

PHYSICAL CHEMISTRY
OF SOLUTIONS

Complexation of Silver(I) with Benzylpenicilline and Oxacilline

V. G. Alekseev and K. A. Nilova

Tver State University, ul. Zhelyabova 33, Tver, 170100 Russia

e-mail: vg_alekseev@rambler.ru

Received November 20, 2013

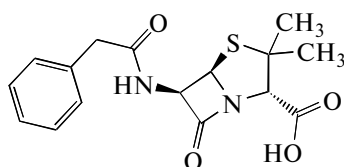
Abstract—The complexation of Ag^+ ions with anions of β -lactam antibiotics, such as benzylpenicilline (Bzp^-) and oxacilline (Oxa^-), in aqueous solution at 25°C and an ionic strength of 0.1 (KNO_3) was studied potentiometrically using a silver indicator electrode. The formation constants of the complexes AgBzp ($\log\beta = 2.21 \pm 0.01$), AgBzp_2^- ($\log\beta = 3.91 \pm 0.02$), Ag_2Oxa^+ ($\log\beta = 4.89 \pm 0.01$), AgOxa ($\log\beta = 2.88 \pm 0.01$), AgOxa_2^- ($\log\beta = 5.43 \pm 0.01$) were determined.

DOI: 10.1134/S0036023614090022

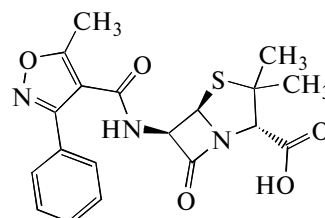
In recent years, there has been a growing interest in silver complexes with different bioactive molecules as potential broad-spectrum antimicrobials, which do not give rise to fungal diseases and microbial “tolerance” [1]. In addition to well-known lapis (AgNO_3 solution), there are produced and applied medications such as Collargolum (colloid silver), Protargolum (silver proteinate, a silver complex with proteins), Argosulfan and its analogues which represent silver derivatives of sulfatizole and sulfadiazine sulfanylamides [2]. Argacryl (a silver(I) complex with polyacrylic acid) has been patented [3, 4]. Silver complexes with amino

acids [5–7], gels based on silver complexes with cysteine [8] and oxacilline [9], and polymeric silver nanocomposites [10] have been proposed for application. The earlier performed studies show that β -lactam penicillin antibiotics can form stable complexes with metal cations [11].

The objective of this work is to determine the composition and stability of the complexes formed in aqueous solution via reaction between Ag^+ ions and benzylpenicilline (Bzp^-) and oxacilline (Oxa^-) anions.



Benzylpenicilline (HBzp)



Oxacilline (HOxa)

EXPERIMENTAL

Experiments were performed using pharmaceutical preparations of sodium salts of benzylpenicilline (NaBzp) and oxacilline (NaOxa) (OAO Sintez, Kurgan, Russia). The purity of the preparations was verified by elemental analysis on a PerkinElmer 2400 Series II CHNS analyzer (table).

Solutions containing 0.1 and 1.0 M KNO_3 and 0.1 M AgNO_3 were prepared from weighed portions of chemically pure salts. All the solutions were prepared using bidistilled water. The electromotive force and pH were measured on pH-410 ion meters with silver

and glass indicator electrodes and a silver/silver chloride reference electrode. The silver electrode was manufactured by us and represented a silver wire piece soldered into a glass tube. The surface of the electrode was cleaned with strong nitric acid before experiment.

