

Supporting Information for
A Reversible pH-Dependent Intramolecular Pyridine-Aldehyde Cyclization

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Experimental Section

Materials and Methods for Synthesis.

Solvents for synthesis were of reagent grade or better. All other reagents for synthesis were purchased and used as received. Silica gel (230 – 400 mesh, EMD Chemical Inc.) or RP-18 silica gel (Aldrich) was used for column chromatography. Analytical thin layer chromatography was performed by using Merck60 F254 silica gel plates (precoated sheets, 0.25 mm thick). ^1H -NMR and ^{13}C -NMR spectra were collected in CD_2Cl_2 , CD_3OD or D_2O at 25 °C on a 400 MHz spectrometer. All chemical shifts were calibrated to residual solvent peaks.

X-ray Crystallographic Studies

Intensity data were collected on a Bruker (formerly Siemens) SMART APEX CCD diffractometer with graphite-monochromated Mo $\text{K}\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$), controlled by a Pentium-based PC running the SMART software package.¹ A single crystal was mounted on the tip of a glass fiber, coated with paratone oil, and cooled to 173 K under a stream of N_2 maintained by a KRYO-FLEX low-temperature apparatus. Data collection and reduction protocols are described elsewhere². The structure of $(\mathbf{12})\text{Cl}_2$ was solved by direct methods and refined on F^2 by using the SHELXTL-97 software³ incorporated in the SHELXTL software package.⁴ An empirical absorption correction was applied by using the SADABS program.⁵ All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were either located directly from a difference Fourier

map or assigned to the idealized position with a thermal parameter equivalent to 1.2 times the thermal parameter of the atom to which it was attached. The C(8)-O(1) bond appeared in two positions and was modeled by refining two sets of coordinates at 80% and 20% occupancies, respectively. (see **Figs. S2** and **S3**)

NMR Titration

A 1.0 ml solution of 10 mM **12**-Cl₂ in MeOH-*d*₆ was the starting point of this experiment. A stock solution of 1 M tetramethylguanidine (TMG) in MeOH-*d*₆ was prepared and added to the solution of **12** by syringe at various volumes. ¹H-NMR spectra were recorded at different ratios of **12** to TMG. The ratio was confirmed by the integration of ¹H-NMR signal intensities. ¹H-NMR data were collected on a 400 MHz spectrometer. The same receiver gain value was applied for acquiring each spectrum, and the temperature was maintained at 25 °C over the length of the titration. The chemical shifts were calibrated against residual solvent peaks.

UV Titration

Millipore water was used for this spectroscopic study. A 50 ml aqueous solution of **12** (20 μM) in 0.1 M KCl was titrated with HCl and KOH stock solutions to achieve the desired pH. Different concentrations of acid and base stock solutions were employed at different pH regions in order to minimize volume and concentration (< 1%) variations. A 3-ml aliquot was transferred to a 1×1 cm quartz cuvette for UV measurement at each point in the titration, and the aliquot was returned to the mother solution for the next measurement point. A glass electrode for determining pH was calibrated by standard

buffer solutions before use. The experimental data were fit to a model involving two separate protonation steps, using Origin® 7.0 SR0 (OriginLab Corporation, Northampton, MA).

References

- (1) *SMART v5.626: Software for the CCD Detector System*; Bruker AXS: Madison, WI, 2000.
- (2) Kuzelka, J.; Mukhopadhyay, S.; Spingler, B.; Lippard, S. J. *Inorg. Chem.* **2004**, *43*, 1751-1761.
- (3) Sheldrick, G. M. *SHELXTL97-2: Program for Refinement of Crystal Structures*; University of Goettingen: Goettingen, Germany, 1997.
- (4) *SHELXTL v5.10: Program Library for Structure Solution and Molecular Graphics*; Bruker AXS: Madison, WI, 1998.
- (5) Sheldrick, G. M. *SADABS: Area-Detector Absorption Correction*; University of Goettingen: Goettingen, Germany, 1997.

