Polymer Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/polymers

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Highly pH-Sensitive Polyurethane Exhibiting Shape Memory and Drug Release

HongmeiChen,[a,b] Ying Li, [a]YeLiu,[a] Tao Gong,[a] Lin Wang[a] and Shaobing Zhou*[a]

Received (in XXX, XXX) XthXXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

In this study, a highly pH-sensitive polymer is synthesised by introducing pyridine rings into the backbone of polyurethane. The chemical structure of the resulting materials is confirmed by FT-IR and ^{1}H-NMR. To analyse the mechanism of the pH sensitivity of this polymer, its structural transformations under acidic and basic conditions are studied by FT-IR, theoretical calculation and ^{1}H-NMR. We observe that the mechanism of pH responsiveness isthe formation of a hydrogen bond interaction between the N atom of the pyridine ring and the H-N of urethane in neutral or alkaline environments which is disrupted under acidic conditions due to the protonation of the pyridine ring. The pH-sensitivity is demonstrated by simply adjusting the pH value of the environment, which can act as a switch to control shape memory and drug release. Unlike other systems with thermally sensitive behaviour, the shape memory functionality of this material is independent of temperature, which is dependent only on the variation in the pH of the environment. This strategy provides a potent tool for the design of multifunctional materials based on the physiological environment tofulfil the complex requirements of drug delivery and tissue engineering systems.

Introduction

Stimulus-responsive materials can undergo conformational or phase changes in response to environmental signals.[1] The materials represent one of the most exciting emerging areas of science[2] due to their promising applications in suchfields as actuator systems,[3] tissue engineering[4] and programmable delivery systems.[5] Although some progress has been made in recent years, the design and engineering of a synthetic material with an ability to respond to stimuli in a controllable and predictable fashion remains a challenge. Among these responsive materials, shape memory polymers (SMPs) have attracted increasing attention for their potential medical applications.[6, 7]SMPs can change from their permanent shape into a temporary shape, and recover to their permanent shape upon application of an appropriate stimulus such as temperature,[8,9] light,[10,11] water,[12,13] magnetic field [14] or chemicals. [15] Thermally induced SMPs are the most widely studied, but their biomedical applications are sometimes limited because the switching temperature should be in the range from room temperature to body temperature.

For biomedical applications, an ideal stimulus must be chosen based on the physiological environment.Variations in physiological pH exist among different sites in the body including the gastrointestinal tract, vagina and blood vessels; on the other hand, a sharp pH gradient generally appears across biological systems on both the cellular and systemic levels in pathological states which differ from the physiological pH of 7.4.[16]Thus, the pH stimulus is a good choice for thedesign of shape memorypolymers with potential applications in medicine.Zhang et al. reported a pH-sensitive shape memory polymer prepared with β-cyclodextrin modified alginate and diethylenetriamine modified alginate.[17]This material can be processed into a temporary shape at pH 11.5 and recover to its initial shape at pH 7. But as far as we know, SMPs stimulated by acidic conditions have not been reported. And inspired by research in drug deliver, pH stimuli can also be used as a reversible switch turning drug release on and off, thus we aim to produce a novel multi-functional shape memory material.

Hydrogen bond interactions have been used to synthesise new shape memory polymer networks.[18] The reversibility of hydrogen bond association endows polymers with athermallyinduced shape memory function, with the rate of shape recovery strongly dependent on temperature becauseweak hydrogen bondinteractions are highly sensitive to heat.[18] To date, little work has beenpublished to describe the precise control of shape memory function via the dissociation and association of hydrogen bonds by simply changing the pH value of the external environment.

In this study, we synthesise a highly pH-sensitive polymer byintroducingpyridineringsintothebackboneofpolyurethane. Polyurethane has great potential for medical applications due to its excellent shape memory andbiocompatibility.[19] Pyridine is a Lewis base, and the N atom of the pyridine ring can readily combine with H^+ toform an NH^+ in acidic conditions, with H^+removed under basic conditions. In this system, the polymer will exhibit high pH sensitivity through the association and dissociation of the hydrogen bond interactions between the H of urethane and the N atom of the pyridine ring via the

deprotonation and protonation of the pyridine ring (**Fig. 1**). The H^+ sensitive part of pyridine can be used as a switch to shift the polymer shape, while the hydrogen bonded urethane segments insensitive to H^+ can be used as the fixed domain to hold the original shape. Unlike other systems with thermally sensitive functions, this shape memory function is independent of temperature and only dependent on the pH value of the environment.This pH sensitivity can be exploited fordrug delivery to reversibly switchdrug release on and off.Additionally, unlike other drug delivery systems such as polymer-drug conjugate nanoparticles that irreversibly de-assemble to release drug via the cleavage of pH-sensitive linkages in the polymeric backbone inthe acidic microenvironment,[20, 21]this system can release drugon demand while maintaininga stable structure due to the reversible hydrogen bond interactions.

