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Annika Kroning

Leibniz-Institut für Analytische Wissenschaften

Andreas Furchner

Leibniz-Institut für Analytische Wissenschaften, andreas.furchner@isas.de

Stefan Adam

Leibniz-Institut für Polymerforschung Dresden

Petra Uhlmann

University of Nebraska–Lincoln

Karsten Hinrichs

Leibniz-Institut für Analytische Wissenschaften

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Probing carbonyl–water hydrogen-bond interactions in thin polyoxazoline brushes

Annika Kroning and Andreas Furchner^{a)}

Leibniz-Institut für Analytische Wissenschaften – ISAS – e. V., Department Berlin, Schwarzschildstraße 8, 12489 Berlin, Germany

Stefan Adam

Leibniz-Institut für Polymerforschung Dresden e. V., Hohe Str. 6, 01069 Dresden, Germany and Faculty of Science, Department of Chemistry, Chair of Physical Chemistry of Polymeric Materials, Technische Universität Dresden, Bergstr. 66, 01069 Dresden, Germany

Petra Uhlmann

Leibniz-Institut für Polymerforschung Dresden e. V., Hohe Str. 6, 01069 Dresden, Germany and Department of Chemistry, University of Nebraska–Lincoln, Hamilton Hall, 639 North 12th Street, Lincoln, Nebraska 68588

Karsten Hinrichs

Leibniz-Institut für Analytische Wissenschaften – ISAS – e. V., Department Berlin, Schwarzschildstraße 8, 12489 Berlin, Germany

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Temperature-responsive oxazoline-based polymer brushes have gained increased attention as biocompatible surfaces. In aqueous environment, they can be tuned between hydrophilic and hydrophobic behavior triggered by a temperature stimulus. This transition is connected with changes in molecule–solvent interactions and results in a switching of the brushes between swollen and collapsed states. This work studies the temperature-dependent interactions between poly(2-oxazoline) brushes and water. In detail, thermoresponsive poly(2-cyclopropyl-2-oxazoline), nonresponsive hydrophilic poly(2-methyl-2-oxazoline), as well as a copolymer of the two were investigated with *in situ* infrared ellipsometry. Focus was put on interactions of the brushes' carbonyl groups with water molecules. Different polymer–water interactions could be observed and assigned to hydrogen bonding between C=O groups and water molecules. The switching behavior of the brushes in the range of 20–45 °C was identified by frequency shifts and intensity changes of the amide I band. © 2016 Author(s). All article content, except where otherwise noted, is licensed under a Creative Commons Attribution 3.0 Unported License. [<http://dx.doi.org/10.1116/1.4939249>]

I. INTRODUCTION

Temperature-responsive polymer brushes have been of wide fundamental and technological interest in the last two decades, in particular, for potential biotechnological applications like bioactive surfaces and drug-delivery systems.^{1–4} A popular example of a thermoresponsive polymer is poly(*N*-isopropylacrylamide) (PNIPAAm), which has been extensively studied in solution as well as in the form of thin layers on a substrate.^{5–7} In the past years, another class of temperature-responsive polymers has been used to fabricate biocompatible switchable surfaces, namely, poly(2-alkyl-2-oxazoline)s (POx).^{8,9} POx were first synthesized in the 1960s,^{10–13} but their potential use in surface modification has been explored only recently.¹⁴ The thermoresponsive behavior of POx and PNIPAAm involves changes in polymer–polymer and polymer–water interactions around the polymers' lower critical solution temperatures (LCST). PNIPAAm has an LCST around 31 °C,¹⁵ but also POx with a propyl group in their side chain have LCSTs in the physiological temperature range¹⁵ and are therefore promising

candidates for the use as surfaces in tissue engineering and other biomedical applications.

Interactions of POx with water depend on the specific side-chain chemistry. Different alkyl groups can lead to more hydrophilic or more hydrophobic POx, or to an LCST behavior often tunable via parameters like molecular weight. Poly(2-methyl-2-oxazoline) (PMeOx), for example, is hydrophilic but not thermoresponsive, whereas poly(2-*n*-propyl-2-oxazoline) (P*n*PrOx) as well as its isomers are thermoresponsive with a reversible temperature-dependent transition from hydrophilic to hydrophobic in a certain temperature range.^{16–20} Katsumoto *et al.* showed that poly(2-isopropyl-2-oxazoline) (PiPrOx) in solution undergoes a gradual reversible dehydration between 20 and 40 °C.¹⁸ However, a drawback of PiPrOx is its irreversible crystallization when the polymer is kept above 40 °C for longer periods of time.^{18,21,22} Other temperature-responsive POx have quite a low glass transition temperature ($T_g < 45$ °C), which is a severe disadvantage in sample handling and storage.^{16,17} For these reasons, Bloksma *et al.* have introduced poly(2-cyclopropyl-2-oxazoline) (PcPrOx), an amorphous polymer with a reversible phase transition in solution as well as a T_g of about 80 °C, which is sufficiently high for biomedical applications.¹⁶

