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SYNTHESIS OF STAR-SHAPED POLYMERS BASED ON 2-ALKYL-2-OXAZOLINE WITH A CALIX[8]ARENE CENTRAL CORE AND THE STUDY OF THEIR HEAT-SENSITIVE PROPERTIES

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This work describes the synthesis of thermosensitive eight-point star-shaped polymers with a central core comprised of residual octa-ester-tert-butylcalix[8]arene with oligo-2-ethyl-2-oxazoline-block-2-isopropyl-2-oxazoline rays. It is found that, despite the presence of two blocks with substantially different temperatures of the coil – globule transition, block copolymers exhibit only one lower critical solution temperature (LCST), and the phase transition is observed at a temperature close to the transition temperature of the homopolymer with a lower LCST. For the first time it is found that, upon incubating for some time in an aqueous solution above the LCST, star polymers with temperature-sensitive polyoxazoline rays self-assemble to form nanofibers and structures with more complex morphology.

In the last three decades the attention of researchers has been drawn to so-called "smart polymers," which is due to wide possibilities of their application. Especially notable are temperature and pH-sensitive polymers with complex architecture – many-ray stars, hyperbranched polymers, and molecular brushes. Extensive possibilities of directional changes in the structure, the amount, and the distribution of functional groups in the bulk macromolecules offer unique opportunities for controlling the properties of polymers with complex architecture and for the design of supramolecular structures [1-4].

The introduction into the polymer structure of fragments ready for effective binding of inorganic ions and organic compounds is a new strategy for the construction of colloidal supramolecular structures. This allows modeling of processes occurring in nature. It is shown that the transition from linear to star-shaped macromolecules significantly increases the molecular recognition abilities of the polymer [5]. Macrocyclic compounds, such as calixarenes, are structures that can form complexes with low molecular weight compounds and metal ions, capable of molecular recognition and the formation of supramolecular structures. At the same time, structural features of calixarenes make it possible to use them as the central elements of star polymers.

Of particular interest are heat-sensitive polymers with lower critical solution temperature (LCST) close to human body temperature, therefore having good prospects for applications in medicine, in particular, for targeted drug delivery [6]. Within this group is poly-2-isopropyl-2-oxazoline, which is a structural analog of polypeptides. Poly-2-isopropyl-2-oxazoline is biocompatible, biodegradable, has low toxicity, and is quite stable in biological environments. The use of polymers containing 2-isopropyl-2-oxazoline for biomedical applications requires further study of their complexing properties and the association processes of such polymers with low molecular weight compounds, the thermal reversibility of complex formation and associative phenomena, and the impact on them of the solvent composition. Moreover, the behavior of poly-2-isopropyl-2-oxazoline in aqueous solutions is largely dependent on the solvent composition, the presence therein of low molecular weight functional additives, the thermal history of poly-2-isopropyl-2-oxazoline, and the molecular weight of the polymer.

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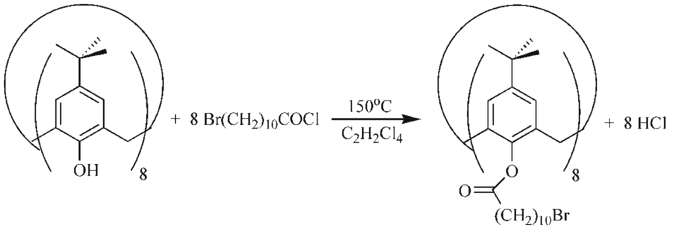


Fig. 1. Preparation of octa(11-bromoundecanoate) octa-p-*tert*-butylcalix[8]arene.

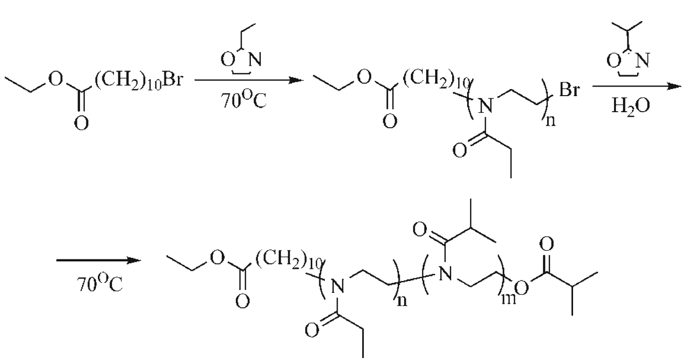


Fig. 2. Preparation of the model ω-ethoxycarbonylundecanoil-poly-2-ethyl-2-oxazoline-*block*-2-isopropyl-2-oxazoline.

