Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2023, **33**, 360–361

Mendeleev Communications

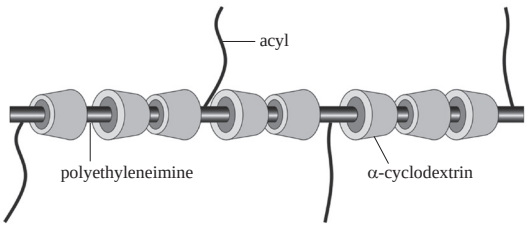
New type polyrotaxanes based on polyethyleneimine and α-cyclodextrin

Mikhail P. Kurlykin,* Mariya A. Golovina and Andrey V. Tenkovtsev

Institute of Macromolecular Compounds, Russian Academy of Sciences, 199004 St. Petersburg, Russian Federation. E-mail: mike_x@mail.ru

DOI: 10.1016/j.mencom.2023.04.020

Functional polyrotaxanes of *N*-alkanoylpolyethyleneimine@α-cyclodextrin type are synthesized by acylation of the polypseudorotaxane precursor, namely, a polyethylenimine@α-cyclodextrin inclusion complex, with excess of carboxylic acid anhydrides. In the course of the processing, α-cyclodextrin moieties are also fully *O*-acylated. The introduction of acyl moieties into polyethyleneimine backbone prevents the expulsion of α-cyclodextrin rings from this backbone.



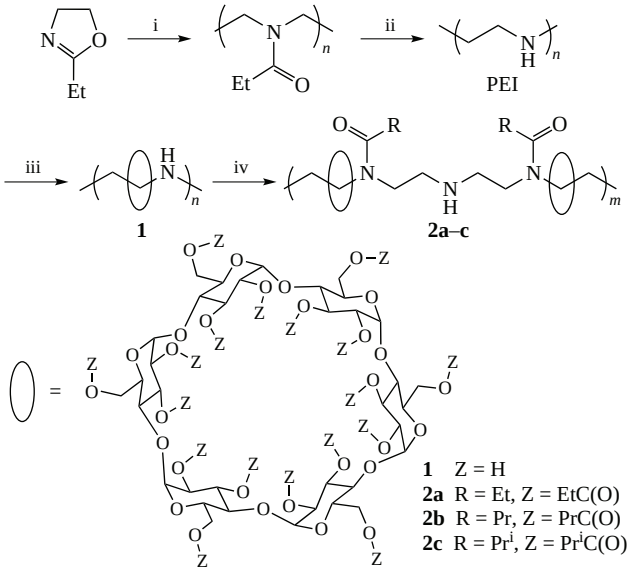
Keywords: polyrotaxane, polyoxazolines, cyclodextrin, polyethyleneimine, complexes, inclusion compounds, acylation.

Due to its successful transfection performance *in vitro* and inherent ability to efficiently condense genetic materials, polyethyleneimine (PEI), a commercially available gene transfection reagent, can be regarded as a promising nonviral vector. However, its low transfection efficiency *in vivo*, along with high cytotoxicity, limits its further application in gene therapy. In the meantime, polyrotaxane based on linear PEI and α-cyclodextrin (α-CD) showed better transfection efficiency and lower cytotoxicity.[1–4] Rotaxanes belong to supramolecular compounds consisting of interlocked macrocycles threaded onto backbone macromolecule.[5–11] Rotaxane synthesis is generally not easy because of multistep procedures, labor-intensive purification and low yields of the resulting compounds. Hence, the search for high-yield and labor-saving methods for rotaxane synthesis is an important problem of supramolecular chemistry.

