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GENERAL REGULARITIES IN THE SORPTION OF ANTIBIOTICS OF THE TETR--ETC(U)  
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GENERAL REGULARITIES IN THE SORPTION OF ANTIBIOTICS OF THE  
TETRACYCLINE SERIES BY ION-EXCHANGE RESINS

By

V. Ya. Vorob'yeva, L. V. Dmitrenko, G. V. Samsonov



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А а	<b>А а</b>	A, a	Р р	<b>Р р</b>	R, r
Б б	<b>Б б</b>	B, b	С с	<b>С с</b>	S, s
В в	<b>В в</b>	V, v	Т т	<b>Т т</b>	T, t
Г г	<b>Г г</b>	G, g	У у	<b>У у</b>	U, u
Д д	<b>Д д</b>	D, d	Ф ф	<b>Ф ф</b>	F, f
Е е	<b>Е е</b>	Ye, ye; E, e*	Х х	<b>Х х</b>	Kh, kh
Ж ж	<b>Ж ж</b>	Zh, zh	Ц ц	<b>Ц ц</b>	Ts, ts
З з	<b>З з</b>	Z, z	Ч ч	<b>Ч ч</b>	Ch, ch
И и	<b>И и</b>	I, i	Ш ш	<b>Ш ш</b>	Sh, sh
Й й	<b>Й й</b>	Y, y	Щ щ	<b>Щ щ</b>	Shch, shch
К к	<b>К к</b>	K, k	Ъ ъ	<b>Ъ ъ</b>	"
Л л	<b>Л л</b>	L, l	Ы ы	<b>Ы ы</b>	Y, y
М м	<b>М м</b>	M, m	Ь ь	<b>Ь ь</b>	'
Н н	<b>Н н</b>	N, n	Э э	<b>Э э</b>	E, e
О о	<b>О о</b>	O, o	Ю ю	<b>Ю ю</b>	Yu, yu
П п	<b>П п</b>	P, p	Я я	<b>Я я</b>	Ya, ya

\*ye initially, after vowels, and after ь, ь; e elsewhere.  
When written as ë in Russian, transliterate as yë or ë.

RUSSIAN AND ENGLISH TRIGONOMETRIC FUNCTIONS

Russian	English	Russian	English	Russian	English
sin	sin	sh	sinh	arc sh	sinh <sup>-1</sup>
cos	cos	ch	cosh	arc ch	cosh <sup>-1</sup>
tg	tan	th	tanh	arc th	tanh <sup>-1</sup>
ctg	cot	cth	coth	arc cth	coth <sup>-1</sup>
sec	sec	sch	sech	arc sch	sech <sup>-1</sup>
cosec	csc	csch	csch	arc csch	csch <sup>-1</sup>

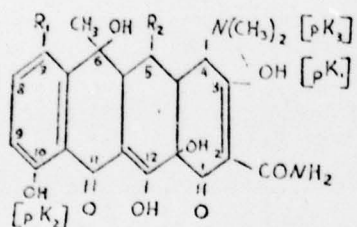
Russian      English

rot      curl  
lg      log

GENERAL REGULARITIES IN THE SORPTION OF ANTIBIOTICS OF THE TETRACYCLINE SERIES BY ION-EXCHANGE RESINS

V. Ya. Vorob'yeva, L. V. Dmitrenko, G. V. Samsonov

The antibiotics of the tetracycline series (ATR) [ATP] include tetracycline (TTs) [TЦ], oxytetracycline (OTTs) [OTЦ] and chlor-tetracycline (KhTTs) [XTЦ], which are substances which are very close in the structure of their molecules and in many chemical and biochemical properties.

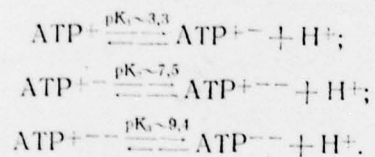


TT:  $R_1 = H; R_2 = H;$   
 OTT:  $R_1 = H; R_2 = OH;$   
 XTT:  $R_1 = Cl; R_2 = H.$

Their value in medical practice is exceedingly great and can be compared in the extent of application with penicillin and streptomycin [1]. The electrochemical properties of ATR have still not been studied sufficiently, which is connected with the complexity of structure of ATR and their ions, which carry both positive and negative ions. The purpose of the present article is an analysis from this point of view of the processes of ion-exchange sorption of ATR by anion-exchange and cation-exchange resins under different

