ZIRCONIUM OXYCHLORIDE OCTAHYDRATE CONTAINING HYDROGEN-BONDED POLYMER MULTILAYER FILMS

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ABSTRACT

ZIRCONIUM OXYCHLORIDE OCTAHYDRATE CONTAINING HYDROGEN-BONDED POLYMER MULTILAYER FILMS

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A facile approach is developed to enhance the pH-stability and controlling destruction kinetics of purely hydrogen-bonded multilayers using ZrOCl₂.8H₂O. To produce layer-by-layer (LbL) films, coordination complexes of a polyphenol, Tannic Acid (TA) and ZrOCl₂.8H₂O ((TA+Zr) complexes) were produced and then they were self-assembled at the surface with neutral polymers such as PVCL, PNIPAM and PEO through hydrogen bonding interactions at pH 2. It was shown that incorporation of (TA+Zr) complexes into hydrogen-bonded multilayers provided excellent pH-stability. Stabilization of the films against pH can be explained by the high affinity of Zr⁴⁺ for phenolate oxygens of TA assuring the charge balance within the multilayers at increasing pH values. In addition, enhanced association between (TA+Zr) complexes with increasing pH could have also contributed to the stability of multilayers. More importantly, (TA+Zr) complexes allowed controlling kinetics of dissolution. The onset of disintegration of PNIPAM and (TA+Zr) multilayers could be delayed for approximately 10 hours at pH 7.5. In addition, incorporation of (TA+Zr) complexes into multilayers extended the disintegration time period. In contrast to multilayers of PNIPAM and TA which eroded exponentially at pH 7.5, multilayers of PNIPAM and (TA+Zr) complexes disintegrated in a linear fashion in longer periods of time. Such hydrogen-bonded multilayers may be promising for controlled drug release applications from surfaces.

Keywords: Layer-by-layer technique, hydrogen-bonded multilayers films, stability of multilayer films

ZİRKONYUM OKSİKLORÜR OKTAHİDRAT İÇEREN HİDROJEN BAĞLI POLİMER ÇOK-KATMANLI FİLMLER

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Hidrojen bağlı çok-katmanlı filmlerin pH-kararlılığını iyileştirmek ve çözünme kinetiklerini kontrol edilebilir hale getirmek için zirkonyum oksiklorür oktahidrat (ZrOCl₂.8H₂O) kullanarak yeni ve kolay bir yaklaşım geliştirilmiştir. Bir polifenol olan tanik asit (TA) ve ZrOCl₂.8H₂O'dan elde edilen koordinasyon komplekslerinin (TA+Zr), PVCL, PNIPAM ve PEO gibi nötral polimerler ile hidrojen bağları aracılığıyla pH 2'de yüzeyde biriktirilmesi suretiyle katman-katman filmler elde edilmiştir. (TA+Zr) komplekslerini çok-katmanlı hidrojen bağlı polimer içerisine yerleştirerek pH kararlıkları yüksek filmler elde edilebileceği gösterilmiştir. Filmlerin pH'a karşı kararlıkları Zr⁴⁺ katyonlarının TA'nın fenolat oksijenlerine olan eğilimi ve böylelikle film yapısı içerisinde sağlanan yük dengesi ile açıklanabilir. Ayrıca, pH yükselmesi ile (TA+Zr) kompleksleri arasındaki etkileşimin artması da pH kararlığının artmasına etki etmiş olabilir. Daha da önemlisi, (TA+Zr) komplekslerinin çok-katmanlı filmler içerisine yerleştirilmesi ile filmlerin çözünme kinetiklerinin kontrol edilebilmesi mümkün kılınmıştır. PNIPAM ve (TA+Zr) komplekslerinden oluşan filmlerin çözünmesi pH 7.5'te yaklaşık 10 saat süreyle ertelenmiştir. Ayrıca, (TA+Zr) kompleksleri sayesinde filmlerin çözünme süresi de uzamıştır. pH 7.5'te üssel olarak çözünen PNIPAM ve TA çok-katmanlı filmlerinin aksine, PNIPAM ve (TA+Zr) komplekslerinden oluşmuş filmler doğrusal olarak

daha uzun sürede çözünmüşlerdir. Bu tür hidrojen bağlı çok-katmanlı polimer filmler kontrollü ilaç salımı uygulamaları için umut verici malzemeler olabilir.

Anahtar kelimeler: Katman-katman film oluşturma tekniği, hidrojen bağlı çok katmanlıfilmler, çok katmanlıfilmlerde kararlılık

To my family,

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TABLE OF CONTENT

PLAGIARISMiv
ABSTRACTv
ÖZvii
ACKNOWLEGMENTS x
TABLE OF CONTENTSxi
LIST OF TABLES
LIST OF FIGURES xiv
LIST OF SCHEMES xvi
CHAPTER
1.INTRODUCTION
1.1. Layer-by-layer Self-Assembly of Charged Polymers
1.2. Stimuli-Responsive Multilayer Films
1.2.1. Stimuli-Responsive Electrostatic LbL Films
1.2.2. Stimuli-Responsive Hydrogen-bonded LbL Films
1.2.2.1. Factors Affecting the Properties of Hydrogen-Bonded Multilayer
Films7
1.2.2.1.1 Effect of Chemical Structure of Polymers7
1.2.2.1.2 Effect of pH of Polymer Deposition Solutions
1.2.2.1.3 Effect of Ionic Strength of Polymer Deposition Solution
1.2.2.1.4 Effect of Molecular Weight of Hydrogen Accepting Neutral
Polymers
1.2.2.1.5 Effect of Temperature of the Polymer Solutions

1.2.2.2 Effect of pH and Temperature on the Properties of Hydrogen-
Bonded Films at the Post-assembly Step12
1.2.2.2.1 Response of Hydrogen-bonded Systems to pH12
1.2.2.2.2 Response of Hydrogen-bonded Systems to Temperature
1.2.2.3 Loading/Release of Functional Molecules into/from Hydrogen-
Bonded Multilayers14
1.2.2.4. Limitations of Hydrogen-Bonded Multilayer Films
1.2.2.5. Improving pH-stability of Hydrogen-Bonded Multilayer Films15
1.3. Aim of the Study
2. EXPERIMENTAL PART
2.1. Materials
2.2. Preparation and characterization of (TA+Zr) complexes
2.3 Deposition of multilayers
2.4 Apparatus and measurement
3. RESULTS AND DISCUSSION
3.1. Aqueous Solution Properties of ZrOCl ₂ .8H ₂ O25
3.2. Zr(IV) complexes of TA in solution
3.3. Preparation of Multilayers Containing (TA+Zr) complexes
3.4. pH-Triggered Dissolution of Multilayers Containing (TA+Zr) complexes 41
3.5. Kinetics of Dissolution
4. CONCLUSION
REFERENCES

LIST OF TABLES

TABLES

 Table 2.1Chemical structures of polymers.
 20

Table 3.1	rms re	ough	ness	values	s and	fractio	n retai	ned at	the	surface	of	12-	bila	yer
PVCL/(TA	A+Zr)	and	12-b	ilayer	PNIP	PAM/(T	A+Zr)	films	after	expos	sure	to	pН	12
buffer solu	itions.		•••••				•••••		•••••	•••••				44

LIST OF FIGURES

FIGURES

Figure 1.1 Number of SCI journals searched by SCI Finder under the titles of 'L'	bL
assembly' and 'polymer multilayer films' [6]	2
Figure 1.2 Schematic representation of (a) LbL film fabrication process,	(b)
adsorption steps during the LbL deposition on the surface [6]	3
Figure 1.3 Chemical structures of polymers represented in Table 1.1 [54]	9

Figure 3.1 Hydrodynamic size of $[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ as a function of pH......27 Figure 3.2 UV-vis absorption spectrum of TA and (TA+Zr) complexes at pH 2. Inset is obtained from reference [74] and shows UV-vis spectrum of TA at acidic and 3.4 Film thickness of PVCL/(TA+Zr) complexes Figure (Panel A): PNIPAM/(TA+Zr) complexes (Panel B) and PEO/(TA+Zr) complexes (Panel C) as a function of bilayer number. Thickness values of PVCL/TA (Panel A); PNIPAM/TA Figure 3.5 AFM topography images (2x2 µm) of silicon wafers coated with 12bilayers of PVCL/(TA+Zr) complexes and PVCL/TA (Panel A); 12-bilayers of PNIPAM/(TA+Zr) complexes and PNIPAM/TA (Panel B) and 5-bilayers of PEO/(TA+Zr) complexes and PEO/TA (Panel C). Panel D contrasts rms roughness

Figure 3.5 (continued)AFM topography images (2x2 μ m) of silicon wafers coated
with 12-bilayers of PVCL/(TA+Zr) complexes and PVCL/TA (Panel A); 12-bilayers
of PNIPAM/(TA+Zr) complexes and PNIPAM/TA (Panel B) and 5-bilayers of
PEO/(TA+Zr) complexes and PEO/TA (Panel C). Panel D contrasts rms roughness
values of the films
Figure 3.6 Thickness of PVCL/(TA+Zr)films as a function of number of bilayers which were prepared using (TA+Zr) complexes with different compositions
Figure 3.7 pH-induced disintegration of PVCL/(TA+Zr) films. Films were prepared at pH 2 using (TA+Zr) complexes with different compositions
Figure 3.8 pH-triggered dissolution of 12-bilayer PVCL/(TA+Zr) and PVCL/TA

Figure 3.9 Thick	cness of [Z	$Zr_4(OH)_8(H)$	$(1_2O)_{16}]^{8+}/TA$	film	as a	function	of	number	of
bilayers at pH 2.									45

Figure 3.11 Fraction retained at the surface of $[Zr_4(OH)_8(H_2O)_{16}]^{8+}/TA$ film as the acidity decreased. 47

Figure 3.12 Fraction retained at the surface of $PVCL/[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ film as the acidity decreased.

