Supporting Information

Synthesis and pH-dependent hydrolysis profiles of mono- and dialkyl substituted maleamic acids

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Fig. S1 ¹H NMR spectra of the reaction of n-butyl amine to 2, 3-dimethylmaleic anhydride with various solvents and basic catalysts. ..................................................................................................................................................................2
Fig. S2 ¹H NMR spectra of the reaction of n-butyl amine to 2, 3-dimethylmaleic anhydride with various TEA amounts. ....2
Scheme S1 Synthesis of compounds M1, M2-α/β, and M3 ..........................................................................................................................................................................................3
Fig. S3 ¹H NMR and ¹³C NMR spectra of M1. .................................................................................................................................................................................................3
Fig. S4 ESI-MS spectrum of M1. ........................................................................................................................................................................................................4
Fig. S5 ¹H NMR and ¹³C NMR spectra of M2-33/67 ..........................................................................................................................................................................................4
Fig. S6 ESI-MS spectrum of M2-33/67 ..................................................................................................................................................................................................5
Fig. S7 ¹H NMR and ¹³C NMR spectra of M2-94/6 ..........................................................................................................................................................................................5
Fig. S8 ESI-MS spectrum of M2-94/6 ..................................................................................................................................................................................................6
Fig. S9 ¹H NMR and ¹³C NMR spectra of M3 ..................................................................................................................................................................................................6
Fig. S10 ESI-MS spectrum of M3 ........................................................................................................................................................................................................7
Fig. S11 ¹H NMR spectra of M1 monitored during the hydrolysis process in phosphate buffer (PB) solution (pH 5.5) .......7
Fig. S12 The detailed ¹H NMR spectra of M2-33/67 monitored during the hydrolysis process in buffered D₂O (pH 5.5)....8
Fig. S13 ¹H NMR spectra of M2-94/6 monitored during the hydrolysis process in buffered D₂O (pH 5.5) ......................8
Fig. S14 MS spectra of the hydrolysis products of compound M2-33/67 in buffered D₂O (pH 5.5) .............................9
Fig. S15 ¹H NMR spectra of M3 monitored during the hydrolysis process in buffered D₂O (pH 5.5) ...........................9
Fig. S16 ¹H NMR spectra of M3 monitored during the hydrolysis process in buffered D₂O (pH 6.5) ..........................9
Fig. S17 The detailed ¹H NMR spectra of M3 monitored during the hydrolysis process in buffered D₂O (pH 7.4) .........10
Fig. S18 MS spectra of the hydrolysis products of compound M3 in buffered D₂O (pH 5.5) .................................11
Fig. S19 MS spectra of the hydrolysis products of compound M3 in buffered D₂O (pH 6.5) .................................11
Fig. S20 MS spectra of the hydrolysis products of compound M3 in buffered D₂O (pH 7.4) .................................12
Fig. S1 $^1$H NMR spectra of the reaction mixture of n-butyl amine and 2,3-dimethylmaleic anhydride under various conditions, 30 °C, 4 h. The percent content of the amidic acid, the imide and the anhydride was estimated by comparing the integrals of peak c, f and b.

Fig. S2 $^1$H NMR spectra of the reaction mixture of n-butyl amine and 2,3-dimethylmaleic anhydride with various TEA equivalents in DMF, 30 °C, 4 h.
Scheme S1 Synthesis of compounds M1, M2-α/β, and M3.

Fig. S3 $^1$H NMR and $^{13}$C NMR spectra of M1.
Fig. S4 ESI-MS spectrum of M1.

Fig. S5 $^1$H NMR and $^{13}$C NMR spectra of M2-33/67.
Fig. S6 ESI-MS spectrum of M2-33/67.

Fig. S7 $^1$H NMR and $^{13}$C NMR spectra of M2-94/6.
Fig. S8 ESI-MS spectrum of M2-94/6.

Fig. S9 $^1$H NMR and $^{13}$C NMR spectra of M3.
Fig. S10 ESI-MS spectrum of M3.

