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α-Diimine Homologues of Cisplatin: Synthesis, Speciation in DMSO/Water and Cytotoxicity

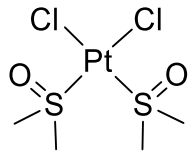
Lorenzo Biancalana, Lucinda K. Batchelor, Paul J. Dyson, Stefano Zacchini, Silvia Schoch, Guido Pampaloni and Fabio Marchetti

Supporting Information

Table of contents *Page/s*

Synthesis and characterization of *cis*-[$PtCl_2(\kappa S\text{-}DMSO)_2$] (Chart S1) [1]

Chart S1. Structure of *cis*-[$PtCl_2(\kappa S\text{-}DMSO)_2$].

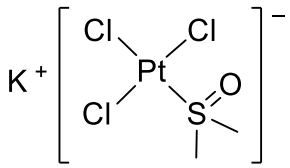


An orange-red solution of $K_2[PtCl_4]$ (570 mg, 1.37 mmol) in H_2O (5 mL) was treated with DMSO (0.40 mL, 5.6 mmol) then stirred at room temperature for 20 hours. The resulting suspension (colourless solid + pale yellow solution) was filtered and the solid was washed with H_2O (2 mL), EtOH (1 mL), Et_2O then dried under vacuum (50°C). Yield: 530 mg, 91%. IR (solid state): $\tilde{\upsilon}/cm^{-1}$ = 3037w, 3010w, 2995w, 2991w, 2926w-sh, 2917w, 2907w-sh, 1412w-sh, 1400w, 1384w, 1315w, 1305w-sh, 1299m, 1153s ($\nu_{S=O}$), 1131s ($\nu_{S=O}$), 1114m-sh, 1030m-sh, 981m, 941m, 919m, 736m, 689m. ^1H NMR (acetone-d_6): δ/ppm = 3.58 (s + satellites, $^3J_{HPt}$ = 22 Hz, CH_3). $^{13}C\{^1H\}$ NMR (acetone-d_6): δ/ppm = 44.9 (CH_3).^1H NMR (CD_3OD): δ/ppm = 3.57 (s + satellites, $^3J_{HPt}$ = 23 Hz, CH_3). $^{195}Pt\{^1H\}$ NMR (DMSO-d_6): δ/ppm = − 3444.

Precipitation of the title compound begins shortly after (*ca.* 15-20 min) the addition of DMSO; note that ageing of the precipitate is important. Performing the filtration after 4 hours, as reported in the literature[1a,b] afforded a pale yellow solid (87% yield) with minor differences in the IR spectrum. However, lower yields of Pt-α-diimine complexes **1**-**4** were obtained when using this material as precursor.

Synthesis and characterization of K[PtCl$_3$(κ*S*-DMSO)] (Chart S2) [2]

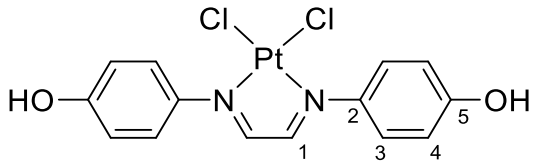
Chart S2. Structure of K[PtCl$_3$(κ*S*-DMSO)].



A suspension of $K_2[PtCl_4]$ (29 mg, 0.071 mmol) and *cis*-[$PtCl_2$(κ*S*-DMSO)$_2$] (30 mg, 0.071 mmol) in H_2O (3 mL) was stirred at 90°C for 3 hours. The resulting yellow solution was cooled to room temperature and volatiles were removed under vacuum. The yellow solid was suspended in MeOH and filtered, washed with MeOH, Et_2O and dried under vacuum (50°C over P_2O_5). Yield: 30 mg, 51%. K[$PtCl_3$(κ*S*-DMSO)] is soluble in DMSO, water, poorly soluble in MeOH and insoluble in Et_2O. Anal. Calcd. for $C_2H_6Cl_3KOPtS$: C, 5.74; H, 1.44. Found: C, 6.30; H, 1.52. IR (solid state): $\tilde{\upsilon}/cm^{-1}$ = 3026w-sh, 3014m, 2925w, 1405w, 1316m, 1300w-sh, 1100s ($\nu_{S=O}$), 1030s, 976m, 942m, 928m, 734w, 692m. $^{195}Pt\{^1H\}$ NMR (D_2O): δ/ppm = − 2982. An additional, minor signal in the $^{195}Pt\{^1H\}$ spectrum was observed (– 2848 ppm), presumably due to [$PtCl_2(H_2O)$(DMSO)] or [$PtCl_2$(OH)(DMSO)]$^-$.[3]

Synthesis and characterization of $[PtCl_2\{\kappa^2N\text{-}(HCN(4\text{-}C_6H_4OH))_2\}]$ acetone solvate, $4\cdot(Me_2CO)_n$ (Chart S3)

Chart S3. Structure of **4** (numbering refers to C atoms).



A suspension of *cis*-$[PtCl_2(\kappa S\text{-}DMSO)_2]$ and **L4** (1:1 mol. ratio) in acetone was stirred at reflux for 1.5-6.5 hours. The reaction mixture (purple red solid + dark red solution) was cooled to room temperature and filtered. The solid was washed with acetone (2 mL, − 20 °C), CH_2Cl_2, Et_2O and dried under vacuum (55°C). The isolated material, **$4\cdot(Me_2CO)_n$**, contains variable amounts of acetone, depending on the reaction time and reactant concentration (acetone : **4** molar ratios = 0.5−4; ^{1}H NMR, CD_3OD). Compound **$4\cdot(Me_2CO)_n$** has similar solubility features as **4**; slightly higher solubility in MeOH and THF. IR (solid state): $\tilde{\upsilon}/cm^{-1}$ = 3292m (ν_{O-H}), 3061m, 3009w, 2958w, 1698s ($\nu_{C=O}$), 1693s ($\nu_{C=O}$), 1607m-sh, 1592s ($\nu_{C=N}$), 1560m, 1501s, 1486s, 1454m, 1366m, 1353m-sh, 1328m, 1299w, 1275m, 1259m, 1233s, 1194m, 1166s, 1109m, 1088m, 1064m, 1010w, 958w, 938m, 884w, 867w, 846w-sh, 834s, 824s-sh, 810s, 752w-br, 723w, 681w-sh, 673w. ^{1}H NMR (CD_3OD): δ/ppm = 8.81 (s + satellites, $^3J_{HPt}$ = 90 Hz, 2H, C1-H), 7.45 (d, $^3J_{HH}$ = 8.7 Hz, 4H, C3-H), 6.84 (d, $^3J_{HH}$ = 8.8 Hz, 4H), 2.16 (s, Me_2CO); the set of signals for the α-diimine ligand is identical to that of **4**.

Acetone can be removed from **$4\cdot(Me_2CO)_n$** either by suspending the solid in refluxing CH_2Cl_2 or by heating the solid to 110°C under vacuum, as described in the main text. Comparison of IR spectra of **$4\cdot(Me_2CO)_n$** and **4**, obtained by the two procedures described above, is shown in Figure S10.

Table S1. Selected bond distances (Å) and angles (°) for **4·THF**.

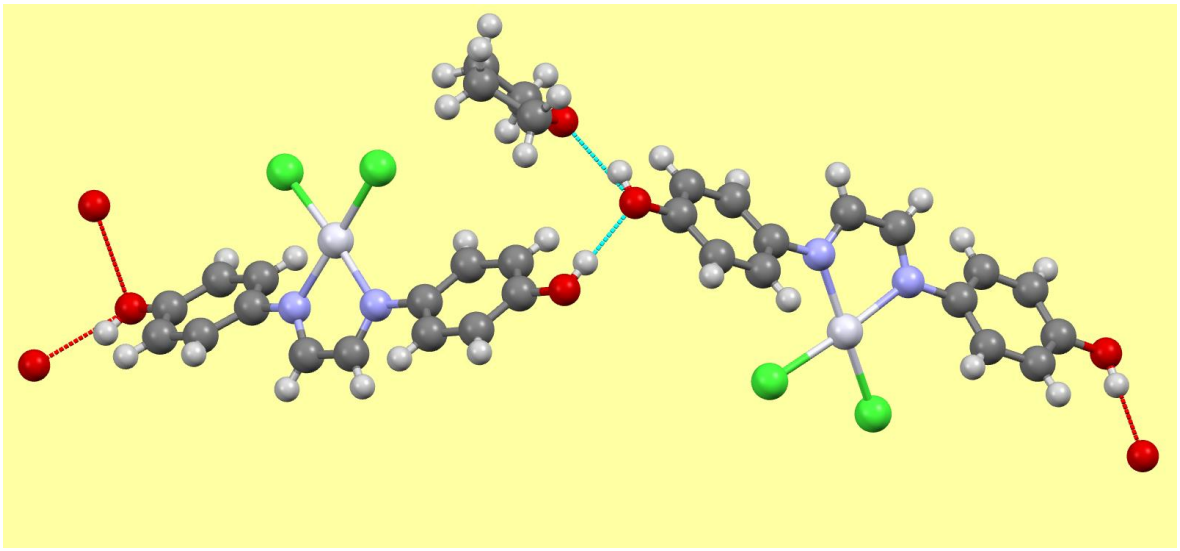
Pt(1)−Cl(1)	2.287(3)	Pt(1)−Cl(2)	2.288(3)
Pt(1)−N(1)	2.025(9)	Pt(1)−N(2)	2.028(8)
N(1)−C(1)	1.290(15)	N(2)−C(2)	1.295(15)
N(1)−C(3)	1.442(15)	N(2)−C(9)	1.420(14)
C(1)−C(2)	1.433(17)		
Cl(1)−Pt(1)−Cl(2)	87.38(11)	N(1)−Pt(1)−N(2)	79.6(4)
Pt(1)−N(1)−C(1)	113.0(8)	N(1)−C(1)−C(2)	116.5(11)
C(1)−C(2)−N(2)	116.9(11)	C(2)−N(2)−Pt(1)	112.6(7)

Table S2. Selected bond distances (Å) and angles (°) for **5**.

Pt(1)−Cl(1)	2.300(2)	Pt(1)−Cl(2)	2.296(2)
Pt(1)−N(1)	1.991(7)	Pt(1)−N(2)	1.966(7)
N(1)−O(1)	1.360(9)	N(2)−O(2)	1.394(9)
C(1)−C(3)	1.481(11)	C(2)−C(4)	1.479(11)
C(1)−C(2)	1.478(11)		
Cl(1)−Pt(1)−Cl(2)	94.51(8)	N(1)−Pt(1)−N(2)	77.5(3)
Pt(1)−N(1)−C(1)	117.5(5)	N(1)−C(1)−C(2)	113.9(7)
C(1)−C(2)−N(2)	111.7(7)	C(2)−N(2)−Pt(1)	119.4(6)

Figure S1. H-bond network present in the solid state structure of **4·THF**: (a) the basic unit involving two **4** molecules and one THF molecule; (b) the resulting infinite chain.

(a)



(b)

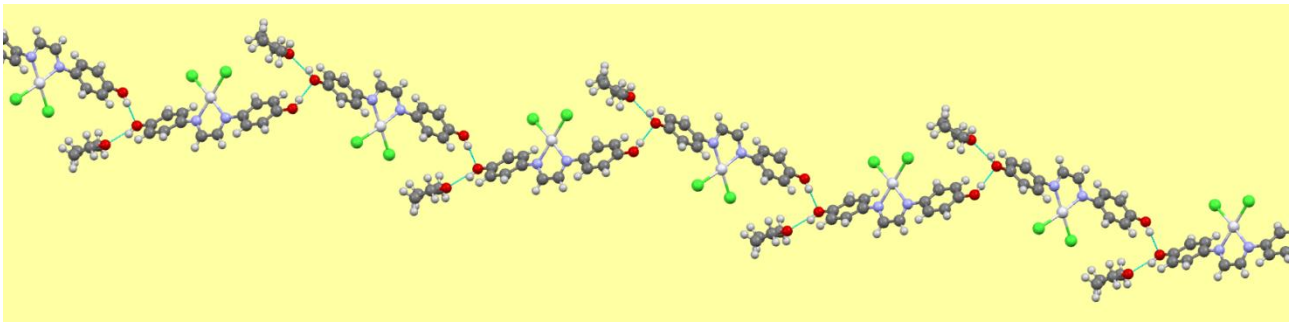


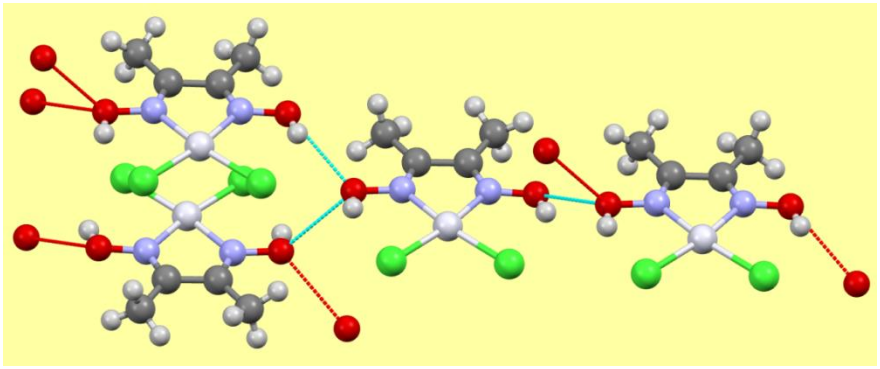
Table S3. Hydrogen bonds for **4·THF** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1)...O(2)#1	0.84	1.90	2.741(13)	178.0
O(2)-H(2)...O(21)	0.84	1.86	2.66(2)	159.2
O(2)-H(2)...O(31)	0.84	1.86	2.61(4)	147.3

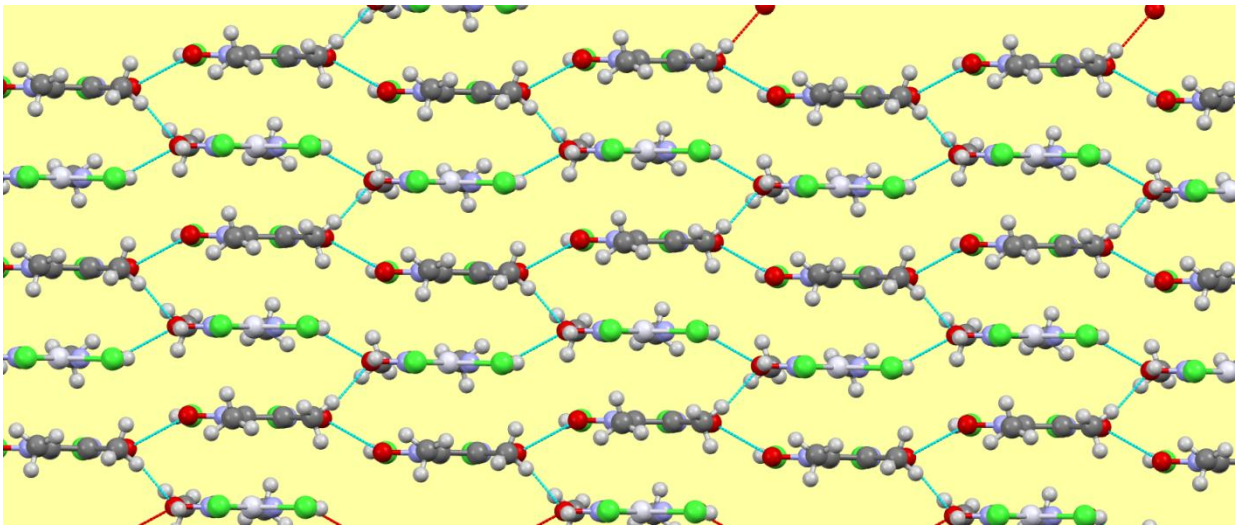
Symmetry transformations used to generate equivalent atoms: #1 -x+3/2,-y+1,z+1/2

Figure S2. H-bond network present in the solid state structure of **5**: (a) the basic unit involving four **5** molecules; (b) and (c) the resulting 2-D network.

