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Star-shaped thermosensitive poly-*N*-acyl-1,3-propylenimines with trianglamine core

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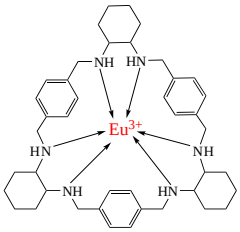
Thermosensitive star-shaped poly-*N*-acyl-1,3-propylenimines with a macrocyclic trianglamine core were synthesized using a 'grafting-on' approach involving polymerization of 2-alkyl-5,6-dihydro-4*H*-oxazines at free trianglamine. The resulting polymers form complexes with europium ions and curcumin and can be used in the creation of delivery systems for drugs as well as contrast agents for NMR tomography.



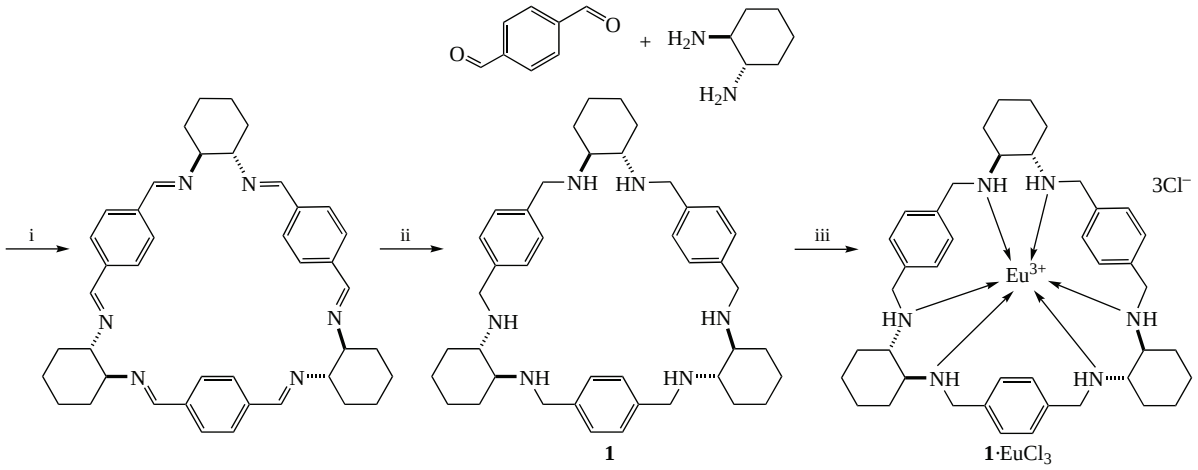
Keywords: star-shaped thermosensitive polymers, polyoxazine, trianglamine, complexes, grafting-on, cationic polymerization, europium complexes.

Hexaaza[2_6]orthoparacyclophanes proposed by Kwit[1] can be obtained in high yield and in preparative quantities, including enantiomerically pure form, by the reduction of the corresponding macrocyclic Schiff bases, which are formed during the [3 + 3] cyclocondensation of aromatic dialdehydes with diamines.[2] These compounds and their hydrogenated derivatives (macrocyclic polyamines) form stable complexes of a certain stoichiometry with various aromatic compounds,[3] and their non-racemic complexes with copper and zinc salts allow stereospecific transformations, *e.g.*, aldol condensation, to occur, with *ee* values of the products up to 85%.[4,5] Moreover, trianglamine forms crystalline molecular complexes of varying stoichiometry with a wide range of aromatic compounds, which may be of interest for biomedical application. Significant limitation for the use of such a macrocycle in biological systems is its insolubility in water. This difficulty can be overcome by using trianglamine as the core of star-shaped polymers whose arms would provide the solubility of the object, while the core provides the complexation ability of the polymer. One of the most well-studied classes of thermosensitive pseudo-polypeptoids is poly-2-alkyl-2-oxazolines. They demonstrate low-critical solubility temperature in aqueous solutions while their phase transition temperatures depend on the length of the side substituent and can range from practically zero to 100 °C.[6] Due to their biocompatibility and stability in biological media, they found applications in medicine and biotechnology. In particular, complexes of linear poly-2-alkyl-2-oxazolines with low molecular weight are used as delivery systems for drugs, DNA, as well as materials for creating biocompatible composite structures.[7] Poly-2-alkyl-5,6-dihydro-4*H*-oxazines are homologs of poly-2-alkyl-2-oxazolines. The presence of an additional methylene group in the monomer unit makes them more hydrophobic than poly-2-alkyl-2-oxazolines.[8] It should be noted that poly-2-alkyl-5,6-dihydro-4*H*-oxazines have a number of advantages over poly-2-alkyl-2-oxazolines. For example, they do not undergo irreversible crystallization in water upon prolonged heating above the phase separation temperature, which is characteristic of poly-2-isopropyl-2-oxazoline.[9] It seems even more significant that they possess better binding of water-insoluble medicinal compounds.[10] In our opinion, thermosensitive star-shaped polymers with a trianglamine core can be useful nanocontainers for europium and gadolinium ions and can be employed as contrast agents for magnetic resonance imaging studies, given the possibility of concentrating the contrast agent near the affected organ, the temperature of which is often higher than the temperature of the surrounding tissues. Such polymers can also be used for the solubilization of hydrophobic biologically active substances.