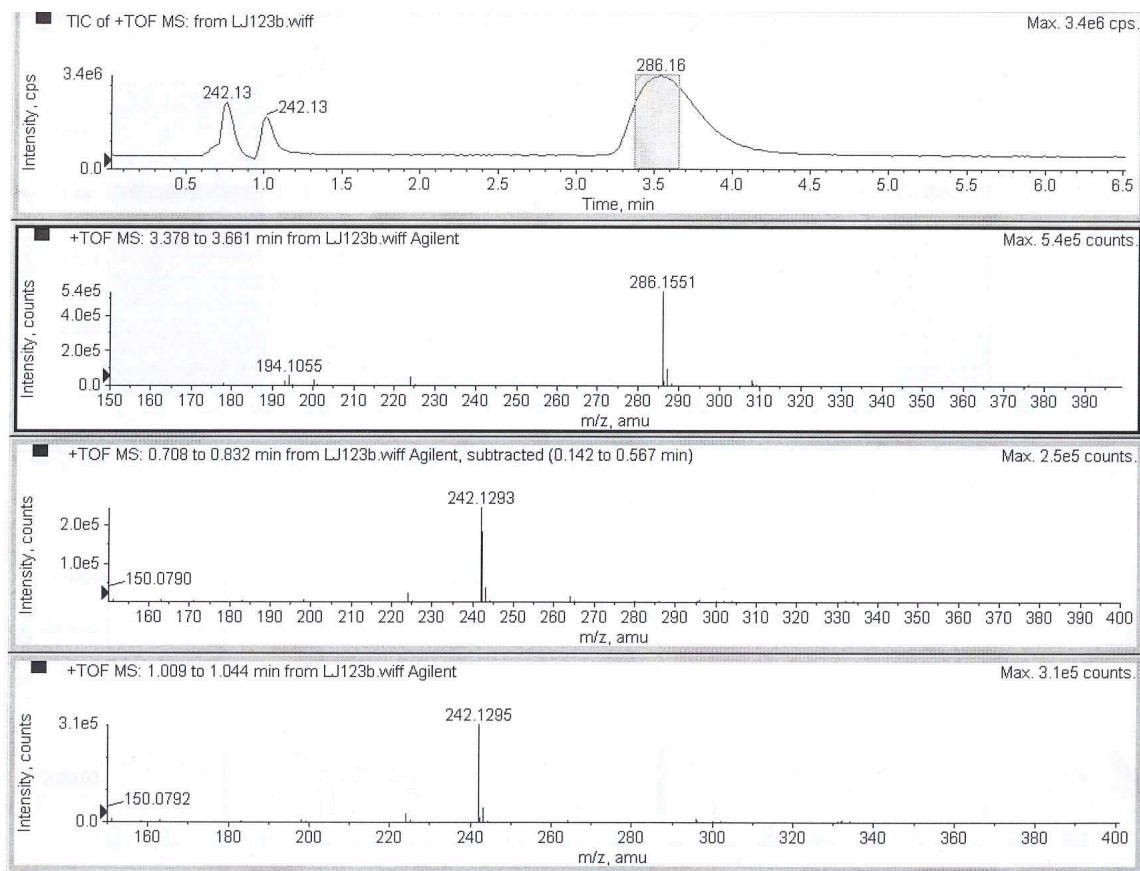


Fig. S1. High resolution LC-TOFMS spectrum of the reaction mixture for deprotecting **6** in acidic solution.

