Synthesis and supramolecular assembly of fluorinated biogenic amine recognition host polymers†

Ervin Kovács, János Deme, Gábor Turczel, Tibor Nagy, Vajk Farkas, Sándor Kéki, László Tríf, Sándor Kéki, Péter Huszthy and Robert Tuba*

Copolymers containing hydroxyl (i.e. vinyl alcohol, VA) or fluorine functionalities are synthetic macromolecules having promising biomedical applications. The concentration of hydroxyl groups along the polymer backbone as a side-chain. They can be involved in the main chain or attached covalently to a polymer backbone as a side-chain. The synthesis of such host polymers can be carried out not only by classical polymerization methods but also via ring opening metathesis polymerization (ROMP) reactions. Crown ethers can form stable complexes not only with metal cations but also with protonated amines. This possibility has prompted many studies of CEs with peptides and proteins. The utilization of CEs in medical applications is emerging. For example, amino-crown ethers have been utilized for the delivery of 5-fluorouracil (5-FU), an anticancer agent used for the treatment of metastatic carcinomas of pancreas and breast. Moreover, several 18-crown-6-ethers have shown antitumor activity and reversal effect on multidrug resistance.

We have recently reported the synthesis of vinyl alcohol (VA) copolymers having fine tuneable polarities, which are considered as emerging nanocomposite materials for drug delivery applications. Fine tuning of the polarity of drug delivery polymers may enable preprogrammed and sustained drug release. Moreover, it is envisioned that the fine tuning of the polarity of the CEs containing host polymers should make possible the transport of highly hydrophilic biogenic amines in a non-polar environment using a well-adjusted lipophilic polymer/nano-

Introduction

Supramolecular chemistry utilizes reversible non-covalent bonding for the assembly of molecular architectures. Crown ethers (CEs) are well-known host molecules in supramolecular chemistry. Due to their excellent selectivity, crown ether-based molecular recognition motifs are widely used to synthesize polymers with unique properties. They can be involved either in the main chain or attached covalently to a polymer backbone as a side-chain. The synthesis of such host polymers can be carried out not only by classical polymerization methods but also via ring opening metathesis polymerization (ROMP) reactions. Crown ethers can form stable complexes not only with metal cations but also with protonated amines.

This possibility has prompted many studies of CEs with peptides and proteins. The utilization of CEs in medical applications is emerging. For example, amino-crown ethers have been utilized for the delivery of 5-fluorouracil (5-FU), an anticancer agent used for the treatment of metastatic carcinomas of pancreas and breast. Moreover, several 18-crown-6-ethers have shown antitumor activity and reversal effect on multidrug resistance.

We have recently reported the synthesis of vinyl alcohol (VA) copolymers having fine tuneable polarities, which are considered as emerging nanocomposite materials for drug delivery applications. Fine tuning of the polarity of drug delivery polymers may enable preprogrammed and sustained drug release. Moreover, it is envisioned that the fine tuning of the polarity of the CEs containing host polymers should make possible the transport of highly hydrophilic biogenic amines in a non-polar environment using a well-adjusted lipophilic polymer/nano-

*Institute of Materials and Environmental Chemistry, Research Centre for Natural Sciences, Hungarian Academy of Sciences, Magyar tudósok körútja 2, P.O. Box 286, H-1519 Budapest, Hungary. E-mail: tuba.robert@ttk.mta.hu
†Department of Applied Chemistry, University of Debrecen, Egyetem tér 1, H-4032 Debrecen, Hungary
‡Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, Szent Gellért tér 4, H-1111 Budapest, Hungary
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composite matrix. For example, it is tentatively supposed that tagging of dopamine via non-covalent reversible bonds to semi- or non-polar host polymers may enable its direct transport through the blood–brain barrier, leading to alternative treatment of Parkinson’s disease.\textsuperscript{15,16} Furthermore, the introduction of perfluorinated organic moieties may open the way to magnetic resonance imaging (MRI) active properties of the potential drug carrier macromolecules.\textsuperscript{17} Here, we report the synthesis and supramolecular assembly of hydroxyl and fluorine functionalized biogenic amine recognition host polymers.

