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MECHANISM OF POLYMERIZATION OF COLCHICIDYL-L-LYSINE N-CARBOXYANHYDRIDE

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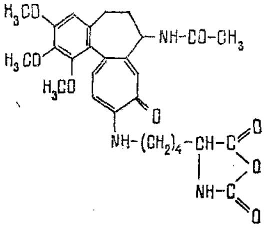
It has been shown that the polymerization of colchicidyl-L-lysine N-carboxyhydride under the action of amines obeys the general laws of the occurrence of anionic polymerization and is described, when primary amines are used, by a mechanism of "normal" amine addition and, when tertiary amines are used by the "activated monomer" mechanism.

Colchicine and its derivatives are attracting the attentions of research workers by their extremely interesting properties and, in the first place, their very strong cytostatic effect [1]. Many investigations have been devoted to the replacement of the tropolone methoxy group by various amino and alkylamine groups, including amino acid residues [2-4]. The introduction of amino acid residues into the molecule provides the possibility of obtaining polypeptides biodegradable in the organism under the action of proteases. The possibility of the gradual disruption of the polymeric chain ensures a prolongation of the action of drugs [5]. The initial monomers are α-amino acid N-carboxyanhydrides (CAs), since synthesis based on them permits a wide variation of the molecular mass of the polymers and the complete exclusion of racemization [6].

In order to elucidate the influence of the structure of the alkaloid on the process of anionic polymerization of CAs, we investigated the mechanism of initiation and chain growth in the polymerization of colchicidyl-L-lysine N-carboxyanhydride, which had been obtained previously [7].



Since the polymerization of CAs is a direct method of obtaining polypeptides, and the polymerization reaction may be brought about by various initiators (amines, metal alkoxides, aprotic bases [8]), the mechanism of initiation and chain growth largely depends on the nature of the initiating agent. As a rule, in the polymerization of CAs in the presence of primary amines the reaction takes place in the manner of a "normal" amine addition [9], and the polymer obtained contains a fragment of the initiator as the terminal group.

A different pattern is observed in the case where tertiary amines are used. The molecule of an aprotic base initiates the reaction by splitting out a proton from a CA molecule, and the particle formed – an "activated" monomer – interacts with the following CA molecule

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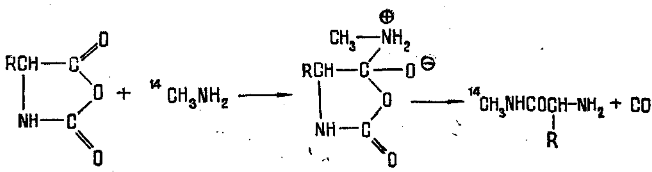
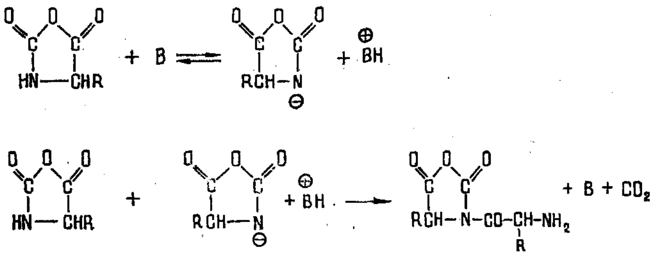
and forms a polymeric chain [10]. This polymerization mechanism is characterized by the absence of the inclusion of a fragment of the tertiary amine in the macromolecule of the polymer, the initiator being regenerated during the process. It is therefore particularly important to establish the mechanism of the polymerization of the CAs intended to produce polymers for medical purposes in connection with the creation of polymeric compounds harmless for the organism.

The polymerization of the CA of colchicidyl-L-lysine was investigated in the presence of labeled amines synthesized for this purpose. As the primary amine we used [^{14}C]methylamine obtained by a modification of the method of Jones and Skraba [11] by the hydrogenation of $K^{14}CN$ with Adams catalyst in an acid medium. The tertiary amine [^{3}H]pyridine was obtained by an exchange reaction in tritiated water solution. Polymerization was performed in dioxane in an inert gas atmosphere at room temperature. In the presence of [^{14}C]methylamine as initiator, the proportion of the inclusion of the isotopic label in the polymer amounted to 89.8%. Consequently, the scheme of initiation can be represented in the following way:



The absence of radioactivity in the polymer obtained in the presence of [^{3}H]pyridine showed a different mechanism of initiation, which takes place by the following scheme:



R-colchicidyl-L-lysine residue   B-[^{3}H]pyridine molecule

EXPERIMENTAL

The labeled compounds synthesized were identified on the basis of a comparison of their physicochemical properties with published characteristics. Radiochemical purity was determined on a NZQ-901 radiochromatograph (Czechoslovakia). The radioactivities of the samples were measured with the aid of a Beta-1 liquid scintillation counter.

[^{14}C]Methylamine. The hydrogenation of 0.26 g (0.004 mole) of potassium cyanide with a total activity of 400 MBq in 5 ml of 25% sulfuric acid was performed in the presence of 0.1 g of platinum oxide. The reaction mixture was then made alkaline, and the amine obtained was distilled off into a receiver containing 20 ml of 5% hydrochloric acid. After evaporation to dryness, the [^{14}C]methylamine hydrochloride was recrystallized from a mixture of absolute ethanol and ether. Yield 0.23 g (87%), mp 225-227°C, molar activity 115 MBq/mmole. Immediately before the performance of the polymerization reaction, the [^{14}C]-hydrochloride was dissolved in the minimum volume of water, and the solution was made alkaline and extracted with ether. An aliquot of the ethereal solution with a measured radioactivity was used for initiating polymerization.

[^{3}H]Pyridine. A solution of 0.5 ml (0.006 mole) of pyridine in 1 ml of tritiated water (specific radioactivity 2 TBq/ml) was treated with 0.1 g of platinum catalyst (PtO_2), and the tube was sealed and was heated with shaking at 100-110°C for 40 h. After the end of the reaction, the catalyst was filtered off, the filtrate was acidified, and the tritiated water was distilled off. After the elimination of labile tritium, the pyridine hydrochloride was recrystallized from absolute ethanol and was converted into the base.

Radiochemical purities were determined by PC in the water–butanol–acetic acid (4:1:5) solvent system followed by the scanning of the chromatogram on a NZQ-901 radiochromatograph. $R_f \cdot 100 = 34$; yield 29%, specific radioactivity 23.2 GBq/mole; radiochemical purity 97%.

Polymerization of Colchicidyl-L-lysine N-Carboxyanhydride. A thermostated round-bottomed flask fitted with a gas-inlet tube and a reflux condenser with a calcium chloride tube was charged with a solution of 0.5 g of colchicidyl-L-lysine CA in 10 ml of absolute dioxane. Then the labeled amine, with a total activity of 10 MBq, was added. Polymerization was carried out at room temperature in a current of nitrogen for 48 h. The product obtained was isolated by precipitation with acetone and was washed free from residual impurities, radiolysis products, and initiator residues with selective solvents.

CONCLUSIONS

It has been shown that polymerization of colchicidyl-L-lysine N-carboxyanhydride under the action of amines obeys the usual laws for the occurrence of anionic polymerization and, when primary amines are used, is described by a mechanism of "normal" amine addition and, when tertiary amines are used, by the "activated" monomer mechanism.

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