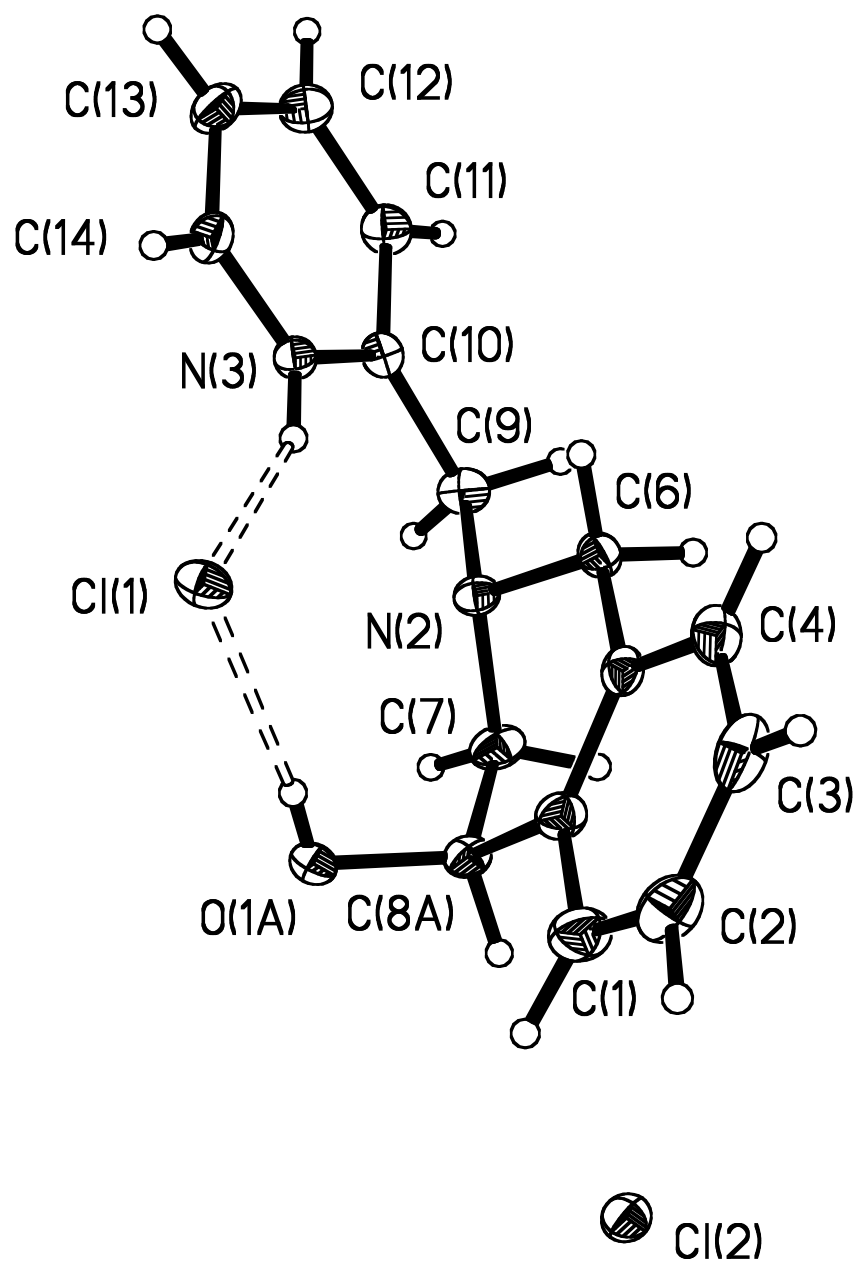


Fig. S2. Structure of (12A)Cl₂.

