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Multifunctional Fe(III)-Binding Polyethers from Hydroxamic Acid-Based Epoxide Monomers

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Multiple hydroxamic acids are introduced at poly(ethylene glycol) (PEG) via copolymerization of ethylene oxide with a novel epoxide monomer containing a 1,4,2-dioxazole-protected hydroxamic acid (HAAGE). AB- and ABA-type di- and triblock copolymers as well as statistical copolymers of HAAGE and ethylene oxide are prepared in a molecular weight range between 2600 and 12 000 g mol^{-1} with low dispersities ($Đ < 1.2$). Cleavage of the acetal protecting group after the polymerization is achieved by mild acidic treatment, releasing multiple free hydroxamic acids tethered to the polyether backbone. The chelation properties of different polymer architectures (statistical versus diblock and ABA triblock) are investigated and compared with regard to the number and position of hydroxamic acids. Separation of the hydroxamic acid units by at least 5 ethylene glycol monomer units is found to be essential for high Fe(III) binding efficiency, while block copolymers are observed to be the best-suited architecture for polymer network and hydrogel formation via Fe(III) chelation.

In many biomolecules metal ions play a fundamental role to enable a specific function. Nature has exploited this combination of organic molecules with metal ions for a long time, for example, for efficient catalysis or for the formation of composite structures with enhanced mechanical properties.[1] Iron is one of the most prominent metals and is of crucial importance in nature. Iron metabolism disorders are associated with a variety of severe or even fatal diseases.[2] Iron is a highly abundant and essential element for all living organisms.[2] Nevertheless, the bioavailability of iron is limited. Hence, in nature various molecules, the so-called siderophores, enable efficient uptake of iron.[3,4] Siderophores are based on moieties that form strong chelate complexes with iron, such as catechols, hydroxamic acids (HAs), or hydroxy carboxylate groups.[4,5] In the last decade, an increasing number of works focused on the development of biomimetic materials by combining synthetic polymers with chelating groups. Especially catechol-bearing polymers have been investigated, for instance as mussel-mimicking structures, exploiting their excellent interaction with different surfaces.[6,7] A broad scope of applications such as self-healing hydrogels,[8–10] polymeric materials for adhesion,[11] solubilization of nanoparticles,[12] or anchoring of polymers with anti-fouling properties via catechols[13] has been demonstrated in recent years. However, catechols are prone to oxidation due to their phenol-type structure and high electron density in the aromatic system. Contact with air under aqueous basic or even neutral conditions rapidly leads to quinone structures, reducing their chelation properties.[14] This issue was tackled by the development of oxidation stable catechol derivatives, such as 3-hydroxy-4-pyridinone (HOPO)[9] or catechol-derivatives with electron withdrawing groups such as nitrocatechols[15] or chlorocatechols.[16] However, none of these improved catechol-based structures are amenable to direct polymerization to date.

In a recent, conceptual work we described HAs as an alternative to catechols for synthetic polymers.[17] HAs feature excellent chelation properties similar to catechols; however, they are oxidatively stable under physiological conditions.[18] Additionally, they are capable of forming stable complexes with various metal ions in a wide pH range (2 to 12).[19] First examples of poly-HAs were given by Du Pont as early as 1942.[20] Winston and coworkers prepared several poly-HAs by post-polymerization modification of poly(methacrylate) derivatives with hydroxylamine in the 1980ies,[21–23] which is a common principle used to tether HAs to polymers. Except for the in-depth investigation of Winston and coworkers regarding the preparation of poly-HAs, all studies focused solely on the application of HA-modified polymers. Scavenging of rare earth metals[24] as well as medical applications using poly-HAs, for example, for the inhibition of matrix metalloproteases[25] and the development of alternatives to low molecular weight chelators for the treatment of iron overload diseases by employing polymers bearing multiple HA groups[26] have been reported. Very recently, the scavenging of f-block elements by synthetic low molecular weight siderophores and HA-based resins was also demonstrated.[27] In our recent conceptual work we introduced a general approach for the introduction of HAs to polymers and demonstrated the preparation of α-functional polyethers.[17] The current report focuses on introducing multiple hydroxamic moieties to poly(ethylene glycol) (PEG) for

