Electronic Supplementary Material (ESI) for ChemComm.

Electronic Supporting Information

Molecular protection of fatty acid methyl esters within a supramolecular nano-capsule

Kaiya Wang,[1] Jacobs Jordan,[2] Bruce C. Gibb[2]*

[1]College Of Material Science & Technology, Nanjing University of Aeronautics and Astronautics, Nanjing 211100, China

[2]Department of Chemistry, Tulane University, New Orleans, LA, 70118

Table of Contents

1 Materials and Instrumentation

Host **1** was synthesized following previously reported procedures.[1] All NMR spectra were recorded on a Bruker 500 MHz spectrometer at 25 ˚C unless otherwise stated. Spectral processing was carried out using Mnova software (Mestrelab Research S.L). All reagents and guests **2** and **5-10** (Figure S1) were purchased from Aldrich and were used without purification. Guests **3**, **4**, **11** and **12** were synthesized as previously reported.[2] For reference, Figure S2 shows the ^{1}H NMR spectrum of a 1 mM solution of free host **1** in 10 mM NaOH/D_2O. ^{18}O-labeled water (purity 95%, Marshall Isotope Inc.) was a gift from Prof. Mike Watkinson (Keel University, UK. Thanks Mike!). ESI-MS spectra were collected using a Bruker microTOF mass spectrometer.

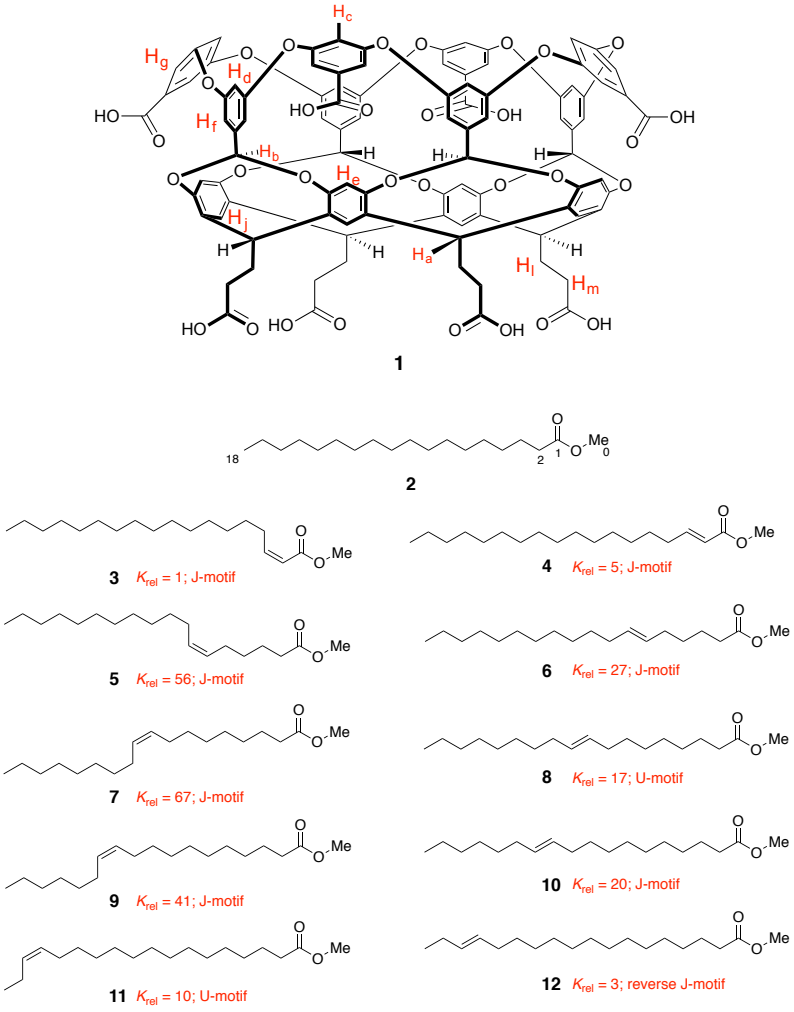


Figure S1: Chemical structures of host **1** and guests **2-12.**

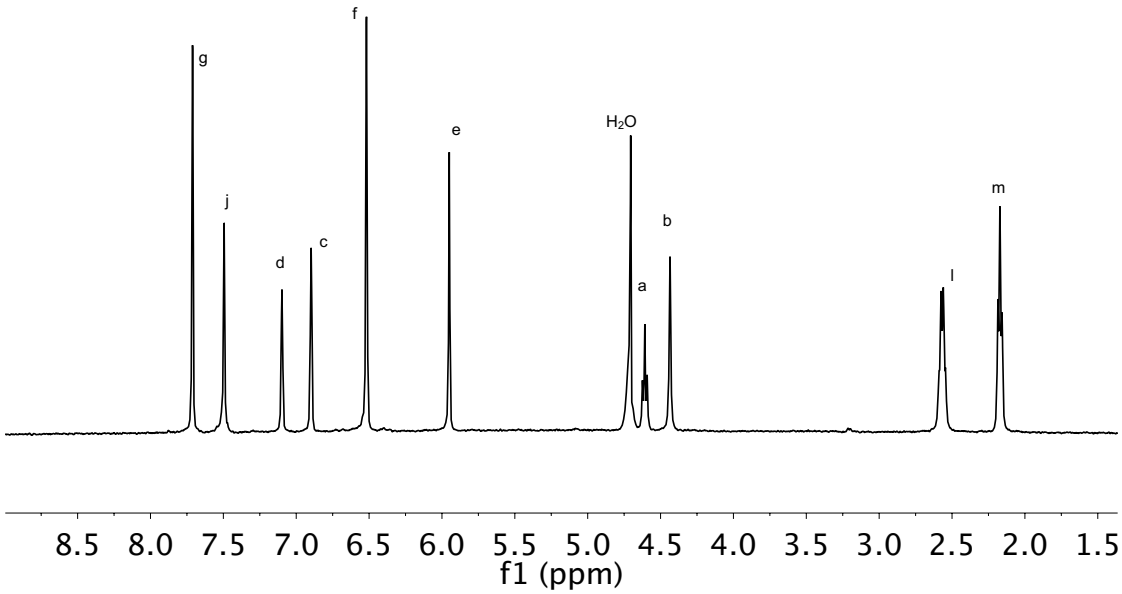


Figure S2: ^{1}H NMR spectrum of 1 mM **1** in 10 mM NaOH/D_2O (See Figure S1 for peak assignments).

2 ^{1}H NMR analysis of the hydrolysis of free esters 3-12

For the hydrolyses of the free esters **3-12** a 40:60 acetone-d_6:D_2O solution was required to ensure homogeneity ([ester] = 0.5 mM, [NaOH] = 150 mM, T = 25 ˚C). Hydrolysis was monitored by ^{1}H NMR spectroscopy by integration of the –OCH_3 group of the ester (δ ≈ 3.63 ppm) and the corresponding methoxy signal from the methanol side-product (δ ≈ 3.34 ppm). Each hydrolysis was carried out in duplicate, with representative NMR spectra for the hydrolysis of free esters **3-12** shown in Figures S3-S12.

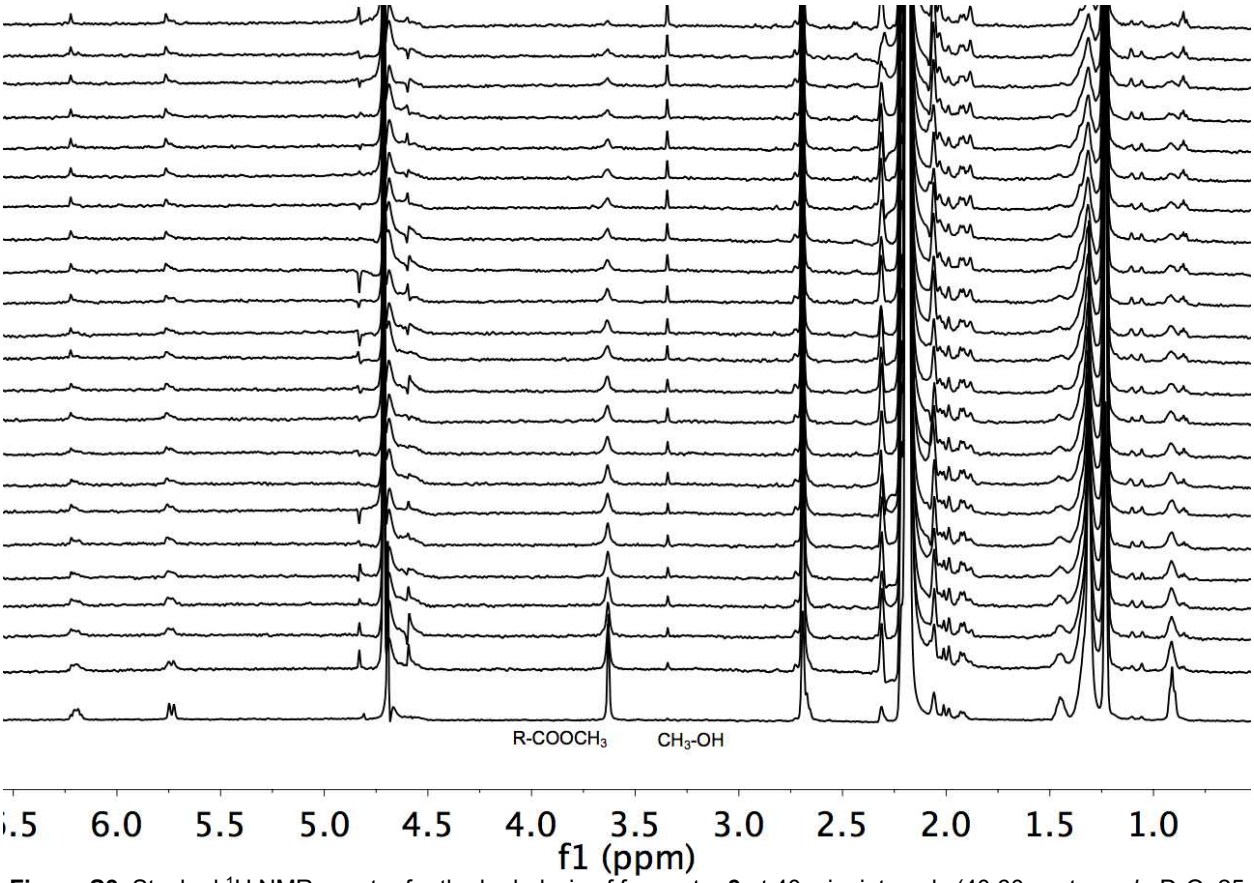


Figure S3: Stacked ^{1}H NMR spectra for the hydrolysis of free ester **3** at 40 min. intervals (40:60 acetone-d_6: D_2O, 25 ˚C, [Ester **3**] = 0.5 mM, [NaOH] =150 mM).

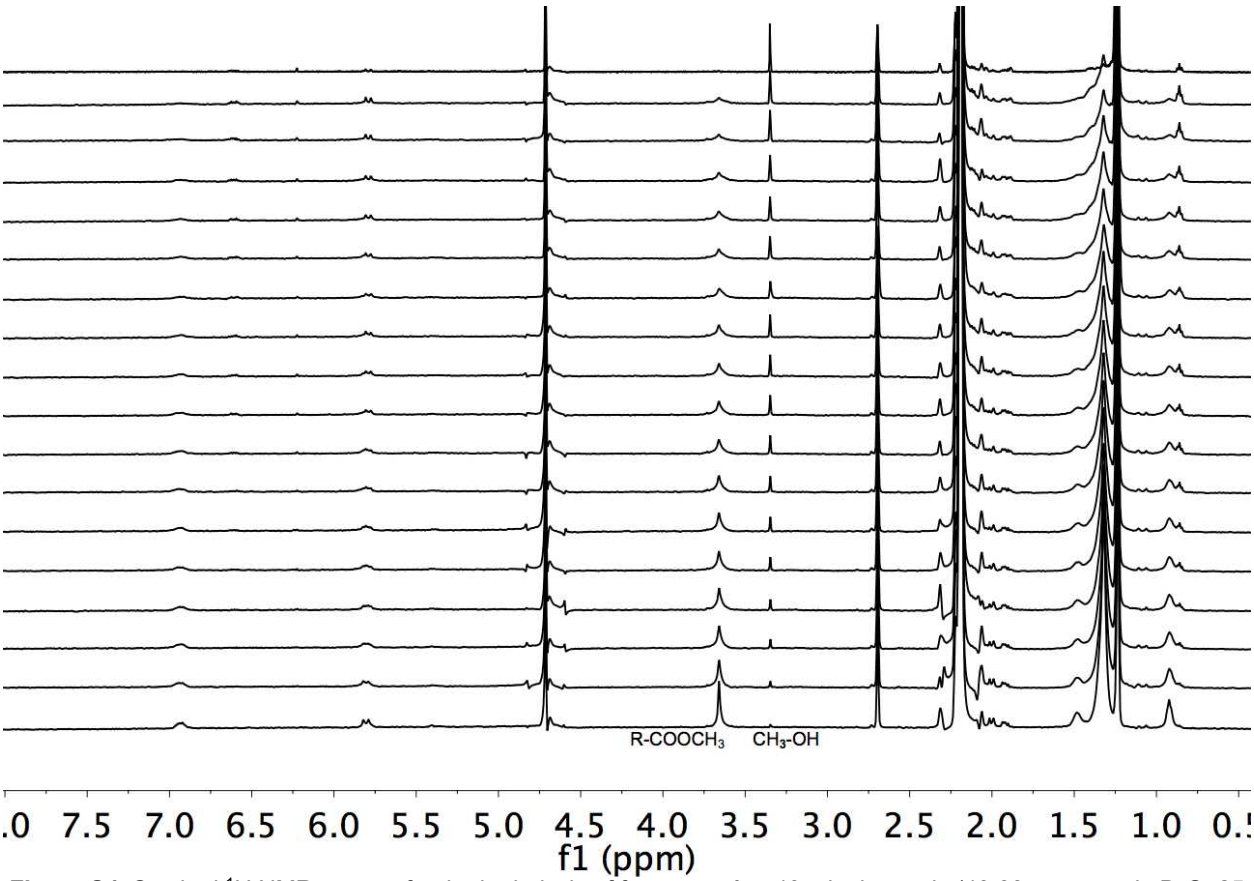


Figure S4: Stacked ^{1}H NMR spectra for the hydrolysis of free ester **4** at 40 min. intervals (40:60 acetone-d_6: D_2O, 25 $^{\circ}$C, [Ester **4**] = 0.5 mM, [NaOH] =150 mM).

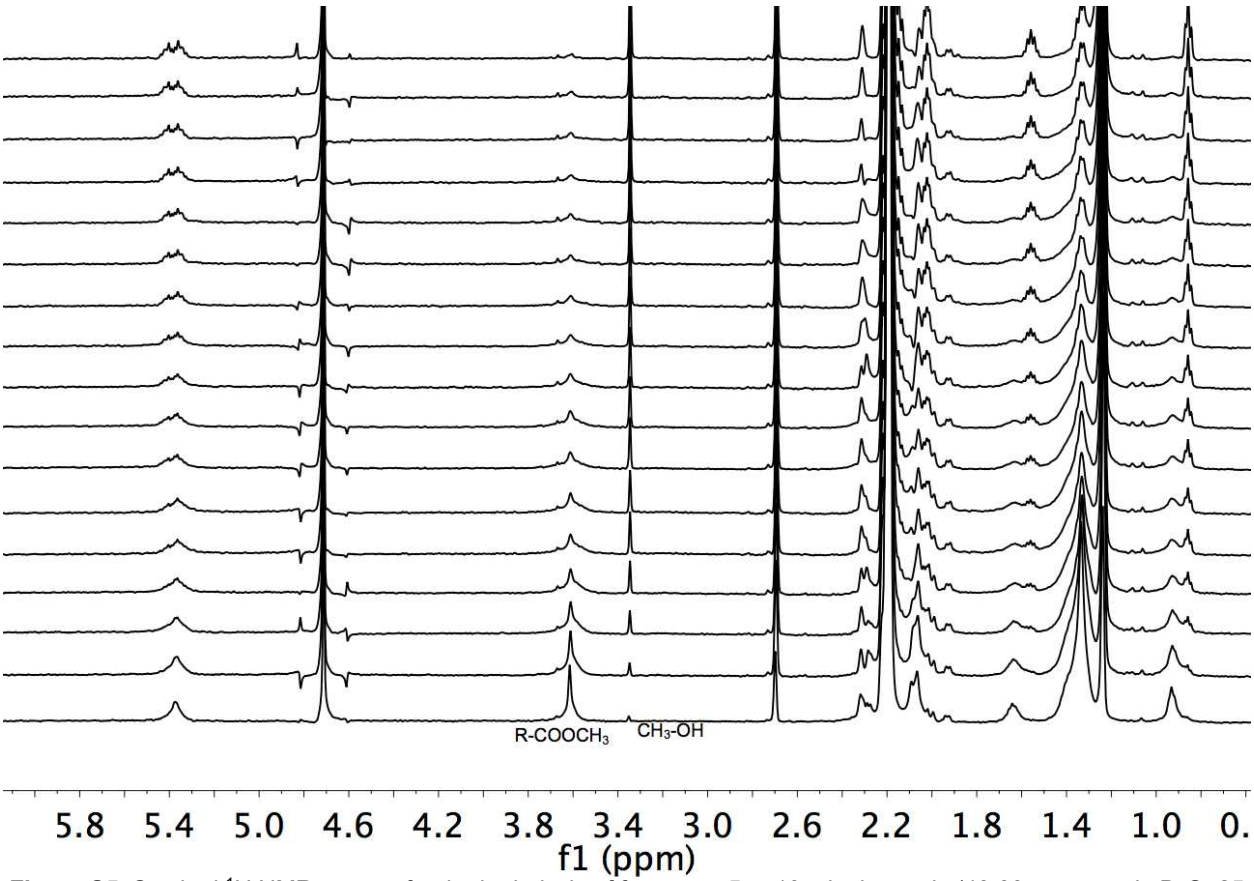


Figure S5: Stacked ^{1}H NMR spectra for the hydrolysis of free ester **5** at 10 min. intervals (40:60 acetone-d_6: D_2O, 25 $^{\circ}$C, [Ester **5**] = 0.5 mM, [NaOH] =150 mM).

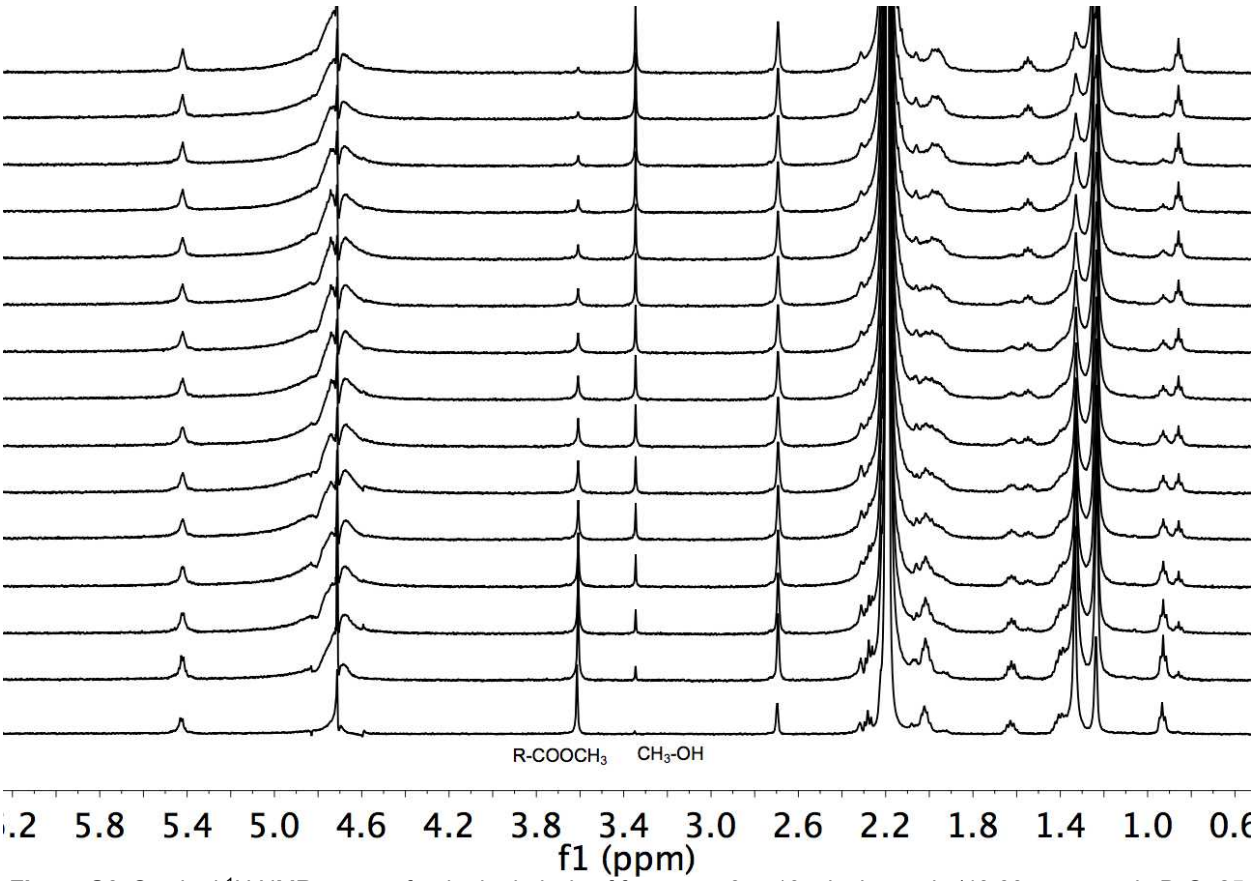


Figure S6: Stacked ^{1}H NMR spectra for the hydrolysis of free ester **6** at 10 min. intervals (40:60 acetone-d_6: D_2O, 25 $^{\circ}$C, [Ester **6**] = 0.5 mM, [NaOH] =150 mM).