^{a)}Electronic mail: andreas.furchner@isas.de

The previously mentioned studies address POx in solution. Only a few publications exist about the switching behavior of thin POx films,^{8,9} and these involve only noncyclic poly(2-oxazoline)s like PiPrOx. In the present study, *in situ* infrared spectroscopic ellipsometry (IRSE) was applied to characterize the thermoresponsive behavior of POx brush films consisting of either PcPrOx or a statistical copolymer containing 75% *c*PrOx and 25% MeOx. The temperature sensitivity of the brushes was monitored between 20 and 45 °C via the characteristic amide I carbonyl vibrational band.¹⁸ This band is a direct measure for changes in polymer–water interactions since its frequency shifts when the polymer's N–C=O groups are involved in hydrogen bonding.

II. EXPERIMENT

A. Synthesis and characterization of the poly(2-oxazoline)s

PMeOx ($M_n = 22.0$ kg/mol, dispersity = 1.27) was purchased from Polymer Source, Inc., Canada. The monomer 2-methyl-2-oxazoline (MeOx, 98%) was purchased from Sigma-Aldrich. The monomers 2-cyclopropyl-2-oxazoline (*c*PrOx) and methyl-3-(oxazol-2-yl) propionate (EsterOx) were synthesized at the IPF in Dresden as described elsewhere.^{16,23} PcPrOx and the copolymer of MeOx and *c*PrOx with 25% MeOx were synthesized via a microwave-assisted cationic ring-opening polymerization in benzonitrile. Both polymers bear a short EsterOx functional chain end (2–4 units) as the starting block for the polymerization. After converting the methyl ester groups into free carboxylic groups via basic hydrolysis, these end blocks served for chain attachment to the substrate in the brush preparation step. The cationic chain ends of all POx were terminated with piperidine groups. A detailed description of polymer synthesis and purification is given by Adam *et al.*²⁴

The molecular weights of the resulting polymers were determined with size exclusion chromatography [Agilent Technologies (USA) 1200 series HPLC pump and Polar Gel M column, K-2301 refractive-index detector (Knauer, Germany), miniDAWN light-scattering detector (Wyatt Technology, USA), *N,N*-dimethylacetamide containing 2 vol. % H₂O and 3 g l⁻¹ LiCl used as eluent with 1 ml min⁻¹ flow rate]. $M_n = 43.4$ kg/mol (dispersity = 1.16) was determined for PcPrOx and $M_n = 61.3$ kg/mol (dispersity = 1.41) for the copolymer. Chemical structures of the poly(2-oxazoline)s are displayed in Fig. 1.

B. Brush preparation

Thin POx brushes were prepared on infrared-transparent silicon wedges (1.5°, 2.35 mm thickness) purchased from Vario GmbH, Germany. The cleaned substrates were first activated in an oxygen plasma and subsequently modified with a 2 nm thin poly(glycidylmethacrylate) (PGMA, $M_n = 17.5$ kg/mol, dispersity = 1.7, Polymer Source) anchoring layer.⁷ Next, brush layers were prepared in a grafting-to