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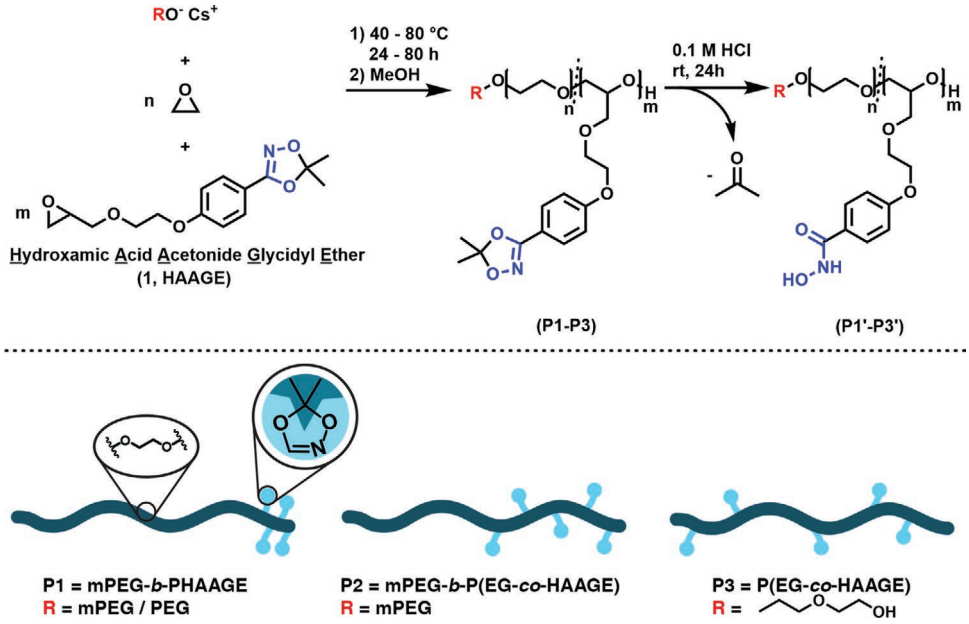
the interaction with metal ions, demonstrated at the example of Fe(III). PEG is the "gold standard" polymer for medical and pharmaceutical application.[28]

Related to the scope of this Special Issue of MRC, we emphasize that pioneering work on poly(ethylene glycol) was carried out as early as 1929 by Hermann Staudinger and Otto Schweitzer, which in fact initiated the research on this key polymer.[29] In our current publication multifunctional polyethers have been prepared by the anionic ring-opening (co) polymerization (AROP) of a novel functional monomer consisting of a protected HA and an epoxide group. The functional monomer "HA acetonide glycidyl ether" (**Scheme 1**, compound 1 designated HAAGE) was prepared by etherification of a hydroxyl functional 1,4,2-dioxazole with epichlorohydrin via phase-transfer catalysis in high yields of 81% on a scale of 20 g (see Figures S1–S5, Supporting Information, for NMR analysis). The hydroxyl-1,4,2-dioxazole precursor was optimized in a previous work of our group to withstand the harsh conditions of an oxyanionic polymerization, while featuring facile release of the free HA moiety by acidic treatment subsequent to polymerization. Hence, the general approach to obtain HA functional polyethers starts with the anionic ring-opening (co)polymerization of HAAGE, employing an alkoxide initiator. Subsequent cleavage of the protecting group after polymerization by the addition of 0.1 M HCl liberates the HA structures.[17]

Three different polymer architectures have been prepared to investigate the influence of the position of the HAs moieties in the polyether chains on their complexation efficiency (Scheme 1). AB and ABA di- and triblock copolymers have been synthesized, based on an (m)PEG macroinitiator (B), in which the A-block represents either a PHAAGE homopolymer (type **P1**) or a P(EG-*co*-HAAGE) (type **P2**) copolymer. Furthermore, statistical copolymers of both monomers EO and HAAGE without the use of an mPEG macroinitiator were synthesized, affording P(EG-*co*-HAAGE) (type **P3**). The copolymerization of glycidyl ethers and ethylene oxide is generally characterized by both reactivity ratios being close to $r = 1$, and thus the formation of ideally random copolymers of HAAGE and EO can be expected.[30] The polymer architectures were systematically varied to alter the density of HAs along the polymer backbone. As already reported by Winston et al., the flexibility and separation of the HA moieties by spacers within the polymer backbone or side chains plays a crucial role to obtain stable octahedral complexes with iron(III).[22]