In the course of experiment, the silver and glass electrodes were placed into a beaker with a solution to be titrated. The reference electrode was placed into another beaker with a 0.1 M KNO_3 solution. The beakers were connected to an electrolytic bridge that represented a silicone tube filled with an agar gel prepared with the use of 0.1 M KNO_3 solution. Both beakers

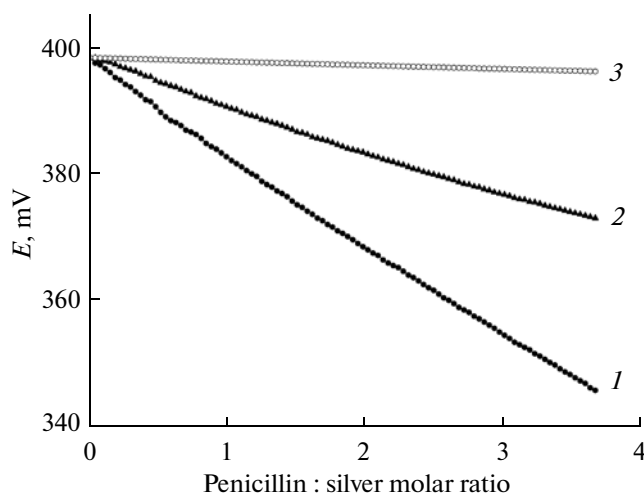


Fig. 1. Change in silver electrode potential during the titration of a 0.02913 M AgNO_3 solution with (1) a 0.0868 M NaOxa solution and (2) a 0.1114 M NaBzp solution in comparison with (3) the theoretical dependence at 25°C and $I = 0.1$ (KNO_3).

were placed in temperature-controlled cells to maintain a temperature of 25°C. The ion meter was adjusted to pH measurement with the glass electrode using $\text{Na}_2\text{B}_4\text{O}_7$ and $\text{KH}_3(\text{C}_2\text{O}_4)_2$ buffer solutions (pH 9.18 and 1.68, respectively, at 25°C). The measurement accuracy was ± 0.02 for pH and ± 2 mV for the silver electrode potential.

The performance of the silver electrode was checked using a series of AgNO_3 solutions, which had known concentrations and were prepared by consecutive dilution of a 0.1 M AgNO_3 solution. The electrode function of the silver electrode was described by the equation $E = 534.86 + 53.71 \log[\text{Ag}]$, which was obtained by the Origin software (OriginLab Corp.) [12] using standard linearization procedures. Hence, the electrode demonstrated satisfactory characteristics and was used in the work.

RESULTS AND DISCUSSION

In order to study the interaction between Ag^+ ions and Bzp^- and Oxa^- anions, the potentiometric titration of a 0.02913 M AgNO_3 solution was performed against the background of 0.1 M KNO_3 (to maintain a constant ionic strength) using a 0.1114 M NaBzp solu-

tion and a 0.0868 M NaOxa solution. The silver electrode potential and pH of the titrated solution were measured simultaneously. The obtained potentiometric curves are plotted in Fig. 1 in comparison with the theoretical curve, i.e., the potentials that were calculated from the electrode function equation of the silver electrode and were generated by the change in silver ion concentration upon dilution of the solution in the course of titration, under the assumption of the absence of interaction between silver ions and penicilline.

The introduction of penicillines into solution decreases the silver electrode potential in comparison with its theoretical value, thus indicating the bonding of silver ions into complexes. The pH remains nearly constant during titration in both cases and lies in the neutral region. Hence, the formation of complexes does not lead to the displacement of protons from the functional groups of penicillines (e.g., the amide group), and penicillines themselves exist in solution in the form of anions in compliance with the known values of $\text{p}K_a$, namely, $\text{p}K(\text{HBzp}) = 3.11$, and $\text{p}K(\text{HOxa}) = 2.69$ [13].

Equilibria in the studied $\text{Ag}^+ - \text{Bzp}^-$ and $\text{Ag}^+ - \text{Oxa}^-$ systems were calculated using the specialized software New DALSFEEK [14].

