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An Optical Sensor Based on a Photonic Polymer Film to Detect Calcium in Serum

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An optical calcium sensor is fabricated based on a cholesteric liquid crystalline (CLC) polymer containing benzoic acid metal binding sites. A chiral imprinted CLC polymer is made which is subsequently treated with KOH to yield a responsive green reflecting film. On investigation of various metal ions, the polymer film shows a high optical response, and selectivity for calcium ions, which is related to the preorganized binding sites in the ordered liquid crystalline phase, leading to a blue reflecting film. The photonic polymer film is sensitive to Ca^{2+} within the physiologically relevant concentration range of 10^{-4} to 10^{-2} M. Measurement of total calcium concentration in serum is also investigated using the film. The optical responses of normal serum and samples mimicking hypocalcemia and hypercalcemia can be clearly distinguished, providing a cheap, battery-free, and easy-to-use alternative for calcium determination in clinical diagnostics.

sensors. Such sensors do not require batteries, are not prone to photobleaching, and the optical readout is discernable by the naked eye. Hydrogel-based photonic crystals have been used to design various metal sensors,^[6–8] whereby selectivity was introduced by incorporating different molecular recognition groups such as crown ether^[9–12] and 8-hydroxyquinoline.^[13] Due to their 1D photonic structure and ease of fabrication, cholesteric liquid crystals^[14–17] have also attracted much attention as optical sensors.^[18–21] To date, a few metal sensors from cholesteric liquid crystalline (CLC) materials have been reported by incorporating crown ether moieties for the detection of metal cations in aqueous solutions.^[22,23] The fabrication

1. Introduction

Detection and quantification of metal ions is important in many fields including medical diagnosis, clinical toxicology, environmental monitoring, and waste water management.^[1] Several techniques, such as atomic absorption spectroscopy, inductively coupled plasma mass spectroscopy, and inductively coupled plasma optical emission spectroscopy are employed for determination of the amount of metal ions with great precision. Besides requiring specialized equipment, these techniques require complex sample preparation and are typically expensive. Therefore, development of an affordable, quick, and easy-to-use technology that enables detection of metal ions even in areas where access to laboratory facilities is limited remains of continued interest. In this respect, a test strip with an optical readout discernable by the naked eye is appealing.

Photonic crystals^[2–5] that are able to reflect light have emerged as an attractive material for the development of optical

of an optical metal sensor that shows a high selectivity and sensitivity remains a challenge, however.

We now report on a metal sensor based on CLC polymer film that demonstrates a remarkable selectivity and optical response toward calcium, which is related to the preorganized binding sites in the liquid crystalline photonic film. Varying the Ca^{2+} concentration between 10^{-4} and 10^{-2} M induced a robust optical response that was clearly visible to the naked eye. The sensor could also be used as a test strip for detection of calcium in human serum.

2. Results and Discussion

2.1. Preparation of the Polymer Optical Sensor

The cholesteric liquid crystal mixture (**Scheme 1**) used in this study is based on the mixture reported by Shibaev et al.^[24] It consists of a monoacrylate (RM 105, 27.7 wt%) mesogen and a diacrylate (RM 257, 22.5 wt%) mesogen. Benzoic acid group functionalized polymerizable molecules viz. 6OBA (16.4 wt%) and 6OBAM (16.4 wt%) were incorporated to bind metal ions. Two different benzoic acids were used to prevent crystallization of the CLC mixture at room temperature. Nonpolymerizable dicarboxylic acid, R-(+)-3-methyladipic acid (MAA, 16.4 wt%) acts as the chiral dopant to induce formation of chiral nematic liquid crystalline phase. Irgacure 369 (0.6 wt%) acts as the initiator for photopolymerization. The planar alignment of the CLC mixture was achieved by shearing between a methacrylate functionalized glass substrate (lower) and a fluorinated alkylsilane functionalized glass slide (upper). The CLC mixture was

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Scheme 1. CLC mixture used for the fabrication of photonic polymer films.