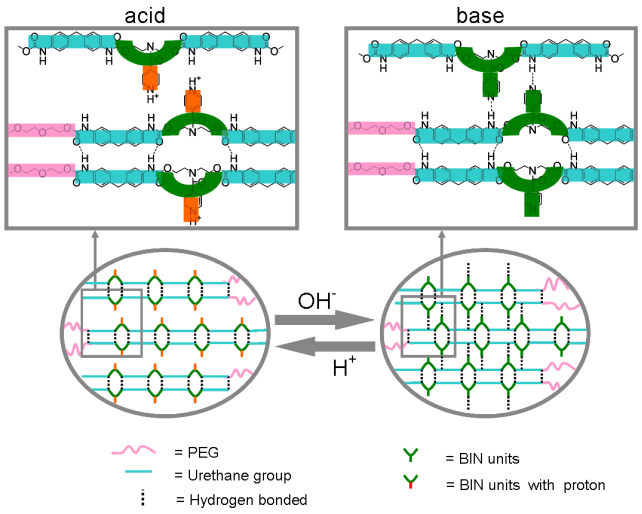


Fig.1 Schematic of the pH sensitivity of the PEG4000-MDI-BIN polymer. The pyridine rings in this polyurethane are protonated to disturb the hydrogen bond interactions in acid and deprotonated to formhydrogen bonds in neutral or basic conditions, enablingreversibleswitching ofboth shape memory and drug release.

Experimental Section

Materials

Unless otherwise noted, all chemical reagents were obtained from commercial suppliers and used without further purification. 4,4-diphenylmethane diisocyanate (MDI) was purchased from Tokyo Chemical Industry Co. LTD. Poly(ethylene glycol) (PEG,4000D), *N,N*-dimethyl formamide (DMF), and isonicotinic acid were purchased from Kelong Chemical Reagent Factory in Chengdu. DMF was dried over CaH_2 for 2 days at room temperature, distilled under vacuum, and stored in the presence of 4 Å molecular sieves. *N,N*-bis(2-hydroxylethyl)isonicotinamine (BIN) was synthesised as previously described in the literature. [22]

Instruments and Procedures

FT-IR spectroscopic analysis was carried out with a Nicolet 5700 FT-IR spectrometer (Thermo Electron, U.S.) by the ATR method. Each sample for infrared analysis was prepared by a film. The software *2Dshige(c)* written by Shigeaki Morita (Kwasei-Gakuin University) was used for two-dimensional correlation analysis. ^{1}H NMR experiments were performed on a Varian 400 NMR spectrometer. Dynamic mechanical thermal analysis experiments were performed using a TA Instruments DMA-Q800 under N_2 with liquid N_2 cooling and heated at a rate of 3 ℃ min^{-1} and 1 Hz. Thermal analysis was conducted by TA DSC-Q100 at heating and cooling rates of 10 ℃ min^{-1}. The molecular weight of the polymer was tested in DMF solution using the Breeze 2 HPLC system. The drug release content was measured using a Shimadzu UV-2550 spectrophotometer. Fluorescence photographs were taken with a Olympus CKX41 fluorescence microscope.

Synthesis of PEG4000-MDI-BIN

PEG (1 mmol), MDI (2 mmol) and DMF (50 ml) were added to a dried flask and reacted for approximately 2 h at 80 – 85 ℃. Then, BIN (22 mmol) and MDI (21 mmol) were added successively, with the reaction maintained at the same temperature for an additional 2 h. The solution was poured out and evaporated at 80 ℃ for 8 h.Theobtained films were further dried under vacuum at room temperature for another 48 h. The BIN content in the polymer is 32wt%.

Swelling Measurements

A piece of dried PEG4000-MDI-BIN film was weighed (M_d) and immersed in acid at a constant temperature (20 ℃). After 60 min, the film was removed from the acid and the mass (M_s) of the swelling film was recorded. The swelling ratio (S_r) was defined as $(M_s-M_d)/M_d$.

Shape-Memory Property Characterisation

PEG4000-MDI-BIN films were cut into rectangular strips with dimensions of 15.0mm×0.5mm×0.1mm. First, a straight strip was immersed in acid to induce swelling, the swollen strip was deformed to an angle θ_i by external force and immersed in base. A few minutes later the force was removed and the angle θ_f was maintained. The fixity ratio (R_r) was defined as θ_f/θ_i. The deformed sample was immersed in acid for a period of time and the residual angle θ_r was recorded. The shape recovery ratio (R_r) was defined as $(\theta_f - \theta_r)/\theta_f$.

Computer Simulation

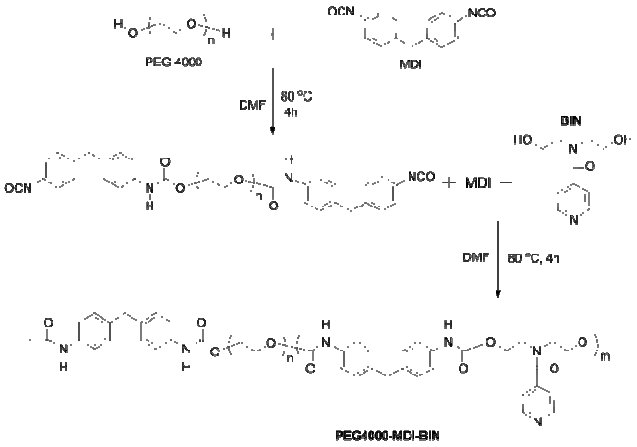
All the computation was carried out using the Gaussian 09 software package. [23] Products were optimised at the density functional level of theory using the hybrid B3LYP function together with the 6-31+G (d) basis set.