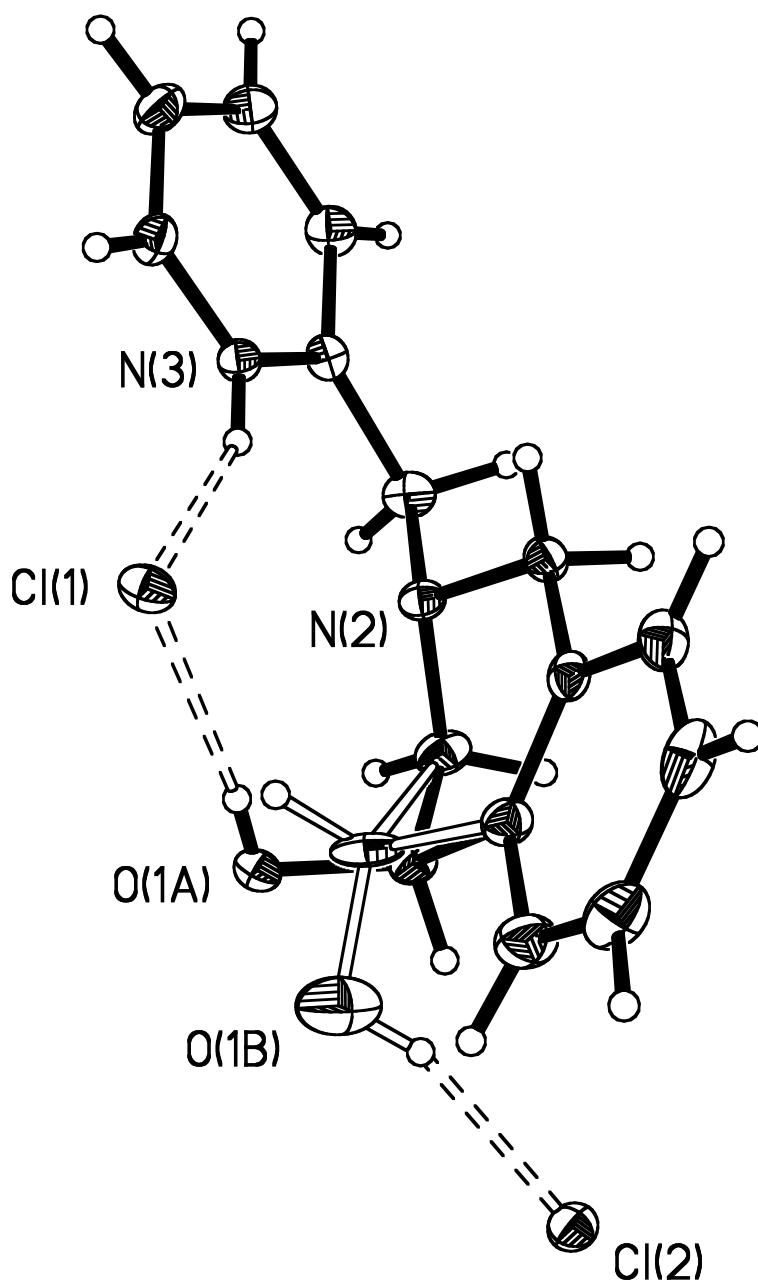


Fig. S3. Structure of (12)Cl₂ showing the position of the second, low occupancy (see text) orientation of the hydroxyl group.

Table S1. Summary of X-ray Crystallographic Data

Empirical formula	C14 H17 Cl2 N3 O	
Formula weight	314.21	
Temperature	426(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 9.3529(6) Å	
	b = 12.6172(8) Å	β = 109.7010(10)°.
	c = 13.3481(9) Å	
Volume	1482.97(17) Å ³	
Z	4	
Density (calculated)	1.407 Mg/m ³	
Absorption coefficient	0.437 mm ⁻¹	
F(000)	656	
Crystal size	0.40 x 0.34 x 0.30 mm ³	
Theta range for data collection	2.29 to 27.49°.	
Index ranges	-12 ≤ h ≤ 12, -16 ≤ k ≤ 16, -17 ≤ l ≤ 17	
Reflections collected	12477	
Independent reflections	3387 [R(int) = 0.0307]	
Completeness to theta = 27.49°	99.6 %	
Absorption correction	Empirical	
Max. and min. transmission	0.8802 and 0.8447	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	3387 / 0 / 267	
Goodness-of-fit on F ²	1.121	
Final R indices [I > 2σ(I)]	R1 = 0.0468, wR2 = 0.1112	
R indices (all data)	R1 = 0.0514, wR2 = 0.1142	
Largest diff. peak and hole	0.477 and -0.196 e.Å ⁻³	

