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Thermal Properties of Oligo(2-ethyl-2-oxazoline) Containing Comb and Graft Copolymers and their Aqueous Solutions

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Summary: The cationic ring opening polymerization of 2-ethyl-2-oxazoline (EtOx) was applied for the synthesis of methacrylate end-functionalized well-defined macromonomers that could be polymerized in a controlled manner using reversible addition-fragmentation chain transfer polymerization. The obtained comb polymers revealed lower critical solution temperature behavior in aqueous solution. The cloud points of these solutions could be tuned in a range from 35 °C to 85 °C by the incorporation of hydrophobic methyl methacrylate comonomer in varying amounts into the graft copolymers whereas copolymerization with methacrylic acid rendered temperature and pH sensitive copolymers. Thermo-gravimetric analysis showed a two-step decomposition of the graft copolymers and differential scanning calorimetry revealed glass transition temperatures that are significantly lowered in comparison to linear PEtOx.

Keywords: cationic ring-opening polymerization; comb polymer; lower critical solution temperature; macromonomer; reversible addition fragmentation chain transfer (RAFT)

Introduction

Certain polymers, which consist of both hydrophilic and hydrophobic moieties and are able to form hydrogen bonds with water, are known to exhibit a phase transition in aqueous solution at their lower critical solution temperature (LCST).[1,2] The thermo-responsive properties of such polymers allow the reversible "switching" between hydrophilic and hydrophobic behavior by changing the temperature resulting in a wide range of potential applications, e.g. in drug delivery systems, for solubilization or precipitation of nanoparticles and in selective membranes.[3,4] Next to the most frequently investigated systems based on poly(*N-iso*-propylacrylamide), poly(2-oxazoline)s have a great potential due to the fact that they can be polymerized in a living manner,[5–7] providing a perfect tool for introduction of functional groups[8,9] as well as for fine-tuning of the transition temperature by copolymerization of different monomers.[10–12] In addition, the combination of the cationic ring opening polymerization (CROP) with vinylic monomers enables various synthetic strategies to obtain more complex polymer structures such as graft copolymers.[13–15]

This contribution describes a versatile synthetic strategy towards comb and graft copolymers containing hydrophilic oligo(2-ethyl-2-oxazoline) side chains and a hydrophobic methacrylate backbone using the

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macromonomer method. For this purpose, the living CROP of 2-ethyl-2-oxazoline (EtOx) was terminated with *in situ* formed triethyl ammonium methacrylate.[16] The thus obtained oligo(2-ethyl-2-oxazoline)-methacrylate (OEtOxMA) macromonomers were subsequently polymerized using the reversible addition–fragmentation chain transfer (RAFT) polymerization technique[17] yielding poly-[oligo(2-ethyl-2-oxazoline)methacrylate] (POEtOxMA) comb polymers (Scheme 1).[18] In addition, RAFT copolymerization of OEtOxMA with MMA or MAA resulted in well-defined graft copolymers.[18,19] The thermal properties of the POEtOxMA-based polymers in bulk as well as in aqueous solution are investigated by means of thermo-gravimetrical analysis (TGA), differential scanning calorimetry (DSC) and turbidimetry, respectively.

Experimental Part

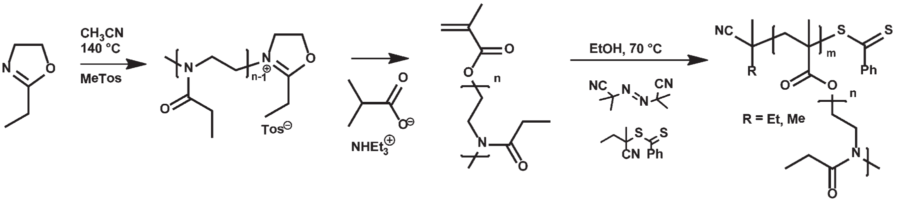
The synthesis of the OEtOxMA macromonomers has been described in a previous publication[16] as well as their RAFT polymerization and turbidity measurements of the POEtOxMA based comb and graft copolymers.[18,19]

Differential scanning calorimetry was performed on a Netzsch DSC 204 F1 Phoenix under nitrogen atmosphere with a heating rate of 20 K min^{-1} from –100 °C to 200 °C. T_g values are reported from the second heating run. Thermo-gravimetrical analyses were performed under nitrogen atmosphere in a Netzsch TG 209 F1 Iris in the range from room temperature to 500 °C with a heating rate of 10 K min^{-1}. Cloud points were determined on a Crystal 16™ from Avantium Technologies being connected to a chiller (Julabo FP 40) using a wavelength of 500 nm and a heating ramp of 1 K min^{-1}. The concentration of the polymer was kept constant at 5 mg mL^{-1}.