Results and Discussion

Characterization of Polymer PEG4000-MDI-BIN

The route used to synthesise the designed pH sensitive polymer, PEG4000-MDI-BIN, is shown in **Scheme 1**. The polymer was synthesised through solution polymerisation by poly(ethylene glycol) (PEG, M_n: 4000 $gmol^{-1}$), diphenylmethanediisocyanate (MDI) and *N, N*-bis(2-hydroxylethyl) isonicotinamine (BIN). The polymer contains 32wt% BIN to introduce the pH sensitive pyridine ring, with 27wt% PEG to increase the polymer hydrophilicity. The chemical structure of the resulting materials was confirmed by FT-IR and ^{1}H-NMR analysis. The FT-IR spectra in **Fig. S1** in the Supporting Information (SI) clearly show that the designed polymer was successfully synthesised. No isocyanate (-NCO) peak occurred at 2270 cm^{-1}, indicating that the reaction was complete. Two obvious bands appear at 3280 and 1724 cm^{-1} assigned to the stretching vibrations of N–H and C=O

of urethane, respectively, demonstrating the formation of the urethane group (–NHCOO–). The bands at 1624 and 1599 cm^{-1} are ascribed to the stretching vibration of the C=O group beside the pyridine ring and the C-N-C stretching of the pyridine ring in the BIN groups, respectively. The peak at 1536 cm^{-1} should be assigned to the C-N stretching vibration of the urethane groups according to the literature.[24]1H-NMR spectra in **Fig. S2** further confirmed the structure of PEG4000-MDI-BIN.GPCresults indicate that the averagemolecular weight (M_n) anditsdistribution are 1.2×10^4 g mol^{-1} and 1.27, respectively.



Scheme 1. Synthetic route of the polymer PEG4000-MDI-BIN.

pH-sensitive ShapeMemory Effect

The shape fixing and recovery of PEG4000-MDI-BIN is demonstrated in**Fig. 2** and **Movie S1** in the SI. To clearly observe the pH change, the pH indicator bromocresol green was added to the polymer film. First, a stripe of PEG4000-MDI-BIN film was swollen in acid at pH 1.3 and thendeformed to a ring and immersed in base at pH 10 to fix this shape. After 20 minutes, the ring shape was fixed and the colour of the film became blue. Next, the fixed ring was returned to acid at pH 1.3, the shape was gradually recovered to a strip again, and the colour turned to yellow in 60 minutes. Repeating the above procedures demonstrate a cycle of shape fixing and recovery. The experimental temperature was set at 20 ℃. As shown in **Fig.2(a)**, the polymer swells well in acid, especially at pH 1.3, where the swelling ratio (S_r) can reach 176% due to the introduction of the pyridine rings in the BIN groups. In turn, swelling causes shape recovery with a recovery ratio (R_r) of 81%. To confirm the role of BIN groups in this recovery,we replaced the BIN groups with 1,4-butanediol (BDO) to synthesise the polymer PEG4000-MDI-BDO, and found that it did not swelling or exhibit shape recovery in acid, suggesting the dominant role of the BIN groups. When PEG4000-MDI-BIN previously treated in acid was immersed in a solution at pH 10, the shape fixity ratio (F_r) reached up to 83%.

Temperature is well-known to be a key factor in shape memory for thermally triggered shape memory polyurethane. [25] Here, the glass transition temperature (T_g) of PEG4000-MDI-BIN is approximately 20 ℃ based on the DSC results in **Fig. S3** and the DMA curves in **Fig. 3**. To detect whether temperature has an effect on the solution-induced shape memory effect at different pH values, the shape recovery and fixing properties are studied at room temperature (20 ℃) and body temperature (37 ℃) respectively,as shown in **Fig. 2(b)** and **2(c)**.We find that both $F_r$in pH 10 and $R_r$in pH 1.3at 37 ℃ were greater than 90%, higher than those at 20 ℃. As is well known, the deformed shape of thermally induced shape memory polymers cannot be fixed at a temperature higher than the transition temperature, but this polymer demonstrate a higher$F_r$at 37 ℃ abovetransition temperature. Thus the shape memory effect of PEG4000-MDI-BIN can be confirmed to be induced by pH only,not by heat. Therefore, we can conclude that unlike other systems induced by heat, the shape memory function of this system is independent of temperature. This is very important for shape fixation, especially when the polymer is used in smart medical devices.

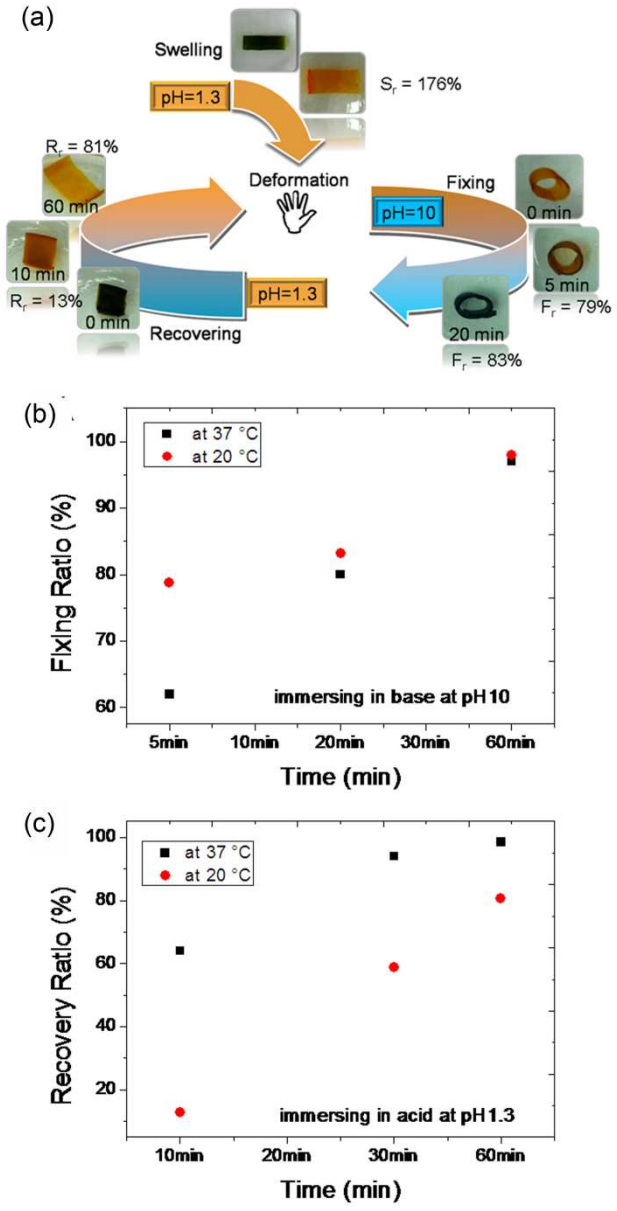
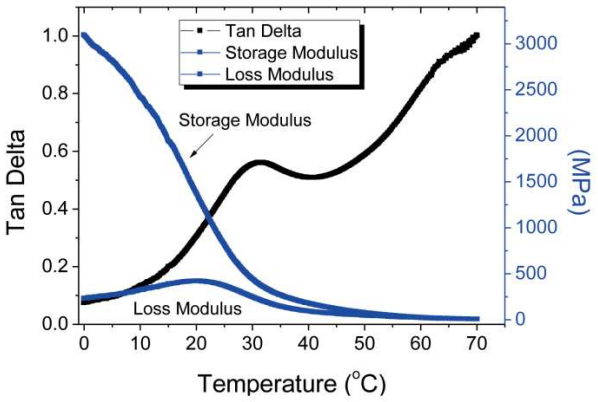


