PHYSICAL CHEMISTRY 2014

12th International Conference
on Fundamental and Applied Aspects of
Physical Chemistry

The Conference is dedicated to the
25. Anniversary of the Society of Physical Chemists of Serbia

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THE EFFECTS OF ANOINIC AND CATIONIC SURFACTANTS ON ACID-BASE EQUILIBRIA OF IRBESARTAN

M. Popović [1], M. Grujić[1], G. Popović [2] and D. Agbaba [1]

[1]*Department of Pharmaceutical Chemistry Faculty of Pharmacy,*
[2]*Department of General and Inorganic Chemistry,*
University of Belgrade, Vojvode Stepe 450, 11000 Belgrade, Serbia
(marija.popovic@pharmacy.bg.ac.rs)

ABSTRACT

In this study pK_a values of irbesartan, an angiotensin receptor blocker, were determined by potentiometry and the effects of sodium dodecyl sulfate (SDS) and cetyl trimethyl ammonium bromide (CTAB) on its protolytic equilibria have been investigated. It was observed that shift in pK_a values is a result of complex electrostatic and hydrophobic interactions with the micelar solutions. Based on the obtained results drug interactions with biomolecules can be evaluated.

INTRODUCTION

Irbesartan (IRB), 2-butyl-3-[[2'-(tetrazol-5-yl)biphenyl-4-yl]-methyl]-1,3-diazaspiro[4,4]non-1-en-4-one (Figure 1), is a potent and selective antagonist of angiotensin II at AT_1 receptor. IRB is indicated for use in therapy of hypertension and also for the treatment of renal disease in patients with type 2 diabetes mellitus and nephropathy [1]. Drugs in the sartan class specifically interact with the receptor, in the two-step process which involves incorporating into the membrane and diffusion to the receptor [2]. It is assumed that biological membranes play an important role in the stabilization of the IRB active form.

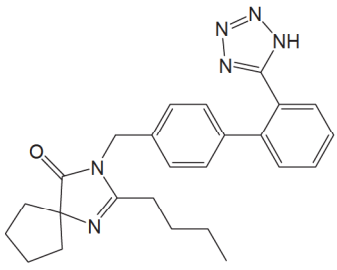

Figure 1. Chemical structure of irbesartan

Chemical structure of IRB contains three ionizable centers, one acidic center (N1 of tetrazole – pK_{a2}) and two basic centers (imidazole – pK_{a3} and N4 of tetrazole – pK_{a1}). Tetrazol ring is a part of the molecule which is required for the pharmacological action because it is analogous to the terminal end of angiotensin II. The overall charge of the drugs under the physiological conditions depends on their pK_a values and

thereby the bioavailability of the active form which is required for the receptor binding [3]. However, expected ionization extent of the drug can be distinguish in terms of *in vivo* environment as a result of interactions with a variety of biomolecules that may be present on the membrane surface and in body fluids. Since biological membranes are extremely complex structures, much less complex surfactant micelles have been used as a model systems [4].

The main aim of this study was to determine the pK_a values of IRB in the presence of micellar solution of anionic surfactant SDS and cationic surfactant CTAB and compared with the values defined for aqueous solution in order to estimate their effect of the acid-base equilibria of IRB.

EXPERIMENTAL

The pK_a values of IRB in the absence and in the presence of the 10^{-2} M surfactant (SDS and CTAB) were determined by potentiometry. A titration system 798 MPT Titrino with a combined electrode (LL unitrode Pt1000, Metrohm) was used for performing potentiometric titrations. All measurements were carried out at 25 ^{o}C and constant ionic strength was adjusted to 0.1 M with NaCl. According to poor water solubility of IRB apparent dissociation constants pK_a^* were obtained in different methanol–water mixtures 40 %, 45 %, 50 %, and 55 %, (w/w). To 40 mL (5×10^{-4} - 10^{-3} M) solutions of IRB in the absence (methanol–water mixtures) and in the presence of surfactants, 1.0 mL of HCl solution (0.10414 M) was added and titrated with standard NaOH solution (0.099564 M). Based on data obtained by potentiometric titrations pK_a values were calculated using a computer program Hyperquad, which enables determination of equilibrium constants in complex systems containing overlapped acid–base equilibria.