Results and Discussion

The living CROP of EtOx was performed using methyl tosylate as initiator in a 4 molar solution in acetonitrile at 140 °C using microwave irradiation as heating source. The advantage of such a living polymerization is the possibility to end-functionalize the living oligo(2-oxazolinium) species with a suitable nucleophile, which was in this case *in situ* formed triethyl ammonium methacrylate. Using a variety of [monomer] to [initiator] ratios, from 3 to 22 (**M1** = 3; **M2** = 5; **M3** = 7; **M4** = 10; **M5** = 15; **M6** = 22), a series of well-defined OEtOxMA macromonomers was synthesized and characterized by means of SEC (see Figure 1A), ^{1}H-NMR spectroscopy as well as matrix assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry (see Figure 1B).[16]

The OEtOxMA macromonomers were polymerized via RAFT polymerization utilizing 2,2′-azo-*bis*-(2-methylpropionitrile) (AIBN) as initiator and 2-cyanobutan-2-yl dithio-benzoate (CBDB) as chain transfer agent with a [CBDB]:[AIBN] ratio of 4:1 in a 0.5 M solution in ethanol at 70 °C. Using this technique, a series of comb polymers



Scheme 1.
Schematic representation of the synthesis route towards poly[oligo(2-ethyl-2-oxazoline)methacrylate]s (POEtOxMA).

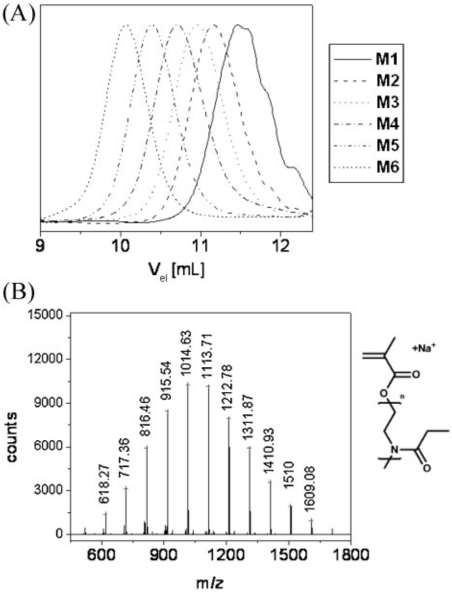


Figure 1.

A: SEC traces ($CHCl_3$:NEt_3:2-propanol = 94:4:2) of the OEtOxMA macro-monomers. B: MALDI-TOF mass spectrum (dithranol, NaI) of **M5** and schematic representation of the assigned structure.

was synthesized with a degree of polymerization (DP) of approximately 30 for the backbone but varying DP (3 to 22) of side chains. However, it was also possible to obtain a longer comb polymer with a DP of 86 as well as a shorter one with a DP of 11, which was suitable for MALDI-TOF MS analysis of the comb polymer class.[18] The SEC characterization of the POEtOxMA comb polymers is summarized in Table 1.

In addition, **M2** was copolymerized with methyl methacrylate (MMA) as well as with methacrylic acid (MAA) resulting in a series of graft copolymers with a side chain DP of 5 and varying content of MMA (see Table 2 for characterization results from SEC and ^{1}H-NMR spectroscopy) or MAA, respectively (see Table 3).

A comparison between the ^{1}H-NMR spectra of these graft-copolymers with the spectrum of the according macromonomer and a comb polymer as well as the assignment of the observed peaks to the structure of the polymers is shown in Figure 2.

Table 1.

Selected characterization results of the POEtOxMA comb polymers.