LIST OF SCHEMES

SCHEMES

Scheme 2.1 Schematic representation of deposition of multilayers					
Scheme 3.1 Chemical structure of tetrameric [Zr ₄ (OH) ₈ (H ₂ O) ₁₆] ⁸⁺ units					
Scheme 3.2 Schematic representation of hydrolysis (Panel A) and polymerization $of[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ in aqueous solution (Panel B)					
Scheme 3.3 Chemical Structure of Tannic Acid					
Scheme 3.4Schematic representation of association between tetrameric $[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ units and TA molecules at pH 2. Drawing is based on the mol					
ratio of Zr ⁴⁺ cations to hydroxyl groups of TA in the coordination complex					

LIST OF ABBREVIATIONS

LbL	Layer-by-layer
НВ	Hydrogen-bonded
ТА	Tannic Acid
ZrOCl ₂ .8H ₂ O	Zirconium oxychloride octahydrate
PEO	Poly(ethylene oxide)
BPEI	Branched poly(ethylenimine)
PVCL	Poly(N-vinylcaprolactam)
PNIPAM	Poly(N-isopropylacrylamide)
DI	Deionized
rms	Root mean square

CHAPTER 1

INTRODUCTION

Functionalization of surfaces via polymer coatings has been of growing interest due to potential use of these coating in the field of electronics, biomedical engineering, optics, etc. Langmuir-Blodgett (LB) technique is one of the oldest techniques used to functionalize surfaces. It is based on deposition of a monolayer which has previously been formed at the gas-liquid interface onto a solid substrate. [1,2] However, its use is limited due to requirement for molecules with surfactant-like properties, relatively expensive instrumentation, difficulty in keeping the surface pressure constant, low thermal and mechanical stability of the films. [3]

Another technique used to functionalize surfaces is layer-by-layer (LbL) selfassembly technique. It is based on alternating deposition of oppositely charged species at the surface. LbL technique was first discovered by Iler in 1966 [4]. They have demonstrated successful deposition of oppositely charged colloids at the surface of a glass in an alternating fashion. LbL technique did not have significant impact on the concerned research field until its rediscovery by Decher et al. in the beginning of 1990s using charged polymers [5]. The number of publications on LbL polymer films has been increasing tremendously in the last 20 years due to wide application areas of LbL films (Figure 1.1) [6].



Figure 1.1 Number of SCI journals searched by SCI Finder under the titles of 'LbL assembly' and 'polymer multilayer films' [6].

1.1. Layer-by-layer Self-Assembly of Charged Polymers

Multilayer films via LbL self-assembly of charged polymers at the surface can be prepared through the following steps: 1) A substrate is dipped into a positively charged polyelectrolyte solution;, 2) the substrate is rinsed with DI water to remove loosely bound polymers to avoid contamination of the polymer solutions; 3) the substrate is immersed into the negatively charged polyelectrolyte solution; 4) the substrate is again rinsed with DI water to get rid of the loosely bound polymers. This deposition cycle is repeated until desired number of layers is deposited at the surface. Note that at each deposition step, coating of the surface by the polymer chains continues until the surface charge is compensated. Schematic representation of layer-by-layer film fabrication technique is shown below.



Figure 1.2 Schematic representation of (a) LbL film fabrication process, (b) adsorption steps during the LbL deposition on the surface [6].

LbL self-assembly technique has several advantages making this method powerful for the fabrication of ultra-thin polymer films. The very first one is the simplicity of the technique. LbL assembly is a robust technique which does not require sophisticated equipment and precise stoichiometry [5]. Thus, it can be considered as a relatively cheap film fabrication method. Second, there is no need for complex reactions. The technique relies on formation of multilayer films through electrostatic association between the layers. Third, it is possible to precisely control the surface morphology and properties of the films by varying the film deposition conditions such as pH, temperature, ionic strength, polymer concentration, deposition time, etc. For example, when salt is added into polyelectrolyte deposition solutions, polymers are adsorbed at the surface more in coiled conformation due to shielding of the charges by the salt ions leading to formation of thicker layers [7]. LbL technique also allows incorporation of a wide range of materials into the multilayers. These materials include but are not limited to inorganic molecular clusters [8,9], nanoparticles (NPs) [10], nanotubes and nanowires [11,12], nanoplates [13,14] organic dyes [15], dendrimers [16], porphyrins [17], biological polysaccharides [18,19], polypeptides [20,21], nucleic acids and DNA [22], proteins [23-26] and viruses[27]. This feature of LbL technique is specifically important to enhance the functionality of the surfaces [11].

Another advantage of LbL films is the variety of the solid supports that can be used as a substrate for multilayer deposition. There is no limitation for size and shape of the substrate. In addition to commonly used 2D substrates such as glass, quartz, silicon wafer or mica [29], 3D substrates can also be used to prepare hollow capsules or nanotube structures composed of polyelectrolyte multilayers [30,31].

Finally, use of aqueous polymer solutions makes LbL technique specifically promising for biomedical applications [32].

1.2. Stimuli-Responsive Multilayer Films

LbL films can also be rendered responsive to changes in environmental conditions such as pH, temperature, light, electric- and magnetic- field when weak polyelectrolyte(s) and/or stimuli-responsive polymers are used as building blocks during the film construction. Stimuli-responsive LbL films exhibit structural changes and/or conformational rearrangement within the multilayers when exposed to a change in energetic (light, electric field) and or chemical (pH, temperature, ionic strength, biological environment) conditions. In this way, film properties such as permeability, wettability, color, solubility could be altered easily [33]. Such a feature is specifically important for biomedical applications such as drug delivery, tissue engineering and biosensing [34-39]. In addition, stimuli-responsive LbL films also find applications in preparation of nonlinear optics [40], solid-state ion conducting materials [41], solar energy conversions [42] and separation membranes [43].

Among these triggering mechanisms, pH and temperature have been the most studied ones. By taking advantage of the pH variations in different tissues and regions of the body, pH-responsive LbL films can be used as a platform to load/release drug molecules [44,45]. Multilayers composed of temperature-responsive polymers which have critical temperature around physiological temperature have also been extensively investigated for controlled drug delivery applications [46].

Stimuli responsive LbL films can be categorized into 2 groups: 1) stimuli-responsive electrostatic LbL films; 2) stimuli-responsive hydrogen-bonded LbL films.

1.2.1. Stimuli-Responsive Electrostatic LbL Films

Different from a strong polyelectrolyte which ionizes completely in aqueous solution, a weak polyelectrolyte has a dissociation constant (pK_a or pK_b) and the polymer's charge density can be tuned by changing the solution pH. Therefore, polyelectrolyte multilayer films which are fabricated using weak polyelectrolytes display response to changes in pH [32]. For example, at low pH values, polyacids become protonated and are in non-ionized state. Increasing pH above the pK_a of the polyacid results in ionization of the acid moieties and swelling of the LbL films. This phenomenon is observed due to an increase in the amount of negative charges and electrostatic repulsion between the layers as well as an increase, counterions penetrate into the multilayers to compensate the negative charge which is followed by penetration of water molecules to balance the osmotic pressure and finally ends up with swelling of the multilayers. Similar phenomenon is also observed for polybasic polymers, however at acidic pH region, below the pK_b of the polymer [46].

It was demonstrated that PAA/PAH films had interesting pH-response [92]. The films were produced from partially charged PAA (pH: 3.5) and PAH (pH: 7.5). A loopy structure, which can produce porous structures with pH arrangements, was obtained. For example, while pore sizes changes from 20 to 40 nm when the film is

treated with pH 1.8 solution, pore sizes increase to 1 micron when pH of the solution is increased from 1.8 to 2.4. When the film was immersed sequentially to the pH 1.8 and 2.4 solutions, a structure with honeycomb appearance was observed with tens of micron sized pores [92].

1.2.2. Stimuli-Responsive Hydrogen-bonded LbL Films

Similar to electrostatic association between the polymers which drives the LbL film assembly, hydrogen bonding interactions between the polymer pairs can also drive the multilayer assembly. Instead of oppositely charged polymer pairs, polymer pairs with hydrogen accepting and hydrogen donor groups are used as building blocks. Hydrogen-bonded systems are of interest specifically for biomedical applications due to use of neutral polymers which are reported to be less toxic than their polycation counterparts as well as pH-response of the films to mild pH conditions. In addition many temperature responsive polymers are neutral and can be incorporated into the multilayers through hydrogen bonding interactions.

