ELSEVIER

Journal of Pharmaceutical and Biomedical Analysis
15 (1997) 1667–1678

JOURNAL OF
PHARMACEUTICAL
AND BIOMEDICAL
ANALYSIS

Protolytic constants of nizatidine, ranitidine and *N*,*N*′-dimethyl-2-nitro-1,1-ethenediamine; spectrophotometric and theoretical investigation

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Received 18 June 1996; accepted 30 October 1996

Abstract

The prototropic exchange equilibria of two drugs, nizatidine (I) and ranitidine (II), and also of structurally related the *N*,*N*′-dimethyl-2-nitro-1,1-ethenediamine molecule (III) were investigated. From the changes in electronic spectra in media of various acidity several protonation constants were determined. For nizatidine p*K* values were −0.82, 1.95, and 6.67; for ranitidine p*K* values were 1.95 and 8.13; and for III was 2.60. The hydroxylation equilibrium constant in strongly alkaline media was determined too. Corresponding pK_a values were 13.23 for I, 13.26 for II and 13.76 for III. Molecular orbital calculations of electronic spectra confirmed that p*K* 1.95 for I and II, and p*K* 2.60 for III, are associated with C-protonation of nitroethenediamine fragment, while all pK_a values correspond to the addition of HO^- anion at the same double bond. © 1997 Elsevier Science B.V.

Keywords: Nizatidine; Ranitidine; *N*,*N*′-dimethyl-2-nitro-1,1-ethenediamine; Protolytic constants; UV spectra; MNDO-PM3 and ZINDO/S calculations

1. Introduction

Nizatidine, *N*-[2-[[[2-[(dimethylamino)methyl]-4-thiazolyl]methyl]thio]ethyl]-*N*′-methyl-2-nitro-1, 1-ethenediamine (I) and ranitidine, *N*-[2-[[[5-[(dimethylamino) methyl]-2-furanyl] methyl]thio] ethyl]-*N*′-methyl-2-nitro-1,1-ethenediamine (II) are selective H_2-receptor antagonists and powerful inhibitors of gastric acid secretion introduced for the treatment of peptic ulcers and related disorders [1–4]. The first synthesis of ranitidine was reported in 1978 [5] and nizatidine in 1983 [6]. These two drugs are structurally related and differ in the type of heterocyclic ring. A key feature of both structures is *N*,*N*′-dialkyl-2-nitro-1,1-ethenediamine moiety [7], since nizatidine (I) contains the thiazolyl, while

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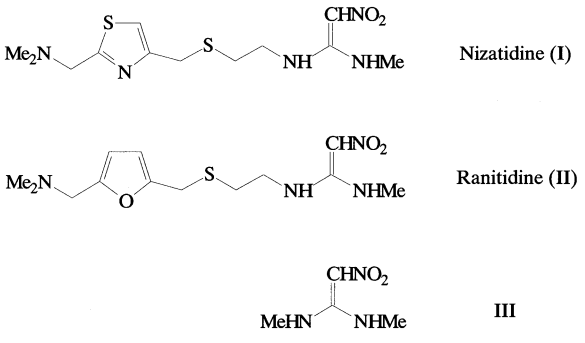
PII S0731-7085(96)01977-2

ranitidine (II) contains the furan ring (Scheme 1). To make the clear distinction between the effects of two moieties, the *N*,*N*′-dimethyl-2-nitro-1,1-ethenediamine molecule (III) was investigated too.

Besides the medical importance of nizatidine and ranitidine, these compounds offer a challenging structural problem of the determination of the reactivity of various sites suitable for prototropic exchange.

The p*K* values for the protonation process of nizatidine [8] and ranitidine [9], which occur in neutral media (pH 6–8) have been determined potentiometrically [8,9]. The protonation constant on a 2-nitroethenediamine moiety of nizatidine [8] as well as of ranitidine [9–11] was determined spectrophotometrically [8–11]. In this paper, the study of protolytic equilibria was extended to include the spectrophotometric and theoretical investigations of the protolytic processes in aqueous, in sulphuric acid aqueous solutions and in alkaline media.

For the molecular orbital calculations of the ground-state geometries the PM3-MNDO method was used [12], as most accurate, particularly for the nitro compounds. All the calculations were done on the compound III. Due to the complex structure of this compound there are certain ambiguities in the assignment of the measured spectra to the particular ionic form. Using ZINDO/S MO method, spectra of III and of various ionic species derived from it were calculated. The calculated approximate spectra are used to make definite assignments of measured spectra.



Scheme 1.

