

# 4-Substituted 2-nitrophenylguanidines

## II. Acid-base properties and structure

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Received 10 April 1986

Accepted for publication 10 November 1987

*Dedicated to Professor RNDr. J. Hadáček, in honour of his 80th birthday*

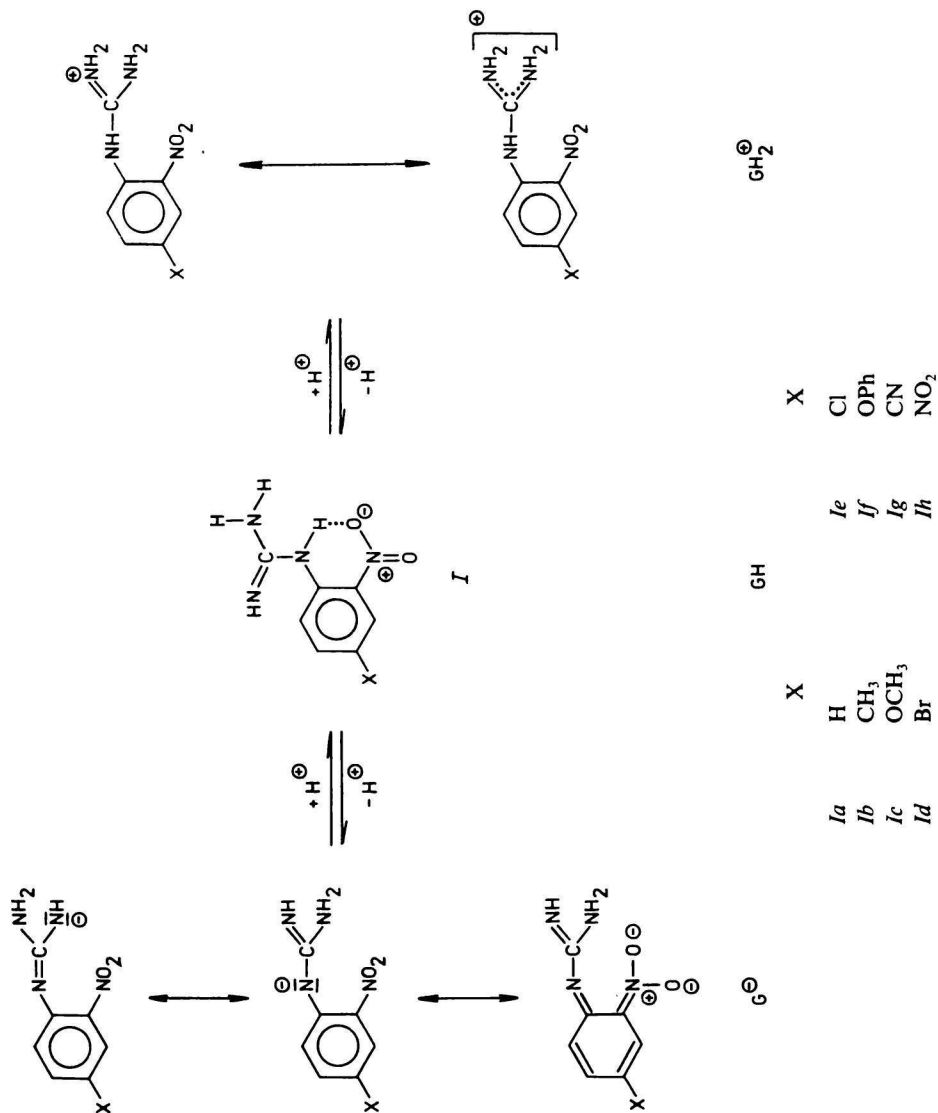
Dissociation constants  $K_I$  of the dissociation of 4-X-2-nitrophenylguanidinium cation in water ( $X = \text{H}, \text{CH}_3, \text{OCH}_3, \text{Br}, \text{Cl}, \text{OPh}, \text{CN}, \text{NO}_2$ ) were measured by potentiometry. A linear dependence of  $\text{p}K_I$  on the Hammett constants  $\sigma_p$  of the substituents X with the value  $\rho = -0.522$  was found.

Dissociation constants  $K'_{II}$  which characterize the dissociation of 4-X-2-nitrophenylguanidine were measured by the UV VIS spectrophotometric method. A linear dependence was found of  $\text{p}K'_{II}$  on Hammett constants  $\sigma_p^-$  of the substituent X with the value  $\rho = 1.143$  and a linear correlation between  $\text{p}K'_{II}$  and the value of the chemical shift  $\delta$  of the hydrogen atom H-4.