Preparation of hydrogen-bonded LbL films in aqueous environment was first demonstrated by Rubner and co-workers. They have self-assembled polyaniline (PAni) at the surface with various neutral polymers such as polyvinylpyrrolidone (PVPON), poly(vinyl alcohol) (PVA), poly(acrylamide) (PAAm), and polyethylene glycol (PEG) [47]. Simultaneously, preparation of hydrogen-bonded films in organic solvents or mixtures of organic solvents and water was also demonstrated [48-51]. Considering the fact that electrostatic multilayers could only be prepared using water-soluble polyelectrolytes, use of organic solvents during film deposition paves the way for the use of water-insoluble materials, thus extends the range of materials that could be incorporated into the multilayers.

The discovery of "erasable hydrogen-bonded multilayers" by Sukhishvili and Granick had tremendous impact in the field of LbL films. They found that hydrogenbonded multilayers of neutral polymers and polycarboxylic acids which were deposited at acidic conditions can be totally erased from the surface by disrupting the hydrogen bonds between the layers through a pH-trigger [52]. The pH at which onset of multilayer disintegration is observed is called "critical disintegration pH". This critical pH value is closely related with the p K_a of the polycarboxylic acid. However, other parameters such as strength of hydrogen bonding between the layers, chemical nature and hydrophobicity of the neutral polymers also affect the critical disintegration pH of the hydrogen-bonded multilayers. This feature of hydrogenbonded films draw special attention due to their emerging potential in controlled delivery of functional molecules such as wound healing applications. For example, a wound patch coated with hydrogen-bonded multilayers which was loaded previously with drug molecules may dissolve and release the drug molecules when exposed to physiological pH.

1.2.2.1. Factors Affecting the Properties of Hydrogen-Bonded Multilayer Films

1.2.2.1.1. Effect of Chemical Structure of Polymers

The thickness of hydrogen bonded films is related with the extent of interpolymer association between the layers [53]. As the extent of interaction between the layers increases, polymers bind through higher number of binding points resulting in more intense and thinner films. A review by Kharlampieva et al. clearly explains the effect of chemical nature of neutral polymer components on the film thickness [54]. For example it was reported that when poly (methacrylic acid) (PMAA) was self-assembled at the surface with various neutral polymers such as poly (ethylene oxide)

(PEO), poly(vinyl methyl ether) (PVME), poly(N-isopropyl acrylamide) (PNIPAM), poly(N-vinylpyrrolidone) (PVPON), poly(2-hydroxyethylacrylate) (PHEA), the highest bilayer thickness was obtained for PEO/PMAA multilayers. However, bilayer thickness for PVCL/PMMA or PVPON/PMAA films was significantly lower than that of PEO/PMAA (Table 1.1 obtained from ref [54]). The difference was explained by the strength of hydrogen bonds. In PEO/PMAA films, hydrogen bonding occurred between the ether oxygens of PEO and carboxylic acid groups of PMAA, whereas in PVCL/PMAA or PVPON/PMAA films, hydrogen bonding occurs between the carbonyl groups of PVCL or PVPON and carboxylic acid groups of PMAA. Ether oxygens are known to form weaker hydrogen bonds. Therefore, higher thickness of PEO/PMAA films was explained by the weaker association between the layers resulting in lower number of binding points between the layers and looser film structure.

Table 1.1 Average bilayer thickness for PMAA (M_{wt} 150 K) layer-by-layer deposited with PEO (M_{wt} 200 K), PVPON (M_{wt} 360 K), PAAM (M_{wt} 5,000 K), PNIPAAM (M_{wt} 300 K), PVME (M_{wt} 200 K), PVCL (M_{wt} 1.8 K), and PHEA (M_{wt} 600 K) at pH 2 and 23°C [54]

Polymer	PMAA/	PMAA/	PMAA/	PMAA/	PMAA/	PMAA/	PMAA/
system	PEO	PVPON	PAAM	PNIPAAM	PVME	PVCL	PHEA
Bilayer thickness, nm	20	4	7	6	15.6	4.8	13



Figure 1.3 Chemical structures of polymers represented in Table 1.1 [54].

1.2.2.1.2. Effect of pH of Polymer Deposition Solutions

pH of the polymer solutions is critical on the thickness of hydrogen-bonded multilayers. When the film deposition pH is close to the pK_a of the polyacid, drastic decrease in the bilayer thickness is observed [53] due to decrease in the number of protonated carboxylic acid groups and lower extent of association between the polymer pairs. For example, Hammond and co-workers found that when the pH of the polymer solutions' was increased from 2.8 to 3.5 during construction of PEO/poly(acrylic acid) (PAA) films, bilayer thickness decreased significantly (from ~25000 Å to 106 Å for 20 bilayers). When the pH was further increased above pH 3.5, the films could not be constructed at all [55]. Similar phenomenon was observed also for more strongly bound PVPON/PAA [56] and PVPON/PMAA [54] films.

1.2.2.1.3. Effect of Ionic Strength of Polymer Deposition Solution

In contrast to electrostatically bound films, thickness of hydrogen-bonded multilayers is not significantly affected by the salt ions in the polymer solutions. The difference can be explained by the charge density on the polymers. In electrostatically bound films, the salt ions can screen the charges on the polyelectrolytes and the polymer chains adopt a more coiled conformation. This results in an increase in the amount of polymers deposited at the surface. The effect of salt on the growth of hydrogen-bonded multilayers is smaller than that on electrostatically bound multilayers. However, it is more complicated and found to be highly dependent on the chemical structure of the polymers and the salt ions. For example, ionization of polyacids is found to be enhanced in the presence of salt ions. The decrease in the amount of protonated acid groups results in lower extent of association between the polymer pairs and a decrease in bilayer thickness [54].

In contrast, Hammond and co-workers reported that growth of PEO and PAA films was slightly enhanced with increasing amount of lithium triflate when the salt concentration was below 0.5 M. However, when salt concentration was further increased, they found that LbL growth of PEO/PAA films was prohibited. At low salt concentrations (<0.5M), the interaction between the ether oxygens of PEO and salt cations decreased the number of free ether oxygens resulting in weaker binding between PEO/PAA layers and higher film thickness. However, at high salt concentrations, the interaction between ether oxygens and salt cations significantly decreased the number of ether oxygens available for film assembly resulting in inhibition of LbL growth [57].

1.2.2.1.4. Effect of Molecular Weight of Hydrogen Accepting Neutral Polymers

The effect of molecular weight of the polymer on the thickness of hydrogen-bonded multilayers is highly dependent on the extent of association between the polymer pairs. For example, Hammond and co-workers reported that the bilayer thickness of weakly bound PEO/PAA films increased 7 times when the molecular weight of PEO was increased from 1.5 kDa to 20 kDa. However, further increasing the molecular weight had insignificant effect on the film thickness [55].

Similar results were demonstrated by Rubner et al. for poly(acryl amide) (PAAM)/PAA multilayers. They reported that thicker films were obtained using PAAM with molecular weight of 5000 kDa than PAAM with molecular weight of 800 kDa[58].

For strongly bound hydrogen-bonded multilayers such as PVCL/PMAA and PVPON/PMAA, changing molecular weight of the neutral polymer did not affect the film thickness [54].

1.2.2.1.5. Effect of Temperature of the Polymer Deposition Solutions

Temperature responsive polymers exhibit change in their physical properties with change in temperature. For example, temperature-responsive polymers adopt expanded coil conformation. At the critical temperature, polymers go into a transition from expanded coil to compact globule conformation. The lower critical solution temperature (LCST) is the temperature above which the polymer solution is biphasic. In contrast, the solution of a polymer with upper critical solution temperature (UCST) is biphasic below the critical temperature [60].

Due to limited number of polymers exhibiting UCST behavior, hydrogen-bonded multilayers of polymers with LCST behavior have been more examined. The effect of deposition temperature on the thickness of hydrogen-bonded multilayers has been first demonstrated by Caruso and co-workers. They found that PNIPAM/PAA films which were deposited at 30°C were thicker than that deposited at 10°C or 21°C (due to decrease in solubility of PNIPAM close to its LCST [61]. Similar phenomenon was also observed for poly(vinyl methyl ether) (PVME) and PVCL with LCST values of 36°C [62]and 35°C [63], respectively [54].

1.2.2.2 Effect of pH and Temperature on the Properties of Hydrogen-Bonded Films at the Post-Assembly Step

1.2.2.2.1. Response of Hydrogen-Bonded Films to pH

As mentioned in Section 1.2.2, hydrogen-bonded multilayers which were deposited at acidic conditions can be totally erased from the surface when exposed to higher pH values. The pH at which the onset of dissolution starts is generally named as "critical dissolution pH". This critical pH value depends primarily on the pK_a of the polyacid, strength of hydrogen bonding interactions between the layers and nature of the neutral polymer.For example, critical dissolution pH values of PEO/PAA and PEO/PMAA multilayers were reported as 3.6 and 4.6, respectively [52]. PAA has a pK_a of 4.28 [64,65] in solution, whereas PMAA has a pK_a of 5.5 [66]. The difference in the pK_a of these 2 polycarboxylic acids is reflected to critical dissolution pH values of the multilayers.

