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Acido-Basic Properties of Proton Pump Inhibitors in Aqueous Solutions

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The pharmacological characteristics of proton pump inhibitors are related to their protolytic behavior estimated by their pK_a values. Lansoprazole is a potent anti-acid drug from this group. Because of its poor stability a rapid spectrophotometric method was developed for the determination of its pK_a values. Three pK_a values were obtained: an acidic pK_{a1} = 8.84 and two basic, pK_{a2} = 4.15 and pK_{a3} = 1.33. These pK_a values were discussed from the point of lansoprazole structure and instability with the aim of locating basic and acidic moieties in the molecule of proton pump inhibitors. They were also compared with experimentally determined pK_a values from the literature and with some pK_a values calculated by different programs.

Keywords proton pump inhibitors; lansoprazole; ionization constants; spectrophotometric method; pK_a values

INTRODUCTION

Proton pump inhibitors are very effective compounds acting at the final enzymatic step of the acid secretory pathway of the parietal cells. The main obstacle of these compounds is their instability, especially in the presence of acids, either in solutions or in dosage form. Their activity is initiated by a series of ionic reactions that lead to the reduction of protonic activity in the parietal cells. Therefore, it is very important to know the acido-basic properties of these compounds in the aqueous environment, as reflected through their pK_a values.

There are various reports in the literature about their acido-basic properties and ionization constants (pK_a values). For omeprazole, different data about its ionization characteristics were published. It was reported that there were two pK_a values determined spectrophotometrically in the neutral to alkaline medium (Yang, Schulman, & Zavala, 2003): 7.1, which corresponds to the dissociation from the protonated pyridine nitrogen of omeprazole, and 14.7, which belongs to the proton dissociation from the nitrogen atom at the 1-position of the benzimidazole ring. At pH < 5 omeprazole decomposes after protonation, these authors determined another pK_a = 3.8, which arises from the protonation at the 3-position of the benzimidazole nitrogen atom. These conclusions differ from the reports of an earlier work, three pK_a values were suggested pK_{a1} of –0.21 assigned to the dissociation of the dication from the protonated nitrogen atom at the 3-position of the benzimidazole ring, pK_{a2} = 3.98 assigned to the monocation dissociating from the protonated nitrogen atom of the pyridine ring, and pK_{a3} of 8.70, which corresponds to the dissociation of the neutral molecule from the nitrogen atom at the 1-position of the benzimidazole ring (Brändström, Bergman, & Grundevik, 1989).

The basic pK_a values for four different proton pump inhibitors: lansoprazole, omeprazole, pantoprazole, and rabeprazole (pK_a values: 4.01, 3.97, 3.96, and 4.9, respectively) were reported also by Hellström and Vitols (2004). It was established that all these compounds have similar potency and efficacy; there is only slightly more rapid onset of acid inhibition for rabeprazole compared with the others (which might be the consequence of the highest basic pK_a value), while the clinical advantage of this seems limited (Hellström & Vitols, 2004).

Latter, another investigation on acido-basic properties of proton pump inhibitors was published (Shin, Cho, & Sachs, 2004). The authors reported pK_a values for omeprazole, lansoprazole, pantoprazole, rabeprazole, and tenatoprazole. All the basic pK_{a1} values, responsible for the pyridine protonation, are in the range from 3.83 for pantoprazole to 4.06 for omeprazole with an outlayer rabeprazole, pK_{a1} = 4.53; similar to the reported values of Hellström and Vitols (2004), while the other set of the basic pK_{a2} values, second protonation of N-3 in benzimidazole moiety, vary in the range from 0.62 for rabeprazole to 0.79 for omeprazole with pantoprazole pK_{a2} = 0.11 and tenatoprazole pK_{a2} = –0.12 deviating from that range.