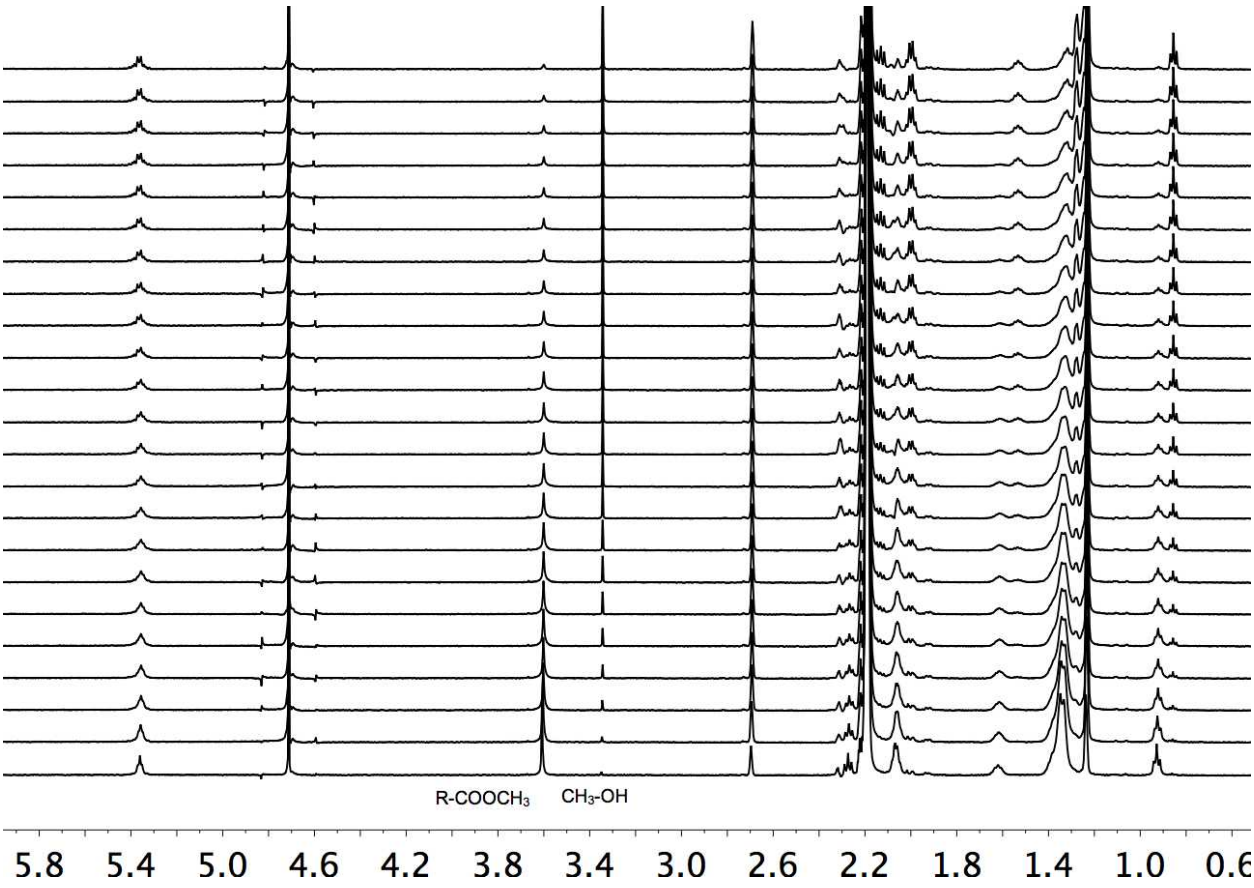


Figure S7: Stacked ^{1}H NMR spectra for the hydrolysis of free ester **7** at 5 min. intervals (40:60 acetone-d_6: D_2O, 25 $^{\circ}$C, [Ester **7**] = 0.5 mM, [NaOH] =150 mM).

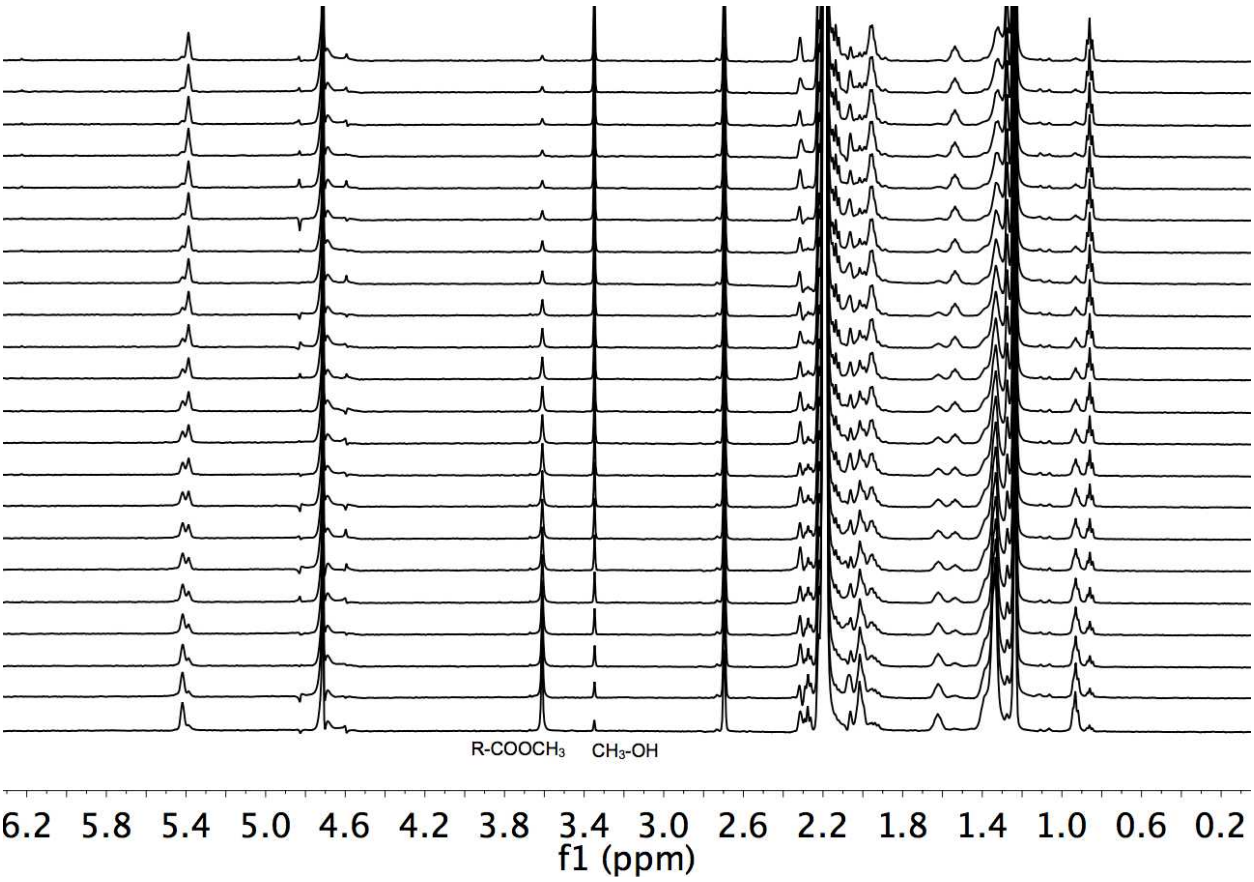


Figure S8: Stacked ^{1}H NMR spectra for the hydrolysis of free ester **8** at 5 min. intervals (40:60 acetone-d_6: D_2O, 25 $^{\circ}$C, [Ester **8**] = 0.5 mM, [NaOH] =150 mM).

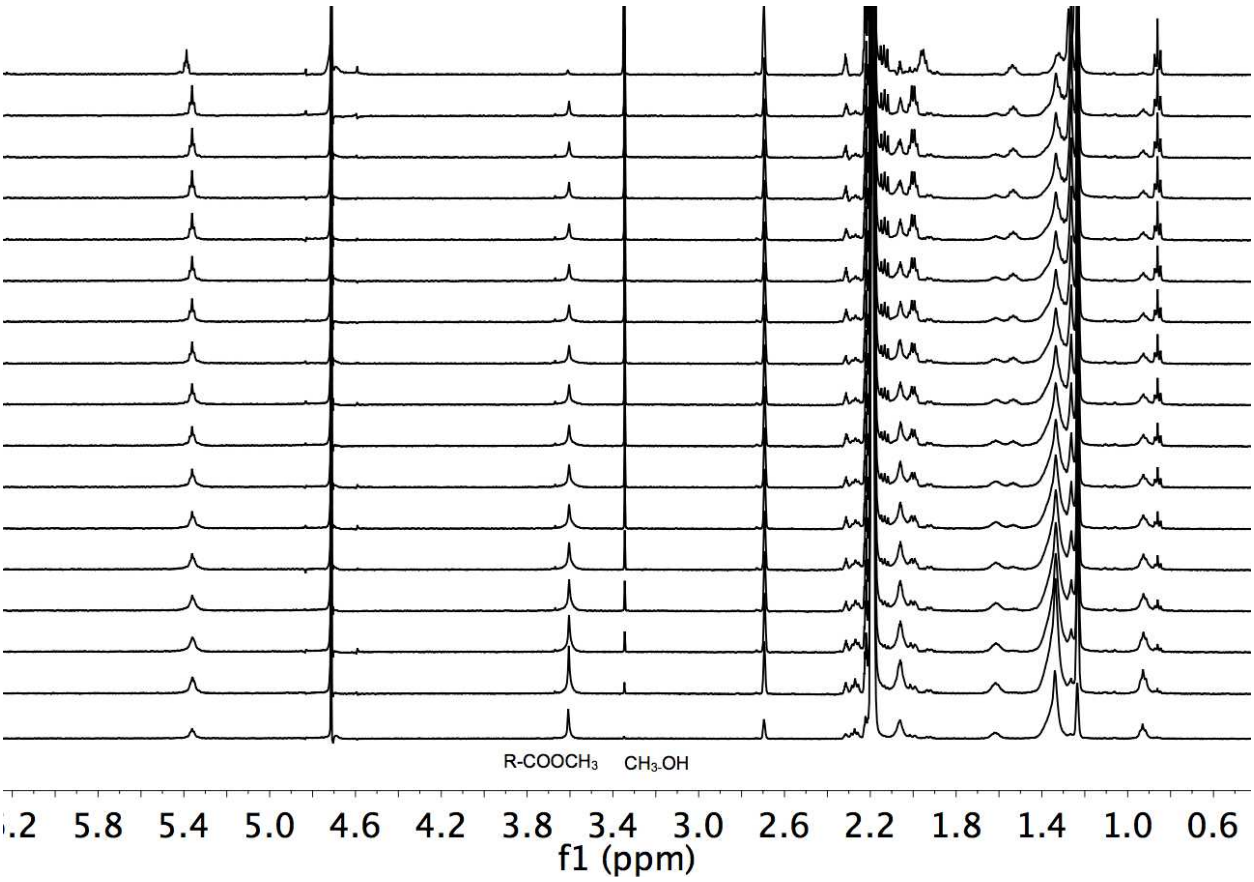


Figure S9: Stacked ^{1}H NMR spectra for the hydrolysis of free ester **9** at 10 min. intervals (40:60 acetone-d_6: D_2O, 25 $^{\circ}$C, [Ester **9**] = 0.5 mM, [NaOH] =150 mM).

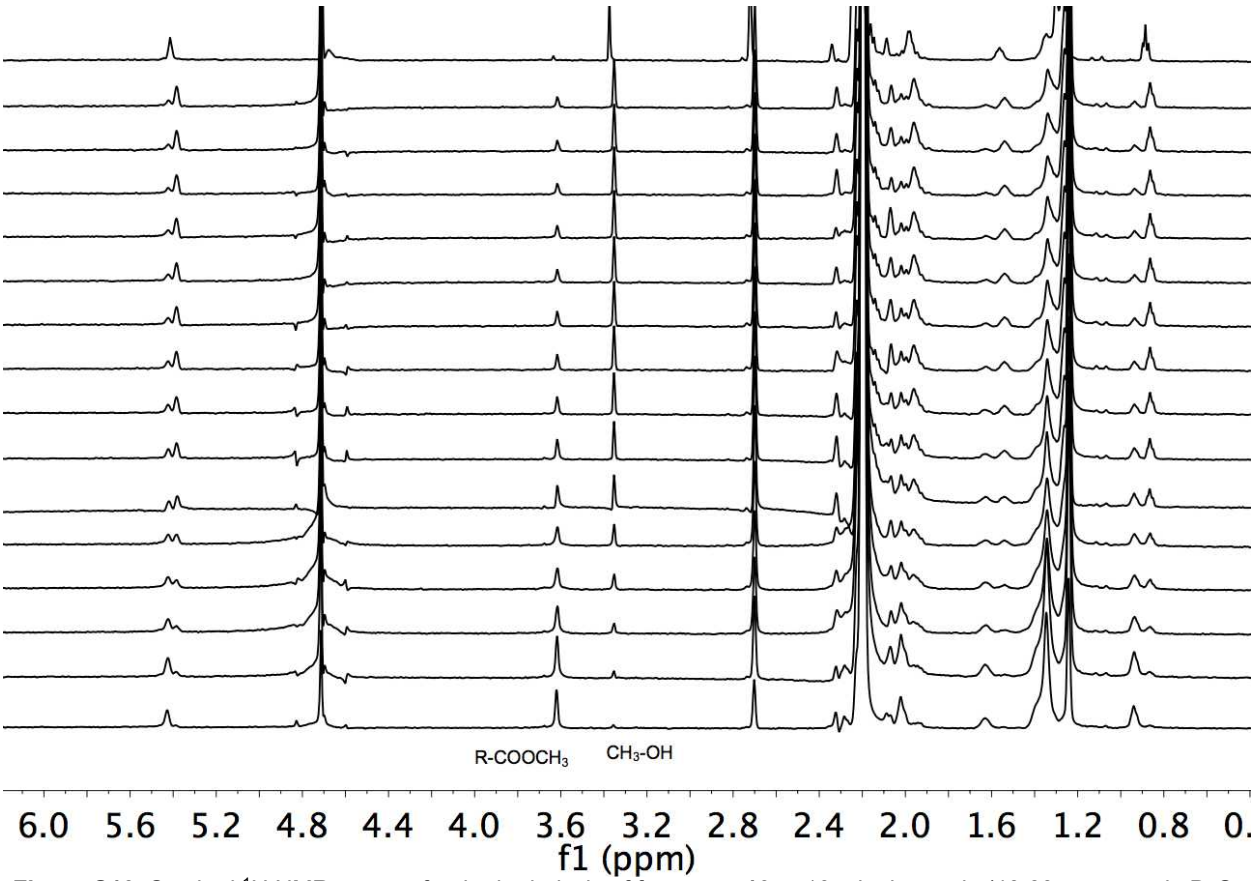


Figure S10: Stacked ^{1}H NMR spectra for the hydrolysis of free ester **10** at 10 min. intervals (40:60 acetone-d_6: D_2O, 25 ˚C, [Ester **10**] = 0.5 mM, [NaOH] =150 mM).

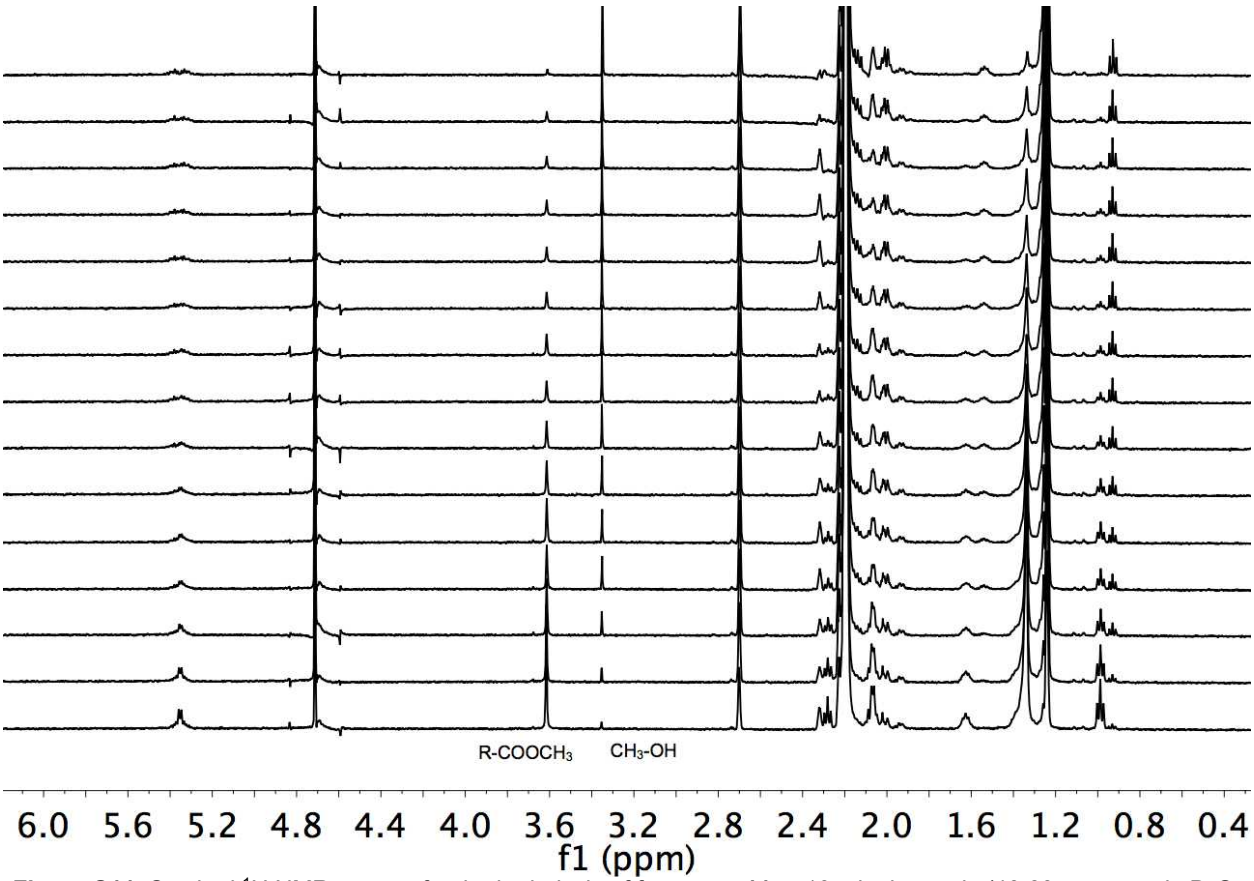


Figure S11: Stacked ^{1}H NMR spectra for the hydrolysis of free ester **11** at 10 min. intervals (40:60 acetone-d_6: D_2O, 25 ˚C, [Ester **11**] = 0.5 mM, [NaOH] =150 mM).

