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Abstract

Full Text

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ON THE NATURE OF THE SPONTANEOUS CHANGE IN THE VISCOSITY OF SALVARSAN SOLUTIONS

(Presented by Academician A. N. Nesmeyanov, 20 IV 1957)

As early as P. Ehrlich and A. Bertheim, in their communication on the synthesis of salvarsan (^1), noted that its aqueous solutions have a rather high viscosity and, without going into an explanation of the reasons for this, stated that salvarsan has colloidal properties. Subsequently a number of works were devoted to the study of the colloidal properties of salvarsan. Klemensiewicz (^2) noted that the viscosity of salvarsan solutions depends on a number of factors: 1) on the method of dissolving the preparation—dissolution at room temperature gives more viscous solutions than dissolution with heating; 2) on the duration of standing of the solution—with time, more concentrated solutions become more viscous, while the viscosity of dilute ones decreases; 3) on a change in temperature before measurement—if the viscosity of a previously cooled or heated solution is measured at the same temperature, then in the latter case considerably smaller values are obtained. Without doubting the structural formula of P. Ehrlich and A. Bertheim, Klemensiewicz believed that, apparently, strong polymerization accompanied by hydration takes place in salvarsan solutions, without specifying what he meant by this. The author considered the changes in viscosity of salvarsan solutions to be irreversible, but later this was refuted (^3). The viscosity of salvarsan solutions depends to a large extent on the manner in which the hydrochloride is prepared: according to P. Ehrlich and A. Bertheim—by adding the calculated amount of HCl to the base of salvarsan in CH_3OH, followed by precipitation with ether, or according to Kober (^4)—by precipitation with an excess of hydrochloric acid. Salvarsan isolated by the latter method always gives considerably more viscous solutions (^5).

Quite recently a paper by I. Stauff, E. Koch, and E. Uhlein appeared (^6), in which the authors study the action of light on salvarsan solutions. The authors regard salvarsan as a substance that gives colloidal solutions by virtue of molecular association. These authors observed that salvarsan solutions differ fundamentally from solutions of all other association colloids in that their viscosity becomes constant only after prolonged standing. Nevertheless, in their investigations these authors proceed from the assumption that salvarsan is the hydrochloride of 3,3′-diamino-4,4′-dioxyarsenobenzene and believe that association occurs through the formation of hydrogen bonds between As atoms and phenolic hydroxyl groups. In the works of our laboratory ([7]-12), devoted to the

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structure of salvarsan and polymeric arseno compounds, a number of quite convincing proofs were presented in favor of the polymeric structure of salvarsan, whereas the formula of 3,3′-diamino-4,4′-dioxyarsenobenzene was proposed only on the basis of the results of elemental analysis and a risky analogy with azo compounds. The spontaneous change in the viscosity of salvarsan solutions, from our point of view (^12), depends on the fact that,

that in solution, depending on concentration, acidity, temperature, etc., the following reactions may occur:

$$m\,\mathrm{HOAs{-}\underset{R}{(As)}{-}As{-}OH} \rightleftarrows$$

$$\mathrm{HOAs{-}\underset{R}{(As)}{-}As{-}}\left[\mathrm{O{-}As{-}\underset{R}{(As)}{-}As}\right]_{m-2}\mathrm{{-}O{-}As{-}\underset{R}{(As)}{-}AsOH} + \frac{m-2}{2}\,\mathrm{H_2O}, \tag{1}$$

where R = [[unclear: aminophenol ring structural formula]],

i.e., in this process the length of the chain of principal valences increases as a result of dehydration ([12]). Such dehydration is more than probable—all compounds with trivalent As are prone to it, for example: $2As(OH)_3 \rightarrow As_2O_3$; $2R_2As{-}OH \rightarrow R_2As{-}O{-}AsR_2$, etc.

[[unclear: aminophenol ring structural formula]]OH.

It is quite natural that under some conditions dehydration may occur, as a result of which the viscosity of the salvarsan solution will increase, while under others, conversely, hydrolytic cleavage of the bonds ≡ As—O—As ≡ may take place, as a result of which the viscosity of the solution will decrease. In order to confirm the proposed assumption, it was necessary to prove that in a salvarsan solution which, with the passage of time, had become more viscous, a polymer with a higher molecular weight had formed, i.e., that another compound had been produced. It is quite obvious that, for this purpose, salvarsan had to be isolated from the solution in the form of some other compound and the viscosity of the isolated substance determined ([13]). The determination would show whether we were dealing with an association-type colloid—in that case the viscosity of the isolated compound would have to differ greatly from the viscosity of the salvarsan solution. If, however, the viscosity of the solution of the compound obtained proved close to the viscosity of the salvarsan solution, this would serve as irrefutable proof that the increase in the viscosity of the salvarsan solution depends on an increase in its molecular weight; thereby our assumption concerning the mechanism of this phenomenon would be proved. Since the salvarsan molecule is very labile, we chose to isolate it in the form of its sulfuric acid salt: it is very sparingly soluble in water, can be readily isolated

