# Supporting Information

## Experimental section:

Figure S1(a), (b), (c), and (d) give the FT-IR spectrum of mPEG, mPEG-Br, mPEG-P*t*BMA, and mPEG-PMAA, respectively. Compared with curves (a) and (b), the disappearance of the absorption peak at 3460 $cm^{-1}$ and the appearance of the peak at 1730 $cm^{-1}$ in Figure S1(c) and (d) indicate that the –OH groups of mPEG changed to ester groups. According to curve (c), the strong peaks at 1724 $cm^{-1}$ (C=O stretching of ester) and 2978 $cm^{-1}$ (C-H stretching of $-CH_3$) suggest that the polymerization was successful. The wide, strong peaks at 3000–3600 $cm^{-1}$ correspond to –COOH groups.

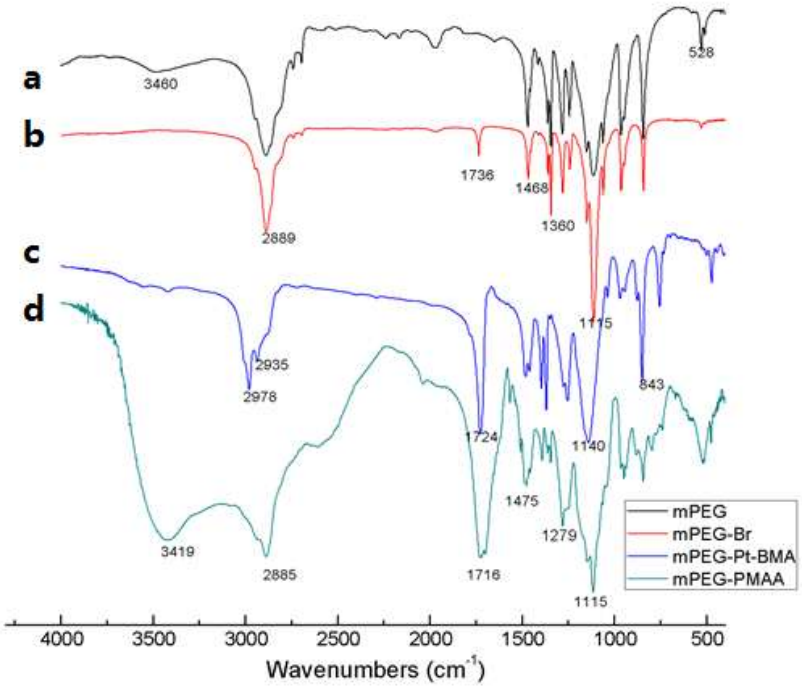


**Figure S1. FT-IR spectra of products during each step of synthesis**

We further confirmed the structure of mPEG-PMAA by the 1H NMR spectrum shown in Figure S2. Using the ratio of the peak area of the proton from the PEG segments (OCH2-CH2, assigned to d) to that of the proton of a (attributed to CH3) and d (attributed to CH2) from the PMAA segments, we calculated the molecular weight to be 9700 Da.

