Functional brush poly(2-ethyl-2-oxazine)s: Synthesis by CROP and RAFT, thermoresponsiveness and grafting onto iron oxide nanoparticles

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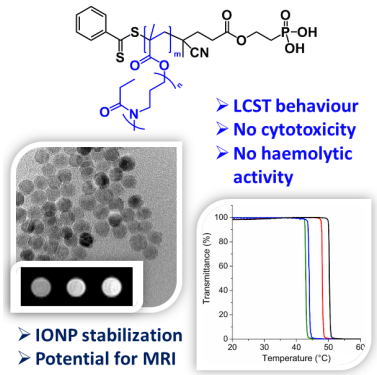

Brush polymers are highly functional polymeric materials combining the properties of different polymer classes, which have found numerous applications, e.g. in nanomedicine. Here, we report the synthesis of functional phosphonate ester bearing brush polymers based on poly(2-oxazine)s through a combination of cationic ring-opening polymerization (CROP) of 2-ethyl-2-oxazine and reversible addition-fragmentation chain transfer (RAFT)

polymerization. In this way, a small library of well-defined ($Đ \leq 1.17$) poly(oligo(2-ethyl-2-oxazine) methacrylate) $P(OEtOzMA)_n$ brushes with tunable lower critical solution temperature (LCST) behavior and negligible cell toxicity was prepared. Upon deprotection, the phosphonic acid end-group of the $P(OEtOzMA)_n$ brush enabled the successful grafting-onto iron oxide nanoparticles (IONPs). Colloidal stability of the particle suspension in combination with suitable magnetic resonance imaging (MRI) relaxivities demonstrate the potential of these particles for future applications as negative MRI contrast agents.

1. Introduction

Poly(cyclic imino ether)s (PCIE) have attracted significant attention in the last decades due to their structural diversity and high functionality.[1] PCIE are obtained by cationic ring-opening polymerization (CROP) of the respective cyclic imino ether, which are heterocyclic compounds possessing the structural motif –N=C(R)-O-. The most prominent member of this polymer family are the poly(2-oxazoline)s (POx),[2] particularly due to the exceptional biomedical properties (e.g., non-cytotoxicity, non-immunogenicity and stealth behavior) of the water-soluble poly(2-methyl-2-oxazoline) (PMeOx) and poly(2-ethyl-2-oxazoline) (PEtOx).[3] The living nature of the CROP as well as the straightforward modulation of the 2-substituent of the monomers enables the synthesis of well-defined tailored POx.[4] Moreover, the possibility to introduce functional groups through the choice of initiators or terminating agents has been exploited to introduce polymerizable groups, such as (meth)acrylates,[5] which makes them available for the design of different polymer architectures. In this context, brush-like/ comb-shaped POx have been prepared and studied (i) for their thermal and aqueous solution properties,[6] (ii) in polymer-biomolecule conjugations,[7] and (iii) as component of multi-layered POx capsules.[8]

In contrast to POx, their higher homologues, namely poly(2-oxazine)s (POz) have received much less attention, despite the simple property modulation offered by the incorporation of an additional methylene group in the polymer backbone.[1a, 9] However, recent reports about the lower critical solution temperature of poly(2-ethyl-2-oxazine) (PEtOz)[10] and the exceptional hydration and bioinertness of poly(2-methyl-2-oxazine) brushes[11] have sparked a renewed interest into this polymer class. POz are also synthesised by CROP and similar to POx their properties can be adjusted by changing the polymer side chain.[9a, 12] Consequently, 2-oxazolines and 2-oxazines can also be combined in the same polymer system as recently reported for linear block copolymers for the fabrication of high capacity based formulations.[13] Moreover, the water-soluble variants PMeOz and PEtOz have been shown to

not affect the cell viability of 3T3 mouse fibroblasts up to a concentration of 100 g L^{-1},[14] indicating their potential as future biomaterials. All these promising results stimulated our interest to further evaluate the potential of POz for nanomedicine applications. Specifically, we were interested to explore POz as component in methacrylate-based brush polymers, which allows us to combine the properties of POz with the modularity of controlled radical polymerizations. To date, only the potential of linear POz has been discussed as outlined above. However, to the best of our knowledge POz have not been exploited for the preparation of other macromolecular architectures or as coating materials for inorganic (nano)particles.

