

Supplementary Information

The 3-*N*-phenyl amide of *all-cis*-cyclopentane-1,2,3,4-tetracarboxylic acid as a potential pH-sensitive amine-releasing prodrug; intervention of imide formation around neutral pH

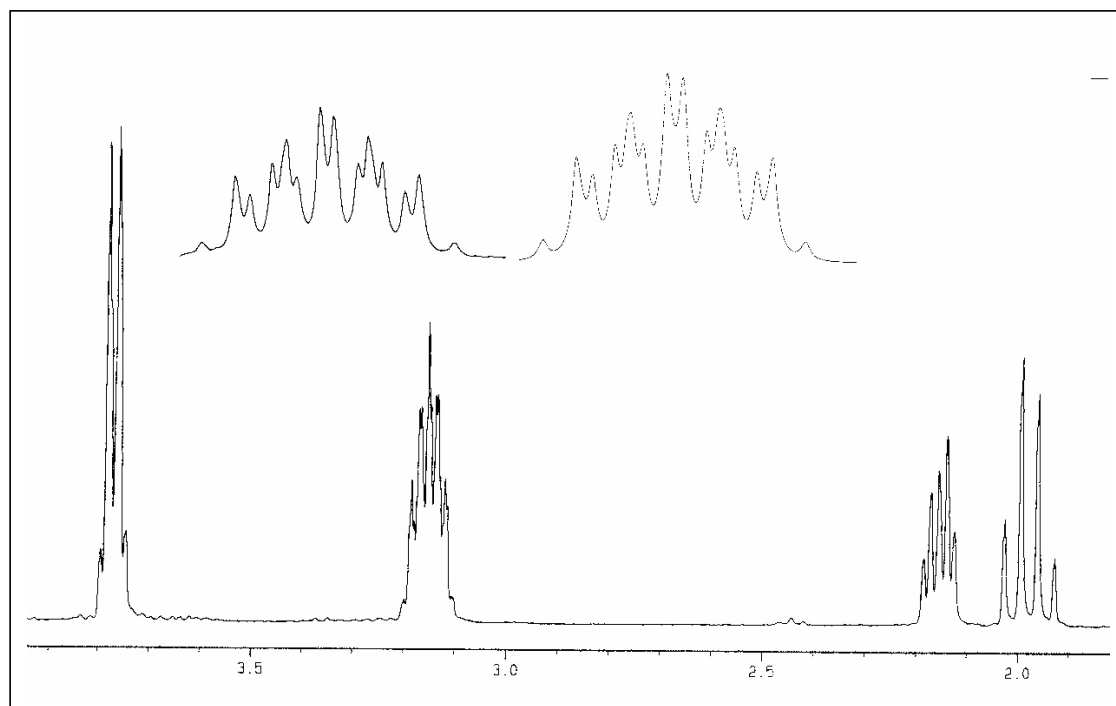
N. Guy Billett,^a Andrew T. Phillis,^a Lyndsay Main,^{a*} Brian K. Nicholson,^a
William A. Denny,^b and Michael P. Hay^b

- S1.** ¹H-NMR spectrum for **13** in D₂O with 1.5 mol equiv. NaOD added
S2. ¹H-NMR spectral changes for **10** in D₂O with 2.7 mol equiv. NaOD added
S3. ¹H-NMR spectral changes for **10** in D₂O buffered with pyrophosphate
S4. ¹H-NMR spectrum for **10** in D₂O buffered with pyrophosphate at completion with product ratio calculation from integration
S5. ¹H-NMR spectrum for **10** in D₂O buffered with deuterioacetate at completion with product ratio calculation by integration

S1. ¹H-NMR spectrum for 13 in D₂O with 1.5 mol equiv. NaOD added, showing expanded multiplet for H_{2,3}

