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# 学 位 論 文 内 容 の 要 旨

博士の専攻分野の名称　博士(ソフトマター科学)　氏　名　猿渡　彩

## 学 位 論 文 題 名

Ionic liquid-polymer composite materials applicable for biomaterials
（バイオマテリアルに適用可能なイオン液体／高分子複合材料）

Ionic liquids (ILs) possess unique properties such as high ion conductivity, (electro)chemical stability, thermal stability, and low volatility, which make them highly suitable for various advanced materials. Ion gels where ILs are involved within polymer network to form self-standing property, have attracted attention for use in applications ranging from electrolyte membranes for batteries, transistors, and supercapacitors, gas absorption/separation membranes, and wearable electronics. This thesis describes IL-poymer composite materials with two main biomaterial targets. First, the research focuses on a stretchable ion gel as an wearable devices such as artificial muscle and ionic skin, realizing toughness and repeated strain resistance. The second target centers on developing a photo-responsive cell scaffold for mechanobiological studies, achieved through the viscoelastic tuning of azobenzene-containing block copolymer. To address the limitations found in conventional azobenzene-based polymer materials, such as cytotoxicity from halmful UV-induced photoisomerization and quick thermal relaxation, the final part of this thesis utilizes an azobenzene possessing four methoxy groups at *ortho*-position, overcoming these challenges to create a safer and more thermally stable scaffold materials for cell culture. Chapter 1 summarizes over view of related research fields noted above.

In Chapter 2, a tough and stretchable ion gel was prepared through a straightforward procedure. Methyl methacrylate (MMA) as a monomer and ethylene glycol dimethacrylate (EGDMA) as a cross-linker were combined with 2,2-diethoxyacetophenone (DEAP) as a photoinitiator and mixed with the IL, 1-ethyl-3-methylimidazolium trifluoromethylsulfonylimide ([$C_2$mim][TFSI]). After deoxidation, this mixture was irradiated with UV light, producing a transparent ion gel. The ion gel exhibited a maximum toughness of 1 MJ $m^{-3}$ at a cross-linker concentration of 0.01 mol% with only 0.02 mol% of initiator. Previous work by our group demonstrated that ultrahigh-molecular weight (UHMW) PMMA could be prepared with a low concentration of initiator due to the enhanced propagation reaction rate of free radical polymerization in ILs. This UHMW PMMA formed an ion gel with abundant polymer chain entanglements. The synergistic effect of numerous physical cross-links from polymer chain entanglements and a minimal amount of permanent chemical cross-links contributed to both the toughness and stretchability of the gel. Such a low concentration of chemical cross-linkers (one chemical cross-linker per every 10000 repeating units of MMA) also extended the relaxation time 10-fold and suppressed residual strain by more than half after 80 successive loading–unloading cycles, indicating an improvement in long-term durability.

In addition to the above applications, our group recently explored the use of ILs as liquid cell scaffolds. ILs are called as “designer solvents” because they offer a wide range of customizable chemical structures and physicochemical properties, unlike conventional liquids. Among these, certain ILs, such as tributylmethylphosphonium trifluoromethylsulfonylimide ([P4,4,4,1][TFSI]) and tetraoctylphosphonium trifluoromethylsulfonylimide ([P8,8,8,8][TFSI]), have been shown to be non-cytotoxic (non-cytotoxic ILs: NCILs). Cell culture at liquid | liquid interfaces has attracted attention in mechanobiology because such interfaces enabled distinct cellular behaviors, including selective neural differentiation and the maintenance of the undifferentiated state of human mesenchymal stem cells (hMSCs). Traditionally, cell culture at the interface of fluorocarbons or silicone and the culture medium relies on “interfacial engineering” of protein nanolayers. In contrast, NCILs provide a new approach “bulk manipulation” that leverages both the solubility of polymers in ILs and their hydrophobicity, opening avenues beyond traditional “interfacial engineering”.

ILs also served as unique platforms for stimuli-responsive polymers. For instance, poly(*N*-isopropylacrylamide) (PNIPAm), widely studied for its lower critical solution temperature (LCST)-type phase behavior in water, exhibits the opposite upper critical solution temperature (UCST)-type phase transition in certain hydrophobic ILs, including imidazolium-based ILs. When NIPAm was randomly copolymerized with methacrylate monomers bearing azobenzene side chains (P(AzoMA-*r*-NIPAm)), the cloud point in 1-butyl-3-methylimidazolium hexafluorophosphate ([$C_4$mim][$PF_6$]) changed depending on the photoisomerization state of AzoMA allowing solubility to be reversibly controlled by light illumination. An ABA triblock copolymer, with P(AzoMA-*r*-NIPAm) as the A block, exhibited reversible sol-gel transitions under light stimuli: crosslinking points formed under UV light and dissolved under visible light. However, the use of [$C_4$mim][$PF_6$] is limited by its cytotoxicity.