In this contribution, we further expand the PCIE toolbox and introduce brush-like poly(2-ethyl-2-oxazine)s as novel water-soluble thermoresponsive materials capable of stabilizing iron oxide nanoparticles (IONPs). To this end, well-defined oligo(2-ethyl-2-oxazine) methylacrylate (OEtOzMA) macromonomers, obtained by CROP of 2-ethyl-2-oxazine (EtOz), were polymerized via reversible addition-fragmentation chain-transfer (RAFT) polymerization using a phosphonate bearing chain transfer agent (CTA). In this way, well-defined $P(OEtOzMA)_n$ brushes with varying side chain and backbone lengths were obtained and studied with regard to their thermal properties in bulk and aqueous solution. In order to highlight the potential of these brushes, we further demonstrated their ability to stabilize IONPs which are shown to be suitable candidates for negative MRI contrast agents.

2. Results and Discussion

Well-defined oligo(2-ethyl-2-oxazine) methylacrylate (OEtOzMA) macromonomers were synthesized through CROP of 2-ethyl-2-oxazine (EtOz) (**Scheme 1A**). Kinetic investigations of the CROP of EtOz revealed a linear increase of $\ln([M]_0/[M]_t)$ with time as depicted in the pseudo first-order kinetic plot in **Figure 1A**. This suggests a constant concentration of the

propagating species and indicates that the polymerization proceeds in a living manner. With k_p = 0.00017 L (mol s)$^{-1}$ the polymerization of EtOz was found to be an order of magnitude slower than EtOx under similar conditions (data not shown). The linear increase of the molar mass with conversion, as well as low dispersities ($Đ$ ~ 1.2) (**Figure 1B**), further supported the living character of the polymerization.

Based on this kinetic investigation two different OEtOzMA macromonomers with degrees of polymerization (DP) of 4 and 8 were synthesized. Upon near quantitative conversion of the EtOz, the living polymer chains were terminated by methacrylic acid anions formed by the addition of methacrylic acid (MAA) and triethylamine (NEt_3). **Figure 2** depicts the ^{1}H NMR (A) and MALDI ToF MS (B) spectrum of the purified OEtOz$_4$MA macromonomer. In the ^{1}H NMR spectrum the signals corresponding to the methacrylate functionality are clearly visible between 5.5 and 6.5 ppm (double bond; H^1, H^2) and 1.9 ppm (methyl group; H^3). The comparison of the integrals of the double bond and the backbone (3.1 – 3.5 ppm) suggested near quantitative introduction of the methacrylate end-group. The molecular composition was further confirmed by MALDI ToF MS. The individual peaks of the spectrum could be assigned to CH_3-initiated and methacrylic acid-terminated EtOz. The two distributions observed are referred to ionization with H^+ or Na^+ ($CH_3(C_6H_{11}NO)_nCOOC_2H_5 + H^+/Na^+$). The molar mass increments within individual distributions were found to correspond to the EtOz repeating unit (113.1 g mol^{-1}).

Subsequent RAFT polymerizations of the macromonomers were performed using a protected phosphonate ester CTA. The kinetic study of the OEtOz$_4$MA polymerization revealed a linear first order kinetic behavior up to 70-80% conversion (**Figure 1C**). Moreover, a linear increase of the molar mass with conversion and low dispersity values (< 1.25) indicated good control of the polymerization under the chosen conditions (**Figure 1D**).

To study their thermal behavior in bulk and aqueous solution a library of brush P(OEtOzMA)$_n$ was prepared. All polymerizations were stopped at < 70% conversion, which resulted in well-

defined brush polymers with narrow molecular weight distributions (**Figure 2C**, **Table 1**). Four different P(OEtOz$_4$MA)$_n$ of varying DPs (**P1a**-**P1d**: n = 16, 25, 47, 70) and one P(OEtOz$_8$MA)$_{18}$ (**P2a**) were synthesized.