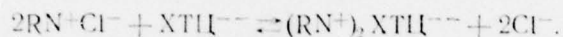
conditions and the exposure of the main factors which lead to the great selectivity of ATR in comparison with the rival mineral ions. These questions are of significant interest both from a practical aspect (for the isolation and purification of the antibiotics), and also from scientific (for the purpose of exposing the main regularities of the interaction of organic ions with polyelectrolytes). A study of these regularities can also be useful for an understanding of the mechanism of action of ATR in an organism. Furthermore, one of the methods of prolonging the action of ATR can also be connected with the formation of complexes with natural or synthetic polymers.

ATR have three groups which are capable of ionization:  $pK_1$  - in the area around 3.3;  $pK_2$  - in the area of 7.3-7.7; and  $pK_3$  in the area of 9.1-9.7. As was shown by us [2],  $pK_1$  and  $pK_2$  are related to acid, and  $pK_3$  - to base groupings. Depending on the value of the pH-solution, the picture of dissociation of ATR can be presented in the following form:



Consequently, in the acid range ( $\text{pH} < 3.0$ ) ATR are found in solution primarily in the form of univalent cations, in the alkaline range  $\text{pH} > 10.0$  - in the form of bivalent anions, and in the intermediate - in the form of zwitterions, carrying one positive (dimethylammonium group) and one (in the area of pH 4-6) or two (in the area of pH 8-9) negative charges (correspondingly the alcohol hydroxyl with the  $C_3$ -atom and the phenol hydroxyl with the  $C_{10}$ -atom). Such a distribution of charges, depending on the pH, makes it possible to make a selection of ionites for the sorption of these antibiotics. The sorbents, capable of absorbing ATR, should contain only strongly acid groupings of the sulfo-group type for cation-exchange resins, and strongly or moderately basic groupings of the type of tertiary and quaternary ammonium bases for anion-exchange resins.

Initially let us consider the interaction of ATR with anion-exchange resins. In the area of  $\text{pH} > \text{pK}_3$ , where ATR are two-charge anions, equivalent ion exchange takes place, in which for 1 mole of KhTTs 2 moles of  $\text{Cl}^-$  are given off into solution [3, 4]:



With a switch to neutral and acid solutions the average total charge of KhTTs ions changes, the number of negatively charged groups drops, which is also observed in the sorption experiment as a lessening of the sorption capacity of an antibiotic with a lowering of the pH value of the solution. Figure 1 shows the dependence, obtained under dynamic conditions, of the sorption capacity of KhTTs on the strongly basic AV-27 resin depending on the pH of the solution. It is evident from the graph that with a lessening of the pH value two significant drops of capacity are observed - at  $\text{pH} \sim 3.3$  and 7.5, i.e., in areas corresponding to  $\text{pK}_1$  and  $\text{pK}_2$  values of acid groupings of the antibiotic. Analogous results were obtained on the moderately basic EDE-10 resin [2]. However, it should be noted that the selectivity of sorption of ATR on anionites is not great and capacity is lowered sharply in the presence of rival anions [3], and even when switching from resins which are found in the base form to the salt forms of anionites [4]. Moreover, in an alkaline medium ATR are not very stable. These factors also specified the circumstance that considerably greater attention is given to cation-exchange processes, taking place with the participation of ATR, than to anion-exchange.

Let us consider the main regularities of the interaction of ATR with cationites. Since ATR are found in the form of cations only in an acid medium, where they are moreover more stable, sorption processes are usually studied with  $\text{pH} < 3$  using strongly acid cationites, as a rule containing sulfo groups. With an increase of pH and the appearance of negative charges on the ATR molecules, the sorption capacity is lowered considerably [2].