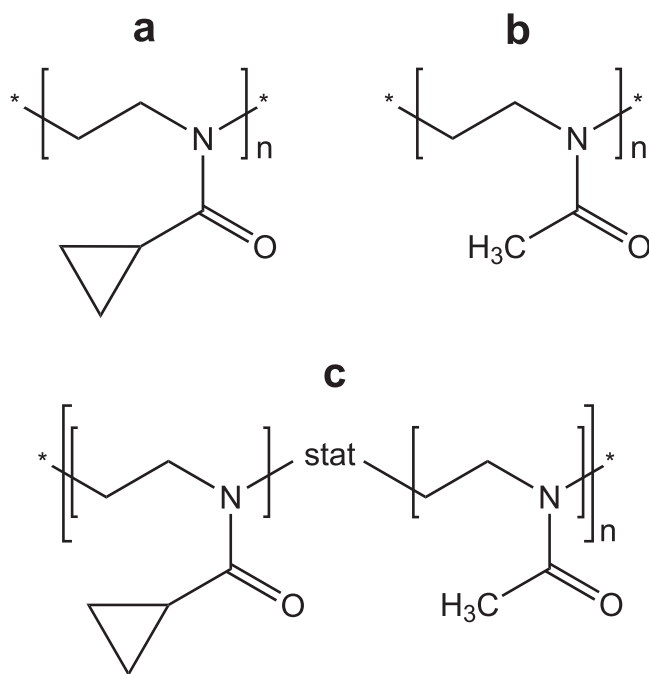


Fig. 1. Chemical structures of the poly(2-oxazoline)s used in this work. (a) PcPrOx, (b) PMeOx, (c) copolymer with 75% *c*PrOx and 25% MeOx. All POx are piperidine-terminated.

process²⁵ by a repeated procedure of spin-coating the polymer from a 0.5 wt. % solution in CHCl₃, annealing in a vacuum oven at 150 °C for 2 h, and removing unbound POx by rinsing in CHCl₃. In the annealing step, POx chains covalently attach to the PGMA layer by reaction of COOH groups of the functional end blocks with epoxy groups of PGMA.

Comparable brushes were prepared on PGMA-functionalized Si(100) wafers. Corresponding layer thicknesses in dry state and hydrated states at 20 and 45 °C in H₂O were determined with visible ellipsometry (alpha-SE, J.A. Woollam Co., Inc., USA) using a multilayer box model. The swollen layers were modeled with an effective medium approximation according to Bruggeman.^{24,26}

C. IRSE setup and measurements

IRSE can measure the change in polarization state of incident linearly polarized light upon reflection at a sample, expressed by the ratio $\tan \Psi e^{i\Delta} = r_p/r_s$, with r_p and r_s being the complex reflection coefficients parallel and perpendicular to the plane of incidence. The custom-built ellipsometer,²⁷ attached to a Bruker Vertex 70 FT-IR spectrometer, was equipped with a photovoltaic MCT detector for maximum linearity of the detected signals, recording at 4 cm⁻¹ spectral resolution. The whole set-up was constantly purged with dry air (relative humidity $\ll 0.1\%$), ensuring that measured spectra were free of water-vapor influence. Along with IRSE brush spectra, $\tan \Psi_{\text{brush}}$, reference spectra of a clean silicon wedge, $\tan \Psi_{\text{Si}}$, were always measured under the same experimental conditions.

Ex situ IRSE brush measurements were performed at the polymer–air interface under an incidence angle of 65° after drying the brushes in water-vapor-free atmosphere for at least 1 h. *In situ* ellipsometric measurements in H_2O and D_2O were carried out with a specifically designed flow cell^{28–30} in backside illumination of the infrared-transparent silicon substrates under an incidence angle of 52.5° at the air–silicon interface, resulting in a $\approx 13^\circ$ angle at the silicon–brush and brush–solution interface.³¹ The *in situ* cell was equipped with a Peltier element, PID-temperature-controlled via a Pt1000 temperature sensor with a stability of $\pm 0.05^\circ C$ (PS01, OsTech GmbH i. G., Germany). After equilibration at the respective temperatures, the POx brushes were measured in incremental steps between $20^\circ C$ and $45^\circ C$.

Second-derivative analysis of referenced *in situ* $\tan \Psi$ spectra was done after smoothing the spectra using cubic splines to preserve the correct band positions.

III. RESULTS AND DISCUSSION

A. *Ex situ* characterization via IRSE

After sufficiently long exposure to dry atmosphere, the polymer brushes were first measured in dry state to characterize the vibrational bands without any interplay with water. The focus was put on the amide I carbonyl infrared signature¹⁸ originating from the POx N–C=O groups, as well as on the influence of the PGMA anchoring layers on the POx amide I bands. Figure 2 shows IRSE spectra in the carbonyl-stretching region of the PMeOx, PcPrOx, and copolymer brushes. The $\nu(C=O)$ band around 1735 cm^{-1} is associated with PGMA and does not change with the chemistry of the brush toplayers. Furthermore, it does not overlap with $\nu(C=O)$ of the brushes, which are located at much lower wavenumbers because of mesomeric effects within the N–C=O groups.³² $\nu(C=O)_{POx}$ is positioned at 1659 cm^{-1} , 1651 cm^{-1} , and 1654 cm^{-1} for PMeOx, PcPrOx, and