Fig. 2(a) The pH sensitivity of PEG-MDI-BIN was tested by first swelling the polymer in acid, fixing its shape in base and then recovering its shape in acid at 20□.**(b)** Shape fixing ratio in base at pH 10 and **(c)**shape recovery ratio in acid at pH 1.3 for PEG4000-MDI-BIN as

immersion time increased at 20□ and 37□, respectively.



Figu. 3. DMA curves of PEG4000-MDI-BIN.

Mechanism of pH-sensitive

It is well known that pyridine accepts H^+, becoming protonated in acid. The protonated N atom in the polymer causes an increasing of hydrophilia, and H_2O molecules permeate into the polymer, leading to swelling. When in base, the H^+ was neutralised by OH^-, N atom was deprotonated and the hydrophilia of polymer decreased, resulting in the diffusion of H_2O molecules out of the polymer. To confirm whether the protonation and deprotonation of the pyridine ring is a critical factor in determining the pH sensitivity, we performed FT-IR, ^{1}H-NMR and theoretical calculations for PEG4000-MDI-BIN treated at pH 1.3 and pH 10.

PEG4000-MDI-BIN contains two types of hydrogen bonds. One is the hydrogen bonds between the N–H and C=O of urethane groups similar to prior reports, [26]another is that between N-H and the pyridine ring.

In water, the hydrogen bonds are mainly influenced H_2O, as shown in **Fig. S4**in the SI. The hydrogen bond between the N-H and C=O groups has been reported to be weakened by the absorbed water. [27] Some H_2O molecules absorbed in the polyurethane SMP may bridge the gaps between the hydrogen bonded N-H and C=O groups, as shown in **Fig. S4 (a)** in the SI. On the other hand, some absorbed H_2O molecules can form double hydrogen bonds with the hydrogen-bonded C=O groups[27], as shown in **Fig. S4 (b)** and **(c)**. FT-IR spectra of PEG4000-MDI-BIN measured over immersion time in water are showed in**Fig.4(a)**.We find that the band of hydrogen-bonded C=O at 1708 cm^{-1} shifts to 1712 cm^{-1}, indicating that the hydrogen bonded N–H and C=O groups are mainly bridged by H_2O, shown as the (a) type in **Fig. S4**. While no new band are observed in the lower wavenumber range, which proved the (b) and (c) type double hydrogen bonds are not exist. It is also note that the band of all free C=O groups of urethane at 1724 cm^{-1} shifts to1712 cm^{-1}representing hydrogen-bonded C=O, suggesting that the C=O groups are bonded to H_2O molecules.The pyridine ring tends to be protonated by H_2O as shown in **Fig. S4 (d)**, or linked via hydrogen bonds with bridging H_2O molecules as shown in **Fig.S4 (e)** and **(f)** in the SI. [24]In **Fig. 4(a)**the vibration bands of the pyridine ring at 1598 cm^{-1}shift to higher frequencies of 1602 cm^{-1}, which indicates H_2O affect the hydrogen bondbetween N-H and the pyridine ring as (d), (e) and (f) types shown in **Fig. S4.**