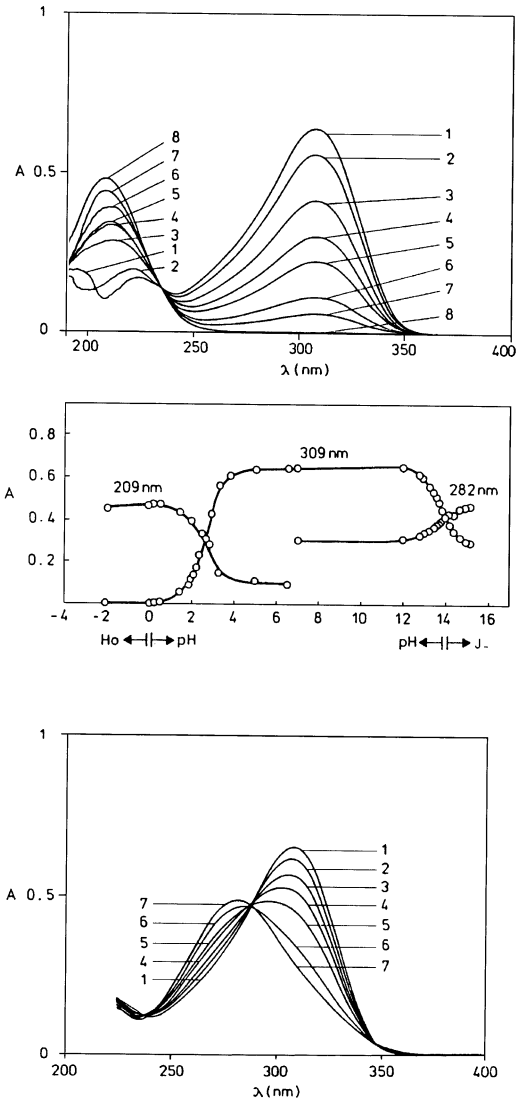


Fig. 1. (a)Absorption spectra of III (4×10^{-5} M) in solutions of different pH: 1, 6.59 (B); 2, 3.29; 3, 2.87; 4, 2.56; 5, 2.36; 6, 1.98; 7, 1.42; 8, 0.23 (BH^+).(b) Absorbance of III (4×10^{-5} M) at 209, 309 and 282 nm as a function of H_0, pH and J_.(c) Absorption spectra of III (4×10^{-5} M) in solutions of different pH and J_: 1, 12.00 (B); 2, 12.80; 3, 13.30; 4, 13.60; 5, 13.85; 6, 14.40; 7, 15.20 (BOH^-).

The knowledge and use of prototropic exchange equilibria and stereoelectronic properties of pharmacologically important subunits of drugs is profoundly important for successful analytical

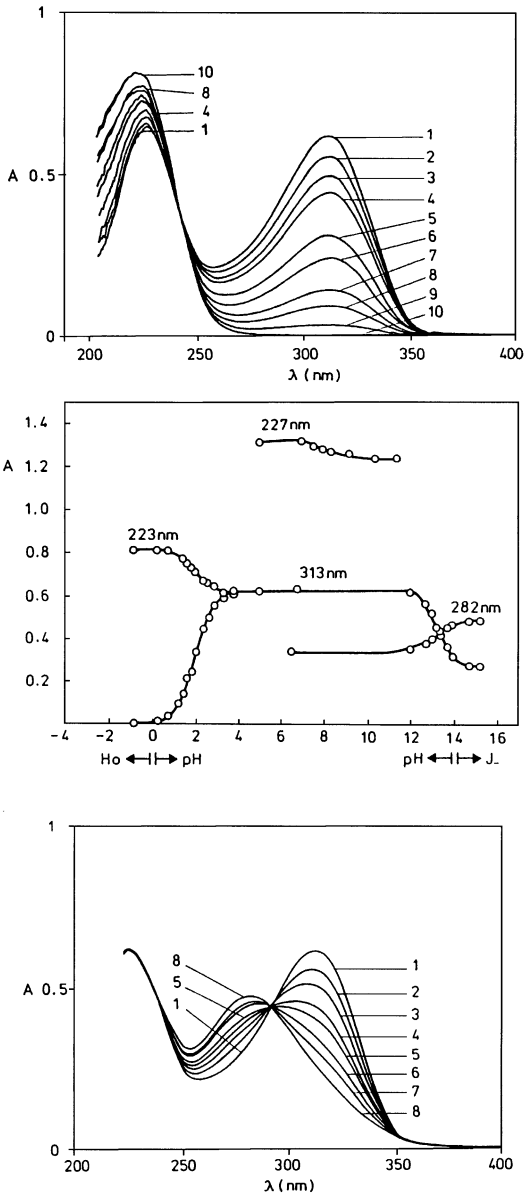


Fig. 2. (a) Absorption spectra of ranitidine, II, (4×10^{-5} M) in solutions of different pH and H_0: 1, 5.02 (BH^+); 2, 2.87; 3, 2.56; 4, 2.36; 5, 1.98 6, 1.81; 7, 1,40; 8, 1.20; 9, 0.70; 10, −0.91 (BH_2^{2+}).(b) Absorbance of II, (4×10^{-5} M) at 223, 313 and 282 nm, and of 8×10^{-5} M at 227 nm, as a function of H_0, pH and J_.(c) Absorption spectra of II (4×10^{-5} M) in solutions of different pH and J_: 1, 12.00 (B); 2, 12.70; 3, 13.00; 4, 13.20; 5, 13.35; 6, 13.70; 7, 13.95; 8, 15.20 (BOH^-).