	DP Side chain	DP[a] Backbone	Conversion[b] [%]	M_n(theo)[a] [g mol^{-1}]	M_n(SEC)[c] [g mol^{-1}]	PDI[c]
P1	3	89	43	35,600	10,600[d]	1.29[d]
P2	5	11	18	6,600	5,700	1.10
P3	5	39	65	23,400	11,600	1.27
P4	7	30	50	24,000	9,200	1.27
P5	10	29	48	31,900	7,400	1.06
P6	15	34	57	54,400	14,500	1.17
P7	22	25	42	57,500	23,200	1.11

[a]calculated from the used ratio of [OEtOxMA] to [CBDB] and the conversion.[b]obtained from the peak areas of OEtOxMA and POEtOxMA in the SEC traces from the reaction solution.[c]obtained from SEC ($CHCl_3$:NEt_3:2-propanol = 94:4:2, PMMA calibration).[d]obtained from SEC (2.1% LiCl in DMA, PMMA calibration).

Table 2.

Selected characterization results of the P(OEtOxMA-*stat*-MMA) graft copolymers.

	[**M2**]: [MMA]: [CBDB][a]	M_n[b] [g mol^{-1}]	PDI[b]	Conversion[c] [**M2**]:[MMA] [%]	DP[d] [**M2**]:[MMA]	[**M2**]:[MMA] (^{1}H-NMR)[e] [%]
C1	60:15:1	15,700	1.29	67:96	40:14	56:44
C2	60:60:1	12,800	1.23	41:66	25:39	38:62
C3	60:240:1	25,200	1.25	61:71	36:170	21:79

[a]feed ratio.[b]obtained from SEC ($CHCl_3$:NEt_3:2-propanol = 94:4:2, PMMA calibration).[c]calculated from suitable peak integrals in the ^{1}H-NMR spectra of the reaction solution (t_0 and t_{end} sample).[d]calculated from the used ratio of [M2]:[MMA]:[CBDB] and the conversion.[e]polymer composition determined by ^{1}H-NMR spectroscopy of the purified products.

Table 3.
Selected characterization results of the P(OEtOxMA-*stat*-MAA) graft copolymers.

	[**M2**]: [MAA]: [CBDB][a]	M_n[b] [g mol^{-1}]	PDI[b]	Conversion[c] [**M2**]:[MMA] [%]	DP[d] [**M2**]:[MMA]	[**M2**]:[MMA][e] [%]
C4	20:40:1	5,500	1.29	21:11	4:4	56:44
C5	40:20:1	8,200	1.26	34:38	14:8	38:62
C6	15:45:1	8,000	1.23	32:30	5:14	21:79

[a] feed ratio. [b] obtained from SEC (2.1% LiCl in DMA, PMMA calibration). [c] calculated from suitable peak integrals in the ^{1}H-NMR spectra of the reaction solution (t_0 and t_{end} sample). [d] calculated from the used ratio of [M2]:[MMA]:[CBDB] and the conversion. [e] polymer composition determined by acid/base titration (0.1 M NaOH) of the purified products.

Although all spectra are dominated by the large amount of protons in the OEtOxMA side chains the signals from the vinylic protons of the methacrylate in the macromonomer (5.6 ppm and 6.1 ppm) are not visible in the spectra of the comb and graft copolymers anymore. The amount of MMA in **C1–C2** can be calculated using the integral of the O-CH_3 signal at 3.6 ppm which is overlapping with OEtOx backbone signal at 3.4 ppm whereas the proton signal of the COOH moieties can be used for this purpose in the case of **C4-C6**.

The LCST behavior of the synthesized comb and graft copolymers was investigated by turbidity measurements of their aqueous solutions utilizing a polymer concentration of 5 mg mL^{-1} and a heating rate of 1 K min^{-1}. All of the POEtOxMA comb polymer solutions revealed cloud points in a temperature range from 60 °C to 80 °C. The phase transitions were fully reversible for all polymer solutions revealing only a minor heating-cooling hysteresis of the turbidity curves (less than 2 °C; see Figure 3A). Since no trend in the cloud points of the solutions of the POEtOxMA comb polymers with varying side chain length could be observed it is proposed that the methacrylate backbone is shielded by the densely packed OEtOx side chains. This