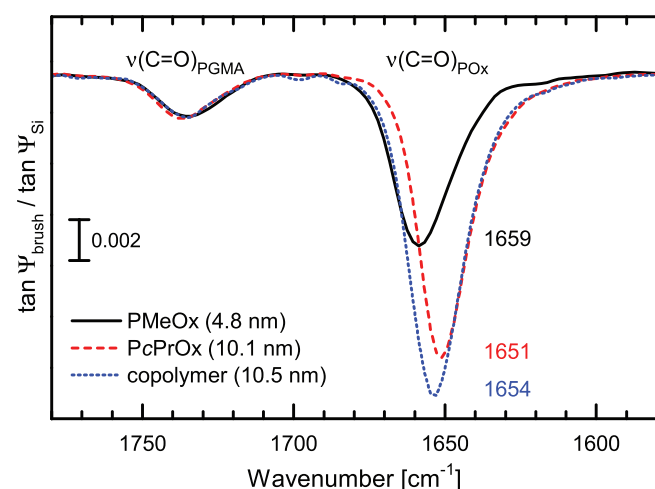


Fig. 2. *Ex situ* IRSE spectra of the poly(2-oxazoline) brushes in dry state. Marked carbonyl band frequencies correspond to the respective peak minima.

copolymer, respectively. The shift to lower wavenumbers of the latter two POx compared to methyl oxazoline is due to the electron withdrawing effect of the cyclopropyl group.^{16,33}

Since POx are tertiary amides, they do not contain N–H groups that could possibly form intra- or intermolecular hydrogen bonds with carbonyl groups. The measured $\nu(C=O)$ bands of dry POx therefore contain only one component corresponding to *free*, that is, non-interacting carbonyl groups. Importantly, for further band analysis of *in situ* spectra, no PGMA bands are overlapping the carbonyl band of the brushes.³⁴

B. *In situ* IRSE

Temperature-dependent infrared ellipsometric spectra of the POx brushes were measured at the solid–water interface in order to study the vibrational characteristics of the carbonyl group in the presence of polymer–water interactions. An overview of *in situ* spectra (each brush at low and high temperature in H_2O) is displayed in Fig. 3. The upward-pointing polymer bands are overlapped by the downward-pointing water-bending vibrational band between 1700 and 1600 cm^{-1} . The monitored C=O stretching vibration is particularly sensitive to variations in hydrogen bonding. The band is shifted to lower wavenumbers in all POx compared to the dry state positions because of the decreased electron density of the carbonyl groups when C=O \cdots H $_2$ O hydrogen bonds are forming.

$\nu(C=O)_{PMeOx}$ is shifted from 1659 cm^{-1} in dry environment to 1618 cm^{-1} in H_2O at $20^\circ C$. The spectrum, however, does not change between cold and warm water, indicating that carbonyl–water interactions within PMeOx do not exhibit temperature-sensitive changes, in accordance with

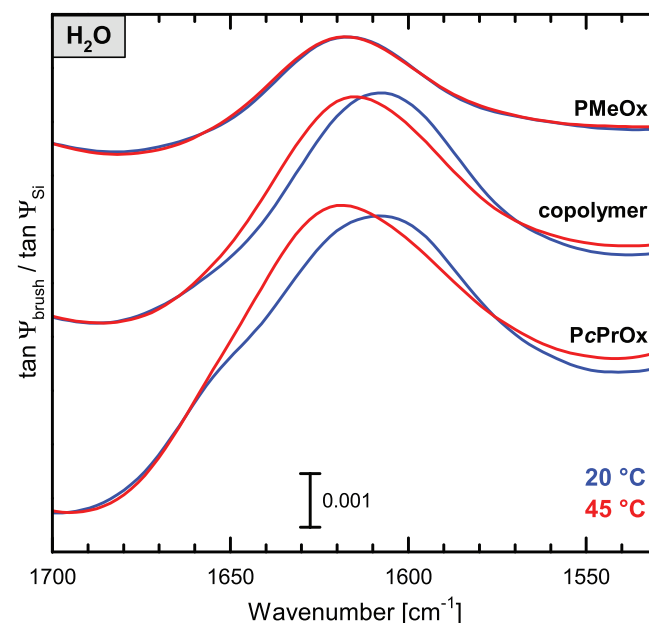


Fig. 3. *In situ* IRSE spectra of poly(2-oxazoline) brushes in H_2O at $20^\circ C$ (blue) and $45^\circ C$ (red).