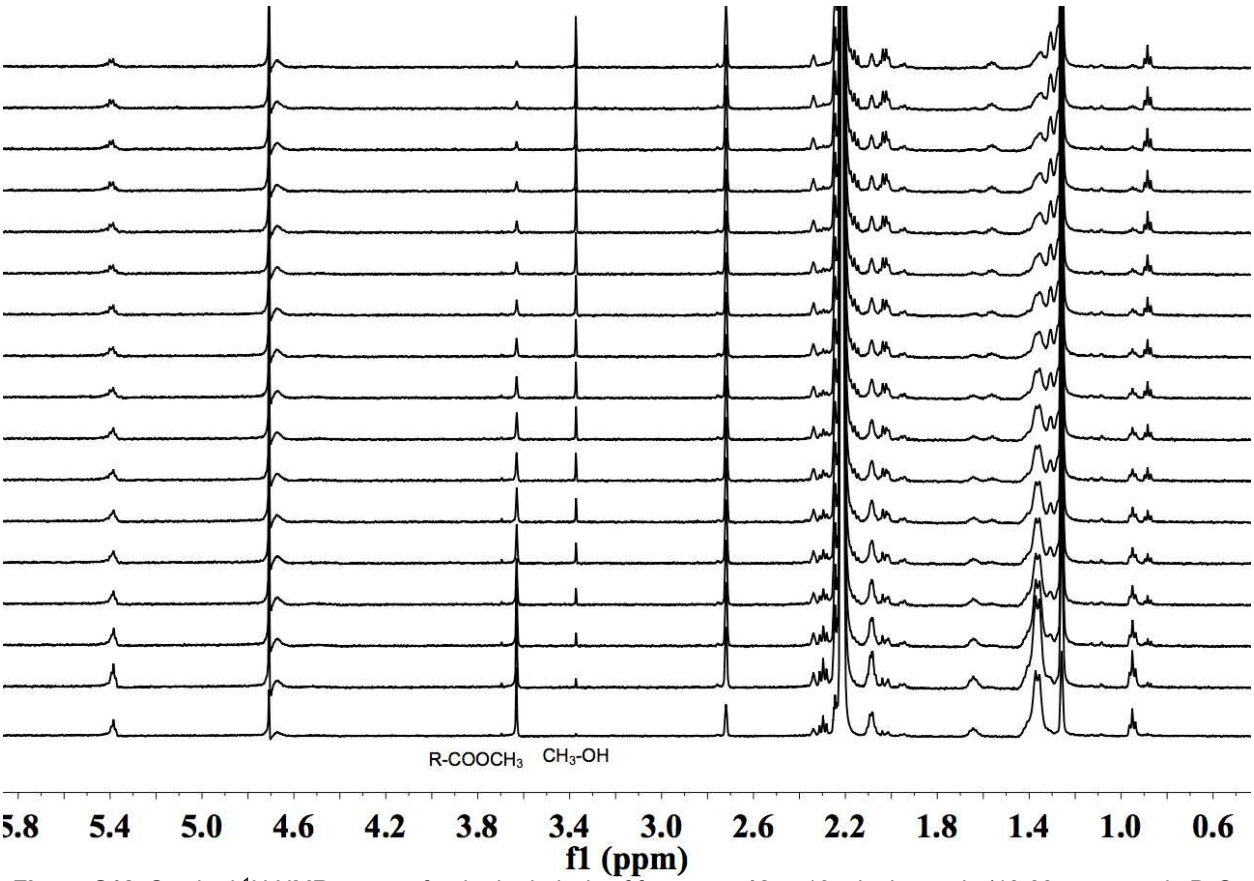


Figure S12: Stacked ^{1}H NMR spectra for the hydrolysis of free ester **12** at 10 min. intervals (40:60 acetone-d_6: D_2O, 25 ˚C, [Ester **12**] = 0.5 mM, [NaOH] =150 mM).

3 ^{1}H NMR analysis of the hydrolysis of esters 2-12 encapsulated within 1_2

The complexes were prepared in D_2O (ester = 0.5 mM, host = 1 mM, NaOH = 150 mM, T = 25 ˚C) using the previously reported methods.[3] The hydrolysis of each encapsulated ester **2-12** was monitored by ^{1}H NMR (Figures S13-23); in cases where the signal of the terminal $–CH_3$ group of the ester and acid product were well-defined, integration gave the extent of hydrolysis as a function of time. If this was not possible to use these signals, integration of the host peaks 'm' or 'l' peak and the terminal $–CH_3$ group of the acid were used instead.

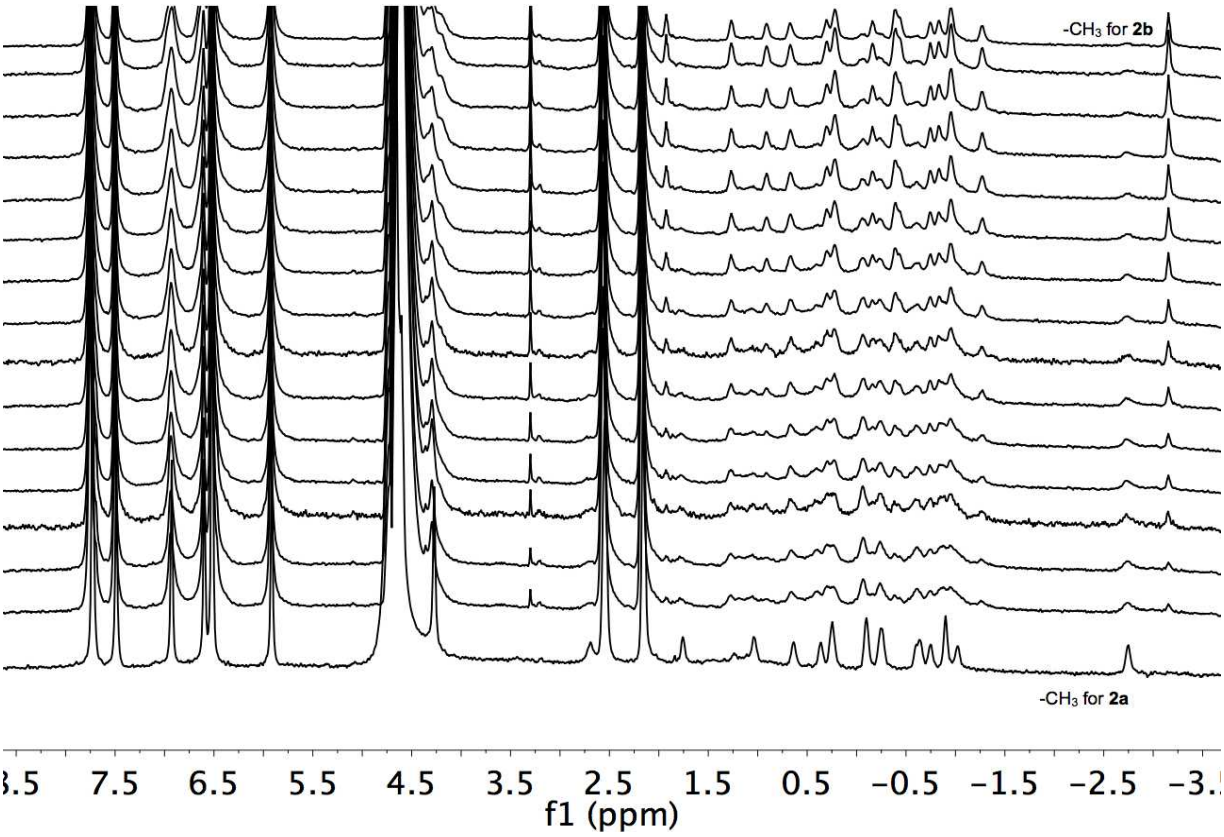


Figure S13: Stacked ^{1}H NMR spectra for the hydrolysis of encapsulated ester **2** at 10 min. intervals (D_2O, 25 ˚C, [Ester **2**] = 0.5 mM, [NaOH] =150 mM, [host] = 1 mM).

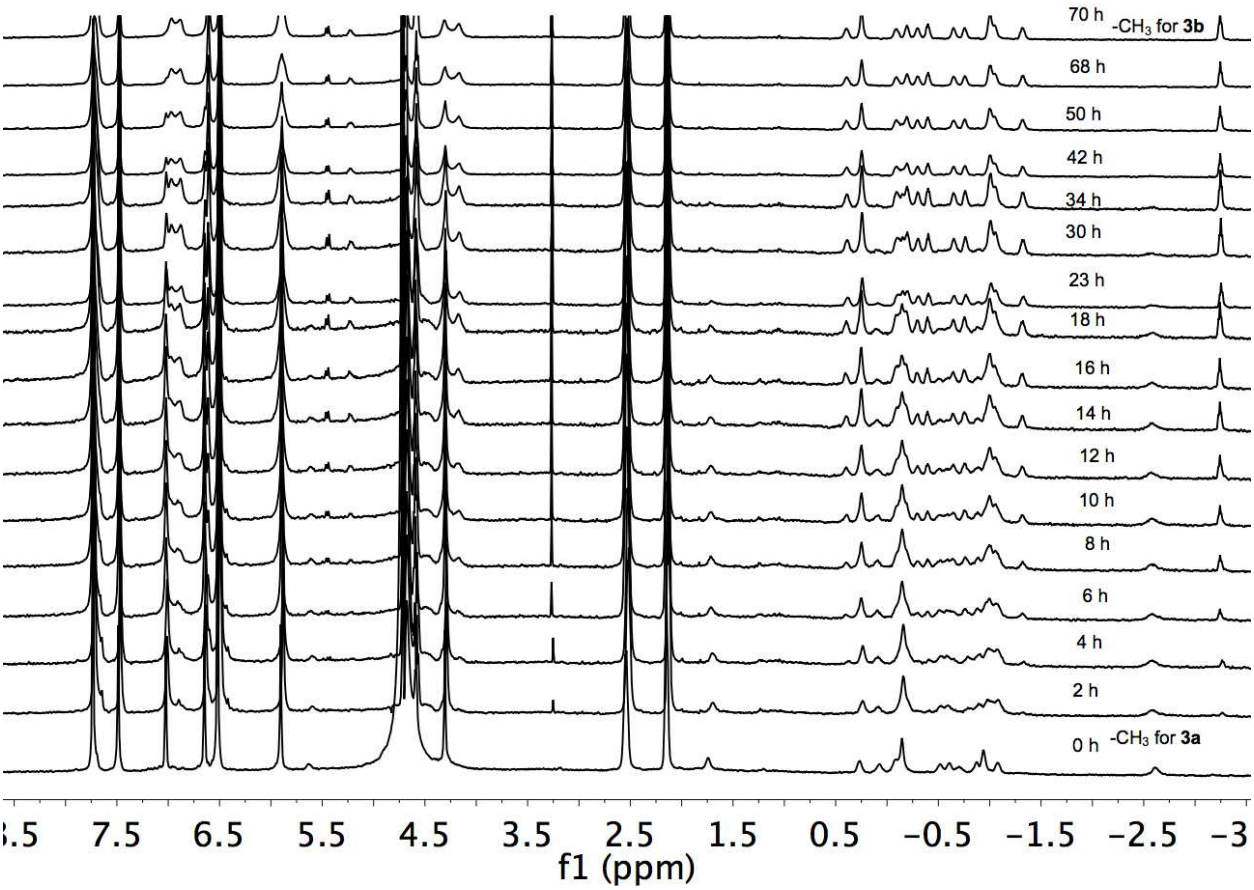


Figure S14: Stacked ^{1}H NMR spectra for the hydrolysis of encapsulated ester **3** (D_2O, 25 ˚C, [Ester **3**] = 0.5 mM, [NaOH] =150 mM, [host] = 1 mM).

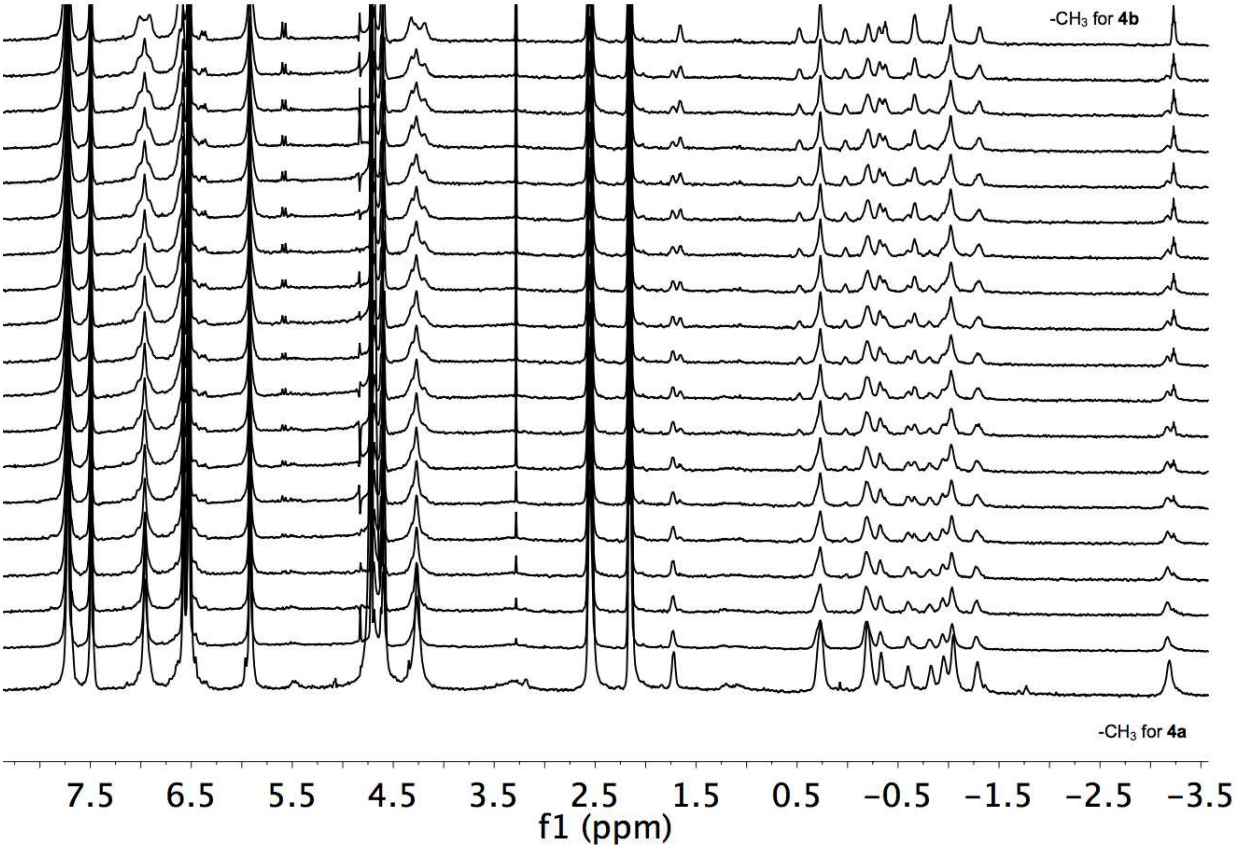


Figure S15: Stacked ^{1}H NMR spectra for the hydrolysis of encapsulated ester **4** at 40 min. intervals (D_2O, 25 ˚C, [Ester **4**] = 0.5 mM, [NaOH] =150 mM, [host] = 1 mM).

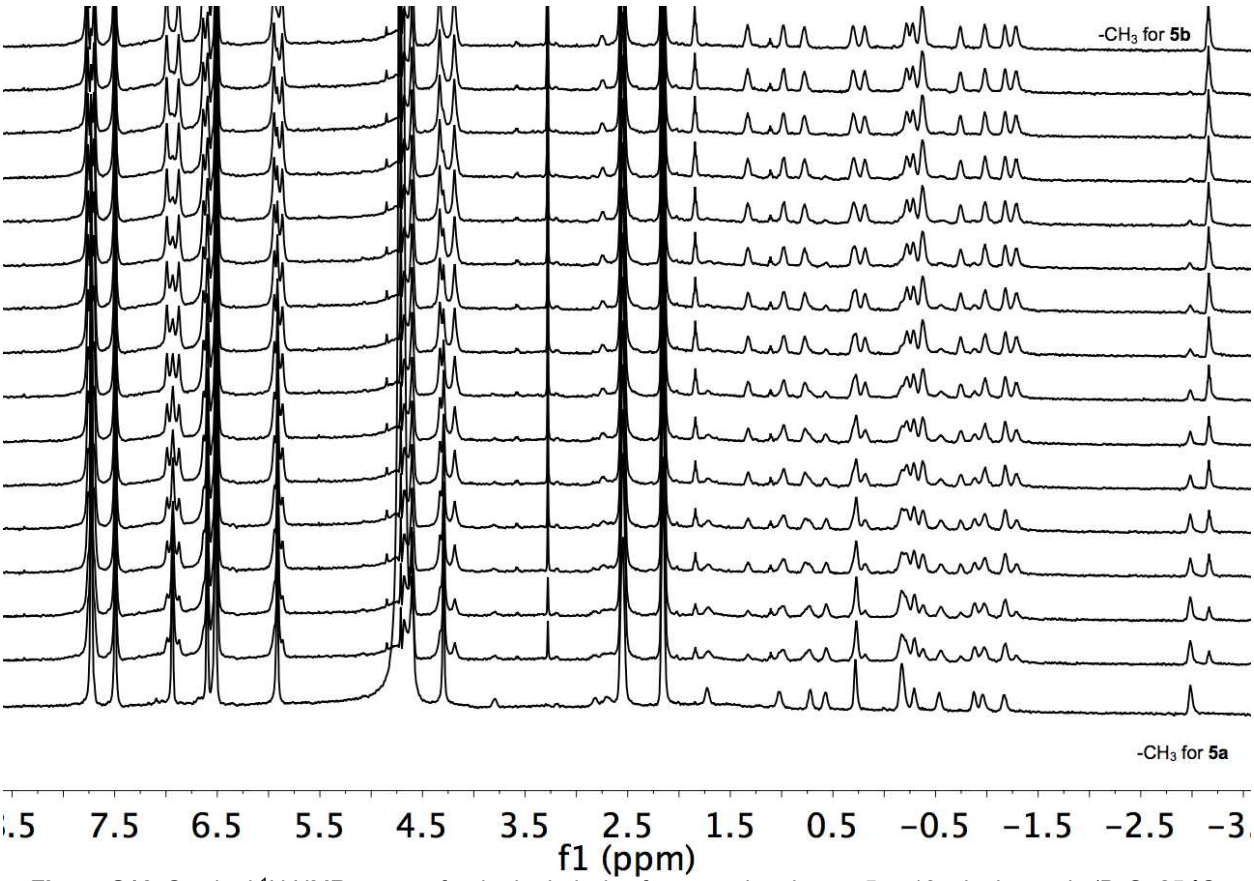


Figure S16: Stacked ^{1}H NMR spectra for the hydrolysis of encapsulated ester **5** at 10 min. intervals (D_2O, 25 ˚C, [Ester **5**] = 0.5 mM, [NaOH] =150 mM, [host] = 1 mM).