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from dilute solutions ([1]), and, what is very important, its preparation does not require a change in temperature, which could cause hydrolytic cleavage of the bonds ≡ As—O—As ≡ that had formed.

All operations, in order to avoid oxidation of salvarsan, were carried out in an atmosphere of CO_2. We isolated the sulfuric acid salt as follows: by adding a soda solution to neutral reaction (litmus), the salvarsan base was precipitated; the precipitate was filtered off on a folded filter (filtration with vacuum takes much longer), and to the resulting paste, with stirring, 25% sulfuric acid was added until an acid reaction to Congo red was obtained. The sulfuric acid salt was filtered off (vacuum) and washed first with 0.5% H_2SO_4, then with water until a weakly acidic reaction to Congo red, and finally with alcohol and ether. The salt obtained was dried in vacuum over H_2SO_4. For the study, a 1% salvarsan solution in $1N$ and $2N$ HCl was used. The use of a 1% solution was due to the fact that more dilute solutions are very readily oxidized by atmospheric oxygen ([14]), while more concentrated ones have a very high viscosity, especially samples prepared by Kober' s method. The use of $1N$ HCl made it possible to obtain well reproducible results. The use of $2N$ HCl for hydrolytic cleavage of the bonds ≡ As—O—As ≡ was due to the fact that in such acid, especially at 35°,

the reaction proceeds faster than in $1N$ HCl. The salvarsan used for the study was obtained by reduction of 3-amino-4-hydroxyphenylarsonic acid with $Na_2S_2O_4$, since this method gives a purer preparation than that obtained by reduction of the corresponding nitro acid ([15]). The salvarsan base obtained in this way was converted into the hydrochloride both by Ehrlich' s method and by Kober' s method. The isolated hydrochloride salts ("salvarsan" of Ehrlich), as well as the sulfate salts obtained from them, were dried, as before, under mild conditions—without heating, in vacuo over H_2SO_4 and KOH for 15 hours—in order to avoid the above-mentioned dehydration. Naturally, the preparations dried in this way contained a certain amount of moisture and differed somewhat in As content (within the range 29.80–31.60% As), but this was of no significance for the subsequent work: the iodine constant of salvarsan was calculated by the formula $J_k = 14.95 \cdot J : p$, where J is the iodine number of salvarsan, expressed in ml of $0.1N$ J, required for oxidation of 0.1000 g of salvarsan, and p is the percentage of As in the sample studied ([7,11]). Solutions for viscosity determinations were always prepared with allowance for the As content in the sample studied—so that 100 ml of solution contained 0.120 g As (a 0.4% solution of salvarsan containing 30.00% As). The method of isolating the hydrochloride salt (by Ehrlich or by Kober) does not affect the magnitude of the iodine constant of salvarsan (and, consequently, the number of As atoms in the elementary unit), which depends only on the reduction conditions. Salvarsan obtained by reduction of 3-amino-4-hydroxyphenylarsonic acid with $Na_2S_2O_4$ always has $J_k = 7.8$ ([11]) and, consequently, its elementary unit contains $n = 4 : (8 - J_k) = 20$ residues of $AsC_6H_3(OH)(NH_2)$. Investigation of the salvarsan samples obtained gave the following results.

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Salvarsan isolated by the method of Ehrlich and Bertheim contained 29.8% As. Flow time of a 0.4% solution (Ostwald viscometer, $t = 27°$) 0 min. 43 sec. Flow time of 1N HCl 0 min. 40.08 sec.; $\eta_{\text{rel}} = 1.075$, $\eta_{\text{sp}} = 0.075$; mol. wt. = 7200 ([12]).