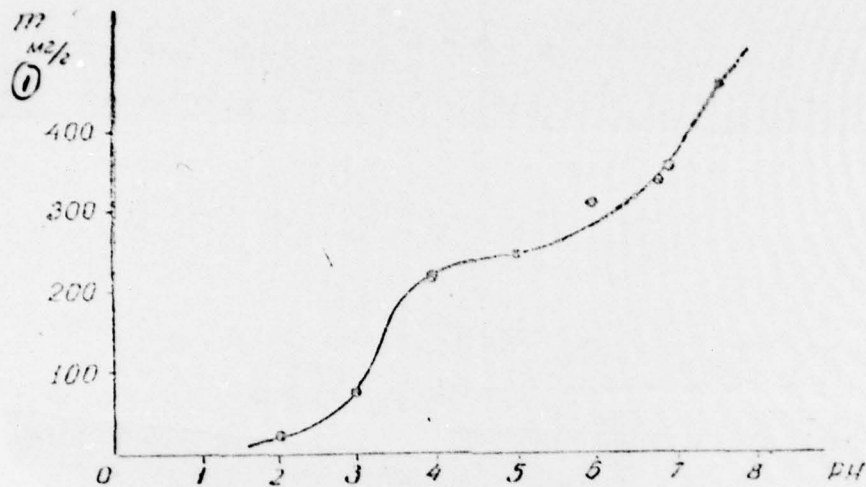


Figure 1. Sorption capacity of KhTTs on the strongly basic AV-27 resin, depending on pH.

Key: (1) mg/g.

The reaction of ion exchange, taking place with the participation of ATP, for an acid medium can be written in the form:



The coefficient of selectivity of sorption  $K$  is calculated using the ordinary equation (3)

$$K = \frac{\bar{c}_{\text{ATP}^+} \cdot c_{\text{H}^+}}{c_{\text{H}^+} \cdot \bar{c}_{\text{ATP}^+}}$$

where  $\bar{c}_{\text{ATP}^+}$  and  $\bar{c}_{\text{H}^+}$  - concentrations of antibiotic and hydrogen ion in the ionite phase,  $c_{\text{ATP}^+}$  and  $c_{\text{H}^+}$  - concentrations in solution. Subsequently we will also use the variable  $X$  - degree of filling

of the ionite with ions of antibiotic  $X = \frac{\bar{c}_{\text{ATP}^+}}{\bar{c}_0}$ , where  $\bar{c}_0$  - total exchange capacity of the ionite (POE) [ΠОЕ], and

$X^I = \frac{\bar{c}_{ATP^+}}{\bar{c}_0}$  - relative degree of filling of the ionite, where

$\bar{c}_0'$  - maximum amount of organic ion, capable of being adsorbed by an ionite with a tendency on the part of the concentration of organic ion in the solution to infinity, and the rival ion - to zero. The last phenomenon - the impossibility of filling all the sorption centers of the ionite - is connected unambiguously with the density of the sorbent matrix, regulated by the percentage of cross-linking agent during synthesis.

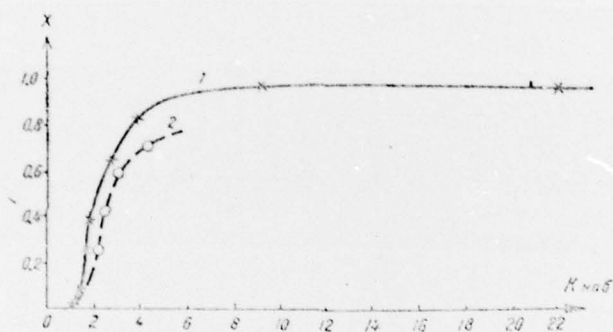


Figure 2. Dependence of the maximum degree of filling of the ionite ( $X$ ) on the coefficient of swelling  $K_{HaO}$  in the case of sorption: 1 - OTTs on Dowex 50 ionite; 2 - OTTs on the SDV-T ionite.

However, it is more convenient to use the swelling capacity or the coefficient of swelling  $K_{HaO}$ , defined as the ratio of the volume of the swollen ionite to the volume of the dry [ionite]. The maximum filling of an ionite with organic ion in a specific interval depends sharply on  $K_{HaO}$ , as this is shown, for example, in the sorption of TTs on the SBS ionite [3, p 141] or OTTs on the Dowex 50 ionite (Figure 2 - solid curve). It follows from Figure 2 that noticeable adsorption is observed only with  $K_{HaO} > 1.5$ , and with  $K_{HaO} > 6.0$  practically all the sorption centers are filled with OTTs. Analogous results were also obtained for the SDV-T ionite (Figure 2, broken curve). In the case of incomplete filling -  $\bar{c}_0' < \bar{c}_0$  into

the calculation of the coefficient of selectivity  $K$  it is possible to introduce in place of  $\bar{c}_0$  the variable  $\bar{c}_0'$ , and then we obtain the relative coefficient of selectivity of sorption  $K'$  [3, p 142].