A typical approach to polyrotaxanes is a preliminary synthesis of polypseudorotaxanes based on a spontaneous formation of a supramolecular inclusion complex between a linear polymer and CD by simple mixing of aqueous solutions of components. Such complexes are dynamic systems and exist in equilibrium with the initial components in the solution. To avoid dethreading, pseudorotaxane end groups are usually capped with bulky groups or polymers. This article debates a new alternative way to prevent dethreading of macrocycles by partial acylation of the PEI backbone of polypseudorotaxane. Beyond that, the proposed approach prevents the aggregation of CD moieties, thus making the products water insolubile.[12,13]

The starting linear PEI was synthesized as reproted[14] by comprising cationic ring opening polymerization of 2-ethyl-2-oxazoline (Scheme 1, stage i). Methyl tosylate was used as a polymerization initiator, and acetonitrile was used as a solvent.† Keeping in mind that conventional heating hardly gives macromolecular products,[15–17] the reaction was carried out under microwave irradiation.[18–20] Based on the static light scattering data, the resulting poly(*N*-propionylethyleneimine) had an average molecular weight M_w = 16000 D, *i.e.*, had a degree of polymerization of about 150–160 and, according to the GPC data, the polydispersity coefficient M_w/M_n was 1.12. The subsequent acidic hydrolysis of intermediate poly(*N*-propionylethyleneimine) afforded linear PEI (see Scheme 1, stage ii).

It is known[21] that the polypseudorotaxane formation highly depends on the pH value (see Scheme 1, stage iii). No complex formation was observed for the mixture of CD and PEI homopolymer below pH 9 due to energetically unfavorable interaction between the cavities of CD molecules and the ionized PEI chains. The polypseudorotaxane formation is closely related to the protonation of secondary amine groups of PEI. In order to synthesize the desired polypseudorotaxane **1**, aqueous solutions of PEI and CD were mixed, and the pH value was then adjusted to 12 with 5 M NaOH followed by subsequent sonification at 60 °C for 20 min. Under these highly basic conditions, polypseudorotaxane partially precipitated that prevented dethreading of the macrocycles. Large excess of carboxylic acid



Scheme 1 *Reagents and conditions*: i, TsOMe, MeCN, MW, 80 °C, 48 h; ii, HCl, 100 °C, 12 h; iii, α-cyclodextrin, H_2O, NaOH (pH 12), 60 °C, sonication, 10 min; iv, $(RCO)_2O$, H_2O, 3–5 °C, 1 h.

† For the synthesis and characterization of polymers **1** and **2a–c**, see Online Supplementary Materials.

anhydride (propionic, butyric or isobutyric added to the reaction mixture caused acylation of amine groups of PEI (stage iv) to produce polyrotaxanes **2a**–**c**. This would arrange the sterical hindrance along the polymer backbone and makes supramolecular complex destruction impossible. Importantly, in the course of the acylation, CD moieties also acquired acyl groups onto oxygen atoms.

The structure of polyrotaxanes **2a**–**c** was verified by NMR spectroscopy. For instance, in the ^{1}H NMR spectrum of rotaxane propionyl–PEI@CD **2a**, multiplets at 5.52–3.44 ppm can be attributed to acetylated CD moieties, while signals of the acylated PEI chain locate at 3.36 ($CH_2C\mathit{H}_2N$), 2.28 ($CO–C\mathit{H}_2–CH_3$) and 0.96 ($CO–CH_2–C\mathit{H}_3$). The ^{13}C NMR spectrum contains signals at 174.43 (COO), 173.78 (CON), 27.14 ($CO–\mathit{C}H_2–CH_3$) and 9.45 ($NCO–CH_2–\mathit{C}H_3$) assigned to propionyl groups along with signals for the CD ring at 99.1 (C^1), 73.7 (C^4), 72.4 (C^2), 72.3 (C^3), 69.4 (C^5) and 63.4 (C^6). The GPC data show that the obtained samples are monomodal, which, combined with the spectral data, confirms the polyrotaxane structures **2a**–**c**. Additionally, the 1D DOSY NMR spectrum confirms the equal diffusion coefficient of all components in the supramolecular structure. It is necessary to point out that according to ^{1}H NMR data the threading density of macrocycles onto PEI backbone is about one CD molecule per seven PEI monomeric unites.

In conclusion, the present method provides an expedient route for polyrotaxane synthesis with an easy one-step high-yield preparation of desired structures at low cost and with a potential for large-scale manufacturing of polyrotaxanes.

This work was supported by Russian Science Foundation (grant no. 22-23-00280).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.04.020.