6 g of the salvarsan under study were dissolved in 600 ml 1N HCl. The flow time of the solution under the same conditions was 0 min. 49.6 sec. The solution was left standing without access of air (CO_2 atmosphere) at room temperature for 3 days. After this the flow time was 1 min. 50 sec. The sulfate salt, isolated as indicated above, contained 31.2% As. Flow time of a 1% solution (same conditions) 1 min. 35 sec. Flow time of a 0.4% solution 0 min. 55.6 sec.; $\eta_{\text{rel}} = 1.39$, $\eta_{\text{sp}} = 0.39$; mol. wt. = 37 000. Thus, the viscosity of a 1% solution of the sulfate salt does not differ appreciably from the viscosity of the solution of the hydrochloride salt that had stood for 3 days, and is considerably greater than the viscosity of the solution of the original salvarsan. Such a simple treatment of salvarsan leads to a fivefold increase in its molecular weight. Evidently, 4 new bonds =As−O−As= were formed in this process. It was of great interest to determine whether it is possible in a similar way to increase the MW of salvarsan isolated by Kober—by precipitating an alkaline solution ("salvarsan phenolate") with an excess of strong hydrochloric acid. Salvarsan obtained in this way has a very high molecular weight and gives very viscous solutions. The sample we obtained contained 30.8% As. In water and 1N HCl it dissolves very slowly, swelling and forming transparent, jelly-like clots. Complete dissolution requires many hours of shaking. In view of the fact that the viscosity of a 1% solution in 1N HCl was too high (flow time under the same conditions 22 min. 30 sec.), a 0.4% solution was prepared. Its flow time was 2 min. 02 sec.; $\eta_{\text{rel}} = 3.05$; $\eta_{\text{sp}} = 2.05$; mol. wt. $\approx$ 193 000. After 3 days the sulfate salt was isolated. Flow time of a 0.4% solution 7 min. 54 sec.; $\eta_{\text{rel}} = 11.8$; $\eta_{\text{sp}} = 10.8$, whence mol. wt. $\approx$ 1 000 000. It is interesting to note that in the case of salvarsan isolated by Kober as well, the molecular weight increased by approximately the same factor as did the molecular weight of salvarsan isolated ···

according to P. Ehrlich—by approximately 5 times. It is also of great interest to determine whether salvarsan isolated according to Kober, i.e., yielding very viscous solutions, can be converted into salvarsan that readily dissolves in water with the formation of low-viscosity solutions, the same as is obtained when it is isolated by Ehrlich' s method. Hydrolysis of such high-molecular salvarsan was carried out as follows: 5 g of the salvarsan described above, isolated according to Kober (30.8% As; η_{rel} (0.4% solution) = 3.05; mol. wt. $\approx$ 193 000), was dissolved in 500 ml of 2N HCl. The outflow time of this solution under the conditions described above was 22 min. 30.8 sec. After standing for many days at 35-36°, the outflow time of this solution decreased to 1 min. 00.4 sec. The sulfite salt was isolated as described above. Four grams of salt containing 30.4% As were obtained. The outflow time of a 0.4% solution in an Ostwald viscometer at 27° was 0 min. 47.6 sec.; the outflow time of a 0.4% solution of salvarsan isolated according to Ehrlich was 0 min. 43 sec. In order to show that this

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treatment did not produce profound changes in the structure of the elementary unit, the sulfite salt obtained was again converted, according to Kober, into the hydrochloride salt. For this purpose, 2.2 g of the sulfite salt was dissolved in 16 ml of a 10% NaOH solution. The solution was left until the following day (protection from oxidation—vacuum). The next day, 70 ml of 18% hydrochloric acid was added to the solution. The precipitated salvarsan was filtered off, washed with 18% hydrochloric acid, then with a mixture of hydrochloric acid and alcohol, with a mixture of alcohol and ether, and finally with ether. It was dried in vacuo over H_2SO_4 and KOH. 1.65 g of salvarsan was obtained. It contained 31.6% As. The outflow time of a 0.4% solution under the conditions described above was 6 min. 14.2 sec. The experiments presented convincingly show that spontaneous changes in the viscosity of salvarsan solutions are, first, governed by definite regularities and, second, once again demonstrate that the viscosity of salvarsan solutions depends not on the formation of associates, but on the fact that salvarsan is a true high-molecular compound whose structure is represented by equation (1). In aqueous solutions, depending on the conditions (pH, temperature, concentration), the molecular weight may either increase through dehydration (elimination of H_2O by terminal groups of the molecule), or decrease through hydrolytic cleavage of the bonds = As—O—As =. It is very probable that most of the "arseno compounds" described in the literature are in fact analogous polymers, with the exception, of course, of those that are colorless and have a crystalline form (arsenobenzene, arsenotoluene, and some others). However, a very large number of such "arseno compounds" have been described, and they have no practical significance. An exception is, of course, neosalvarsan, questions of whose structure we hope to clarify further.

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