Потенциометрически определены константы диссоциации  $K_I$  катиона 4-X-2-нитрофенилгуанидиния в воде ( $X = \text{H}, \text{CH}_3, \text{OCH}_3, \text{Br}, \text{Cl}, \text{OPh}, \text{CN}, \text{NO}_2$ ) и установлена линейная зависимость  $\text{p}K_I$  от констант Гамметта  $\sigma_p$  заместителей X со значением  $\rho = -0,522$ .

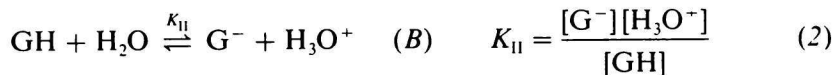
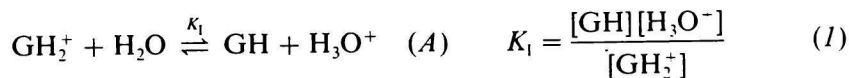
Константы диссоциации  $K'_{II}$ , характеризующие диссоциацию 4-X-2-нитрофенилгуанидина были измерены методом спектрофотометрии УФ и в видимой области. Установлена линейная зависимость  $\text{p}K'_{II}$  от констант Гамметта  $\sigma_p^-$  заместителя X со значением  $\rho = 1,143$  и линейная корреляция между  $\text{p}K'_{II}$  и величиной химического сдвига  $\delta$  водородного атома H-4.

Guanidine is known to be one of the strong bases ( $\text{p}K_b = 0.5$ ). Its basicity is a function of a substitution. Therefore, we can expect 4-substituted 2-nitrophenylguanidine to exhibit base properties. On the other hand, it can also show acid properties — there is a possibility of proton abstraction from the guanidine group because the negative charge of the anion so formed may be delocalized on either the 2-nitrophenyl group or the guanidine part of the molecule (Scheme 1).



Scheme 1

We could describe the acid-base behaviour of 4-X-2-nitrophenylguanidine in the following summary equations



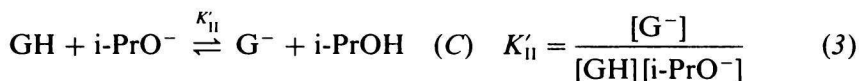
Potentiometric titrations of 4-X-2-nitrophenylguanidinium nitrates with sodium hydroxide aqueous solution showed that there are two potential jumps on the potentiometric titration curve. These correspond to the ionization equilibria mentioned above that are characterized by the dissociation constants  $K_1$ ,  $K_{II}$ . Values of the negative decadic logarithm of the dissociation constants  $\text{p}K_1$  were determined for the individual derivatives from the potentiometric titration curves. It was very difficult to determine the  $\text{p}K_{II}$  from the potentiometric or derived potentiometric curves because of a negligible change in the surroundings of the inflexion point.

Therefore we tried to determine  $\text{p}K_{II}$  by spectrophotometry. The measurement of the electronic spectra of the studied 2-nitrophenylguanidines *Ia—Ih* in dependence on pH showed that the proton abstraction from the molecule of 2-nitrophenylguanidine with sodium hydroxide in water is accompanied by a bathochromic and hyperchromic shift of the longwavelength band.

But in view of the fact that compounds *Ia—Ih* are very little acidic, the full dissociation in the aqueous solution does not take place and the spectrophotometric method of the acidity determination cannot be used.

The constants of dissociation  $\text{p}K'_{II}$  were therefore determined in a medium of 2-propanol in the presence of the sodium 2-propoxide base where the full dissociation may occur.

In this medium the equilibrium and its equilibrium constant may be expressed by the following equation



The correlation of the values  $\text{p}K_1$  and  $\text{p}K'_{II}$  with Hammett  $\sigma_p$  and  $\sigma_p^-$  constants of the substituents X was carried out.

From the linear dependence  $\text{p}K_1 = (-0.522 \pm 0.041) \cdot \sigma_p + (5.07 \pm 0.02)$  with the coefficient of correlation  $r = -0.998$  it resulted that the protonation of 2-nitrophenylguanidine probably occurs at the nitrogen of the imino group and that the influence of a substituent on the imino group basicity is not very significant. A cation thus formed may be stabilized by the mesomery (Scheme 1).

On the other hand, the influence of substituents in the position 4 on the  $pK_{II}'$  values is very significant ( $pK_{II}' = (1.143 \pm 0.198) \cdot \sigma_p^- + (13.54 \pm 0.02)$ ). This indicates that the proton is split off from the nitrogen atom bonded immediately at the 2-nitrophenyl system. The anion arisen by the proton abstraction may be stabilized either by the delocalization of the negative charge at the 2-nitrophenyl part of the molecule forming a quinoid structure or by the delocalization at the guanidine group (Scheme 1).

These conclusions obtained by the acid-base study were confirmed and specified by the results of IR and  $^1\text{H}$  NMR spectroscopy.

