

## The Influence Of Nonionic Surfactants And B-Cyclodextrin On The State Of 5-Phenylthio-8-Mercaptoquinoline In Aqueous Media

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**Abstract-** Using spectrophotometry method the condition of 5-phenylthio-8-mercaptoquinoline within a wide pH range (pH 0-10) was studied in water, the aqueous solutions of a nonionic surfactant Brij35 and  $\beta$ -cyclodextrin ( $\beta$ CD). It was found that in water within the range of pH = 2-6 5-phenylthio-8-mercaptoquinoline is poorly soluble after the self-association of zwitterionic (HR  $\pm$ ) reagent forms. In other areas of pH the aqueous solutions of the reagent are transparent due to the transition of zwitterions in protonated (H<sub>2</sub>R<sup>+</sup>) or anionic (R<sup>-</sup>) form. The spectral parameters of mercaptoquinoline in surfactant solutions or cyclodextrin were similar to the observed ones in aqueous, strongly acidic and alkaline environments. However, in neutral and slightly acidic pH areas the spectra of the reagent differed greatly in the presence of  $\beta$ CD and Brij35. The latter allowed to suggest that due to the different polarity of the mercaptoquinoline microenvironment in surfactant solutions and  $\beta$ CD various tautomeric forms of the reagent are stabilized. The molecular form (HR) is realized in the micellar environment, and the presence of cyclodextrin stabilizes the zwitterionic form ( $\pm$  HR), which proves the presence of a chromophore node in an aqueous medium. By varying the ratio of Brij35 and  $\beta$ CD in the neutral pH range, it is possible to observe the corresponding tautomeric transition.

The comparison of 5-phenylthio-8-mercaptoquinoline absorption spectra results in various environments allowed to identify the spectral parameters and pH range of different reagent forms. The mathematical processing of optical density absorbance dependencies on pH showed that Brij35 supplements, unlike  $\beta$ CD ones, change the acid-base properties of a reagent by micelle solubilization. The influence of cyclodextrin is explained by the formation of "guest-host" complex with the phenyl substitute of 5-phenylthio-8-mercaptoquinoline. As micelle forming surfactants so as cyclodextrins may be used to increase the solubility of 8-mercaptoquinoline aromatic derivatives in water.

**Keywords:** 5-phenylthio-8-mercaptoquinoline, nonionic surfactant,  $\beta$ -cyclodextrin, solubilization.

### 1. INTRODUCTION

8 mercaptoquinolines are the known highly selective analytical reagents for the quantitative detection of transition metal ions. The presence of several absorption bands changing their position depending on different degrees of reagent protonation allows you to explore these systems spectrophotometrically. Mercaptoquinoline derivatives and their metal complexes are hardly soluble in water, which necessitate to use toxic organic solvents for their study [1]. However, the solubility in water may be also improved through the use of supramolecular systems: surfactant micelles, and host-guest complexes. There is no data for the study of mercaptoquinoline derivative state in aqueous solutions of micelle-forming surfactants and the macrocycles in the literature. It is known that certain derivatives of 8-mercaptoquinoline and their complexes have an antibacterial activity [2]. From this viewpoint, the identification of 8-mercaptoquinoline derivative solubility increase possibility by diphilic surfactant molecules and cyclodextrins is interesting for enhancement of such drugs bioavailability.

It is known that mercaptoquinolines exist as a mixture of molecular (thiol) (HR) and zwitterionic (HR  $\pm$ ) forms weakly acidic and neutral areas [1]. The concentration ratio of zwitterionic and thiol forms is continuous, does not depend on pH medium and is determined mainly by the solvent polarity. The zwitterionic forms are capable of self-assembly caused by electrostatic and  $\pi$ -stacking interactions between the aromatic reagent fragments. Such interactions, clearly pronounced in polar solvents (water), disappear at the transition to a less polar environment - organic solvents with low dielectric permeability, or ultra micro heterogeneous media. For example, the complex formation with cyclodextrin leads to the destruction of such aggregates as surfactant micelles [3] or ionic associates with the participation of diphilic compounds [4]. We also know that mononuclear aromatic reagents

form relatively strong inclusion complexes with  $\beta$ -cyclodextrin ( $\lg K = 2-3$  [5]).

Cyclodextrins (CD) are cyclic glucose oligomers with a hydrophilic surface and a hydrophobic cavity. Such compounds are also able to change the properties and the spectral parameters of many analytical reagents, forming with them such compounds as guest-host. According to [6], the van-der-Waals and hydrophobic interactions are the main driving forces of cyclodextrin complex formation, while electrostatic interactions and hydrogen bonding may have a significant effect on the conformation of inclusion complexes.