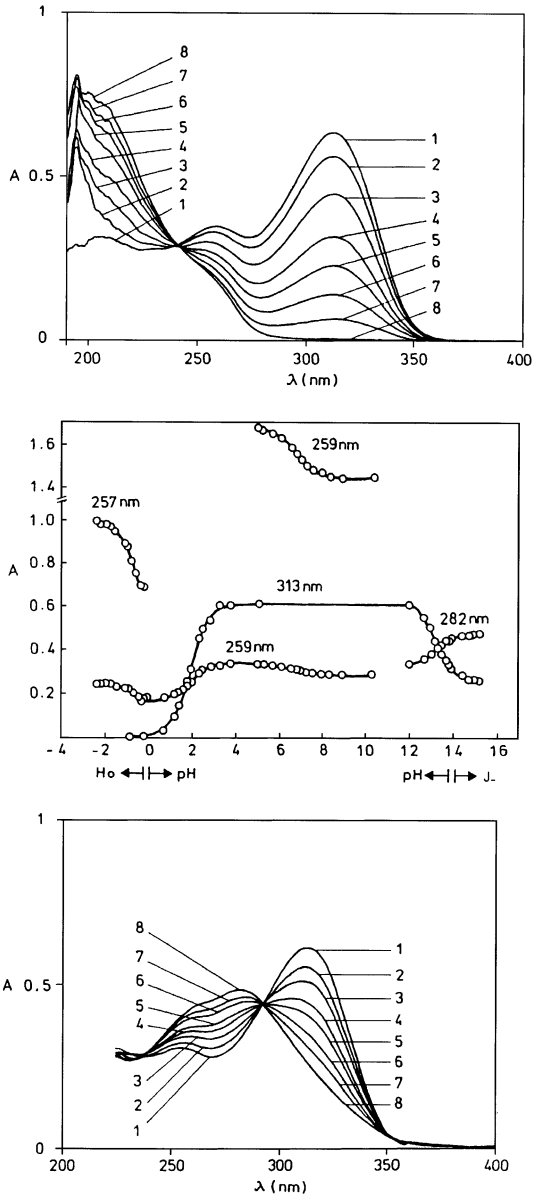


Fig. 3. (a) Absorption spectra of nizatidine, I, (4×10^{-5} M) in solutions of different pH: 1, 5.02 (BH^+); 2, 2.87; 3, 2.36; 4, 1.98; 5, 1.70; 6, 1.40; 7, 1.00; 8, 0.0 (BH_2^{2+}).(b) Absorbance of I, (4×10^{-5} M) at 259, 313 and 282 nm of 2×10^{-4} M at 259 nm and of 1.6×10^{-4} M at 257 nm, as a function of H_0, pH and J_.(c) Absorption spectra of I (4×10^{-5} M) in solutions of different pH and J_: 1, 12.00 (B); 2, 12.70; 3, 13.00; 4, 13.20; 5, 13.35; 6, 13.70; 7, 13.95; 8, 15.20 (BOH^-).

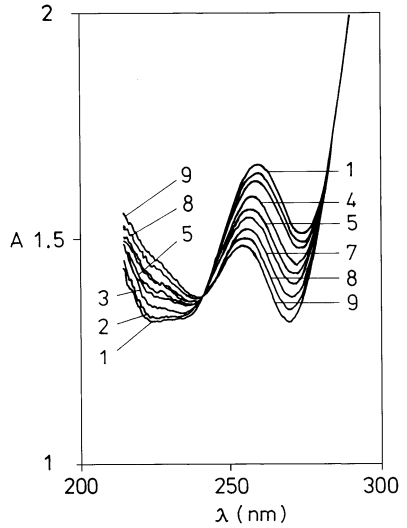


Fig. 4. Absorption spectra of nizatidine, I, (2×10^{-4} M) in solutions of different pH: 1, 5.02 (BH^+); 2, 5.72; 3, 6.09; 4, 6.59; 5, 6.80; 6, 7.00; 7, 7.24 8, 7.54; 9, 8.36–10.38(B).

procedures, for the selection of optimal conditions for synthesis, isolation, and purification. It is essential in the realm of pharmaceutical technology, pharmacokinetics, clinical medicine, etc.