All brush polymers were found to exhibit glass transition temperatures (T_g's) below room temperature (Table 1). The DP of the brush backbone only had a marginal effect on the T_g, whereas an increase in the side chain length resulted in a significant higher T_g. The latter can be assigned to the decreased chain mobility. Similar to their linear analogues,[10] EtOz-based brush systems possess lower T_g's than EtOx based ones. This is due to the additional methylene group in the EtOz repeating unit, resulting in increased chain mobility. A similar trend was recently observed for brush polymers based on *N*-acylated poly(aminoester)s, obtained by the spontaneous zwitterionic copolymerization (SZWIP) of EtOx and EtOz.[15] In contrast, the thermal properties of the brush polymers in aqueous solution revealed a more significant dependency on the brush backbone length. The polymers were dissolved in deionized water or phosphate buffered saline (PBS) at a concentration of 5 mg mL^{-1}, and the phase transitions were studied by turbidimetry (**Figure 2D**). Previously it was shown that linear PEtOz below DP 50 does not possess any thermo-responsive behaviour in water.[10] For the brush P(OEtOzMA)$_n$, a trend towards lower cloud point temperatures (T_{cp}) for longer methacrylate backbones was observed, similar to brush-like P(OEtOxMA), both in deionized water and PBS. T_{cp} values in PBS were found to be lower than in water, indicating a salt dependency of the phase transition. An increase of EtOz repeating units in the side chain of the brush polymers (**P1a** versus **P2a**) did not lead to a significant change in its T_{cp}. As previously stated by Weber *et al.*, this observation might indicate that the hydrophobic methacrylate backbone is sufficiently shielded by the hydrophilic OEtOz side chains, and thus cannot be accessed by water molecules, which endows the brush polymers with poly(2-oxazine)-like properties.[6b]

Upon the study of the polymerization of OEtOzMA macromonomers and the thermal properties of the resulting brush polymers, the potential of the $P(OEtOzMA)_n$ to stabilize IONPs in aqueous solution was investigated. Non-functionalized IONPs are colloidally unstable under physiological conditions resulting in agglomeration, which limits their application.[16] Steric stabilization of IONPs is hence commonly performed via physisorption or chemisorption of hydrophilic and biocompatible stealth polymers.[17] In general, there is only a very limited number of reports about the use of PCIEs for the steric stabilization of IONPs despite their promising properties.[18] A larger batch of **P1b**, referred to as **P1b*** (DP 27, $M_{n,SEC}$ = 16500 g mol^{-1}, $Đ$ = 1.09), was synthesized and the terminal phosphonate ester moieties of the RAFT end-group were cleaved in the presence of an excess of trimethylsilylbromide. Subsequent methanolysis yielded phosphonic acid groups.[19] The successful deprotection could be confirmed via ^{1}H and ^{31}P NMR by the disappearance of the methoxy group signals at 3.75 ppm and the shift of the phosphorous signal from 30.9 ppm to 26.6 ppm (**Figure S1**, Supporting Information). No detectable change upon cleavage could be observed in the respective SEC chromatograms.

The **P1b*** brushes before and after phosphonate ester cleavage were exemplarily examined regarding their cytotoxicity and hemocompatibility. To this end, the cytotoxicity against 3T3 fibroblast and N27 neural cells was investigated using an AlamarBlue assay (**Figure S2**, Supporting Information). Only a negligible cytotoxicity could be observed in the concentration range from $7.8 \cdot 10^{-3}$ mg mL^{-1} to 1 mg mL^{-1}. Similarly, **P1b*** did not trigger any detectable hemolysis indicating no observable damage of the erythrocyte membrane (**Figure S3**, Supporting Information).