**Results and discussion**

**Norbornene-functionalized pyridino-18-crown-6 ether (7)** synthesis

As shown in Scheme 1, norbornene-functionalized pyridino-18-crown-6 ether 7 was synthesized via chelidonic acid (1) in 15\% overall yield. 1 was prepared from diethyl oxalate and acetone in the presence of sodium ethoxide according to literature sources.\textsuperscript{18} Treatment of 1 with aqueous concentrated ammonium hydroxide resulted in chelidamic acid (2).\textsuperscript{19} Esterification was carried out with thionyl chloride and methanol leading to chelidamic acid dimethyl ester (3).\textsuperscript{20} Following the Mitsunobu reaction of 3 with the endo norbornene derivative 4, the ether 5 could be obtained by column chromatography. The reduction of 5 to diol 6 followed by macrocyclization gave the crown ether 7 in moderate yield (42\%). When the mixture of endo/exo isomers of 5 was used without separation, the product 7 contained endo and exo stereoisomers in 74\% and 26\% ratios, respectively.

**Complexation of pyridino-18-crown-6 ether (7) with biogenic amines**

The complexation of crown ether (7) with dopamine hydrochloride (12) (Fig. 1, 2 and Fig. S47†) and \textit{l}-alanyl-\textit{l}-lysine dipeptide hydrochloride (13) (Fig. 2 and Fig. S48†) has been investigated. Upon mixing 7 with 12, the C(py)-CH\textsubscript{2}-O proton signals of 7 shifted upfield significantly from 4.64 to 4.57 ppm (Fig. 1). This is aligned with the literature data reported for the complexation of organic ammonium salts and similar pyridino-18-crown-6 ethers.\textsuperscript{21–24} The titration of 7 with 12 indicated a gradually increasing upfield shift of C(py)-CH\textsubscript{2}-O signals of 7 (4.64 ppm) until reaching the stoichiometric ratio. However, as the stoichiometric ratio has been achieved there was no further significant shifts observed for the C(py)-CH\textsubscript{2}-O signal in \textit{1H} NMR spectra (Fig. 1). Based on the chemical shift changes, log $K$ = 4.3 ± 0.6 could be calculated,\textsuperscript{25} which is consistent with the reported data for similar complexes shown in Fig. S54.† Izatt et al. found a slightly lower log $K$ value of 3.62 for the complexation of a bulkier isoalkyl-ammonium ion, (R)-1-phenylethylamine with a less flexible dimethylated pyridino-18-crown-6 ether molecule (see details of calculation in the ESI).\textsuperscript{25} The $K$ values for complexation of crown ethers using ammonium salts are in general high, and the equilibrium is shifted toward the complex formation side.\textsuperscript{21–24} Reproduction of the complexation using dipeptide 13 resulted in a similar supramolecular complex formation (see also ESI Fig. S48†).

**Scheme 1** Synthesis of norbornene-functionalized pyridino-18-crown-6 ether (7).

**Fig. 1** Investigation of the complexation of 7 (endo/exo mixture) with 12 by a titration \textit{1H} NMR method. Chemical shifts of pyridino-18-crown-6 ether methylidene protons (red) vs. 12: 7 molar ratios. Black: 0; brown: 0.3; green: 0.6; light blue: 1.0; dark blue: 1.5; red: 2.0 (MeOD–CD\textsubscript{2}Cl\textsubscript{2} 1:1 mixture, [7] = [12] = 0.01 mmol mL\textsuperscript{−1}).
Electronic structure calculations using Gaussian 09 program package\textsuperscript{26} were carried out to determine the lowest-energy conformers of 7 and its complexes formed with dopamine·HCl (12) and L-alanyl-L-lysine dipeptide·HCl (13) at the M06-2X/cc-pVDZ level of density functional theory (DFT)\textsuperscript{27,28} using the SMD implicit solvent model.\textsuperscript{29} Coordinates of optimized geometries are listed in the ESI.\textsuperscript{†} Molecular dynamics (MD) studies with explicit solvent molecules and accurately parameterized solvent–solute interaction are needed to account for such a complex environment.\textsuperscript{30} Implicit solvent models do not allow the realistic treatment of solvent mixtures, especially in the case of different solvent types (e.g., protic vs. aprotic, highly polar vs. slightly polar/apolar).