PMeOx in solution.²⁰ $\nu(\text{C}=\text{O})_{\text{PcPrOx}}$ and $\nu(\text{C}=\text{O})_{\text{copolymer}}$ are measured at 1608 cm^{-1} at 20°C , and shift to 1619 cm^{-1} and 1615 cm^{-1} , respectively, after raising the temperature to 45°C . These upward shifts are related to a dehydration of the carbonyl groups with a loss of hydrogen bonds, which is followed by diffusion of water molecules out of the collapsing brushes. The smaller band shift in the copolymer compared to PcPrOx suggests that more water is retained within the copolymer brush, hinting at an overall higher water content. This observation is in agreement with the swelling degrees of comparable brushes determined via *in situ* VIS ellipsometry (see Table I), showing higher swelling of the copolymer brush.

The overall $\nu(\text{C}=\text{O})$ band shapes of PcPrOx and the copolymer in Fig. 3 indicate that the band envelope comprises several components related to different hydration states. However, the $\nu(\text{C}=\text{O})$ band is also overlapped by the downward-pointing $\delta(\text{H}_2\text{O})$ mode of water around 1650 cm^{-1} , which might obscure the total band shift of the carbonyl mode. In order to identify the switching behavior more unambiguously, measurements were performed in H_2O and additionally in D_2O . The band related to the bending vibration of heavy water occurs at $\sim 1215\text{ cm}^{-1}$, thus allowing for a clear analysis of the $\nu(\text{C}=\text{O})$ band components.

Figure 4 shows *in situ* IRSE spectra of the two temperature-responsive PcPrOx and copolymer polyoxazoline brushes in water and heavy water. Additionally, second-derivative spectra are plotted to reveal components within the carbonyl bands.

Within the broad carbonyl band of PcPrOx in H_2O (Fig. 4, top left), three components are identified at approximately 1655 cm^{-1} , 1622 cm^{-1} , and 1599 cm^{-1} . Since the latter two are at lower frequencies compared to the free-carbonyl position in dry state (see Fig. 2), they can be attributed to hydrated $\text{C}=\text{O}$ groups involved in hydrogen bonding. Based on measurements of polyacrylamides by Katsumoto *et al.*,³⁵ we assign the components at 1622 cm^{-1} and 1599 cm^{-1} to weakly and strongly hydrated $\text{C}=\text{O}$ groups that form hydrogen bonds to either one or two water molecules, respectively. The weakly hydrated component probably arises when $\text{C}=\text{O}$ hydration is inhibited by steric-hindrance effects or interchain association.³⁵ With increasing temperature, the strongly hydrated component decreases and the weakly hydrated component increases. This transformation of the polymer–water interactions is related to the brush turning from hydrophilic to

more hydrophobic. Note again that PcPrOx is a tertiary amide that does not allow for intramolecular hydrogen bonding between neighboring monomer units. This is contrary to secondary amides like PNIPAAm, which exhibit additional vibrational bands associated with hydrated H–N-bonded $\text{C}=\text{O}$ groups.³⁶

Similar to the dry states, the PcPrOx band component at 1655 cm^{-1} might be attributed to free $\text{C}=\text{O}$ groups. Interestingly, it also diminishes with the increasing temperature. A possible reason is that, when one hydrogen bond of a strongly hydrated $\text{C}=\text{O}$ group is broken, the corresponding water molecule forms a new hydrogen bond to a neighboring free $\text{C}=\text{O}$ group. This assignment, however, is ambiguous due to the overlapping contribution of the water-bending vibration at 1650 cm^{-1} . Since no 1655 cm^{-1} component is observed for PcPrOx in D_2O (Fig. 4, bottom left), it is also possible that $\delta(\text{H}_2\text{O})$ is the major contribution to the 1655 cm^{-1} component in H_2O . Its change in intensity could then be related to the change in water content and thickness of the collapsing brush.

The $\nu(\text{C}=\text{O})$ band of the copolymer in H_2O (Fig. 4, top right) only displays two major components in its second derivatives, namely, the weakly and strongly hydrated one around 1619 cm^{-1} and 1600 cm^{-1} , respectively. This shows that all $\text{C}=\text{O}$ groups are involved in hydrogen bonding. The brush is more hydrophilic owing to the incorporation of 25% MeOx in the copolymer, leading to a higher water content compared to the PcPrOx brush, which is in agreement with VIS ellipsometry measurements²⁴ (see Table I). However, the temperature-responsive change of the distribution between weakly and strongly hydrated $\text{C}=\text{O}$ groups is smaller than for PcPrOx.