Table S2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for (12)Cl₂. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl(1)	9115(1)	7677(1)	3529(1)	31(1)
Cl(2)	2130(1)	5054(1)	2436(1)	34(1)
O(1A)	5710(2)	7135(2)	2509(2)	29(1)
O(1B)	4498(12)	6609(11)	2629(9)	75(3)
N(1)	6525(2)	5395(1)	3036(1)	31(1)
N(2)	7327(2)	5995(1)	1302(1)	25(1)
N(3)	9756(2)	7199(1)	1432(1)	24(1)
C(1)	6157(3)	5268(2)	3926(2)	43(1)
C(2)	7063(3)	4670(2)	4757(2)	45(1)
C(3)	8335(3)	4187(2)	4663(2)	43(1)
C(4)	8677(3)	4320(2)	3744(2)	36(1)
C(5)	7770(2)	4950(2)	2927(2)	27(1)
C(6)	8132(2)	5100(2)	1929(2)	28(1)
C(7)	5719(2)	5897(2)	1154(2)	34(1)
C(8A)	5450(4)	6086(3)	2154(3)	26(1)
C(8B)	5810(20)	6380(20)	2427(14)	38(5)
C(9)	7665(2)	6111(2)	319(2)	31(1)
C(10)	9173(2)	6650(2)	524(1)	25(1)
C(11)	9964(3)	6633(2)	-186(2)	34(1)
C(12)	11330(3)	7166(2)	67(2)	38(1)
C(13)	11895(3)	7715(2)	1017(2)	38(1)
C(14)	11081(2)	7719(2)	1697(2)	31(1)

Table S3. Bond lengths [\AA] and angles [Deg] for (12)Cl₂..

O(1A)-C(8A)	1.400(4)
O(1B)-C(8B)	1.37(2)
N(1)-C(5)	1.344(3)
N(1)-C(1)	1.354(3)
N(1)-C(8B)	1.51(2)
N(1)-C(8A)	1.536(4)
N(2)-C(7)	1.454(2)
N(2)-C(6)	1.455(2)
N(2)-C(9)	1.456(2)
N(3)-C(14)	1.339(3)
N(3)-C(10)	1.341(2)
C(1)-C(2)	1.373(4)
C(2)-C(3)	1.379(4)
C(3)-C(4)	1.379(4)
C(4)-C(5)	1.384(3)
C(5)-C(6)	1.493(3)
C(7)-C(8A)	1.459(5)
C(7)-C(8B)	1.780(18)
C(9)-C(10)	1.506(3)
C(10)-C(11)	1.385(3)
C(11)-C(12)	1.381(3)
C(12)-C(13)	1.384(3)
C(13)-C(14)	1.368(3)
C(8B)-O(1B)-Cl(2)	123.0(13)
C(5)-N(1)-C(1)	122.15(19)
C(5)-N(1)-C(8B)	121.8(7)
C(1)-N(1)-C(8B)	111.8(7)
C(5)-N(1)-C(8A)	121.4(2)
C(1)-N(1)-C(8A)	116.5(2)
C(7)-N(2)-C(6)	108.84(16)
C(7)-N(2)-C(9)	114.51(15)
C(6)-N(2)-C(9)	111.61(16)
C(14)-N(3)-C(10)	123.35(17)