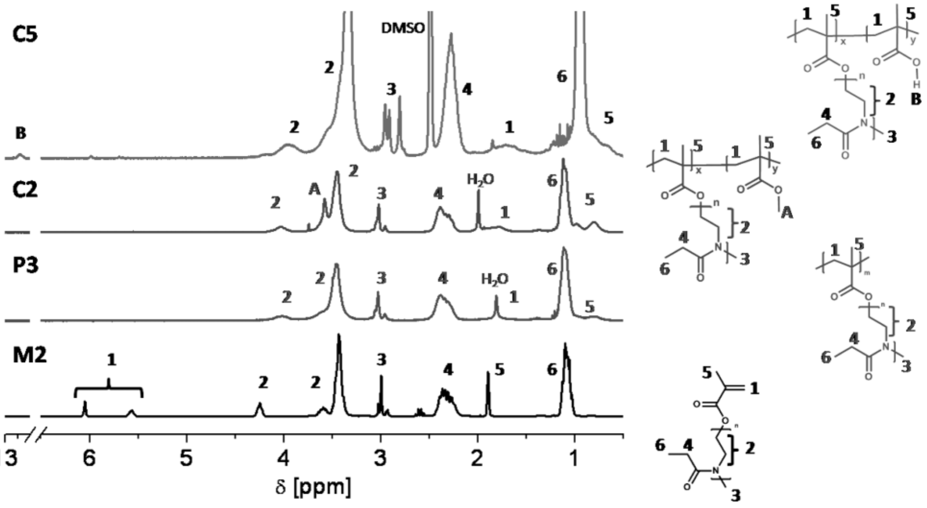


Figure 2.
^{1}H-NMR spectra (250 MHz, $CHCl_3$) of POEtOxMA comb and graft copolymers and the corresponding macromonomer. Bottom: OEtOxMA macromonomer **M2**; center: POEtOxMA comb polymer **P3**; top: P(OEtOxMA-*stat*-MMA) graft copolymer **C2** and P(OEtOxMA-*stat*-MAA) graft copolymer **C5** (solvent: DMSO-d_6).

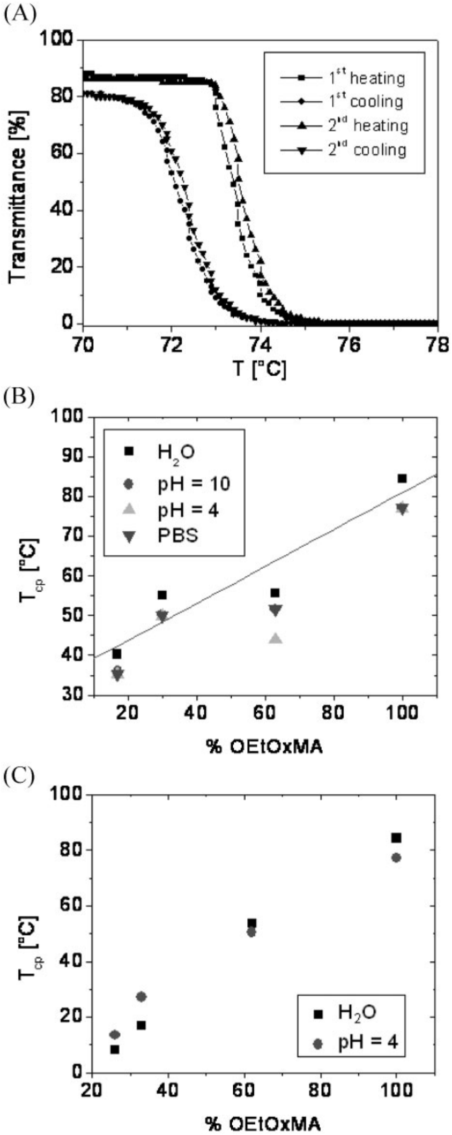


Figure 3.