Subsequently, IONPs sterically stabilized with oleic acid and with an average diameter of 15 nm were functionalized with phosphonic acid terminated **P1b*** by the *grafting-onto* approach exploiting the strong affinity of the phosphonic acid moiety towards IONP surfaces (**Scheme 1B**). The ligand exchange reaction was performed in a methanol/chloroform mixture at 37 °C

overnight followed by nanoparticle purification via precipitation and several centrifugal washing cycles. The presence of **P1b*** on the IONP surface was confirmed using ATR-FTIR and TGA. ATR-FTIR spectra displayed vibrational bands for ester and tertiary amide bonds at 1720 and 1630 cm^{-1}, respectively, in addition to an absorbance at 750 and 660 cm^{-1} originating from the IONPs (**Figure S4**, Supporting Information). A grafting density of 0.13 nm^{-2} was calculated from the observed weight loss in TGA (**Figure S5**, Supporting Information) and the molecular weights of **P1b*** ($M_{n,NMR}$ = 15200 g mol^{-1}). TEM measurements revealed the presence of well-dispersed IONPs after modification in aqueous media (**Figure 3A**).

The **P1b*** stabilized IONPs were subsequently tested for their performance as negative MRI contrast agents. To this end, MRI relaxivities were measured using a 9.4 T high field animal MR scanner. Different concentrations of particles dispersed in water were immobilized in agarose gels and the relaxivities r_1 and r_2 were determined from T_1 and T_2 mappings, respectively (**Figure 3B**). The r_2 value was found to be ~ 115 s^{-1} mM^{-1}, which is within the expected range for polymer-coated IONPs of similar size.[20] The r_1 relaxivity (0.54 s^{-1} mM^{-1}) was found to be similar to poly(PEGMA) coated IONPs.[21] This led to a r_2/r_1 ratio - an important indicator for negative contrast agent - of ~ 214, a value which is similar to the commercial product Resovist (r_2/r_1 = 224).

3. Conclusions

We report the synthesis of water-soluble and thermoresponsive brush poly(2-ethyl-2-oxazine)s capable of stabilizing IONPs and demonstrate their potential for future MRI applications. To this end, oligo(2-ethyl-2-oxazine) methacrylate (OEtOzMA) macromonomers were synthesized via living cationic ring-opening polymerization (CROP) and subsequently polymerized via reversible addition-fragmentation chain transfer (RAFT) polymerization to yield well-defined P(OEtOzMA) brushes. The brushes were found to

exhibit tunable LCST behaviour, negligible cytotoxicity and be capable of stabilizing IONPs due to their phosphonic acid end groups introduced via a phosphonate ester bearing chain transfer agent. Relaxivity studies of P(OEtOzMA)@IONPs revealed a r_2/r_1 ratio comparable to commercial contrast agents. Further in-depth MRI studies of POz stabilised IONPs are currently performed in our laboratory.

In summary, this study further expands the poly(cyclic imino ether) toolbox and introduces poly(2-oxazine) based brush polymers as promising materials for future biomedical applications.