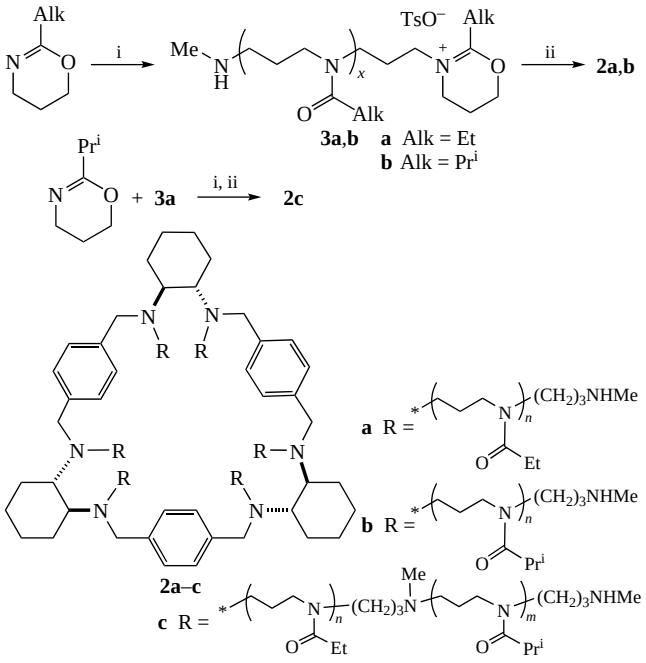
In this study, we aimed to obtain some new star-shaped polymers. Initially, according to the known procedure,[3] we synthesized trianglamine **1** by the [3 + 3] cyclocondensation of terephthalic aldehyde and *trans*-1,2-cyclohexanediamine followed by the reduction of the intermediate Schiff base with sodium tri(acetoxy)borohydride (Scheme 1). When trianglamine **1** was treated with excess $EuCl_3$ in an NMR tube, the Job's plot analysis clearly showed the 1 : 1 complex **1** · $EuCl_3$ formation; the similar phenomenon was observed for curcumin. The latter is a promising drug candidate with pleiotropic antineoplastic activity whose exceptionally low aqueous solubility prevents its medical applications. The double reciprocal Benesi–Hildebrand plot shows that the binding constant in this system is about 2.1×10^5.

A grafting-on approach was used to prepare star-shaped polymers **2a–c** with a trianglamine core and thermosensitive poly-5,6-dihydro-4*H*-oxazine arms. In this case, the preliminarily synthesized arms **3a**,**b** were reacted with core **1** containing amino functions complementary to the terminal groups of the arms (Scheme 2). 'Mixed' arm with both Et and Pr^i groups was prepared by elongation of 'living' polymer **3a** with 2-isopropyl-5,6-dihydro-4*H*-oxazine; its final termination with triaglamine **1** afforded 'mixed' star **2c**.

It is well known[11] that amino groups are effective terminators of growing chains of 2-alkyl-2-oxazolines as well as 5,6-dihydro-4*H*-oxazines, although steric hindrances in the case of a triangular amine require the selection of conditions that ensure



Scheme 1 *Reagents and conditions*: i, MeOH, room temperature, 12 h; ii, $NaBH(OAc)_3$; iii, $CDCl_3$, room temperature, anhydrous $EuCl_3$ (2 molar excess).