For all polymers a monomodal, narrow molecular weight distribution ($Đ < 1.2$) was obtained with HA contents of 3–9 mol% in the molecular weight range of 3000 to 12 000 g mol^{-1} (**Table 1**, Figure S12, Supporting Information), supporting the stability of the dioxazole-protected HA-based glycidyl ethers under the harsh conditions of the AROP and confirming the living nature of the copolymerization. At least three terminal HA groups were targeted in the polymers to enable the formation of a tris(hydroxamato)iron(III) complex by a single polymer chain, keeping polymerization statistics in mind. Underestimation of the molecular weights by SEC is ascribed to the structural deviation of the polymers from the PEG calibration standard. Nevertheless, good control over the molecular structure was achieved. ^{1}H NMR analysis (Figure S6, S8, S10, Supporting Information) confirms the incorporation of HAAGE as well as the stability of the 1,4,2-dioxazole group (singlet at 1.6 ppm) against the harsh conditions of the AROP. Multiple incorporation of HAAGE and formation of a (block) copolymer were also confirmed by MALDI-ToF-MS characterization (**Figure 1**, Figures S13c, S14a,b, Supporting Information). Both repeating units (M_{HAAGE} = 297.32 g mol^{-1}; M_{EO} = 44.05 g mol^{-1}) can be detected and assigned. In the case of mPEG$_{118}$-*b*-PHAAGE$_3$ the subdistributions can be assigned as well, confirming the formation of the block copolymer. In the case of higher PHAAGE



Scheme 1. Synthetic approach for the introduction of multiple HA groups (blue) at polyethers (**P1-P3**), providing different polyether topologies (**P1′–P3′**) that enable interaction with various metal ions. The polymer architectures were systematically varied, adjusting the position and distribution of the HAAGE units along the polyether backbone.

Table 1. Overview of the HAAGE-based (block) copolymers **P1–P3**.

Type	Polymer	$Mn^{a)}$ [g mol^{-1}]	$Mn^{b)}$ [g mol^{-1}]	$Đ^{b)}$	T_g [°C]	T_m [°C]	ΔH [J g^{-1}]	mol% $HA_{,theo}$	mol% $HA_{,exp}$	$n_{EG}{}^{c)}/n_{HA}$
P1a	$mPEG_{44}$-*b*-$PHAAGE_3$	2900	2600	1.04	n.d.[d)]	49	82	8.3	6.4	0
P1a	$mPEG_{118}$-*b*-$PHAAGE_3$	6100	6000	1.03	n.d.[d)]	54	101	3.3	2.5	0
P1b	$PHAAGE_{3.5}$-*b*-PEG_{227}-*b*-$PHAAGE_{3.5}$	12 100	13 500	1.05	n.d.[d)]	52	110	3.4	3.0	0
P2	$mPEG_{44}$-*b*-$P(EG_{33}$-*co*-$HAAGE_4)$	4600	3700	1.11	–33	38	68	5.1	4.9	8.3
P2	$mPEG_{44}$-*b*-$P(EG_{34}$-*co*-$HAAGE_6)$	5200	3800	1.06	–34	34	56	9.6	7.1	5.7
P3	$P(EG_{88}$-*co*-$HAAGE_6)$	5700	3800	1.22	–55	24	42	6.3	6.4	14.7
P3	$P(EG_{100}$-*co*-$HAAGE_{10})$	7400	4500	1.20	–47	19	30	6.3	9.1	10.00

[a)]Determined via ^{1}H end group analysis. In case of P1b the size of the PEG block was determined via SEC (PEG, calibration) and used for normalization of the integrals in ^{1}H NMR; [b)]Determined via SEC (DMF, PEG calibration); [c)]Number of ethylene glycol repeating units per HA in the HA (co)polymer part of the total polymer; [d)]n.d. = not detectable.

content (**P2, P3**) the spectra become too complex for detailed assignment due to the high number of linear combinations of the ethylene glycol and HAAGE repeating units.