Fig. S11 $^1$H NMR spectra of M1 monitored during the hydrolysis process in deuterated phosphate buffer (PB) solution (pH 5.5) at 37 °C. The extent of hydrolysis ($E_d$) of M1 was estimated by comparing the integrals of peaks a + b + c + d and a’+b’ ($E_d = I_{a'+b'}/(I_{a+b+c+d} + I_{a'+b'})$).
Fig. S12 The detailed $^1$H NMR spectra of M2-33/67 monitored during the hydrolysis process in buffered D$_2$O (pH 5.5) at 37 °C. The $E_d$ of M2 was estimated by comparing the integrals of peaks $a_1$, $a_2$ and $a'$ ($E_d = I_{a'}/(I_{a'} + I_{a1} + I_{a2})$).

Fig. S13 $^1$H NMR spectra of M2-94/6 monitored during the hydrolysis process in buffered D$_2$O (pH 5.5) at 37 °C.
Fig. S14 MS spectra of the hydrolysis products of the mixture M2-33/67 in buffered D₂O (pH 5.5). Positive ion mode (left): mPEG₂-NH₂ (C₉H₂₁NO₄ + H⁺), calcd: 208.15; found: 208.36. (C₉H₂₃NO₄ + Na⁺), calcd: 230.14; found: 230.37. Negative ion mode (right): citraconic acid (C₅H₅O₄⁻), calcd: 129.02; found: 129.33.

Fig. S15 ¹H NMR spectra of M3 monitored during the hydrolysis process in buffered D₂O (pH 5.5) at 37 °C. The $E_d$ of M3 was estimated by comparing the integrals of peaks a₁, a₂ and a' (a*) ($E_d = (I_{a'} + I_{a'})/(I_{a} + I_{a+s} + I_{a'})$).
Fig. S16 ¹H NMR spectra of M3 monitored during the hydrolysis process in buffered D₂O (pH 6.5) at 37 °C.

Fig. S17 The detailed ¹H NMR spectra of M3 monitored during the hydrolysis process in buffered D₂O (pH 7.4) at 37 °C, $E_i$ is the percent content of M3-imide. The $E_d$ and $E_i$ of M3 were estimated by comparing the integrals of peaks $a_1$, $a_2$, $a'$ and $a''$ ($E_d = I_{a'}/(I_{a'} + I_{a''} + I_{a_1+a_2})$; $E_i = I_{a''}/(I_{a'} + I_{a''} + I_{a_1+a_2})$).
Fig. S18 MS spectra of the hydrolysis products of compound **M3** in buffered D$_2$O (pH 5.5). Positive ion mode (left): mPEG$_4$-NH$_2$ (C$_9$H$_{21}$NO$_4$ + H$^+$), calcd: 208.15; found: 208.37. (C$_9$H$_{21}$NO$_4$ + Na$^+$), calcd: 230.14; found: 230.37. Negative ion mode (right): 2,3-dimethyl maleic acid (C$_6$H$_7$O$_4$), calcd: 143.03; found: 143.33.

Fig. S19 MS spectra of the hydrolysis products of compound **M3** in buffered D$_2$O (pH 6.5). Positive ion mode (left): mPEG$_4$-NH$_2$ (C$_9$H$_{21}$NO$_4$ + H$^+$), calcd: 208.15; found: 208.43. (C$_9$H$_{21}$NO$_4$ + Na$^+$), calcd: 230.14; found: 230.39. Negative ion mode (right): 2,3-dimethyl maleic acid (C$_6$H$_7$O$_4$), calcd: 143.03; found: 143.33.
Fig. S20 MS spectra of the hydrolysis products of compound M3 in buffered D$_2$O (pH 7.4). Positive ion mode (left): mPEG-NH$_2$ (C$_9$H$_{21}$NO$_4$ + H$^+$), calcd: 208.15; found: 208.36. (C$_9$H$_{21}$NO$_4$ + Na$^+$), calcd: 230.14; found: 230.40. M3-imide (C$_{15}$H$_{25}$NO$_6$ + Na$^+$), calcd: 338.16; found: 338.39. Negative ion mode (right): 2,3-dimethylmaleic acid (C$_6$H$_7$O$_4$), calcd: 143.03; found: 143.33.