The aqueous solutions of surfactants are also a unique environment, combining the areas of different polarity. At a certain surfactant concentration, called the critical concentration of micelle development (CCM) the diluted aqueous solutions develop micelles [7]. In surfactant solutions low polar substrates may transfer from an aqueous phase into different areas of micelles: a non-polar nucleus, polar head groups or boundary layers.

Thus, surfactant additives and cyclodextrins may increase the water-solubility of analytical reagents by multiple non-covalent interactions.

## 2. MATERIALS AND METHODS

As the main object of the study 5-phenylthio-8-mercaptoquinoline (HR) was chosen. It was synthesized at the Institute of Inorganic Chemistry of the Republic of Latvia. The selection of reagent was conditioned primarily by its higher affinity to an organic phase ( $\text{CHCl}_3$  for  $KD = 390000$ , [1]) as compared to, for example, with 5-methylthio-8-mercaptoquinoline ( $KD = 8300$ ). In all experiments, the concentration of 5-phenylthio-8-mercaptoquinoline was equal to 0.06 mM.

The paper also used the hydrate of  $\beta$ -cyclodextrin ( $\beta\text{CD}$ , "Acros Organics"), containing 10 water molecules according to the thermogravimetric analysis data. Ethoxylated dodecanol (23 EO groups)

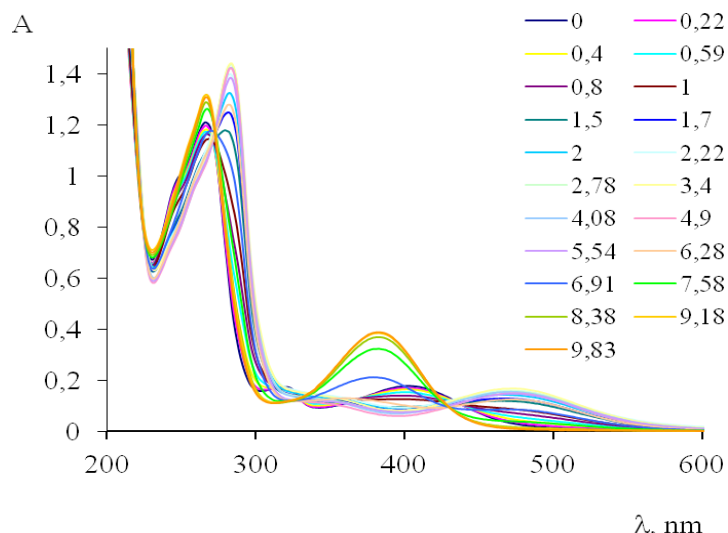
Brij35 ("ICN Biomedicals") was used as a nonionic surfactant, which forms micelles in aqueous solutions at the concentration of more than 0.09 mM [7].

All experiments were performed at 298 K. The solutions were prepared of more concentrated ones by dilution or rigging. The absorption spectra were recorded using the device "Lambda EZ210" (Perkin Elmer) in the wavelength range of 200-900 nm, in quartz cuvettes with the thickness of 1 cm compared with water.

The values of equilibrium constants were obtained by the development of the studied system mathematical models, including equilibria schemes (with stoichiometric coefficients at reagents), the values of complex formation equilibrium constants and the extinction coefficients  $\epsilon$ . The optimization of number parameters was carried out by the computer program CPESP [8] with the assessment of reliability according to the Fisher criterion.

## 3. RESULTS AND THEIR DISCUSSION

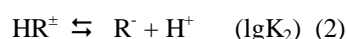
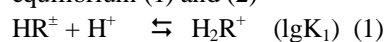
During the study of the acid-base properties of 5-phenylthio-8-mercaptoquinoline in water within the range of pH 2-6 a strong opalescence and precipitation were revealed and absorption spectra may be obtained for the solutions beyond the specified pH range. However, the presence of  $\beta\text{CD}$  caused the disappearance of light scattering effect in the slightly acidic and neutral pH ranges. The performance of experiments involving  $\beta\text{CD}$  showed that the absorption maxima of the reagent in a strongly acidic ( $\lambda_{\text{max}}$  at 475 nm and 280 nm) and a strongly alkaline media ( $\lambda_{\text{max}}$  at 415 nm and 270 nm) are identical to those that were observed in aqueous medium. The absorption spectra of the prepared solutions at different pH values are shown on Fig. 1.