(a)



(b)



(c)

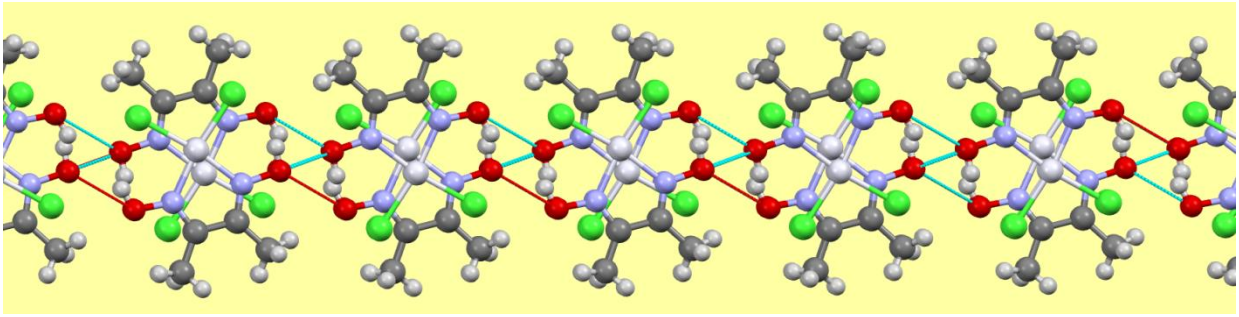


Table S4. Hydrogen bonds for **5** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1)...O(2)#1	0.839(10)	2.30(8)	2.926(8)	132(9)

Symmetry transformations used to generate equivalent atoms: #1 x+1/2,-y+1/2,z+1/

Stability studies in DMSO-d_6 and DMSO-d_6:D_2O solutions

Reference data (^1H NMR). NMR spectra of the following compounds were recorded in DMSO-d_6 or in DMSO-d_6:D_2O 9:1 *v*/*v* and used for assignments. **L1**. ^{1}H NMR (DMSO-d_6): δ/ppm = 7.88 (s, 2H), 3.19 (t, *J* = 11.1 Hz, 2H), 1.72 (s, 4H), 1.61 (s, 6H), 1.46–1.35 (m, 4H), 1.35–1.16 (m, 6H). **L2**. ^{1}H NMR (DMSO-d_6): δ/ppm = 7.88 (s, 2H), 4.49 (s, 2H), 3.49–3.37 (m, 2H), 3.20–3.08 (m, 2H), 1.90–1.79 (m, 4H), 1.67–1.57 (m, 4H), 1.52–1.40 (m, 4H), 1.31–1.18 (m, 4H). **L3**. ^{1}H NMR (DMSO-d_6): δ/ppm = 8.44 (s, 2H), 7.31 (d, *J* = 7.9 Hz, 4H), 7.26 (d, *J* = 8.2 Hz, 4H), 2.34 (s, 6H). ^{1}H NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 8.40 (s, 2H), 7.26 (pseudo-q, *J* = 8.6 Hz, 8H), 2.31 (s, 6H). **L4**. ^{1}H NMR (DMSO-d_6): δ/ppm = 9.79 (s-br, 2H), 8.40 (s, 2H), 7.32 (d, *J* = 8.6 Hz, 4H), 6.82 (d, *J* = 8.6 Hz, 4H). ^{1}H NMR (DMSO:D_2O 9:1): δ/ppm = 8.37 (s, 2H), 7.30 (d, *J* = 8.7 Hz, 4H), 6.83 (d, *J* = 8.7 Hz, 4H). **dmgH$_2$**. ^{1}H NMR (DMSO-d_6): δ/ppm = 11.37 (s, 2H), 1.92 (s, 6H). ^{1}H NMR (DMSO-d_6:D_2O 9:1): δ/ppm = 1.89 (s, 6H). ***p*-HOC$_6$H$_4$NH$_2$**. ^{1}H NMR (DMSO-d_6): δ/ppm = 6.48 (pseudo-q, *J* = 8.7 Hz, 4H). ***p*-CH$_3$C$_6$H$_4$NH$_2$**. ^{1}H NMR ($CDCl_3$): δ/ppm = 6.95 (d, *J* = 7.8 Hz, 4H), 6.56 (m, 4H), 2.22 (s, 6H).[4]

Reference data (^{195}Pt NMR). NMR data were taken from the literature.

[PtCl$_4$]$^{2-}$. ^{195}Pt{^{1}H} NMR (D_2O): δ/ppm = – 1620.[5]

K[PtCl$_3$(DMSO)]. ^{195}Pt{^{1}H} NMR (D_2O): δ/ppm = – 2990.5 ^{195}Pt{^{1}H} NMR (DMSO-d_6): δ/ppm = – 2965;[6] – 2969.3

***cis*-[PtCl$_2$(DMSO)$_2$]**. ^{195}Pt{^{1}H} NMR (D_2O): δ/ppm = –3442.[7]

***trans*-[PtCl$_2$(DMSO)$_2$]**. ^{195}Pt{^{1}H} NMR (D_2O): δ/ppm = –3650.3

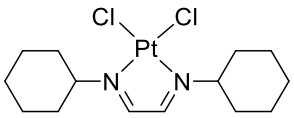
[PtCl(DMSO)$_3$]$^+$. ^{195}Pt{^{1}H} NMR (D_2O): δ/ppm = – 3845.3

***cis*-[PtCl$_2$(DMSO)(OH)]$^-$**. ^{195}Pt{^{1}H} NMR (DMSO-d_6): δ/ppm = – 2811.3

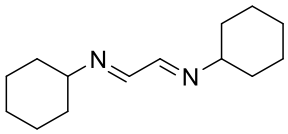
*Stability studies: compound **1***. Yellow solution (0-72 h, DMSO-d_6); yellow solution + orange solid (0-72 h, DMSO-d_6/D_2O/NaCl), the compound is not completely soluble under the selected conditions (S = $2.6 \cdot 10^{-4}$ M). Data are reported in Table S5, NMR detected species are shown in Chart S4.

1. ^{1}H NMR (DMSO-d_6): δ/ppm = 8.66 (s + sat., *J* = 102 Hz, 2H), 4.39 (t, *J* = 11.2 Hz, 2H), 2.11 (d, *J* = 10.2 Hz, 4H), 1.80 (d, *J* = 13.0 Hz, 4H), 1.65 (d, *J* = 12.7 Hz, 2H), 1.44 (q, *J* = 11.9 Hz, 4H), 1.31 (q, *J* = 12.8 Hz, 4H), 1.20−1.08 (m, 2H). ^{1}H NMR (DMSO-d_6/D_2O 9:1): δ/ppm = 8.63 (s, 2H), 4.33 (t, *J* = 10.7 Hz, 2H), 2.08 (d, *J* = 13.6 Hz, 4H), 1.78 (d, *J* = 13.9 Hz, 4H), 1.62 (d, *J* = 13.2 Hz, 2H), 1.41 (q, *J* = 11.5 Hz, 4H), 1.28 (q, *J* = 13.3 Hz, 4H), 1.17–1.04 (m, 2H).

Chart S4, Table S5. NMR detected species a function of time for DMSO-d_6 or DMSO-d_6/D_2O/NaCl solutions of **1** at 37°C. Data for the DMSO-d_6/D_2O/NaCl solution are given in parentheses.



1



L1

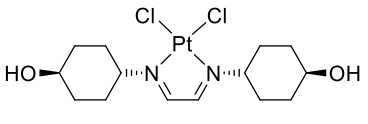
time		0 [a]	72 h
% NMR	**1**	100 (100)	96 (100)
	L1	0 (0)	4 (0)

[a] NMR spectra were recorded shortly after dissolution (t < 10 min).

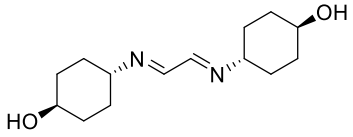
*Stability studies: compound **2**.* Yellow solution (0-72 h, DMSO-d_6); yellow solution + orange solid (0-72 h, DMSO-d_6/D_2O/NaCl), the compound is not completely soluble under the selected conditions (S = $3.9 \cdot 10^{-3}$ M). Data are reported in Table S6, NMR detected species are shown in Chart S5.

2. ^{1}H NMR (DMSO-d_6): δ/ppm = 8.68 (s + sat., *J* = 102 Hz, 2H), 4.65 (d, *J* = 4.4 Hz, 2H), 4.39 (t, *J* = 10.0 Hz, 2H), 3.47–3.37 (m, 2H), 2.07 (d, *J* = 11.2 Hz, 4H), 1.90 (d, *J* = 10.8 Hz, 4H), 1.56 (q, *J* = 11.6 Hz, 4H), 1.25 (q, *J* = 11.8 Hz, 4H). ^{1}H NMR (DMSO-d_6/D_2O 9:1): δ/ppm = 8.64 (s + sat., *J* = 89 Hz, 2H), 4.32 (t, *J* = 10.9 Hz, 2H), 3.51–3.36 (m, 2H), 2.05 (d, *J* = 10.2 Hz, 4H), 1.89 (d, *J* = 10.4 Hz, 4H), 1.53 (q, *J* = 12.0 Hz, 4H), 1.22 (q, *J* = 11.0 Hz, 4H).

Chart S5, Table S6. NMR detected species a function of time for DMSO-d_6 or DMSO-d_6/D_2O/NaCl solutions of **2** at 37°C. Data for the DMSO-d_6/D_2O/NaCl solution are given in parentheses.



2



L2

time		0 [a]	72 h
% NMR	**2**	100 (100)	96 (100)
	L2	0 (0)	4 (0)

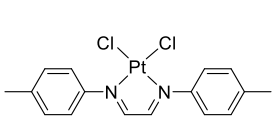
[a] NMR spectra were recorded shortly after dissolution (t < 10 min).

*Stability studies: compound **3**.* Red-orange solution (0-72 h, DMSO-d_6); yellow solution + red solid (0-72 h, DMSO-d_6/D_2O/NaCl), the compound is not completely soluble under the selected conditions. Data are reported in Table S7, NMR detected species are shown in Chart S6.

3. ^{1}H NMR (DMSO-d_6): δ/ppm = 9.09 (s, 2H), 7.41 (d, *J* = 8.0 Hz, 4H), 7.38 (d, *J* = 8.7 Hz, 4H), 2.39 (s, 6H). ^{1}H NMR (DMSO-d_6/D_2O 9:1): δ/ppm = 8.98 (s, 2H), 7.37 (d, *J* = 6.5 Hz, 4H), 7.29 (d, *J* = 7.8 Hz, 4H), 2.35 (s, 6H). **3A**.[8] ^{1}H NMR (DMSO-d_6): δ/ppm = 9.64 (d, *J* = 8.0 Hz, 1H), 8.89 (d, *J* = 7.8 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 2H), 7.63 (br, 3H), 7.49 (d, *J* = 7.9 Hz, 2H), [7.32 (d, *J* = 8.4 Hz, 4H)], [2.40 (s)]. ^{1}H NMR (DMSO-d_6/D_2O 9:1): δ/ppm = 9.59 (d, *J* = 6.9 Hz, 1H), 8.82 (d, *J* = 7.0 Hz, 1H), 7.83 (d, *J* = 6.7 Hz, 2H), 7.64–7.56 (m, 2H), 7.47–7.43 (m, 2H). **Other compounds**. ^{1}H NMR (DMSO-d_6; 17-72 h): δ/ppm = 7.48–6.55 (m), 2.38–2.14 (m). ^{1}H NMR (DMSO-d_6/D_2O 9:1; 72 h): δ/ppm = 9.86, 8.93 (d, *J* = 6.7 Hz), 8.64, 8.18, 8.12, 7.75 (d, *J* = 8.4 Hz), 7.12 (t, *J* = 8.1 Hz), 7.08–6.95 (m), 6.93–6.84 (m), 6.86–6.78 (m), 6.48 (t, *J* = 7.1 Hz), 5.45, 5.31 (d, *J* = 12.0 Hz), 5.11–5.03 (m), 4.79, 4.70, 4.53, 4.44, 2.24, 2.21, 2.18, 2.16, 2.12 (m), 2.10, 2.06. ***p*-$CH_3C_6H_4NH_2$**. ^{1}H NMR (DMSO-d_6/D_2O 9:1): δ/ppm = 6.89 (d, *J* = 7.9 Hz, 4H), 6.61 (d, *J* = 8.1 Hz, 4H), 2.13 (s, 6H).

^{195}Pt{^{1}H} NMR (DMSO-d_6; 72 h): δ/ppm = – 2951, – 3096, – 3444 (major, *cis*-$[PtCl_2(DMSO)_2]$). ^{195}Pt{^{1}H} NMR (DMSO-d_6/D_2O 9:1; 72 h): δ/ppm = – 2956 (major, $[PtCl_3(DMSO)]^-$), – 2997, – 3102, – 3361, –3447 (*cis*-$[PtCl_2(DMSO)_2]$).

Chart S6, Table S7. NMR detected species a function of time for DMSO-d_6 or DMSO-d_6/D_2O/NaCl solutions of **3** at 37°C. Data for the DMSO-d_6/D_2O/NaCl solution are given in parentheses.



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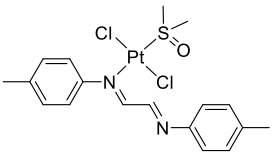
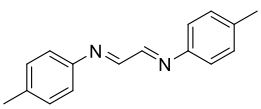
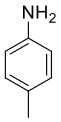
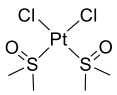


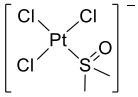
3A



L3







time		0 [a]	17 h	72 h
% NMR	**3**	55 (74)	0 (< 1)	0 (0)
	3A	20 (20)	0 (0)	0 (0)
	L3	25 (6)	73 (21)	47 (1)
	***p*-$CH_3C_6H_4NH_2$**	0 (0)	0 (4)	0 (20)
	Other compounds [b]	0 (0)	27 (75)	53 (79)

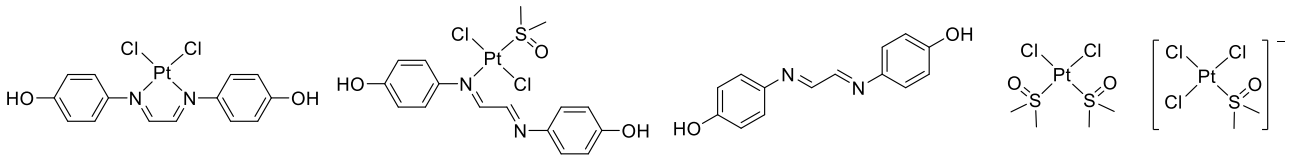
[a] NMR spectra were recorded shortly after dissolution (t < 10 min). [b] Based on the integration of CH_3 signals.

*Stability studies: compound **4**.* Red solution (0 h, DMSO-d_6); orange solution (17-72 h, DMSO-d_6); dark red solution (0-72 h, DMSO-d_6/D_2O/NaCl). Data are reported in Table S8, NMR detected species are shown in Chart S7.

4. ^{1}H NMR (DMSO-d_6): δ/ppm = 10.26–10.07 (m-br, 2H), 8.93 (s, 2H), 7.39 (d, *J* = 8.4 Hz, 4H), 6.95 (d, *J* = 8.5 Hz, 4H). ^{1}H NMR (DMSO-d_6/D_2O 9:1): δ/ppm = 8.86 (s, 2H), 7.37 (d, *J* = 7.7 Hz, 4H), 6.84 (d, *J* = 7.1 Hz, 4H). **4A**.8 ^{1}H NMR (DMSO-d_6): δ/ppm = [10.26–10.07 (m-br)], 9.62 (d, *J* = 7.2 Hz, 1H), 8.70 (d, *J* = 7.4 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 2H), 7.67 (s-br, 2H), 7.52 (d, *J* = 8.5 Hz, 2H), 6.93–6.88 (m, 4H). ^{1}H NMR (DMSO-d_6/D_2O 9:1): δ/ppm = 9.59 (d, *J* = 6.8 Hz, 1H), 8.65 (d, *J* = 6.9 Hz, 1H), 7.83 (d, *J* = 6.6 Hz, 2H), 7.65 (m-br, 2H), 7.50 (d, *J* = 7.5 Hz, 2H), [6.99–6.89 (m, 4H)]. **Other compounds**. ^{1}H NMR (DMSO-d_6/D_2O 9:1, 72 h): δ/ppm = 10.01, 9.58, 8.91 (d, *J* = 6.6 Hz), 8.12, 7.91, 7.82, 7.69–7.60 (m), 7.53–7.42 (m), 7.35 (d, *J* = 9.1 Hz), 7.18 (d, *J* = 8.7 Hz), 7.07 (d, *J* = 8.7 Hz), 6.96–6.91 (m), 6.75–6.64 (m), 5.50, 5.37–5.34 (m), 5.18 (d, *J* = 19.6 Hz), 4.44. ^{195}Pt{^{1}H} NMR (DMSO-d_6, 72 h): δ/ppm = – 3445 (*cis*-[$PtCl_2(DMSO)_2$]).

^{195}Pt{^{1}H} NMR (DMSO-d_6/D_2O 9:1, 72 h): δ/ppm = – 2956 (major, [$PtCl_3(DMSO)]^-$), – 2956, – 3001, – 3102, – 3360, – 3447 (*cis*-[$PtCl_2(DMSO)_2$]).

