A New Comonomer Design for Enhancing pH-Triggered LCST Shift of Thermosensitive Polymers

Hu Zhang, Thomas Marmin, Étienne Cuierrier, Armand Soldera, Yves Dory^{*}, Yue Zhao^{*} Département de chimie, Université de Sherbrooke, Sherbrooke, Québec, J1K 2R1, Canada

1. Synthesis of the comonomer



t-Butyl 2-(hydroxymethyl)acrylate 3. Water (30 mL), paraformaldehyde (3.03 g, 100 mmol) then MeCN (50 mL) were successively added to DABCO (5.6 g, 50 mmol) in a 250 mL round-bottom flask and with stirring. The resulting mixture was heated at 80 °C until the reaction mixture became homogeneous. *t*-Butyl acrylate 2 (7.3 mL, 6.4 g, 50 mmol) was then added all at once. The solution was heated at 80 °C for 2.5 h and left to cool down to room temperature. The reaction mixture was extracted twice with DCM (2 × 100 mL). The combined DCM layer was washed with 1 N aqueous HCl (100 mL) followed by brine (50 mL); it was dried (MgSO₄) and the solvent was removed under reduced pressure. The crude oil was purified by flash chromatography (hexane:EtOAc 8:2) to yield the title product as a colorless liquid (5.9 g, 75%). ¹H-NMR (300 MHz, CDCl₃): $\delta = 1.45$ (s, 9H), 2.90 (t, *J* = 6.0 Hz, 1H), 4.25 (d, *J* = 6.0 Hz, 2H), 5.75 (s, 1H), 6.16 (s, 1H). ¹³C-NMR (75 MHz, CDCl₃): $\delta = 28.00$, 62.30, 81.20, 124.00, 140.90,

165.60. **IR**: 3400, 2975, 2931, 1703, 1639, 1460, 1370, 1314, 1283, 1260, 1145, 1050, 945, 846, 820, 760 cm⁻¹. **HRMS** (EI, 70eV): calcd for C₇H₁₁O₃ : 143.0708; found :143.0630 [M⁺ - CH₃].

<u>t-Butyl 2-(bromomethyl)acrylate 4</u>. PBr₃ (1.4 mL, 3.97 g, 14.66 mmol) was added, with stirring, to a cold (-30 °C) solution of alcohol **3** (5.8 g, 36.70 mmol) in anhydrous Et₂O (40 mL). The mixture left to warm up to 0 °C over a 3 h period, then cooled again to -10 °C. Water (2.5 mL) was added and the resulting mixture was allowed to reach room temperature. The organic layer was collected, dried (MgSO₄.) and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (hexane:EtOAc 5:1) to afford the title product (6.1 g, 75 %) as a colorless liquid.

¹**H-NMR** (300 MHz, CDCl₃): $\delta = 1.45$ (s, 9H), 4.07 (d, J = 1.0 Hz, 2H), 5.78 (d, J = 1.0 Hz, 1H), 6.15 (d, J = 1.0 Hz, 1H). ¹³**C-NMR** (75 MHz, CDCl₃): $\delta = 27.90$, 29.80, 81.70, 127.80, 138.60, 163.90. **IR**: 2970, 2930, 1710, 1635, 1390, 1370, 1340, 1320, 1226, 1148, 950, 845, 810, 720 cm⁻¹.

<u>*t*-Butyl 4-(3-(*t*-butoxy)-2-methylidene-3-oxopropoxy)benzoate 1</u>. Potassium carbonate (3.50 g, 51.60 mmol) and allylic bromide 4 (5.70 g, 25.80 mmol) were added to a solution of *t*-butyl *p*-hydroxybenzoate 5 (5.00 g, 25.80 mmol) in acetone (50 mL). The mixture was refluxed for 3h with stirring. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (hexane:EtOAc 9:1) to give the title compound as a white solid (7.42 g, 86%).

¹**H-NMR** (300 MHz, CDCl₃): $\delta = 1.54$ (s, 9H), 1.60 (s, 9H), 4.78 (s, 2H), 5.91 (d, J = 1.3 Hz, 1H), 6.33 (d, J = 1.3 Hz, 1H), 6.95 (d, J = 9.0 Hz, 2H), 7.96 (d, J = 9.0 Hz, 2H). ¹³**C-NMR** (75 MHz, CDCl₃): $\delta = 28.09$, 28.26, 66.27, 80.57, 81.48, 114.17, 124.87, 125.52, 131.39, 136.88, 161.72, 164.58, 165.52. **HRMS** (ESI-Q-Tof): calcd for [MNa⁺]: 357.1672; found: 357.1664.

<u>4-((2-Carboxyallyl)oxy)benzoic acid CBA</u>. A solution of diester 1 (1.00 g, 2.99 mmol) in a mixture of TFA and DCM (1:1, 18 mL) was stirred at room temperature for 2 h. The solvent was removed under reduced pressure 3 times after addition of some toluene each time. The residue was purified by flash chromatography (CH₂Cl₂:MeOH 95:5) to give the title compound as a white solid (651 mg, 98%).

2. ¹H NMR spectra



Fig.S1 The ¹H NMR spectrum of synthesized CBA monomer in d_6 -DMSO.