Elemental analysis results for sodium salts of benzylpenicilline and oxacilline

Sample	Bulk formula	Content (found/calcd.)			
		C	H	N	S
NaBzp	$\text{C}_{16}\text{H}_{17}\text{N}_2\text{O}_4\text{SNa}$	53.51/53.92	4.70/4.81	7.87/7.86	9.20/9.00
NaOxa · H ₂ O	$\text{C}_{19}\text{H}_{20}\text{N}_3\text{O}_6\text{SNa}$	50.36/51.70	4.45/4.57	9.23/9.52	7.60/7.26

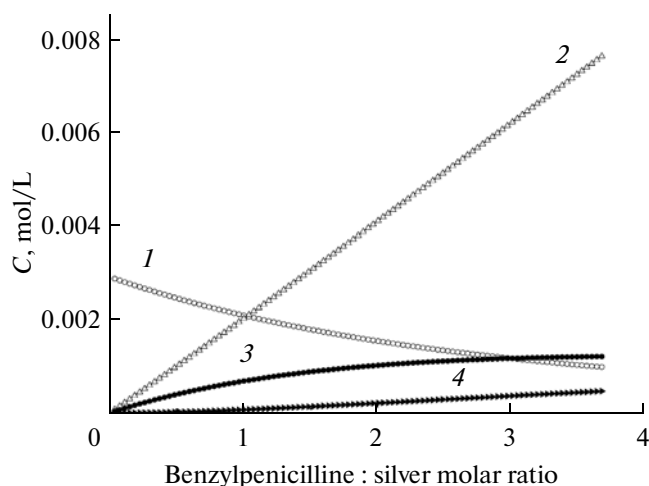
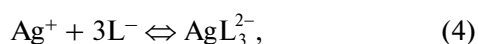
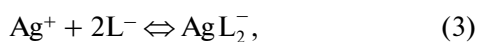
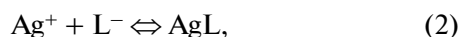
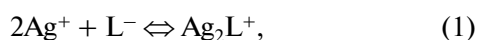


Fig. 2. Distribution of equilibrium species concentrations in the Ag^+ - Bzp^- system versus component molar ratio: (1) Ag^+ , (2) Bzp^- , (3) AgBzp , and (4) AgBzp_2^- .

Since the anions (Bzp^- and Oxa^-) have several donor atoms, which can coordinate to silver(I), and the molar ratio of components is varied within a wide range during titration, it was necessary to take into account the possibility of formation of different complexes in the systems. The model for calculation included the following equilibria:



where $\text{L}^- = \text{Bzp}^-$, Oxa^- .

As a result of calculation, the complexes AgBzp , AgBzp_2^- , Ag_2Oxa^+ , AgOxa , and AgOxa_2^- were found to form. The corresponding formation constants β were determined: $\log\beta(\text{AgBzp}) = 2.21 \pm 0.01$, $\log\beta(\text{AgBzp}_2^-) = 3.91 \pm 0.02$, $\log\beta(\text{Ag}_2\text{Oxa}^+) = 4.89 \pm 0.01$, $\log\beta(\text{AgOxa}) = 2.88 \pm 0.01$, and $\log\beta(\text{AgOxa}_2^-) = 5.43 \pm 0.01$. The Ag_2Bzp^+ , AgBzp_3^{2-} , and AgOxa_3^{2-} species were estimated by the program to be negligible. In both cases, the experimental and calculated titration curves nearly coincided, and the convergence criterion (the sum of squared deviations) had a very small value of ~ 0.001 .

Taking into account the found formation constants of the complexes, the equilibrium concentrations of species in the Ag^+ - Bzp^- and Ag^+ - Oxa^- systems were calculated and plotted in Figs. 2 and 3. It can be seen that an appreciable equilibrium concentration of free