Chart S7, Table S8. NMR detected species a function of time for DMSO-d_6 or DMSO-d_6/D_2O/NaCl solutions of **4** at 37°C. Data for the DMSO-d_6/D_2O/NaCl solution are given in parentheses.



4 **4A** **L4**

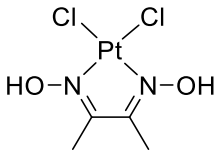
time		0 [a]	17 h	72 h
% NMR	**4**	26 (43)	6 (6)	4 (4)
	4A	46 (52)	6 (3)	4 (0)
	L4	28 (5)	88 (50)	88 (30)
	Other compounds [b]	0 (0)	0 (41)	4 (66)

[a] NMR spectra were recorded shortly after dissolution (t < 10 min). [b] Based on the integration of aromatic CH signals.

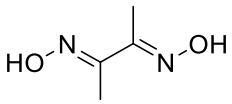
*Stability studies: compound **5**.* Pale yellow solution + brown solid (0-72 h, DMSO-d_6 and DMSO-d_6/D_2O/NaCl), the compound is not completely soluble under the selected conditions. Data are reported in Table S9, NMR detected species are shown in Chart S8.

5. ^{1}H NMR (DMSO-d_6): δ/ppm = 2.21 (s, 6H). ^{1}H NMR (DMSO-d_6/D_2O 9:1): δ/ppm = 2.16 (s, 6H). **Other species**. ^{1}H NMR (DMSO-d_6): δ/ppm = 2.16 (s; 17-72 h), 1.78 (s; 0-72 h). ^{1}H NMR (DMSO-d_6/D_2O 9:1): δ/ppm = 2.22 (s; 72h) 1.94 (s; 0-72 h), 1.77 (s; 0-72 h).

Chart S8, Table S9. NMR detected species a function of time for DMSO-d_6 or DMSO-d_6/D_2O/NaCl solutions of **5** at 37°C. Data for the DMSO-d_6/D_2O/NaCl solution are given in parentheses.



5



dmgH$_2$

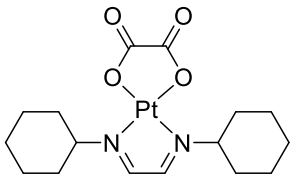
time		0 [a]	17 h	72 h
% NMR	**5**	13 (11)	10	4 (4)
	dmgH$_2$	73 (66)	78	87 (88)
	Other species [b]	14 (23)	12	9 (8)

[a] NMR spectra were recorded shortly after dissolution (t < 10 min). [b] Based on the integration of CH_3 signals.

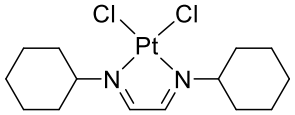
*Stability studies: compound **6***. Pale yellow solution + orange solid (0-72 h, DMSO-d_6 and DMSO-d_6/D_2O/NaCl), the compound is not completely soluble under the selected conditions (S = $1.5 \cdot 10^{-4}$ M in the DMSO-d_6/D_2O/NaCl solution). Data are reported in Table S10, NMR detected species are shown in Chart S9.

6. ^1H (DMSO-d_6): δ/ppm = 8.79 (s + sat., *J* = 99 Hz, 2H), 3.90–3.80 (m, 2H), 1.97 (d, *J* = 11.2 Hz, 4H), 1.83 (d, *J* = 15.4 Hz, 4H), 1.81–1.71 (m, 4H), 1.66 (d, *J* = 11.7 Hz, 2H), 1.34 (q, *J* = 12.5 Hz, 4H), 1.21–1.13 (m, 2H).^1H NMR (DMSO-d_6/D_2O 9:1): δ/ppm = 8.71 (s), 2.00–1.93 (m), 1.75–1.69 (m), 1.09–1.00 (m).

Chart S9, Table S10. NMR detected species a function of time for DMSO-d_6 or DMSO-d_6/D_2O/NaCl solutions of **6** at 37°C. Data for the DMSO-d_6/D_2O/NaCl solution are given in parentheses.



6



1

time		0 [a]	20 h	72 h
% NMR	**6**	100 (100)	100 (13)	100 (14)
	1	0 (0)	0 (87)	0 (86)

[a] NMR spectra were recorded shortly after dissolution (t < 10 min).

Stability studies: cis-[PtCl$_2$(κS-DMSO)$_2$]. Pale yellow solutions (0-72 h, DMSO-d$_6$ and DMSO-d$_6$/D$_2$O/NaCl). NMR detected species are shown in Chart S10. A single ^{195}Pt{^{1}H} NMR signal was observed in the DMSO-d$_6$ solution, attributed to the starting material *cis*-[PtCl$_2$(κ*S*-DMSO)$_2$]; no changes were observed after 66 hours at 37 °C. Two ^{195}Pt{^{1}H} NMR signals were observed in the DMSO-d$_6$/D$_2$O/NaCl solution, due to *cis*-[PtCl$_2$(κ*S*-DMSO)$_2$] and [PtCl$_3$(κ*S*-DMSO)]$^-$ (relative integral *ca*. 1:9); no changes were observed after 88 hours at 37 °C.

***cis*-[PtCl$_2$(κ*S*-DMSO)$_2$]**. ^{195}Pt{^{1}H} NMR (DMSO-d$_6$): δ/ppm = − 3444. ^{195}Pt{^{1}H} NMR (DMSO-d$_6$:D$_2$O 9:1): δ/ppm = − 3445. **[PtCl$_3$(κ*S*-DMSO)]$^-$**. ^{195}Pt{^{1}H} NMR (DMSO-d$_6$:D$_2$O 9:1): δ/ppm = − 2956.

Chart S10. NMR detected species for DMSO-d$_6$ or DMSO-d$_6$/D$_2$O/NaCl solutions of *cis*-[PtCl$_2$(κ*S*-DMSO)$_2$] at 37°C.

Chloride/solvent exchange experiment for compound 1

A suspension of **1** (53 mg, 0.11 mmol) and AgOTf (56 mg, 0.22 mmol) in EtOH:H_2O 1:1 *v*/*v* (18 mL) was stirred at reflux temperature for 3 hours in the dark. The resulting mixture (orange-yellow solution + colourless solid) was filtered over celite then volatiles were removed from the filtrate solution, affording an ochre yellow-orange solid (yield: 68.5 mg).

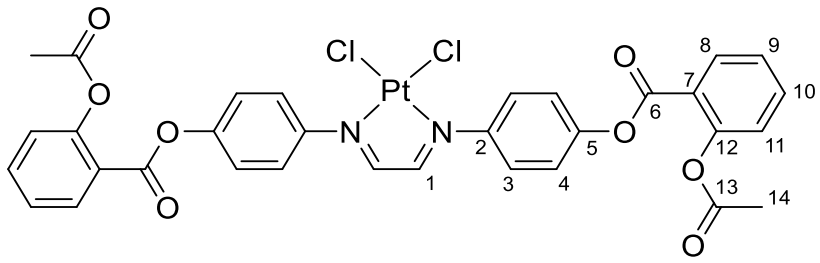
This material was analyzed by NMR spectroscopy in DMSO-d_6 and DMSO-d_6/D_2O 9:1 *v*/*v* + NaCl (0.11 M), the solutions employed for the stability studies of compounds **1**-**6**.

DMSO-d_6. Yellow solution. Mixture of species; 4 set of signals. ^{1}H NMR (DMSO-d_6): δ/ppm = 8.73, 8.53, 8.49, 8.43 (s, 2H); 4.38–4.21, 4.18–4.07, 3.74–3.64, 3.64–3.55 (m, 2H); 2.12–1.99 (m, 4H), 1.90–1.76 (m, 4H), 1.71–1.59 (m, 2H), 1.57–1.33 (m, 6H), 1.31–1.10 (m, 4H). ^{19}F{^{1}H} NMR (DMSO-d_6): δ/ppm = – 77.8 ($CF_3SO_3^-$).

DMSO-d_6/D_2O/NaCl. Yellow solution + orange solid. ^{1}H NMR (DMSO-d_6:D_2O 9:1): quantitative formation of **1**. ^{19}F{^{1}H} NMR (DMSO-d_6:D_2O 9:1): δ/ppm = – 77.8 ($CF_3SO_3^-$).

Synthesis of $[PtCl_2\{\kappa^2N\text{-}(HCN(4\text{-}C_6H_4OCOasp))_2\}]$, 7 (Chart S11)

Chart S11. Structure of **7** (numbering refers to C atoms).



In a 25-mL Schlenk tube, NEt_3 (45 μL, 0.32 mmol) and **4** (55 mg, 0.11 mmol) were added to a solution of freshly-prepared aspirin acyl chloride (aspCOCl, 0.31 mmol) in THF (5 mL). The red suspension was stirred at room temperature for 24 hours and then filtered. The resulting orange-brown solid was thoroughly washed with Et_2O, water then dried under vacuum (40 °C). ^{1}H NMR analysis of this solid revealed a mixture of **7** and **4** (3:1 mol. ratio, CD_3CN). NMR and IR data for **7** are given below. All attempts to isolate the product were unsuccessful. IR (solid state; in admixture with **4**): $\tilde{\upsilon}/cm^{-1}$ = 1768w-sh ($\nu_{C=O}$), 1740m ($\nu_{C=O}$), 1732m ($\nu_{C=O}$), 1605s ($\nu_{C=N}$), 1592s ($\nu_{C=N}$), 1564m. ^{1}H NMR (CD_3CN): δ/ppm = 9.02 (s + satellites, $^3J_{HPt}$ = 89 Hz, 2H, C1-H), 8.25 (dd, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.5 Hz, 2H, C8-H), 7.75 (td, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.6 Hz, 2H, C10-H), 7.62 (d, $^3J_{HH}$ = 8.7 Hz, 4H, C3-H), 7.49 (td, $^3J_{HH}$ = 7.7, $^4J_{HH}$ = 1.1 Hz, 2H, C9-H), 7.37 (d, $^3J_{HH}$ = 8.8 Hz, 4H, C4-H), 7.27 (d, $^3J_{HH}$ = 7.5 Hz, 2H, C11-H), 2.28 (s, 6H, C14-H).

Figure S3. Solid-state IR spectrum (250-4000 cm^{-1}) of $[PtCl_2\{\kappa^2N\text{-}(HCN(C_6H_{11}))_2\}]$, **1**.

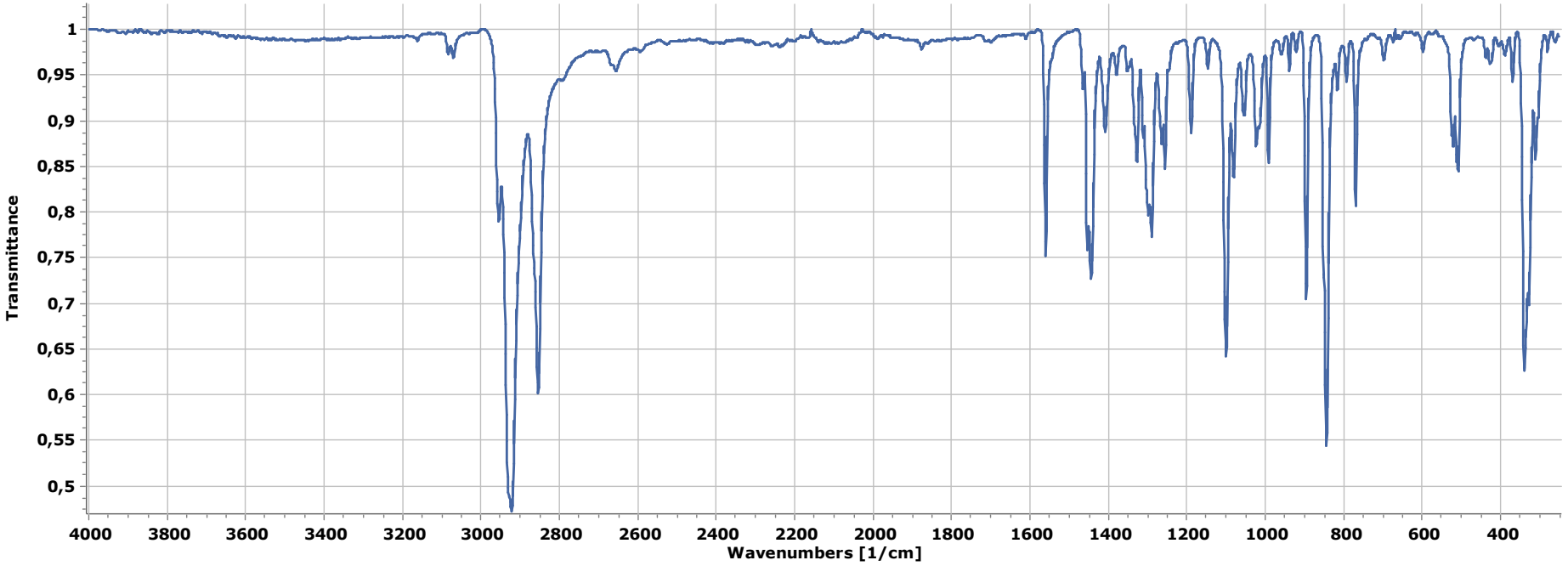


Figure S4. Solid-state IR spectrum (250-4000 cm^{-1}) of $[PtCl_2\{\kappa^2N\text{-}(HCN(4\text{-}C_6H_{10}OH))_2\}]$, **2**.

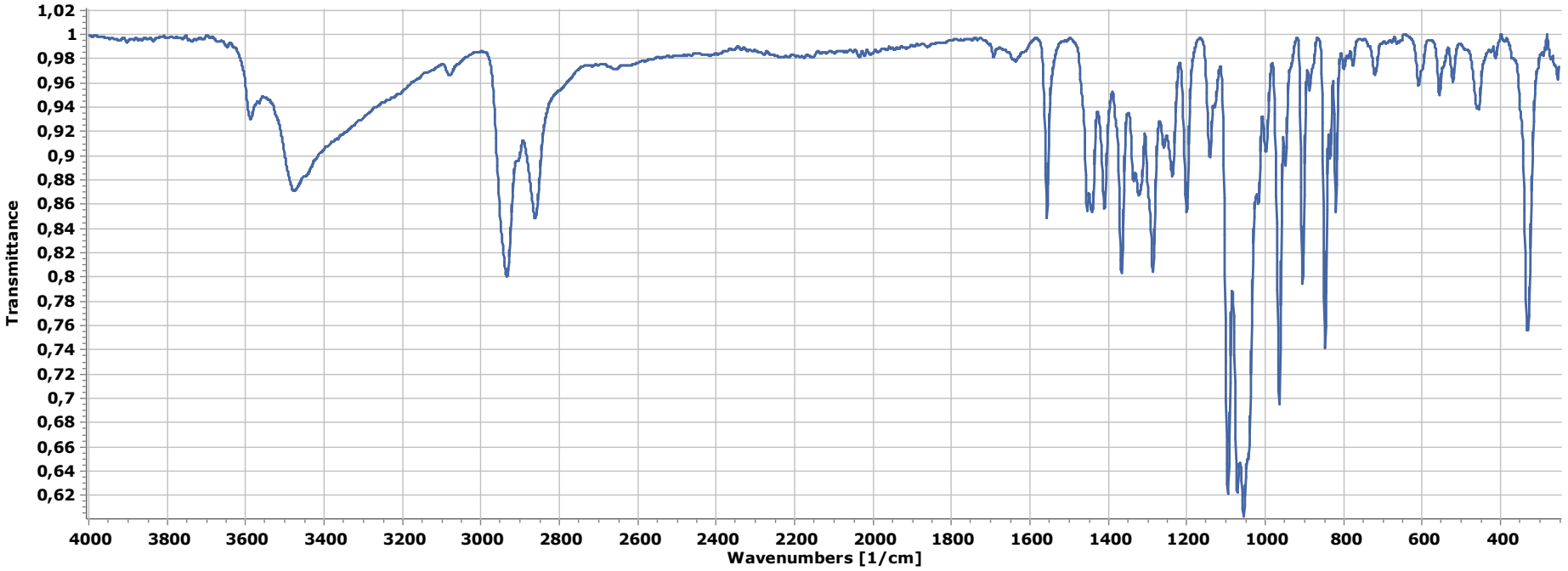


Figure S5. Solid-state IR spectrum (250-4000 cm^{-1}) of $[PtCl_2\{\kappa^2N\text{-}(HCN(4\text{-}C_6H_4CH_3))_2\}]$, **3**.