The recent MD study of Benay and Wipff investigated solvation and complexation of alkali cations (picrate salts) by 18-crown-6 in a 90:10 chloroform/methanol mixture and found that the ions and the highly polar moieties are surrounded mainly by the polar and protic methanol molecules.\textsuperscript{30} Accordingly, they found that the calculated free energy change of complexation in the solvent mixture was very much like in pure methanol as intense interaction energies of polar and ionic groups dominated the energy change of the process. While specific MD studies are beyond the scope of the present work, these findings allow a realistic treatment of the complexation in methanol/dichloromethane and methanol/chloroform 50/50 solvent mixtures even with an implicit solvent model if pure methanol solvent is assumed.

Consequently, all electronic structure calculations presented here were carried out using methanol as an implicit solvent. A systematic (though probably non-exhaustive) DFT exploration of the high-dimensional conformational space of the crown ether ring identified several low-energy conformers for 7.

The one with the lowest energy is shown in three perpendicular directions in Fig. 2 (top three 3D structures). The minimum energy structure of the pyridino-18-crown-6 ether ring is largely different from the regular chair-type $S_6$-symmetric structure expected for 18-crown-6 ethers. Driven by secondary interactions, the crown shrinks and folds back over the pyridine ring. Complexation of 7 with dopamine and L-alanyl-L-lysine dipeptide hydrochloride (12 and 13) was investigated in methanol as an implicit solvent without explicit consideration of the chloride ion and by assuming a zwitterionic form for the dipeptide (Fig. 2).

During complexation, the crown ether folds out, and the cavity of the macrocycle expands and takes on a much more regular shape that can host the primary ammonium cations. Complexation of 12 proceeds by forming three H-bonds (distributed at every $\sim$120°) with the crown ether by two different ways: either involving the nitrogen atom of the pyridine ring (7+12 complex I) or without it (7+12 complex II) (Fig. 2 middle two 3D structures). The former is energetically favored when no other interactions of the ligand with the crown ether are considered. However, when the nitrogen atom is not involved in the complexation, the conformational motion of the dopamine allows the aromatic ring of the dopamine to fold back over the pyridine ring (Fig. 2 middle right) and this structure
is stabilized by π-π interactions.25 The protonated dipeptide cation can form a complex with the crown ether via either its lysine side chain (7+13 complex I) or its N-terminal (7+13 complex II) (Fig. 2 bottom two 3D structures). The formation of the intramolecular H-bond on the one hand significantly lowers the energy of the latter structure, and on the other hand, it hinders its conformational motion. The crown ether (7) and all complexes of 7+12 and 7+13 turned out to be very flexible as they have several low-energy very low-frequency vibrational modes (∼20 cm⁻¹). Thus, to assess their relative stability through their standard free energy differences, full conformational sampling using MD simulations30 would be required. This, however, is beyond the scope of this study. Nevertheless, one can conclude that in proteins, which are the main targets of the proposed application, complexation through the lysine side chain will be dominant statistically as the number of lysine residues in them is usually much higher than one.

**Polymer synthesis**

Cycloolefin-functionalized crown ethers are expected to participate in polymerization and co-polymerization reactions such as ruthenium-catalyzed ring-opening metathesis polymerization (ROMP).31,32 Indeed, it was found that the norbornene-functionalized pyridino-18-crown-6 ether can readily be polymerized using commercially available ruthenium metathesis catalysts G2 (Grubbs 2nd generation catalyst) and G3 (Grubbs 3rd generation catalyst). Although G2 provides polynorbornene having a moderate polydispersity (D > 1.5) – especially at relatively high catalyst loading – it has a higher functional group tolerance compared to the G3 metathesis catalysts.33 The ROMP reactions of norbornenes, in general, are relatively straightforward reactions, and they can be carried out at a low catalyst loading in any common organic solvent giving insoluble high molecular weight polymers.34