To understand the effect of strength of hydrogen bonding between the layers and the chemical structure of neutral polymer on the pH-stability of the multilayers, a comparison between the critical dissolution pH of various hydrogen-bonded multilayers which have common hydrogen donating polyacid was demonstrated in a review by Kharlampieva and Sukhishvili. Table 1.2, which is obtained from ref [54], shows critical dissolution pH of hydrogen-bonded multilayers of PMAA and various neutral polymers. PEO/PMAA which is a weakly bound film has a critical dissolution pH of 4.6, whereas a strongly bound PVCL/PMAA film has a significantly higher critical pH value of 6.95. This was reported to be due to difference in strength of hydrogen bonding interactions between the layers in these two film systems. The strength of hydrogen bonding interactions between hydrogen accepting carbonyl groups of PVCL and hydrogen donating carboxylic acid groups of PMAA was greater than that between ether oxygens of PEO and carboxylic acid

groups of PMAA [54]. Interestingly, multilayer film of another polyether, PVME and PMAA had a critical dissolution pH of 6.0 which is 1.4 pH units higher than the critical dissolution pH of PEO/PMAA. Although both films have polyethers as the neutral polymer, the difference in critical dissolution pH values was correlated with the difference in the hydrophobicity of the polymers. PVME which has more hydrocarbon moieties than PEO is more hydrophobic and leads to enhanced hydrophobic interactions between the layers and significantly contributes to the stabilization of multilayers [54]. Similar phenomenon was also observed when a comparison between the critical pH values of PVPON/PMAA (pH ~ 6.4) and PVCL/PMAA (pH ~ 6.95) was performed in the same study [54]. It was reported that 2 more methylene groups of PVCL contributed to stronger hydrophobic interactions between the layers resulting in higher pH-stability of PVCL/PMAA multilayers.

Table 1.2 Critical dissolution pH values of several hydrogen-bonded polymer multilayer systems. Critical pH values were determined as the value at which less than 10% of the film dissolved in one hour. Critical ionization values present the PMAA ionization at the critical pH [54].

Polymer system	Critical dissolution pH	Critical ionization
PMAA/PHEA	4.0	$\sim \! 1\%$
PMAA/PEO	4.6	$\sim \! 1\%$
PMAA/PAAM	5.0	${\sim}4\%$
PMAA/PVME	6.0	${\sim}2\%$
PMAA/PNIPAAM	6.2	$\sim \! 3\%$
PMAA/PVPON	6.4	$\sim\!\!8{-}10\%$
PMAA/PVCL	6.95	30%

1.2.2.2.2 Response of Hydrogen-Bonded Films to Temperature

Studies have shown that hydrogen-bonded multilayers containing polymers with LCST exhibited enhanced dye permeability with increasing temperature below their

LCST [59]. This is probably due to conformational changes that the polymer goes through when approaching close to its LCST.

1.2.2.3 Loading/Release of Functional Molecules into/from Hydrogen-Bonded Multilayers

In general, 2 different strategies are applied to load functional molecules into the multilayers. First, functional molecules are loaded into the multilayers during film assembly by adding the functional molecules into the polyacid solution. However, the functional molecules should be positively charged and mixed with the polyacid solution when polyacid is slightly negatively charged so that functional molecules can associate with the polyacid through electrostatic interactions. Molecules can be released from the multilayers when the pH is increased above the critical dissolution pH. For example, Sukhishvili and Granick loaded a model dye, Rhodamin 6G into PEO/PMAA multilayers by using a mixture of Rhodamin 6G and PMAA solution for LbL deposition of PEO at pH 4. Rhodamin 6G could be released from the multilayers at pH above the critical dissolution pH of the multilayers (Scheme 1.1) [52].

Second, functional molecules can be incorporated into the multilayers at the postassembly step. Multilayers which are deposited at strongly acidic conditions are exposed to the solution containing positively charged functional molecules at a pH which is slightly higher than the film deposition pH. The reason for choosing a higher pH value is to induce slight ionization within the multilayers so that functional molecules can be incorporated within the film structure through electrostatic interactions. Sukhishvili also showed that Rhodamin 6G could be incorporated into PEO/PMAA multilayers by immersing PEO/PMAA films which were constructed at pH 2 into Rhodamin 6G containing solution at either pH 3.8 or pH 4.2 (Scheme 1.2) [67].

1.2.2.4. Limitations of Hydrogen-Bonded Multilayer Films

As mentioned in Section 1.2.2, hydrogen-bonded multilayers attract great attention for biomedical applications. In addition to use of neutral polymers, another significant property of hydrogen-bonded multilayers which make them unique is the pH-response of multilayers, making such systems promising for controlled drug delivery applications. However, there is one major drawback of hydrogen-bonded neutral polymer/polycarboxylic acid multilayers which is the lack of stability of multilayer films at high pH values, significantly at physiological conditions. Hydrogen-bonded neutral polymer/polycarboxylic acid multilayers completely disintegrate at physiological conditions because almost all polycarboxylic acids have pK_a valueslower than 7 [13,36]. When a fast release of molecules from the surface is desired, this feature of the hydrogen-bonded multilayers is advantageous, e.g. wound-healing applications. However, if the release of functional molecules in extended time is expected, hydrogen-bonded neutral polymer/polycarboxylic acid multilayers are not suitable due to fast disintegration of the films above their critical dissolution pH.

There are several strategies which have been reported to enhance the pH-stability of hydrogen-bonded multilayers.

1.2.2.5. Improving pH-stability of Hydrogen-Bonded Multilayer Films

Yang and Rubner indicated that pH-stability of hydrogen-bonded multilayer films could be increased by introducing covalent bonds between the layers through thermal-or photo-crosslinking methods. They used two different approaches for crosslinking of PAA and PAAm multilayers. Firstly, the temperature of the film was increased to 175°C. That process resulted with two different crosslinking between multilayers. One of them was thermal imidization reaction between the amide groups

of the PAAm and the carboxylic groups of the PAA, and the other one was an anhydride formation between carboxylic acid groups. In contrast to anhydride linkages which were hydrolyzed under exposure to water at pH=7, the imide groups were stable at longer period of time at elevated pH values. The second approach of Yang and Rubner was based on using PAA which is functionalized with a UV-crosslinkable moiety (an α -hydroxybenzoyl group) as the topmost layer. This moiety produced free radicals upon UV-irradiationfollowed by crosslinkingwithin the multilayers [68].

Crosslinking of hydrogen-bonded multilayers was also demonstrated by Sukhishvili and co-workers. They took advantage of carbodiimide chemistry to introduce covalent crosslinks between multilayers of poly(methacrylic acid) (PMAA) and PVPON or PEO [69]. Following this work, same group also demonstrated fabrication of single-component PMAA hydrogels derived through chemical crosslinking of hydrogen-bonded multilayers of PVPON and PMAA [70,71].

In another study, pH-stability of hydrogen-bonded films was improved by depositing hydrogen-bonded and electrostatically bound multilayer stacks in an alternating fashion at the surface. Different from the previously mentioned chemical crosslinking studies, this method does not require chemical crosslinking but tuned the critical dissolution pH of a heterogeneous system through the number of hydrogen-bonded stacks inserted within the electrostatically bound multilayers [72].

Another approach was reported by Quinn et al. The study was based on introducing multivalent ions (Ce^{4+} or Fe^{3+}) into multilayers at the post-assembly step. This method was limited only to hydrogen-bonded films containing free strong acid groups. Therefore, use of a copolyacid containing both strong and weak acid functional groups was required for film stability [73].

As it is discussed before in Section 1.2.1, pK_a of the polyacid is one of the most critical parameters affecting the critical dissolution pH of hydrogen-bonded multilayers. Erel and Sukhishvili demonstrated that pH-stability of hydrogen-bonded multilayers of neutral polymer/polyacid systems can be increased when a watersoluble polyphenol, Tannic Acid (TA), is used as an alternative to polycarboxylic acids. This enhancement in the pH-stability of hydrogen-bonded multilayers relies on the fact that TA has relatively higher pK_a (~ 8.5) than most of the polycarboxylic acids traditionally used in the fabrication of hydrogen-bonded multilayers [74]. Same researchers have also demonstrated that critical dissolution pH of hydrogen-bonded multilayers of polyacids with low acidity could be shifted to higher values when polyacids with low acidity and high acidity are assembled together resulting in hybrid multilayers [75]. Another study by Erel et al has shown that pH-stability of hydrogen-bonded multilayers of poly(2-isopropyl-2-oxazoline) (PIPOX) and TA could be enhanced by using PIPOX with amino end-groups as the hydrogen accepting polymer [91]. Electrostatic interactions between the ionized TA molecules and ammonium groups at the PIPOX-amino chain-ends increased the pH stability of the multilayer films and shifted the critical disintegration pH of the multilayers to slightly higher pH values. However, this method required an end-group modification of the neutral polymer.