Scheme 2 *Reagents and conditions*: i, MeOTs, sulfolane, 70 °C, 48 h; ii, trianglamine **1**, Cs_2CO_3, sulfolane, 100 °C, 2 h.

the addition of all six arms. It was found that carrying out the reaction with a 3-fold excess of oligo-5,6-dihydro-4*H*-oxazines **3a**,**b** in the presence of cesium carbonate made it possible to achieve a degree of functionalization of 0.95–0.97, if the reaction is performed in thermodynamically 'good' solvents, both for poly-5,6-dihydro-4*H*-oxazines and for a triangular amine, for example, sulfolane.[12,13] Otherwise, the yield of the target product decreases along with completeness of the functionalization of the core with polyoxazine arms.

In the prepared star-shaped polymers **2a**–**c**, molar masses of the arms (M_{arm}) were obtained from the GPC data (Table 1). It can be seen that their polydispersity indices $Đ$ are low. The M_w values of polymers **2a**–**c** were measured by the light scattering method in 2-nitropropane (see Table 1). Comparison of molar masses of single arms and full molecules **2a**–**c** confirmed the six-arm structure of the latter.

Table 1 Molecular weight characteristics of polymers.

Sample	M_w/g mol^{-1}	M_{arm}/g mol^{-1}	$Đ_{arm}$	T_1/°C
2a	12 500	1900	1.12	65
2b	12 200	1750	1.22	25
2c	19 300	2050	1.31	42

Thermoresponsive behavior was studied using light scattering and turbidimetry methods at a given concentration $c = 0.005$ g cm^{-3}. It was shown that the phase separation temperature T_1 for sample **2c** differs between samples with homopolymer arms.

We also attempted the complexation of polymers **2a**–**c** with $EuCl_3$, analogously to non-modified triaglamine **1** (see Scheme 1). Predictably, due to strong broadening of the characteristic signals for benzylic protons it was difficult to quantify the changes in the chemical shifts when the $CDCl_3$ solutions of **2a**–**c** were treated with $EuCl_3$; however, the spectra of free polymers and those treated with $EuCl_3$ slightly differed. The complexation of polymers **2a**–**c** with rare-earth cations will be the topic of our future research. In conclusion, the present polymers seem of interest for different biomedical applications like NMR tomography, drug delivery systems, *etc*.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.09.038.

References

1 J. Gawronski, H. Kolbon, M. Kwit and A. Katrusiak, *J. Org. Chem.*, 2000, **65**, 5768.
2 N. E. Borisova, M. D. Reshetova and Y. A. Ustynyuk, *Chem. Rev.*, 2007, **107**, 46.
3 J. Gawronski, K. Gawronska, J. Grajewski, M. Kwit, A. Plutecka and U. Rychlewska, *Chem. – Eur. J.*, 2006, **12**, 1807.
4 J. Gao and A. E. Martell, *Org. Biomol. Chem.*, 2003, **1**, 2795.
5 K. Tanaka and S. Hachiken, *Tetrahedron Lett.*, 2008, **49**, 2533.
6 T. Lorson, M. M. Lübtow, E. Wegener, M. S. Haider, S. Borova, D. Nahm, R. Jordan, M. Sokolski-Papkov, A. V. Kabanov and R. Luxenhofer, *Biomaterials*, 2018, **178**, 204.
7 O. Sedlacek and R. Hoogenboom, *Adv. Ther.*, 2019, **3**, 1900168.
8 M. M. Lübtow, L. Hahn, M. S. Haider and R. Luxenhofer, *J. Am. Chem. Soc.*, 2017, **139**, 10980.
9 A. Zahoranova and R. Luxenhofer, *Adv. Healthcare Mater.*, 2021, **10**, 2001382.
10 Z. Varanaraja, J. Kim and C. R. Becer, *Eur. Polym. J.*, 2021, **147**, 110299.
11 O. Nuyken, G. Maiec and A. Gross, *Macromol. Chem. Phys.*, 1996, **191**, 83.
12 A. N. Blokhin, T. Yu. Kirila, N. D. Kozina, A. B. Razina, A. P. Filippov and A. V. Tenkovtsev, *Mendeleev Commun.*, 2022, **32**, 247.
13 A. Smirnova, T. Kirila, A. Blokhin, N. Kozina, M. Kurlykin, A. Tenkovtsev and A. Filippov, *Eur. Polym. J.*, 2021, **156**, 110637.

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