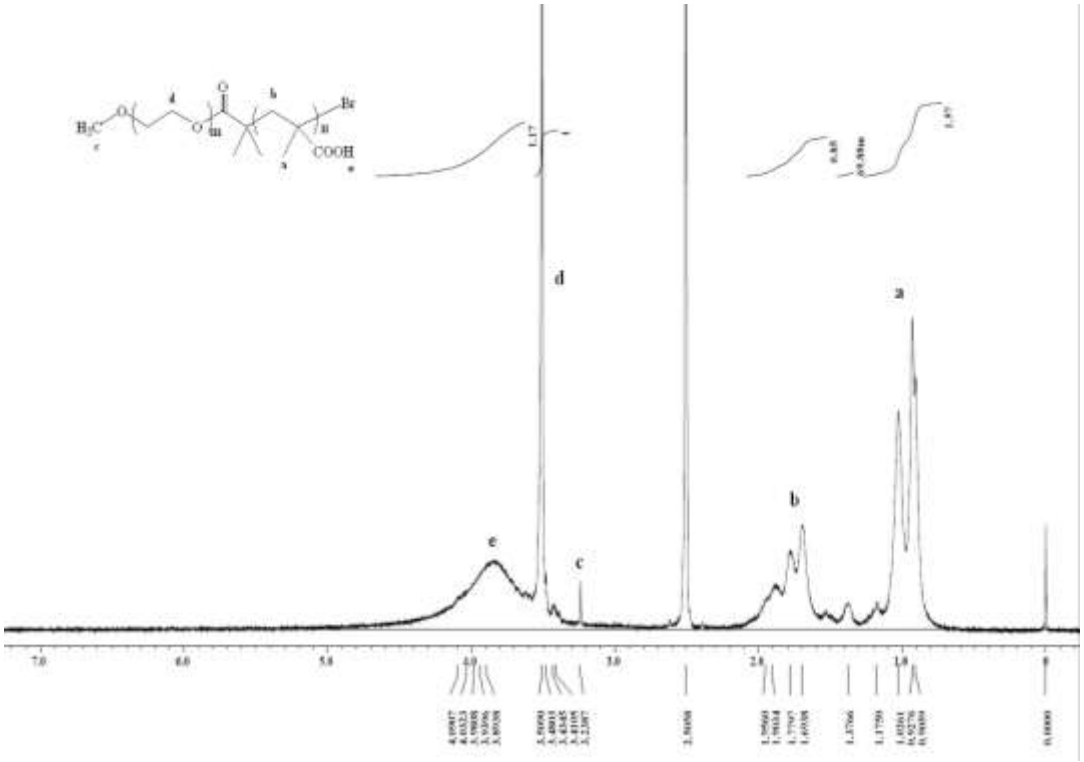


**Figure S2. $^{1}$H NMR spectrum of mPEG-PMAA**

**Titration of mPEG-PMAA**

The total number of carboxyl groups on the PMAA segment and the apparent charges of mPEG-PMAA at different pH values were determined by titrating mPEG-PMAA, as shown in Figure S3. Because of the poor solubility of mPEG-PMAA in pure water, we used back-titration procedure. To summarize, we

dissolved 40.6 mg mPEG-*b*-PMAA in a 0.052 mol/L NaOH solution and then slowly added the titrant 0.127 mol/L HCl solution. Using the titration test and the $M_n$ of PEG-PMAA, the ionization degree of mPEG-PMAA can be calculated, as shown in Figure S4.