1.3. Aim of the Thesis

In this thesis, improving pH-stability of neutral polymer/polycarboxylic acid hydrogen-bonded multilayers by using a polymerizable salt, zirconium oxychloride octahydrate (ZrOCl₂.8H₂O) was aimed. Poly(N-vinylcaprolactam) (PVCL), poly(Nisopropylacrylamide) (PNIPAM) and poly(ethylene oxide) (PEO) were used as hydrogen accepting polymers for film construction. To be used as hydrogen donor, coordination complexes of TA and ZrOCl₂.8H₂O (TA+Zr) were prepared. Hydrogenbonded multilayers were then constructed by layer-by-layer depositing (TA+Zr) complexes and hydrogen accepting polymers (PVCL, PNIPAM or PEO) at the surface at acidic pH. Multilayers containing (TA+Zr) showed significant improvement in pH-stability than the multilayers containing only TA. This improvement in pH-stability can be correlated with the high affinity of Zr^{4+} to phenolate anions which are formed with the ionization of TA with increasing pH. Another factor which might have affected the pH-stability of the multilayers was the strong association between the (TA+Zr) complexes as the acidity decreased. This might have also enhanced the association between the multilayers resulting in more stable films at basic conditions. Incorporation of (TA+Zr) complexes within the multilayers also allowed controlling the kinetics of pH-induced disintegration. Onset of disintegration could be delayed for ~ 10 hours. In addition, in contrast to multilayers of TA which eroded exponentially at neutral pH, (TA+Zr) containing multilayers disintegrated with a linear fashion in a longer period of time. These features of (TA+Zr) multilayers are specifically important for controlled drug delivery applications from surfaces.
CHAPTER 2

EXPERIMENTAL PART

2.1. Materials

Poly(ethylene oxide) (PEO; M_w200,000); branched poly(ethylenimine) (BPEI; M_w25,000); sodium hydroxide; dibasic sodium phosphate and hydrochloric acid were purchased from Sigma-Aldrich Chemical Co. Tannic acid (TA; M_w 1701.20); Zirconium oxychloride octahydrate (ZrOCl₂.8H₂O) and monobasic sodium phosphatewere purchased from Merck Chemicals. Poly(*N*-vinylcaprolactam) (PVCL; M_w1800) was purchased from Polymer Source Inc. Poly(*N*-isopropylacrylamide) (PNIPAM; M_n7100) was provided by Dr. Helmut Schlaad's Research Laboratory (Max Planck Institute of Colloids and Interfaces, Potsdam, Brandenburg, Germany). All chemicals were used as received. All solutions were prepared with deionized water (DI), which was purified with a Milli-Q system (Millipore).

Molecule	Structure	Details	Manufacturer
	$* \begin{pmatrix} H_2 \\ C \end{pmatrix} = \begin{pmatrix} H_2 \\ C \end{pmatrix} + *$	Poly	Sigma-Aldrich
PEO	\neg	(ethylene	Chemical Co.
		oxide)	
		M _w =200,000	
PVCL	$*-\underbrace{(-C^2-CH)^{*}}_{n}$	Poly(<i>N</i> -vinyl caprolactam) M _w 1800	Polymer Source Inc.
	H_2 H h_3	Poly	
PNIPAM	$-\sqrt{-\frac{1}{n}}$	(N-isopropyl	Donated by Dr.
	o	acrylamide)	Helmut Schlaad
		M _n 7100	
	йн СН		
	н₃с сн₃		
		Branched poly	Sigma-Aldrich
BPEI	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	(ethylenimine)	Chemical Co.
		M _w =25,000	

 Table 2.1 Chemical structures of polymers.

2.2. Preparation and characterization of (TA+Zr) complexes

Aqueous solution of TA with a concentration of 2 mg/mL at pH 2 was prepared. It was then added dropwise into aqueous solution of 2 mg/mL ZrOCl₂.8H₂O under vigorous stirring. Mixing volume ratio was 1:0.65(ZrOCl₂.8H₂O:TA). This mixing composition corresponded to ~ 8:1 mol ratio of ZrOCl₂.8H₂O:TA and ~ 1:3 mol ratio of Zr⁴⁺:OH groups of TA. Note that TA has 25 hydroxyl groups per molecule. pH was readjusted to 2 because of the slight decrease in the pH after mixing TA and ZrOCl₂.8H₂O.

2.3. Deposition of Multilayers

Multilayer films were assembled on silicon wafers. Silicon wafers were cut into 1x1 cm² pieces and then they were treated with concentrated sulfuric acid for 1 hour and 25 minutes to remove organic impurities from the surface. After that they were rinsed first with tap water and then DI water. Then, wafers were immersed into 0.25 M NaOH solution for 10 minutes. After this treatment, wafers were rinsed again with tap water and DI water, respectively. Wafers were blown dried with flow of nitrogen.

PVCL, PNIPAM, PEO, TA and ZrOCl₂.8H₂O were dissolved in DI water with pH 2. Concentration of neutral polymers was 0.5 mg/mL. Concentrations of TA and ZrOCl₂.8H₂O solutions were 2 mg/mL and (TA+Zr) complexes were prepared as described in Section 2.2. Neutral polymer/(TA+Zr) multilayers were fabricated at pH 2 by immersing the silicon wafers alternately into neutral polymer and (TA+Zr) solutions for 15 minutes. There were 2 intermediate rinsing steps between each layer deposition. For neutral polymer/TA films, concentration of neutral polymers and TA were 0.5 mg/mL and 0.78 mg/mL, respectively. Only for

PNIPAM/TA films, precursor layers of BPEI and TA were deposited at pH 7.5 and pH 5.5, respectively. Concentrations of precursor polymers (BPEI and TA) were 0.5

mg/mL. pH-stability of the films was followed by monitoring the change in film thickness after the multilayers were exposed to 0.01 M phosphate buffer solutions with increasing pH. Waiting period in buffer solution was for 30 minutes at every pH.



Scheme 2.1 Schematic representation of deposition of multilayers

2.4 Apparatus and Measurement

UV/Vis spectroscopy: 100Bio-Cary Varian UV-Visible Spectrophotometer was used to follow the association of TA with ZrOCl₂.8H₂O in aqueous solution.Concentration of both TA and ZrOCl₂.8H₂O was 0.01 mg/mL. Experiments were carried out in 3.0 mL quartz cuvettes.

Dynamic light scattering (DLS): Number average hydrodynamic sizes of ZrOCl₂.8H₂O solution and (TA+Zr) complexes were measured via dynamic light scattering technique using a Zetasizer Nano-ZS (Malvern Instruments Ltd.). Number average hydrodynamic sizes were obtained by cumulative analysis of autocorrelation data.

Ellipsometry: A Spectroscopic Ellipsometer of Optosense, USA (OPT-S6000) was used to follow the film growth and pH-stability of the multilayers. The reported values in this study were the average of the measurements taken at least from four different locations on a wafer.

Atomic force microscopy (AFM): The changes in morphology of the multilayers were followed using AFM. AFM imaging of the multilayers was performed using Nanomagnetics Instruments, Ambient AFM in dynamic mode.

CHAPTER 3

RESULTS AND DISCUSSION

3.1 Aqueous Solution Properties of ZrOCl₂.8H₂O

Zr is a transition element. It has 4 valence electrons and its electronic configuration is $5s^24d^2$. Zirconium has an oxidation number of 4+ in its compounds. It can take a maximum coordination number of 8. In ZrOCl₂.8H₂O, zirconium ion is connected to 4 OH and 4 H₂O groups [83]. The chemical structure of ZrOCl₂.8H₂O was demonstrated by Clearfield and Vaughan [87]. They showed that four Zr⁴⁺ions were connected to each other through 2 OH groups locate at the corners of a square and each Zr⁴⁺ formed coordinate bonds with 4 aqua ligands forming a cyclic tetrameric structure [83,84].The composition of the tetrameric structures in the unit cell was found as [Zr₄(OH)₈(H₂O)₁₆]⁸⁺. Subsequently, Muha and Vaughan showed that same cyclic tetrameric species as described by the formula [Zr₄(OH)₈(H₂O)₁₆]⁸⁺ formed when zirconium oxychloride was dissolved in water [85]. Scheme 3.1 shows chemical structure of ZrOCl₂.8H₂O.

To investigate the aqueous solution behavior of $ZrOCl_2.8H_2O$, hydrodynamic size measurements of $ZrOCl_2.8H_2O$ with increasing pH values were performed via dynamic light scattering technique. It has been seen that, while the pH value was increasing, there was an obvious increase in the turbidity of the solution. Also, as it is seen in Figure 3.1, hydrodynamic size of $[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ increased gradually with increasing pH values.



Scheme 3.1 Chemical structure of tetrameric $[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ units.

Particle size measurements of $[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ tetrameric units as a function of pH were monitored to understand the pH-dependent aqueous solution behavior of ZrOCl₂.8H₂O. 3.1 Figure shows the change in particle size of $[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ with increasing pH. It has been seen that the hydrodynamic sizes of tetrameric units increased gradually while the acidity of the solution was decreased. There occurred a turbidity and precipitation in the solution with increasing pH. After pH 6, a sharp increase in the hydrodynamic size was recorded. Above pH 9, a gelatinous precipitate on the wall of the vial was observed.