Thermal properties (differential scanning calorimetry, DSC) showed the perturbation of the crystalline PEG domains by the HAAGE repeating units in the case of polymers formed by the statistical copolymerization of EO and HAAGE, namely mPEG-*b*-P(EG-*co*-HAAGE) **(P2)** and P(EG-*co*-HAAGE) **(P3)** (Figures S16 and S17, Supporting Information). As expected, with increasing HAAGE content both the melting point and melting enthalpy decrease. This is especially pronounced in case of P(EG-*co*-HAAGE) (**P3**) copolymers, in which no (m)PEG macroinitiator is present. Assuming an ideally random copolymer formation, every 10 to 15 ethylene glycol repeating units one HA group interrupts the PEG homopolymer segments. Hence, the degree of crystallization of statistical (**P3**) polymers is low (T_m = 19–24 °C, ΔH = 30–40 J g^{-1}), leading to incomplete crystallization of the PEG segments during the cooling cycle and hence the additional occurrence of a crystallization period during the second heating cycle (Figure S17, Supporting Information). Additionally, due to increased amorphous content, the glass transition is more pronounced in random P(EG-*co*-HAAGE) (**P3**) copolymers. As expected, the thermal properties of the copolymers support a random copolymerization ($r_1 = r_2 = 1$) behavior of HAAGE with ethylene oxide (EO).[30] In contrast, no influence of the HAAGE repeating units on the degree of crystallization of PEG was observed for the AB and ABA block copolymers (**P1**) (Figure S15, Supporting Information).

Cleavage of the protecting group was achieved by treatment of the HAAGE containing polymers **P1–P3** with 0.1 M HCl at room temperature for 24 h to obtain the free HA bearing polymers (HA glycidyl ether, **HAGE) (P1′-P3′)**. Successful deprotection is confirmed by the disappearance of the CH_3-singlet of the 1,4,2-dioxazole group at 1.6 ppm (Figure 1, red) and simultaneous occurrence of the NH and OH signals of the free HAs (Figure 1, blue) in ^{1}H NMR spectrum (see Figures S7, S9, and S11, Supporting Information, for additional ^{1}H NMR spectra of **P1′–P3′**). Additionally, the molecular weight distributions of the polymers are shifted to lower molecular weights due to the loss of 40.07 g mol^{-1} per HAAGE repeating unit (M_{HAGE} = 253.25 g mol^{-1}) (Figures S13a and S14c,d, Supporting Information). Both repeating units can be assigned in the mass spectra. In the case of $mPEG_{118}$-*b*-$PHAAGE_3$ the subdistributions can also be assigned in analogy to the polymer before cleavage of the protecting group (Figure S13b, Supporting Information). No significant influence on the thermal properties was detected