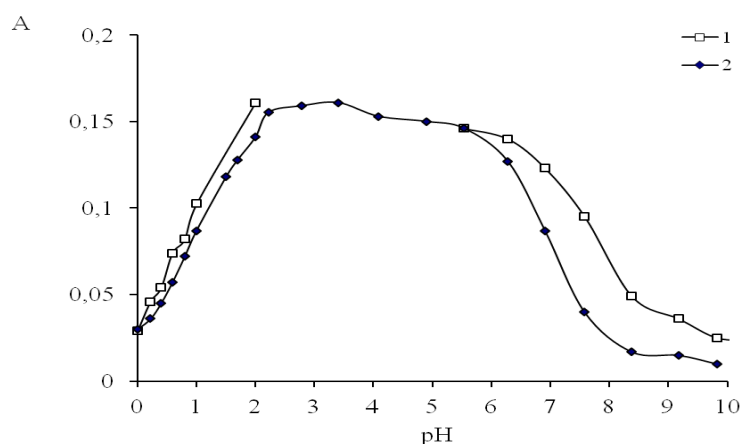
**Fig. (1).** – The absorption spectra of 5-phenylthio-8-mercaptoquinoline in aqueous solution of  $\beta$ CD ( $C_{HR}$  0,06 mM,  $C_{\beta CD}$  2 mM, pH 0-9,83)

The increase of 5-phenylthio-8-mercaptoquinoline solubility in the presence of cyclodextrin may be explained by the formation of such complexes as "host-guest" between  $\beta$ CD and the phenyl group of the reagent. The entry of the reagent quinoline nucleus is not possible due to steric hindrance of  $\beta$ CD cavity to a given substrate. Furthermore, the identity of the absorption spectra for less hydrophobic 5-methylthio-8-mercaptoquinoline from pH media in water and in solutions with  $\beta$ -cyclodextrin additives confirmed the absence of quinoline nucleus interaction with the macrocycle. Thus the lack of light scattering in aqueous solutions of mercaptoquinoline with  $\beta$ CD is explained by the violation of  $\pi$ -stacking interactions and multiple electrostatic interactions between zwitterionic forms of a reagent in its microcrystals.

The mathematical processing of optical density dependencies on pH (Fig. 2) in accordance with the equilibrium (1) and (2)



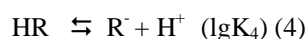
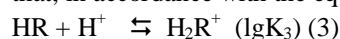
showed that the inclusion of the phenyl reagent substituent in the cavity of a cyclodextrin almost does not influence on the zwitterionic protonation in an acidic medium and even makes the deprotonation in alkaline pH region easier. So, for aquatic media the constants of equilibrium are equal to  $\lg K_1 = 1,0 \pm 0,3$  and  $\lg K_2 = -7,5 \pm 0,3$ , while in the presence of  $\beta$ CD they made  $\lg K_1 = 1,1 \pm 0,1$  and  $\lg K_2 = -6,9 \pm 0,1$ .



**Fig. (2).** – The optical density dependence on pH of 5-phenylthio-8-mercaptoquinoline aqueous solutions in water (curve 1) and a  $\beta$ CD (curve 2) at 475 nm ( $C_{HR}$  0.06 mM, 2 mM  $C_{\beta CD}$ )

It is interesting to note, that in micellar surfactant solutions, unlike  $\beta$ CD, non zwitterionic ( $\lambda_{\max}$  286 and 477 nm), but the molecular form of the reagent was revealed ( $\lambda_{\max}$  257 and 355 nm), which exists in the media with low dielectric permeability [1]. Thus, in the case of  $\beta$ CD the chromophoric part of the reagent molecule is outside the macrocycle cavity, i.e. in a more polar environment, than in the core of a surfactant micelle.

The spectrophotometric measurements showed that, in aqueous solution Brij35 the molecular form is stabilized in a wide pH range (pH = 1-8) and only in the strongly alkaline and strongly acidic medium the reagent ionization is observed. Calculations showed that, in accordance with the equations:



the values of equilibrium constants make  $\text{lg}K_3 = -0,1 \pm 0,1$  и  $\text{lg}K_4 = -9,1 \pm 0,1$ . Comparing the values of equilibrium constants in water and surfactant micelles, one may conclude that the additive Brij35 considerably facilitates the protonation in an acid medium and hinders the formation of a reagent anionic form in alkaline medium.

Analyzing the obtained data one may suggest that at the simultaneous finding of surfactants and cyclodextrin in a solution the co-existence of two tautomeric forms of 5-phenylthio-8-mercaptoquinoline in neutral and mildly acidic medium is possible. Indeed, by varying the ratio of Brij35 and  $\beta$ CD the changes in the spectra are observed, which correspond to the mutual transition of molecular (HR) and zwitterionic ( $\text{HR}^{\pm}$ ) form of 5-phenylthio-8-mercaptoquinoline, in accordance with the following scheme:

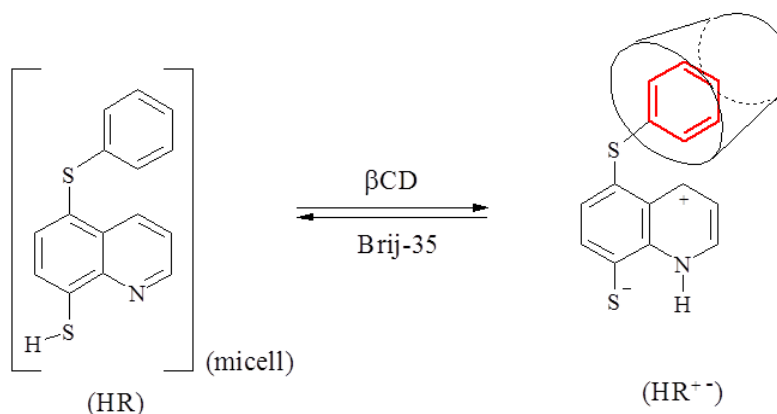


Figure 3 shows the absorption spectra of mercaptoquinoline in isomolar series containing the same concentration of surfactant and  $\beta$ -cyclodextrin in total.