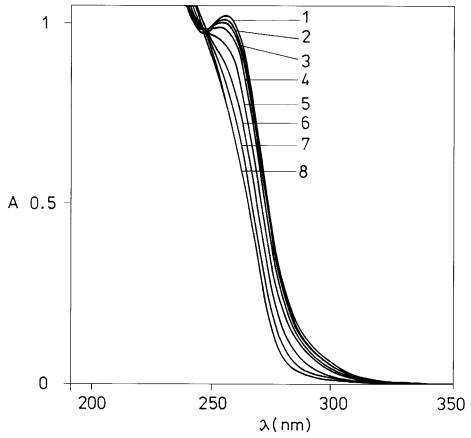


Fig. 5. Absorption spectra of nizatidine, I, (1.6×10^{-4} M) in solutions of different H_0: 1, −2.50 (BH_3^{3+}); 2, −2.23; 3, −1.78; 4, −1.50; 5, −1.10; 6, −0.83; 7, −0.62; 8, −0.30; 9, −0.20 (BH_2^{2+}).

2. Experimental

2.1. Materials

Nizatidine (CAS No. 76 963-41-2) (I), supplied from ICN Galenika (Belgrade, Yugoslavia), ranitidine (II) hydrochloride (CAS No. 66 357-59-3), obtained from Zdravlje (Leskovac, Yugoslavia) and *N*,*N*′-dimethyl-2-nitro-1,1-ethenediamine (CAS No. 54 252-45-8) (III), product of Uquifa (Barcelona, Spain), were used without further purification. Substrate stock solutions of 1×10^{-3} M were prepared in water. The concentrations of substrates for the determination of p*K* values were 4×10^{-5}–2×10^{-4} M. The other chemicals (H_2SO_4, NaOH) were of reagent grade quality. The acidity of the solutions in the pH range 2–12 was adjusted by addition of Britton–Robinson buffer. The acidity of concentrated H_2SO_4 solutions was characterized by Hammett acidity function, H_o [13]. The basicity of concentrated NaOH solutions was described using J_- function [14].

2.2. Spectroscopic and pH measurements

UV spectra were recorded, immediately after preparing the solutions, on a spectrophotometer Shimadzu UV Model 260. The concentration of sulfuric acid was determined from the density measured at 25°C, using the precise density meter. Acid solutions of various acid concentration were made by diluting H_2SO_4 to obtain desired acidity. To check the possible existence of the non-protolytic processes, the absorption spectra were recorded again after 1 h standing and no changes were found. On the subsequent dilution of solutions in 8 M H_2SO_4 and in 5 M NaOH, the spectra were identical to those of the control solutions in dilute acids or in neutral media.

2.3. Method of computation

Ground state structures of III and ions derived from it were calculated by MNDO-PM3 semiempirical molecular orbital method [12], included in MOPAC program package, Version 7.01. The simulation of polar medium was performed using COSMO facility. The calculation of electronic

Table 1
Heats of formation calculated by MNDO-PM3 and spectral transitions (calculated by ZINDO/S) for N,N′-dimethyl-2-nitro-1,1-ethenediamine, III and ionic species derived from it

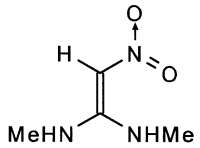
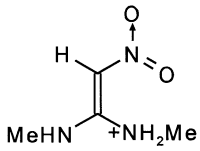
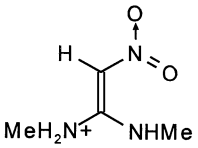
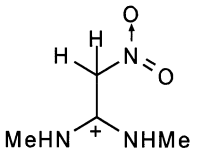
Structure	ΔH_f/kcal mol^{-1}		Spectral transition wavelengths (nm) (calculated oscillator strengths are given in parentheses)	
	In vacuum	In water	In vacuum	In water
III 	−1.656	−28.455	192 (0.538) 200 (0.137) 206 (0.237) 314 (0.0455)	193 (0.636) 200 (0.145) 205 (0.183) 313 (0.382)
IIIa 	170.853	89.260	188 (0.226) 300 (0.988)	188 (0.217) 293 (0.285) 308 (0.285)
IIIb 	175.299	88.079	180 (0.527) 208 (0.149) 211 (0.147) 267 (0.302)	172 (0.475) 177 (0.162) 182 (0.184) 207 (0.137) 215 (0.172) 269 (0.284)
IIIc 	158.250	81.840	187 (0.358) 191 (0.418) 215 (0.196)	190 (0.653) 194 (0.107) 221 (0.280)

Table 1 (continued)