then photopolymerized at room temperature during which the polymer film becomes covalently bonded to the methacrylate functionalized glass substrate as well. The upper glass slide was then removed to obtain a circular CLC polymer film with a diameter ≈ 2 cm and a thickness of ≈ 10 μm and the green selective reflection band (SRB) was centered around $\lambda = 512$ nm (Figure 1). The FT-IR (Fourier Transform Infrared) spectrum of the polymer film (see Figure S1, Supporting Information) showed the absence of C=C double bond of the acrylate as no peaks are present at 809 or 985 cm^{-1} .^[25] A highly intense peak centered at 1696 cm^{-1} was observed due to the stretching vibration of hydrogen bonded C=O. The broad nature of this peak suggests the presence of more than one type of H-bonded carboxylic acids,^[26] i.e., H-bonded MAAs, H-bonded benzoic acids, and mixed MAA-benzoic acid complexes. It should be noted that since the molar concentration of MAA with respect to each benzoic acid is double, not all the carboxylic acid moieties of the MAA molecules are bound to the polymer network. Thermogravimetric analysis (TGA) showed a weight loss of 16.5% in the temperature range of 120–200 $^{\circ}\text{C}$ (Figure S2, Supporting Information), which can be attributed to evaporation of MAA.

In order to enhance the optical response of the polymer film, the chiral molecule MAA was removed by extracting using an organic solvent (tetrahydrofuran).^[27] The TGA profile (Figure S2, Supporting Information) of this more flexible

polymer film did not show any loss in weight below 300 $^{\circ}\text{C}$, which is consistent with complete removal of MAA. The FT-IR spectrum showed a sharp vibration peak at 1680 cm^{-1} indicating the presence of H-bonded dimer of 6OBA and 6OBAM (Figure S1, Supporting Information).^[25] Upon removal of the chiral dopant, the reflection band shifted to $\lambda \approx 380$ nm indicating that the helical structure is still present and that a chiral-imprinted polymer network has been formed (Figure 1a,b). The blue shift of ≈ 130 nm of the SRB suggests a collapse of the polymer coating which resulted in a decrease in pitch length as the number of pitches is invariant after polymerization.^[28] The remarkable wavelength shift of 25% is higher than the weight fraction of the chiral dopant (16.4 wt%), suggesting that the shrinkage in the polymer film, having covalently linked to the glass substrate, mainly takes place in the vertical direction.

In order to make the polymer film responsive to metal ions, the chiral imprinted film was treated with KOH to convert the benzoic acid units to potassium benzoate derivatives. FT-IR analysis of this KOH-treated film showed the disappearance of a stretching vibration peak due to H-bonded C=O at 1680 cm^{-1} (Figure S1, Supporting Information). The peak at 1728 cm^{-1} due to the carbonyl of ester groups remained identical implying that KOH treatment does not affect the alkyl ester moieties. Two new peaks appeared at 1543 and 1382 cm^{-1} , corresponding to the asymmetric and symmetric stretching of

Figure 1. a) Photographs and b) UV-vis transmission spectra of the CLC polymer film at the different preparation steps.

COO^- ,^[25] which is consistent with complete deprotonation of the benzoic acid groups to form a K^+ -carboxylate salt.^[24,25,29,30] This polymer potassium salt film swells by absorbing water from KOH solution leading to an increase in pitch and thus a change in color with the reflection band at $\lambda = 540$ nm (Figure 1), which is around the same wavelength as the pristine film. The bandwidth is narrower which might be due to the absorbed water lowering the birefringence in the film.^[31] This SRB is red shifted by 160 nm with respect to the chiral imprinted film showing the ability of the flexible polymer film to reversibly change its optical properties over a large spectral range. When the film was placed in deionized water, a small blue shift (≈ 17 nm) of the green reflection band was observed.

2.2. Detection of Metal Ions in Water

To investigate the binding efficacy of the polymer potassium salt film toward metal cations, they were exposed to 0.75 mL of 0.1 M of monovalent and divalent cations such as Na^+ , Mg^{2+} , Ca^{2+} , Zn^{2+} , Cd^{2+} , and Pb^{2+} for 60 min and the optical response was monitored with UV-vis spectroscopy. It was observed that in all cases the reflection band of the films undergoes a blue shift to different extents (Figure 2a,b). Interestingly, a close examination of the blue shift, $\Delta\lambda$, of the SRB (Figure 2b), reveals that Ca^{2+} gives the highest $\Delta\lambda$ of 70 nm yielding a blue reflecting film whose color change can be clearly seen by the naked eye