To date, the information about the properties of water-soluble heat-sensitive star polymers is limited and often contradictory. Therefore, many important issues have no clear answer. It primarily relates to the possibility of regulating the LCST. One possibility is to use block-copolymers as the rays, each of which has a unique coil - globule transition temperature. The possibility of such an approach has been demonstrated on the example of statistical linear copolymers, but the effect of block structure and branched nature of the macromolecule on its temperature sensitivity has not been investigated.

The purpose of this work is the synthesis of star polymers with a calix[8]arene central core and rays of 2-ethyl- and 2-isopropyloxazoline block copolymers, and the study of their thermal properties.

As shown earlier [7], effective initiation of the growth of rays on multifunctional initiators of the calixarene type is possible only in the presence of a spacer between the macrocycle and the initiating group due to steric hindrance created by the macrocycle. In this regard, octa(11-bromoundecanoate) octa-p-*tert*-butylcalix[8]arene was selected as the initiator.

The initiator – octa(11-bromoundecanoate) octa-p-*tert*-butylcalix[8]arene – was synthesized by reacting octa-p-*tert*-butylcalix[8]arene with 11-bromoundecanoic acid chloride (Fig. 1). An attempt to obtain the desired product under standard Einhorn reaction conditions using pyridine as a catalyst and an HCl acceptor was not successful. Carrying out the reaction for 48 hr, even in 3-fold excess of the reagent, resulted in formation of a mixture of products of incomplete esterification, which is probably due to steric unavailability of some of the calixarene hydroxyl groups. Given the oligomeric character of one of the reaction components, esterification was performed using polycondensation methods, in particular, the high-temperature polycondensation in solution with no acceptor, providing a quantitative yield of ester.

The possibility of preparing block copolymers using the obtained initiator was demonstrated on model reactions of polymerization of 2-ethyl-2-oxazoline using 11-bromoundecanoic acid ethyl ester as the initiator, followed by post-polymerization of 2-isopropyl-2-oxazoline on the obtained polymer according to the diagram in Fig. 2.

The polymerization of 2-ethyl-2-oxazoline was carried out to an almost complete exhaustion of the monomer. Completeness of the reaction was determined by the disappearance of the 2-ethyl-2-oxazoline signal at 4.18 ppm (signals of the methylene protons of the ring). Then 2-isopropyl-2-oxazoline was added to the reaction mixture, and the synthesis continued until complete consumption of the monomer. Similarly, the polymer with the reverse order of the sequence of blocks was synthesized.

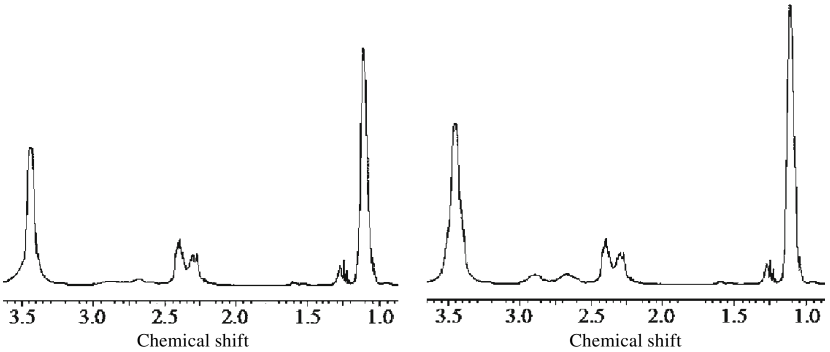


Fig. 3. NMR-spectra of ω-ethoxycarbonylundecanoil-poly-2-ethyl-2-oxazoline and ω-ethoxycarbonylundecanoil-poly-2-ethyl-2-oxazoline-*block*-2-isopropyl-2-oxazoline.