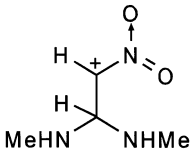
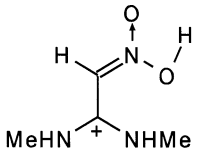
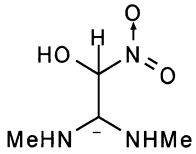
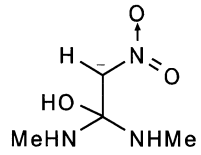
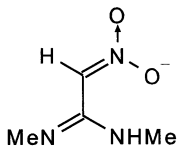
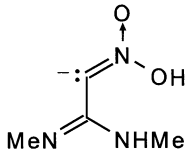
Structure		ΔH_f/kcal mol^{-1}		Spectral transition wavelengths (nm) (calculated oscillator strengths are given in parentheses)	
		In vacuum	In water	In vacuum	In water
	IIId	247.106	167.527	Partial geometry optimization was done (C–H bond angle was not optimized). See discussion.	
					
	IIIe	156.521	90.233	173 (0.220) 237 (0.273) 294 (0.923)	202 (0.159) 205 (0.426) 320 (0.713)
					
	IIIf	−72.293	−141.745	201 (0.472) 205 (0.120) 247 (0.241) 673 (0.198)	202 (0.428) 204 (0.130) 254 (0.239) 448 (0.113) 661 (0.222)
					
	IIIg	−97.912	−153.042	208 (0.277) 247 (0.562)	207 (0.303) 259 (0.281) 269 (0.137)
					

Table 1 (continued)

Structure	ΔH_f/kcal mol^{-1}		Spectral transition wavelengths (nm) (calculated oscillator strengths are given in parentheses)	
	In vacuum	In water	In vacuum	In water
IIIh 	−49.443	−127.493	170 (0.172) 207 (0.331) 307 (0.779)	220 (0.159) 205 (0.426) 320 (0.713)
IIIi 	−20.446	−107.351	344.96 (0.154) 264.19 (0.345) 221.67 (0.216) 204.23 (0.339)	302.31 (0.290) 265.13 (0.259) 208.98 (0.184) 195.07 (0.216)

transitions was done with ZINDO/S program. Configurational space for the excited state calculations was formed of all monoexcitations up to 20 eV cutoff energy.

3. Results and discussion

3.1. Absorption spectra

The absorption spectra of the compounds I–III were recorded in water solutions of the various acidity, from 8 M H_2SO_4 to 5 M NaOH.

The absorption spectra of the model substance III in neutral media show the absorption bands with the maxima at 223 and 309 nm (Fig. 1). In acidic solutions (pH 5–0) the protonation of 2-nitroethenediamine moiety caused the hypsochromic shift of the absorption maximum from 223 to 209 nm while the absorption maximum at 309 nm disappeared (Fig. 1(a,b)). With the increasing NaOH concentration up to 5 M, the longer wavelength maximum was shifted hypsochromically from 309 to 282 nm (Fig. 1(b,c)).

The absorption spectra of ranitidine (Fig. 2) and nizatidine (Fig. 3) in aqueous solutions (pH 4–11) show two main absorption bands. The short wavelength maximum at 227–259 nm stems mainly from the heterocyclic ring chromophore, with the contribution from the 2-nitroethenediamine chromophore. The other one has main absorption at 313 nm. The absorption spectra of both drugs in acidic media (pH 4–0) show the changes similar to the change exerted by III. Disappearance of the absorption band at 313 nm, assignable to the substituted conjugated 2-nitroethenediamine chromopohore, is followed by the increase in intensity and by the hypsochromic shift of the short wavelength maximum, at 223 nm for ranitidine (Fig. 2(a,b)), and 207 nm for nizatidine (Fig. 3a). The increase of pH from 11 to 15.5, leads to the hypsochromic shift of the other absorption maximum from 313

Table 2
Spectral characteristics of nizatidine (I), ranitidine (II) and *N*,*N*′-dimethyl-2-nitro-1,1-ethenediamine (III) molecular species

Compound	Ionic form	Optimal acidity	λ_{max} (nm)	$10^{-4} \times \varepsilon$ (mol^{-1} dm^3 cm^{-1})
Nizatidine	BH_3^{3+}	$H_0 = -2.5 - -3.0$	207	1.70
			257	0.67
	BH_2^{2+}	pH = 0.0–0.5	207	1.84
			257	0.50
	BH^+	pH = 4.0–5.1	259	0.87
			313	1.59
	B	pH = 9.5–11.5	255	0.77
			313	1.59
	BOH^-	$J_- = 15.2–15.4$	262	1.10
			282	1.23
Ranitidine	BH_2^{2+}	$H_0 = -1.0$–pH = 0.0	223	2.15
	BH^+	pH = 4.0–6.0	227	1.73
			313	1.65
	B	pH = 10.3–11.5	227	1.63
			313	1.66
	BOH^-	$J_- = 15.2–15.4$	227	1.55
			282	1.26
III	BH^+	pH = 0.0–0.3	209	1.20
	B	pH = 5.0–11.5	223	0.45
			309	1.59
	BOH^-	$J_- = 15.2–15.4$	282	1.20

to 282 nm (Fig. 2(b,c) and 3(b,c)); again the behavior similar to that of III.