EXPERIMENTAL

In our previous work (Kristl & Vrečer, 2000), we spectrophotometrically (Lambda 15, Perkin Elmer, USA) determined pK_a values of lansoprazole (Figure 1), structurally

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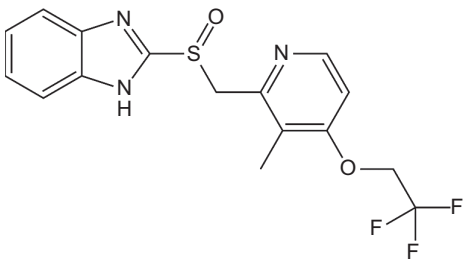

FIGURE 1. Structural formulae of lansoprazole.

very similar to omeprazole. Because of lansoprazole instability, its stock solution was prepared in methanol and then diluted with appropriate buffer (1:50, vol/vol, phosphate, citrate, or borate buffer) to obtain the final lansoprazole concentrations about 3×10^{-5}M. All the buffer solutions used had the same ionic strength (μ = 0.1 M). The absorbance measurement was performed after a short period of time, 30 s, even if 10–15% of lansoprazole decomposes at pH = 1.

First, we examined the absorbances of lansoprazole aqueous solutions in the whole pH range 1.0–14.0 (at λ = 245 nm) with the aim to estimate all the possible lansoprazole pK_a values in water (Figure 2). It is evident from Figure 2 that the curve has three different slopes in the pH ranges from 0.5 to 2.0, from 3.0 to 4.0, and from 8.0 to 10.0. Consequently, lansoprazole possesses three different ionization constants.

For more precise determination of pK_a values different wavelengths were used—for acidic pK_{a1} (pH range 8.0–10.0), λ_1 = 261 nm and λ_1' = 300 nm; for basic pK_{a2} (pH range 3.0–4.0), λ_2= 245 nm and λ_2' = 310 nm, and for basic pK_{a3} (pH range 0.5–2.0), λ_3 = 245 nm and λ_3' = 270 nm. For better statistics, the pK_a values were not determined only at one specific wavelength (i.e., λ = 261) but at different values changing only 0.5 nm (i.e., λ = 260.5 nm; 261.5 nm).

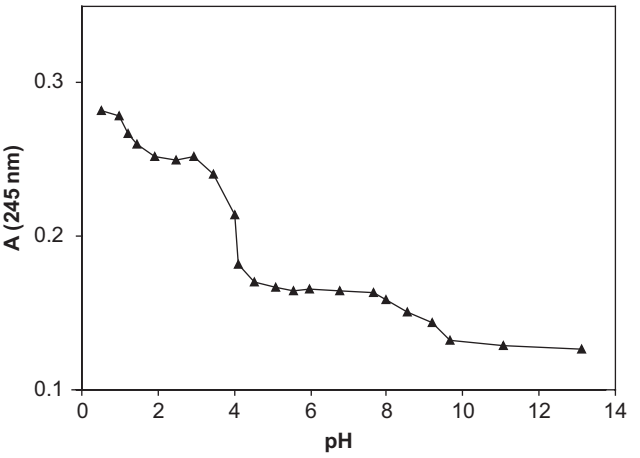

FIGURE 2. Absorbances of lansoprazole in buffer solutions at various pH, in 0.5 M HCl and in 0.5 M NaOH at λ = 245 nm.

For the calculation of pK_a, the equations 1 (for acidic pK_{a1}) and 2 (for basic pK_{a2} and pK_{a3}) were used:

$$pK_a = pH + \log (A_i - A)/(A - A_n) \quad (1)$$

$$pK_a = pH + \log (A - A_n)/(A_i - A) \quad (2)$$

where A_i is the absorbance of the ionized form, A_n is the absorbance of the nonionized form, and A is the absorbance measured at various pH values.