(Figure 2a). To determine the selectivity of the polymer potassium salt film, Na^+ , Mg^{2+} , Ca^{2+} , Zn^{2+} , and Cd^{2+} ions were dissolved together in water such that the concentration of each of the nitrate salts was 0.1 M. On exposing the polymer salt film to this metal ions solution, the SRB undergoes a blue shift of 65 nm which is very close to $\Delta\lambda$ ($= 70$ nm) observed for Ca^{2+} (Figure 3a). This suggests that Ca^{2+} ions have the highest binding affinity for the polymer film relative to the other metal ions. To further test the Ca^{2+} selectivity, a Ca^{2+} polymer film (vide infra) was exposed to Zn^{2+} , Mg^{2+} , Cd^{2+} , and Na^+ solutions (each of 1 M concentration, 0.75 mL) consecutively. There was no change in the reflection band (Figure 3b), confirming that calcium is strongly bound in the polymer film (vide infra). From these studies it can be concluded that Ca^{2+} binds selectively and strongly to the polymer film over all the other metal ions studied. The binding of Ca^{2+} apparently results in a large decrease in the length of helical pitch which may be due to dehydration of the film leading to polymer shrinkage.^[32] The bound Ca^{2+} ions can be washed away by treating the film with dilute HNO_3 and the resulting film can be reused. Moreover, the polymer potassium salt films can be stored at ambient conditions for days.

2.3. Detection of Calcium in Water

To investigate the calcium selectivity and sensitivity in more detail, the kinetics of the exchange reaction of K^+ by Ca^{2+} was

Figure 2. a) UV-vis transmission spectrum of the polymer potassium salt film in water and after exposure to 0.1 M Ca^{2+} solution. The inset shows photographs of the film before and after exposure to 0.1 M Ca^{2+} solution. b) Blue shift observed for the reflection band of polymer potassium salt film after exposure to 0.75 mL of 0.1 M NaNO_3 , $\text{Mg}(\text{NO}_3)_2$, $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$, $\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$, $\text{Cd}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$, and $\text{Pb}(\text{NO}_3)_2$. Error bar indicates mean $\pm$ standard deviation for five measurements at different places on the film. Duration of exposure to the metal ions solution was 60 min.

investigated. The polymer potassium salt film was treated with Ca^{2+} (0.1 M) and the change of the reflection band was monitored by UV-vis spectroscopy. Within a minute of exposure, the SRB of the wet polymer film underwent a blue shift of ≈ 60 nm (Figure 4a). An additional blue shift of 10 nm was observed in the next 60 min, which did not change any further. This reveals that exchange between K^+ and Ca^{2+} is rapid and apparently this exchange reaction is accompanied by release of absorbed water from the film and hence a blue shift of the SRB. FT-IR measurements showed an increase in the symmetric stretching frequency of COO^- from 1385 to 1394 cm^{-1} and decrease in the asymmetric stretching frequency of COO^- from 1543 to 1531 cm^{-1} (Figure S1, Supporting Information) indicating binding of COO^- to Ca^{2+} .^[33,34]

In order to determine the stoichiometry of calcium complexation, polymer potassium salt films were exposed to different concentration of Ca^{2+} ions. Figure 4b shows the blue shift of the SRB as a function of the ratio of Ca^{2+} ions to available benzoate

Figure 3. UV-vis transmission spectrum of a) polymer potassium salt film before and after exposure to mixture of equimolar metal ions Na^+ , Mg^{2+} , Ca^{2+} , Zn^{2+} , Cd^{2+} , and Pb^{2+} (0.1 M each). b) Calcium polymer salt film on successive exposure to 1 M of Zn^{2+} , Mg^{2+} , Cd^{2+} , and Na^+ solutions. Duration of exposure to the metal ions solution was 60 min.

binding sites (2.5×10^{18} per film). With an increased amount of Ca^{2+} ions, an increase in the blue shift is observed before saturation of the COO^- sites takes place. A sharp inflection point is observed when the amount of calcium is ≈ 0.5 with respect to the binding sites indicating that two COO^- are binding one Ca^{2+} ion and that the binding is strong.^[35] The TGA profile of fully saturated Ca^{2+} -polymer film showed a content of 4 wt% at temperature above 600 $^{\circ}\text{C}$ (Figure S2, Supporting Information) which corresponds to the amount of CaCO_3 that is formed when Ca^{2+} binds to two COO^- binding sites and is heated up.^[36]