Figure 3.1 Hydrodynamic size of $[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ as a function of pH.

The increase in the hydrodynamic size of the complexes with increasing pH could be the consequence of the association of tetrameric $[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ units. Muha and Vaughan also reported on formation of larger species and found that the molecular weight of these larger species increased with rising pH due to enhanced association among $[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ units, so called "polymerization reaction" ongoing in ZrOCl₂.8H₂O solution [84,85].

The polymerization mechanism of $\text{ZrOCl}_2.8\text{H}_2\text{O}$ in aqueous solution was suggested by Rijnten et al. They reported that the aqueous solution of $\text{ZrOCl}_2.8\text{H}_2\text{O}$ was acidic because of hydrolysis of the tetrameric $[\text{Zr}_4(\text{OH})_8(\text{H}_2\text{O})_{16}]^{8+}$ units. As a result of the hydrolysis reaction, overall charge of the tetrameric unit was reduced to 4+.(Scheme 3.2A). This corresponded to +1 charge on each zirconium site. There are four zirconium ions in every tetrameric unit which can hydrolyze independently. If one of the zirconium ions could further hydrolyze, one of the zirconium sites could become electrically neutral and the rest 3 zirconium sites could carry an overall charge of 3+ for the complex (Scheme 3.2B). It was claimed by Rijnten et al. that the neutral site could be the starting point for the polymerization of $[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ in the solution. It could react with a 1+ charged site of another tetrameric unit resulting in a connection of two tetrameric units by 2 OH groups as bridging ligands (Scheme 2B). This was how tetrameric units were connected to each other and, polymerization reaction of ZrOCl₂.8H₂O proceeded in the solution.



Scheme 3.2 Schematic representation of hydrolysis (Panel A) and polymerization $of[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ in aqueous solution (Panel B).

3.2. Zr(IV) complexes of TA in solution

TA is a molecule which has ability to make multiple hydrogen bonding through numerous terminal hydroxyl groups. Actually it is not a true acid because it does not have carboxyl groups which all organic acids have (–COOH). Instead of that, TA has phenolic hydroxyl groups, so it is indeed a polyphenol.

As it is described in Section 3.1, each Zr^{4+} ion formed coordinate bondingwith H₂O molecules in the tetrameric, $[Zr_4(OH)_8(H_2O)_{16}]^{8+}$. These aqua ligands can be replaced by other ligands such as OH⁻, F⁻, PO₄³⁻, C₂O₄²⁻, SO₄²⁻, NO₃⁻, Cl⁻[86,87]. Since TA has 25 hydroxyl groups per molecule (Scheme 3.3), it is possible that phenolic hydroxyl groups of TA could replace some of the aqua ligands of $[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ and form coordinate bonding to Zr^{4+} ions with the lone pairs on oxygen atom.



Scheme 3.3 Chemical Structure of Tannic Acid.

(TA+Zr) complexes were prepared by drop wise addition of TA into ZrOCl₂.8H₂O solution with 1:3 mol ratio of Zr⁴⁺:OH groups of TA under vigorous stirring at pH 2 (Section 2.2). After mixing of TA and ZrOCl₂.8H₂O solutions, a 0.2 pH unit decrease in the solution was recorded. That is probably because of the hydrolysis reactions of the tetrameric $[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ units (discussed in Section 3.1). When ZrOCl₂.8H₂O is dissolved in water, at least one mole of HCl comes out per mole of salt resulting in a slight decrease in the pH of the (TA+Zr) solution. For that reason, pH of the complexes was readjusted to 2 prior to using. Also, different compositions of (TA+Zr) complexes were tested (Figure 3.4). The best solution stability was obtained when complexes were prepared at 1:3 mol ratio of Zr⁴⁺: OH groups of TA. Therefore, the mol ratio of Zr⁴⁺to OH groups of TA was optimized as 1:3. Similar to solution stability, the highest pH-stability of multilayers was obtained when multilayers were prepared using complexes which were also prepared at 1:3 mol ratio of Zr⁴⁺: OH groups of TA. These findings will be discussed in Section 3.4 (Figure 3.6).

To understand the interaction among TA and $[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ units, UV-Visible spectra of TA and (TA+Zr) complexes were recorded at pH 2(Figure 3.2). Pure TA solution exhibits 2 peaks at 214 nm and 276 nm. These 2 peaksare correlated with the protonated form of TA [74,88]. It has been found that the intensities of these two peaks decreased in the spectrum of (TA+Zr) complexes which was recorded at the same pH. The decrease in the intensity of the two peaks at 214 nm and 276 nm in the spectrum of (TA+Zr) complexes can be correlated with the decrease in the number of free protonated phenolic hydroxyl groups upon complexation. Note that, $[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ has no absorption bands between 200 and 600 nm. Also, peaks which are correlated with the ionized form of TA have not been recorded. It was reported that the ionized form of TA exhibited two additional peaks at higher wavelengths and a decrease in the intensity of the first two peaks were seen (See inset of Figure 3.2 obtained from ref [74]) [74,88]. Therefore, absence of additional peaks in the spectrum of (TA+Zr) complexes showed that TA was mostly in the non-ionized form and the coordinate bonding occurred between phenolic hydroxyl groups of TA and Zr^{4+} . Scheme 4 shows the association between $[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ and TA molecules. Schematic is drawn based on the approximate mol ratio of Zr^{4+} cations to hydroxyl groups of TA in the mixture.



Figure 3.2 UV-Vis absorption spectrum of TA and (TA+Zr) complexes at pH 2. Inset is obtained from reference [74] and shows UV-Vis spectrum of TA at acidic and basic pH values.



(TA+Zr) complexes

Scheme 3.4 Schematic representation of association between tetrameric $[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ units and TA molecules at pH 2. Drawing is based on the mol ratio of Zr^{4+} cations to hydroxyl groups of TA in the coordination complex.

pH-dependent hydrodynamic size measurements of (TA+Zr) complexes were also measured to understand the aqueous solution behavior of (TA+Zr) complexes with changing pH. We found a sharp increase in hydrodynamic size of (TA+Zr)complexes at a lower pH when compared to the pH at which a sharp increase in hydrodynamic size was observed for $[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ units. This difference in the aqueous solution behavior of (TA+Zr) and $[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ units was attributed to higher tendency of (TA+Zr) complexes for polymerization. This is probably due to hydrophobic and π - π stacking interactions induced by TA molecules which enhanced the association among (TA+Zr) complexes. These results limited the film preparation pH to strongly acidic conditions. To avoid the polymerization of (TA+Zr)complexes, pH 2 was selected as the film deposition pH. Another reason to prepare multilayers at strongly acidic conditions was to ensure sufficient number of protonated phenolic hydroxyl groups of TA. Phenolic hydroxyl groups which did not participate in the complexation process could further be used as hydrogen donors for multilayer assembly.



Figure 3.3 Hydrodynamic size of (TA+Zr) complexes as a function of pH.

3.3. Preparation of Multilayers Containing (TA+Zr) complexes

(TA+Zr) complexes were layer-by-layer deposited with neutral polymers, poly(N-vinylcaprolactam) (PVCL), poly(N-isopropylacrylamide) (PNIPAM) or poly(ethylene oxide) (PEO) through hydrogen bonding interactions at pH 2. Hydrogen bonding interactions take place between the hydrogen-accepting groups of the neutral polymers, which are carbonyl groups of PVCL and PNIPAM and ether oxygens of PEO, and protonated phenolic hydroxyl groups of TA. As it was mentioned at Section 3.2, (TA+Zr) complexes were prepared with a 1:3 mol ratio of Zr^{+4} : OH groups of TA during the film deposition since higher solution stability and pH-stability of the multilayers were observed at this composition.

Figure 3.4 shows multilayer growth of PVCL/(TA+Zr) and PVCL/TA (Panel A); PNIPAM/(TA+Zr) and PNIPAM/TA (Panel B), PEO/(TA+Zr) and PEO/TA (Panel C) films at pH 2. Note that LbL deposition of TA with PVCL, PNIPAM or PEO and pH-induced disintegration of the films have earlier been reported by Erel and Sukhishvili [74]. Films that contain (TA+Zr) complexes are thinner than multilayers of TA and the corresponding neutral polymer. Also, (TA+Zr) containing films were smoother with lower rms (root mean square) roughness values. Figure 3.5A, 3.5B and 3.5C show AFM height images of PVCL/(TA+Zr) and PVCL/TA, PNIPAM/(TA+Zr)and PNIPAM/TA, PEO/(TA+Zr) and PEO/TA respectively. Figure 3.5D contrasts the surface roughness values of multilayers of neutral polymer/(TA+Zr) complexes and multilayers of neutral polymer/TA.



Figure 3.4 Film thickness of PVCL/(TA+Zr) complexes (Panel A); PNIPAM/(TA+Zr) complexes (Panel B) and PEO/(TA+Zr) complexes (Panel C) as a function of bilayer number. Thickness values of PVCL/TA (Panel A); PNIPAM/TA (Panel B); PEO/TA (Panel C) are plotted for comparison.