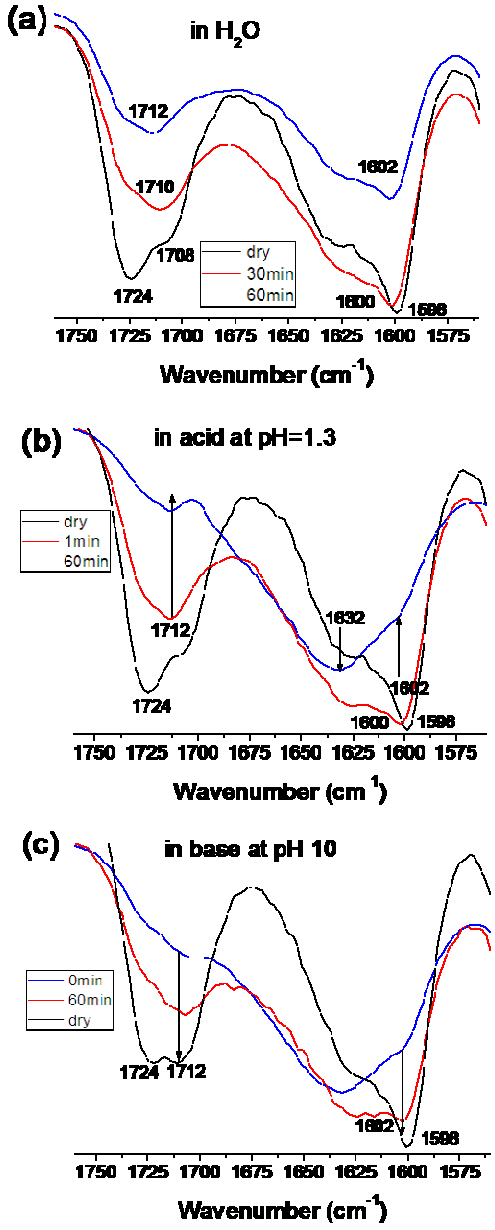


Fig.4FTIR spectra of PEG4000-MDI-BIN**(a)** from the dry state to immersion in H_2O for 30 and 60 min; **(b)**in solution at pH1.3 for 60 minutes;**(c)**continuously in solution at pH10 for 60 minutes and then dried in air**.**

Under acidic condition, not only the H_2O affect the hydrogen bodings as above, but also the effects of H^+ should be considered, as shown in **Fig. S5**in the SI.The N atom of the pyridine ring has a high tendency to accept free H^+. The pyridine ring can be easily protonated by the H^+ in acid. Comparing the FT-IR spectra of polymer immersed in H_2O and acid at pH1.3 for 60 minutes, as shown in **Fig. 4(a)** and **4(b)**, the vibration peak of the pyridine ring at 1598 cm^{-1} disappeared in acid, while that peak remaining present and only shifting to 1602 cm^{-1} in H_2O. This may demonstrated that hydrogen bond between N-H and pyridine ring was preferentially destroyed by protonation of pyridine in acidas

shown in Fig.S5(h),not as the (d), (e) and (f) types shown in Fig.S4.The theoretical calculation results in **Fig. 5** showed that the molecular energy of H^+ bonded to O atom in C=O is 58KJ mol^{-1} higher than that of H^+ bonded to Natom in the pyridine ring. This result demonstrates that in acid, the H^+ prefers to bond with the N atom in the pyridine ring by protonation rather than by bonding with the O atom in C=O, which corresponding to the above IR results.Thus, there is only one type hydrogen bond as Fig.S4(a)showedin the acid condition.

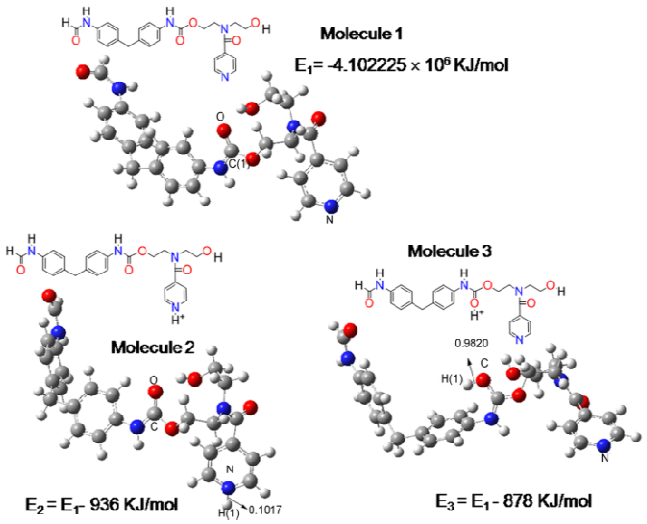


Fig. 5 The structure of **Molecule 1**designed by computer simulation, with the proton bonding to the N atom of pyridine ring in Molecule 1 to form**molecule 2**, and the proton bonding to the oxygen of C=O in molecule 1 to form**molecule 3**, **E**represent the molecular energy.

Under basic condition, the H^+ of the NH^+ group in the pyridine ring is neutralised, and the FT-IR spectra of this procedure are recorded in **Fig.4(c)**. In contrast to the FT-IR spectra in Fig.4(b) and 4(c), the band approximately 1600 cm^{-1} assigned to the C-N-C stretching of pyridine ring gradually disappeared with immersion timeincreasingin acid, then gradually appearing again upon immersion in base at pH 10, and even reverting to its original state upon the complete evaporation of water. It showed a reversible protonated and disprotonated procedure. The hydrogen bond between N-H and the pyridine ring can be associated and disassociated by changing the pH value of the external environment.

The synchronous contour plots varied over time for the spectral region from 1780 cm^{-1} to 1560 cm^{-1} in **Fig.6(a)** also demonstrate the same tendency. The peaks at the diagonal demonstrate that the corresponding groups are affected by the stimulus. For example, in diagonal the peak at 1600 cm^{-1}, assigned to the C-N-C stretching of the pyridine ring, is not obvious in the first 5 minutes but is obvious after 20 minutes in acid. Then, this peak gradually disappears as the immersion time increasing in base.

The structural transformation of the polymer in acid and base is further studied by ^{1}H-NMR as shownin **Fig.6(b)**. In Fig. 6 (b), the chemical shifts at 8.48 ppm (**b**) and 7.32ppm (**c**) are attributed to the protons of pyridine. After immersed in solution at pH1.3, these two peaks shift to higher ppm values at 8.67 ppm (**b'**) and 7.70 ppm (**c'**) due to the protonation of pyridine rings. Then the sample was immersed in solution at pH10, the chemical shifts attributed to the protons of pyridine ring back to the initial position at 8.48 ppm (**b**) and 7.34 ppm (**c**) again.