The association constants of benzoic acid toward a variety of metal ions in solution do not show any preference for Ca^{2+} .^[37] It is well known that divalent calcium prefers bidentate over monodentate binding of carboxylate.^[38] In the CLC polymer film, the benzoic acid groups are planarly aligned pointing toward each other by hydrogen bond interactions (vide supra). Most likely this preorganized planar-like geometry facilitated strong binding of calcium.^[39] Calcium-carboxylate complexes

Figure 4. a) UV-vis transmission spectrum of the polymer potassium salt film on exposure to 0.1 M Ca^{2+} solution taken at different time. b) Blue shift of the reflection band of polymer potassium salt film after exposure to different concentration of Ca^{2+} (inset: schematic illustration of the expected stoichiometry of Ca-carboxylate complex). The X-axis represents the molar ratio of Ca^{2+} to COO^- binding sites. Error bar indicates mean $\pm$ standard deviation for five measurements at different places on the film. Duration of exposure to the Ca^{2+} solution was 60 min.

have been shown to be less hydrated,^[38,40] compared to other metal-carboxylate complexes, which is attributed to their low polarizing power of bound first shell water molecules.^[41] This could explain the release of large amount of water leading to a large color change of the polymer film upon binding to Ca^{2+} . Presumably, it is the preorganization that is causing the strong, fast, and selective binding of Ca^{2+} with subsequent dehydration of the film.

2.4. Detection of Calcium in Serum

To determine the effective range of calcium concentrations for which the polymer film is most sensitive, the $\Delta\lambda$ of the SRB was plotted versus the logarithm of different Ca^{2+} concentrations ($\log[\text{Ca}^{2+}]$) (Figure 5a). It can be seen that the increase

Figure 5. a) Blue shift of the reflection band of polymer potassium salt film after exposure to different molar concentration of Ca^{2+} ions [Ca^{2+}]. Error bar indicates mean $\pm$ standard deviation for five measurements at different places on a film. b) Blue shift of the reflection band of polymer potassium salt film after exposure to normal serum, hypocalcemia (hypoCa-1 and hypoCa-2), and hypercalcemia (hyperCa) samples. HypoCa-1 and HypoCa-2 were prepared by supplementing normal serum with 0.5 and 1×10^{-3} M EDTA, respectively. Error bar indicates mean $\pm$ standard deviation for measurements of three different films. The inset shows photograph of the films after exposure to normal serum, hypocalcemia, and hypercalcemia samples.

in $\Delta\lambda$ occurs between 10^{-4} and 10^{-2} M concentration of Ca^{2+} . It should be noted that this sensitivity, however, will depend on the number of binding sites and the thickness of the film. Interestingly, for a healthy human the amount of total calcium in blood occurs in the range of 2.1×10^{-3} to 2.6×10^{-3} M^[42] precisely in the range where the film is most sensitive, indicating that perhaps our film could be used as an alternative readout system for this important diagnostic parameter.^[43–51] For a healthy human, total magnesium levels in blood are in the range of 0.7×10^{-3} to 1×10^{-3} M.^[52] In order to determine the sensitivity of our sensor toward calcium, a Mg^{2+} -polymer film was treated with a 1 M Ca^{2+} solution (0.75 mL). A blue