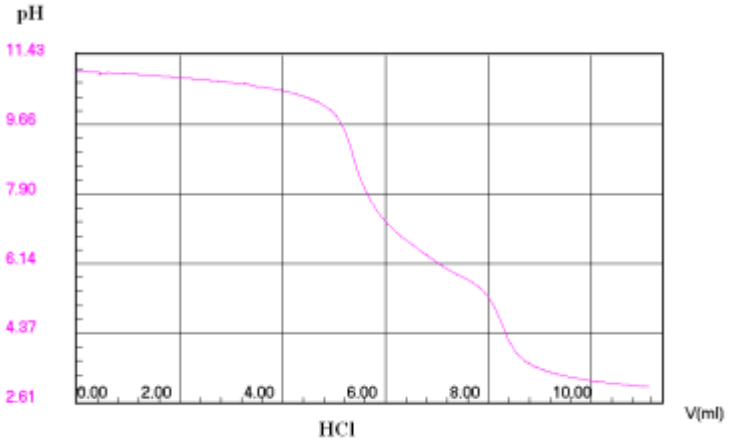


**Figure S3. Titration of mPEG-PMAA**

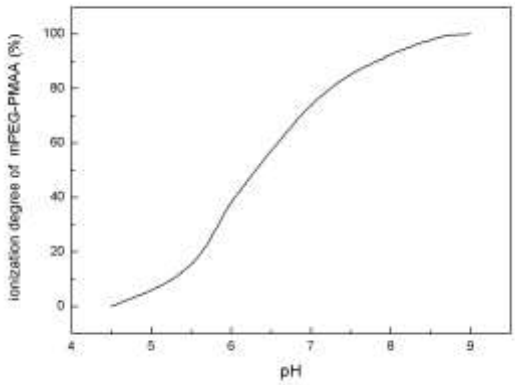


**Figure S4. Ionization degree of mPEG-PMAA**

We took fluorescence spectra an excitation wavelength of 280 nm and an emission wavelength range of 280–400 nm at room temperature. As figure S5 shows, all of the peak points of each maximum fluorescence intensity of the free lysozyme solution at different pH values are near ~340 nm. In the mixture of polymer and lysozyme, the

fluorescence spectrum shows distinct blue-shifts at pH 5 (~330 nm) and pH 6 (~336 nm), but not at pH 7, 8, or 9.

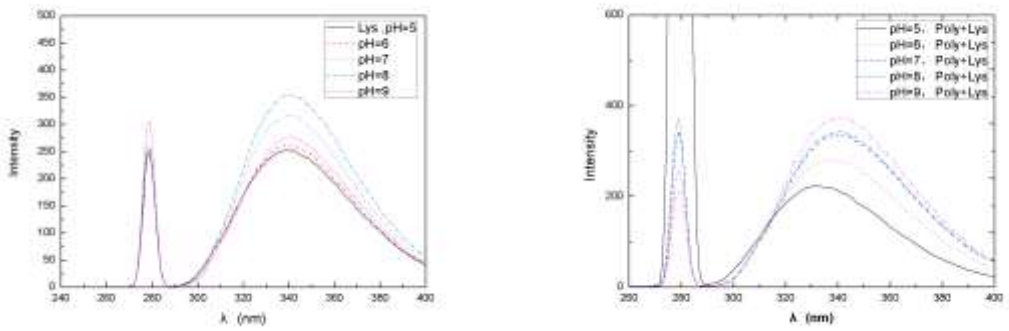


**Figure S5. Fluorescence spectra of polymer/lysozyme mixtures: (a) Lysozyme solution (0.08mg/mL); (b) mixture of polymer (1mg/mL) and lysozyme (0.08mg/mL), molar ratio is 18 in pH range from 5 to 9.**

**Molecular dynamics simulation section:**

**Determining the charge distribution of lysozyme**

To determine the charge distributions of lysozyme at different pH values, we calculated the internal pKa values of the titratable amino acids using the H++ web tool (http://biophysics.cs.vt.edu). For lysine, once the pKa value is higher than the target pH value, the protonated state is selected; otherwise, the neutral state is selected. For aspartate and glutamate, if the pKa value is higher than the target pH value, the protonated state is selected (neutral state); otherwise, the unprotonated state is selected. For histine, the proton can be either on ND1, on NE2, or on both, which is also

determined by the difference between pKa and the target pH value. The detailed input file of lysozyme at pH 5 is given in the Appendix.

**Determining the charge and geometry of mPEG-b-PMAA**

The charge and structure of $–CH_2$-$CH_2$-O, $–CH_2$-C(COO)($CH_3$)-O–, and –C(Br)($CH_3$)-C(COO)$CH_3$)-O– are calculated by optimizing geometry using Gaussian 03 with DFT theory and 6-31+g(d,p) base. The output of the geometry is accepted and fixed in the input file of Gromacs. The charge distribution of the titratable group of MAA, i.e., the COOH group, is predicted according to the experimental data shown in Figure S4. The ionization degree of COOH is affected by pH, e.g., the charge of O changed from −0.2793 to −0.793 as the pH changed from 5 to 9. The charges of other groups or atom are sourced from unmodified data from the Gaussian 03 calculation. The input file of PEG-MMA at pH 9.0 for the MD simulation is given in the Appendix.