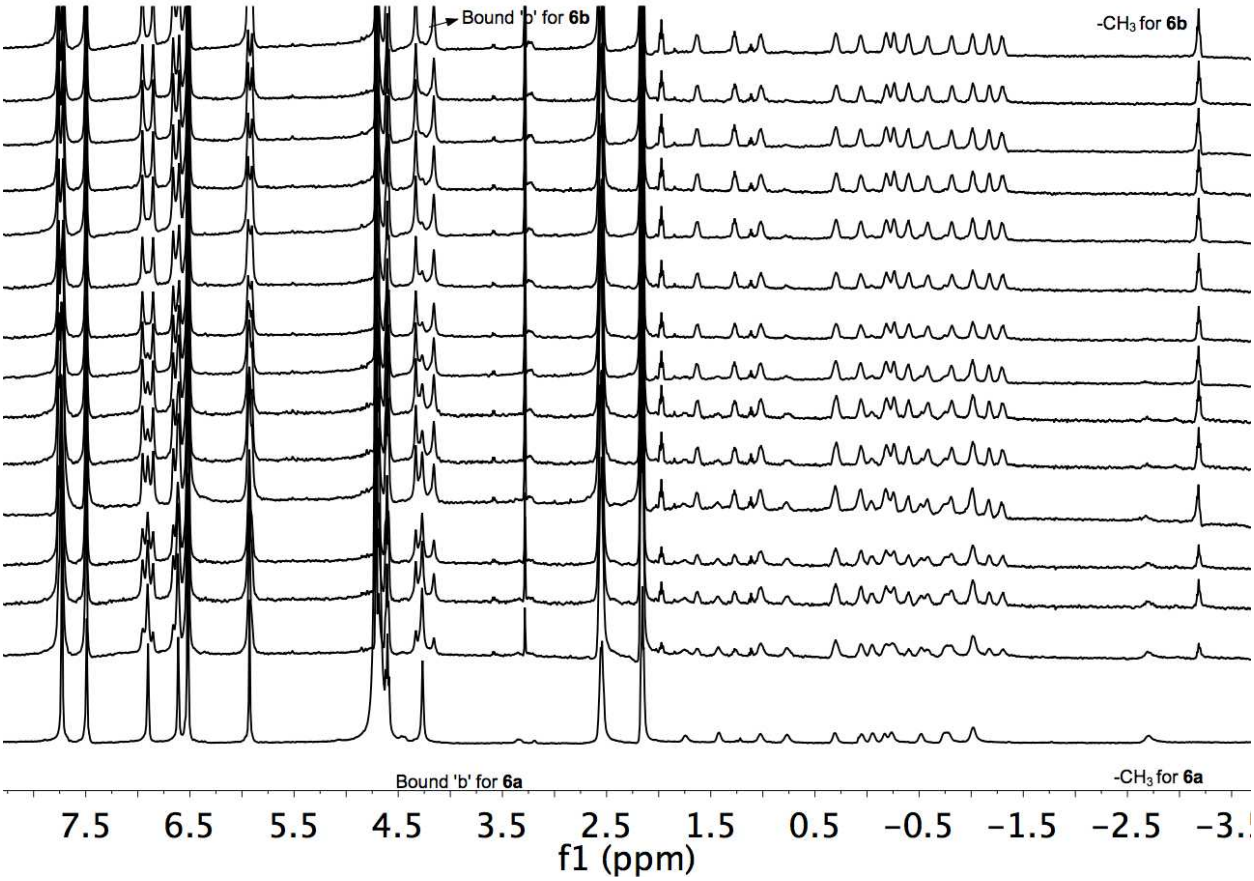


Figure S17: Stacked ^{1}H NMR spectra for the hydrolysis of encapsulated ester **6** at 10 min. intervals (D_2O, 25 ˚C, [Ester **6**] = 0.5 mM, [NaOH] =150 mM, [host] = 1 mM).

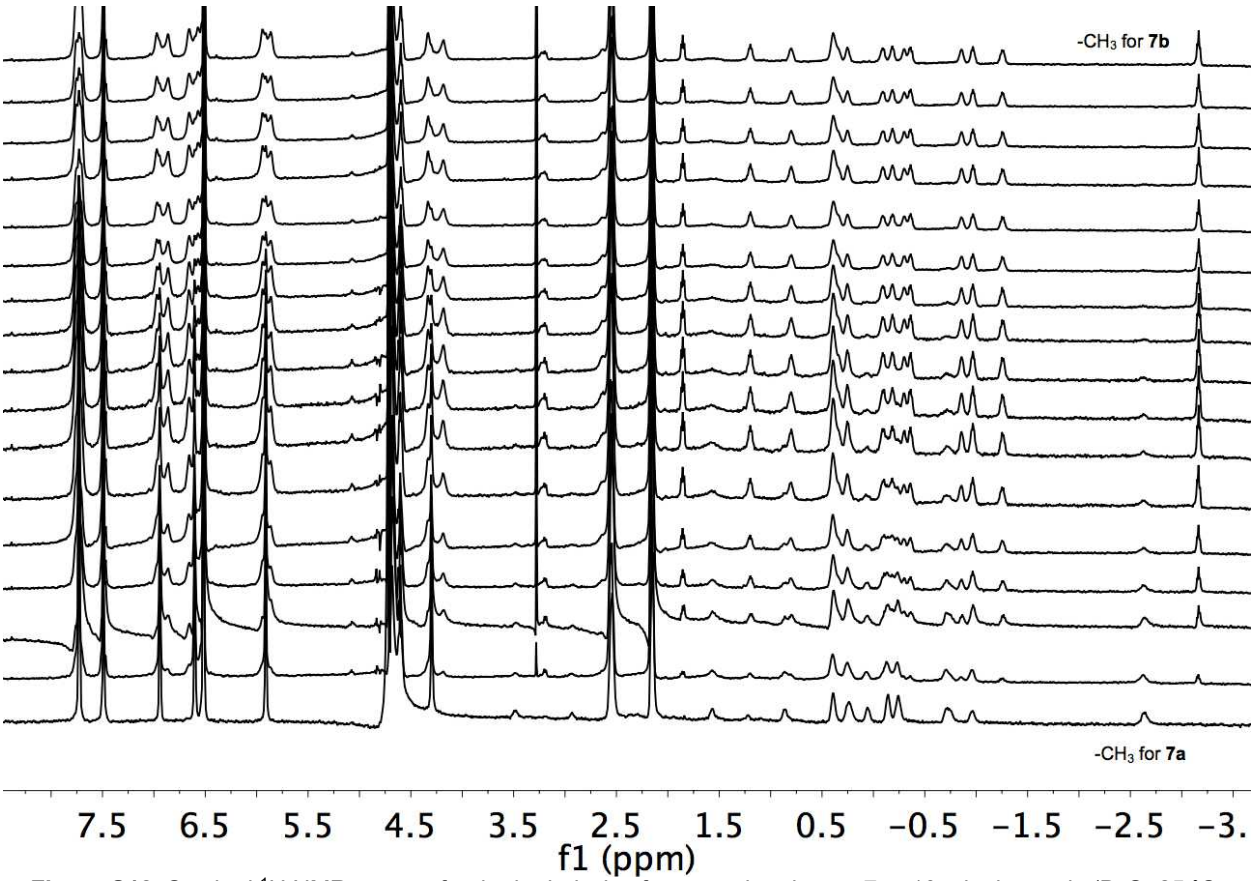


Figure S18: Stacked ^{1}H NMR spectra for the hydrolysis of encapsulated ester **7** at 10 min. intervals (D_2O, 25 ˚C, [Ester **7**] = 0.5 mM, [NaOH] =150 mM, [host] = 1 mM).

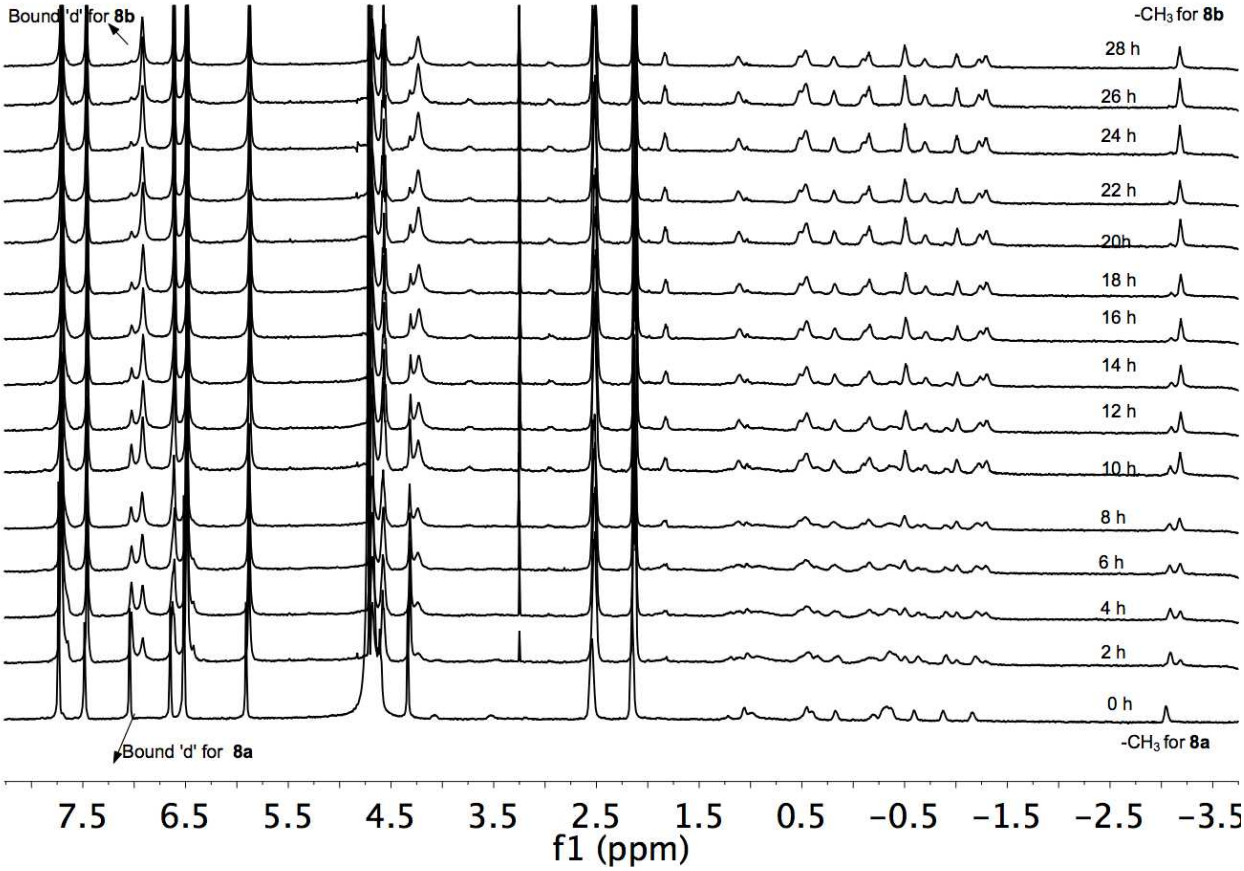


Figure S19: Stacked ^{1}H NMR spectra for the hydrolysis of encapsulated ester **8** at 2 h. intervals (D_2O, 25 ˚C, [Ester **8**] = 0.5 mM, [NaOH] =150 mM, [host] = 1 mM).

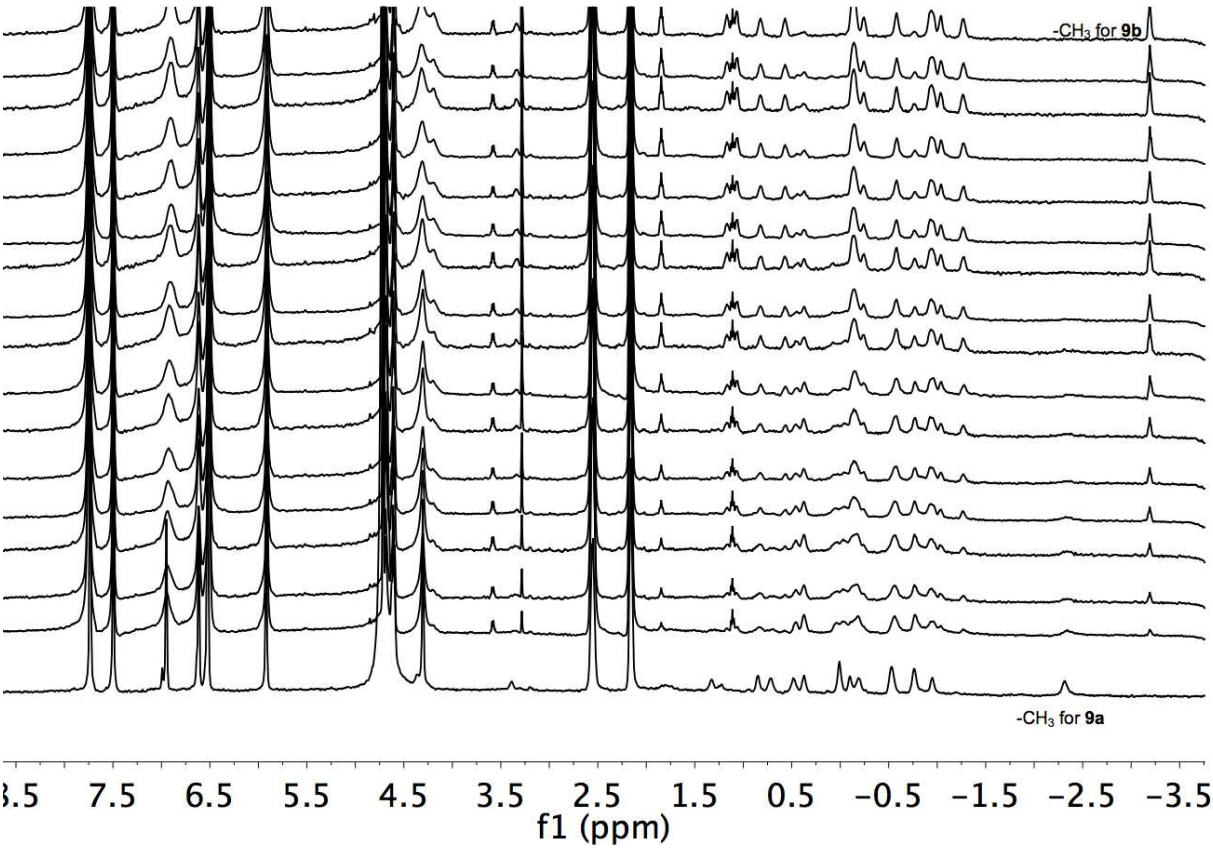


Figure S20: Stacked ^{1}H NMR spectra for the hydrolysis of encapsulated ester **9** at 10 min. intervals (D_2O, 25 ˚C, [Ester **9**] = 0.5 mM, [NaOH] =150 mM, [host] = 1 mM).

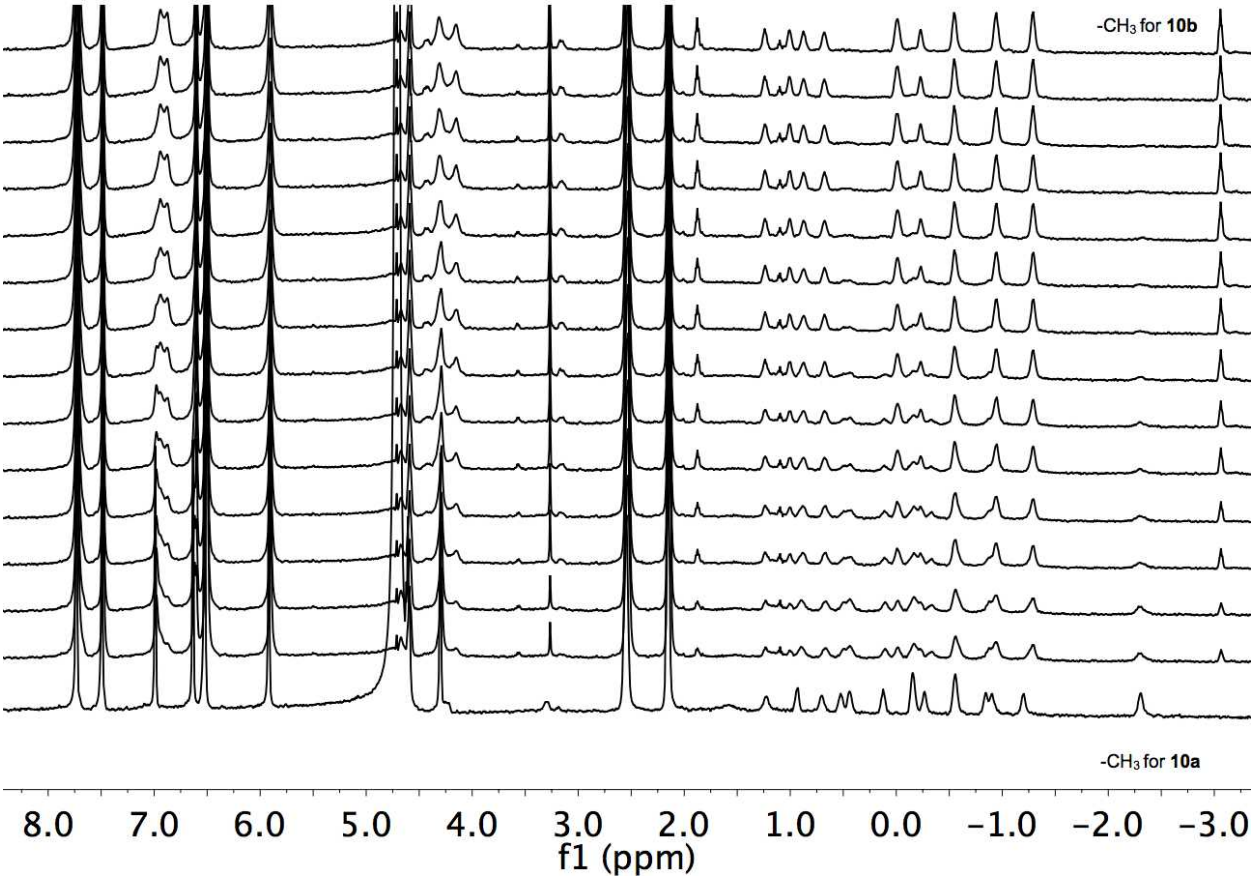


Figure S21: Stacked ^{1}H NMR spectra for the hydrolysis of encapsulated ester **10** at 10 min. intervals (D_2O, 25 ˚C, [Ester **10**] = 0.5 mM, [NaOH] =150 mM, [host] = 1 mM).

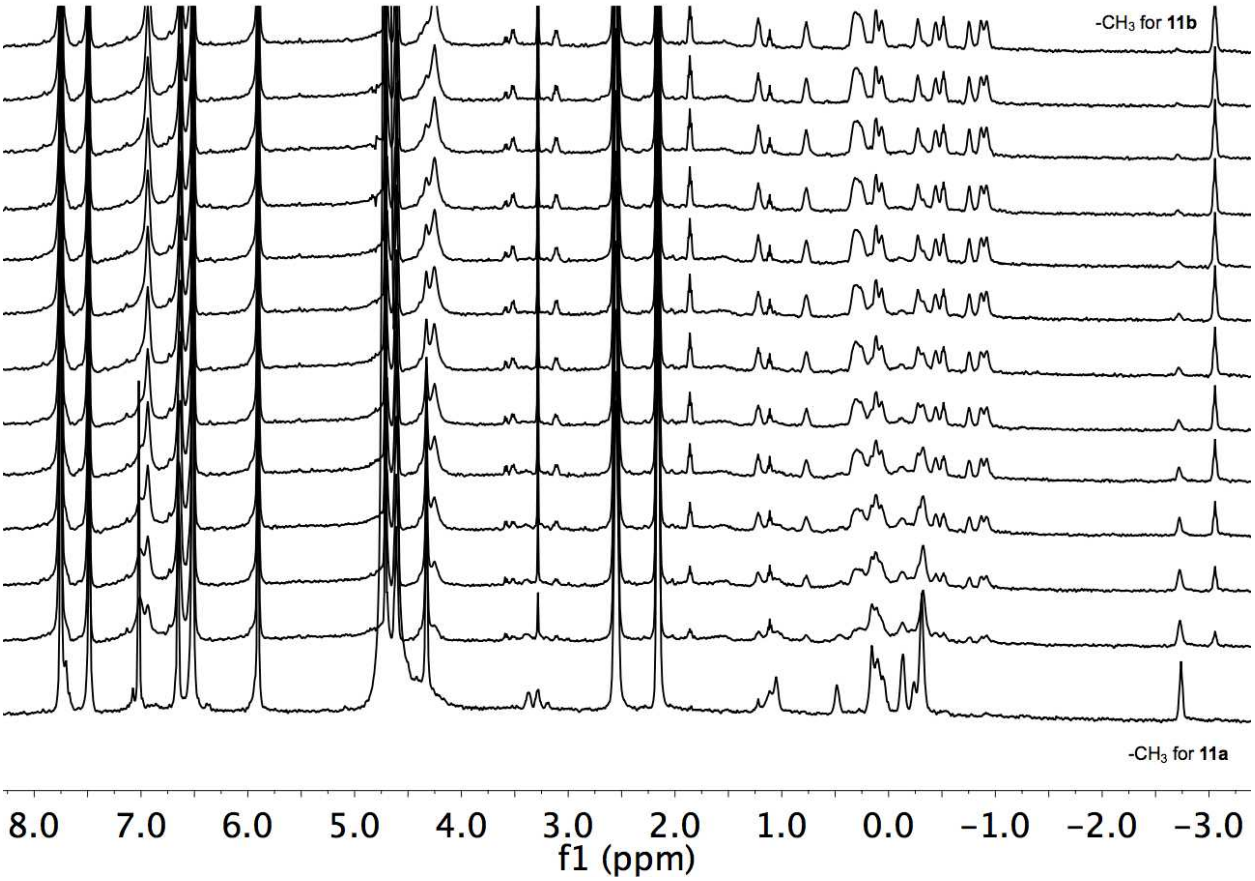


Figure S22: Stacked ^{1}H NMR spectra for the hydrolysis of encapsulated ester **11** at 40 min. intervals (D_2O, 25 ˚C, [Ester **11**] = 0.5 mM, [NaOH] =150 mM, [host] = 1 mM).