Figure 3.5 AFM topography images (2x2 μm) of silicon wafers coated with 12-bilayers of PVCL/(TA+Zr) complexes and PVCL/TA (Panel A); 12-bilayers of PNIPAM/(TA+Zr) complexes and PNIPAM/TA (Panel B) and 5-bilayers of PEO/(TA+Zr) complexes and PEO/TA (Panel C). Panel D contrasts rms roughness values of the films.



Figure 3.5 (continued)AFM topography images (2x2 μm) of silicon wafers coated with 12bilayers of PVCL/(TA+Zr) complexes and PVCL/TA (Panel A); 12-bilayers of PNIPAM/(TA+Zr) complexes and PNIPAM/TA (Panel B) and 5-bilayers of PEO/(TA+Zr) complexes and PEO/TA (Panel C). Panel D contrasts rms roughness values of the films.

There could be several reasons of the differences in film thicknesses between the neutral polymer/(TA+Zr) and neutral polymer/TA films. Firstly, it can be correlated by a decrease in the number of free hydroxyl groups of TA after complexation. Since the complexation occurred between the $[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ ions and the hydroxyl groups of TA, the number of free hydroxyl groups on TA molecules decreased. This decrease in the number of free hydroxyl groups resulted in lower extent of association between the neutral polymer and TA molecules. This is also supported by the thickness values of the films which were prepared using different mol ratios of Zr⁴⁺ and OH groups of TA. As it is shown in Fig. 3.6, thicker filmswere obtained when the amount of TA in (TA+Zr) complexes is increased. These results are in good agreement withthe findings obtained from UV-Vis spectra of (TA+Zr) complexes. As shown in Fig. 3.2.the intensity of the peaks of TA decreased when TA was complexed with $[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ units due to coordinate bonding of TA molecules to Zr⁴⁺ through hydroxyl groups and a decrease in the number of free phenolic hydroxyl groups.



Figure 3.6 Thickness of PVCL/(TA+Zr)films as a function of number of bilayers which were prepared using (TA+Zr) complexes with different compositions.

There might be other factors leading to formation of thinner films when (TA+Zr) complexes were incorporated within the multilayers rather than TA alone. For example, all the hydrogen accepting neutral polymers have lone electron pairs on their oxygen atoms (carbonyl oxygen of PVCL and PNIPAM and ether oxygen of PEO). Therefore, it could be possible that there was an association between the Zr^{4+} cations and neutral polymers which contributed to the binding strength between the layers. Stronger binding between the layers resulted in thinner and denser film. To further understand this phenomenon, PVCL and $[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ films were deposited at the surface. As layer-by-layer shown in 3.9. Fig. $PVCL/[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ films could be grown up with ~0.5 nm/bilayer thickness. This clearly shows the association between PVCL and Zr⁴⁺cations. When layer-bylayer deposition of $[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ was tried with PNIPAM and PEO instead of PVCL, the films could not be constructed. It can be correlated with lower extent of association between Zr⁴⁺cations and PNIPAM or PEO. Also, similar to the association between Zr^{4+} cations and the neutral polymers, association of Zr^{4+} with neighboring TA layers might be possible and might have contributed to the binding strength between the layers.

3.4. pH-Triggered Dissolution of Multilayers Containing (TA+Zr) complexes

pH stability of the multilayers was determined by exposing the multilayers to buffer solutions of increasing pH values for 30 minutes followed by measurement of the dry film thicknesses. As it is mentioned before in Section 3.2, the most stable films against pH were obtained when the composition of the complex was 1:3 mol ratio of Zr⁴⁺:OH groups of TA (Figure 3.7). When the amount of TA was increased in the complex, it did not result infurther enhancement in the stability of the films. Thus, all of the multilayer films were prepared with a 1:3 mol ratio of Zr⁴⁺:OH groups of TA. pH-induced dissolution of PVCL/(TA+Zr)(Panel A); PNIPAM/(TA+Zr)(Panel B); PEO/(TA+Zr)(Panel C) films were shown in Figure 3.8. Neutral polymer/TA films were plotted for comparison. All of the dissolution experiments were done under the same conditions.



Figure 3.7 pH-induced disintegration of PVCL/(TA+Zr) films. Films were prepared at pH 2 using (TA+Zr) complexes with different compositions.



Figure 3.8 pH-triggered dissolution of 12-bilayer PVCL/(TA+Zr) and PVCL/TA (Panel A); 12-bilayer PNIPAM/(TA+Zr) and PNIPAM/TA (Panel B) and 5-bilayer PEO/(TA+Zr) and PEO/TA (Panel C).

It could be seen clearly in Figure 3.8 that when (TA+Zr) was used as a film component instead of only TA, pH-stability of the film increased dramatically. In contrast to PVCL/TA films which dissolved completely at pH 10, only ~ 9 % of PVCL/(TA+Zr) released from the surface at the same conditions. Further increasing pH to 11 resulted in removal of only ~ 20 % of the film. Note that, slight swelling of the multilayers between pH 2.5 and 7 could be correlated with the ionization of TA resulting in an increase in the hydrophilicity of the matrix and entrapment of water molecules within the multilayers.

PNIPAM/(TA+Zr)films showed a similar trend. When PNIPAM/TA films were exposed to pH 10, significant amount (~80%) of the film was removed from the surface. However, only 5% of the film was lost when PNIPAM/(TA+Zr) films were exposed to pH 10. After exposing of PNIPAM/TA+Zr films to the pH 11, ~40% of the material was lost from the surface.

The most significant difference was observed in PEO systems. No erosion was seen for PEO/(TA+Zr) multilayers between pH 2 to 7, while ~30% of PEO/TA film dissolved within the same pH range. Furthermore, when the films were exposed to pH 10, there were no loss in the PEO/(TA+Zr) film, while almost all of PEO/TA film released from the surface at the same conditions. Even after exposure to pH 11, only 5% of PEO/(TA+Zr) film dissolved. It should also be mentioned that both PEO/TA and PEO/(TA+Zr) films were 5 bilayers. Because thickness of films with higher number of layers could not be measured using ellipsometry due to very high thickness of PEO/TA films which do not allow reliable thickness measurements. It was also found that the loss was greater when 12-bilayers of PEO/(TA+Zr) film was exposed to increasing pH conditions. This was probably due to mechanical destruction of the films after drying steps. Such a behavior was not observed for PVCL/(TA+Zr) and PNIPAM/(TA+Zr) films. Additionally, rms roughness values of 12-bilayer (TA+Zr) containing films after construction at pH 2 and exposure to pH 12 were contrasted. In contrast to relatively small amounts of loss of PVCL/(TA+Zr) and PNIPAM/(TA+Zr) films after exposure to basic conditions, significant change in rms roughness values was recorded for PVCL/(TA+Zr) and PNIPAM/(TA+Zr) films (Table 3.1). This was probably an indication of a restructuring within the multilayers which resultedin smoother films at basic conditions. That experiment could not be performed for PEO/(TA+Zr) system because 12-bilayer PEO/(TA+Zr) film had highly rough surface so, it did not give any reliable measurements of surface roughness.

Table 3.1 rms roughness values and fraction retained at the surface of 12-bilayerPVCL/(TA+Zr) and 12-bilayer PNIPAM/(TA+Zr) films after exposure to pH 12 buffersolutions.

	PVCL/(TA+Zr)	PNIPAM/(TA+Zr)
Rms roughness at pH 2	6.30 ± 1.20	8.21 ± 3.75
Rms roughness at pH 12	1.60 ± 0.18	2.81 ±1.271
Fraction retained at pH 12	0.73 ± 0.04	0.63 ± 0.08

The mechanism for pH-induced disintegration of hydrogen-bonded multilayers can be explained as follows: increased ionization of polyacid within the film results in an increase in the amount of negative charges within the film matrix and electrostatic repulsion between the layers. During this phenomenon, salt cations also penetrate into the film to compensate the negative charges. Penetrations of the salt ions into the multilayer matrix increase the osmotic pressure and leads penetration of also water molecules into the multilayers. Finally, multilayers swell and completely disintegrate [75,89,90]. However, different phenomenon should have taken place in (TA+Zr) containing multilayers so that multilayers were quite stable at basic conditions.

To understand the pH stability of multilayers in detail, multilayers of $[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ and TA (Figure 3.8) and PVCL and $[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ (Figure 3.9) were prepared at pH 2.



Figure 3.9 Thickness of $[Zr_4(OH)_8(H_2O)_{16}]^{8+}/TA$ film as a function of number of bilayers at pH 2.



Figure 3.10 Thickness of $PVCL/[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ film as a function of number of bilayers at pH 2.

When $[Zr_4(OH)_8(H_2O)_{16}]^{8+}/TA$ film was exposed to increasing pH values, only ~5% loss of film was recorded (Figure 3.11). This result could be explained by; i) compensation of the excess negative charge arising from ionization of TA by Zr^{4+} cations, preventing the disintegration of multilayers; ii) polymerization of $[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ within the multilayers. As it was mentioned in Section 3.1, tetrameric $[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ units associate in aqueous solution with increasing pH. Similar phenomenon could have been occurred within the multilayers, resulting in enhanced association between the layers and more stable films against pH.