**Simulation protocol to achieve equilibrium conformation**

Lysozyme was placed in the center of a simulation box with dimensions of 17nm × 17nm × 17nm. Ten mPEG-b-PMAA molecules were then randomly placed into the simulation box with different conformations. Finally, 156660 water molecules were filled into the simulation box to achieve a water density of 0.98g/l, and ions were added to neutralize system. The system containing lysozyme, mPEG-b-PMAA, water, and ions minimized its energy using 1000 steps of steepest-descent minimization to converge to a value lower than 500 kJ $mol^{-1}$ $nm^{-1}$ at 300 K. If the procedure failed, we used a combined conjugate gradient algorithm, which performed one steepest-descent

step for every 100 conjugate gradient energy steps until the energy converged. We then performed a 1 ns position-restrained MD simulation by fixing the protein and the mPEG-b-PMAA molecules to achieve solvent equilibrium. The simulated annealing procedure was used to optimize the conformation of the lysozyme-mPEG-*b*-PMAA complex, and a leapfrog algorithm was used to integrate the Newtonian equations of motion. An example of the procedure is increasing 300 to 400 K linearly within 1.0 ns and equilibrating at 400 K for 1.0 ns, increasing the temperature to 450 K linearly over an additional 0.5 ns, equilibrating at 450 K for 1.0 ns, and then linearly decreasing the temperature symmetrically and stabilizing at 300 K for an additional 10 ns. Finally, we conducted an additional 10 ns MD simulation at 300 K for equilibrium simulation. This method was used in our previous study (Yang et al., Biochemistry, 2011, 50, 2585).

In order to avoid illusory results, we performed three independent simulations with each condition. In other words, different initial conformations, in which mPEG-b-PMAA and the solvent were randomly distributed around lysozyme, were used at each pH value.

**Interactions between the active site and the polymer**

In order to investigate the interactions between the active site of lysozyme and mPEG-b-PMAA at different pH values, we calculated the minimal dynamic distance between the active site of lysozyme and mPEG-b-PMAA as function of time. The results are shown in Figure S6.

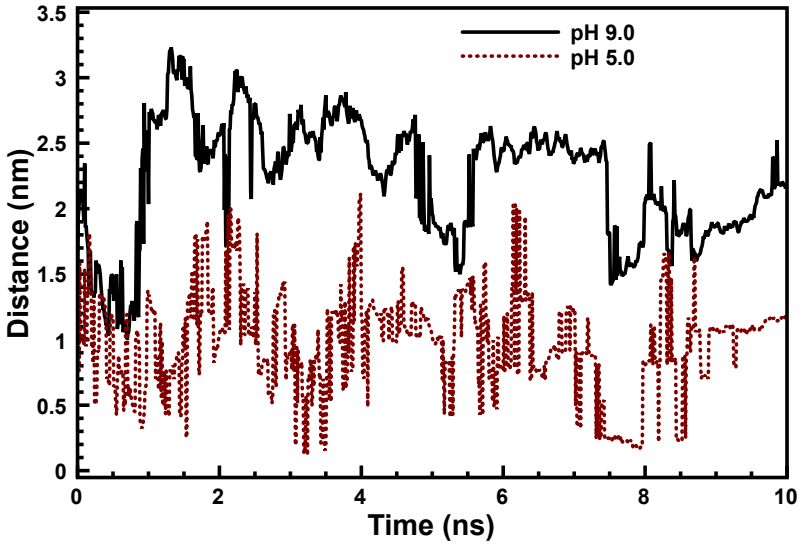


Figure S6. The minimum distance between the active site and mPEG-b-PMAA at different pH values.

The starting conformation is the same and the minimal distance between the active site and mPEG-b-PMAA is 1.5 nm.

The interaction between mPEG-b-PMAA and the active site of lysozyme differs as the pH varies. At a high pH such as pH = 9.0, the repulsive force between mPEG-b-PMAA and lysozyme results in the departure of the polymer to the active site of lysozyme, with an average distance of 2.1 nm. At a low pH such as pH = 5.0, however, the attractive force between mPEG-b-PMAA and lysozyme results in the association of the polymer and the active site of lysozyme, with average distance of 0.82 nm, indicating that the active site becomes shielded at pH 5.0. This behavior is consistent with the results shown in Figure 3 and Figure 6.