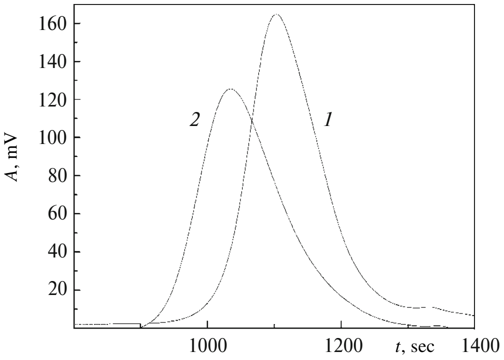


Fig. 4. Chromatograms of ω-ethoxycarbonylundecanoil-poly-2-ethyl-2-oxazoline (*1*) and ω-ethoxycarbonylundecanoil-poly-2-isopropyl-2-oxazoline-*block*-2-ethyl-2-oxazoline (*2*).

Table 1. Molar Mass Characteristics of the Model Polymers

Polymer	M_n^{PEG}	M_w^{PEG}	M_w/M_n
Et – iPr	5700	6500	1.30
iPr – Et	5500	6200	1.24

Figs. 3 and 4 show NMR spectra and chromatograms of ω-ethoxycarbonylundecanoilpoly-2-ethyl-2-oxazoline (Et – iPr) and ω-ethoxycarbonylundecanoilpoly-2-ethyl-2-oxazoline-*block*-2-isopropyl-2-oxazoline (iPr – Et) samples obtained in the post-polymerization process. As can be seen from the figures, the addition to the reaction mixture of 2-isopropyl-2-oxazoline (after the complete consumption of 2-ethyl-2-oxazoline) leads to an increase in the molecular weight of the product, while maintaining its monomodal molecular weight distribution. In the NMR^{1}H spectrum there are signals of both the ethyl and the isopropyl groups, which, together with gel permeation chromatography (GPC) data, proves the formation of poly-2-ethyl-2-oxazoline-*block*-2-isopropyl-2-oxazoline and, hence, the absence of the irreversible chain termination reaction.

The resulting molecular-mass characteristics of the model polymers are given in Table 1. The evaluation of the molecular weights of the polymers and the hydrolysis products was carried out on a Shimadzu LC-20AD chromatograph equipped with the TSKgel G5000HHR column (5 microns, 7.8·300 mm, "Tosoh Bioscience") and the corresponding precolumn, using a refractometric detector. For the mobile phase we used a solution of LiBr (0.1 mol/L) in DMF at 60 °C, flow rate $V = 0.75$ mL/min, pressure $P = 3.9$ MPa. Polymer solutions for the analysis (3 g/L) were prepared 2-3 hours before measuring and were filtered through a syringe filter (Membrane Solutions, PTFE, 0.45 microns). Column calibration was performed using polyethylene glycol standards ($M_w = 6 \cdot 10^{-2} - 4 \cdot 10^{-4}$), according to the cubic dependence. Calculation