In these tests, however, a relatively high (2 mol%) catalyst loading was applied to obtain relatively short polymers (M_w (mass-average molar mass) < 20 kDa) with reasonable THF solubility for GPC analysis. The ROMP of 7 was carried out at room temperature in dichloromethane using the G2 catalyst giving the homopolymer poly-7 in 99% isolated yield (Table 1). The formed polymer was sparingly soluble in CDCl₃, CD₂Cl₂ and CD₂Cl₂/MeOD mixture (1:1); however, it was poorly soluble in THF, which did not allow its GPC analysis. When the polymerization was carried out using the G3 catalyst, the product showed increased THF solubility (M_w 1.53 × 10³ Da, D (dispersity): 1.17). This observation can be explained by the significantly faster initiation and living polymerization character of the G3 catalyst leading to polymers with lower M_w values and narrow dispersity (D).33 MALDI-TOF MS measurements showed molecular weights corresponding to the oligomers containing 7 units (m/z: 419, Fig. S15f). Preliminary co-polymerizations of 7 have been carried out with norbornene (8) at 1:1 and 1:5 molar ratios using the G3 catalyst.33 The M_w of the copolymers were 4.49 × 10³ Da (D: 1.68) at 7:8 = 1:1 and 7.19 × 10³ Da, (D: 1.87) at 7:8 = 1:5 molar ratio, respectively. Co-polymerization carried out at the 7:8 = 1:1 molar ratio with the G2 catalyst resulted in a non-THF soluble polymer (98% yield) (Scheme 2). However, the co-polymerization of 7 and 8 at the 1:5 molar monomer ratio led to a THF soluble polymer in 97% yield with a comparable molecular weight (M_w: 5.97 × 10³ Da) and higher polydispersity (D: 1.80). The MALDI-TOF MS measurements indicate that the oligomers are comprised of both 7 (m/z: 419) and 8 (m/z: 94) monomer units (Fig. S23f), as expected. Considering the observed molecular weights for cp-7-8 polymers (Table 1), it can be concluded that these data are consistent with the M_w value of polynorbornene synthesized under the similar condition and a slightly lower catalyst loading (0.6 mol%).35

Following the preliminary co-polymerization tests with 8, the incorporation of hydroxyl and perfluoro-tert-butyl groups into the host polymer chain was investigated. Perfluorinated moieties containing monomer 10 was synthesized by the reaction of the tosyl ester derivative of 4 (Tos-4)-16 with the sodium salt of nonafluoro-tert-butyl alcohol37 in reasonable yield (60%). Meanwhile, the bis-perfluorinated moieties containing monomer 11 has been synthesized by the Mitsunobu reaction38 via the reaction of 9 and nonafluoro-tert-butyl alcohol in moderate yield (27%). The co-polymerization of crown ether 7 with 4 and 9 and perfluoro-tert-butyl-functionalized norbornene 10 and 11 gave copolymers having randomly distributed dyads.

The co-polymerization of 7 with 4 in the stoichiometric ratio resulted in the cp-7-4 copolymer in quantitative yield. The polymer does not render any THF solubility. However, it is

### Table 1 MW, polydispersity (D) and glass transition (T_g) and decomposition (T_d) temperature of the synthetized host polymers

| Entry | Polymer | Yield (%) | Cp–M–M′/M/M′ | Catalysts | THF solubility | M_w (Da) × 10³ | D | T_g (°C) | T_d (°C) |
|-------|---------|-----------|--------------|-----------|---------------|----------------|---|---------|---------|
| 1     | poly-7  | 99        | NA           | G2        | Poor          | —              | — | —       | 36      | 347     |
| 2     | poly-7  | 93        | NA           | G3        | Sparing       | 1.53           | 1.17 | —       | —       | —       |
| 3     | cp-7-8  | 98        | 1/1          | G2        | Poor          | —              | — | 14.9    | 329     |
| 4     | cp-7-8  | 95        | 1/1          | G3        | Moderate      | 4.19           | 1.68 | —       | —       | —       |
| 5     | cp-7-8  | 91        | 1/5          | G3        | Moderate      | 7.19           | 1.87 | —       | —       | —       |
| 6     | cp-7-8  | 97        | 1/5          | G2        | Moderate      | 5.97           | 1.80 | 19.7    | 248     |
| 7     | cp-7-10 | 92        | 1/1          | G2        | Poor          | —              | — | —       | 16      | 295     |
| 8     | cp-7-10 | 98        | 1/5          | G2        | Sparing       | 9.85           | 1.43 | a       | 307     |
| 9     | cp-7-11 | 98        | 1/5          | G2        | Moderate      | 5.59           | 2.16 | a       | 403     |