N(1)-C(1)-C(2)	120.3(2)
C(1)-C(2)-C(3)	119.0(2)
C(4)-C(3)-C(2)	119.6(2)
C(3)-C(4)-C(5)	120.4(2)
N(1)-C(5)-C(4)	118.50(19)
N(1)-C(5)-C(6)	120.61(17)
C(4)-C(5)-C(6)	120.86(19)
N(2)-C(6)-C(5)	112.50(16)
N(2)-C(7)-C(8A)	110.6(2)
N(2)-C(7)-C(8B)	97.3(6)
O(1A)-C(8A)-C(7)	113.6(3)
O(1A)-C(8A)-N(1)	106.5(3)
C(7)-C(8A)-N(1)	109.8(3)
O(1B)-C(8B)-N(1)	109.3(14)
O(1B)-C(8B)-C(7)	120.1(13)
N(1)-C(8B)-C(7)	95.9(12)
N(2)-C(9)-C(10)	110.89(15)
N(3)-C(10)-C(11)	118.51(18)
N(3)-C(10)-C(9)	117.91(17)
C(11)-C(10)-C(9)	123.55(18)
C(12)-C(11)-C(10)	119.3(2)
C(11)-C(12)-C(13)	120.3(2)
C(14)-C(13)-C(12)	118.9(2)
N(3)-C(14)-C(13)	119.7(2)

Table S4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for (12)Cl₂. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U ¹¹	U ²²	U ³³	U ²³	U ¹³	U ¹²
Cl(1)	27(1)	40(1)	24(1)	-5(1)	8(1)	3(1)
Cl(2)	26(1)	34(1)	40(1)	7(1)	9(1)	3(1)
O(1A)	24(1)	29(1)	34(1)	1(1)	11(1)	5(1)
O(1B)	52(6)	96(9)	84(8)	6(7)	33(6)	4(6)
N(1)	29(1)	33(1)	31(1)	6(1)	11(1)	1(1)
N(2)	20(1)	30(1)	22(1)	-1(1)	6(1)	-2(1)
N(3)	28(1)	25(1)	21(1)	0(1)	11(1)	0(1)
C(1)	44(1)	48(1)	44(1)	9(1)	23(1)	2(1)
C(2)	56(2)	50(1)	32(1)	5(1)	16(1)	-9(1)
C(3)	45(1)	35(1)	33(1)	10(1)	-6(1)	-9(1)
C(4)	31(1)	30(1)	39(1)	2(1)	1(1)	1(1)
C(5)	24(1)	22(1)	30(1)	-3(1)	4(1)	-4(1)
C(6)	26(1)	26(1)	32(1)	-4(1)	9(1)	1(1)
C(7)	20(1)	45(1)	35(1)	8(1)	4(1)	-2(1)
C(8A)	15(2)	31(2)	26(2)	5(1)	1(1)	1(1)
C(8B)	24(9)	75(17)	23(8)	-2(8)	16(7)	-5(8)
C(9)	29(1)	42(1)	22(1)	-4(1)	6(1)	-3(1)
C(10)	28(1)	25(1)	22(1)	0(1)	7(1)	2(1)
C(11)	43(1)	38(1)	25(1)	-2(1)	16(1)	0(1)
C(12)	46(1)	42(1)	38(1)	2(1)	28(1)	-2(1)
C(13)	38(1)	36(1)	44(1)	1(1)	19(1)	-10(1)
C(14)	35(1)	27(1)	30(1)	-4(1)	11(1)	-7(1)

Table S5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for (12)Cl₂.

	x	y	z	U(eq)
H(1B)	6500(40)	7240(30)	2650(30)	39(10)
H(1BA)	3930	6064	2508	90
H(1A)	9280(30)	7196(18)	1869(19)	32(6)
H(1)	5270(30)	5650(20)	3930(20)	54(8)
H(2)	6820(30)	4640(20)	5400(20)	52(8)
H(3)	8910(30)	3830(20)	5170(20)	56(8)
H(4)	9480(30)	4010(20)	3670(20)	43(7)
H(6B)	7860(30)	4450(20)	1545(19)	36(6)
H(6A)	9210(30)	5198(17)	2105(18)	29(6)
H(7B)	5160(30)	6414(19)	662(19)	37(6)
H(7A)	5350(30)	5190(20)	960(20)	47(7)
H(8A)	4460(30)	5893(18)	2101(18)	9(5)
H(8BA)	6519	6976	2636	46
H(9B)	7670(30)	5410(20)	-61(19)	37(6)
H(9A)	6910(30)	6523(19)	-140(20)	38(6)
H(11)	9510(30)	6260(20)	-830(20)	47(7)
H(12)	11820(30)	7170(20)	-420(20)	48(7)
H(13)	12760(30)	8080(20)	1200(20)	47(7)
H(14)	11410(30)	8041(18)	2329(18)	28(6)