In situ measurements of PcPrOx and the copolymer brushes in heavy water (Fig. 4, bottom) show that the deswelling behavior takes place gradually and is stretched over the entire measured temperature range. This is in contrast to the steplike phase transition of poly(2-oxazoline)s in solution,^{24,37} and also to PNIPAAm, which shows a steplike transition around the LCST both in solution⁶ and in the form of brushes.^{7,31} For PcPrOx in D_2O , two hydrated carbonyl-stretching components are measured at $1618\text{--}1628\text{ cm}^{-1}$ and 1600 cm^{-1} . While the strongly hydrated component at 1600 cm^{-1} clearly decreases with increasing temperature, the other component increases and seems to shift from 1618 cm^{-1} at 20°C to 1628 cm^{-1} at 45°C . A possible explanation for this shift is a gradual change from a state of hydrogen bonding with water molecules bound to other water molecules to a state of hydrogen bonding with water molecules forming a bridge between two $\text{C}=\text{O}$ groups. Formation of the latter could be a result of interchain association and steric hindrance within the brush layer.¹⁸ For PiPrOx in solution, the frequency of the bridging hydrogen bonds is supposed to be around 1630 cm^{-1} ,^{18,37} which is close to the observed 1628 cm^{-1} position for PcPrOx.

Second-derivative spectra of the copolymer in D_2O (Fig. 4, bottom right) do not show two distinct carbonyl components but rather a gradual shift of the carbonyl band,

TABLE I. Thicknesses, H_2O volume fraction, and swelling degrees of PcPrOx and copolymer brushes on PGMA-functionalized Si wafers in dry state as well as in hydrated states in H_2O , determined from VIS ellipsometry.

Polymer	Thickness d (nm)			H_2O content (vol. %)		Swelling degree	
	Dry	20°C	45°C	20°C	45°C	$d_{20^\circ\text{C}}/d_{\text{dry}}$	$d_{45^\circ\text{C}}/d_{\text{dry}}$
PcPrOx	8.5	20.2	14.0	52	32	240%	160%
Copolymer	9.4	32.4	20.4	64	51	340%	220%