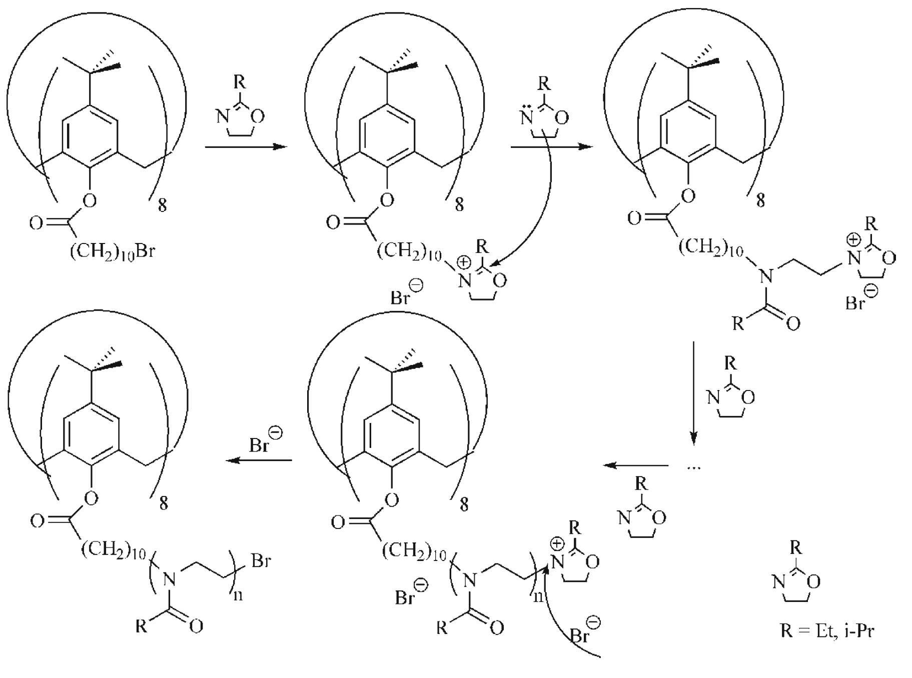


Fig. 5. Reaction mechanism for producing star-shaped poly-2-alkyl-2-oxazolines based on calix[8]arene.

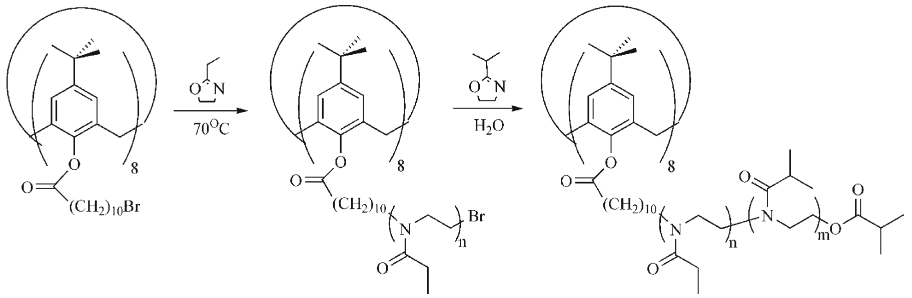


Fig. 6. Diagram describing the production of octa-p-*tert*-butylcalix[8]arene-11-bromundecanoate-poly-2-ethyl-2-oxazoline-*block*-2-isopropyl-2-oxazoline.

of the average molecular weight (M_w) and the polydispersity index ($Đ = M_w/M_n$) was performed using the software package "Shimadzu LCsolution."

Star polymers based on octa-p-*tert*-butylcalix[8]arene-11-bromundecanoate with eight rays, which are poly(2-ethyl-2-oxazoline-*block*-2-isopropyl-2-oxazoline) and poly(2-isopropyl-2-oxazoline-*block*-2-ethyl-2-oxazoline), were prepared by sequential polymerization of 2-alkyl-2-oxazolines on the indicated initiator (Fig. 5).

For the synthesis of the polymer with rays of poly-2-ethyloxazoline-*block*-2-isopropyloxazoline, a mixture of the initiator and 2-ethyloxazoline in a 1:240 molar ratio was dissolved in acetonitrile and was polymerized at 70 °C for two weeks. 2-isopropyl-2-oxazoline was added to this reaction mixture, and polymerization was continued under the same conditions (Fig. 6).

In the spectrum of the synthesized polymer along with the signals of the methylene protons of ethyl groups there are methine proton signals of isopropyl groups (Fig. 7), which, given the monomodal nature of the peaks in the chromatograms of the rays obtained by hydrolysis of the star polymer, indicates their block character. Furthermore, the proton signals of the ethyl and isopropyl groups are well separated, which allows to evaluate the ratio of the lengths of each block, which was close to 1:1.3.

It is well known [8] that a complete description of star polymers is impossible without determining the number and the molecular weight distribution of the rays. For this purpose, samples of obtained star polymers were subjected to

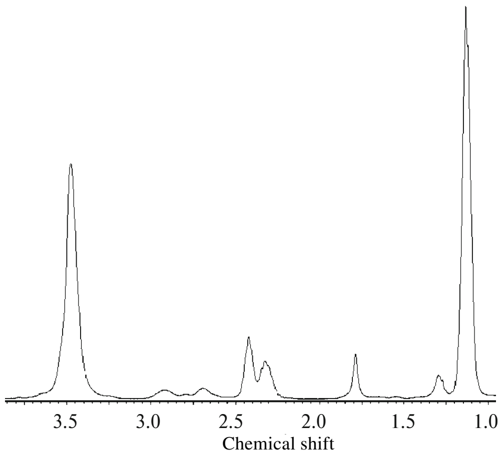


Fig. 7. ^{1}H NMR spectrum of octa-p-*tert*-butylcalix[8]arene-11-bromundecanoate-poly-2-ethyl-2-oxazoline-*block*-2-isopropyl-2-oxazoline.