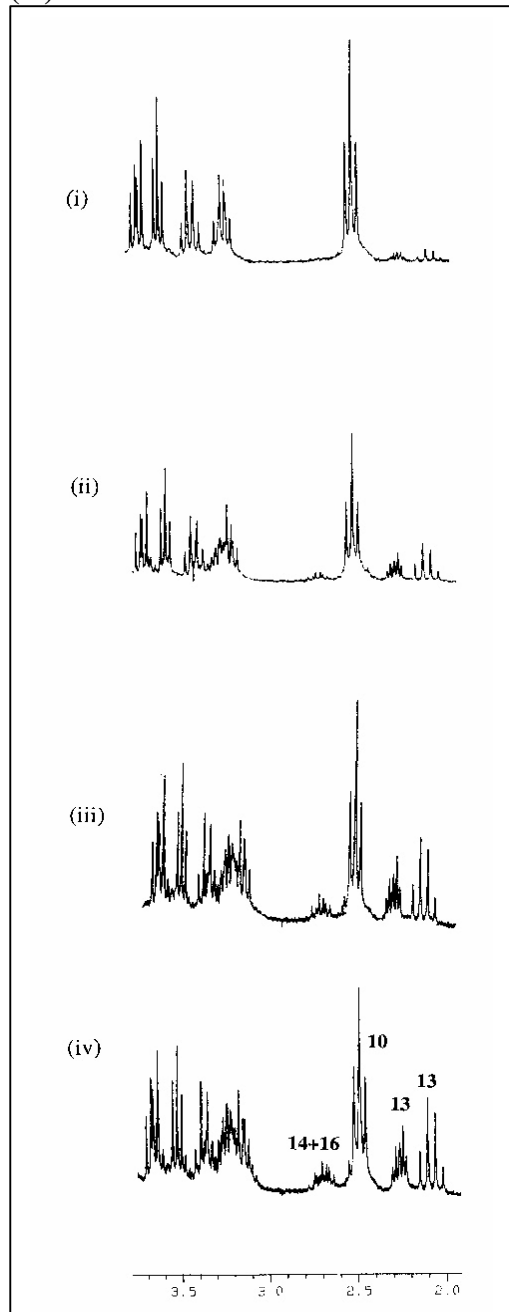
- *experimental* (on left)

- *simulated* (on right, based on coupling constants in the text)



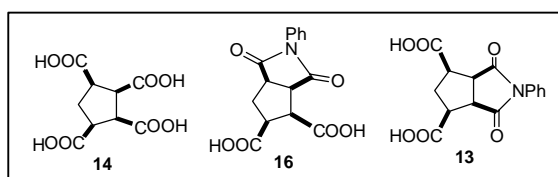
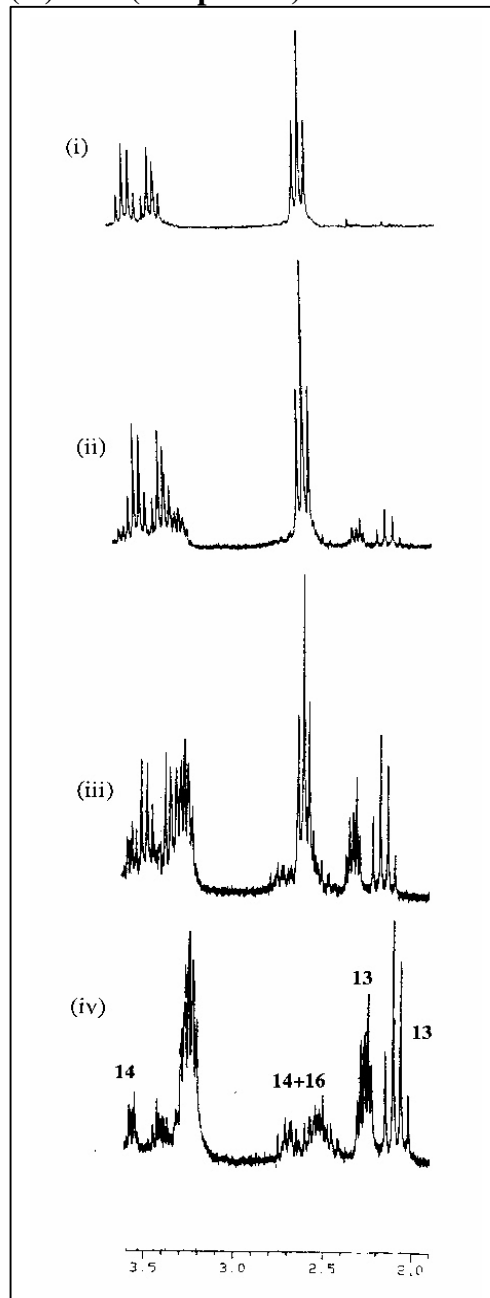
S2