In the IR spectrum [1] of the studied compounds *Ia—Ih* there is a band corresponding to the stretching vibration  $\nu(\text{N—H})$  in the  $\tilde{\nu}$  range from 3280 to 3330  $\text{cm}^{-1}$ . This low position of the N—H bond vibration, which is not dependent on the 2-nitrophenylguanidine concentration, is a proof of an intramolecular hydrogen bond between N—H group and nitro group at the benzene ring. The hydrogen bridge is relatively strong due to the relatively high acidity of the hydrogen atom bonded at the nitrogen in the neighbourhood of 2-nitrophenyl. The shift of wavenumbers of  $\nu(\text{N—H})$  vibration which accompanies the bridge formation is relatively high.

This affirmation is in good agreement with the results of an electrochemical study of 2-nitrophenylguanidines in acetonitrile [2], where a disconnection of this hydrogen bond was proved as well as with the conclusions about the effect of the intramolecular hydrogen bridge in ortho derivatives of aniline summarized in the monograph [3].

It follows from the  $^1\text{H}$  NMR spectra of 4-X-2-nitrophenylguanidines *Ia—Ih* (Table 3) that the hydrogen atom H-4, in comparison with hydrogen atoms H-5, is less shielded and has a higher value of the chemical shift  $\delta$ . A more pronounced electronic effect of the substituents X on the chemical shift of the atom H-4 appeared during the correlation with Hammett constants  $\sigma_p$  when compared with the effect on the chemical shift of the atoms H-5 ( $\delta_{\text{H-4}}/\text{ppm} = (1.639 \pm 0.428) \cdot \sigma_p + (5.17 \pm 0.17)$ ;  $r = 0.967$ ).

The values of the chemical shift of the atom H-4 are linearly dependent on  $pK_{II}'$  ( $\delta_{\text{H-4}}/\text{ppm} = (-1.000 \pm 0.085) \cdot pK_{II}' + (18.66 \pm 1.22)$ ;  $r = -0.923$ ). An analysis of 4-X-2-nitrophenylguanidine  $^1\text{H}$  NMR spectra led us to the conclusion that both hydrogen atoms H-5 are equal (giving only one signal of the integral intensity of 3) and from this we concluded that both end nitrogen atoms of the guanidine group are equal. This might be explained by the fast tautomeric equilibrium in a polar solvent.

## Experimental

Dissociation constants  $K_I$  were determined with autotitrator TT2 with automatic burette ABU 12 (Radiometer, Copenhagen). Electronic spectra were recorded with

Unicam SP 1800 in a 1 cm quartz cell. IR spectra were taken on Unicam SP 1000,  $^1\text{H}$ NMR spectra on Tesla BS 567 instrument (100 MHz). IR spectra were measured in bromoform solution,  $^1\text{H}$ NMR spectra in DMSO- $d_6$  solution of concentration about  $1 \text{ mol dm}^{-3}$  using HMDSO as internal standard.

### Potentiometric determination of $\text{p}K_1$

A volume from 5 to 10  $\text{cm}^3$  of 4-X-2-nitrophenylguanidinium nitrate ( $c \approx 1 \times 10^{-2} \text{ mol dm}^{-3}$ ) in water was titrated with NaOH aqueous solution ( $c \approx 0.05 \text{ mol dm}^{-3}$ ) at the temperature of 22–23 °C. pH Value was indicated by a combined glass electrode against SCE. The dependence of pH on the added volume  $V$  of the hydroxide solution was recorded. The  $\text{p}K_1$  was evaluated from the potentiometric titration curve and from the equation  $\Delta\text{pH}/\Delta V = f(V)$ . The results are presented in Table 1.

Table 1

Results of the potentiometrically determined values  $\text{p}K_1$  and photometrically determined values  $\text{p}K'_1$

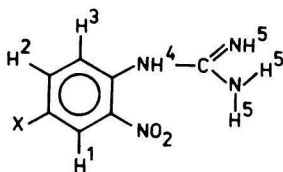
Compound	$\sigma_p$	Ref.	$\sigma_p^-$	Ref.	$\text{p}K_1$	$\text{p}K'_1$
<i>Ia</i>	0.00		0.00		$5.05 \pm 0.01$	$13.52 \pm 0.08$
<i>Ib</i>	-0.15	[4]	-0.15	[6]	$5.14 \pm 0.01$	$13.78 \pm 0.09$
<i>Ic</i>	-0.27	[5]	-0.12	[6]	$5.23 \pm 0.02$	$13.70 \pm 0.08$
<i>Id</i>	0.23	[4, 5]	0.26	[6]	$4.95 \pm 0.01$	$13.20 \pm 0.09$
<i>Ie</i>	0.22	[4, 6]	0.24	[6]	$4.98 \pm 0.01$	$13.28 \pm 0.08$
<i>If</i>	-0.03	[4, 5]	0.05	[6]	$5.08 \pm 0.01$	$13.45 \pm 0.10$
<i>Ig</i>	0.68	[4]	0.99	[6]	$4.73 \pm 0.01$	$12.38 \pm 0.09$
<i>Ih</i>	0.80	[4]	1.25	[6]	$4.64 \pm 0.02$	$12.16 \pm 0.08$

