 2.5	8.15	231(12.9) 272(10.6)	228(14.0) 280(13.8)
18	CH_3	4-Cl	135–136	7.70	224(16.9) 268(10.4)	278(14.9)
19	CH_3	4-Br	118–120	7.73	228(17.0) 267(10.1)	275(11.7)
20	CH_3	4-NO_2	142–143	7.10	266(16.7) 335(5.4)	279(19.2)

[a] Recorded on a Specord M-40 spectrophotometer

Table 2. pK_a values and ultraviolet absorption data of 2,4-*bis*-dimethylamino-6-methyl-5-substituted pyrimidines



	R	m.p. (°C) or b.p. (°C/torr)	pK_a (20 °C)	Ultraviolet absorption[a]	
				Neutral species λ_{max} ($\varepsilon \times 10^{-3}$)	Monocation λ_{max} ($\varepsilon \times 10^{-3}$)
21	H	158 / 31	8.73	228(23.0) 298(8.3)	229(26.0) 255(13.3)
22	CH_3	140 / 31	8.68	242(18.8) 309(7.5)	230(21.1) 264(12.4)
23	C_2H_5	160 / 28	8.71	244(18.6) 311(7.0)	231(22.7) 266(12.3)
24	$(CH_3)_2CH$	163 / 31	8.57	243(18.8) 311(6.1)	233(22.5) 267(11.6)
25	C_6H_5	86–87	8.37	236(21.4) 308(7.9)	234(30.6)
26	$4\text{-}CH_3\text{-}C_6H_4$	88–90	8.64	235(19.9) 307(6.9)	235(28.6) 290(8.0)
27	$3\text{-}Cl\text{-}C_6H_4$	68–69	8.12	239(17.3) 305(6.9)	235(27.8)
28	$4\text{-}Cl\text{-}C_6H_4$	126–128	8.22	243(12.0) 307(9.3)	235(32.8)
29	$3\text{-}NO_2\text{-}C_6H_4$	134–135	7.94	239(17.8) 273(11.6) 300(8.9)	236(26.1) 260(22.0)
30	$3\text{-}CH_3\text{-}C_6H_4$	220 / 31	8.48	237(25.6) 308(10.5)	235(30.6)

[a] Recorded on a Specord M-40 spectrophotometer

Table 3. Correlation of pK_a values with *Hammett* σ constants for compounds **1**–**30**

	ρ	r^2	n
4-amino-2,6-dimethyl-5-phenylpyrimidine derivatives (**1**–**10**)	−0.64	0.992	10
4-dimethylamino-2,6-dimethyl-5-phenyl-pyrimidine derivatives (**11**–**20**)	−0.92	0.973	10
2,4-*bis*-dimethylamino-6-methyl-5-phenyl-pyrimidine derivatives (**25**–**30**)	−0.75	0.958	6

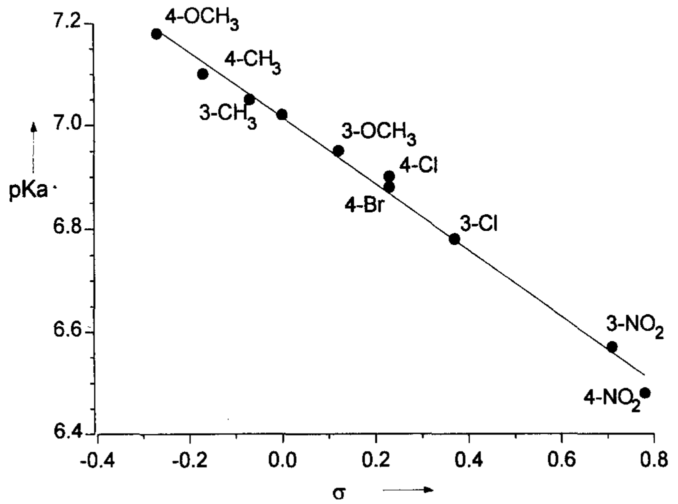


Fig. 1. Plot of pK_a values of 4-amino-2,6-dimethyl-5-phenylpyrimidine derivatives (**1**–**10**) *vs.* *Hammett* constants