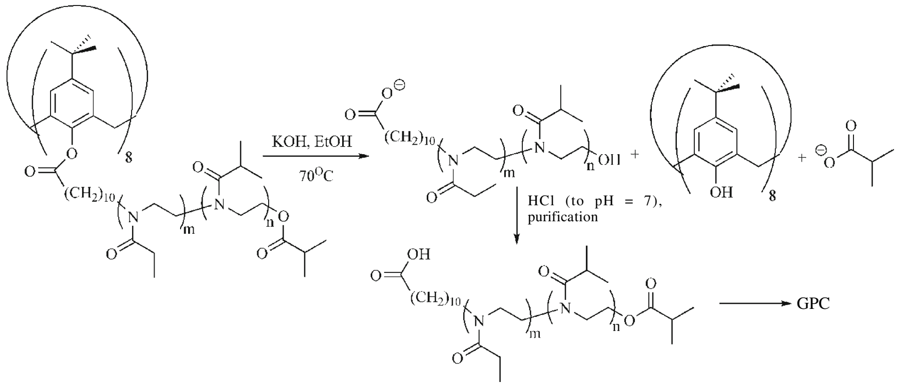


Fig. 8. Diagram describing the hydrolysis of octa-p-*tert*-butylcalix[8]arene-11-bromundecanoate-poly-2-ethyl-2-oxazoline-*block*-2-isopropyl-2-oxazoline.

Table 2. Molar Mass Characteristics of Star-Shaped Poly-2-Alkyl-2-Oxazolines

Polymer	M_w (SD)	Ratio Et : i-Pr	M_n of the rays	M_w/M_n of the rays
Et - iPr	48000	1:1.3	4400	5700
iPr - Et	27000	1:1.0	2300	3200

hydrolysis under conditions that provide complete hydrolysis of the ester groups while preserving the amide groups [9]. For this, samples of the studied polymers were heated in sealed ampoules in one molar alcohol solution of KOH at 70 °C for three days (Fig. 8).

As can be seen from Table 2, the average molecular weight of the star polymers is about 8 times greater than the average weight of the rays obtained by hydrolysis of the polymer, which confirms the formation of the eight-ray polymer, and the narrow molecular weight distribution of the rays ($M_w/M_n = 1.3$) indicates the simultaneous initiation of all active sites.

Thermal sensitivity of the obtained star polymers was examined by thermo nephelometry. For this we determined the temperature dependence of the optical density of aqueous polymer solutions of different concentrations at = 625 nm.

It was possible to assume that in the case of block copolymer nature of the rays, the polymer will have two LCSTs corresponding to the coil – globule transition in each of the blocks. However, in the case of block-copolymers there is only one structural transition at a temperature close to the cloud point of the homopolymer solution with a lower LCST (Fig. 9). Given the fact that the ratio of the lengths of the blocks in the studied polymers is close to 1:1 (according to NMR), it can be assumed that there is a possibility of regulating the transition temperature by varying the relative lengths of the blocks.

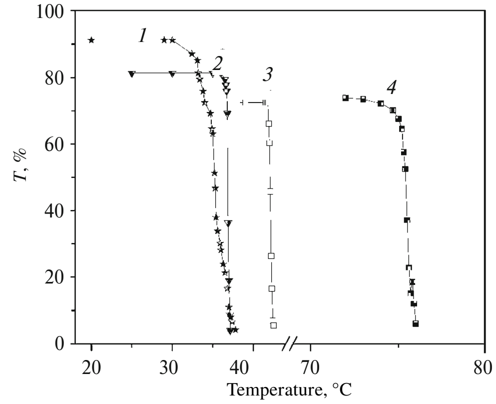


Fig. 9.