For the three compounds studied the spectral changes exert clear isosbestic points, in acidic solutions at 242 nm(I), 243 nm (II), 235 nm (III) and in alkaline solutions at 238 and 292 nm (I), 240 and 292 nm (II), 238 and 288 nm (III). Corollarly, these protolytic processes involve the same reaction sites on 2-nitroethenediamine moiety.

By increasing pH from 4 to 10 the compounds I and II show the spectral changes that are minute but visible. The decrease of the intensity of the absorption at 259 nm of I (Fig. 3b/upper curve and Fig. 4) and at 227 nm of II (Fig. 2b/upper curve) was accompanied by the appearance of the clear isosbestic points and hypsochromic shift of the absorption maximum.

The increase of acidity from pH 0 to $H_0 - 3$, decreases the absorption of component I at 257 nm (Fig. 3b, Fig. 5).

3.2. Molecular orbital calculations

The results of the molecular orbital calculations are summarized in Table 1. Details on various conformers of III, are not given, because of their close resemblance to the results previously obtained by MNDO-AM1 method [15]. The structures IIIa–IIIe represent all the possible protonated forms of III. (The full geometry optimization was not performed for structure IIId. If bond angle of new C–H is not constrained it ends as structure IIIc). In the reference [9] very convincing evidences in favor of *C*-protonation were given. The calculations confirm it. The calculations both on isolated and on solvated ions reveal rather low heats of formation for two *C*-protonated species, IIIc and IIId and *O*-protonated species IIIe. The semiempirical MNDO-PM3 calculation shows that IIId can not exist. Distinction between IIIc and IIIe is clearly detectable in UV spectra. Only the electronic transitions calculated for IIIc conform to the experimental spectrum, because IIIe should have

Table 3
The pK values of nizatidine (I), ranitidine (II) and N,N'-dimethyl-2-nitro-1,1-ethenediamine (III), determined spectrophotometrically

Ionic form	Reaction site	pK_n	pK		
			Nizatidine	Ranitidine	III
BH_3^{3+}	Heterocyclic ring	pK_3	-0.82 ± 0.07		
BH_2^{2+}([a])	2-nitroethene diamine	pK_2	1.95 ± 0.02 2.1 [8]	1.95 ± 0.01 2.3 [9] 2.19 ± 0.04 [10,11]	2.60 ± 0.02
BH^+	Dimethyl amino group	pK_1	6.67 ± 0.01 6.80[b]	8.13 ± 0.05 8.20[c]	
BOH^-	2-nitroethene diamine	pK_a	13.23 ± 0.02	13.26 ± 0.04	13.76 ± 0.02

[a] For compound III this is actually BH^+ due to lack of dimethyl amino group.
[b] Value 6.80 was found by potentiometric titration [8].
[c] Value 8.20 was found by potentiometric titration [9].

considerable absorption at longer wavelengths.

Anionic species can be produced either by the proton abstraction (IIIh and IIIi) [9], or by the hydroxyl anion addition (IIIf and IIIg). The calculations show that IIIf has the lowest heat of formation. The key feature of the UV spectral changes in alkaline solutions of III is hypsochromic and hypochromic shifts of the long wavelength peak. Again, the calculated electronic transitions for IIIg most closely fit the observed effect. This structure is already suggested in the literature [16], and we hope that our calculations bear the conclusive evidence for it.

3.3. The ionic forms and calculation of protolytic constants

The changes in the absorption spectra due to the variable media acidity, are the consequences of the changed ionic form of the compound. The absorbance versus acidity curves were produced for the investigated acidity range. Table 2 summarizes the pH and intervals of the acid concentrations where no change of the absorbance takes place (optimal acidity for particular molecular species), together with the wavelength and molar absorptivity of the peak absorption of the corresponding molecular species.

Taking into accounts that there are different basic sites, the multiple protonation equilibria in the acidity range from pH 10 to 8 M H_2SO_4 occur:

$$BH_{n-1}^{(n-1)+} + nH^+ \leftrightarrows BH_n^{n+} \quad (1)$$

$$K_n = \frac{[BH_n^{n+}]}{[BH_{n-1}^{(n-1)+}]\,[H^+]^n} \qquad n = 1, 2, 3 \quad (2)$$

The protonation constant, K_1, of the dimethyl amino group for compounds I and II was well established and determined by potentiometric titration [8,9]. Although the spectral changes in the acidity range from pH 5 to 10 were small, the pK_1 values of monoprotonated molecules I and II have been calculated from the dependence of the absorbance versus pH curves at several wavelengths according to the known spectrophotometric method [17].

$$pK = pH + \log I \quad (3)$$

$$I = \frac{[BH_n^{n+}]}{[BH_{n-1}^{(n-1)+}]} = \frac{A - A_1}{A_0 - A} \quad (4)$$

where A_0 and A_1 are the absorbancies of the pure forms of the compounds. The spectrophotometrically obtained results agree very well with the potentiometric data [8,9] (Table 3).