*Crystalline structure, no T_g data were obtained. Cp–M–M′: copolymer of monomer 1 (M) and monomer 2 (M′). M/M′: theoretical monomer 1 and monomer 2 ratio in the copolymer.*
sparingly soluble in the methylene chloride–methanol mixture. The co-polymerization of 7 with 9 led to the formation of entirely insoluble copolymer cp-7-9. These observations are consistent with literature data reporting that poly-4 and poly-9 have minimal solubility in common organic solvents.39 However, the introduction of perfluoro-tert-butyl units has significantly improved the copolymer solubility even in tetrahydrofuran. The co-polymerization of 7 has been carried out with 10 at 1 : 1 and 1 : 5 molar ratios using the G2 catalyst (cp-7-10 (1 : 1): 92% and cp-7-10 (1 : 5): 98% yield) in dichloromethane solution. cp-7-10 (1 : 1) was only sparingly soluble in THF; however, cp-7-10 (1 : 5) rendered reasonable THF solubility. The GPC tests of cp-7-10 (1 : 5) revealed a reasonable Mw = 9.85 × 10³ Da (Đ: 1.43) value (Table 1). As it was expected, the MALDI-TOF MS investigations have clearly indicated that the copolymers are comprised of both 7 (m/z: 419) and 10 (m/z: 342) monomer units as well (Fig. 3). Polymer cp-7-11 containing the bis-perfluoro-tert-butyl moieties in 1 : 5 = 7 : 11 ratio has been synthesized in high yield (98%). The polymer rendered a similar molecular weight and dispersity (5.59 × 10³ Da, Đ: 2.16) to copolymers cp-7-8 and cp-7-10 synthesized under similar reaction conditions (Table 1). Based on the DSC measurements (Table 1), it can be concluded that the inclusion of side groups increases the Td values (as seen at poly-7: 347 °C and cp-7-11 (1 : 5): 403 °C vs. cp-7-8 (1 : 1): 329 °C; cp-7-8 (1 : 5): 248 °C). The co-polymerization of 7 with 8 at the 1 : 1 monomer ratio significantly increased the Tg value (poly-7 = −36 °C; poly-7-8 (1 : 1) = 14.9 °C). However, increasing the 7 : 8 monomer ratio up to 1 : 5 resulted in only a slight increase of the Tg value (poly-7-8 (1 : 5) = 19.7 °C).

Complexation of pyridino-18-crown-6 ether (7)-functionalized polymers with biogenic amines

The complexation of poly-7 with 12 (Fig. 4 and Fig. S49†) and 13 (Fig. S50†) have been investigated by 1H NMR spectroscopy in the MeOD–CD₂Cl₂ 1 : 1 solvent mixture at 30 °C. As expected, upon complexation the poly-7 broad aromatic proton signals shifted upfield from 6.83 to 6.79 ppm; meanwhile, the aromatic protons of 12 have also shown significant shifts from 6.80 (d), 6.76 (d) and 6.62 (dd) ppm to 6.76, 6.71 and 6.55 ppm, respectively (Fig. 4). These observations are in accordance with the literature data reported for the supramolecular complex formation of pyridino-18-crown-6 ethers with protonated primary amines.21 Similar chemical shift could be clearly observed in the aliphatic proton region as well. The aliphatic CH₂ proton signals of 12 shifted from 3.13 (t) and 2.86 (t) ppm to 3.09 and 2.80 ppm, respectively (Fig. 4). As was expected, the proton signals of 12 significantly broadened upon complexation with the crown ether-functionalized polymer.

The complexation of poly-7 with 13 also revealed significant changes of the chemical shifts of the reacting molecules. The
aromatic proton signals of poly-7 shifted upfield from 6.83 ppm to 6.79 ppm (Fig. S50†). Unlike the complexation of 7 with 12, it can be seen that upon complexation of poly-7 with 13 the most characteristic peaks CH (t) (4.33 ppm) and CH2 (t) (2.95 ppm) of 13 have revealed significant chemical shifts to 4.21 ppm and 2.80 ppm; meanwhile, the CH (q) peak at 3.97 ppm did not show any significant changes (Fig. 5, bottom). This observation indicates that the complexation between poly-7 and 13 most probably occurs exclusively via the lysine –NH3+ group rather than the alanine –NH3+ moiety, unlike the complexation between 7 and 13 where all the three peaks revealed significant upshift indicating that it takes place by both –NH3+ moieties (Fig. 5, top).

Following the investigation of the complexation of homopolymer poly-7 with 12, the complexation of perfluoro tert-butyl group-functionalized copolymer cp-7-10 has been investigated (Fig. 6).

As expected, upon addition of 12 to a MeOD–CD2Cl2 solution of cp-7-10 (1 : 1), the aromatic proton signals of 12 (6.81 (d), 6.75 (d) and 6.62 (dd) ppm) significantly shifted to 6.79 (d), 6.73 (d) and 6.60 (dd) ppm, respectively. Meanwhile, broadening of the proton peaks of 12 was observed.