Figure 3.11 Fraction retained at the surface of $[Zr_4(OH)_8(H_2O)_{16}]^{8+}/TA$ film as the acidity decreased.

As another control experiment, 12-bilayer $PVCL/[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ film was exposed to increasing pH values (Figure 3.12). After exposure of the film to pH 11, 75 % of the film was still on the surface. The 25 % loss could be correlated with the increase in the OH⁻ concentration which disrupted the interaction between Zr^{4+} cations and PVCL.



Figure 3.12 Fraction retained at the surface of $PVCL/[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ film as the acidity decreased.

These results showed that: i) coordinate bonding between Zr^{4+} cations and phenolate anions of TA and ii) the tendency of (TA+Zr) complexes towards polymerization were the major reasons of the improved pH-stability of (TA+Zr) containing multilayers. Note that it was also found that (TA+Zr) complexes have more tendency toward polymerization than $[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ units alone (Section 3.2). Considering the fact that hydrogen-bonded films are interpenetrated rather than stratified, the interaction among the alternating layers could be possible and (TA+Zr) complexes which were at close proximity could have associated bringing an additional stability to the multilayers.

One more deduction could be ade from the pH-induced disintegration data of $[Zr_4(OH)_8(H_2O)_{16}]^{8+}/TA$ and $PVCL/[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ films. When films were exposed to pH 11, the loss of $PVCL/[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ film was greater than that of $[Zr_4(OH)_8(H_2O)_{16}]^{8+}/TA$ film. It indicated that most of the material released from neutral polymer/(TA+Zr) multilayers at basic conditions was the hydrogen accepting neutral component. The reasons of that can be listed as; i) decrease in the extent of association between the neutral polymer and TA layers due to ionization of TA and loss in hydrogen bonding interactions; ii) loss of interaction between neutral polymers and $[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ with increasing pH. The fraction retained at the surface of neutral polymer/(TA+Zr) films at basic conditions supported this assumption. For example, ~ 47 % of PNIPAM/(TA+Zr) film was consisted of PNIPAM and the amount released was ~ 41 % of the total film. Also, 15 % of a 5bilayer PEO/(TA+Zr) film was PEO and the ~5 % of the total film was released. The difference can be correlated with PEO and PNIPAM chains which associated with Zr⁴⁺ and retained within the film.

The highest amount of neutral polymer retained within PVCL/(TA+Zr) films. PVCL composed ~44% of PVCL/(TA+Zr) film. The material released from the multilayers was ~ 20 %. This can be explained by greater association between Zr^{4+} cations and PVCL than that between Zr^{4+} cations and PNIPAM or PEO chains as already discussed in Section 3.3. Note that the changes in surface roughness values of the films after exposure to basic pH (Table 3.1) also indicated a restructuring within the multilayers and supported release of the neutral component.

Quinn and Caruso were also able to improve the stability of hydrogen-bonded multilayersthrough loading a multivalent salt (Ce^{4+})into the multilayers at the post-assembly step. However, such films were stable only up to pH 7.1 and required use of a copolyacid, poly[(styrene sulfonic acid)-*co*-(maleic acid)] (PSSMA).Different from the film systems reported in this study, those films were not neutral and contained free styrene sulfonate groups. In addition, a post-assembly treatment (loading of Ce^{4+} cations into multilayers) was necessary to provide the film stability after disruption of hydrogen-bonding interactions at increasing pH[73].

Lastly, neutral polymer/TA multilayers were prepared at acidic conditions and Zr^{4+} cations were loaded at the post-assembly step rather than film preparation step. Then, pH-stability of the films was examined by exposing the films to increasing pH

values. However, no improvement in pH-stability was recorded, probably due to lower number of free hydroxyl groups within the multilayers available for association with Zr^{4+} cations at the post-assembly step.

3.5. Kinetics of Dissolution

Controlling the dissolution of hydrogen-bonded multilayers above the critical disintegration pH is a hard process because disintegration of the layers happens swiftly [74]. This property makes hydrogen-bonded multilayers improper for applications which require long-term release of film components and/or functional molecules. In addition to improving pH-stability of hydrogen-bonded films, incorporating (TA+Zr) complexes into hydrogen-bonded multilayers had pronounced effect on controlling the kinetics of pH-triggered disintegration of the films.

pH 7.5 was chosen to study the kinetics of pH-triggered dissolution. Note that PNIPAM/TA films have a critical disintegration pH of ~ 8 the pH at which ~10% of the material is lost from the surface. By choosing a slightly lower pH value to study the kinetics of dissolution, fast disintegration of the layers was prevented. Therefore, there was enough time to examine the difference in the kinetics of dissolution between PNIPAM/TA and PNIPAM/(TA+Zr) multilayers.

It has been reported that hydrogen-bonded multilayers showed faster equilibration time with increasing pH [74].Figure 3.13 shows pH-triggered disintegration of 12-bilayer PNIPAM/TA and PNIPAM/(TA+Zr) films. Films were assembled at pH 2 and exposed to pH 7.5. As it is seen from the graph, there was an exponential decrease in film thickness for PNIPAM/TA film. ~ 75% of the film released from the surface in 50 hours. Even if the film was exposed for an additional ~ 45 hours at the same pH value, the rest of it could not be desorbed. Strong association of the remaining layers with the substrate may be the reason of it. On the other side, PNIPAM/(TA+Zr) film exhibited a linear erosion profile. Only ~ 30 % of PNIPAM/(TA+Zr) film was desorbed from the surface within 50 hours. Between 50

and 70 hours, an additional ~ 15 % dissolved. After the process was continued for additional 20 hours, no further dissolution was recorded. Moreover, delaying the onset of PNIPAM/(TA+Zr) film disintegration for ~ 10 hours was achieved. Also (TA+Zr) containing films followed a decelerated dissolution with smaller extent of desorption within the same time period when compared to PNIPAM/TA films. For example, while 50% of PNIPAM/TA film eroded within 24 hours, just 15% of PNIPAM/(TA+Zr) dissolved within the same time period at the same conditions.

The result of this experiment indicated that disintegration period of hydrogen-bonded multilayers was lengthened with incorporation of (TA+Zr) complexes within the multilayers. With the increased pH value, hydroxyl groups of TA ionized and they generated stronger coordination complexes with Zr^{4+} cations. Also, the enhanced association between (TA+Zr) complexes within the multilayers could be another reason of slowed release of macromolecules from the surface. As it was described in Section 3.4, loading Zr^{4+} cations into multilayers after multilayer deposition step did not provide any improvement in the pH-stability of the films. Zr^{4+} loaded multilayers disintegrated in the same manner as PNIPAM/TA films. The reason of it was probably the insufficient amount of Zr^{4+} that could be incorporated within the film structure.



Figure 3.13 Fraction retained at the surface of 12-bilayer PNIPAM/TA and PNIPAM/(TA+Zr) films as a function of time at pH 7.5. Multilayers were constructed at pH 2 and then exposed to pH 7.5 buffer solutions.

Erel and Sukhishvili reported on decelerating the kinetics of disintegration of hydrogen-bonded multilayers through constructing hybrid multilayer systems. They prepared films composed of a neutral polymer (PVCL), a polyacid with low acidity (poly-L-aspartic acid; PLAA) and another polyacid with high acidity (TA). It was demonstrated that film architecture was primarily critical on the kinetics of dissolution and release of the polyacid with low acidity can be slowed down by the presence of the polyacid with higher acidity in the same multilayer system [75]. Also, Cho and Caruso exhibited a similar approach. The kinetics of dissolution of hydrogen-bonded multilayer films was slowed down by constructing hydrogen-bonded multilayer films was slowed down by constructing hydrogen-bonded multilayers between electrostatically bound multilayers [72].

CHAPTER 4

CONCLUSION

Coordination complexes of a natural polyphenol, TA and a polymerizable salt, ZrOCl₂.8H₂O were prepared which were then used as building blocks in the preparation of hydrogen-bonded multilayers. Different from traditional hydrogenbonded multilayers of neutral polymers and polyacids, such multilayers showed improved pH-stability as well as controllable pH-induced disintegration kinetics. Improved pH-stability of the films can be explained by: i) compensation of the excess negative charge arising from ionization of TA with increasing pH by Zr⁴⁺cations and ii) enhanced association of (TA+Zr) complexes with increasing pH. It was shown for the first time that onset of disintegration of hydrogen-bonded multilayers could be retarded for approximately 10 hours at neutral pH. Moreover, in the presence of Zr⁴⁺cations, disintegration kinetics could be slowed down. For example, in contrast to PNIPAM/TA multilayers, which showed exponential erosion at pH 7.5, PNIPAM/(TA+Zr) multilayers dissolved linearly. This study presents a simple approach to improve pH-stability and control disintegration kinetics of hydrogen-bonded multilayers. These films can be promising for controlled release applications from surfaces.
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