In the case of exchange of inorganic ions  $K$  usually does not exceed several units. With switching to organic ions, the coefficient of sorption selectivity of such ions in respect to ions of mineral salts changes in considerably wider limits and can reach hundreds and even thousands [3, p 143]. Such an increase of selectivity can be explained by the presence of an additional, apart from Coulomb, interaction between the organic ion - the sorbate, and the matrix of the ionite - the sorbent [5, 6]. The nature of the additional interaction can be connected with the formation of a hydrogen bond, van der Waals or hydrophobic interaction.

It can be assumed that the chemical structure of both the sorbed organic ions and the matrix of the sorbent should exert a decisive influence on the selectivity of the sorption interaction. Actually even the small differences in the structure of TTs, OTTs and KhTTs have an influence on the selectivity of their sorption by the same resin. On the Dowex 50 ionite KhTTs has a greater selectivity of sorption than OTTs [7], and on the SDV-T ionite at room temperature ( $20^\circ$ ) the coefficient of selectivity  $K$  increases with a switch from OTTs to TTs and KhTTs and is equal respectively to: 83, 130 and 160. However, it should be noted that all three antibiotics have a relatively high degree of selectivity of sorption and the discussion concerns only a lessening or augmentation of the additional interaction.

A change in the chemical structure of the sorbent matrix exerts an analogous influence on the selectivity of sorption. In this case there is a whole number of possibilities of "adjustment" of an ionite for a given organic ion for the purpose of obtaining the most selective adsorption. The main matrix of the ionite is a polymer, constructed from monomeric units, containing ionogenic groups, and a cross-linking agent. Also the process of polymerization can be conducted in the presence of some agent, telogen for example, leading to the breaking of the reaction of polymeri-

zation and disrupting the order along the polymer chain, i.e., changing the structure of the matrix.

Let us consider some connections between the structure of the ionite and selectivity. First of all the very structure of the monomeric unit of the polymer itself exerts a great role. With a switch from the KU-2 polysulfostyrene ionite to the polysulfoacenaphthene KU-6 ionite the coefficient of selectivity of sorption of OTTs increases from 50 to 250, apparently due to the great additional interaction with the naphthalene nuclei of the ionite. In the same manner there is an increase in the coefficient of selectivity of sorption of OTTs from 95 to 340 following switching from the Dowex 50 polysulfostyrene ionite to an ionite on a base of a copolymer of styrene with sulfostyrene (partially sulfonated resins [7]). Evidently benzene nuclei, which do not carry sulfo groups, play an important role in the formation of an additional bond between OTTs and the sorbent matrix. When telogen is added to the polysulfostyrene matrix (SDV-T ionite) there is also an augmentation of selectivity of sorption of OTTs which is proportional to the amount of telogen which is added during synthesis:  $K$  increases from several units (without telogen) to 70 (with 90% telogen) [8]. However, the structure of the matrix can be changed, and with the help of a cross-linking agent - its chemical structure, its length. Thus in the polysulfostyrene ionite the substitution of the cross-linking agent divinylbenzene-ionite SDV for divinyl-ionite SBS leads to an increase in the coefficient of selectivity from 22 to 150 in the case of OTTs sorption [8]. In summing up these results, the conclusion can be made that virtually any disordering, disruption in the regularity of structure of the ionite, or introduction of new radicals into the matrix of the sorbent, leads to an increase in the selectivity of sorption of ATR due to an augmentation of the additional interaction of the sorbent-sorbate type. This interaction is manifested especially well when studying the dependence of the selectivity of ion exchange ( $K$ ) on the degree of filling of the ionite with organic ion ( $X$ ). With an increase of

filling the sorbed organic ions begin to interact with each other (sorbate-sorbate interaction) due to their large dimensions and relatively high concentration.

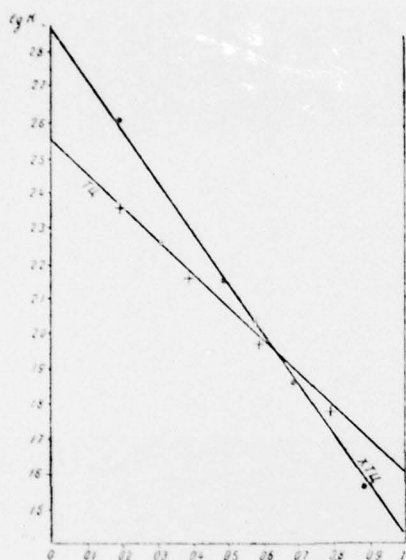


Figure 3. Dependence of the selectivity of sorption on the relative degree of filling ionite during the sorption of TTs and KhTTs on the SBS ionite at room temperature (pH 2.0) in the presence of 0.1 NaCl.