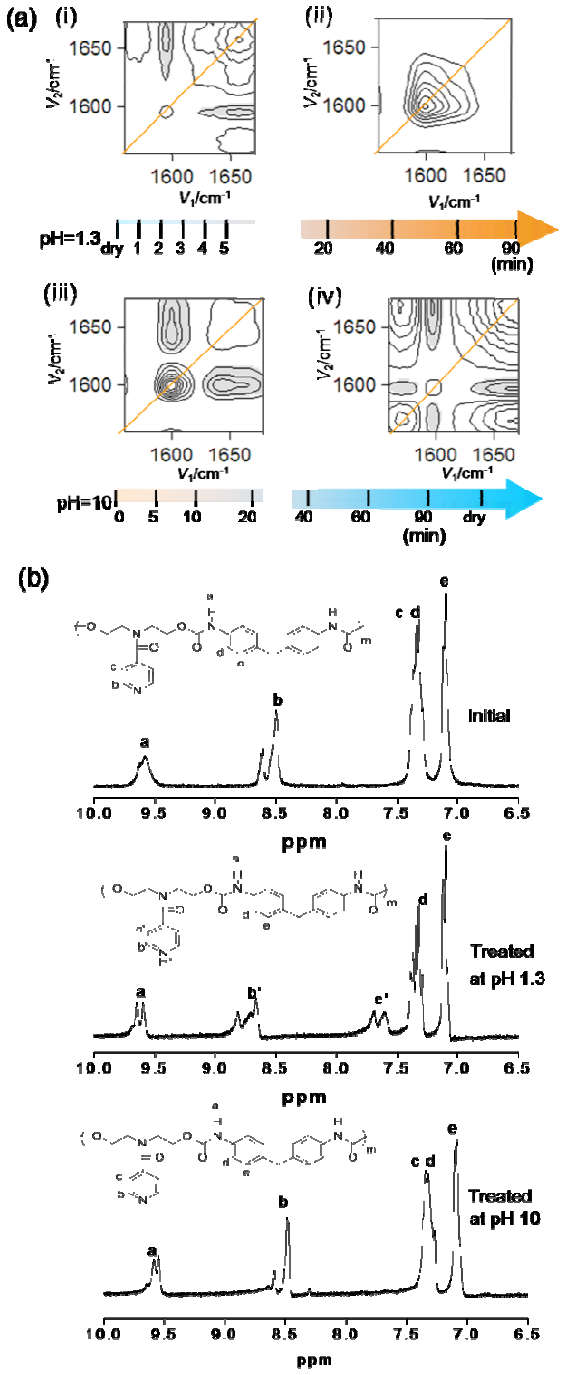


Fig.6(a) The 2D correlation FTIR spectra of synchronous correlation of PEG4000-MDI-BIN immersed in acid atpH1.3 from dry to 5 min(i), from 20 min to 90 min(ii), and then in base at pH10 from 0 min to 20 min(iii), from 40 min to 90 min and dried for 2h(iv).**(b)**^{1}H-NMR spectra of PEG4000-MDI-BIN untreated and treated in solutions at pH 1.3 and pH 10, respectively.

Above results further confirms that the hydrogen bonds between urethane and pyridine rings are formed in base and

broken in acid, while those between urethane groups are not affected in acid or in base, as expected in **Fig. 1**. Thus, in the shape memory procedure, the pyridine part sensitive to H^+ can be used as a switch to shift the polymer shape, while the hydrogen bonded urethane segments insensitive to H^+ can be used as a fixed domain to hold the original shape. Simply adjusting the pH value of the environment leads to a pH-induced shape memory effect for this polymer through the association and dissociation of the hydrogen bond interactions involving pyridine rings.

Drug Delivery

This switching effect can also be used to control drug release. The disturbed hydrogen bond interactions of pyridine rings in acid cause swelling to allow drug release, while hydrogen bond formation leads to de-swelling, suppressing drug release.

It is essential that a material used for drug delivery should be biocompatibility. Osteoblasts cells are culturedon PEG4000-MDI-BIN in pH 7.4 for 5 daysto evaluate the biocompatibilitybased on Alamar Blue assay. From **Fig.7(a)** we can findthat the cell viabilityis over 90%with no significant difference during the 5 daysof culture, indicating the non-cytotoxicity of polymer.To further confirmthe result of Alamar Blue assay, the morphology of osteoblasts is observed by fluorescence microscopy as shown in **Fig.7(b)**. It clearly showed that the osteoblasts grow healthily and attached well on the polymer films. The results suggest that the polymerspossess good biocompatibility, and are potentially suitable for the application of biomaterials.

Green tea polyphenol loaded polymer films are immersed in aqueous solutions at pH 1.2 or pH 7.4 to investigate the effect of pH on the drug release from the polymer matrix. The amount released was measured using a UV-vis spectrophotometer. As shown in **Fig.7(c)**, drug release almost stops in the normal physiological environment at pH 7.4, while release is accelerated in the acid environment. Additionally, the fluorescence intensity measured by fluorescence microscopy remains constant at pH 7.4 but sharply decreases at pH 1.2. The results also demonstrate that this novel highly pH-sensitive polyurethane can be used as a stimulus-responsive drug carrier to reversibly switch drug release on and off. This system is different from other drug delivery systems such as polymer-drug conjugate nanoparticles that irreversibly de-assemble to release drug via the cleavage of pH-sensitive linkages in the polymeric backbone in the acidic microenvironment.[20, 21]

Conclusions

In summary, a highly pH-sensitive polymer was successfully synthesizedby introducing pyridine rings into the backbone of polyurethane. We determined that the pH sensitivity of this material results from the formation of a hydrogen bondinteraction between the N atom of the pyridine ring and the H-N of urethane in neutral or alkaline environments which is broken in acidic environments due to the protonation of the pyridine ring. Consequently, the reversible pH-sensitivity is triggered by simply adjusting the pH value of the environment, which can act as a switch to control the shape memory effect and drug release. Unlike other systems, the shape memory function is only dependent on the pH value of the external environment, independent of temperature. This strategy provides a potent tool for the design of multifunctional materials based on the physiological environment to fulfilthe complex requirements of biomedical applications, including drug delivery and tissue engineering systems.