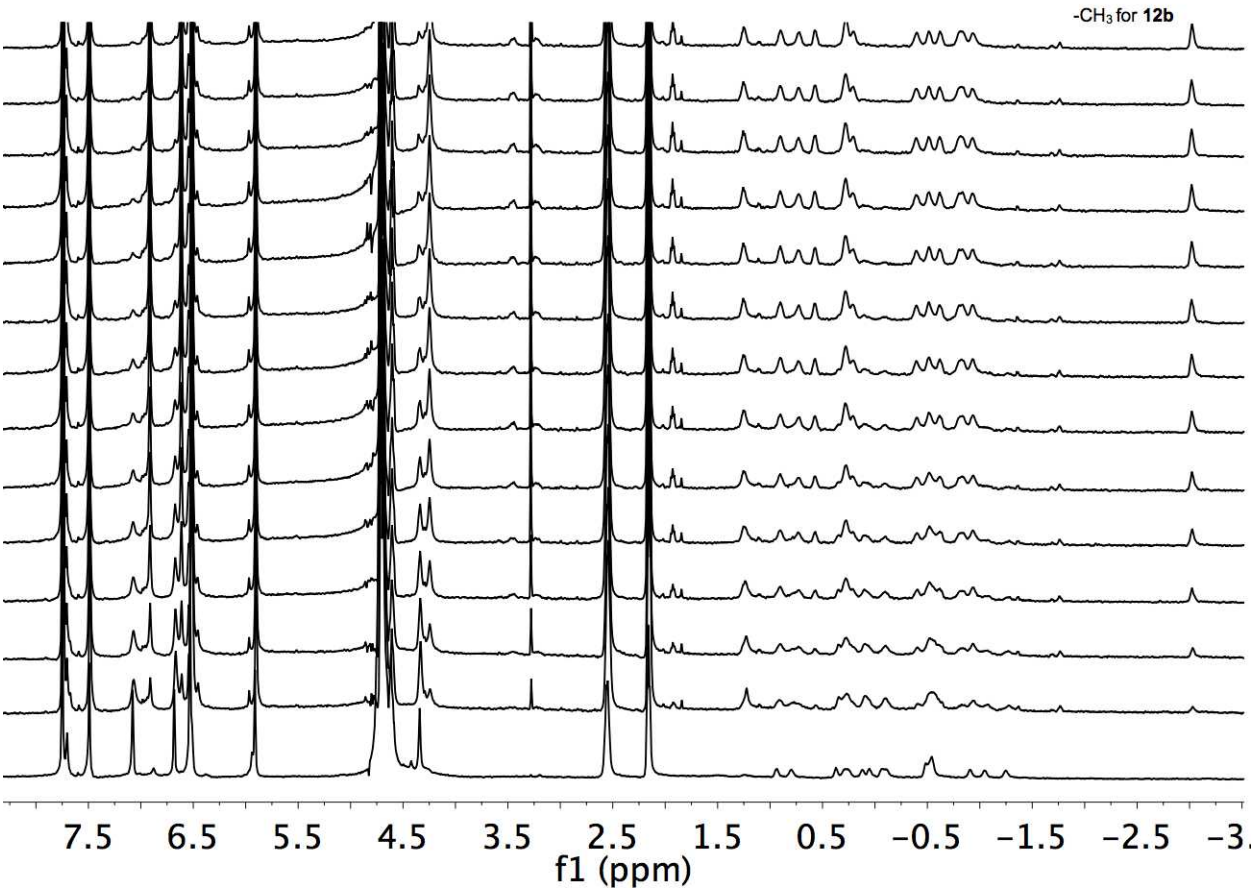


Figure S23: Stacked ^{1}H NMR spectra for the hydrolysis of encapsulated ester **12** at 1 h. intervals (D_2O, 25 ˚C, [Ester **12**] = 0.5 mM, [NaOH] =150 mM, [host] = 1 mM).

4 Kinetic data for the hydrolysis of free and encapsulated ester 3-12

Each hydrolysis experiment was carried out in at least duplicate. Fitting of the data was performed using Origin Pro 2016 (mono-exponential growth function, y = A1*exp(-x/t1)+y0, where the rate constant *k* is the inverse of the life time (t1). In all cases reaction was confirmed to be pseudo-first order. All R^2 values were > 0.99. Figure S25-S34 show the hydrolysis rate of the free ester **3**-**12**. Figure S35-S45 shows the hydrolysis rate of encapsulated ester **2-12**. Table S1 summarizes the hydrolysis rate constant for the free and bound esters, and the corresponding ratio of these rates. A plot of K_{rel} verses k_{free}/k_{bound} is shown in Figure S24.

For non-conjugated esters **5-12**, the free hydrolysis rates (k_{free}) were approximately the same, while the hydrolysis rate k_{bound} varies dependent on the binding conformation of the guest inside the host **1**.

Table S1: Hydrolysis rates of free (k_{free}), encapsulated (k_{bound}), and the k_{free}:k_{bound} ratio for esters **2–12**

Guest	k_{free}[a,b] ($\times 10^{-3}$ min^{-1})	k_{bound}[a,c] ($\times 10^{-3}$ min^{-1})	k_{free} : k_{bound}
2	-[d]	13.37	-
3	2.71	0.61	4.44
4	4.23	1.94	2.18
5	16.65	11.18	1.49
6	17.04	13.38	1.27
7	16.04	11.57	1.39
8	16.72	2.73	6.12
9	14.12	13.14	1.07
10	15.03	11.69	1.29
11	15.38	6.80	2.26
12	14.19	2.45	5.80ß

[a] Average of two trials. Errors < 10%.
[b] 0.5 mM ester in 150 mM NaOH in 40% acetone-d_6/D_2O.
[c] 0.5 mM ester in 150 mM NaOH in D_2O.
[d] High amounts of acetone required to ensure homogeneity, resulted in incompatible data.

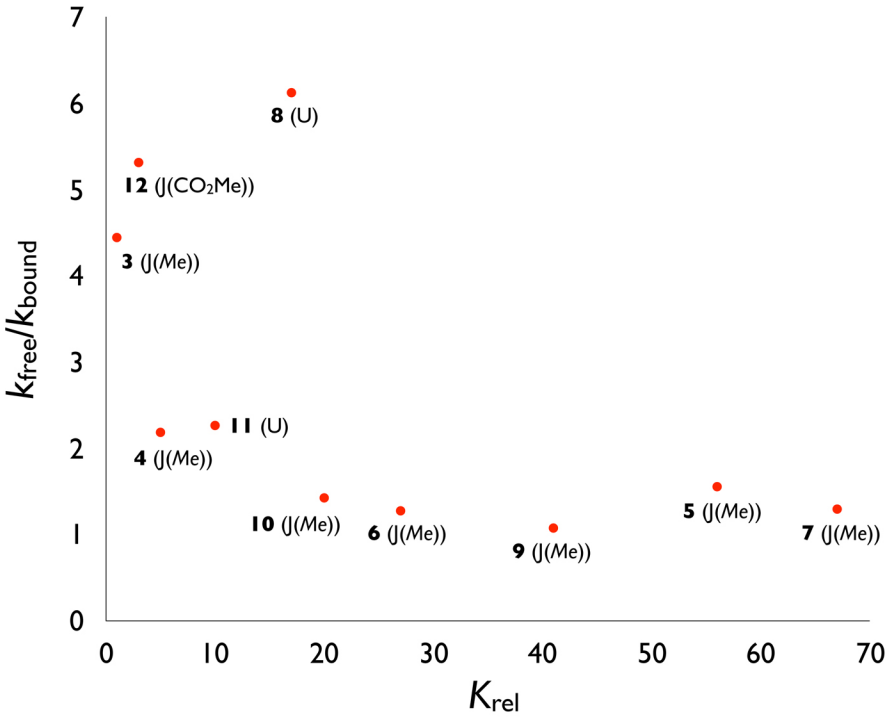


Figure S24: Plot of K_{rel} verses k_{free}/k_{bound}.

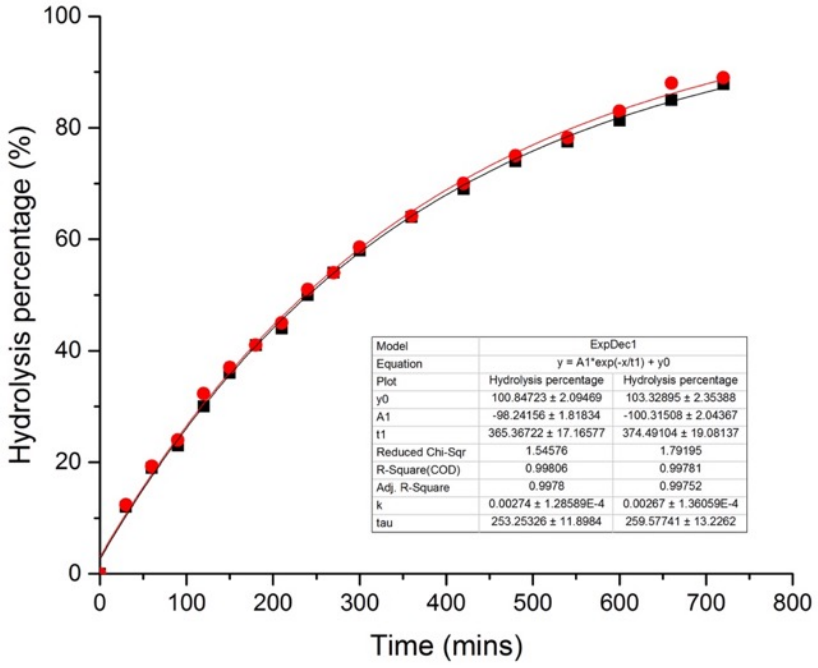
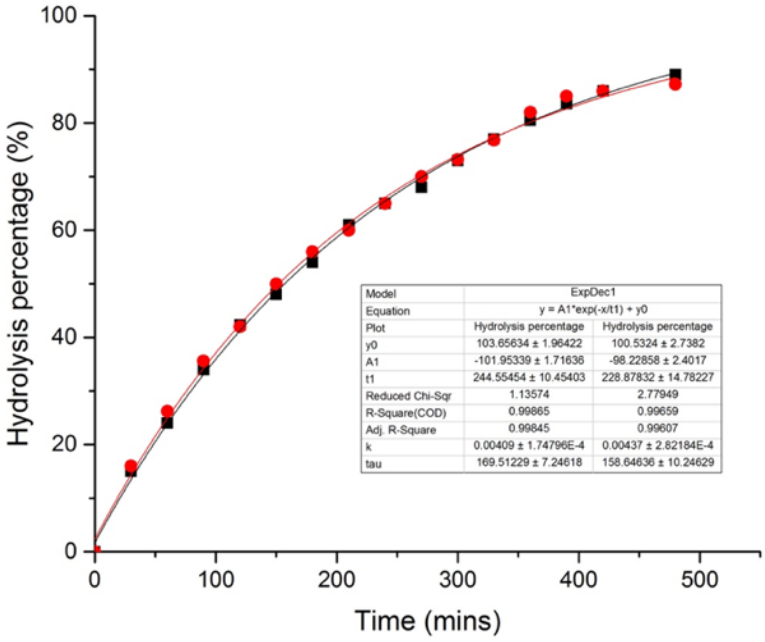
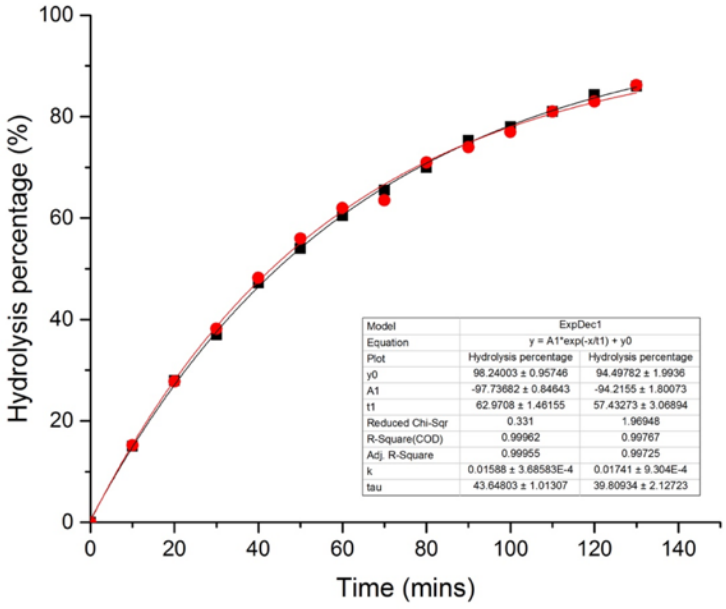


Figure S25: Hydrolysis of 0.5 mM free guest **3** in 150 mM NaOH in 40% acetone-d_6/D_2O (two trials).



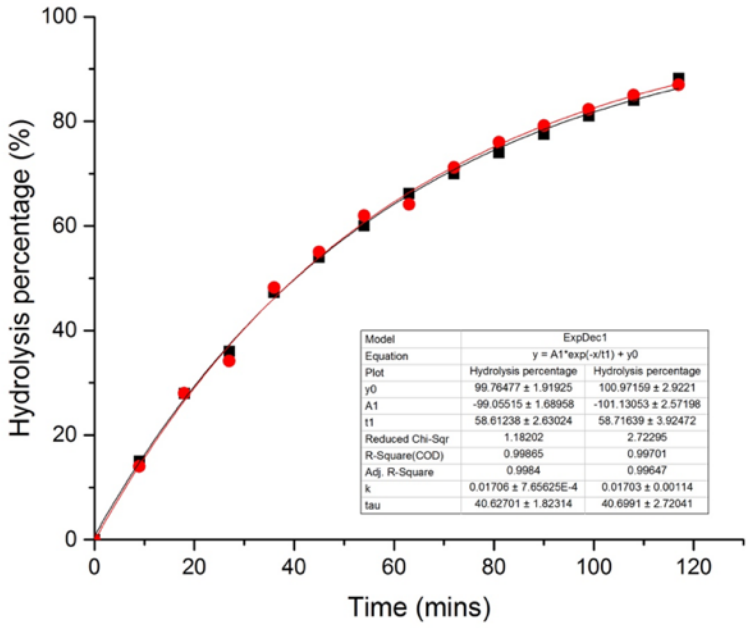
Model	ExpDec1	
Equation	y = A1*exp(-x/t1) + y0	
Plot	Hydrolysis percentage	Hydrolysis percentage
y0	103.65634 ± 1.96422	100.5324 ± 2.7382
A1	-101.95339 ± 1.71636	-98.22858 ± 2.4017
t1	244.55454 ± 10.45403	228.87832 ± 14.78227
Reduced Chi-Sqr	1.13574	2.77949
R-Square(COD)	0.99865	0.99659
Adj. R-Square	0.99845	0.99607
k	0.00409 ± 1.74796E-4	0.00437 ± 2.82184E-4
tau	169.51229 ± 7.24618	158.64636 ± 10.24629

Figure S26: Hydrolysis of 0.5 mM free guest **4** in 150 mM NaOH in 40% acetone-d_6/D_2O (two trials).



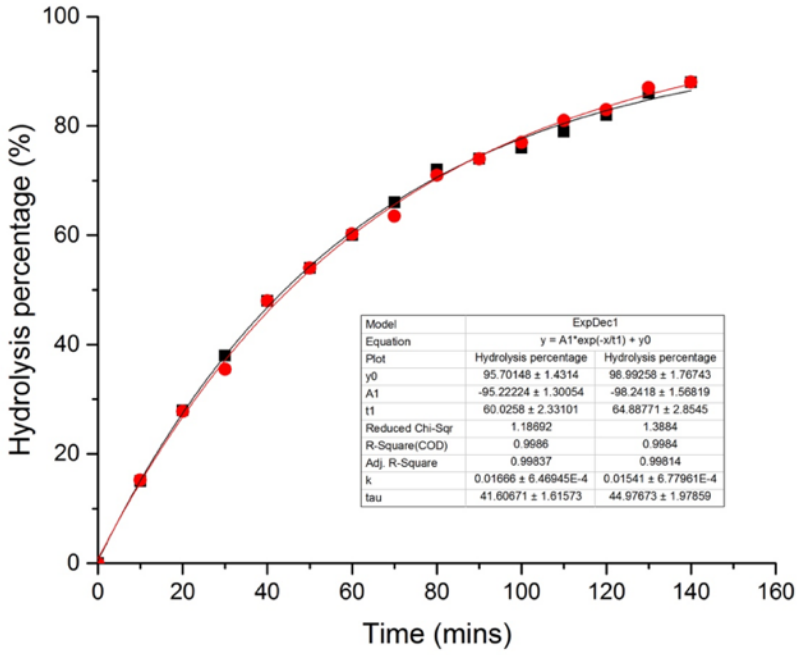
Model	ExpDec1	
Equation	y = A1*exp(-x/t1) + y0	
Plot	Hydrolysis percentage	Hydrolysis percentage
y0	98.24003 ± 0.95746	94.49782 ± 1.9936
A1	-97.73682 ± 0.84643	-94.2155 ± 1.80073
t1	62.9708 ± 1.46155	57.43273 ± 3.06894
Reduced Chi-Sqr	0.331	1.96948
R-Square(COD)	0.99962	0.99767
Adj. R-Square	0.99955	0.99725
k	0.01588 ± 3.68583E-4	0.01741 ± 9.304E-4
tau	43.64803 ± 1.01307	39.80934 ± 2.12723

Figure S27: Hydrolysis of 0.5 mM free guest **5** in 150 mM NaOH in 40% acetone-d_6/D_2O (two trials).



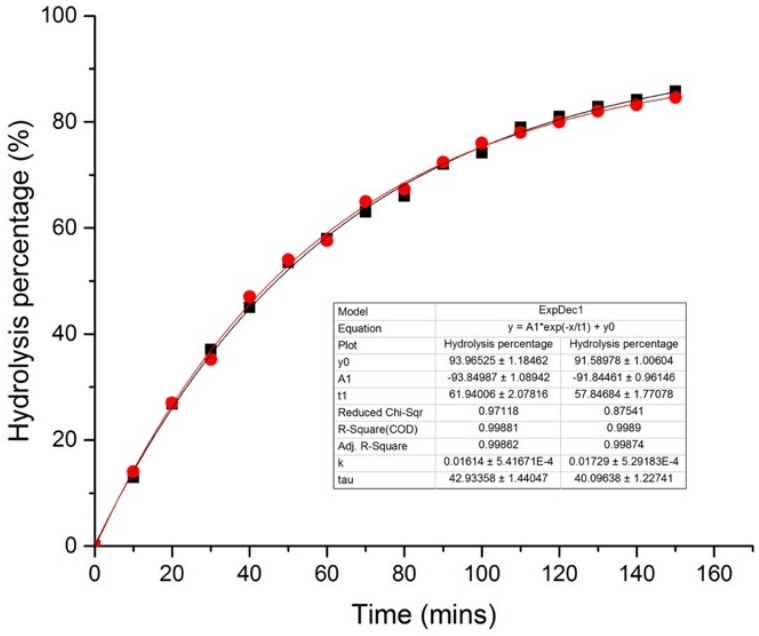
Model	ExpDec1	
Equation	y = A1*exp(-x/t1) + y0	
Plot	Hydrolysis percentage	Hydrolysis percentage
y0	99.76477 ± 1.91925	100.97159 ± 2.9221
A1	-99.05515 ± 1.68958	-101.13053 ± 2.57198
t1	58.61238 ± 2.63024	58.71639 ± 3.92472
Reduced Chi-Sqr	1.18202	2.72295
R-Square(COD)	0.99865	0.99701
Adj. R-Square	0.9984	0.99647
k	0.01706 ± 7.65625E-4	0.01703 ± 0.00114
tau	40.62701 ± 1.82314	40.6991 ± 2.72041

Figure S28: Hydrolysis of 0.5 mM free guest **6** in 150 mM NaOH in 40% acetone-d_6/D_2O (two trials).