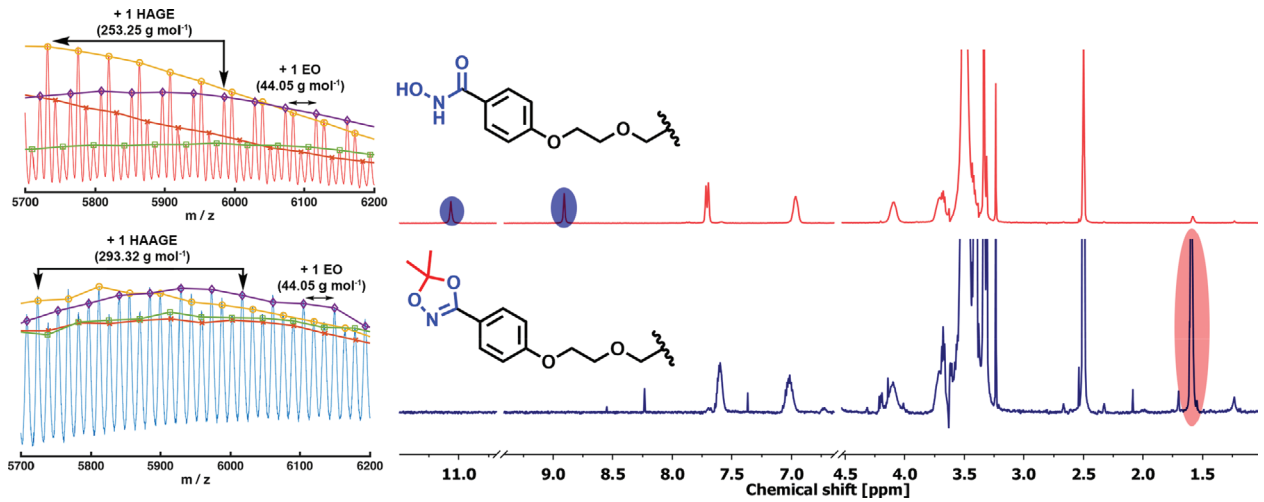


Figure 1. ^{1}H NMR (400 MHz, DMSO-d_6) and representative section of the MALDI-ToF mass spectrum of $mPEG_{118}$-*b*-$PHAAGE_3$ (**P1a**) before (bottom, blue) and after (top, red) cleavage of the protecting group (**P1a'**).

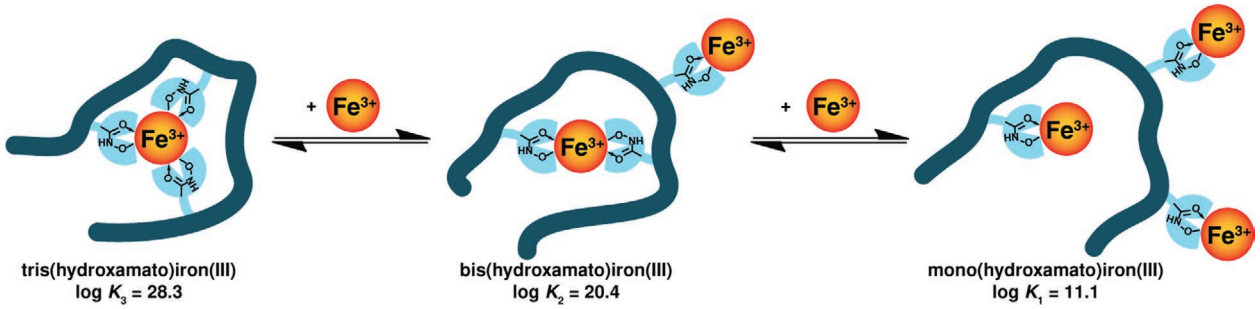


Figure 2. Binding of iron(III) by the HA groups connected to the polyether backbone. Depending on the amount of Fe(III), either the tris-, bis-, or mono(hydroxamato)iron(III) complex is formed. For clarity, only the HA groups of one polymer chain are shown. The stability constants for the low molecular benzo HA complexes are given for comparison.[31]

after the deprotection of the copolymers. A slight increase of the melting point T_m of 0–7 °C can be detected after deprotection (Table S1, Supporting Information) for all samples. However, from these minor changes no structural conclusions can be drawn.

Chelation properties of all polymers (**P1a′**, **P2′**, **P3′**) in aqueous solution (non-buffered) were investigated by UV–vis spectroscopy (Figure 3, Figure S18, Supporting Information), monitoring the formation of the colorful hydroxamato-iron(III) complexes. To reduce intermolecular coordination and to prevent gelation all experiments were performed in high dilution (0.3 µmol mL^{-1} total HA concentration).

The addition of Fe(III) chloride to a solution of P1′–P3′ leads to an instantaneous coloration of the solution due to the formation of tris(hydroxamato)iron(III) complexes ($\lambda_{max} \approx 500$ nm, depending on the molecular architecture) (**Figure 2** and **3**). The absorption increases with further iron(III) addition, until a ratio of Fe(III) per HA group of 1:3 is achieved and all HA groups are complexed.