References

1 L.-Z. Hu, N. Wan, X.-X. Ma, Z.-W. Jing, Y.-X. Zhang, C. Li, Z. S.-Y. Zhou and B.-L. Zhang, *Nanotechnology*, 2017, **28**, 125102.
2 T. Ooya, H. S. Choi, A. Yamashita, N. Yui, Y. Sugaya, A. Kano, A. Maruyama, H. Akita, R. Ito, K. Kogure and H. Harashima, *J. Am. Chem. Soc.*, 2006, **128**, 3852.
3 N. Yui, R. Katoono and A. Yamashita, *Adv. Polym. Sci.*, 2009, **222**, 55.
4 R. Ardeleanu, A. I. Dascalu, A. Neamtu, D. Peptanariu, C. M. Uritu, S. S. Maier, A. Nicolescu, B. C. Simionescu, M. Barboiue and M. Pinteala, *Polym. Chem.*, 2018, **9**, 845.
5 F. Huang and H. W. Gibson, *Prog. Polym. Sci.*, 2005, **30**, 982.
6 (*a*) J. Li, *J. Drug Delivery Sci. Technol.*, 2010, **20**, 399; (*b*) V. D. Badwaik, E. Aicart, Y. A. Mondjinou, M. A. Johnson, V. D. Bowman and D. H. Thompson, *Biomaterials*, 2016, **84**, 86.
7 B. L. Tardy, S. Tan, H. H. Dam, T. Suma, J. Guo, G. G. Qiao and F. Caruso, *Biomacromolecules*, 2017, **18**, 2118.
8 P. Gawel, S. L. Woltering, Y. Xiong, K. E. Christensen and H. L. Anderson, *Angew. Chem., Int. Ed.*, 2021, **60**, 5941.
9 M. Burkeev, S. Fazylov, R. Bakirova, A. Iskineyeva, A. Sarsenbekova, E. Tazhbaev and S. Davrenbekov, *Mendeleev Commun.*, 2021, **31**, 76.
10 M. V. Papezhuk, V. A. Volynkin and V. T. Panyushkin, *Russ. Chem. Bull.*, 2022, **71**, 430.
11 Z. Muldakhmetov, S. Fazylov, O. Nurkenov, M. Burkeev, A. Sarsenbekova, A. Gazaliev, A. Muratbekova and S. Davrenbekov, *Mendeleev Commun.*, 2022, **32**, 816.
12 J. Li, X. Yu, Y. Zhao, H. Zhang, M.-H. Li and J. Hu, *Polym. Chem.*, 2020, **11**, 6492.
13 P. Saokham, C. Muankaew, P. Jansook and T. Loftsson, *Molecules*, 2018, **23**, 1161.
14 H. M. L. Lambermont-Thijs, F. S. van der Woerdt, A. Baumgaertel, L. Bonami, F. E. Du Prez, U. S. Schubert and R. Hoogenboom, *Macromolecules*, 2010, **43**, 927.
15 Z. Varanaraja, J. Kim and C. R. Becer, *Eur. Polym. J.*, 2021, **147**, 110299.
16 R. Hoogenboom, *Macromol. Chem. Phys.*, 2007, **208**, 18.
17 N. Luedecke, S. Weidner and H. Schlaad, *Macromol. Rapid Commun.*, 2020, **41**, 1900404.
18 R. Hoogenboom, M. W. M. Fijten and U. S. Schubert, *Macromol. Rapid Commun.*, 2004, **25**, 339.
19 K. Kempe, A. Baumgaertel, R. Hoogenboom and U. S. Schubert, *J. Polym. Sci., Part A: Polym. Chem.*, 2010, **48**, 5100.
20 M. Kang, S. Y. Lee, H. H. Shin, Y. C. Yu and J. H. Youk, *Polymer*, 2016, **87**, 108.
21 H. S. Choi, T. Ooya, S. C. Lee, S. Sasaki, M. Kurisawa, H. Uyama and N. Yui, *Macromolecules*, 2004, **37**, 6705.

Received: 19th January 2023; Com. 23/7087