RESULTS AND DISCUSSION

All the measured absorbances and calculated pK_{a1}, pK_{a2}, and pK_{a3} values of lansoprazole are given in Tables 1–3, respectively. The mean calculated values including standard deviations are the following: acidic pK_{a1} = 8.84 ± 0.04 and

TABLE 1
Absorbances of Lansoprazole Solutions in Buffers Ranging from pH 7 to 13 (0.1 M NaOH) at Different Wavelengths with Calculated Values of pKa_1

pH	$A_{260.5}$	pK_{a1}	$A_{261.0}$	pK_{a1}	$A_{261.5}$	pK_{a1}	$A_{299.5}$	pK_{a1}	$A_{300.0}$	pK_{a1}	$A_{300.5}$	pK_{a1}
7.0	0.228		0.231		0.234		0.136		0.126		0.117	
8.19	0.214	8.81	0.217	8.81	0.220	8.81	0.183	8.81	0.173	8.81	0.164	8.80
8.44	0.205	8.78	0.208	8.78	0.211	8.78	0.207	8.82	0.197	8.82	0.187	8.83
8.65	0.199	8.83	0.203	8.86	0.206	8.86	0.232	8.83	0.221	8.84	0.213	8.83
8.86	0.192	8.87	0.195	8.87	0.199	8.90	0.260	8.84	0.250	8.84	0.240	8.84
9.08	0.180	8.80	0.183	8.80	0.187	8.82	0.287	8.86	0.277	8.86	0.267	8.86
9.25	0.177	8.88	0.180	8.88	0.183	8.88	0.308	8.86	0.299	8.85	0.288	8.86
9.39	0.174	8.94	0.177	8.94	0.179	8.90	0.322	8.87	0.312	8.87	0.302	8.86
13	0.155		0.158		0.161		0.378		0.368		0.357	

pK_{a1} (average) = 8.84 ± 0.04.

TABLE 2
Absorbances of Lansoprazole Solutions in Buffers Ranging from pH 2.40 to 6.0 at Different Wavelengths with Calculated Values of pK_{a2}

pH	$A_{244.5}$	pK_{a2}	$A_{245.0}$	pK_{a2}	$A_{245.5}$	pK_{a2}	$A_{309.5}$	pK_{a2}	$A_{310.0}$	pK_{a2}	$A_{310.5}$	pK_{a2}
2.40	0.237		0.236		0.234		0.105		0.103		0.100	
3.35	0.224	4.11	0.224	4.13	0.221	4.08	0.094	4.21	0.092	4.20	0.089	4.20
3.57	0.217	4.10	0.217	4.11	0.214	4.07	0.085	4.11	0.082	4.08	0.079	4.07
3.79	0.209	4.11	0.210	4.15	0.207	4.11	0.076	4.11	0.073	4.08	0.071	4.10
3.98	0.203	4.17	0.203	4.18	0.203	4.20	0.073	4.24	0.071	4.23	0.068	4.22
4.17	0.197	4.24	0.197	4.24	0.196	4.24	0.058	4.13	0.056	4.12	0.053	4.11
4.40	0.182	4.16	0.183	4.18	0.185	4.24	0.047	4.14	0.045	4.13	0.044	4.16
4.63	0.172	4.16	0.173	4.17	0.173	4.19	0.036	4.11	0.033	4.06	0.032	4.10
6.0	0.150		0.151		0.151		0.015		0.014		0.012	

pK_{a2} (average) = 4.15 ± 0.06.

TABLE 3
Absorbances of Lansoprazole Solutions in Buffers Ranging from pH 0.50 to 2.40 at Different Wavelengths with Calculated Values of pK_{a3}

pH	$A_{269.0}$	pK_{a3}	$A_{270.0}$	pK_{a3}	$A_{271.0}$	pK_{a3}	pH	$A_{245.0}$	pK_{a3}
0.5–1.0	0.268		0.286		0.269		0.5–1.0	0.281	
1.16	0.275	1.27	0.274	1.42	0.277	1.30	1.17	0.270	1.47
1.27	0.276	1.27	0.275	1.42	0.278	1.32	1.45	0.261	1.26
1.43	0.277	1.32	0.276	1.48	0.280	1.29	1.97	0.254	1.32
1.61	0.279	1.27	0.279	1.35	0.283	1.16	2.40	0.248	
2.40	0.284		0.285		0.288				

pK_{a3} (average) = 1.33 ± 0.09.

