

DISSOCIATION CONSTANTS OF *m*- AND *p*-SUBSTITUTED PHENYLTHIOUREAS AND UREAS IN WATER AND IN METHANOL

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Dissociation constants of nine *m*- and *p*-substituted phenylthioureas, 4-nitrophenylurea, and 1-(4-nitrophenyl)-3,3-dimethylurea have been measured in water and in methanol. The pK_a values in methanol are higher than those in water by about 4 units. The Hammett ρ constant has the values 2.6 and 2.35 in water and in methanol, respectively. The pK_a difference between 4-nitrophenylurea and 4-nitrophenylthiourea is 2.85 in methanol and 3.25 in water.

Hydrogen atom in N—H bond of thiourea derivatives is substantially more acidic than that in the corresponding urea derivatives. So *e.g.* pK_a of 6-methyluracil and its mono-anion¹ (9.76 and 14.07) are higher by more than one unit than the corresponding values of 6-methylthiouracil² (8.15 and 13.01). Still greater differences can be expected with simpler urea and thiourea derivatives. Values of their dissociation constants have not been determined yet, due to their very low acidity. However, the rate constant of the N—H bond splitting by hydroxyl ion was found to be greater by three orders of magnitude in N-methyl thiourea as compared with that of N-methylurea^{3,4}. As the reverse step of this reaction is diffusion-controlled, the difference in pK_a 's of the two compounds is determined by the difference in $\log k$ of the proton transfers.

The aim of the present communication is to determine the dissociation constants of substituted phenylthioureas in water and in methanol and to compare them with the dissociation constants of substituted phenylureas. Acidity of some derivatives in dimethyl sulphoxide was described elsewhere⁵.

EXPERIMENTAL

Preparation of the Substances

The substituted nitrophenylureas were prepared by reaction of substituted phenyl isocyanates with ammonia or dimethylamine. The substituted phenylthioureas were prepared by reaction of benzoyl isothiocyanate⁶ with substituted anilines and subsequent methanolysis. The melting points of the crystallized derivatives of phenylurea and phenylthiourea agreed with literature

data: 4-Nitrophenylurea⁷, 1-(4-nitrophenyl)-3,3-dimethylurea⁸, phenylthiourea⁶, 4-methoxyphenylthiourea⁹, 4-chlorophenylthiourea^{10,11}, 4-methylphenylthiourea¹¹, 4-bromophenylthiourea^{9,11}, 4-nitrophenylthiourea^{9,11}, 3-chlorophenylthiourea^{9,11}, 3-nitrophenylthiourea^{11,12}; 3-acetylphenylthiourea, m.p. 170–171°C, for C₉H₁₀N₂OS (194.2) calculated: 55.66% C, 5.15% H; found: 55.82% C, 5.07% H.

Measurements of the Dissociation Constants

The values of dissociation constants were determined spectrophotometrically¹³ in methanolic sodium methoxide and aqueous sodium hydroxide solutions at 25°C using a Specord UV VIS and VSU 2P apparatus. The dissociation constants of 3- and 4-nitrophenylthiourea in water were also measured in piperidine buffers at ionic strength 0.1. The analytical wavelengths and the measured values of dissociation constants are given in Table I. The calculations were realized according to the general program for factor analysis and analysis of the main components implemented in the language FORTRAN IV using an EC 1033 computer.

RESULTS AND DISCUSSION

The dissociation constants of substituted phenylthioureas in methanol were computed from the relation (1)

$$pK_a = \log I + H_M, \quad (1)$$

TABLE I

pK_a Values of substituted phenylureas and phenylthioureas (R—C₆H₄—NH—CX—NH₂) in water and in methanol at 25°C

R	X	$\lambda_{\text{anal}}, \text{nm}$		pK_a^a	
		water	methanol	water	methanol
H	S	—	320	—	16.95
4-OCH ₃	S	—	250	—	17.14
4-CH ₃	S	—	257	—	17.04
4-Cl	S	310	270	12.30	16.30
4-Br	S	315	272	12.35	16.33
4-NO ₂	S	420	333	10.75	15.05
3-COCH ₃	S	350	—	12.10	—
3-Cl	S	310	268	12.00	16.10
3-NO ₂	S	370	305	11.10	15.32
4-NO ₂	O	420	430	14.0	17.9
4-NO ₂ ^b	O	—	450	—	17.5