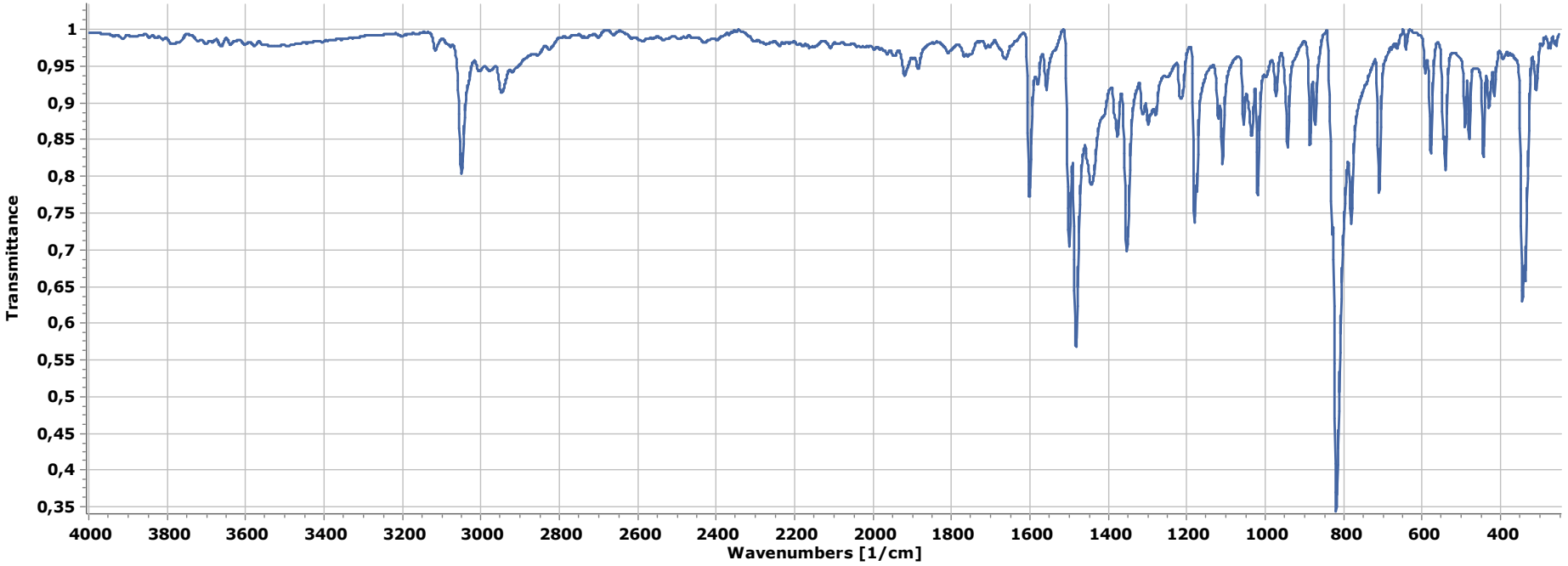


Figure S6. Solid-state IR spectrum (250-4000 cm^{-1}) of $[PtCl_2\{\kappa^2N\text{-}(HCN(4\text{-}C_6H_4OH))_2\}]$, **4**.

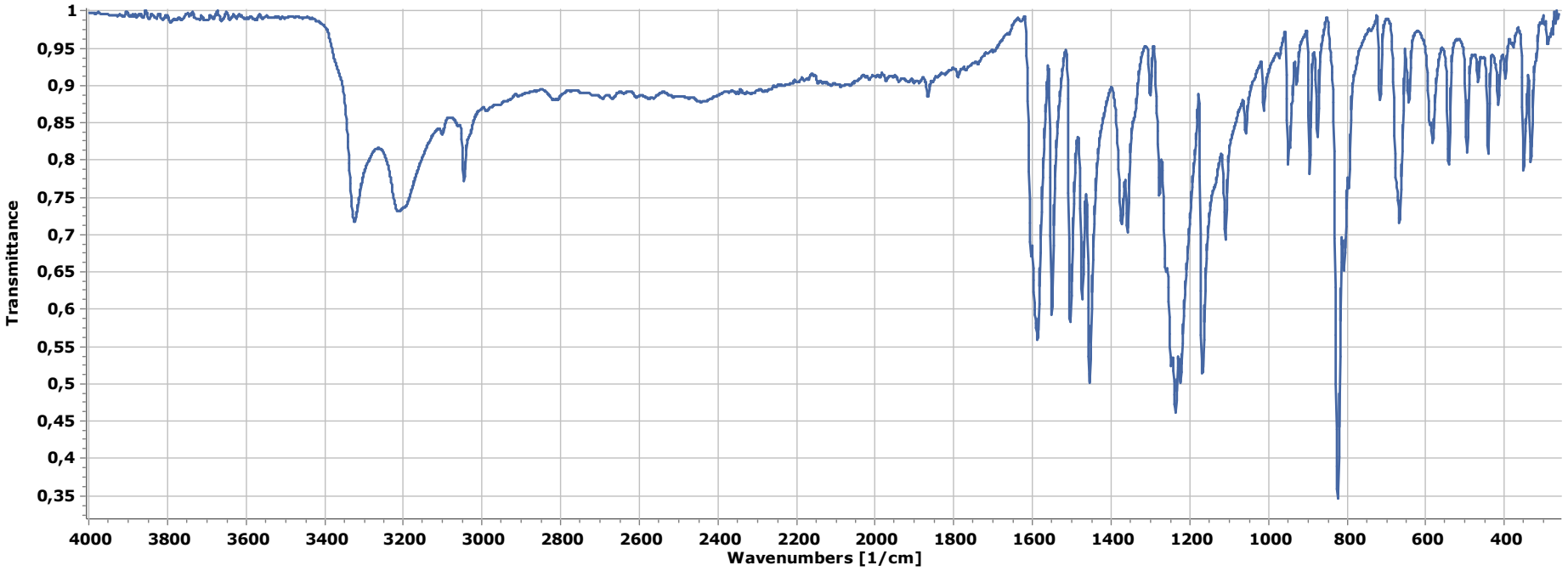


Figure S7. Solid-state IR spectrum (250-4000 cm^{-1}) of [$PtCl_2\{\kappa^2N\text{-}(CH_3CNOH)_2\}$], **5**.

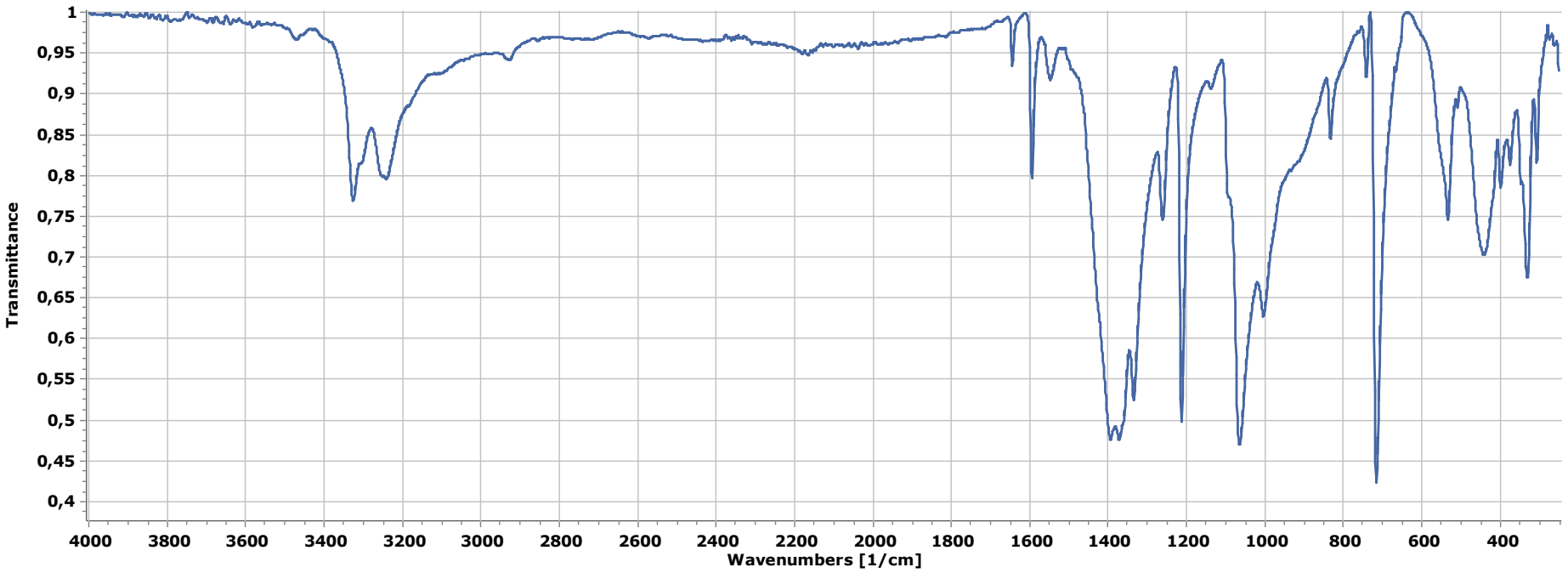


Figure S8. Solid-state IR spectrum (250-4000 cm^{-1}) of [Pt(κ^2*O*-C_2O_4){κ^2*N*-(HCN(C_6H_{11}))$_2$}], **6**.

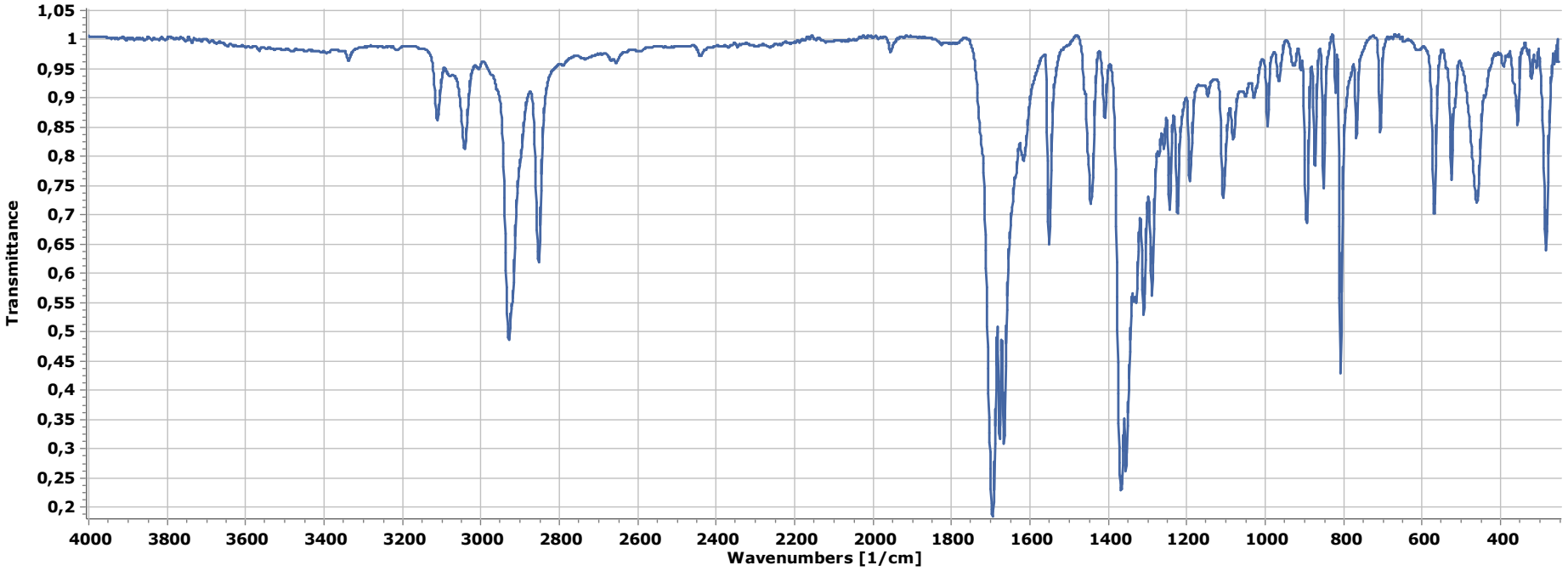


Figure S9. Solid-state IR spectrum (250-4000 cm^{-1}) of [Pt{κ^2*N,N'*-(ONC(CH_3)C(CH_3)NOH)}$_2$], [Pt(dmgH)$_2$].

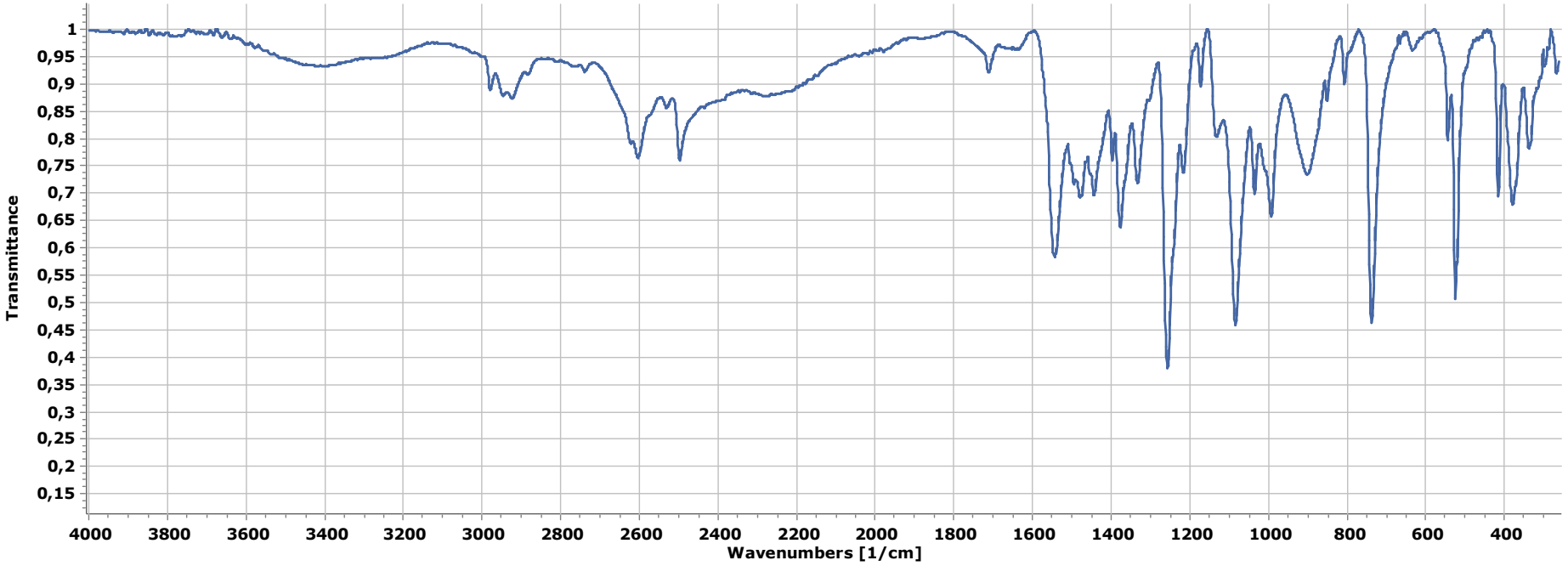


Figure S10. Solid-state IR spectra (650-3600 cm^{-1}) of **4·(Me$_2$CO)$_n$** (red line)and **4** obtained by acetone removal with thermal treatment (green line) or dispersion in CH_2Cl_2 (blue line).