Here if an interaction of the sorbate-sorbate type leads to repulsion, then this alone weakens the interaction of the sorbent-sorbate type due to disruption of steric conformity and the selectivity of sorption drops with an increase of X. Such a picture was observed earlier for a whole series of organic ions [9, 10]. In Figure 3 a similar picture is given for the sorption of TTs and KhTTs on the SBS ionite.

However, in a number of cases the opposite picture can be observed, when the sorbate-sorbate interaction leads to the attraction of molecules, and then the selectivity of ion exchange increases with the filling of the ionite by ions of organic substances.

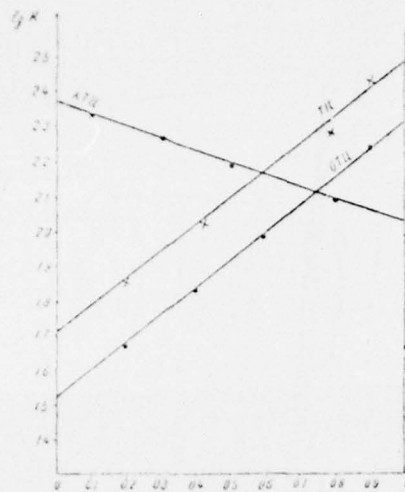


Figure 4. Dependence of the selectivity of sorption of TTs, OTs and KhTTs on the relative filling of the ionite SDV-T.

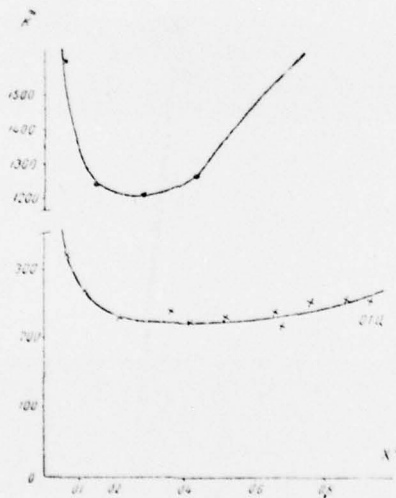


Figure 5. Dependence of the selectivity of sorption of KhTTs on the Dowex 50x6.6 ionite (upper curve) and OTTs on the partially sulfonated Dowex 50 ionite (lower curve) on the relative degree of filling  $X^1$ .

On the Dowex 50 polysulfostyrene ionite the selectivity of sorption increases with filling for OTTs for all samples of ionite, and for KhTTs for strongly swollen samples [7]. For ATR it is possible to observe both types of selectivity on the SDV-T ionite with a coefficient of swelling of 3.0 (Figure 4): selectivity increases with filling for OTTs and TTs and drops for KhTTs. In the case of KhTTs on weakly swelling Dowex 50 ionite, and also OTTs on partially sulfonated Dowex 50 ionite both types of additional interaction are observed simultaneously: sorbent--sorbate - with a low degree of filling the selectivity of sorption drops, and sorbate-sorbate - with a high degree of filling the selectivity of sorption increases [7] (Figure 5).

All the considered regularities of ion exchange of ATR on anionites and cationites, and also the factors which determine the accessibility of sorption centers and the selectivity of sorption of ATR, make it possible to understand the mechanism of ion exchange and the formation of an additional interaction. These results make it possible not only to eliminate empirism in the selection of sorbents in a number of cases, but also to express specific requirements for the chemical structure of the ionite, intended for removal of TTs, OTTs and KhTTs with a high degree of selection of sorption from solutions, which has great practical significance for the technology of purification of ATR.

#### CONCLUSIONS

1. The main regularities of the interaction of tetracycline, oxy and chlortetracycline with anionites and cationites were reviewed.
2. The problem of the formation of an additional interaction on an ionite of the sorbent--sorbate and sorbate--sorbate type was considered, as well as the influence of interaction on the selectivity of sorption of ions of the antibiotics of the tetracycline group.

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