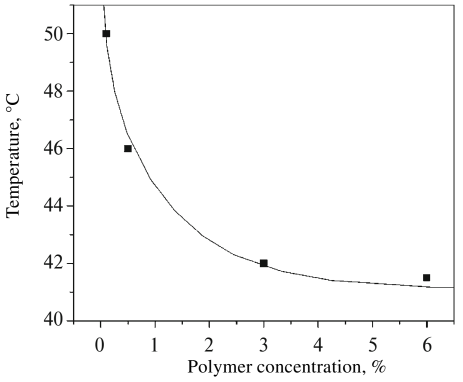
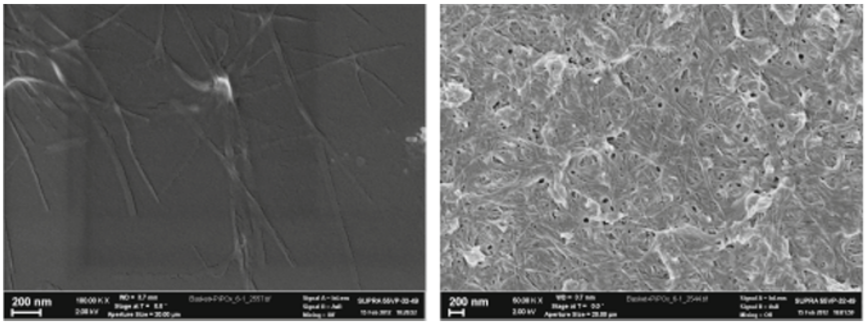


Fig. 10.

Fig. 9. Temperature dependence of light transmittance (λ = 625 nm) of 6% aqueous solutions of star polyoxazolines: *1* – octa-p-*tert*-butylcalix[8]arene-11-bromundecanoate-poly-2-isopropyl-2-oxazoline-*block*-2-ethyl-2-oxazoline; *2* – octa-p-*tert*-butylcalix[8]arene-11-bromundecanoate-poly-2-isopropyl-2-oxazoline; *3* – octa-p-*tert*-butylcalix[8]arene-11-bromundecanoate-poly-2-ethyl-2-oxazoline-*block*-2-isopropyl-2-oxazoline; *4* – octa-p-*tert*-butylcalix[8]arene-11-bromundecanoate-poly-2-ethyl-2-oxazoline.

Fig. 10. Part of the water – octa-p-*tert*-butylcalix[8]arene-11-bromundecanoate-2-ethyl-2-oxazoline-*block*-2-isopropyl-2-oxazoline phase diagram.



a *b*

Fig. 11. Electron micrograph of nanofibers formed by incubating the aqueous solution of star polymer: *a* – after 1 day; *b* – after 3 days.

Fig. 10 shows a portion of the phase diagram of the octa-p-*tert*-butylcalix[8]arene-11-bromundecanoate-poly-2-ethyl-2-oxazoline-*block*-2-isopropyl-2-oxazoline – water system. As can be seen in the figure, the minimum on the temperature – concentration curve corresponding to the LCST is 41 °C, which is 6 degrees above the LCST of a similar polymer with 2-isopropyl-2-oxazoline rays [7] and 44 degrees below the LCST of the polymer with 2-ethyl-2-oxazoline rays.

As seen in Fig. 10, the LCST is close to the cloud point of the 6% solution. It can be assumed that the LCST of the “inverted” star polymer is also close to the cloud point of the 6% solution. Comparing cloud points (41.5 °C for the polymer with 2-ethyl-2-oxazoline-*block*-2-isopropyl-2-oxazoline rays, and 35.0 °C for the polymer with inverted rays) shows that the LCST of block-copolymers depends largely on the LCST of the fragment with the lower phase transition temperature.

Notably, the cloud point of 6% aqueous solutions of the model linear ω-ethoxycarbonylundecanoil-poly-2-isopropyl-2-oxazoline-*block*-2-ethyl-2-oxazoline (41 °C) and the star polymer with rays of similar structure (35 °C) is significantly different, indicating a possible cooperative interaction of the chains of the star polymer at the coil – globule transition.

It is possible that it is the cooperative interactions of polyoxazoline rays of the obtained polymers that facilitate their self-organization in solution. It has been found that prolonged (more than two weeks) incubation of their aqueous solutions above the LCST causes spontaneous formation of water-insoluble nanofibers and structures with more complex morphology (Fig. 11).

Despite the fact that the formation of nanofibers in the crystallization of linear polyoxazolines has been previously described [10], the formation of one-dimentionally ordered structures by the star polymer is very unusual. The reason for this behavior of the obtained polymers is presently the subject of our studies.

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