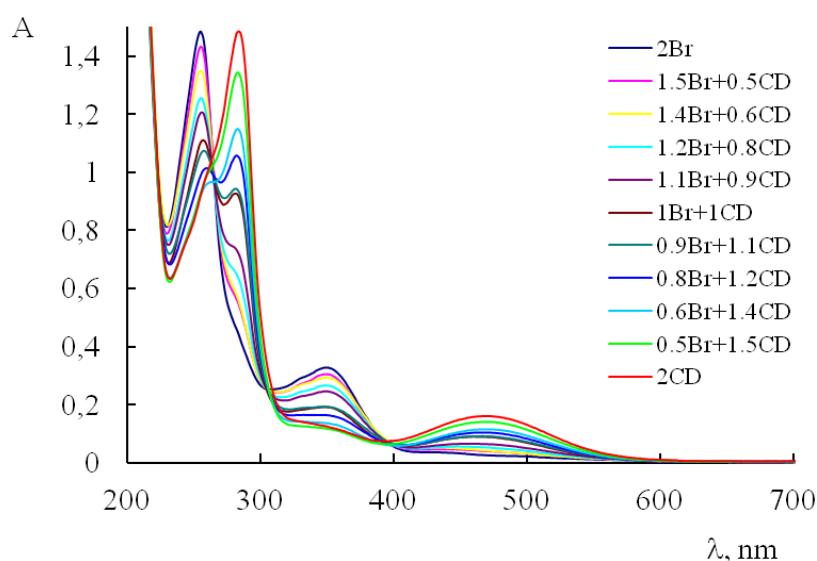


Fig. (3). – Absorption spectra of mercaptoquinoline in isomolar series containing 2 mM of Brij35 and  $\beta$ CD in total.

The lack of clear isobestic points in this series may be attributed to the presence of an additional balance between Brij35 and  $\beta$ CD interaction. The latter is caused by the fact of "guest-host" complex formation for surfactant with  $\beta$ CD known in literature [3-5], by the introduction of alkyl surfactant substituent in a hydrophobic cavity of the macrocycle.

Thus, using the surfactant and  $\beta$ CD one may influence on the acid-base equilibria and tautomeric interconversion of reagents such as amphiphilic derivatives of 8-mercaptoquinoline in aqueous solutions.

#### 4. CONCLUSION

- The micellar solutions of nonionic surfactants, as well as aqueous solutions of cyclodextrin may be used to increase the water solubility of 5-phenylthio-8-mercaptoquinoline.

- In weakly acid aqueous solution of nonionic surfactants the molecular form (HR) of the reagent is stabilized and zwitterionic form ( $\pm$  HR) is realized in water and the solutions of  $\beta$ -cyclodextrin. By varying the ratio of surfactant and cyclodextrin one may observe the corresponding tautomeric transition of a neutral pH region.

- $\beta$ -cyclodextrin develops the complex of guest-host type with the phenyl substituent of the reagent. The introduction of the phenyl group of 5-phenylthio-8-mercaptoquinoline into the cavity  $\beta$ CD was identified through the spectral data testifying to the accumulation of the reagent zwitterionic form.

- The constants of protic equilibria of 5-phenylthio-8-mercaptoquinoline are calculated in water, in the micellar solution of nonionic surfactant Brij35 and in an aqueous solution of  $\beta$ -cyclodextrin.

#### 5. SUMMARY

Micelle forming surfactants and cyclodextrins combine the regions of different polarities and are capable to increase the water solubility of 5-phenylthio-8-mercaptoquinoline by micellar solubilization or inclusion complex development. Such supramolecular systems may influence the acid-base and tautomeric equilibria of reagent in aqueous solutions. The presence of  $\beta$ -cyclodextrin in aqueous solution almost did not influence on the constants of mercaptoquinoline protonation and deprotonation. At the same time the addition of the nonionic surfactant Brij35 considerably facilitated the protonation in acidic media and hindered the formation of the reagent anionic form. At that surfactant micelles stabilized the molecular (thiol) form of the reagent and the additives of  $\beta$ -cyclodextrin stabilized the zwitterionic form of the reagent.

#### 6. ACKNOWLEDGEMENTS

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