Supporting Information

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

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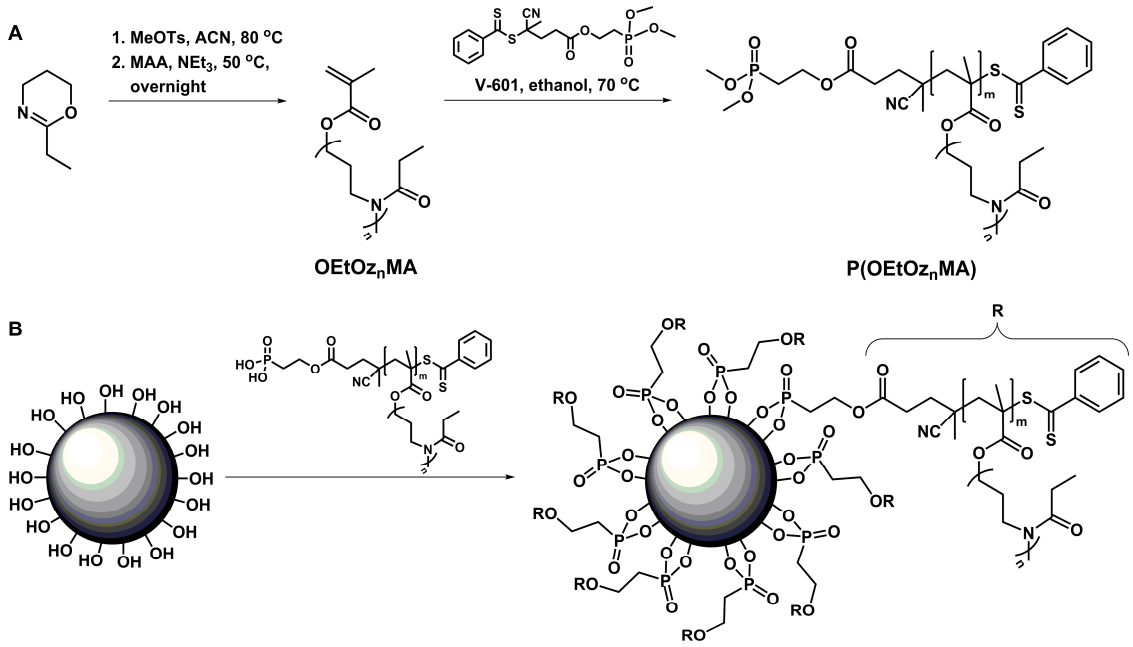
Figures, Schemes, Tables and legends



Scheme 1. Schematic representation of the (A) synthesis of poly(oligo(2-ethyl-2-oxazine) methyl acrylate) (P(OEtOz$_n$MA)) by a combination of CROP and RAFT polymerization using a protected phosphonate chain transfer agent (CTA); (B) grafting of phosphonic acid functional P(OEtOz$_n$MA) to IONPs.