RESULTS AND DISCUSSION

Because of a slight IRB solubility, its apparent pK_a values (pK_a*) in the absence of surfactants were determined in different methanol–water mixtures 40 % to 55 % (w/w). For this purpose, methanol is the solvent of choice because its solvation effect is close to that of pure water [5]. Aqueous pK_a values were calculated by extrapolation of the pK_a* values to zero cosolvent. (Table 1, Figure 2). Precipitation of the drug did not occur in the presence of micelles formation, because the solubilizing effect of the surfactants acted to increase the IRB solubility.

IRB pK_a values are shifted in the presence of micelles which points out that surfactants affect its acid-base equilibrium. Comparison of the results obtained in the presence and in the absence of surfactants (Table 2) indicates

that the most sensitive to the presence of SDS is acid group of tetrazole ($\Delta pK_{a2} = +1.82$), while CTAB the most prominent affects the ionization of base center in tetrazole ($\Delta pK_{a1} = +1.22$).

Table 1. pK_a* values of irbesartan determined in different methanol–water mixtures

% Methanol	pK_{a1}	pK_{a2}	pK_{a3}
40	1.91	3.65	4.88
45	2.64	3.65	-
50	2.47	3.59	4.93
55	2.26	3.61	5.02

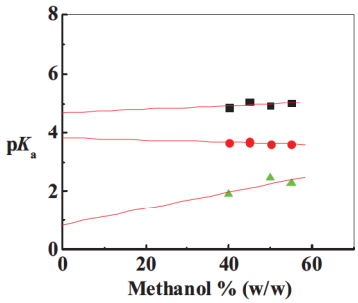

Figure 2. Plots of methanol % (w/w) *vs* pK_a*

Table 2. pK_a values of irbesartan with and without of surfactants

	H_2O	CTAB	ΔpK_a	SDS	ΔpK_a
pK_{a1}	0.86	2.08	+1.22	-	-
pK_{a2}	3.81	2.60	-1.21	5.63	+1.82
pK_{a3}	4.69	3.55	-1.14	6.23	+1.54

Observed changes in pK_a values can be considered in terms of competing different hydrophobic and electrostatic interactions on the surface of the micelles [6]. Due to repulsion of the same charge, negatively charged surface of SDS micelles can stabilize the nonionized form of the acid center shifting the equilibria by decreasing the acidity. At the same time SDS can stabilize the protonated form of the base group causing an increase in pK_a value and basicity ($\Delta pK_{a3} = +1.54$).

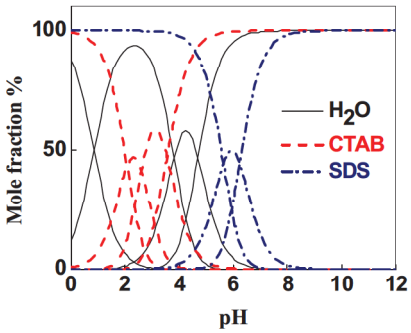

Figure 3. Ionization profiles of irbesartan in water, SDS and CTAB

The opposite effect is expected in the case of CTAB micelles whose surface is positively charged. Consequently, the greater stability of the ionized form of the acid group causes an increase in acidity ($\Delta pK_{a2} = -1.21$), while the greater repulsion of the protonated basic center reduces the basicity (ΔpK_{a3}

= -1.14). However, a significant shift of the pK_{a1} value in the presence of CTAB, which is contrary to the expectations, may indicate that the hydrophobic interactions are predominant, with possible insertions into the micelle.

CONCLUSION

Based on obtained results and the shift in pK_a values it can be concluded that the ionisable centers of IRB participate in complex electrostatic and hydrophobic interactions with the SDS and CTAB micelles. The shift in pK_{a2} and pK_{a3} values probably is a consequence of the dominant electrostatic interactions, whereas the predominant hydrophobic interactions with micelles are responsible for a shift in pK_{a3} value. The results obtained in this study can be used for more detailed investigation of the drug behavior in interaction with the membrane and the receptor, particularly if one takes into account that the presence of surfactants affects the ionization of the groups which are required for activity.

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