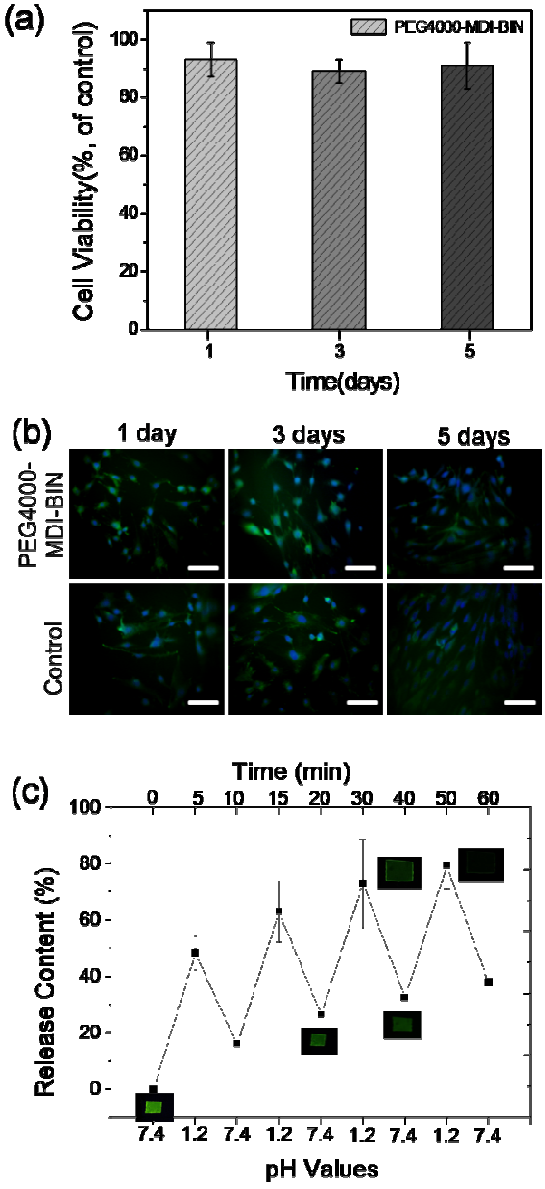


Fig.7(a) Alamar Blue analysis; **(b)**fluorescence microscopy images of osteoblastscultured on PEG4000-MDI-BIN films substrates on day 1, 3, and 5, respectively; blue represent the cell nucleus stained by DIPA and green represent the cytoplasm stained by Rhodamine; all the scale bars represent 50μm **(c)**The release profile of Green Tea Polyphenol releasing from PEG4000-MDI-BIN films immersed in solutions at pH1.2 and pH7.4. The inserts are thefluorescence microscopic images of the films.

Acknowledgments

This work was partially supported by the National Basic Research Program of China (973 Program, 2012CB933600), the National Natural Science Foundation of China (Nos.51173150,51373138), the National Key Project of Scientific and Technical Supporting Programs Funded by MSTC (2012BAI17B06), Research Fund for the Doctoral Program of Higher Education of China (20120184110029) and andConstruction Program for Innovative ResearchTeam ofUniversityin Sichuan Province(14TD0050).

Notes and references

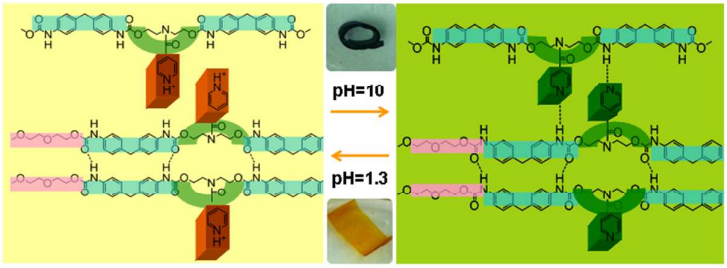
*Corresponding authors

[a]*Key Laboratory of Advanced Technologies of Materials, Ministry of Education, School of Materials Science and Engineering, Southwest Jiaotong University, Chengdu,, P. R. China. Fax: 86-28-87634649; Tel: 86-28-87634068; E-mail: shaobingzhou@swjtu.cn; shaobingzhou@hotmail.com*

[b]*Department of Chemistry and Materials Science, Sichuan Normal University,Chengdu, , P. R. China*

† Electronic Supplementary Information (ESI) available: FT-IR (Fig.S1), ^{1}H NMR (Fig. S2), DSC (Fig. S3). The effects of H_2O (Fig. S4) and H^+ (Fig. S5) on the hydrogen bond between the N–H and C=O of urethane groups and between N-H and the pyridine ring in the polymer.A video of the shape fixity and recovery procedure in acidic and alkaline conditions(Movie S1). See DOI: 10.1039/b000000x/