The pK_2 values of I–III were determined from the absorbance versus pH curves in the acidity range from pH 0 to 5 according to the Eq. (3), and their values are mutually related in the manner expected from structural differences. This agreement suggests that the second protonation process on I and II must be assigned to the 2-nitroethenediamine moiety.

The variation of nizatidine absorbance in a highly acidic media is shown on Fig. 5. The value of the protonation constant of the nitrogen atom in a thiazole ring of I (pK_3) was calculated using the excess acidity method based on the following equation [18]:

$$\log I - \log c_{H^+} = m \cdot X + pK_3 \quad (5)$$

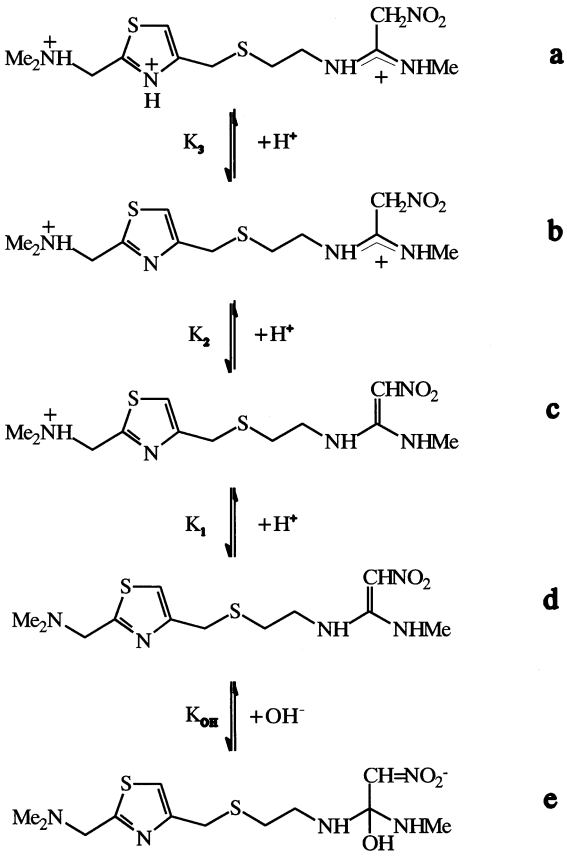
The values for $\log C_{H^+}$ and X are independent of the base present and are taken from the literature data for each H_2SO_4 concentration [18].

The spectroscopic studies of ranitidine in alkaline solutions show that ranitidine, as a weak acid, is completely dissociated in 5 M sodium hydroxide [9]. This protolytic constant has not been accurately measured but suggested that it is of the magnitude 10^{-14}. Presumably, proton loss is from nitrogen, although why it leads to a hypsochromic shift was not clear [9]. However, the report on the investigation of hydrolytic cleavage of ranitidine under strongly basic conditions at reflux temperature [16] was suggested that hydrolytic cleavage occurs via hydroxy ion attack on the β-carbon atom of the 2-nitroethenediamine moiety.

The equilibrium Eq. (6) represents the addition of a hydroxyl ion that can occur at pH > 12:

$$B + OH^- \leftrightarrows BOH^- \quad (6)$$

$$K_{OH^-} = \frac{[BOH^-]}{[B][OH^-]} \quad (7)$$



Scheme 2.

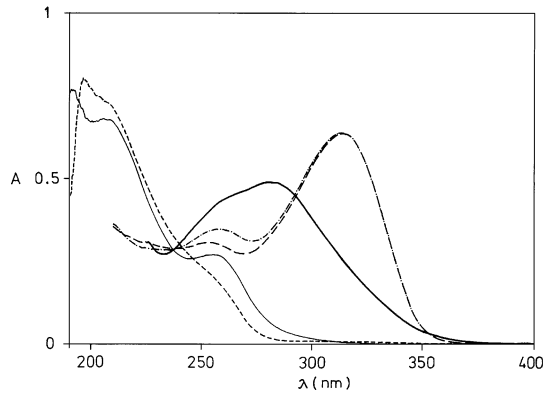


Fig. 6. Absorption spectra of nizatidine, I, (4×10^{-5} M) species: BH_3^{3+} (——) (H_0 −3.0); BH_2^{2+} (- - - -) (pH 0.0); BH^+ (- • - • -) (pH 5.3); B (– – – –) (pH 10.4); and BOH^- (——) (J_ 15.2).