Fig.S2 The ¹H NMR spectra of synthesized copolymers (P1-P5) in d_6 -DMSO.

3. Computational details

All the calculations were performed using the Gaussian09 environment package.^{S1} All the calculations were carried out using DFT approach with the M05-2X functional with the 6-31+g(d,p) basis set. This functional is recognized to represent adequately hydrogen bonding.^{S2} The minimum of energy is free from any negative frequencies. Six water molecules were placed around each carboxylic acid moiety, in order to maximize the hydrogen bonding. The hydration energy was calculated from the difference between the comonomer/water complex, with the comonomer and six water molecules. The electrostatic potential (ESP) surfaces were calculated and mapped on electronic density. The maximum value (in kJ/mol) of a position was considered. To calculate the Gibbs free energy of solvation in water and n-octanol for logP, the SMD solvation model^{S3} was used. Frequency calculations made by Gaussian09's used the default temperature of the package (298.15 K). LogP were calculated from the following equation (T=298.15K):

 $LogP = \frac{(\Delta G_s - \Delta G_{n-octanol})}{2.303RT}$

From this equation, we can observe that a more hydrophilic molecule (highly negative ΔG_s) will lead to a lower value of logP and vice versa. As mentioned in the paper, The calculated values of LogP for the comonomer CBA as well as the two reference molecules MAA and BA do not agree quantitatively with the experimental data. They are all lower than experimental ones, indicating that a possible error comes from an overestimation of ΔG_s or underestimation of $\Delta G_{n-octanol}$.

4. Figures of the hydrogen-bonded molecules (figure realised with CYLview^{S4})





5. pKa analysis and results for the monomer, methacrylic acid and benzoic acid

For pKa calculation, the same equations and thermodynamic cycle as Liptak and Shields were applied [Liptak, M.D.; Shields G.C. *J. Am. Chem. Soc.* **2001**, *123*, 7314-7319]. The thermodynamic cycle is:

$$AH_{gas} \xrightarrow{\Delta G_{gas}} A^{-}_{gas} + H^{+}_{Gas}$$

$$\uparrow -\Delta G_{s}(AH) \qquad \qquad \downarrow \Delta G_{s}(A^{-}) \qquad \qquad \downarrow \Delta G_{s}(H^{+})$$

$$AH_{aq} \xrightarrow{\Delta G_{aq}} A^{-}_{aq} + H^{+}_{aq}$$

Figure S3: Thermodynamic cycle for pKa calculation

pKa can be thus calculated from:

$$pKa = \frac{\Delta G_{aq}}{2.303RT}$$
$$\Delta G_{aq} = \Delta G_{gas} + \Delta \Delta G_s$$
$$\Delta \Delta G_s = \Delta G_s (H^+) + \Delta G_s (A^-) - \Delta G_s (AH)$$

The values of $G(H^+_{gas})$ and $\Delta G_s(H^+)$ are empirical: $G(H^+_{gas})$ = -26.28 kJ/mol and $\Delta G_s(H^+)$ = -1106.13 kJ/mol. Since ΔG_s is a reference state of 1M, and ΔG_{gas} is at 1 atm, to convert ΔG_{gas} from 1atm (24.46 L and 298.15 K) to 1M :

$$\Delta G_{gas}(1M) = \Delta G_{gas}(1atm) + RT \ln(24.46)$$

The global equation for pKa is :

$$pKa = \frac{\left[G(A^{-}_{gas}) - G(AH_{gas}) + \Delta G_{s}(A^{-}) - \Delta G_{s}(AH) - 1124.5\right]}{5.7086}$$

	Monomer (MA)	Monomer (BA)	Methacrylic Acid	Benzoic Acid
Calculated pKa	1) 5.56	1) 7.05	6.68	6.13
	2) 5.90	2) 7.38		
Experimental pKa		4.6*	4.65	4.19

* Para-oxy benzoic acid

Table S1: pKa values

The calculated values of pKa are overestimated by about 2 units. However, the calculation of precise pKa values is not straightforward, since an error of 4.18 kJ/mol in the calculations leads to an error of 0.73 pKa units. A stronger basis set would potentially address this issue, but calculations are very time expensive. The presence of anion implies the use of diffuse functions. However, qualitatively results lead to interesting observations. It is important to note that ionizing the monomer a second time does not significantly increase the pKa (about 0.34), so at a pH of 7, the monomer should have both position ionized for the majority of molecules. Thus, for logP, ESP surfaces and hydrogen-bonding calculation, only the dianion was considered.

References

(S1) Frisch, M. J.; Trucks, G. W.; Schlegel, Hb.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery Jr, J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; et al. Gaussian 03, Revision C. 02; Gaussian. *Inc Wallingford CT* 2004, *4*.

(S2) Zhao, Y.; Schultz, N. E.; Truhlar, D. G. J. Chem. Theory Comput. 2006, 2 (2), 364–382.

(S3) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* 2009, **113** (18), 6378–6396.

(S4) CYLview, 1.0b; Legault, C. Y., Université de Sherbrooke, Québec, Montreal, Canada, 2009 ; (http://www.cylview.org).