shift of 14 nm of the SRB (Figure S3, Supporting Information) was observed indicating Ca^{2+} has replaced Mg^{2+} in the polymer film. These results encouraged us to investigate the ability of the polymer potassium salt film to detect calcium in serum. A blue shift in the SRB of ≈ 68 nm was observed when the polymer film was treated with pooled normal human serum. In an attempt to explore the diagnostic potential of the films, we then conducted experiments treating the films with blood samples supplemented with 0.5×10^{-3} and 1×10^{-3} M ethylenediaminetetraacetic acid (EDTA) (hypoCa-1 and hypoCa-2 respectively) or 1×10^{-3} M CaCl_2 (hyperCa) in order to mimic hypo and hypercalcemic blood samples, respectively (Figure 5b). As expected, films treated with blood samples with a reduced Ca^{2+} concentration display a smaller blue shift (40 nm for hypoCa-1 and 28 nm for hypoCa-2), while films treated with blood samples with elevated Ca^{2+} levels display an increased blue shift (75 nm), slightly higher than the maximum blue shift (≈ 69 nm) observed for aqueous Ca^{2+} which may be due to the difference in osmotic pressure of blood serum compared to water. These results confirm that the film is sensitive to changes in Ca^{2+} levels in the physiologically relevant concentration range and that the film may eventually be used as an alternative, low-cost readout system for the detection and quantification of Ca^{2+} levels in blood serum. The difference in color of the films after exposure to serum simulating hypocalcemia and hypercalcemia cannot be easily observed unaided, however, this can probably be addressed by using a smartphone camera app.

3. Conclusion

An optical calcium sensor has been fabricated based on chiral imprinted cholesteric liquid crystalline polymer. The polymer photonic film shows a remarkable selective response to calcium, with a color change from green to blue. This result is ascribed to liquid crystalline order in the material resulting in a preorganized optimal binding geometry for calcium and the dehydration properties of the calcium complex. It suggests that CLC-based sensors can be constructed that show a selective high optical response toward metal ions without using specific binding moieties. Most likely, the effective sensitivity of the sensor can be further optimized by varying the number of binding sites and the thickness of the polymer film. The calcium sensor could also be used as a test strip for qualitative detection of calcium in serum. Normal serum and samples mimicking hypocalcemia and hypercalcemia showed optical responses which could be distinguished spectroscopically. These optical materials hold promise in fabrication of cheap, easy-to-use, battery-free metal ion sensors for clinical diagnostics.

4. Experimental Section

Materials: RM 257 and RM 105 were obtained from Merck. 6OBA and 6OBAM were purchased from Synthon. Irgacure 369 was purchased from CIBA. Chiral dopant (R)-(+)-3-methyladipic acid, KOH pellets, EDTA, 3-(trimethoxysilyl)propyl methacrylate, 1H, 1H, 2H, 2H-perfluorodecyltriethoxysilane and the metal nitrates NaNO_3 , $\text{Mg}(\text{NO}_3)_2$, $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$, $\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$, $\text{Cd}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$, and $\text{Pb}(\text{NO}_3)_2$ were from Sigma-Aldrich. CaCl_2 was from Merck. The solvents

tetrahydrofuran, isopropanol, and ethanol were obtained from Biosolve. Pooled normal human blood plasma and serum were obtained from Innovative Research Inc.

Equipment: UV-visible studies were carried out in Ocean Optics UV-Visible spectrophotometer HR 2000+. Varian 670 FT-IR spectrometer with slide-on ATR (Ge) was used to record IR spectra. Thermogravimetric analyses were performed in TA TGA Q500. Photopolymerization was carried out with Omnicure series 2000 EXFO lamp.

Functionalization of Glass Slides: Methacrylate functionalized and perfluoro coated glass slides were prepared as reported by Stumpel et al.^[53] Glass slides were first cleaned by sonication (ethanol, 30 min), followed by treatment in a UV-ozone photoreactor (Ultra Violet Products, PR-100, 20 min) to activate the glass surfaces. The glass surfaces were then modified by spin coating (3000 rpm, 45 s) with 3-(trimethoxysilyl)propyl methacrylate solution (1 vol% solution in a 1:1 water-isopropyl alcohol mixture) or 1H, 1H, 2H, 2H-perfluorodecyltriethoxysilane solution (1 vol% solution in ethanol) to obtain methacrylate functionalized and fluorinated alkylsilane functionalized glass substrates, respectively, followed by curing (100 °C, 10 min).

Preparation of CLC Polymer Film: CLC mixture (1 g) consisting of 22.55 wt% of RM 257, 27.70 wt% of RM 105, 16.40 wt% of each of 6OBA, 6OBAM, and (R)-(+)-3-methyladipic acid, and 0.6 wt% of Irgacure 369 was dissolved in tetrahydrofuran (4 mL). 20 μL of this solution was dropped on methacrylate functionalized 3×3 cm glass slide. After evaporating the solvent by heating at 75 °C, a perfluoro coated 3×3 cm glass slide was placed directly on top and cooled to room temperature simultaneously shearing along one direction to obtain a planarly aligned green color film. It was then photopolymerized by shining UV light (48 mW cm^{-2} intensity in the range 320–390 nm) for 5 min after which the upper perfluoro coated glass was removed.