An additional increase in iron(III) concentration (Fe(III)/HA = 1:2) leads to the cleavage of the tris-coordination to obtain bis(hydroxamato)iron(III) complexes. Finally, at equimolar ratios (Fe/HA = 1:1) mono(hydroxamato)iron(III) complexes are formed. This change in the coordination sphere is accompanied by a bathochromic shift and a less pronounced increase in absorbance.[22,23] In all cases no significant change of the pH values by the addition of the iron(III) solution was observed ($pH_{min} = 6.3$), therefore the use of buffers was omitted. Compared to catechols (log $K_{3,Catechol} = 43.8$)[32] the stability constants of HA complexes (Figure 2) are several orders of magnitude lower, enabling this concentration driven change of the coordination. Additionally, the stability of the polymer complexes was found to depend both on the polymer architecture and the distribution of the HAs, as also shown by Winston at the example of PMMA-based poly-HAs. Due to steric effects the formation of tris(hydroxamto)iron(III) complexes may be impeded.[22,23] This behavior was found for all polymers. However, the separation of the HAGE units by ethylene glycol units (n_{EG}/n_{HA}, Table 1) is correlated with the bathochromic shift. The formation of stable tris complexes (Table S2, Supporting Information) was inhibited in the following order:

$\Delta\lambda \rightarrow$ mono-functional PEG "HA-PEG"[17] (λ_{max} = 553 nm) > mPEG-*b*-PHAGE (**P1′**) (λ_{max} = 540 nm) > mPEG-*b*-P(EG-*co*-HAGE) (**P2′**) (λ_{max} = 520 nm) ≈ P(EG-*co*-HAGE) (**P3′**) (λ_{max} = 518 nm).

In summary, separation of HAGE units by at least five ethylene glycol (polymers **P2′**, **P3′**, see Table 1) units was observed to enhance the stability of the formed intramolecular tris(hydroxamato)iron(III) complexes. In the case of block copolymers with a PHAGE block (**P1**), the close proximity of the adjacent HA groups leads to less stable complexes. In addition, due to the nature of the underlying polymer distribution some polymer chains of the mPEG-*b*-$PHAGE_3$ (**P1a**) polymers possess only one terminal HA moiety, which also impedes the formation of intramolecular tris(hydroxamato)iron(III) complexes. However, in every case superior chelation properties were found compared to mono-HA functional PEG.

In a final demonstration, the chelation properties of the HA bearing polymers were utilized to form polymer networks by iron(III) addition (Figure 3, Figure S19, Supporting Information). Gelation occurs instantaneously by the addition of the $FeCl_3$ solution to an aqueous $PHAGE_{3.5}$-*b*-PEG-*b*-$PHAGE_{3.5}$ (**P1b′**) solution (5 wt%). The resulting solution can be converted to a hydrogel within seconds by thorough mixing. Capitalizing on the high rate of complexation, spatial control over the area of gel formation (Figure S19, Supporting Information) can be achieved. However, when adding an excess of Fe(III) in a competition experiment, intramolecular crosslinks are cleaved again, due to the formation of mono(hydroxamato)iron(III) complexes, as described above. It has to be emphasized that the necessary excess of Fe(III) depends on the pH value of the solution. Simultaneously the color changes from the red tris(hydroxamato)iron(III) complexes (λ_{max} = 460–500 nm, dependent on concentration) to the violet mono(hydroxamato) iron(III) ($\lambda_{max} \approx 540$ nm), as observed via the UV–Vis measurements. An important advantage of HA-based networks compared to catechol-based systems is their high stability in a wide pH-range. The prepared $PHAGE_{3.5}$-*b*-PEG-*b*-$PHAGE_{3.5}$ (**P1b′**) gels were stable in a pH range from 2 to 12.[10]

To our surprise, the statistical copolymers mPEG-*b*-P(EG-*co*-HAGE) (**P2′**) and P(EG-*co*-HAGE) (**P3′**) did not form stable hydrogels by $FeCl_3$ addition, and only a slight increase in viscosity of the polymer solution was observed. This unexpected behavior can be explained by the tendency of P2′ and P3′ to favor the formation of intramolecular tris(hydroxamato)