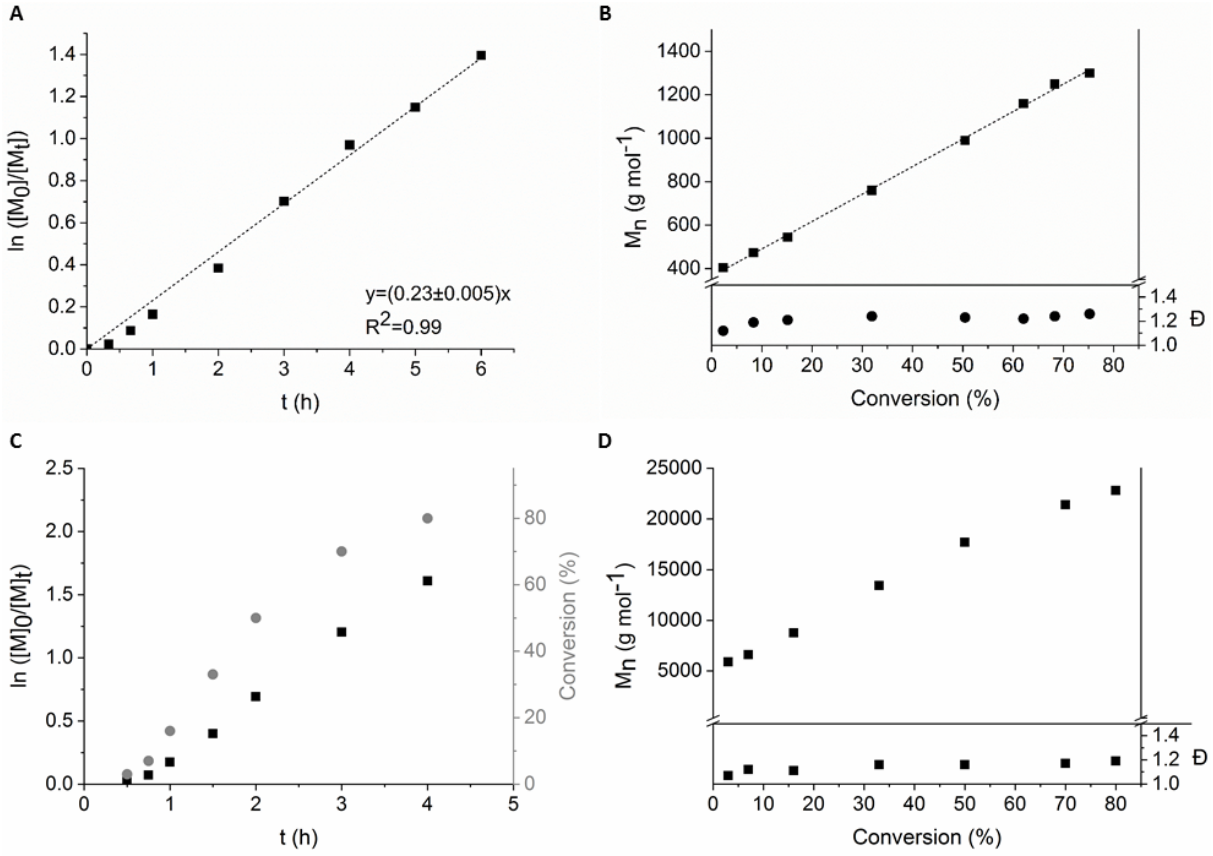


Figure 1. CROP kinetic of EtOz (DP 10) in acetonitrile at 80 °C using MeOTs as initiator, (A) first-order kinetic plot, (B) M_n and $Đ$ against conversion plot; (C, D) RAFT polymerization kinetics of $OEtOz_4MA$ (DP 60) in ethanol at 70 °C using AIBN as initiator.