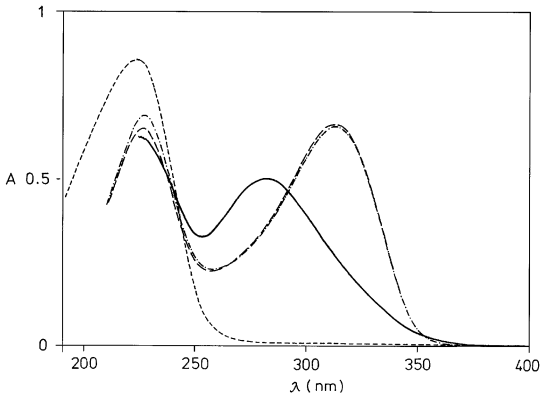


Fig. 7. Absorption spectra of ranitidine, II, (4×10^{-5} M) species: BH_2^{2+} (- - - -) (pH 0.0); BH^+ (- • - • -) (pH 5.3); B (– – – –) (pH 10.4); and BOH^- (——) (J_ 15.2).

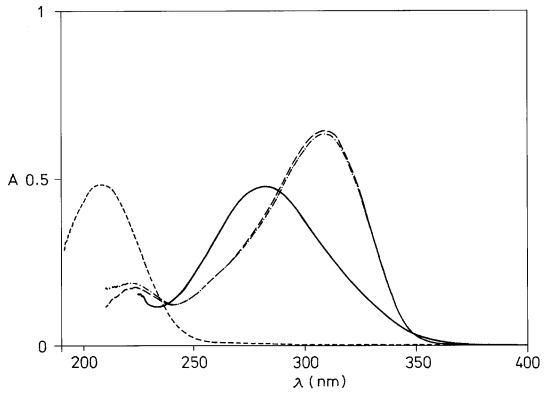


Fig. 8. Absorption spectra of III (4×10^{-5} M) species: BH^+ (- - - -) (pH 0.0); B (- • - • -) (pH 5.3), (– – – –) (pH 10.4); and BOH^- (——) (J_- 15.2).

The symbol B represents a very weakly acidic molecule having no net charge.

For addition of hydroxyl ions (Eq. (6)) the acidity function J_- has been defined [13,14] as:

$$J_- = pK_a + \log\frac{[BOH^-]}{[B]} \quad (8)$$

where $pK_a = pK_{OH^-} + pK_w$; pK_w denotes a negative logarithm of the dissociation constant of water. To calculate values of pK_a by means of equilibrium 8, the value of $\log I$ was determined from spectrophotometric measurements at varying sodium hydroxide concentrations.

The p*K* values for the two drugs, nizatidine and ranitidine, and for the model substance III are summarized in Table 3. The differences found between the successive pK_n values are large enough to justify the assumption in the treating of experimental data that protonation steps take place one at a time.

Scheme 2 shows three steps of protonation equilibria and the process of the addition of a hydroxyl ion on nizatidine.

The structures *d* and *c* in Scheme 2 are easily characterized by UV absorption maximum at ~ 310 nm that is found in uncharged forms of II and III too. The transition $c \rightarrow b$ is characterized by the disappearance of this absorption maximum at approximately 310 nm, implying a major structural change. Some authors [19,20] have proposed a proton exchange resembling the transition III → IIIi. The computed properties of various molecular species, given in Table 1, are clearly against such proton exchange. In common terms, the C–H dissociation in highly acidic medium is not probable. It is well known fact that anionic species have much higher reduction potential than corresponding cation and experimental facts show clear decrease of reduction potential at lower pH. All the effects described in the literature [19,20] are easy to explain by involvement of intermediate IIIc. This is also consistent with the finding that nitrosation of a nitroethenediamine moiety occurs preferentially at a carbon atom [21].

The prototropic exchange $b \rightarrow a$ may involve protonation on several places: oxygen in a nitro group, amine nitrogen in ethenediamine moiety, and nitrogen in a thiazole ring. The lack of analogous protonation in ranitidine suggests that this metathesis is related to the presence of a thiazole ring.

Once the p*K* value is determined, the H_0, pH, or J_- of the medium could be chosen to obtain the maximal concentration of the corresponding molecular species. For nizatidine, ranitidine and compound III, spectra of pure molecular species taken at appropriate acidity values are given in Figs. 6–8.

The knowledge of correct p*K* values of pharmaceuticals has a profound pharmacological relevance, enabling the preparation of most stable and most efficient formulations. The results presented in this work show that spectrophotometric titration coupled with MO calculations offer accurate method for the identification of ionic species derived from complex organic molecules.

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