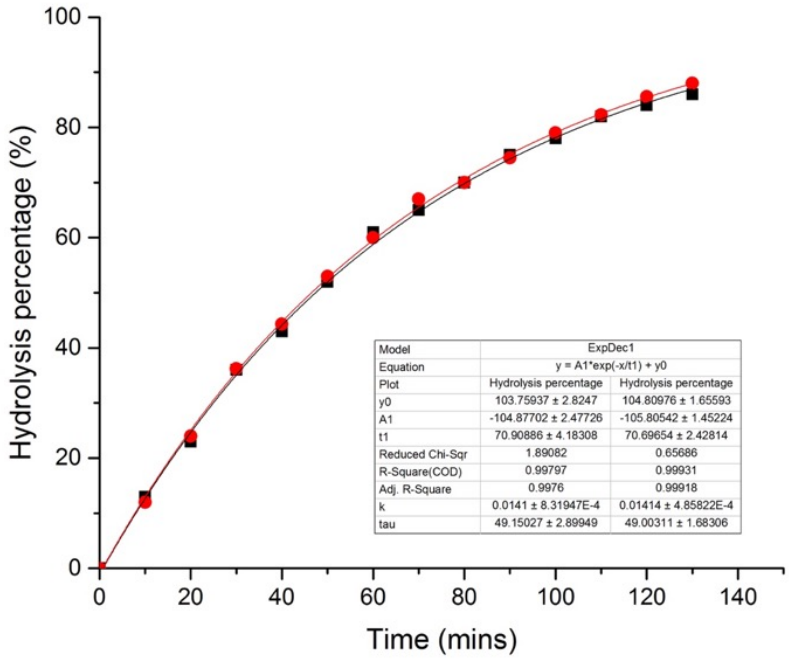
Model	ExpDec1	
Equation	y = A1*exp(-x/t1) + y0	
Plot	Hydrolysis percentage	Hydrolysis percentage
y0	95.70148 ± 1.4314	98.99258 ± 1.76743
A1	-95.22224 ± 1.30054	-98.2418 ± 1.56819
t1	60.0258 ± 2.33101	64.88771 ± 2.8545
Reduced Chi-Sqr	1.18692	1.3884
R-Square(COD)	0.9986	0.9984
Adj. R-Square	0.99837	0.99814
k	0.01666 ± 6.46945E-4	0.01541 ± 6.77961E-4
tau	41.60671 ± 1.61573	44.97673 ± 1.97859

Figure S29: Hydrolysis of 0.5 mM free guest **7** in 150 mM NaOH in 40% acetone-d_6/D_2O (two trials).



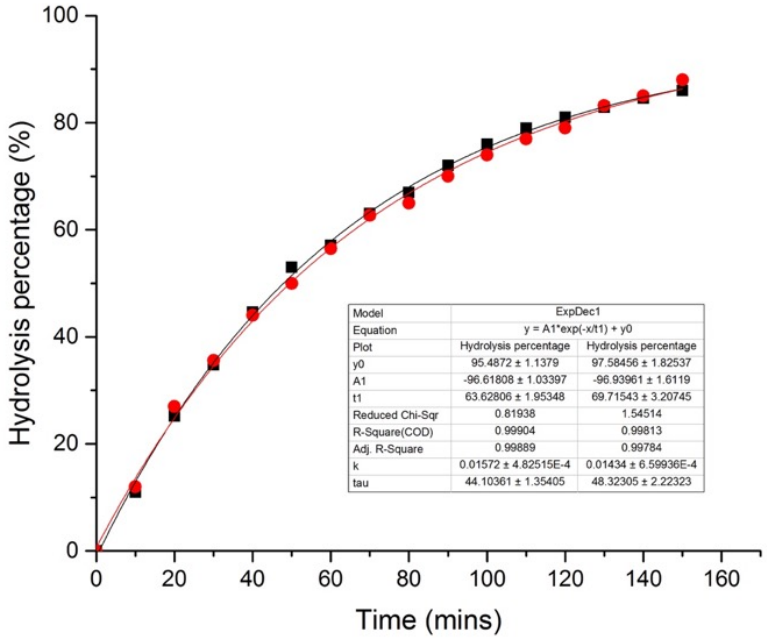
Model	ExpDec1	
Equation	y = A1*exp(-x/t1) + y0	
Plot	Hydrolysis percentage	Hydrolysis percentage
y0	93.96525 ± 1.18462	91.58978 ± 1.00604
A1	-93.84987 ± 1.08942	-91.84461 ± 0.96146
t1	61.94006 ± 2.07816	57.84684 ± 1.77078
Reduced Chi-Sqr	0.97118	0.87541
R-Square(COD)	0.99881	0.9989
Adj. R-Square	0.99862	0.99874
k	0.01614 ± 5.41671E-4	0.01729 ± 5.29183E-4
tau	42.93358 ± 1.44047	40.09638 ± 1.22741

Figure S30: Hydrolysis of 0.5 mM free guest **8** in 150 mM NaOH in 40% acetone-d_6/D_2O (two trials).



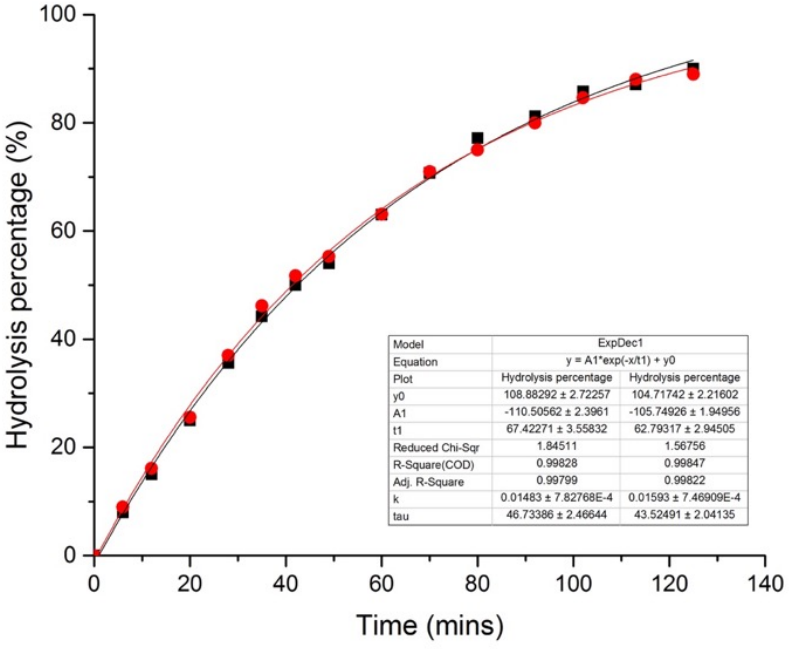
Model	ExpDec1	
Equation	y = A1*exp(-x/t1) + y0	
Plot	Hydrolysis percentage	Hydrolysis percentage
y0	103.75937 ± 2.8247	104.80976 ± 1.65593
A1	-104.87702 ± 2.47726	-105.80542 ± 1.45224
t1	70.90886 ± 4.18308	70.69654 ± 2.42814
Reduced Chi-Sqr	1.89082	0.65686
R-Square(COD)	0.99797	0.99931
Adj. R-Square	0.9976	0.99918
k	0.0141 ± 8.31947E-4	0.01414 ± 4.85822E-4
tau	49.15027 ± 2.89949	49.00311 ± 1.68306

Figure S31: Hydrolysis of 0.5 mM free guest **9** in 150 mM NaOH in 40% acetone-d_6/D_2O (two trials).



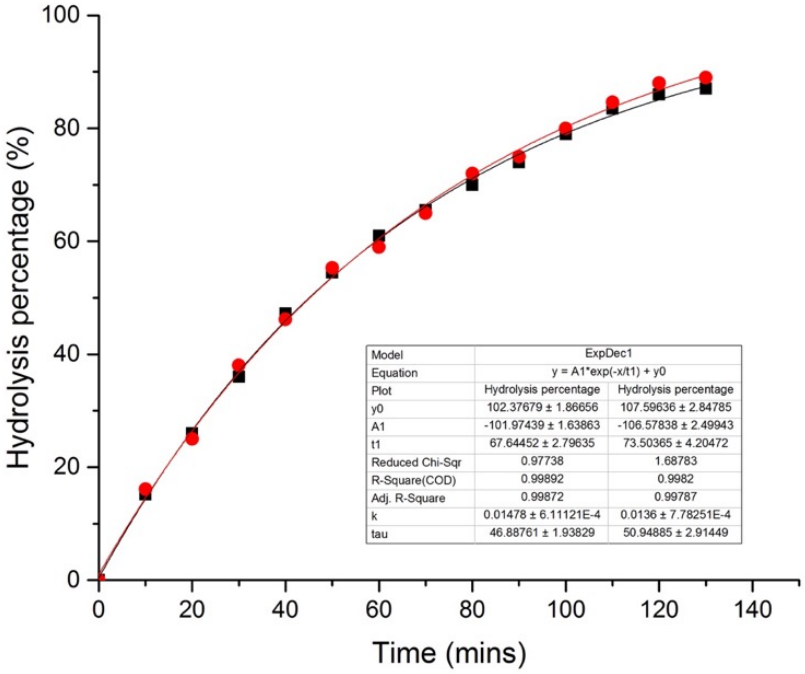
Model	ExpDec1	
Equation	y = A1*exp(-x/t1) + y0	
Plot	Hydrolysis percentage	Hydrolysis percentage
y0	95.4872 ± 1.1379	97.58456 ± 1.82537
A1	-96.61808 ± 1.03397	-96.93961 ± 1.6119
t1	63.62806 ± 1.95348	69.71543 ± 3.20745
Reduced Chi-Sqr	0.81938	1.54514
R-Square(COD)	0.99904	0.99813
Adj. R-Square	0.99889	0.99784
k	0.01572 ± 4.82515E-4	0.01434 ± 6.59936E-4
tau	44.10361 ± 1.35405	48.32305 ± 2.22323

Figure S32: Hydrolysis of 0.5 mM free guest **10** in 150 mM NaOH in 40% acetone-d_6/D_2O (two trials).



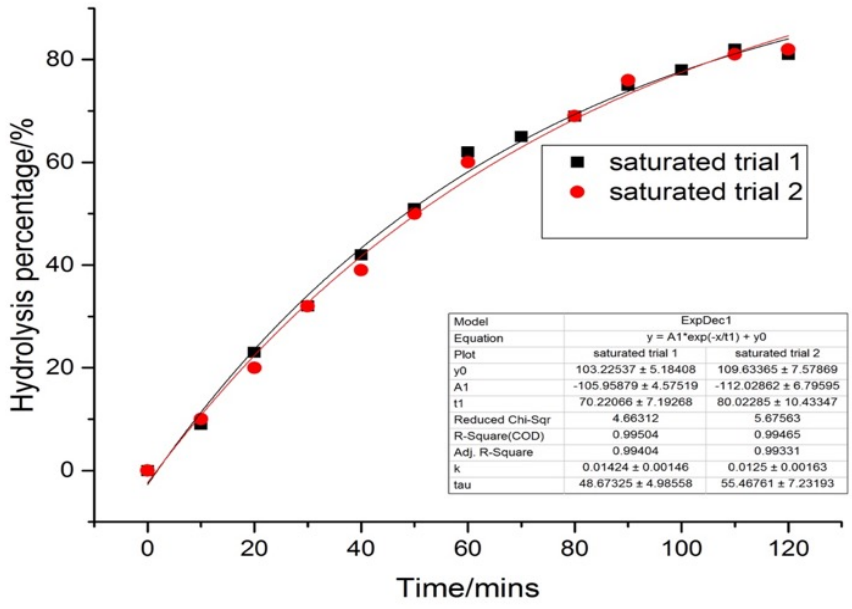
Model	ExpDec1	
Equation	y = A1*exp(-x/t1) + y0	
Plot	Hydrolysis percentage	Hydrolysis percentage
y0	108.88292 ± 2.72257	104.71742 ± 2.21602
A1	-110.50562 ± 2.3961	-105.74926 ± 1.94956
t1	67.42271 ± 3.55832	62.79317 ± 2.94505
Reduced Chi-Sqr	1.84511	1.56756
R-Square(COD)	0.99828	0.99847
Adj. R-Square	0.99799	0.99822
k	0.01483 ± 7.82768E-4	0.01593 ± 7.46909E-4
tau	46.73386 ± 2.46644	43.52491 ± 2.04135

Figure S33: Hydrolysis of 0.5 mM free guest **11** in 150 mM NaOH in 40% acetone-d_6/D_2O (two trials).



Model	ExpDec1	
Equation	y = A1*exp(-x/t1) + y0	
Plot	Hydrolysis percentage	Hydrolysis percentage
y0	102.37679 ± 1.86656	107.59636 ± 2.84785
A1	-101.97439 ± 1.63863	-106.57838 ± 2.49943
t1	67.64452 ± 2.79635	73.50365 ± 4.20472
Reduced Chi-Sqr	0.97738	1.68783
R-Square(COD)	0.99892	0.9982
Adj. R-Square	0.99872	0.99787
k	0.01478 ± 6.11121E-4	0.0136 ± 7.78251E-4
tau	46.88761 ± 1.93829	50.94885 ± 2.91449

Figure S34: Hydrolysis of 0.5 mM free guest **12** in 150 mM NaOH in 40% acetone-d_6/D_2O (two trials).



Model	ExpDec1	
Equation	y = A1*exp(-x/t1) + y0	
Plot	saturated trial 1	saturated trial 2
y0	103.22537 ± 5.18408	109.63365 ± 7.57869
A1	-105.95879 ± 4.57519	-112.02862 ± 6.79595
t1	70.22066 ± 7.19268	80.02285 ± 10.43347
Reduced Chi-Sqr	4.66312	5.67563
R-Square(COD)	0.99504	0.99465
Adj. R-Square	0.99404	0.99331
k	0.01424 ± 0.00146	0.0125 ± 0.00163
tau	48.67325 ± 4.98558	55.46761 ± 7.23193

Figure S35: Hydrolysis of 0.5 mM encapsulated guest **2** in 150 mM NaOH in D_2O (two trials).

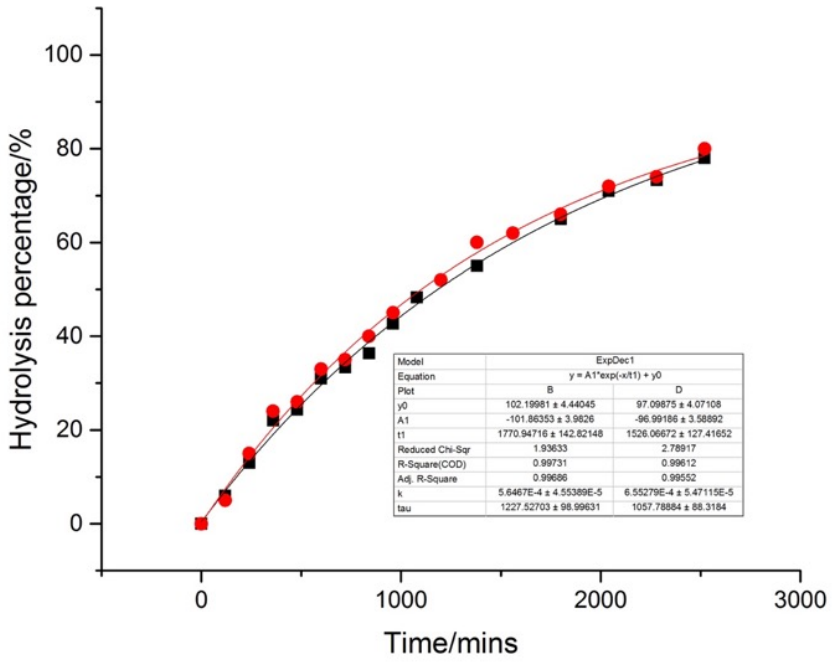


Figure S36: Hydrolysis of 0.5 mM encapsulated guest **3** in 150 mM NaOH in D_2O (two trials).

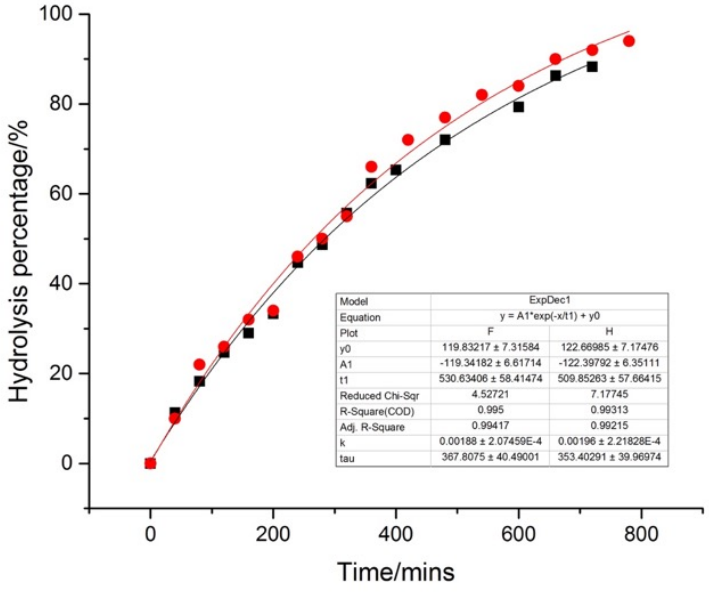
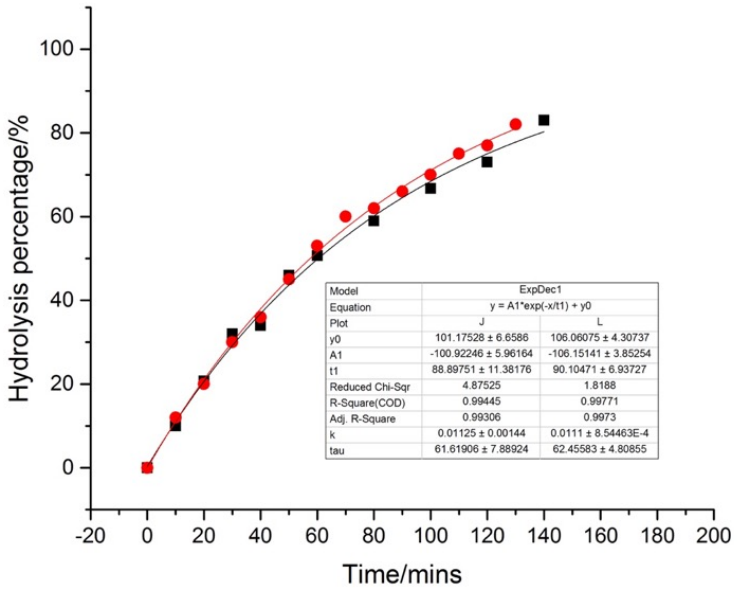
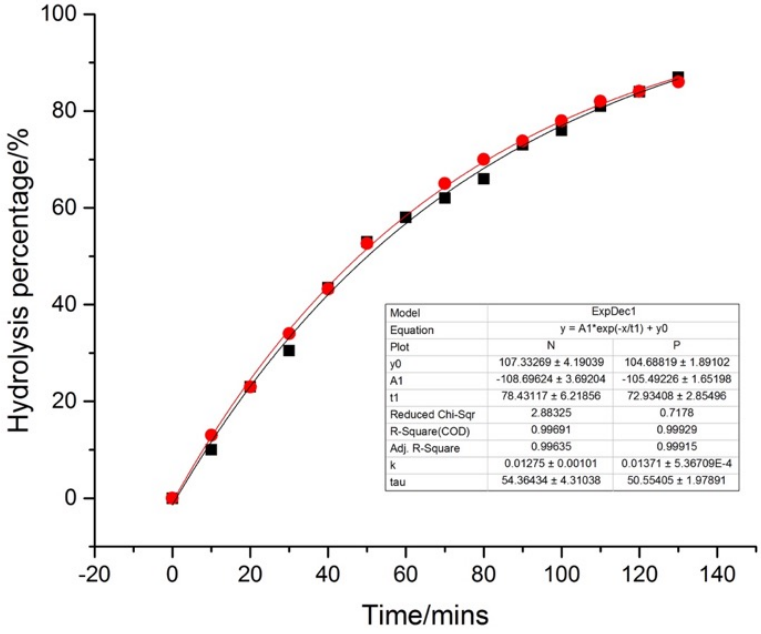


Figure S37: Hydrolysis of 0.5 mM encapsulated guest **4** in 150 mM NaOH in D_2O (two trials).