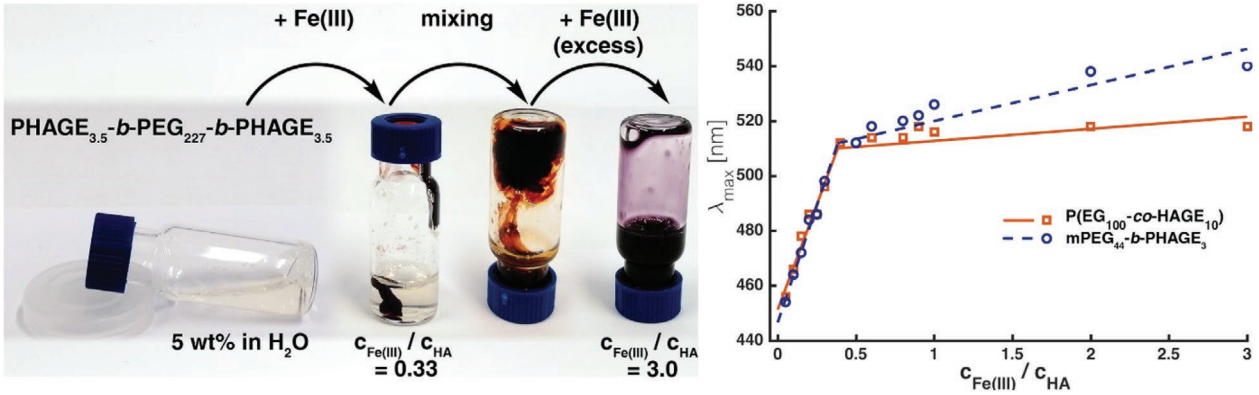


Figure 3. Illustration of Fe(III)induced gelation of ABA block copolymers with PHAGE block (**P1b′**) via complex formation (left image) and the corresponding change in λ_{max} of the absorption spectrum during the course of iron addition to the polymer solution (right).

iron(III) complexes, which is ascribed to the separation of the HAs groups by ethylene glycol repeating units. Hence, little or no crosslinking due to complexation by different polymer chains was observed. In contrast, in the case of ABA-block copolymer **P1b′** intermolecular crosslinking is more likely due to the steric constraints caused by adjacent HAGE units, decreasing the stability of intramolecular tris(hydroxamato) iron(III) complexes.

In conclusion, well-defined polyether copolymers containing multiple HA groups have been prepared for the first time by the anionic ring opening polymerization of a tailored epoxide monomer (HAAGE). Both the concentration as well as the placement of the HAAGE monomers in the chains can be controlled due to the living nature of the epoxide copolymerization. The HAs were liberated by mild acidic treatment without degradation of the polyether backbone. The polymer architecture and distribution of the HA units in the polymers were investigated with respect to their chelation properties. For efficient binding of Fe(III) the separation of HAGE units by at least five ethylene glycol units in random copolymers is beneficial for the intramolecular formation of tris(hydroxamato)iron(III) complexes. In contrast, the proximity of the HAGE units in PHAGE blocks is assumed to favor the formation of intermolecular crosslinks. Hence, for the preparation of hydrogel networks via chelation the use of ABA-block copolymers is proposed. The addition of an excess of Fe(III) dismantles the coordination-based polymer network, leading to a solution again. This responsive behavior is based on the stability of HA complexes (log $K_{3,\text{Hydroxamic acid}} \approx 28$ versus log $K_{3,\text{Catechol}} \approx 43$), which enables efficient complexation of Fe(III), but also features an interesting handle to manipulate the structural properties of these non-covalently crosslinked polymer networks. By using the tailored epoxide HAAGE, the polyether architecture can be precisely controlled. The chelation properties can be optimized to achieve either high iron uptake, when random copolymers are used or instantaneous hydrogel formation in the case of block copolymers. HA-bearing polyethers exhibit high storage stability at physiological conditions without any oxidation, while providing all features known from multiple catechol-based systems.[6] PEG-derived polyethers bearing multiple HAs offer promise as a versatile class of polymeric chelators for biomedical applications, that is, for iron transport and removal in biological systems.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

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