^a Standard deviation ± 0.04 and ± 0.1 for X = S and O, respectively; ^b 1-(4-nitrophenyl)-3,3-dimethylurea.

where I means the ratio of concentrations of the non-dissociated and dissociated forms of thiourea ($I = \frac{[-\text{NH}-]}{[-\text{N}^-]}$), and H_M is the acidity function in methanol. At low alkoxide concentrations Eq. (1) can be expressed in the form (2)¹⁴.

$$\text{p}K_a = 16.916 + \log [\text{CH}_3\text{O}^{(-)}] + \log I. \quad (2)$$

At higher alkoxide concentrations we obtained linear dependence of $\log I$ on the H_M function with the slope equal to 1, if we used the H_M function for anilines and diphenylamine¹⁵. The dependence $\log K_a$ on σ^0 constants¹⁶ was linear with the slope $\rho = 2.3$.

The spectra of 4-nitrophenylurea were measured in the range 250 to 550 nm. The isosbestic point was shifted to longer wavelengths with increasing alkoxide concentration, and at the highest used methoxide concentration (5.5 mol l^{-1}) further spectral changes took place which were considered to be due to dissociation to the second degree. Therefore, we measured, at the same conditions, also 1-(4-nitrophenyl)-3,3-dimethylurea, and we found again a shift of isosbestic point, but no other substantial spectral changes at the highest alkoxide concentrations. To differentiate the effect of protonation from specific effects of medium on electronic spectra of the compounds studied we used the characteristic method of vector analysis (CVA)¹⁷. For the calculation we used the covariance matrix of average data. In the case of 4-nitrophenylurea the absorbance was read at 8 methoxide concentrations and at 8 wavelengths. The first main component involved 99.27% variance, and the second one involved 0.69%. The treatment of the absorbances of 1-(4-nitrophenyl)-3,3-dimethylurea at 12 methoxide concentrations and at 10 wavelengths involved 95.88% and 3.98%

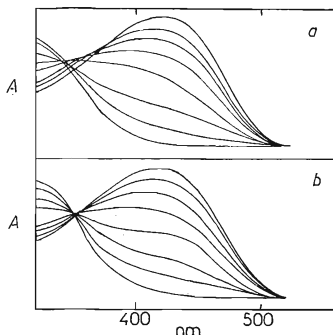


FIG. 1
Electronic spectra measured *a*, recalculated by the CVA method *b*) of 4-nitrophenylthiourea in aqueous sodium hydroxide solutions

variance for the first and the second main component, respectively. Reproduction of the source matrix by means of the first main component gave a spectrum with unequivocal isosbestic point in each of the two cases. These data were used for calculation of the proper pK_a values. In contrast to the thioureas, we obtained the unit slope of the dependence of $\log I$ on the H_M function when using the acidity function derived for indoles¹⁸ (for 4-nitrophenylurea) or for formamides¹⁹ (for 1-(4-nitrophenyl)-3,3-dimethylurea). The difference in pK_a of 4-nitrophenylurea and 4-nitrophenylthiourea is 2.85.

Determination of the dissociation constants of phenyl thioureas in aqueous sodium hydroxide solutions was difficult due to low solubility of the substrate and (except for the 4-nitro derivatives) also due to small spectral changes. With some phenylthiourea derivatives it was quite impossible to obtain reliable pK_a values by the measurements, since the experiments were irreproducible even at the low concentrations used.

Slope of the dependence of $\log K_a$ on σ^* constants has the value 2.6 which agrees, within experimental error, with the ρ value found in methanol.

4-Nitrophenylthiourea also showed a shift of isosbestic point with increasing sodium hydroxide concentration, but the spectral changes at the highest hydroxide concentrations were negligible. The spectra were also recalculated by the CVA method, and the experimental spectra are given in Fig. 1 along with the calculated ones. The pK_a difference between 4-nitrophenylurea and 4-nitrophenylthiourea is 3.25, i.e. practically the same as in methanol.

The pK_a values measured in methanol are higher than those in water by about 4 units (Table I), which agrees with the general rule that dissociation of neutral compounds is less favourable in methanol than in water due to lower permittivity of methanol.

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