Supporting Information

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

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- [1] G. Aragay, J. Pons, A. Merkoçi, *Chem. Rev.* **2011**, *111*, 3433.
- [2] H. Wang, K.-Q. Zhang, *Sensors* **2013**, *13*, 4192.
- [3] C. Fenzl, T. Hirsch, O. S. Wolfbeis, *Angew. Chem. Int. Ed.* **2014**, *53*, 3318.
- [4] J. Ge, Y. Yin, *Angew. Chem. Int. Ed.* **2011**, *50*, 1492.
- [5] L. Wang, Q. Li, *Adv. Funct. Mater.* **2015**, DOI: 10.1002/adfm.201502071.
- [6] D. Arunbabu, A. Sannigrahi, T. Jana, *Soft Matter* **2011**, *7*, 2592.
- [7] N. Gogoi, M. Barooah, G. Majumdar, D. Chowdhury, *ACS Appl. Mater. Interfaces* **2015**, *7*, 3058.
- [8] B.-F. Ye, Y.-J. Zhao, Y. Cheng, T.-T. Li, Z.-Y. Xie, X.-W. Zhao, Z.-Z. Gu, *Nanoscale* **2012**, *4*, 5998.

- [9] S. A. Asher, S. F. Peteu, C. E. Reese, M. X. Lin, D. Finegold, *Anal. Bioanal. Chem.* **2002**, 373, 632.
- [10] J. H. Holtz, S. A. Asher, *Nature* **1997**, 389, 829.
- [11] J. H. J. S. W. Holtz, C. H. Munro, S. A. Asher, *Anal. Chem.* **1998**, 70, 780.
- [12] C. E. Reese, S. A. Asher, *Anal. Chem.* **2003**, 75, 9534.
- [13] S. A. Asher, A. C. Sharma, A. V. Goponenko, M. M. Ward, *Anal. Chem.* **2003**, 75, 1676.
- [14] H. K. Bisoyi, Q. Li, *Acc. Chem. Res.* **2014**, 47, 3184.
- [15] Y. Wang, Q. Li, *Adv. Mater.* **2012**, 24, 1926.
- [16] Q. Li, Y. Li, J. Ma, D. K. Yang, T. J. White, T. J. Bunning, *Adv. Mater.* **2011**, 23, 5069.
- [17] J. Ma, Y. Li, T. White, A. Urbas, Q. Li, *Chem. Commun.* **2010**, 46, 3463.
- [18] R. J. Carlton, J. T. Hunter, D. S. Miller, R. Abbasi, P. C. Mushenheim, L. N. Tan, N. L. Abbott, *Liq. Cryst. Rev.* **2013**, 1, 29.
- [19] D. J. Broer, C. M. W. Bastiaansen, M. G. Debije, A. P. H. J. Schenning, *Angew. Chem. Int. Ed.* **2012**, 51, 7102.
- [20] T. J. White, M. E. McConney, T. J. Bunning, *J. Mater. Chem.* **2010**, 20, 9832.
- [21] M. Mitov, *Adv. Mater.* **2012**, 24, 6260.
- [22] S. Kado, Y. Takeshima, Y. Nakahara, K. Kimura, *J. Incl. Phenom. Macrocycl. Chem.* **2011**, 72, 227.
- [23] V. Stroganov, A. Ryabchun, A. Bobrovsky, V. Shibaev, *Macromol. Rapid Commun.* **2012**, 33, 1875.
- [24] P. V. Shibaev, D. Chiappetta, R. L. Sanford, P. Palfy-Muhoray, M. Moreira, W. Cao, M. M. Green, *Macromolecules* **2006**, 39, 3986.
- [25] J. E. Stumpel, C. Wouters, N. Herzer, J. Ziegler, D. J. Broer, C. W. M. Bastiaansen, A. P. H. J. Schenning, *Adv. Opt. Mater.* **2014**, 2, 459.
- [26] A. Martínez-Felipe, A. G. Cook, M. J. Wallage, C. T. Imrie, *Phase Transitions* **2014**, 87, 1191.