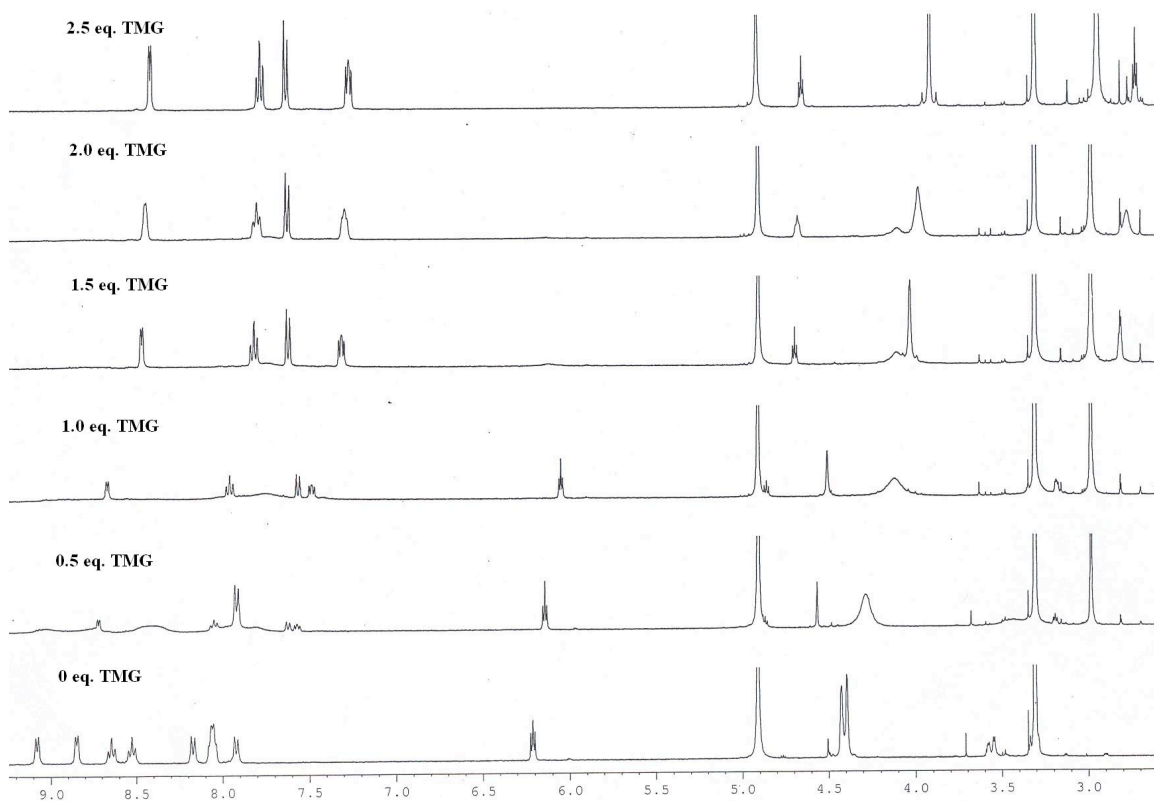


Fig. S4. 400 MHz ¹H-NMR full spectra of 10 mM (12)Cl₂ in MeOH-*d*₄ in the absence (bottom) and presence of increasing amount of TMG.

NMR Spectra