In Chapter 3, a non-cytotoxic ion gel that enables photo-reversible viscoelastic changes was developed for use as a cell scaffold. PNIPAm was found to be compatible with [P4,4,4,1][TFSI] and exhibited a UCST-type phase transition in [P8,8,8,8][TFSI] above 80 ºC, significantly higher than the standard cell culture temperature of 37 ºC. In a blended solution of [P4,4,4,1][TFSI] and [P8,8,8,8][TFSI], the cloud point ($T_c$) decreased linearly with increasing the volume fraction of [P4,4,4,1][TFSI], suggesting that $T_c$ can be precisely controlled by adjusting the blend ratio. Copolymerizing NIPAm with acrylamide monomers containing azobenzene side chains (P(AzoAm-*r*-NIPAm)) enabled $T_c$ to shift according to the photoisomerization state of AzoAm. The low-polarity of [P4,4,4,1][TFSI] and [P8,8,8,8][TFSI] allowed the *trans*-type polymer to have higher solubility (and thus lower $T_c$) under visible light than the *cis*-type polymer under UV light. An ABC triblock copolymer of P(AzoAm-*r*-NIPAm)-*b*-poly(butyl acrylate)-*b*-polystyrene was synthesized and combined with the NCIL blend to create a transparent ion gel. Under UV-light illumination, the ion gel showed higher storage modulus ($G'$), loss modulus ($G''$) and gelation temperature than under visible light. Reversible sol-gel transitions were observed by alternating the light wavelength near the gelation temperature of the *cis*-type ion gel. Cell adhesion and spreading on the ion gel were confirmed, demonstrating the potential of the gel as a cell scaffold. Unlike hydrogels, the NCIL and triblock copolymer components showed minimal dissolution into the culture medium, allowing the ion gel to retain its mechanical properties even in the sol state. This study proposed a non-cytotoxic ion gel capable of providing dynamic mechanical stimuli to cells in both sol and gel states, offering promising applications in mechanobiology.

In Chapter 4, to address the inherent limitations of azobenzene-based materials, a visible light-responsive polymer-NCIL solution was developed. Conventional azobenzene faces two major drawbacks: (1) while azobenzene isomerizes to *cis*-form under UV irradiation, excessive UV exposure poses a risk of cellular damage, and (2) thermal isomerization from the *cis*- to *trans*-form can lead to unintended changes in material properties during cell culture. The introduction of methoxy groups at the *ortho*-position of azobenzene has been reported to impart non-phototoxic visible light responsivity while significantly slowing the thermal relaxation rate. This methoxy azobenzene derivative, (mAzoA), exibited even slower thermal isomerization in [P8,8,8,8][TFSI], with a half-life ($\tau_{1/2}$) of 121 days. Solubility tests revealed that PMMA undergoes a UCST-type phase transition near the cell culture temperature in [P8,8,8,8][TFSI]. Random copolymerization of MMA with mAzo yielded P(mAzoA-*r*-MMA)), which exhibited UCST-type phase separation in [P8,8,8,8][TFSI], with $T_c$ shifting according to the photoisomerization state of mAzo. At appropriate temperature, P(mAzoA-*r*-MMA) reversibly switched its solubility in [P8,8,8,8][TFSI] under visible-light irradiation. This phenomenon enabled repeated changes in the $G''$ of the polymer-NCIL solution in response to light of varying wavelength of visible light. The polymer solution demonstrated no cytotoxicity and showed promise as a liquid cell scaffold due to its water-immisibility. This innovative material introduces a new liquid scaffold platform with stimuli-responsive mechanical properties, offering potential for real time modulating cellular environments in mechanobiological studies.

The findings presented in this thesis demonstrate the versatility of (NC)IL-polymer composites, ranging from highly stretchable ion gels with exceptional toughness and durability for wearable devices to light-responsive cell scaffolds for dynamic mechanobiology. By addressing challenges in material stability, cytotoxicity, and mechanical adaptability, this work bridges the gap between advanced material science and biomedical applications, opening new pathways for innovative technologies in both fields.