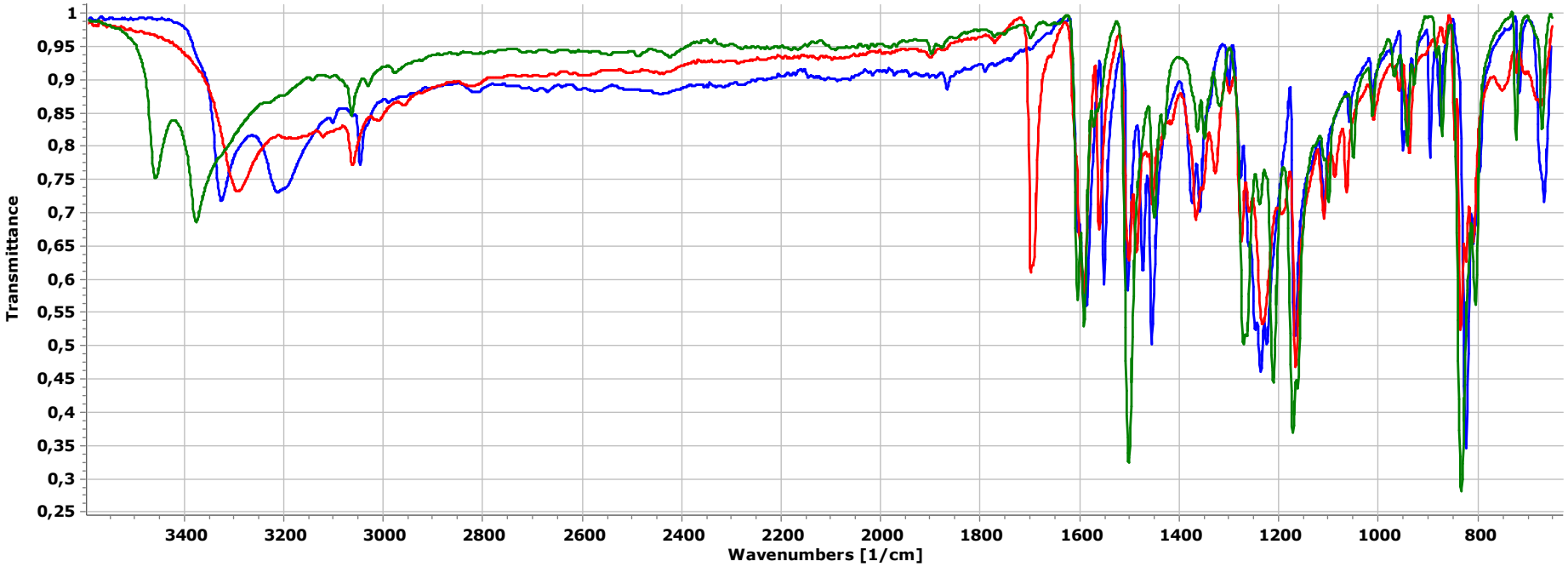


Figure S11. ^{1}H NMR spectrum (401 MHz, DMSO-d$_6$) of [PtCl$_2${κ^2*N*-(HCN(C$_6$H$_{11}$))$_2$}], **1**.

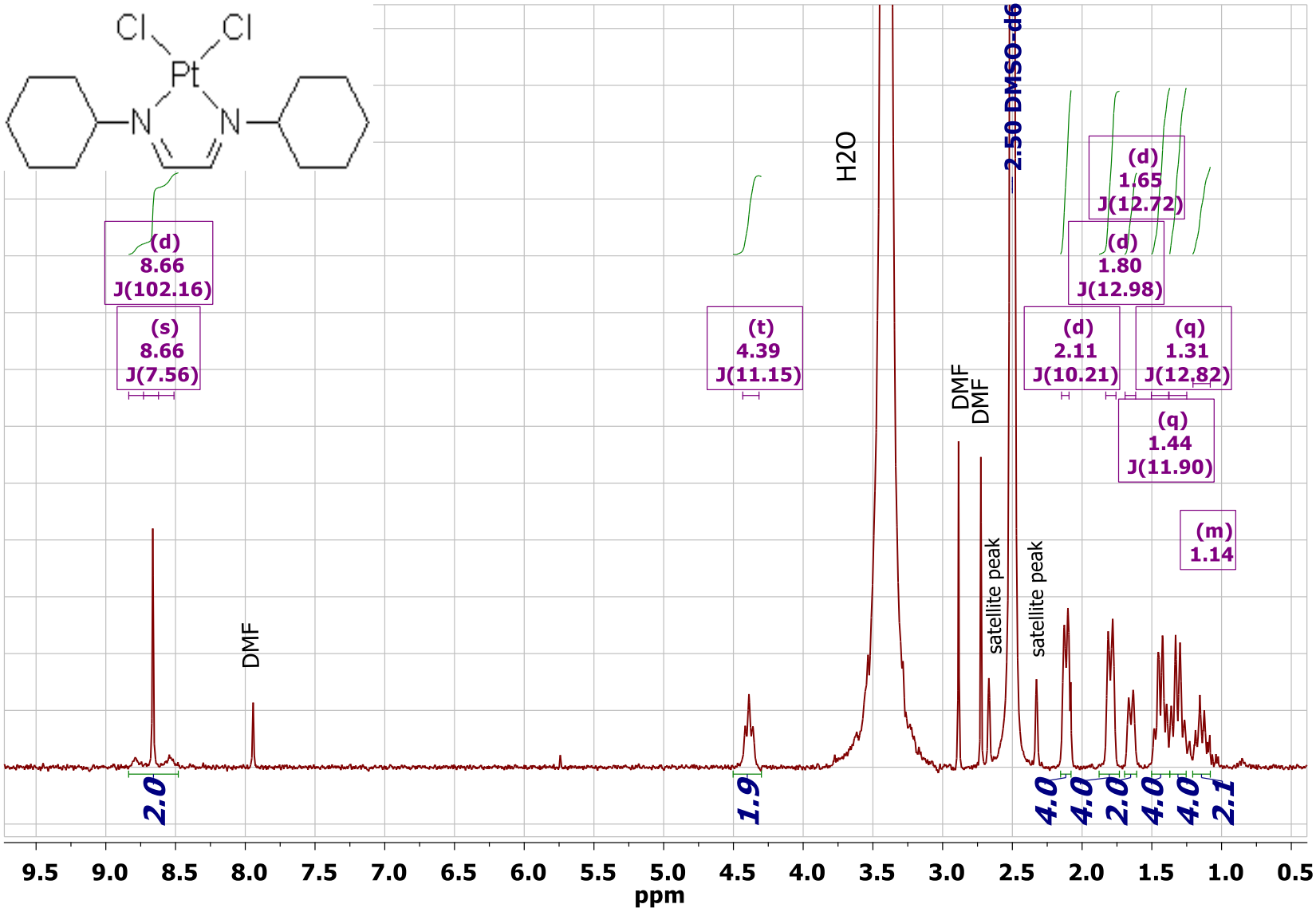


Figure S12. $^{13}C\{^{1}H\}$ NMR spectrum (101 MHz, DMSO-d_6) of $[PtCl_2\{\kappa^2N\text{-}(HCN(C_6H_{11}))_2\}]$, **1**.

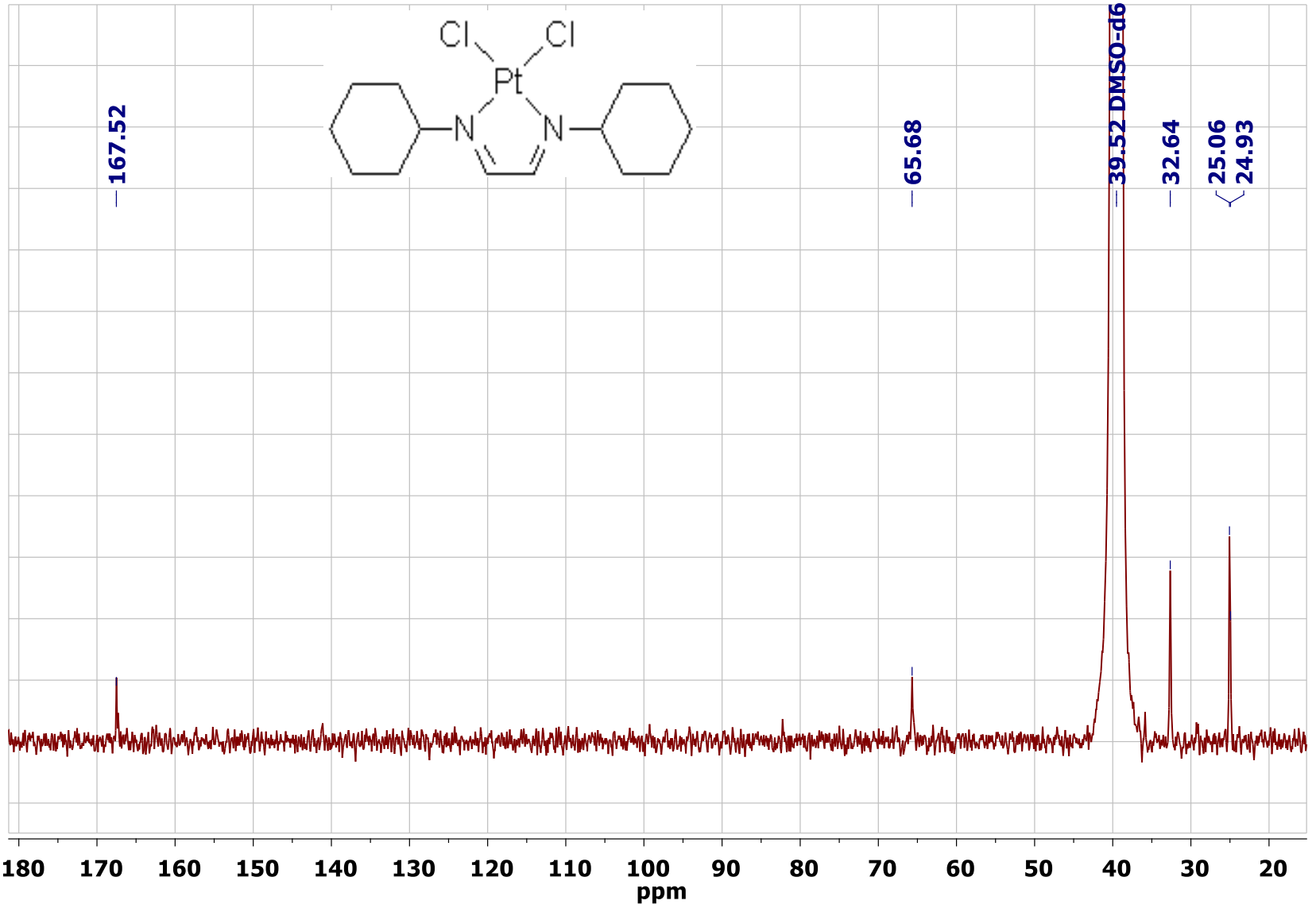


Figure S13. $^{195}Pt\{^{1}H\}$ NMR spectrum (86 MHz, DMSO-d_6) of $[PtCl_2\{\kappa^2N\text{-}(HCN(C_6H_{11}))_2\}]$, **1**.

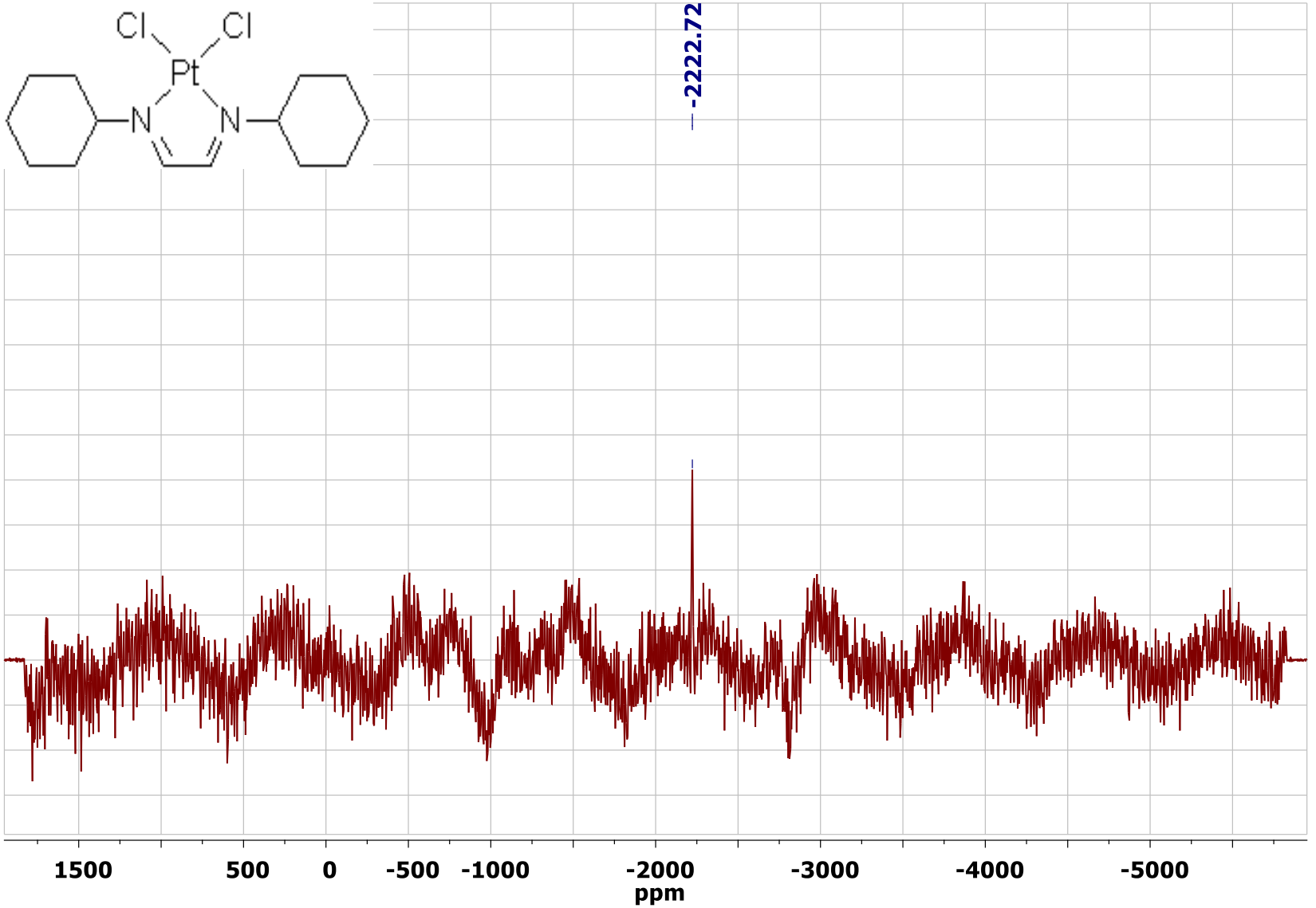


Figure S14. ^{1}H NMR spectrum (401 MHz, DMSO-d$_6$) of [PtCl$_2${κ^2*N*-(HCN(4-C$_6$H$_{10}$OH))$_2$}], **2**.

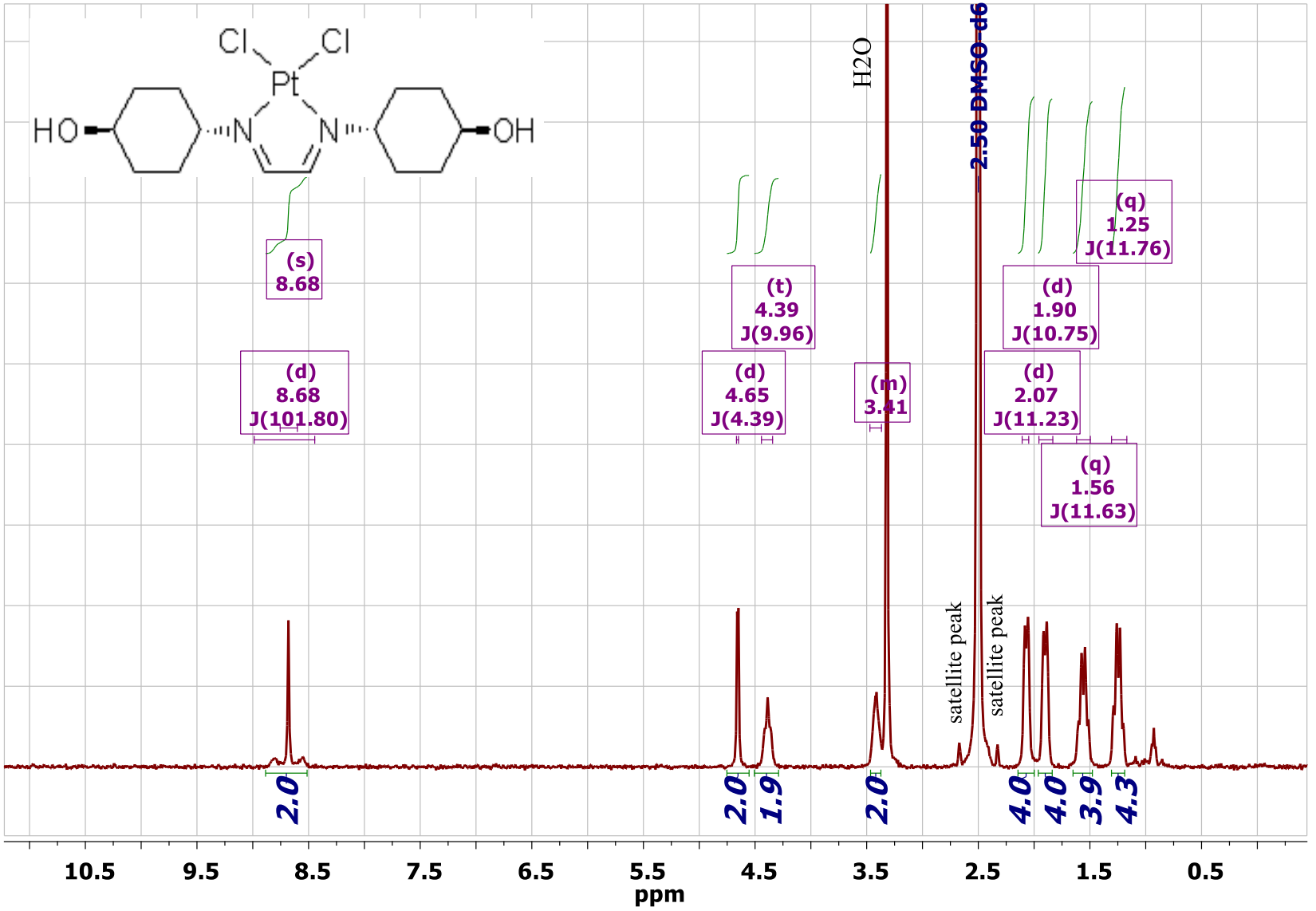


Figure S15. $^{13}C\{^{1}H\}$ NMR spectrum (101 MHz, DMSO-d_6) of $[PtCl_2\{\kappa^2N\text{-}(HCN(4\text{-}C_6H_{10}OH))_2\}]$, **2**.