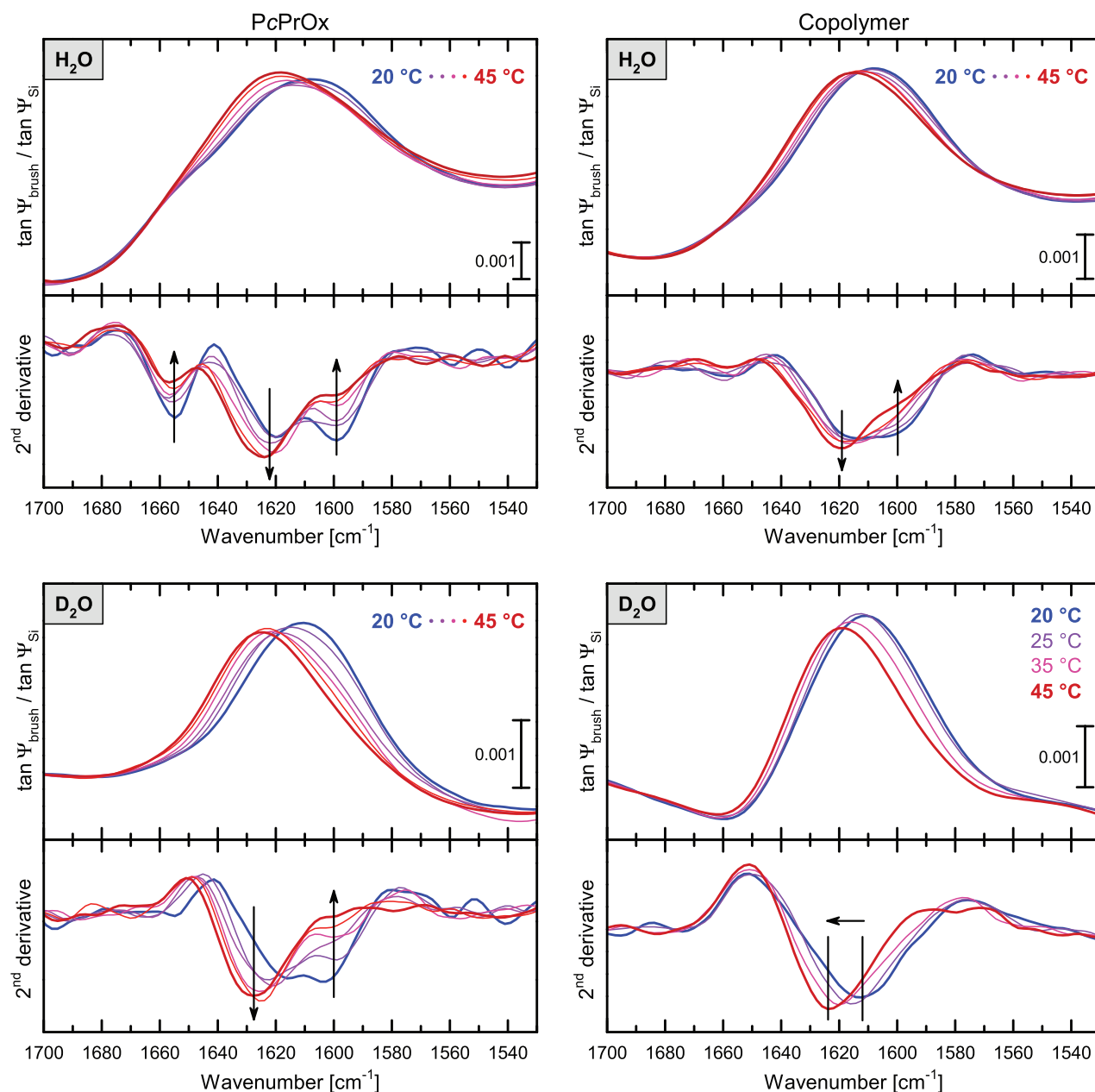


Fig. 4. Temperature-dependent IRSE spectra of POx in H₂O (top) and D₂O (bottom), as well as their second derivatives. Arrows indicate the development of identified components with increasing temperature.

hinting at less pronounced changes in polymer–water interactions. To visualize this, the thermoresponsive transition of the copolymer brush is compared with that of the PcPrOx brush in Fig. 5. The figure displays the temperature-dependent frequency shift of the carbonyl stretching vibration in heavy water, as well as the swelling degrees determined from VIS ellipsometry at 20 °C and 45 °C on comparable brushes. Up to 35 °C, PcPrOx shows a strong, linear shift of its $\nu(\text{C}=\text{O})$ frequency, which then slightly levels off at higher temperatures. An almost linear shift is also observed for the copolymer but with a much smaller incline due to the incorporation of 25% hydrophilic MeOx in the brush. In both cases, the shift takes place gradually over the entire temperature range with the

absolute frequency difference between lowest and highest temperature being greater for the PcPrOx brush. Comparison to the swelling degrees, however, shows a greater collapse of the copolymer brush. We conclude that the more hydrophilic copolymer brush contains a higher amount of additional water molecules that do not interact with C=O groups of the polymer chains via hydrogen bonding. However, they still contribute to the overall swelling of the layer.

A summarizing schematic of the polymer–water interactions within the brushes is depicted in Fig. 6, comparing the swollen and collapsed states in water with the dry state. From the swollen, highly hydrated state at room temperature, the polymer brushes deswell as the temperature rises. This is

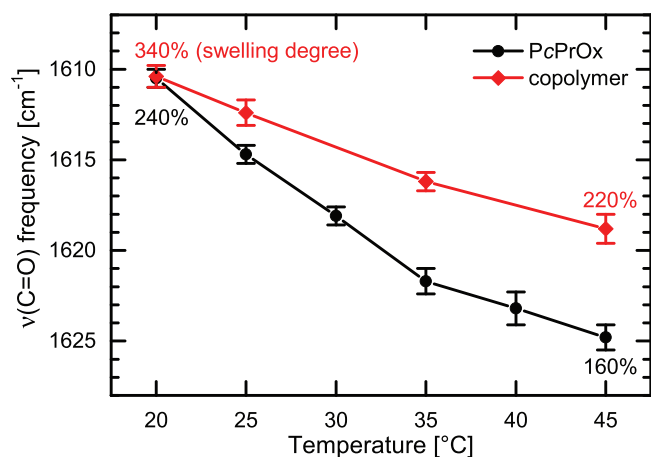


FIG. 5. Temperature-dependent $\nu(\text{C}=\text{O})_{\text{POx}}$ frequencies of the two thermoresponsive PcPrOx (black circles) and copolymer (red diamonds) brushes in D_2O , as well as their swelling degrees (with respect to the dry state) at 20 and 45 °C, determined in H_2O with VIS ellipsometry. Data points were connected to guide the eye.

accompanied by a transition from strongly to weakly hydrated $\text{C}=\text{O}$ groups, in accordance with water molecules diffusing out of the collapsing brushes.