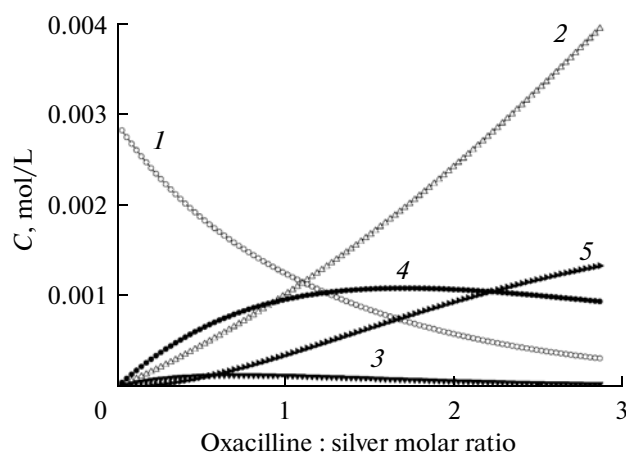


Fig. 3. Distribution of (1) Ag^+ , (2) Oxa^- , (3) Ag_2Oxa^+ , (4) AgOxa , and (5) AgOxa_2^- equilibrium concentrations in the Ag^+ - Oxa^- system depending on the molar ratio of components.

silver ions still exists in both systems even when the ligand is in excess.

We are the first to study the complexation of silver ions with benzylpenicilline and oxacilline anions by direct potentiometry, demonstrated the formation of complexes AgBzp , AgBzp_2^- , Ag_2Oxa^+ , AgOxa , and AgOxa_2^- , determined and their stability constants. The obtained formation constants of the oxacilline silver complexes are in good agreement with the earlier results [15], where pH-metry gave the following values: $\log\beta(\text{AgOxa}) = 3.28 \pm 0.03$, $\log\beta(\text{AgOxa}_2^-) = 6.22 \pm 0.04$. Since the formation of binuclear complexes is observed for oxacilline and is not observed for benzylpenicilline, it may be supposed that the isoxazole group of oxacilline is able to coordinate silver ions.

ACKNOWLEDGMENTS

This work was performed within the framework of the Government assignment to the Tver State University to perform R & D job "Nanostructured Supramolecular Hydrogels of Bioactive Compounds for Medical Use," project no. 3.1841.2011.

REFERENCES

1. A. B. Lansdown, *Adv. Pharm. Sci.* Article ID 91068686 (2010).
2. RLS Alphabetical Index of Drugs. <http://www.rls-net.ru/>.
3. M. G. Voronkov, A. S. Kogan, L. M. Antonik, et al., *Khim.-Farm. Zh.* **35** (5), 19 (2001).
4. M. G. Voronkov, L. M. Antonik, A. S. Kogan, et al., *Khim.-Farm. Zh.* **36** (2), 27 (2002).

5. A. S. Kazachenko, E. V. Legler, and O. V. Per'yanova, *Khim.-Farm. Zh.* **34** (5), 34 (2000).
6. E. V. Legler, A. S. Kazachenko, and V. I. Kazbanov, *Khim.-Farm. Zh.* **35** (9), 35 (2001).
7. G. M. Bobiev, T. D. Sufiev, and A. N. Shakhmatov, *Khim.-Farm. Zh.* **42** (11), 10 (2008).
8. P. M. Pakhomov, M. M. Ovchinnikov, S. D. Khizhnyak, et al., *Vysokomol. Soedin., Ser. A* **53**, 1574 (2011).
9. V. G. Alekseev, E. P. Alekseeva, and P. M. Pakhomov, RU pat. 2484810. *Elektron. Byull. Izobret. Polezn. Models*, No. 17 (2013) http://www1.fips.ru/Electronic_bulletin/Inventions_and_utility_models/17_13/DOC/RUNWC2/000/000/002/484/810/DOCUMENT.PDF.
10. G. Singh, R. B. Patankar, and V. K. Gupta, *Pol.-Plast. Technol. Eng.* **49**, 1329 (2010).
11. V. G. Alekseev and L. V. Demskaya, *Koord. Khim.* **33**, 211 (2007).
12. www.originlab.com.
13. V. G. Alekseev, *Khim.-Farm. Zh.* **44** (1), 16 (2010).
14. <http://sinisha.chat.ru/nonie/products/newdalsfek/>.
15. S. V. Snesarev and E. G. Kulapina, *Izv. Saratovsk. Gos. Univ. Nov. Ser., Ser. Khim. Biol. Ekol.*, **12** No. 1, 17 (2012).

Translated by E. Glushachenkova

SPELL: 1. bioactive, 2. Collargolum, 3. Protargolum