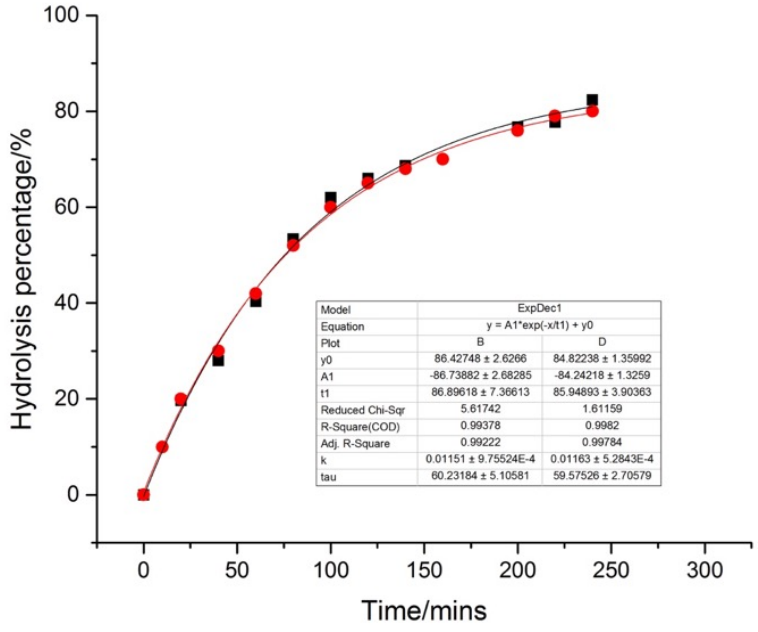
Model	ExpDec1	
Equation	y = A1*exp(-x/t1) + y0	
Plot	J	L
y0	101.17528 ± 6.6586	106.06075 ± 4.30737
A1	-100.92246 ± 5.96164	-106.15141 ± 3.85254
t1	88.89751 ± 11.38176	90.10471 ± 6.93727
Reduced Chi-Sqr	4.87525	1.8188
R-Square(COD)	0.99445	0.99771
Adj. R-Square	0.99306	0.9973
k	0.01125 ± 0.00144	0.0111 ± 8.54463E-4
tau	61.61906 ± 7.88924	62.45583 ± 4.80855

Figure S38: Hydrolysis of 0.5 mM encapsulated guest **5** in 150 mM NaOH in D_2O (two trials).



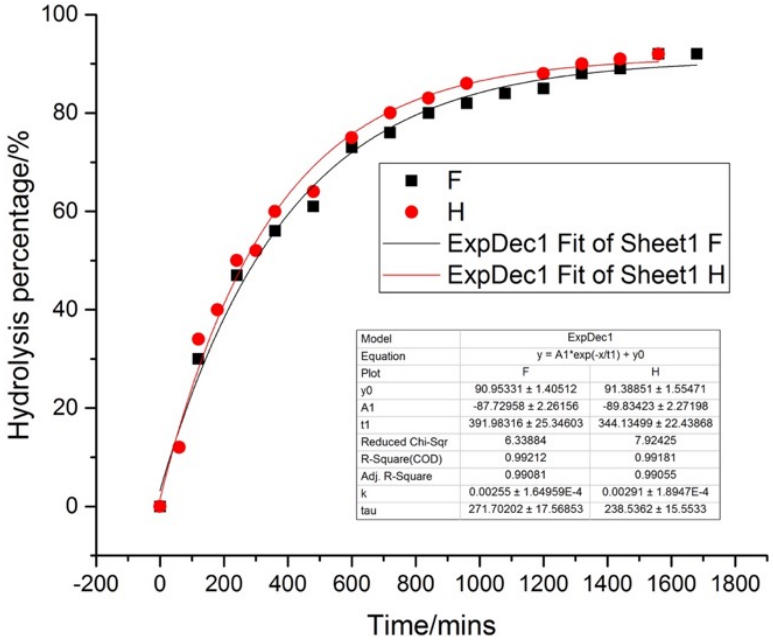
Model	ExpDec1	
Equation	y = A1*exp(-x/t1) + y0	
Plot	N	P
y0	107.33269 ± 4.19039	104.68819 ± 1.89102
A1	-108.69624 ± 3.69204	-105.49226 ± 1.65198
t1	78.43117 ± 6.21856	72.93408 ± 2.85496
Reduced Chi-Sqr	2.88325	0.7178
R-Square(COD)	0.99691	0.99929
Adj. R-Square	0.99635	0.99915
k	0.01275 ± 0.00101	0.01371 ± 5.36709E-4
tau	54.36434 ± 4.31038	50.55405 ± 1.97891

Figure S39: Hydrolysis of 0.5 mM encapsulated guest **6** in 150 mM NaOH in D_2O (two trials).



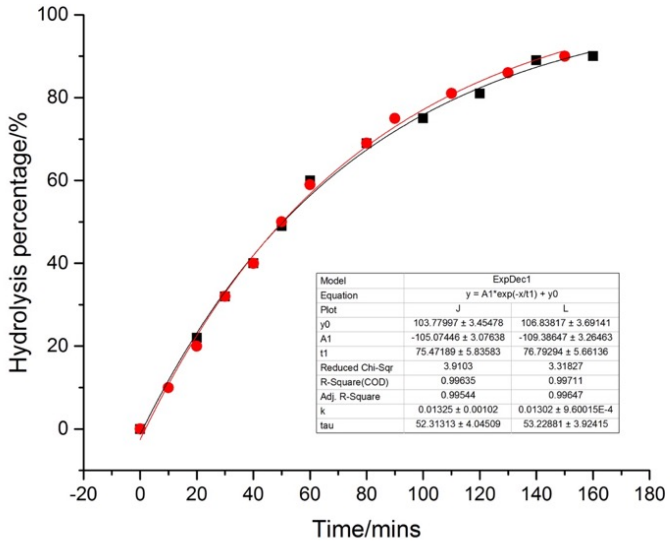
Model	ExpDec1	
Equation	y = A1*exp(-x/t1) + y0	
Plot	B	D
y0	86.42748 ± 2.6266	84.82238 ± 1.35992
A1	-86.73882 ± 2.68285	-84.24218 ± 1.3259
t1	86.89618 ± 7.36613	85.94893 ± 3.90363
Reduced Chi-Sqr	5.61742	1.61159
R-Square(COD)	0.99378	0.9982
Adj. R-Square	0.99222	0.99784
k	0.01151 ± 9.75524E-4	0.01163 ± 5.2843E-4
tau	60.23184 ± 5.10581	59.57526 ± 2.70579

Figure S40: Hydrolysis of 0.5 mM encapsulated guest **7** in 150 mM NaOH in D_2O (two trials).



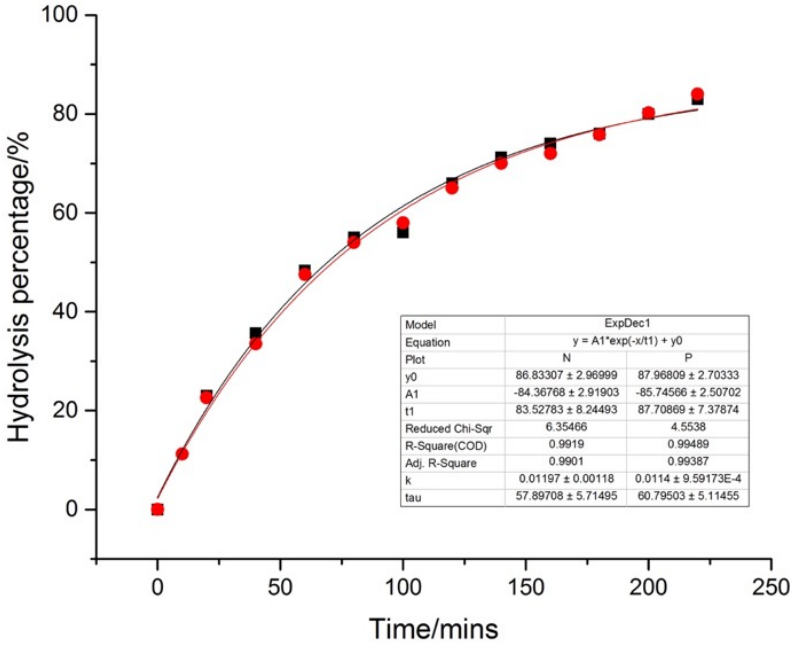
Model	ExpDec1	
Equation	y = A1*exp(-x/t1) + y0	
Plot	F	H
y0	90.95331 ± 1.40512	91.38851 ± 1.55471
A1	-87.72958 ± 2.26156	-89.83423 ± 2.27198
t1	391.98316 ± 25.34603	344.13499 ± 22.43868
Reduced Chi-Sqr	6.33884	7.92425
R-Square(COD)	0.99212	0.99181
Adj. R-Square	0.99081	0.99055
k	0.00255 ± 1.64959E-4	0.00291 ± 1.8947E-4
tau	271.70202 ± 17.56853	238.5362 ± 15.5533

Figure S41: Hydrolysis of 0.5 mM encapsulated guest **8** in 150 mM NaOH in D_2O (two trials).



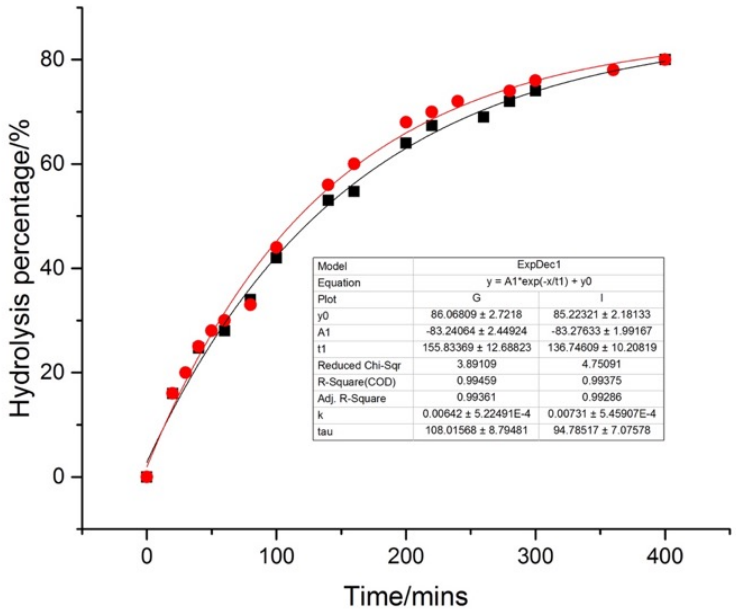
Model	ExpDec1	
Equation	y = A1*exp(-x/t1) + y0	
Plot	J	L
y0	103.77997 ± 3.45478	106.83817 ± 3.69141
A1	-105.07446 ± 3.07638	-109.38647 ± 3.26463
t1	75.47189 ± 5.83583	76.79294 ± 5.66136
Reduced Chi-Sqr	3.9103	3.31827
R-Square(COD)	0.99635	0.99711
Adj. R-Square	0.99544	0.99647
k	0.01325 ± 0.00102	0.01302 ± 9.60015E-4
tau	52.31313 ± 4.04509	53.22881 ± 3.92415

Figure S42: Hydrolysis of 0.5 mM encapsulated guest **9** in 150 mM NaOH in D_2O (two trials).



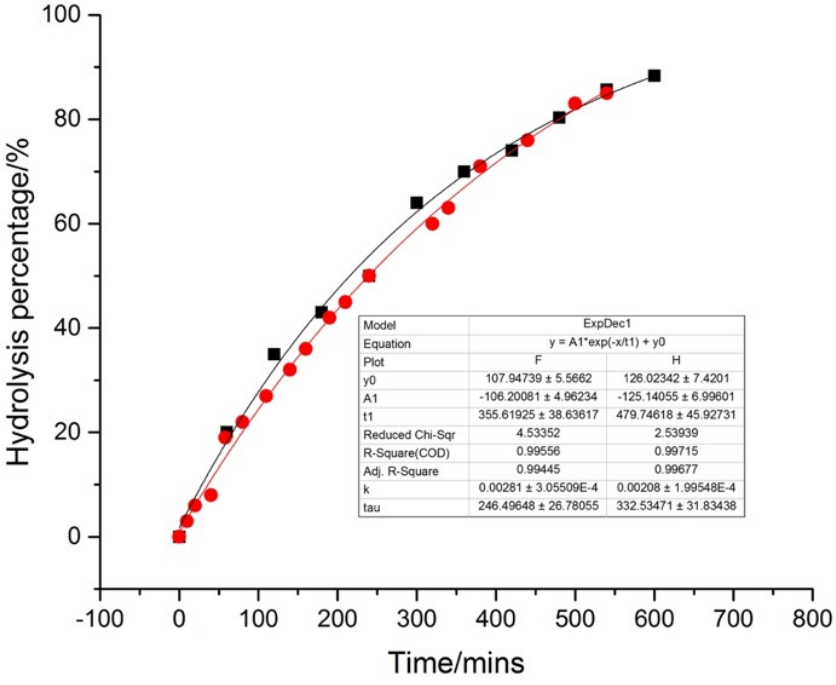
Model	ExpDec1	
Equation	y = A1*exp(-x/t1) + y0	
Plot	N	P
y0	86.83307 ± 2.96999	87.96809 ± 2.70333
A1	-84.36768 ± 2.91903	-85.74566 ± 2.50702
t1	83.52783 ± 8.24493	87.70869 ± 7.37874
Reduced Chi-Sqr	6.35466	4.5538
R-Square(COD)	0.9919	0.99489
Adj. R-Square	0.9901	0.99387
k	0.01197 ± 0.00118	0.0114 ± 9.59173E-4
tau	57.89708 ± 5.71495	60.79503 ± 5.11455

Figure S43: Hydrolysis of 0.5 mM encapsulated guest **10** in 150 mM NaOH in D_2O (two trials).



Model	ExpDec1	
Equation	y = A1*exp(-x/t1) + y0	
Plot	G	I
y0	86.06809 ± 2.7218	85.22321 ± 2.18133
A1	-83.24064 ± 2.44924	-83.27633 ± 1.99167
t1	155.83369 ± 12.68823	136.74609 ± 10.20819
Reduced Chi-Sqr	3.89109	4.75091
R-Square(COD)	0.99459	0.99375
Adj. R-Square	0.99361	0.99286
k	0.00642 ± 5.22491E-4	0.00731 ± 5.45907E-4
tau	108.01568 ± 8.79481	94.78517 ± 7.07578

Figure S44: Hydrolysis of 0.5 mM encapsulated guest **11** in 150 mM NaOH in D_2O (two trials).



Model	ExpDec1	
Equation	y = A1*exp(-x/t1) + y0	
Plot	F	H
y0	107.94739 ± 5.5662	126.02342 ± 7.4201
A1	-106.20081 ± 4.96234	-125.14055 ± 6.99601
t1	355.61925 ± 38.63617	479.74618 ± 45.92731
Reduced Chi-Sqr	4.53352	2.53939
R-Square(COD)	0.99556	0.99715
Adj. R-Square	0.99445	0.99677
k	0.00281 ± 3.05509E-4	0.00208 ± 1.99548E-4
tau	246.49648 ± 26.78055	332.53471 ± 31.83438

Figure S45: Hydrolysis of 0.5 mM encapsulated guest **12** in 150 mM NaOH in D_2O (two trials).

5 Competition experiments

Based on the above results, competition experiments involving the best-protected guest (**8**) with two of the poorest protected guests (**7** and **10**) were carried out. In these experiments, a ratio of host to guests of 4:1:1([host] = 1 mM, [guest 1] = 0.25 mM, [guest 2] =0.25 mM) was required to ensure homogeneity. Integration of the terminal $–CH_3$ group of ester and acid allowed the calculation of the amount of remaining (strongly protected) guest when 100% of the less protected guest had undergone complete hydrolysis. Figure S46 shows the hydrolysis of encapsulated ester **7** and **8** within host **1** as a function of time. When 100% of **7** was hydrolyzed 34% of **8** had been hydrolyzed. Figure S47 shows the corresponding data for **8** and **10**. When 100% of **10** was hydrolyzed, only 32% of **8** was hydrolyzed.

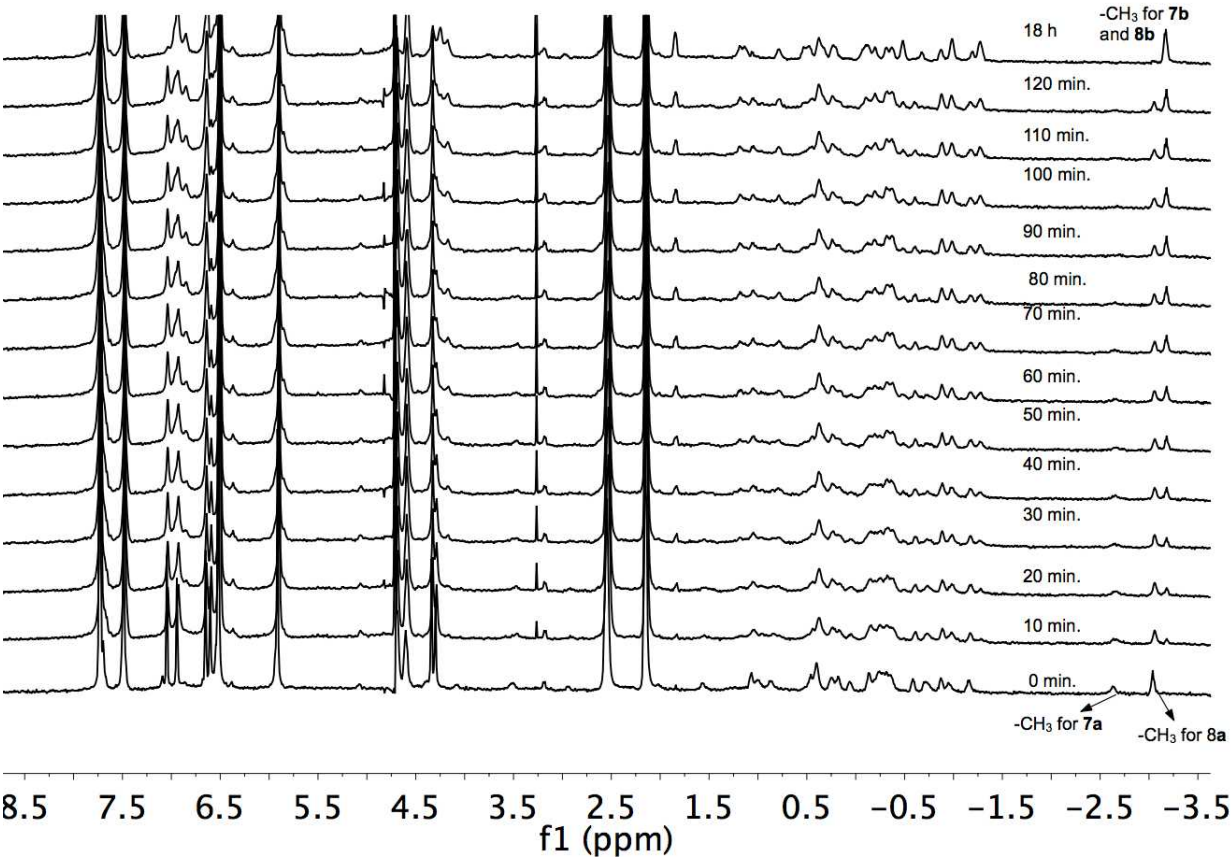


Figure S46: Stacked 1H NMR spectra for the hydrolysis of encapsulated ester **7** and **8** within host **1** as a function of time. (D_2O, 25 ˚C, ([host] = 1 mM, [**7**] = 0.25 mM, [**8**] =0.25 mM).