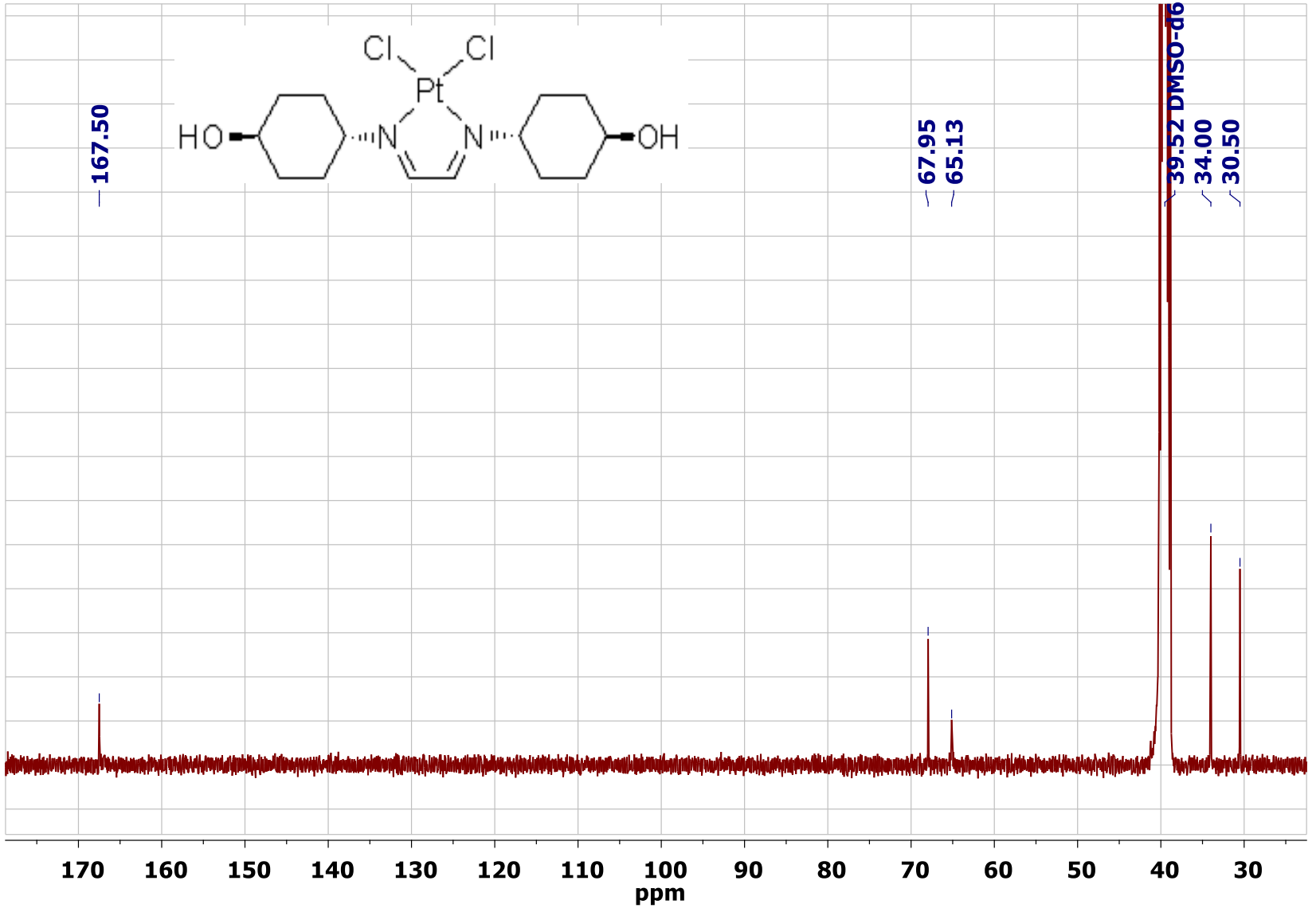


Figure S16. $^{195}Pt\{^{1}H\}$ NMR spectrum (86 MHz, DMSO-d_6) of $[PtCl_2\{\kappa^2N\text{-}(HCN(4\text{-}C_6H_{10}OH))_2\}]$, **2**.

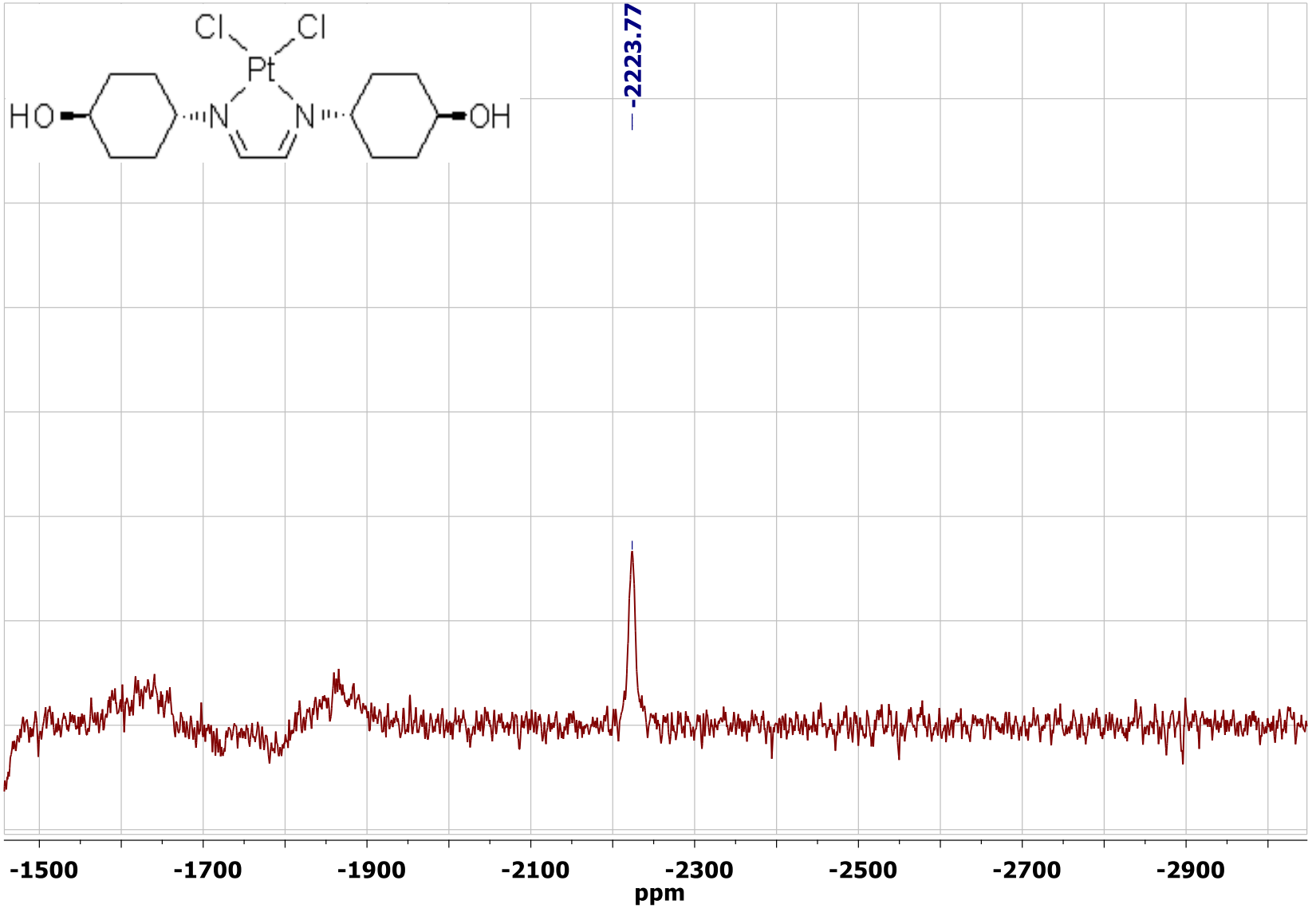


Figure S17. ^{1}H NMR spectrum (401 MHz, CD_2Cl_2) of $[PtCl_2\{\kappa^2N\text{-}(HCN(4\text{-}C_6H_4CH_3))_2\}]$, **3**.

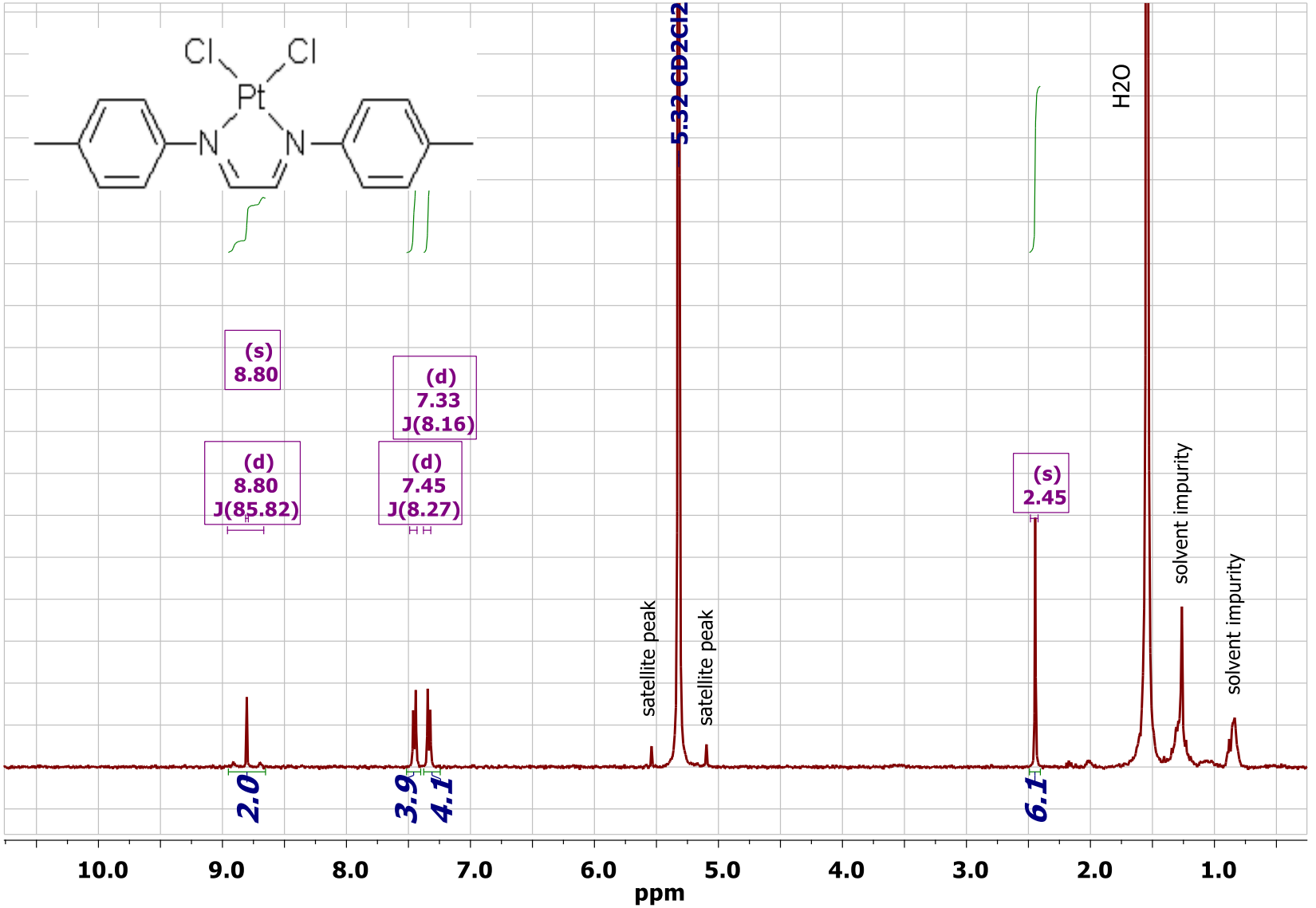


Figure S18. $^{13}C\{^{1}H\}$ NMR spectrum (101 MHz, DMF/C_6D_6 capillary) of [$PtCl_2\{\kappa^2N$-$(HCN(4\text{-}C_6H_4CH_3))_2\}$], **3**.

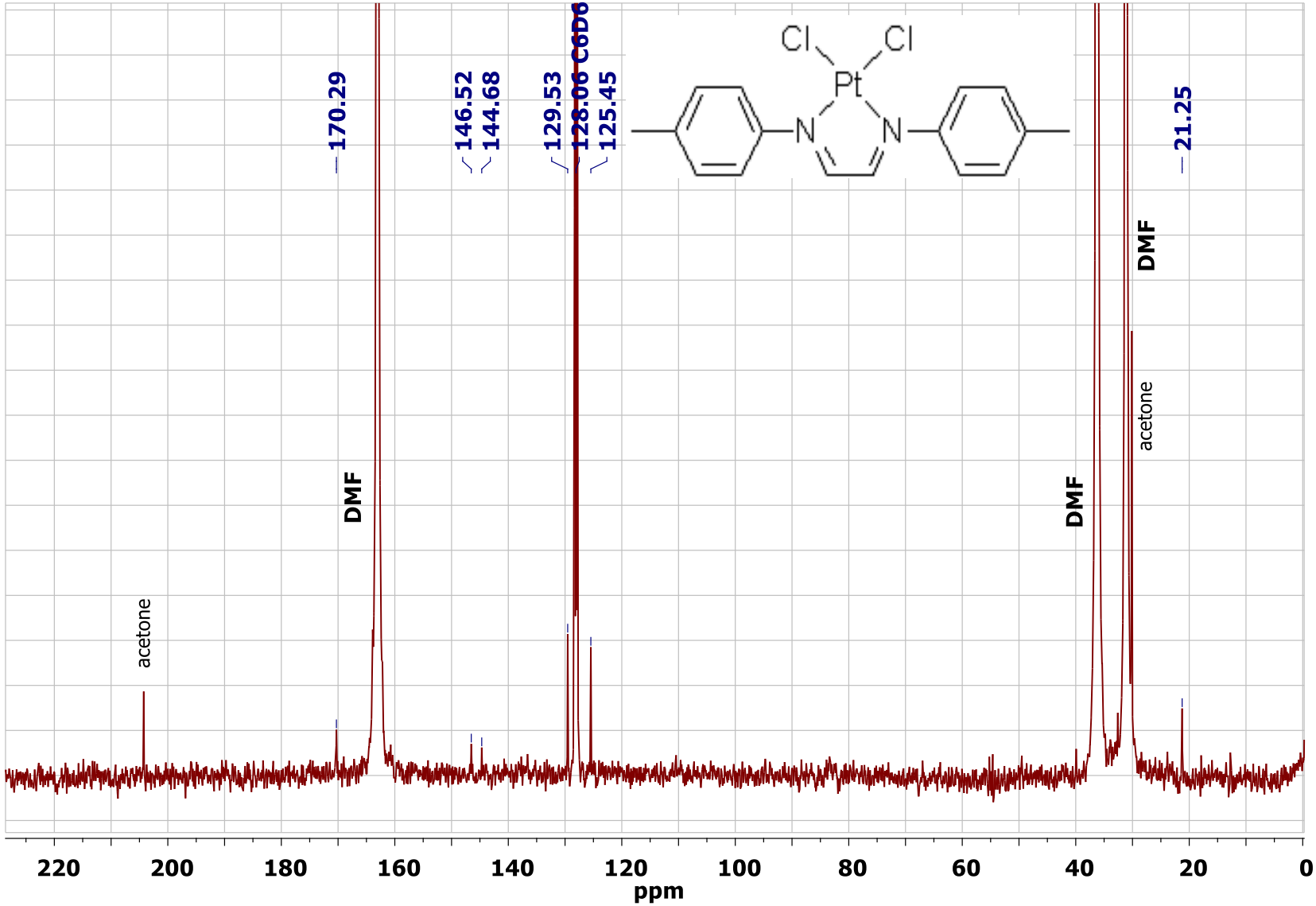


Figure 19. $^{195}Pt\{^{1}H\}$ NMR spectrum (86 MHz, DMF/C_6D_6 capillary) of $[PtCl_2\{\kappa^2N\text{-}(HCN(4\text{-}C_6H_4CH_3))_2\}]$, **3**.