The aliphatic proton signals of 12 have also shifted upfield from 3.13 (t) and 2.86 (t) ppm to 3.12 (t) and 2.84 (t) ppm, respectively (Fig. 6 and Fig. S51†). Meanwhile, the broad aro-
matic CH proton peaks of \textbf{cp-7-10} were also shifted upfield from 6.83 ppm to 6.77 ppm. The observed simultaneous upfield shifts and peak broadenings of 12 clearly indicate an interaction between the polymer (cp-7-10) and Dopamine-HCl (12). The complexation of cp-7-10 with Ala-Lys-HCl (13) led to similar shifts of the pyridino-18-crown-6 ether aromatic protons (from 6.83 (br) to 6.78 (br) ppm) and lysine protons (from 4.33 (t) to 4.26 (br) ppm and from 2.95 (t) to 2.91 (br) ppm) (Fig. S52†). Just as in the case of complexation of cp-7-10 with 12, the proton signal broadening of 13 were unambiguous, indicating the specific intermolecular interaction between cp-7-10 and Ala-Lys-HCl (13). It should be noted that based on the $^1$H NMR spectra, there was significant upshift for the quartet signal of the Ala unit from 3.97 ppm to 3.91 ppm (CH-CH$_3$), indicating that most probably the complexation occurs not only via the protonated lysine side chain but also on the protonated N-terminal alanine dyad (Fig. S52†).

The formed copolymers are not only non-periodic, but also highly flexible; thus, they do not exhibit a well-defined geometry. The all-trans H--(poly-7-10)$_4$--H alternating cooligomer can be considered as the most abundant possible dyad$^{40}$ of the formed host polymers. A local optimum structure of its complex formed with 12 was determined in an implicit methanol solvent using the PM6 semiempirical theory and is shown as an illustration in Fig. 7 to help the reader to visualize them.$^{41}$

Fig. 6 Complexation of poly-7-10 (1:1, bottom) with Dopamine-HCl, 12 (top), and poly-7-10-12 complex (middle) (MeOD–CD$_2$Cl$_2$ 1:1 mixture, 30 °C, [cp-7-10] = [12] = 0.01 mmol mL$^{-1}$).

Fig. 7 A local optimum structure of the all-trans H--(poly-7-10)$_4$--H cooligomer and its complex with 12 (cp-7-(10+12)) determined at the PM6 level of theory in an implicit methanol solvent. Molecular switching to planar structure of pyridino-18-crown-6 ether moieties upon complexation with 12. In the ball and stick representation carbon, nitrogen, oxygen and heteroatom-bound hydrogen atoms are drawn as grey, blue, red and white balls, respectively.
Coordinates of optimized geometries are listed in the ESI.† If no complexation takes place, the strong attraction between the tilted and folded crown ether units aligns them and bends the copolymer chain toward the side groups. In the complex state, the side groups are positively charged due to the presence of the primary ammonium ions. The strong electrostatic repulsion is only partially ameliorated by the methanol solvent (and the scattered, solvated chloride ions). Thus, the side groups tilt away from each other and the polymer chain becomes distorted.

Conclusions

In summary, a wide range of copolymers having host (pyridino-18-crown-6 ether), OH and perfluoro tert-butyl functionalities have been synthesized via ruthenium-catalyzed ring opening metathesis polymerization.

The complexation of poly-7 and its perfluoro-tert-butyl group containing copolymers (poly-7-10) with biogenic amines including dopamine (12) and L-alanyl-L-lysine dipeptide (13) has led to the formation of the supramolecular complexes indicated by $^1$H NMR spectroscopy. Upon complexation, significant upfield shift of the proton signals (0.02–0.06 ppm) of both reactants and peak broadening of the biogenic amines were observed. The investigations have revealed that the complex formation of 13 with monomer 7 and copolymer ep-7-10 may take place via either the lysine or alanine –NH$_2$ moieties. However, in the case of poly-7, the lysine amine group coordination was observed exclusively.

The experimental data have been supported by theoretical calculations, also indicating that the complexation of a biogenic amine to the presented host polymer is straightforward.

It is envisioned that these polymers may have potential to serve as “biogenic amine carriers” opening new alternatives for drug delivery applications.

Conflicts of interest

There are no conflicts to declare.

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