1 C. D. H.Alarcon, S.Pennadam and C.Alexander, *Chem. Soc. Rev.*,2005, **34**, 276.
2 F.Liu and M. W.Urban, *Prog. Polym. Sci.*, 2010, **35**, 3.
3 J.Hoffmann, M.Plotner, D.Kuckling and W. J.Fischer, *Sens Actuators*, 1999, **A77**, 139.
4 R.Langer and D. A. Tirrell, *Nature*,2004, **428**, 487.
5 A. K.Bajpai, S. K.Shukla, S.Bhanu and S.Kankane, *Prog. Polym. Sci.*, 2008, **33**,1088.
6 M.Behl, M. Y.Razzaq andA. Lendlein, *Adv. Mater.*, 2010, **22**, 3388.
7 X.Zheng, S.Zhou, X.Li and J.Weng, *Biomaterials*, 2006, **27**, 4288
8 P.Miaudet, A.Derré, M.Maugey, C.Zakri, P. M.Piccione, R.Inoubli and P.Poulin,*Science*, 2007,**318**,1294.
9 A.Lendlein and S.Kelch, *Angew. Chem. Int. Ed.*, 2002, **41**, 2034.
10 A.Lendlein, H.Jiang,O. Jünger and R. Langer, *Nature*, 2005, **434**, 879.
11 T.Maeda,J. Mamiya, T.Ikeda and Y.Yu, *Angew. Chem. Int. Ed.*, 2007, **46**, 506.
12 J.Cho, Y.Jung, B.Chun and Y.Chung, *J. Appl. Polym. Sci.*, 2004, **92**, 2812.
13 J.Mendez, P. K.Annamalai, S. J.Eichhorn, R.Rusli, S. J.Rowan, E. J.Foster and C.Weder, *Macromolecules*, 2011, **44**, 6827.
14 X.Yu, S.Zhou, X.Zheng, T.Guo, Y.Xiao and B.Song, *Nanotechnology*, 2009, **20**, 235702.
15 J. R.Kumpfer and S. J. Rowan, *J. Am. Chem. Soc.*, 2011, **133**, 12866.
16 E.Fleigea, M. A.Quadirb and R.Haag, *Adv. Drug. Del. Rev.*, 2012, **64**, 866.
17 X. J. Han, Z. Q. Dong, M. M Fan, Y. Liu, J. H.Li,Y. F. Wang, Q. J. Yuan, B. J. Li and S. Zhang. *Macromol. Rapid Commun.,* 2012, **33**, 1055.
18 J.Li, J. A.Viveros, M. H.Wrue and M.Anthamatten,*Adv. Mater.*, 2007, **19**, 2851; G.Liu, X.Ding, Y.Cao, Z.Zheng and Y.Peng, *Macromolecules,* 2004, **37**, 2228.
19 A.Lendlein and R.Langer, *Science*, 2002, **296**, 1673.
20 S.Aryal, M.J.Hu and L.Zhang, *ACS Nano.*, 2010, **4**, 251.
21 R.Tomlinson,J.Heller, S.Brocchini and R. Duncan, *Biconjugate Chem.*, 2003,**14**, 1096.
22 T.Fujii and A.Shimichi, [P] JP 08337560, 1996.
23 M. J.Frisch, G. W.Trucks, H. B.Schlegel, G. E.Scuseria, M. A.Robb, J. A.Cheeseman, G.Scalmani, V.Barone, B. Mennucci, G. A.Petersson, H.Nakatsuji, M.Caricato, X.Li, H. P.Hratchian, A.F.Izmaylov, J.Bloino, G.Zheng, J. L.Sonnenberg, M.Hada, M.Ehara, K.Toyota, R.Fukuda, J.Hasegawa, M.Ishida, A.Nakajima, Y.Honda, O.Kitao, H.Nakai, T.Vreven, J. A.Montgomery, J. E.Peralta, F.Ogliaro, M.Bearpark, J. J.Heyd, E.Brothers, K. N.Kudin, V. N.Staroverov, R. Kobayashi, J.Normand, K.Raghavachari, A.Rendell, J. C.Burant, S. S.Iyengar, J.Tomasi, M.Cossi, N.Rega, J. M.Millam, M.Klene, J. E.Knox, J. B.Cross, V.Bakken, C.Adamo, J.Jaramillo, R.Gomperts, R. E.Stratmann, O.Yazyev, A. J.Austin, R.Cammi, C.Pomelli, J. W.Ochterski, R. L.Martin, K.Morokuma, V. G.Zakrzewski, G. A.Voth, P.Salvador, J. J.Dannenberg, S.Dapprich, A. D.Daniels, O.Farkas, J. B.Foresman, J. V.Ortiz, J.Cioslowski, D. J.Fox, Gaussian 09, Revision A.02, Gaussian, Inc., Wallingford, CT, 2009.
24 S.Chen, J. Hu, C.Yuen and L.Chan, *Polym. Int.*, 2010, **59**, 529.
25 W. M.Huang,B. Yang, Y.Zhao and Z.Ding, *J. Mater. Chem.*, 2010, **20**, 3367.
26 B. C.Chun, T. K.Cho, M. H.Chong and Y.C.Chung, *J. Mater. Sci.*, 2007, **42**, 9045
27 B.Yang, W. M.Huang, C.Li and L.Li, *Polymer*, 2006, **47**, 1348.



A hydrogen bonding interaction is formed and broken between the N of pyridine ring and H-N of urethane in PEG4000-MDI-BIN polymer due to the deprotonation and protonation of pyridine rings by simply changing the pH value of the external environment, and can reversibly switch both the shape memory and drug release.