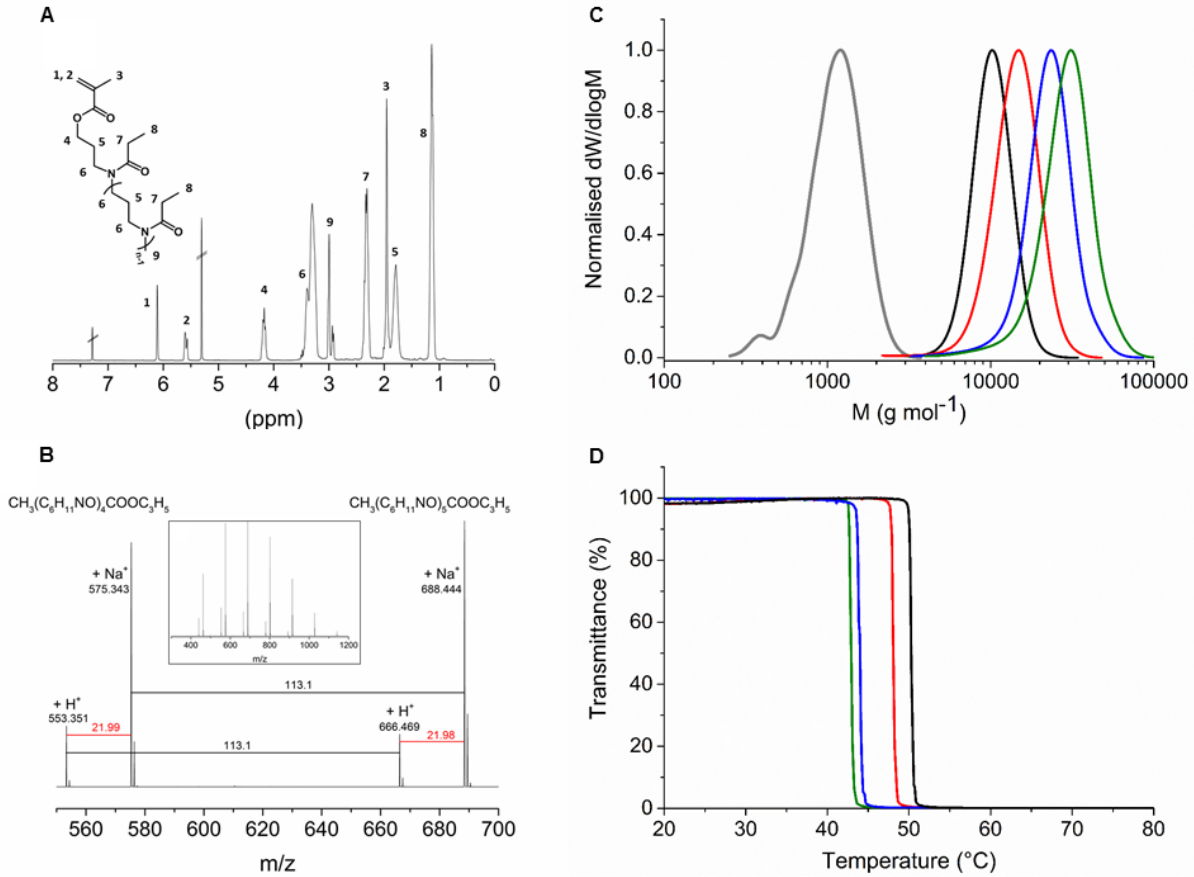


Figure 2. ^{1}H NMR (400 MHz, $CDCl_3$; A) and MALDI TOF MS spectra (B) of the $OEtOz_4MA$ macromonomer. SEC traces of the different P($OEtOz_4MA$) (C) and their corresponding turbidimetry curves (D); black: DP16, red: DP25, blue: DP47, green: DP70.

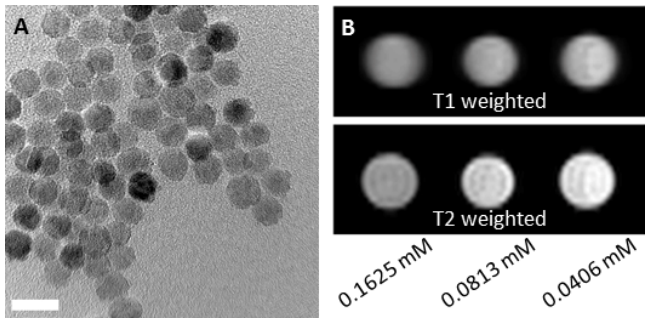


Figure 3. TEM (A; scale bar = 20 nm) and MRI (B) T_1 and T_2 weighted images of **P1b*** modified IONPs at different concentrations.

Table 1. Characterization of the macromonomers (**M1**, **M2**) and brush polymers (**P1a-d, P2a**).

Code	DP^a	$M_{n,\ NMR}$ [g mol^{-1}]^a	$M_{n,\ SEC}$ [g mol^{-1}]^b	$Đ^b$	T_g^c [°C]	T_{cp}^d (H_2O) [°C]	T_{cp}^d (PBS) [°C]
M1	4	553	1000	1.19	n.d.	n.d.	n.d.
M2	8	1005	2100	1.13	n.d.	n.d.	n.d.
P1a	16	9260	9700	1.09	12.4	50.4	39.8
P1b	25	14240	13100	1.14	11.5	48	45.4
P1c	47	26410	20800	1.15	12.6	44.1	41.4
P1d	70	39130	26400	1.17	15.4	42.9	40.7
P2a	18	18510	18500	1.12	20.8	47.7	45.5

[a]Calculated by ^{1}H NMR ($CDCl_3$, 400 MHz) from conversion and molar mass of the monomer (EtOz: 113.16 g mol^{-1}) and macromonomer (M1: 553 g mol^{-1}, M2: 1005 g mol^{-1}), respectively. [b]Determined by SEC (eluent: DMF + NH_4BF_4, standard: PMMA). [c]Determined by DSC (second heating run). [d]Cloud point temperature(5 mg mL^{-1}). n.d., not determined.

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The synthesis and characterization of poly(2-oxazine) based brush polymers is reported. Moreover, the polymers were shown to stabilise IONPs and be suitable contrast agents for future MRI applications.