A: Turbidity measurement for an aqueous solution of **P7** ($c = 5\,\mathrm{mg\,mL^{-1}}$, heating rate $1\,\mathrm{K\,min^{-1}}$). B: Cloud points (at 50% transmittance) of P(OEtOxMA-*stat*-MMA) graft copolymers with varying content of MMA. C: Cloud points of P(OEtOxMA-*stat*-MAA) graft copolymers with varying content of MAA.

results in an LCST behavior of the comb polymers that is comparable to linear PEtOx. Nonetheless, for linear PEtOx the cloud points decrease below 70 °C only when the molar mass exceeds 100,000 $\mathrm{g\,mol^{-1}}$ while this already occurs for POEtOxMA with 60,000 $\mathrm{g\,mol^{-1}}$.[20,21] This difference can be ascribed to fixation of one of the OEtOxMA ends to the hydrophobic methacrylate backbone resulting in decreased solubility as was previously also reported from end-functionalized and block copoly(2-oxazolines).[22,23]

The copolymerization of the OEtOxMA macromonomer **M2** with hydrophobic MMA as comonomer led to a significant decrease of the cloud points of the graft copolymer solutions. By the incorporation of varying amounts of MMA into the copolymer the cloud points of their aqueous solutions can be tuned over a wide temperature range from 40 °C to 85 °C (see Figure 3B). Cloud point measurements in buffered solutions at different pH values showed that the LCST behavior of the investigated polymers is not influenced by the pH value but rather by the salt content of the solution, as indicated by comparison with cloud points in phosphate buffered saline (PBS).

On the other hand, pH responsiveness can be achieved by copolymerization of OEtOxMA with MAA. At $\mathrm{pH} = 4$ the MAA moieties of these copolymers exist in a protonated form and therefore are able to form hydrogen bonds with the hydrogen bond accepting amide groups of the OEtOxMA side chains. In this way they compete for the binding sites with water molecules resulting in a decreased cloud point of the solution when compared to the POEtOxMA homopolymer (Figure 3C). Under basic conditions the acidic functionalities are deprotonated and therefore enhance the solubility of the polymers so that they do not show any LCST behavior in the investigated temperature range anymore.

In addition to the thermal behavior of the polymers in aqueous solution, their thermal properties in bulk were investigated using TGA as well as DSC. The TGA thermograms (see Figure 4A) of the POEtOxMA homopolymers show that the polymers start to decompose at

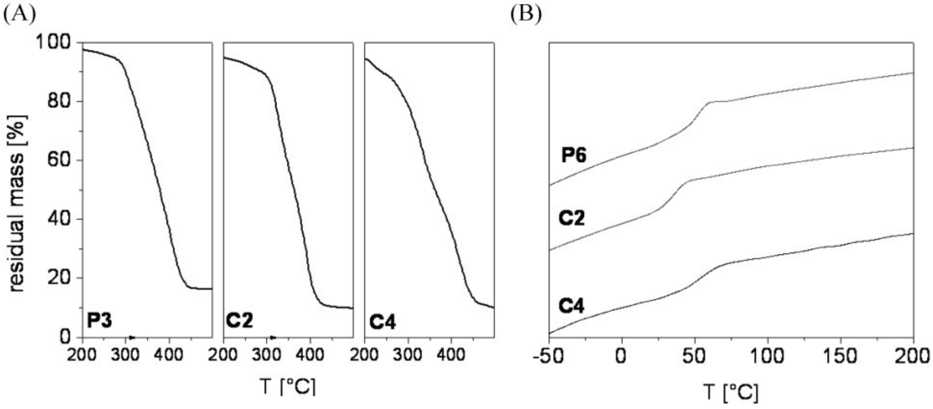


Figure 4.
A: TGA thermograms (10 K min^{-1}) of **P3** (left), **C2** (center) and **C4** (right); B: DSC traces (2nd heating run, 20 K min^{-1}) of a POEtOxMA comb polymer (top), a POEtOxMA-MMA copolymer (center) and a POEtOxMA-MAA copolymer.

300 °C and give no distinct stepwise decomposition of backbone and side chains. However, this becomes visible when the backbone fraction of the polymer is increased by copolymerization with another monomer, as is the case for the copolymers **C1–C3** and **C4–C6**. In these cases a first inflection point can be observed around 330 °C, which most likely corresponds to the decomposition of the OEtOx side chains.[24] In the TGA thermograms of **C1**-**C3** a second inflection point can be detected between 390 °C and 400 °C which is slightly shifted to higher temperatures (420 °C) for **C4–C6** indicating that the second inflection point corresponds to the comonomer. Indeed, the observed second weight loss of **C4** coincides with the inflection point reported in literature for the decomposition of poly(methacrylic acid) (410 °C).[25]