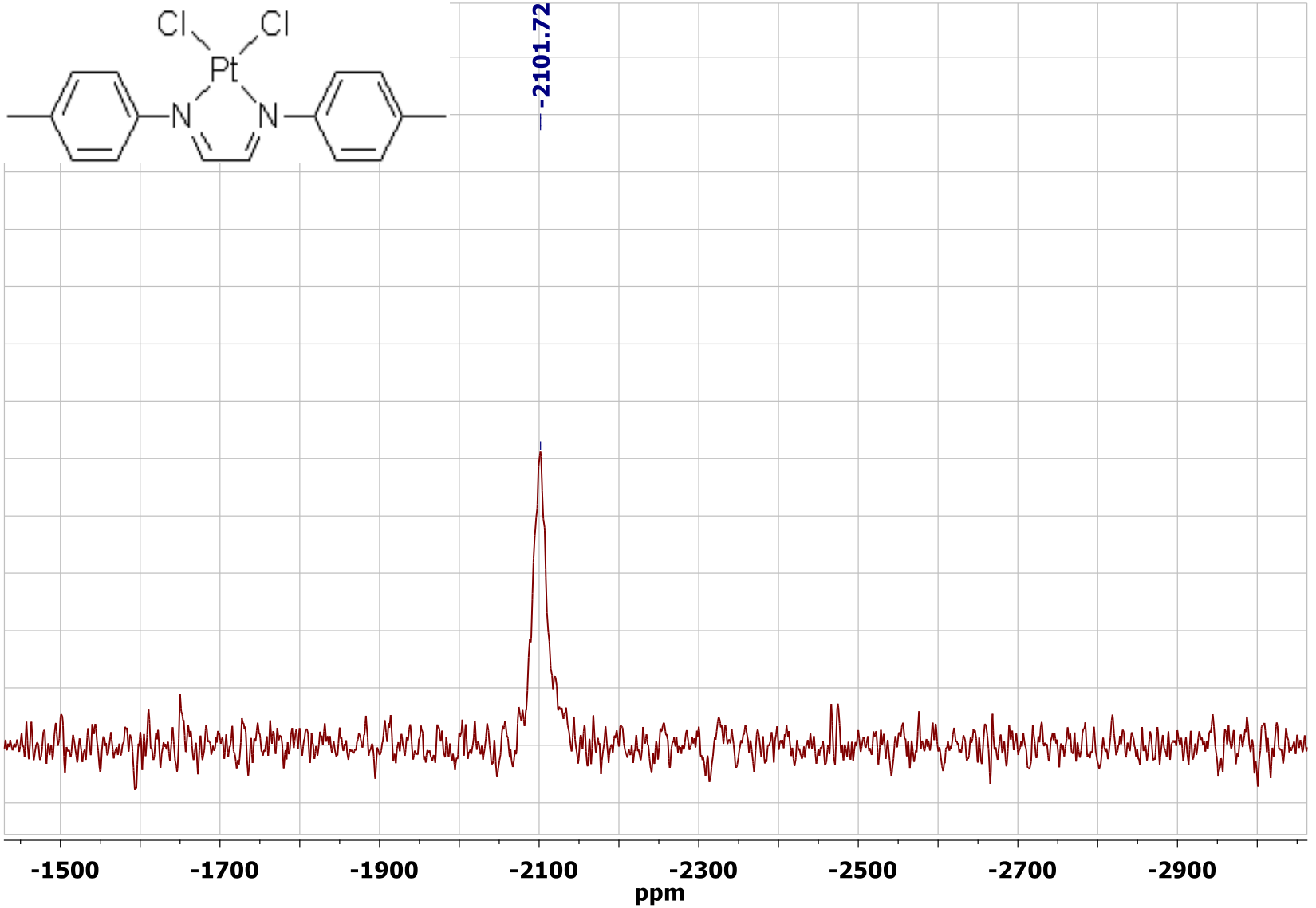


Figure S20. ^{1}H NMR spectrum (401 MHz, CD_3OD) of $[PtCl_2\{\kappa^2N\text{-}(HCN(4\text{-}C_6H_4OH))_2\}]$, **4**.

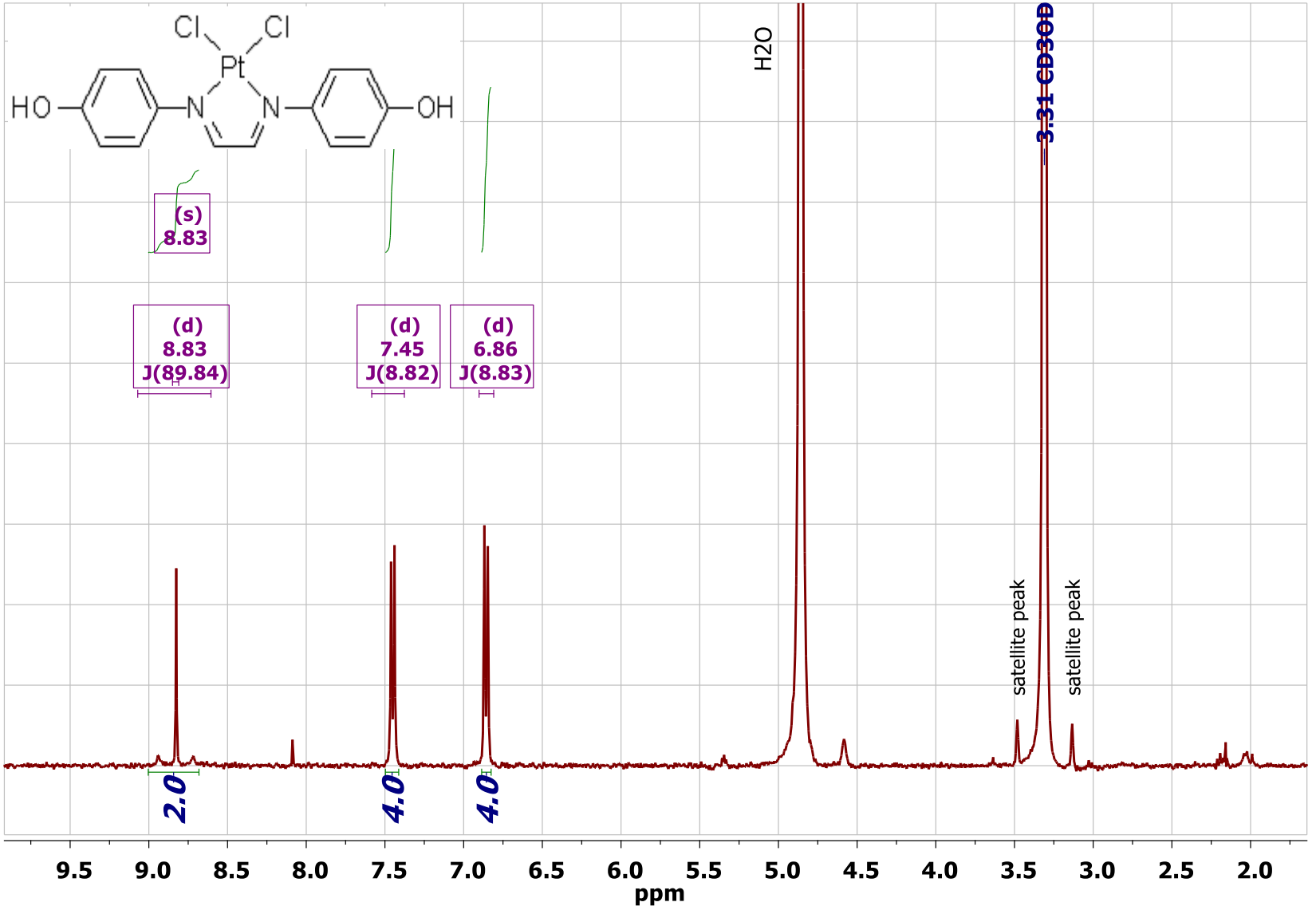


Figure S21. $^{13}C\{^{1}H\}$ NMR spectrum (101 MHz, CD_3OD) of $[PtCl_2\{\kappa^2N\text{-}(HCN(4\text{-}C_6H_4OH))_2\}]$, **4**.

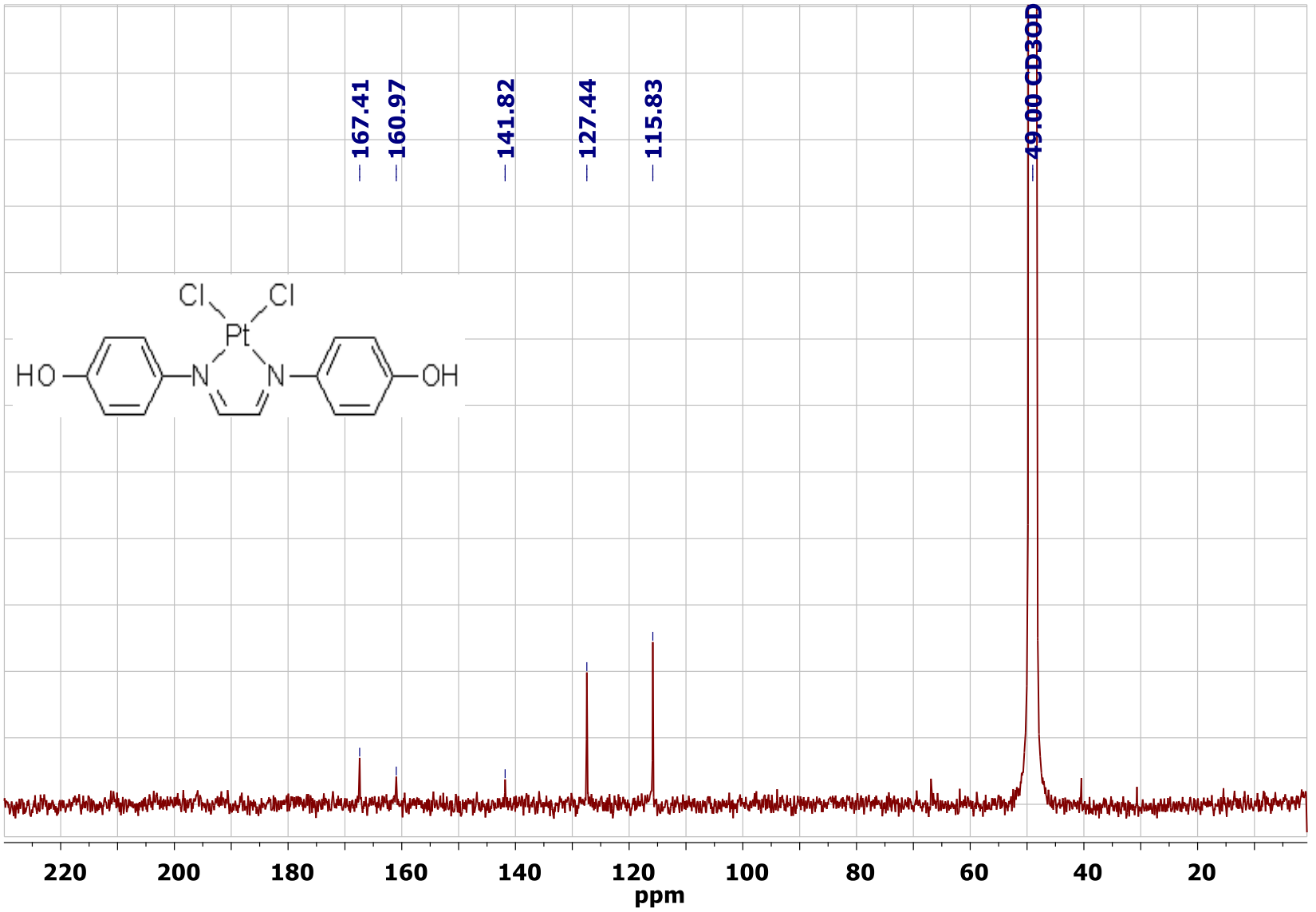


Figure S22. $^{195}Pt\{^{1}H\}$ NMR spectrum (86 MHz, DMF/C_6D_6 capillary) of $[PtCl_2\{\kappa^2N\text{-}(HCN(4\text{-}C_6H_4OH))_2\}]$, **4**.

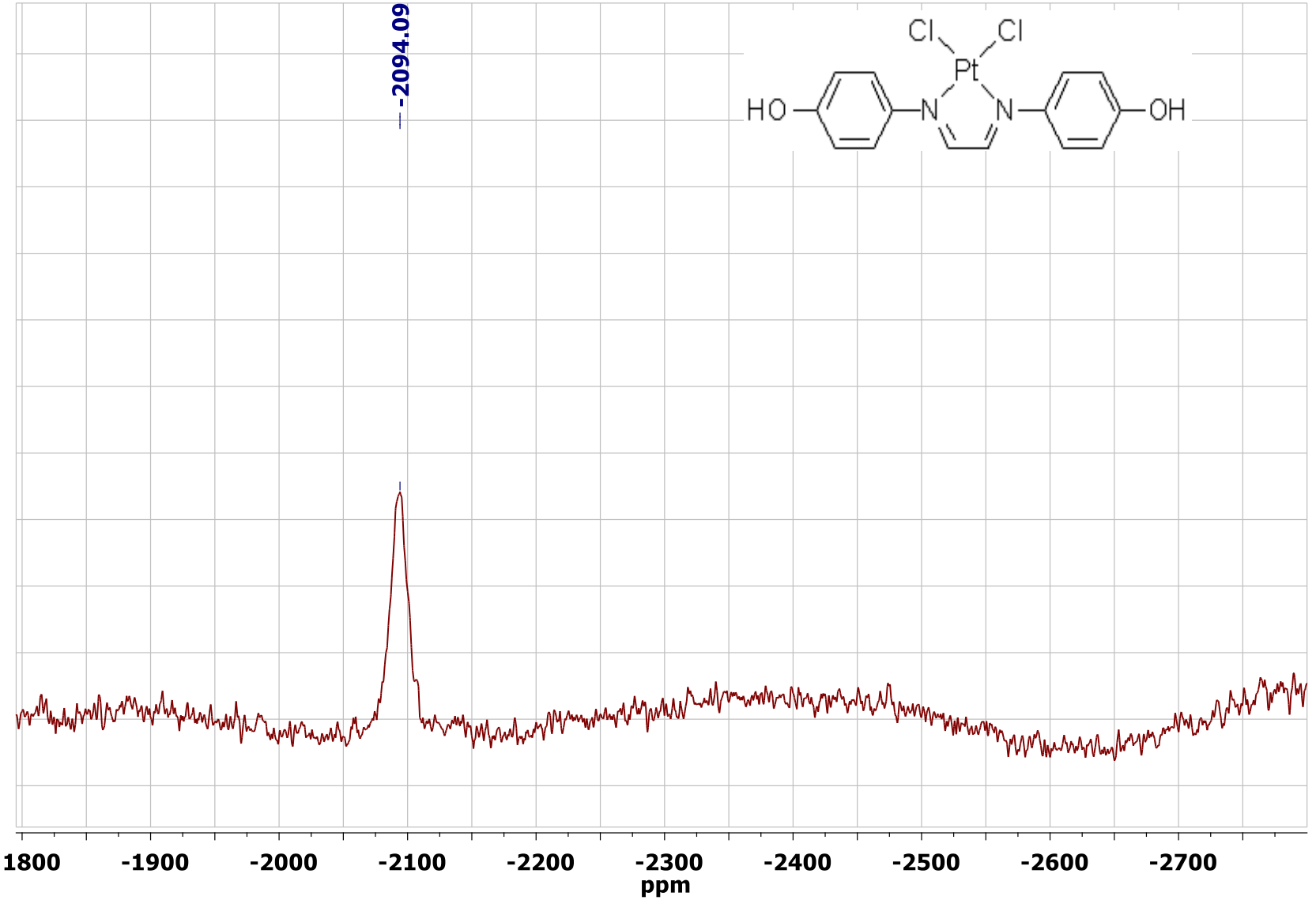


Figure S23. ^{1}H NMR spectrum (401 MHz, acetone-d_6) of $[PtCl_2\{\kappa^2N\text{-}(CH_3CNOH)_2\}]$, **5**. Inset shows the OH resonance (lower integral value due to H/D exchange).