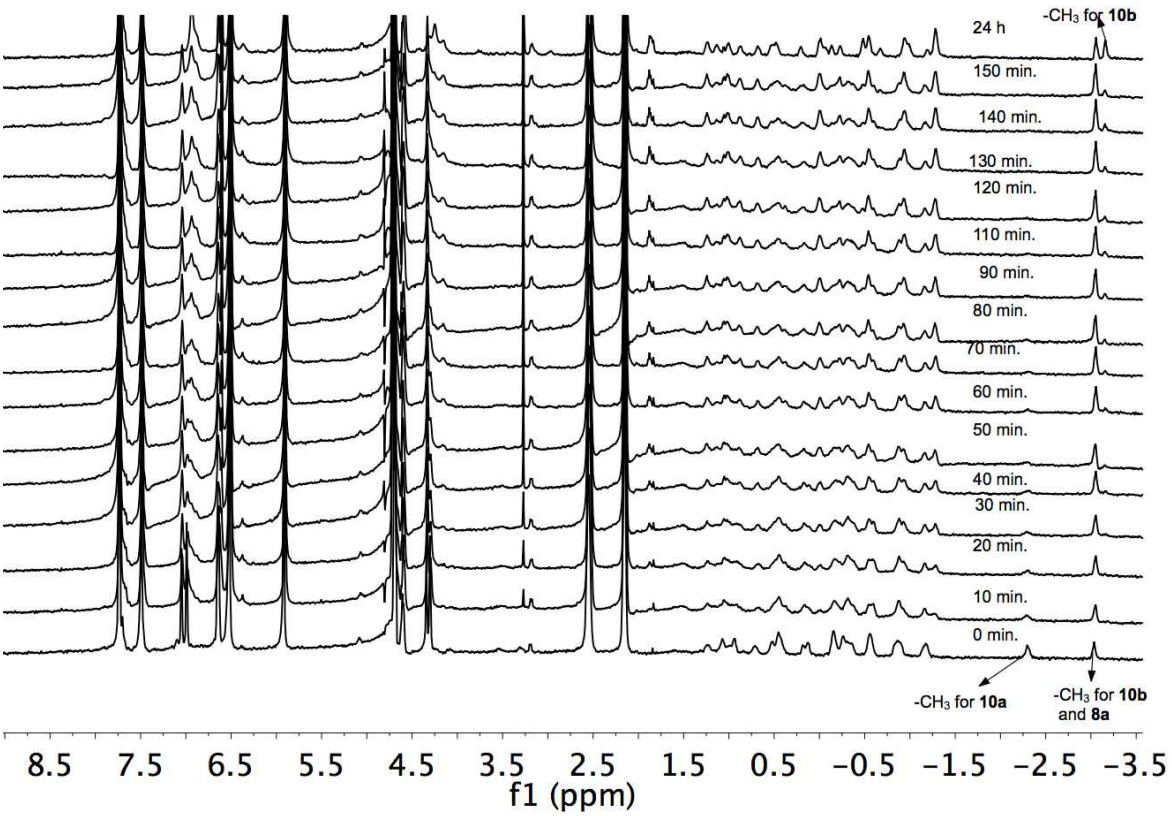


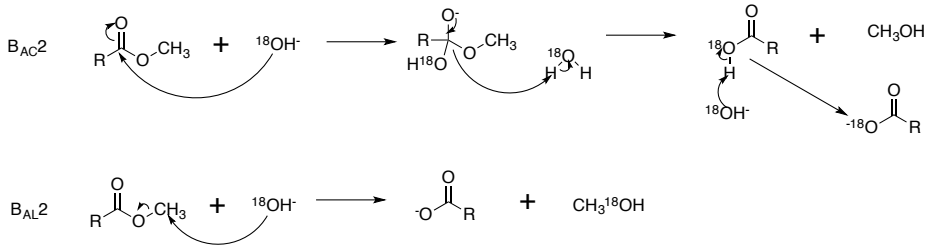
Figure S47: Stacked ^{1}H NMR spectra for the hydrolysis of encapsulated ester **8** and **10** within host **1** as a function of time. (D_2O, 25 ˚C, ([host] = 1 mM, [**8**] = 0.25 mM, [**10**] =0.25 mM).

6 Mechanistic studies of the hydrolysis of encapsulated esters using $H_2{}^{18}O$

The guests esters could in principle be hydrolyzed by as many as four different mechanisms under basic conditions.[4] The $B_{AC}2$ hydrolysis (Scheme S1) is the most common mechanism. However, for methyl esters possessing large, bulky alkyl groups there is also the possibility of hydrolysis occurring through a $B_{AL}2$ mechanism.

To explore the hydrolysis mechanism of encapsulated esters reaction, the hydrolysis of guests **6**, **7**, **8**, **11**, **12** were carried out in $H_2{}^{18}O$. Thus, 92 mg of cleaned sodium metal (washed in pentane to remove mineral oil) was added to 1 mL $H_2{}^{18}O$ to make a 4 M $Na^{18}OH$ stock solution. A 1 mM solution of host **1** in 8 mM $Na^{18}OH$ was then formed using $H_2{}^{18}O$ and the corresponding complex formed by stirring excess guests with the solution of host **1**. This solution/suspension was then filter through a 0.1 μm Durapore Hydrophilic PVDF (polyvinylidene fluoride) filter membrane to get remove excess guest. 30 μL of 4 M $Na^{18}OH$ solution was then added, and the solution stirred gently for 24 h to bring about hydrolysis. Chloroform was then added to extract the hydrolysis product, the organic layer dried with anhydrous magnesium sulfate, and the solvent removed under reduced pressure.

ESI-MS data was collected from methanol solutions of the extract in positive ion mode. Ions were continuously generated by infusing the MeOH solution samples into the source with a syringe pump at flow rates of 6 μL/min. The parameters were adjusted typically as follows: capillary voltage (–4.1 kV); capillary exit voltage (140 V); skimmer voltage (40 V); and drying gas temperature (200 °C). All experiments were carried out with a nebulizer gas pressure of 0.3 Bar and a drying gas flow of 4.0 L/min. Figure S49–S53 shows the resulting data. The unlabeled acid derivatives ($C_{18}H_{34}O_2$, Mw = 282 g/mol) were observed as the carboxylate plus two sodium ions and appeared as m/z 327.2, 328.2 and 329.2 (e.g., Figure S48, upper portion). This matched the predicted MS (Figure S48, lower portion). The m/z shift of 2 Daltons for the ^{18}O isotope labeled sample ($C_{18}H_{33}O^{18}O$ + 2•Na^+) appeared at m/z 329.2, 330.2, and 331.2 and matched the theoretical. For the five samples examined (Figures S49–53, upper portions) the major species observed (> 90%) was the ^{18}O labeled species and not the calculated, unlabeled $C_{18}H_{33}O_2$+2•Na^+ (corresponding lower portions). The small peaks at m/z 327.2 and 328.2 corresponds to the unlabeled water derived from the 5% H_2O present in $H_2{}^{18}O$ sample.



Scheme S1: $B_{AC}2$ and $B_{AL}2$ mechanism for ester hydrolysis.

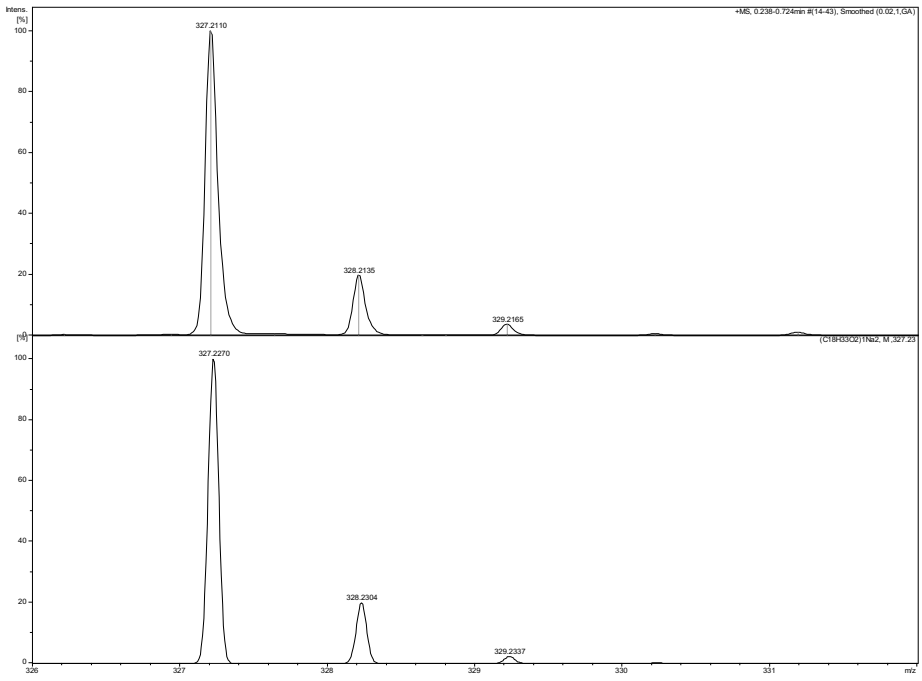


Figure S48: ESI-MS of hydrolysis product from guest **7** (top) in H_2O and theoretical calculations of normal acid **7** (below).

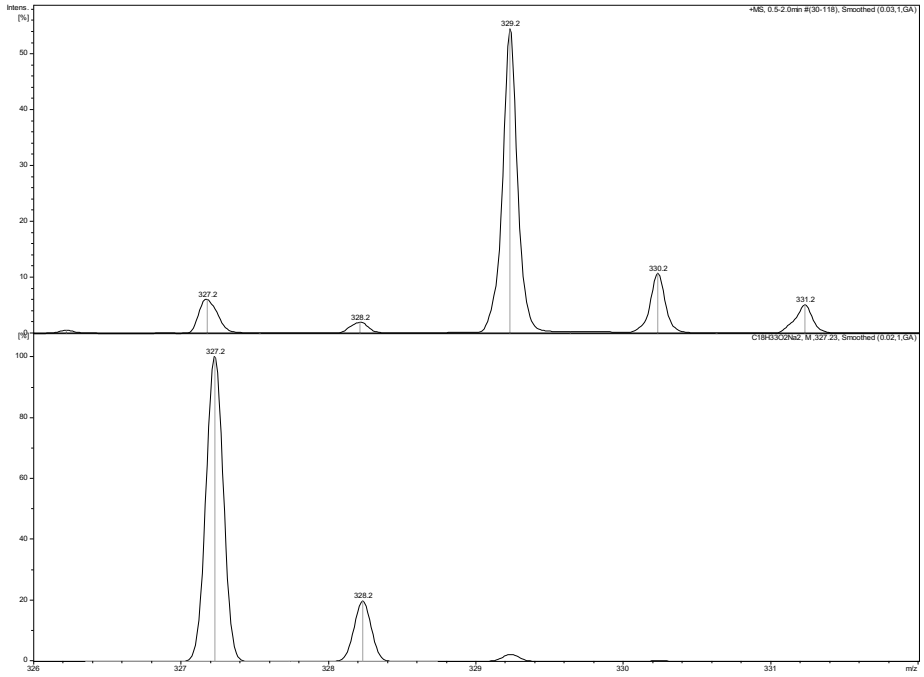


Figure S49: ESI-MS of hydrolysis product from guest **6** (top) in $H_2{}^{18}O$ and theoretical calculations of normal acid **6** (below).

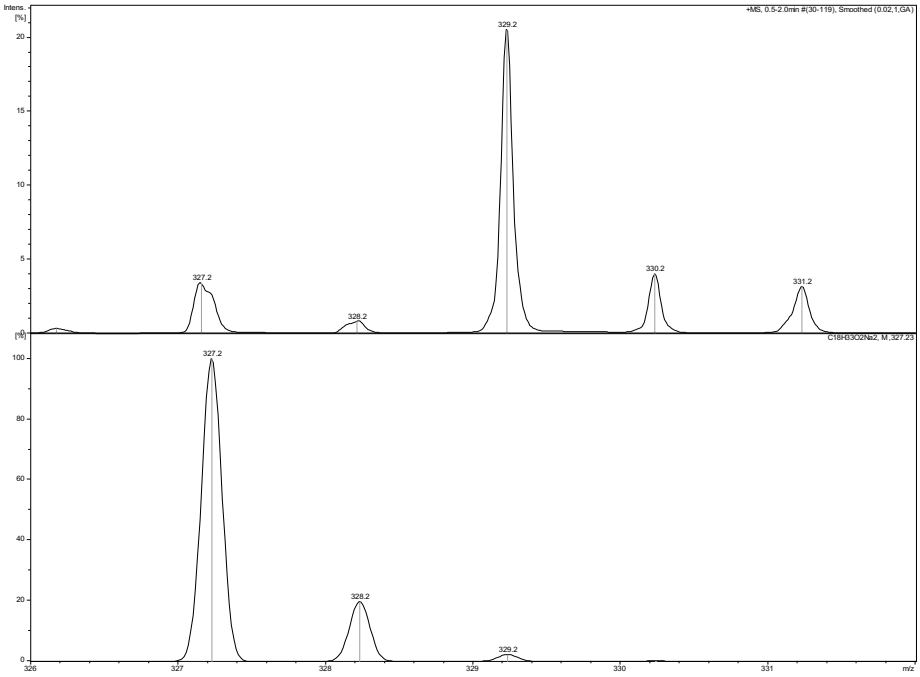


Figure S50: ESI-MS of hydrolysis product from guest **7** (top) in $H_2{}^{18}O$ and theoretical calculations of normal acid **7** (below).

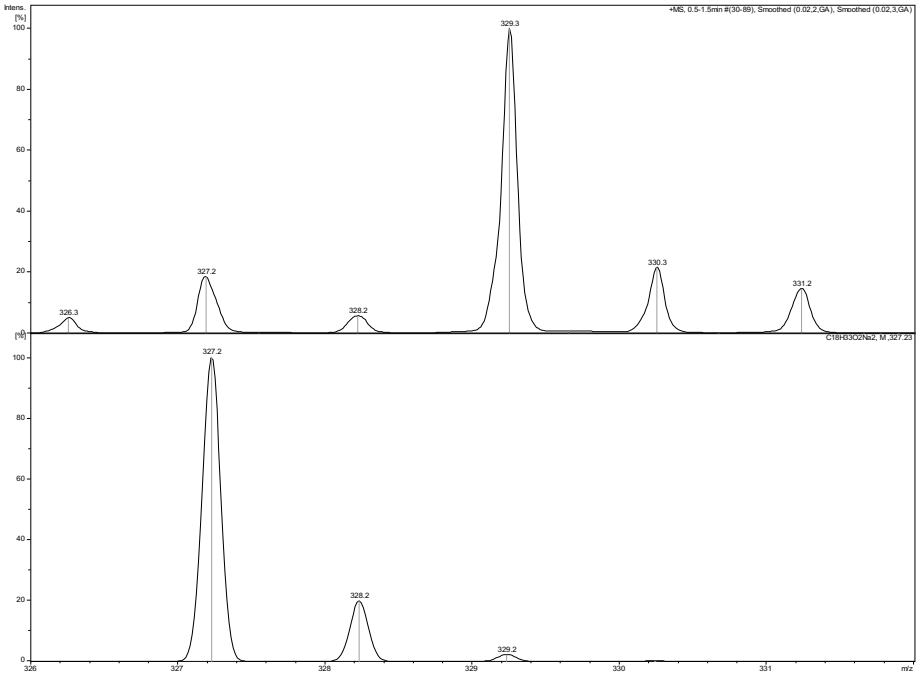


Figure S51: ESI-MS of hydrolysis product from guest **8** (top) in $H_2{}^{18}O$ and theoretical calculations of normal acid **8** (below).

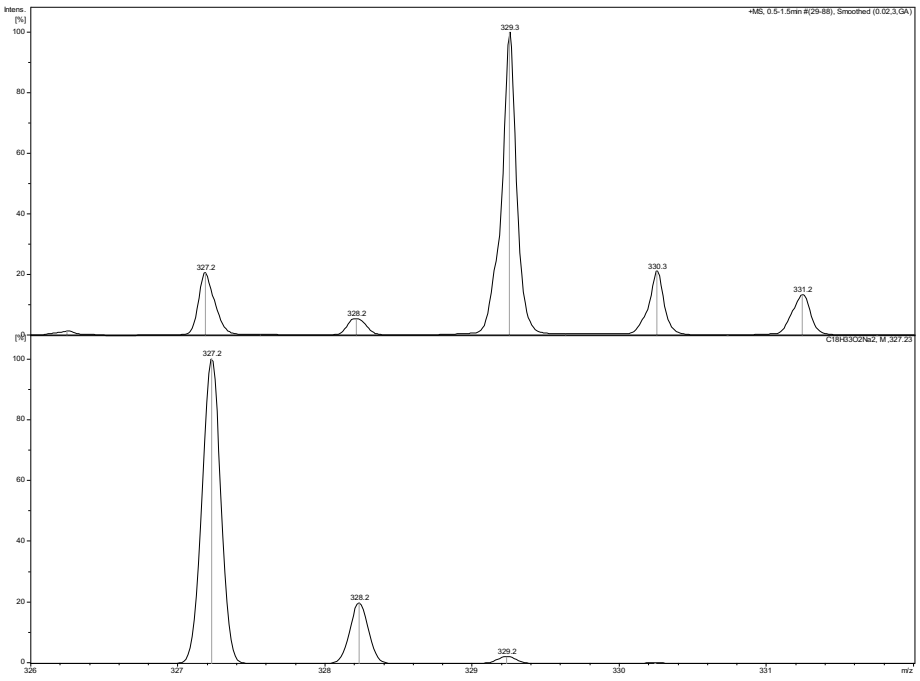


Figure S52: ESI-MS of hydrolysis product from guest **11** (top) in $H_2{}^{18}O$ and theoretical calculations of normal acid **11** (below).

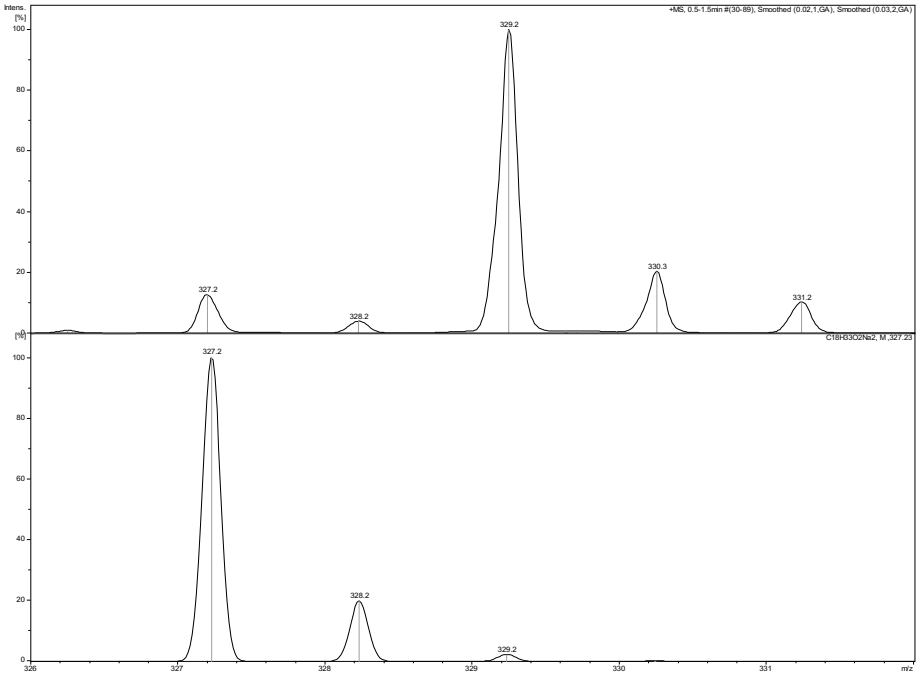


Figure S53: ESI-MS of hydrolysis product from guest **12** (top) in $H_2{}^{18}O$ and theoretical calculations of normal acid **12** (below).

7 References

1. (a) Liu, S.; Whisenhunt-Ioup, S. E.; Gibb, C. L.; Gibb, B. C., *Supramol Chem* **2011,** *23* (6), 480-485; (b) Gibb, C. L.; Gibb, B. C., *J Am Chem Soc* **2004,** *126* (37), 11408-9.
2. Wang, K.; Gibb, B. C., *J Org Chem* **2017**.
3. Liu, S.; Gan, H.; Hermann, A. T.; Rick, S. W.; Gibb, B. C., *Nat Chem* **2010,** *2* (10), 847-52.
4. Douglas, J. E.; Campbell, G.; Wigfield, D. C., *Canadian Journal of Chemistry* **1993,** *71* (11), 1841-1844.