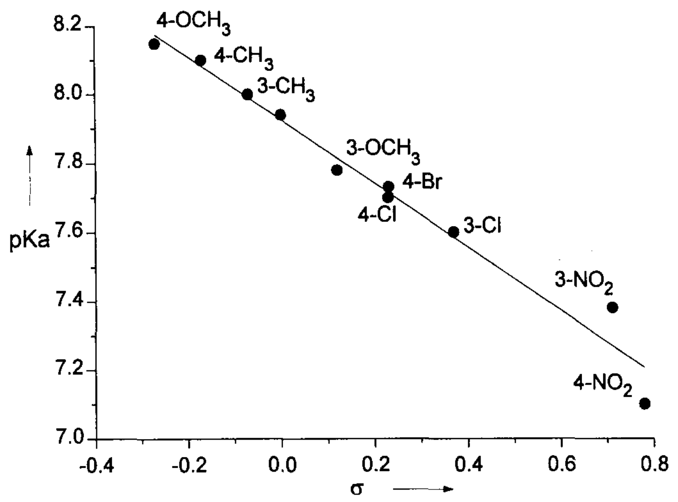


Fig. 2. Plot of pK_a values of 4-dimethylamino-2,6-dimethyl-5-phenylpyrimidine derivatives (**11**–**20**) *vs.* *Hammett* constants (σ)

Results and Discussion

The basic dissociation constants of the aminopyrimidines under investigation were determined by spectrophotometric means, employing a method similar to that reported by *Albert* and *Serjeant* [12]. Because of the poor solubility of the studied compounds in water, the pK_a values were determined at 20 °C in a 2% v/v aqueous methanol solution. The *pH* was adjusted by means of a *Britton* and *Robinson* buffer solution. The UV/Vis spectra of the corresponding pyrimidinium cations were obtained in 0.01 *M* hydrochloric acid solutions; 0.01 *M* sodium hydroxide solutions were applied to obtain the spectra of the non-protonated forms. The dissociation constants and ultraviolet spectroscopic data for 4-amino- and 4-dimethylaminopyrimidine derivatives are given in Table 1. Table 2 shows the corresponding data of the 2,4-*bis*-dimethylaminopyrimidine derivatives.

Least-squares plots of the data from Tables 1 and 2 reveal that for each series of the 4-amino-, 4-dimethylamino-, and 2,4-*bis*-dimethylamino-pyrimidines a good linear correlation exists between the pK_as and the *Hammett* σ values of the

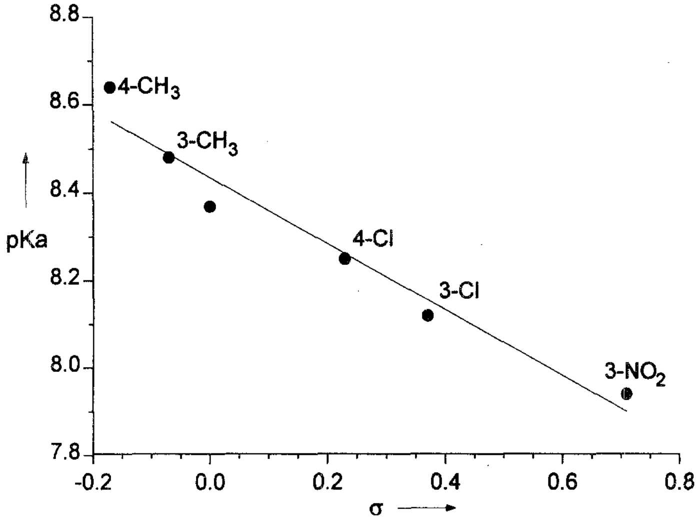


Fig. 3. Plot of pK_a values of 2,4-*bis*-dimethylamino-6-methyl-5-phenylpyrimidine derivatives (**25**–**30**) *vs. Hammett* constants (σ)

substituents at the benzene ring. Table 3 lists the reaction constants obtained from linear regression analysis of Figs. 1–3.

The basicity of the investigated pyrimidines clearly depends on the nature of the substituent at the benzene ring, increasing with increasing electron donating properties. 4-Dimethylamino derivatives **11**–**20** are appreciably stronger bases than 4-amino-derivatives **1**–**10**. 2,4-*bis*-dimethylamino-6-methylpyrimidine (**21**) and 5-alkyl-2,4-*bis*-dimethylamino-6-methylpyrimidines (**22**–**24**) have closely similar basic strengths and are stronger bases than 2,4-*bis*-dimethylamino-6-methyl-5-phenylpyrimidine (**25**). Analysing all data, we can say that the polar effects of the substituents on the base strength of the pyrimidines are proportional to the substituent constants.

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