TABLE 4
pK_a Values of Proton Pump Inhibitors Obtained by Different Researchers. The Predicted Position of the Ionization in the Molecule is Given too

Reference	pK_{a1}	pK_{a2}	pK_{a3}
Brändström et al. (1989)	8.70 (acid) benzimidazole (N_1)	3.98 (base) pyridine	–0.21 (base) benzimidazole (N_3)
Yang et al. (2003)	14.70 (acid) benzimidazole (N_1)	7.10 (base) pyridine	3.80 (base) benzimidazole (N_3)
Shin et al. (2004)		3.83–4.06 (base) pyridine	0.62–0.79 (base) benzimidazole (N_3)
Kristl and Vrečer (2000)	8.84 (acid) benzimidazole (N_1)	4.15 (base) pyridine	1.33 (base) benzimidazole(N_3)

basic pK_{a2} = 4.15 ± 0.06, and pK_{a3} = 1.33 ± 0.09. From the point of lansoprazole instability, despite very fast and careful determinations, only acidic pK_{a1} and basic pK_{a2} were determined exactly, whereas the basic pKa3 can be considered more as an estimate.

If one takes a careful look at the experimentally determined values for pK_a of proton pump inhibitors by different researchers (Table 4) one can see that they are in accordance to some extent, although Shin et al. (2004) determined only two pK_a values and the values determined by Yang et al. (2003) do not fit into this scheme. However, it might be thus questionable which are the correct pK_a values and whether they are ascribed to the proper part of the proton pump molecule.

TABLE 5
Calculated Values of pK_a for Lansoprazole by Different Computer Programs With the Appropriate Acidic or Basic Properties and the Part of the Molecule to Which they Belong

	pK_{a1}	pK_{a2}	pK_{a3}
Marvin	9.30 (acid) benzimidazole (N_1)	6.77 (base) pyridine	3.62 (base) benzimidazole (N_3)
Pallas	12.71 (acid) benzimidazole	5.08 (base) pyridine	2.81 (base) benzimidazole
VCCLAB	8.91 (acid)	3.64 (base)	

With the aim to get some more information about pK_a values of proton pump inhibitors, we determined pK_a values of lansoprazole also by the computational approach using three different methods (Marvin, Pallas, VCCLAB). These calculated values (Table 5) differ although one acidic and at least one basic pK_a were calculated by all programs. Two out of three applied programs predicted also the third basic pK_a value.

Lansoprazole is (like the other proton pump inhibitors) derivative of 2-[[(2-pyridyl) methyl] sulfinyl] benzimidazole. Regarding this structure, the molecule of proton pump inhibitors can possess three dissociation constants in the pH range 1–14, two basic and one acidic. The pK_a of pyridine base is 5.2, whereas the pK_a values of benzimidazole are 5.5 as a base and 12.3 as an acid (Albert, Goldrace, & Philips, 1948). One can thus expect that the pK_a values of proton pump inhibitors should be in the range of those pK_a values for pyridine and benzimidazole and should not differ from them although the introduction of different substituents into the molecule can significantly influence acido-basic properties of the pyridine and benzimidazole moiety. On the basis of these observations, one can clearly see that some experimentally determined values for proton pump inhibitors from the literature must have been wrongly determined. The introduction of 2,2,2-trifluoroethoxy group in the case of lansoprazole and specially of sulfinyl group increases the acidic properties lowers the pK_a values of pyridine and benzimidazole significantly.

Our experimentally determined values are thus in the best accordance with those determined by Brändström et al. (1989) for omeprazole; only the second basic pK_a (–0.21) is significantly lower than ours (pK_{a3} = 1.33), which is questionable because of instability of these compounds in acidic solutions.

CONCLUSION

One can conclude that lansoprazole has three ionization constants; the acidic one pK_{a1} = 8.84 corresponds to the proton dissociation in benzimidazole ring (N_1), the basic pK_{a2} = 4.15 belongs to the pyridine moiety, and the basic pK_{a3} with the estimated value 1.33 could be ascribed to the basic characteristics of benzimidazole ring (N_3).

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