IV. SUMMARY AND CONCLUSIONS

This study researched the interaction of poly(2-cyclopropyl-2-oxazoline) brushes with water in dependence of

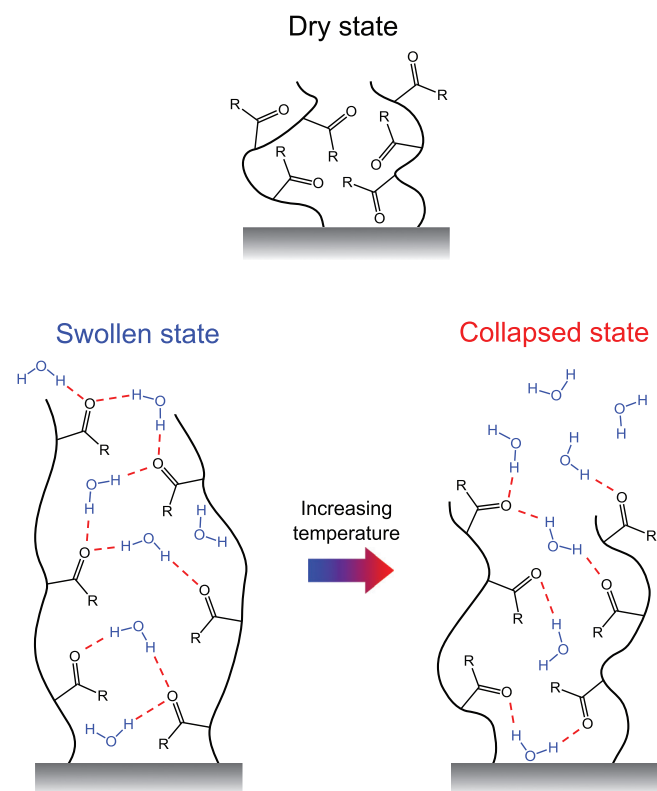


FIG. 6. Scheme of the POx brushes in dry state as well as their proposed interactions in swollen and collapsed state.

temperature variation. Measurements with *in situ* infrared ellipsometry showed downshifts of the amide I carbonyl stretching modes from dry states to hydrated states in aqueous environment, related to $\text{C}=\text{O}$ groups involved in hydrogen bonding with water molecules. Raising the temperature of the brushes in H_2O also significantly changed the carbonyl band envelopes. Frequency upshifts of $\nu(\text{C}=\text{O})$ between 20 °C and 45 °C indicated a collapse of the brushes. The transition of the brushes was clarified by using D_2O to avoid overlapping $\delta(\text{H}_2\text{O})$ contributions in the $\nu(\text{C}=\text{O})$ range. Two hydrated components of the $\nu(\text{C}=\text{O})$ band were identified from second-derivative spectra. One around 1625 cm^{-1} and one around 1600 cm^{-1} , assigned to weakly and strongly hydrated carbonyl groups, respectively.

Interactions in a pure temperature-responsive PcPrOx brush were compared to those in a copolymer brush consisting of a random mixture of cPrOx and the more hydrophilic MeOx. In contrast to the steplike transition of other thermoresponsive polymers, for example, PNIPAAm,^{7,31} the PcPrOx and copolymer brushes showed continuous $\nu(\text{C}=\text{O})$ frequency shifts to higher wavenumbers with increasing temperature, correlating with less polymer–water interactions within the collapsing brushes. Smaller band shifts, but higher swelling degrees, were observed for the copolymer brush, showing that more water molecules are retained in the copolymer brush because of its higher hydrophilicity.

It is known from turbidity measurements that the thermoresponsive behavior of POx in solution strongly depends on molecular weight M_n and concentration.¹⁶ Since *in situ* IRSE on POx brushes revealed that temperature-induced changes in polymer–water interactions are influenced by the brush composition, it would also be interesting for future studies to investigate the dependence on M_n and grafting density. Knowledge of this in combination with the possibility to tune the transition behavior via copolymerization is needed to successfully design temperature-responsive POx brushes for biomedical applications.

In this respect, future studies with *in situ* infrared ellipsometry will focus on more complex POx systems like those with adsorbed peptides or proteins, which are additionally governed by intra- and intermolecular hydrogen bonding. Understanding interactions and hydration states in these systems is of tremendous importance for potential applications, such as antifouling surfaces, drug-delivery systems in the form of polymer–drug conjugates, as well as for stimuli-controlled protein and cell adhesion.

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