Table 2

Molar absorption coefficient values  $\varepsilon$  of the compounds *Ia*–*Ih* and their deprotonated forms in 2-propanol at the wavelength of the maximum absorbance of the deprotonated form  $\lambda_{\text{exp}}$

Compound	$\lambda_{\text{exp}}/\text{nm}$	$\varepsilon_{\text{GH}} \cdot 10^{-3}/(\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1})$	$\varepsilon_{\text{G}^-} \cdot 10^{-3}/(\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1})$
<i>Ia</i>	350	0.842	2.564
<i>Ib</i>	362	0.800	2.540
<i>Ic</i>	382	0.644	2.624
<i>Id</i>	364	0.881	2.797
<i>Ie</i>	364	0.892	2.870
<i>If</i>	386	0.705	3.002
<i>Ig</i>	374	0.660	6.122
<i>Ih</i>	378	0.520	10.281

Table 3

<sup>1</sup>H NMR spectral characteristics of compounds *la–lh*

Compound	$\delta_{H-1}$ /ppm	$\delta_{H-2}$ /ppm	$\delta_{H-3}$ /ppm	$\delta_{H-4}$ /ppm	$\delta_{H-5}$ /ppm	$J_{2,3}$ /Hz	$J_{1,2}$ /Hz
<i>la</i>	7.76	7.67	—	6.83 m	5.20	3.73*	9.0
<i>lb</i>	7.45	7.17	6.80	2.15 <sup>a</sup>	5.22	4.43	9.0 2.5
<i>lc</i>	7.26	7.10	6.88	3.68 <sup>b</sup>	—	—	9.0 2.5
<i>ld</i>	7.85	7.53	6.95	—	5.55	3.62	9.0 2.5
<i>le</i>	7.69	7.35	7.02	—	5.52	3.65	9.0 2.5
<i>lf</i>	7.63	—	—	6.46 m	5.18	3.59	—
<i>lg</i>	7.87	7.49	7.01	—	6.20	3.52	9.0 2.5
<i>lh</i>	8.53	8.08	7.07	—	6.52	3.45	9.0 2.5

a) CH<sub>3</sub>—C<sub>ar</sub>; b) CH<sub>3</sub>O.  
 m — unresolved multiplet.

\* Broad maximum.

*Photometric determination of  $pK'_{II}$* 

The fact that the electronic spectra of the substituted 2-nitrophenylguanidines differ from the spectra of the deprotonated forms in the longwavelength region (Table 2) was used for the determination of  $K'_{II}$  constants.

Hammett acidity function  $H_-$  of 4-X-2-nitrophenylguanidines is given by the relation

$$H_- = pK'_{II} - \log \frac{[GH]}{[G^-]} \quad (4)$$

Hammett acidity function of 2-propanol determined in [7] is given by the equation

$$H_- = 17.95 + \log \{[i\text{-PrO}^-]\} \quad (5)$$

The comparison of both relations and their rearrangement led to the relation for  $pK'_{II}$

$$pK'_{II} = 17.95 + \log \{[i\text{-PrO}^-]\} + \log \frac{[GH]}{[G^-]} \quad (6)$$

The ratio  $[GH]/[G^-]$  may be expressed in the case of photometric determination by the relation from [8]

$$\frac{[GH]}{[G^-]} = \frac{\varepsilon_{G^-} - \varepsilon}{\varepsilon - \varepsilon_{GH}} = \frac{A_{G^-} - A}{A - A_{GH}} \quad (7)$$

where

- $\varepsilon_i$  — molar absorption coefficient of the component  $i$  in the solution;
- $\varepsilon$  — molar absorption coefficient of the solution;
- $A_i$  — absorbance of the component  $i$  in the solution;
- $A$  — absorbance of the measured solution.

The other symbols have the same meaning as in Scheme 1.

The dependence of the molar absorption coefficient of compounds  $Ia—Ih$  in 2-propanol on the sodium 2-propoxide concentration was examined in the concentration region from  $10^{-2}$ — $10^{-4}$  mol dm $^{-3}$ . A set of every measured compound consisted of twelve measurements. A stock solution of sodium 2-propoxide in concentration 1 mol dm $^{-3}$  was prepared by the reaction of 2-propanol with sodium and its concentration was determined by the titration with benzoic acid in anhydrous DMF (indicator thymol blue) [9].  $pK'_{II}$  Values are presented in Table 1.

IR spectral characteristics are presented in [1].  $^1\text{H}$  NMR spectra are in Table 3.

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Translated by M. Potáček