^A ¹H-NMR spectral changes for the reaction of 10 in D₂O with 2.7 mol equiv. NaOD added: (i) 1.5 h; (ii) 6.5 h; (iii) 48 h; (iv) 72 h

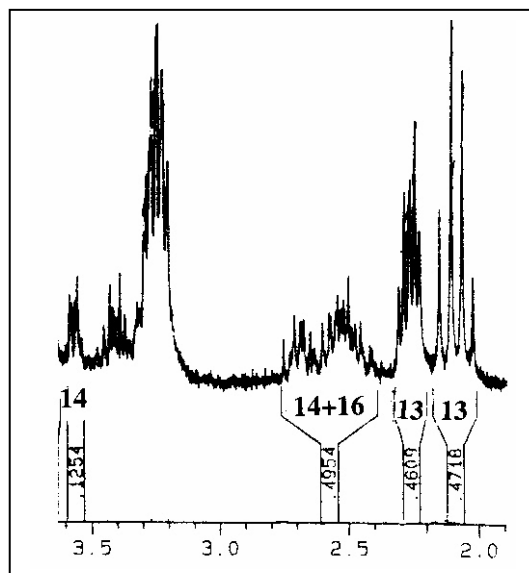
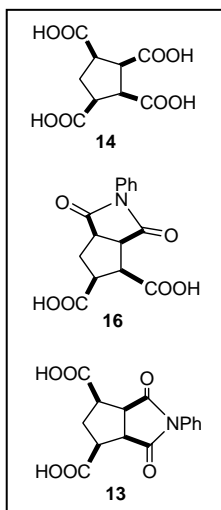


S3

^B ¹H-NMR spectral changes for the reaction of 10 in D₂O buffered with pyrophosphate: (i) 10 min; (ii) 2 h; (iii) 6.5 h (~ t_{1/2}); (iv) 72 h (completion)

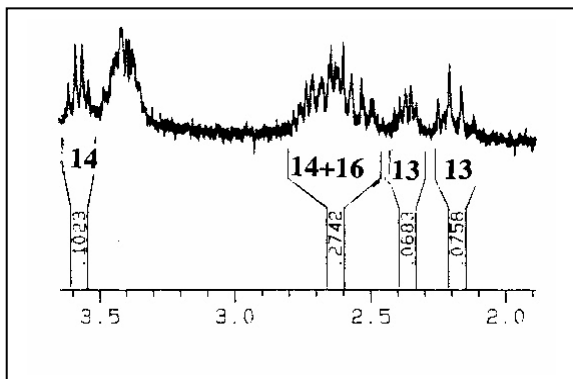


S4. $^1\text{H-NMR}$ spectrum for products from 10 in D_2O buffered with pyrophosphate (pD 6.53) at completion (72h), with product ratio calculation by integration (see table)



Pyrophosphate Buffer	14 (2H)	14 (2H) + 16 (2H)	13 (2H)
Signal (δ)	3.5-3.6	2.4-2.75	2.0-2.3
Integral ratio	1.0	4.0	7.5
Proportionation	1.0	1.0 (14) and 3.0 (16)	7.5
Calculated Percentage (± 5)	10 (14)	10 (14) and 25 (16)	65 (13)

S5. $^1\text{H-NMR}$ spectrum for products from **10** in D_2O buffered with deuterioacetate (pD 5.02) at completion (72h), with product ratio calculation from integration (see table)



Acetate buffer	14 (2H)	14 (2H) + 16 (2H)	13 (2H)
Signal (δ)	3.5-3.65	2.45-2.8	2.05-2.45
Integral ratio	1.0	2.7	1.4
Proportionation	1.0	1.0 (14) and 1.7 (16)	1.4
Calculated Percentage (± 5)	25 (14)	25 (14) and 40 (16)	35 (13)