Representative DSC traces (second heating run, heating rate 20 K min^{-1}) of the comb and graft copolymers are shown in Figure 4B. The glass transition temperatures of the POEtOxMA comb polymers vary in a temperature range from 27 °C to 54 °C and increase with increasing side chain length of the comb polymer (see Figure 5A). This can be explained by the decreased chain mobility with increasing side chain length resulting from the higher molar mass and lower number of end-groups per weight unit. However, the T_g values are significantly lowered when compared to linear PEtOx ($T_g = 62$ °C)[26] as can be commonly observed for polymacromonomers due to the increased number of end groups of the polymer leading to an increase in free volume.[27–29] The methacrylate-like properties of the material emerge when the amount of methacrylate in the polymer structure is increased, as is the case for the copolymers of OEtOxMA with MMA or with MAA, respectively. The T_g values of both polymer series increase with increasing content of MMA or MAA and therefore decreasing number of flexible oligomer side chains. A PMMA with comparable DP of 38 (determined from ^{1}H-NMR spectroscopy, $M_n(SEC) =$ 3,700 g mol^{-1}, $PDI_{SEC} = 1.12$), which was synthesized by RAFT polymerization of MMA, has a T_g of 84 °C (see Figure 5B). The fact that the T_g of PMAA (DP = 29, $M_n(SEC) = 3{,}200$ g mol^{-1}, $PDI_{SEC} = 1.30$) is higher than the T_g of PMMA as well as the possibility of hydrogen bonding in the POEtOx-MAA copolymers result in higher T_g values of **C4–C6** when compared to **C1–C3**.

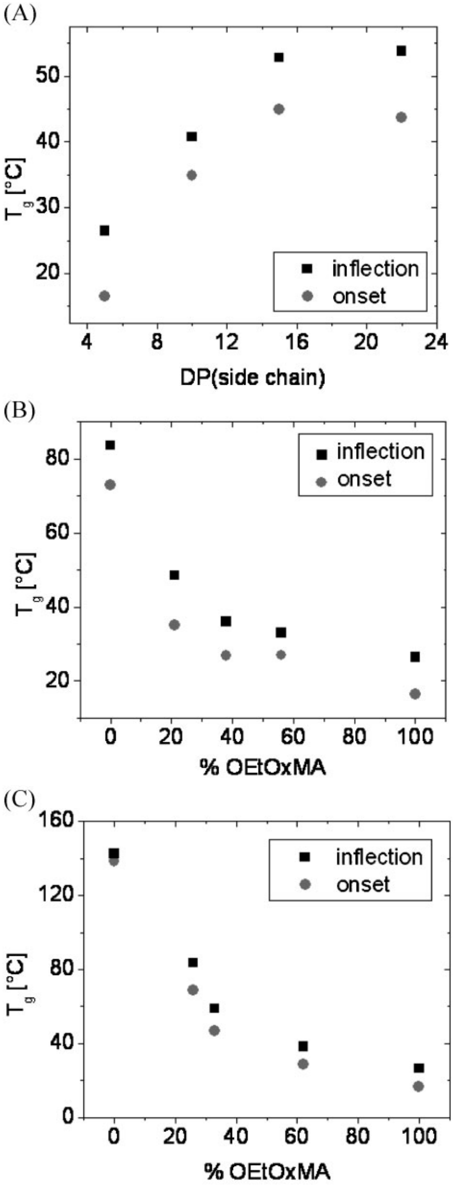


Figure 5.
A: T_g values of the POEtOxMA comb polymers **P3**-**P7**; B: T_g values of POEtOxMA-MMA copolymers **C1**-**C3** in comparison with **P3** and PMMA; C: T_g values of POEtOxMA-MAA copolymers **C4**-**C6** in comparison with **P3** and PMAA.

Conclusion

Various well-defined OEtOxMA containing comb and graft copolymers could be synthesized using a combination of living and controlled polymerization techniques. The investigation of the thermal properties of these polymers in bulk displayed glass transition temperatures that are significantly lowered in comparison to linear PEtOx due to the increased number of chain ends. Turbidity measurements revealed their thermo-responsive properties in aqueous solution. The LCST behavior of the polymers could be tuned by incorporation of hydrophobic MMA into the polymer architecture, whereas the copolymerization with MAA rendered them also pH responsive.

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