- [27] C. K. Chang, C. M. W. Bastiaansen, D. J. Broer, H. L. Kuo, *Adv. Funct. Mater.* **2012**, 22, 2855.
- [28] N. Herzer, H. Guney, D. J. D. Davies, D. Yildirim, A. R. Vaccaro, D. J. Broer, A. P. H. J. Schenning, *J. Am. Chem. Soc.* **2012**, 134, 53.
- [29] P. V. Shibaev, R. L. Sanford, D. Chiappetta, P. Rivera, *Mol. Cryst. Liq. Cryst.* **2007**, 479, 161.
- [30] P. V. Shibaev, J. Madsen, A. Z. Genack, *Chem. Mater.* **2004**, 16, 1397.
- [31] D. Liu, C. W. M. Bastiaansen, J. M. J. den Toonder, D. J. Broer, *Angew. Chem. Int. Ed.* **2012**, 51, 892.
- [32] J. E. Stumpel, D. J. Broer, A. P. H. J. Schenning, *RSC Adv.* **2015**, 5, 94650.
- [33] T. Dudev, C. Lim, *J. Mol. Struct.* **2012**, 1009, 83.
- [34] M. Nara, H. Morii, M. Tanokura, *Biochim. Biophys. Acta, Biomembr.* **2013**, 1828, 2319.
- [35] P. Thordarson, *Chem. Soc. Rev.* **2011**, 40, 1305.
- [36] M. Ghiasi, A. Malekzadeh, *Cryst. Res. Technol.* **2012**, 47, 471.
- [37] A. E. Martell, R. M. Smith, *Other Organic Ligands*, Springer Science+Business Media, New York **1977**.
- [38] T. Dudev, T. Dudev, C. Lim, C. Lim, *J. Phys. Chem. B* **2004**, 108, 4546.
- [39] J.-M. Lehn, *Chem. Soc. Rev.* **2007**, 36, 151.
- [40] T. Dudev, C. Lim, *Chem. Phys.* **2003**, 103, 773.
- [41] T. Dudev, C. Lim, *J. Am. Chem. Soc.* **2013**, 135, 17200.
- [42] S. Kim, J. W. Park, D. Kim, I. H. Lee, S. Jon, *Angew. Chem. Int. Ed.* **2009**, 48, 4138.
- [43] F. M. LaFerla, *Nat. Rev. Neurosci.* **2002**, 3, 862.
- [44] J. M. Lappe, D. Travers-gustafson, K. M. Davies, R. R. Recker, R. P. Heaney, *Am. J. Clin. Nutr.* **2007**, 85, 1586.
- [45] W. D. Fraser, *Lancet* **2015**, 374, 145.
- [46] K. D. Burman, J. M. Monchik, J. M. Earll, L. Wartofsky, *Ann. Intern. Med.* **1976**, 84, 668.
- [47] B. E. C. Nordin, *Nutrition* **1997**, 13, 664.
- [48] S. Kim, J. Kim, N. H. Lee, H. H. Jang, M. S. Han, *Chem. Commun.* **2011**, 47, 10299.
- [49] M. S. Eom, W. Jang, Y. S. Lee, G. Choi, Y.-U. Kwon, M. S. Han, *Chem. Commun.* **2012**, 48, 5566.
- [50] P. Caglar, S. A. Tuncel, N. Malcik, J. P. Landers, J. P. Ferrance, *Anal. Bioanal. Chem.* **2006**, 386, 1303.
- [51] Y. Guo, X. Tong, L. Ji, Z. Wang, H. Wang, J. Hu, R. Pei, *Chem. Commun.* **2015**, 51, 596.
- [52] H. Frankel, R. Haskell, S. Y. Lee, D. Miller, M. Rotondo, C. W. Schwab, *World J. Surg.* **1999**, 23, 966.
- [53] J. E. Stumpel, E. R. Gil, A. B. Spoelstra, C. W. M. Bastiaansen, D. J. Broer, A. P. H. J. Schenning, *Adv. Funct. Mater.* **2015**, 25, 3314.