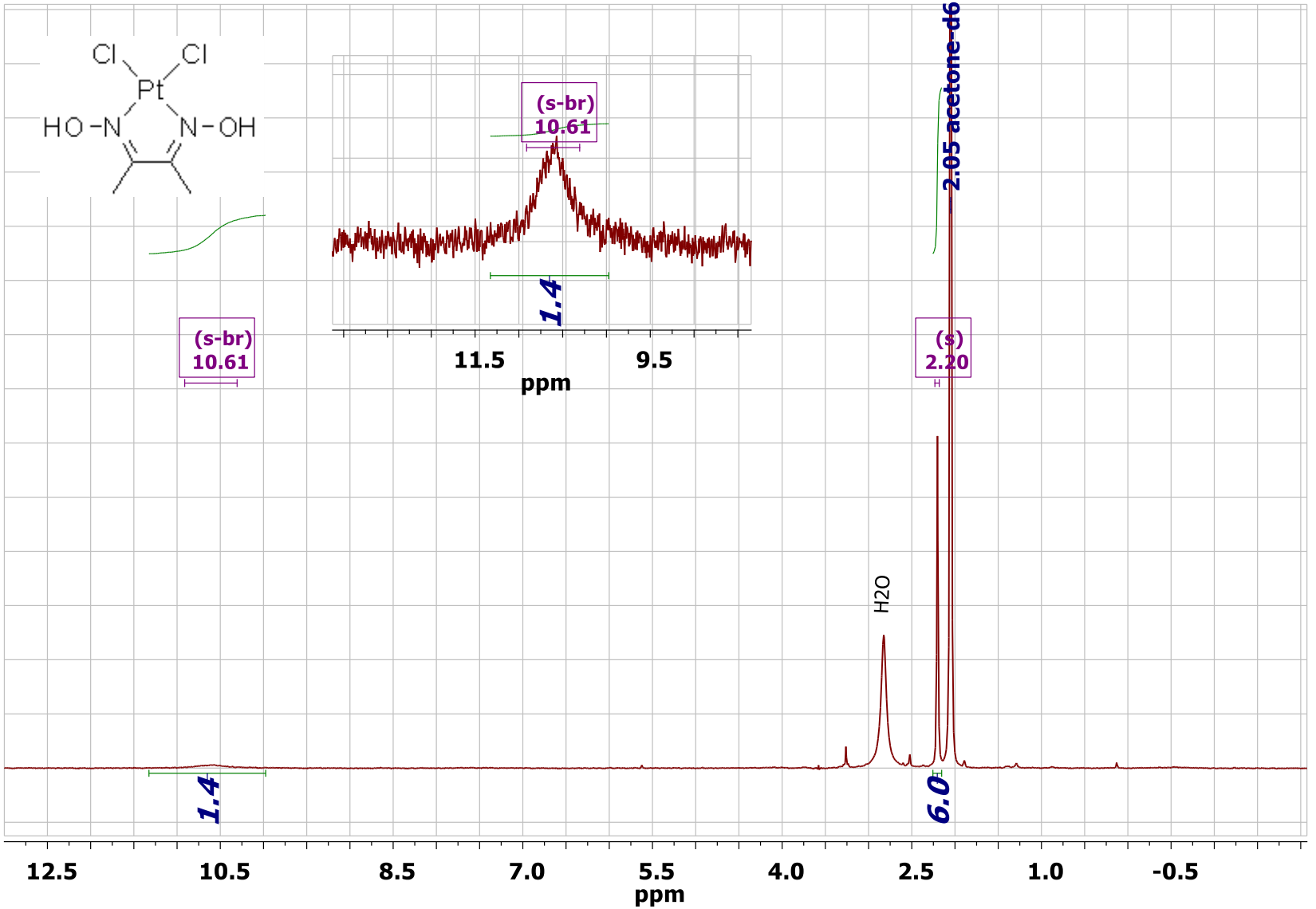


Figure S24. $^{13}C\{^{1}H\}$ NMR spectrum (101 MHz, acetone-d_6) of $[PtCl_2\{\kappa^2N\text{-}(CH_3CNOH)_2\}]$, **5**.

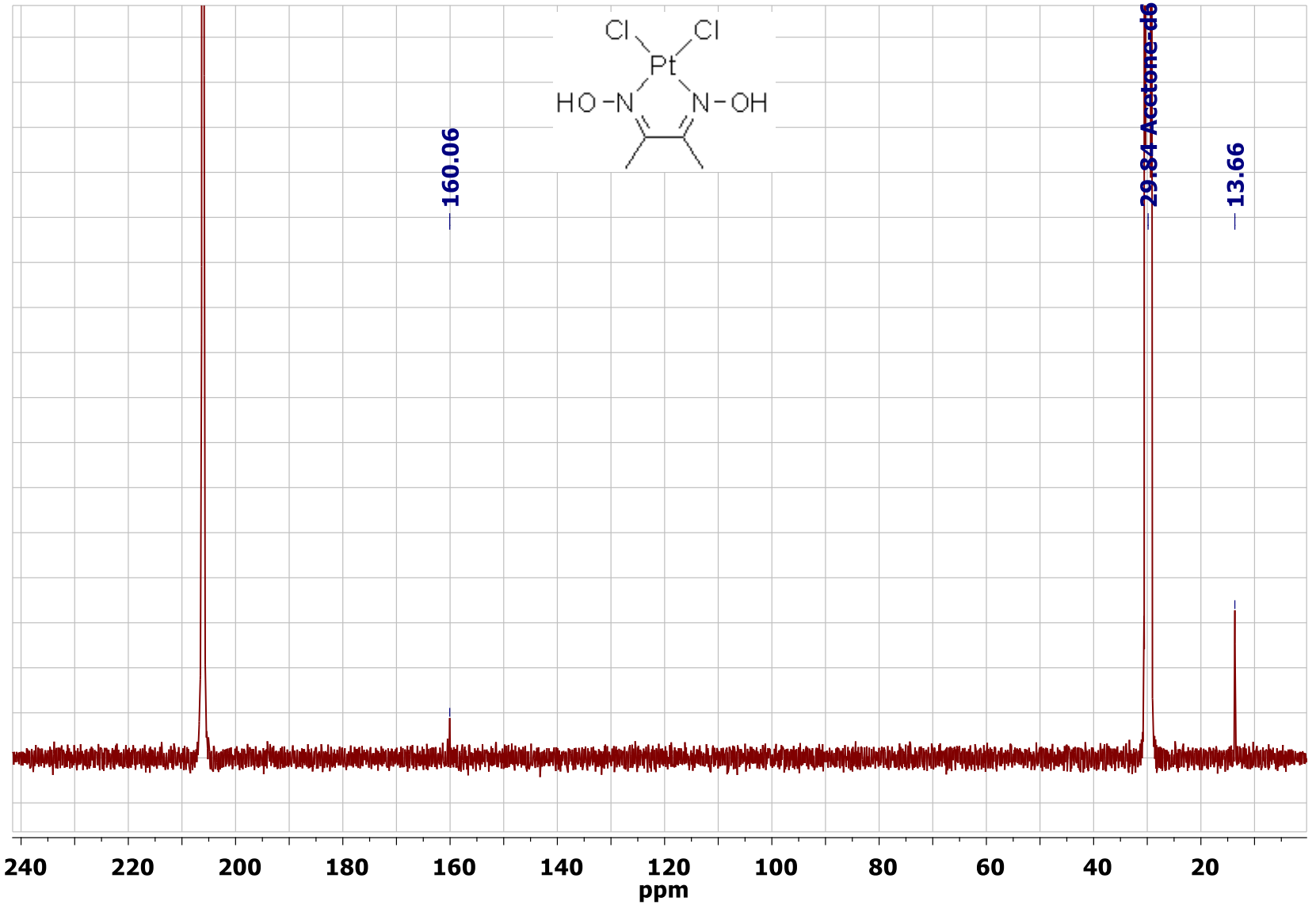


Figure S25. $^{195}Pt\{^{1}H\}$ NMR spectrum (86 MHz, DMF/C_6D_6 capillary) of $[PtCl_2\{\kappa^2N\text{-}(CH_3CNOH)_2\}]$, **5**.

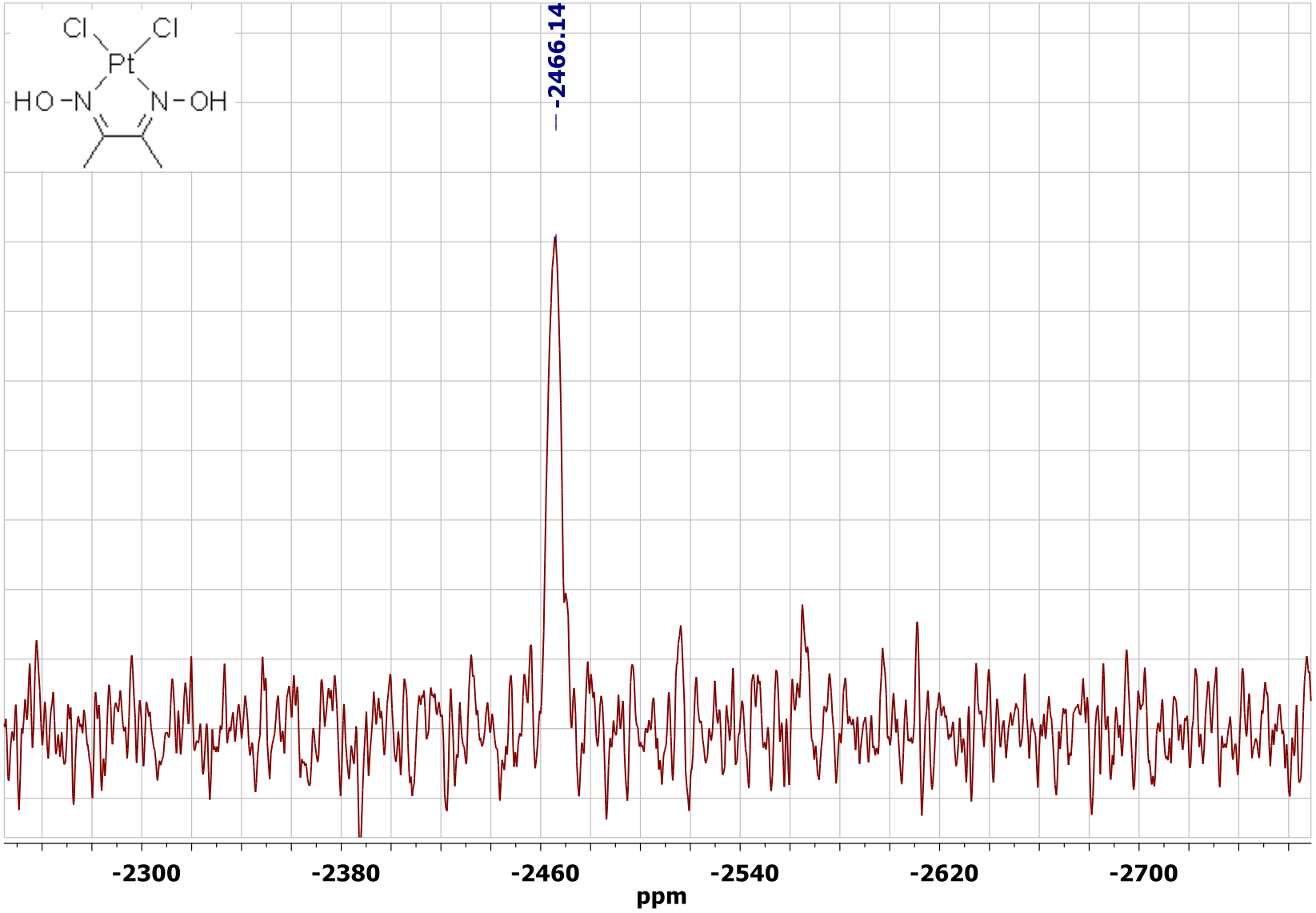


Figure S26. ^{1}H NMR spectrum (401 MHz, CD_2Cl_2) of [Pt(κ^2*O*-C_2O_4){κ^2*N*-(HCN(C_6H_{11}))$_2$}], **6**. Some signals are hidden by the H_2O peak and solvent impurities.

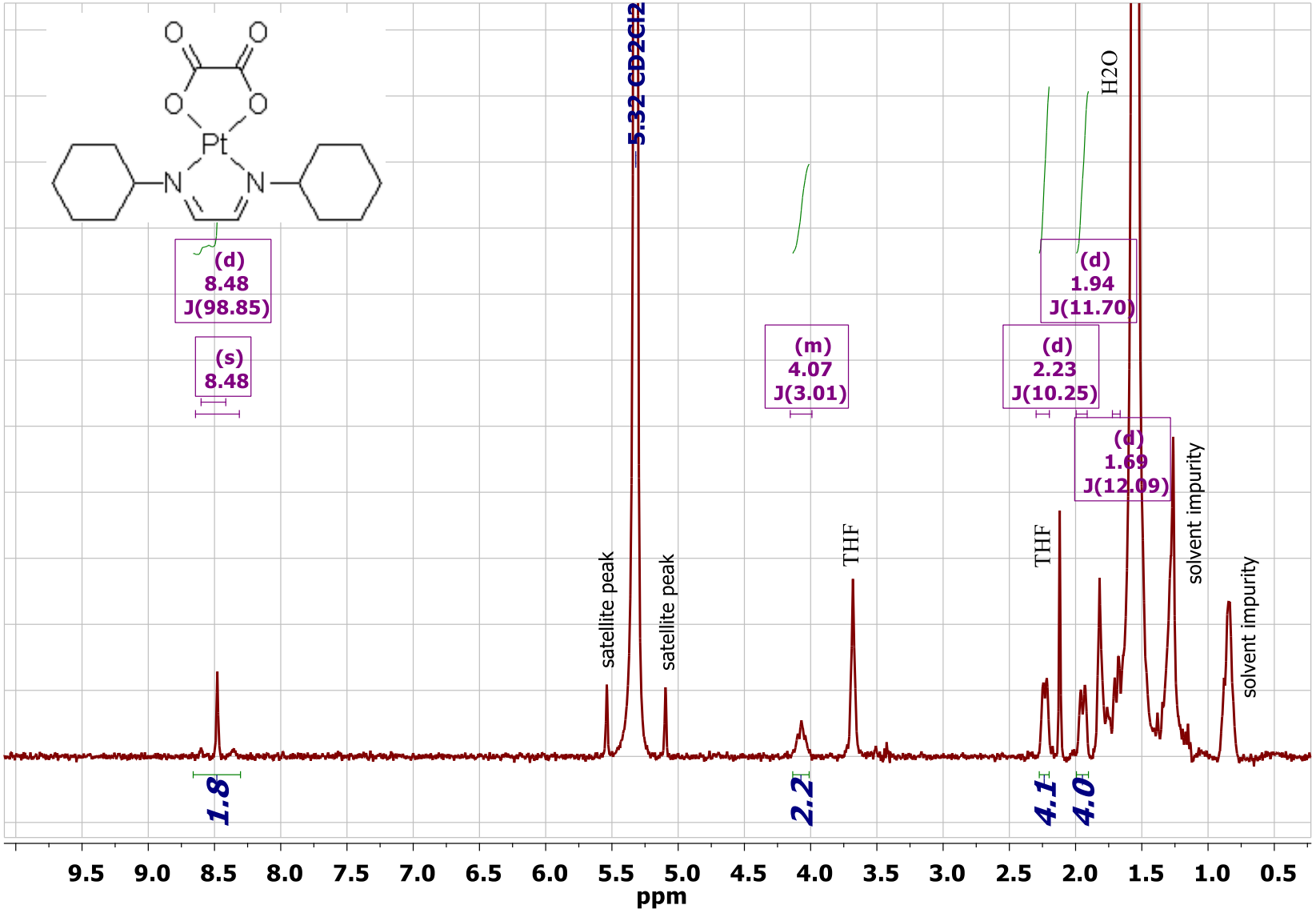
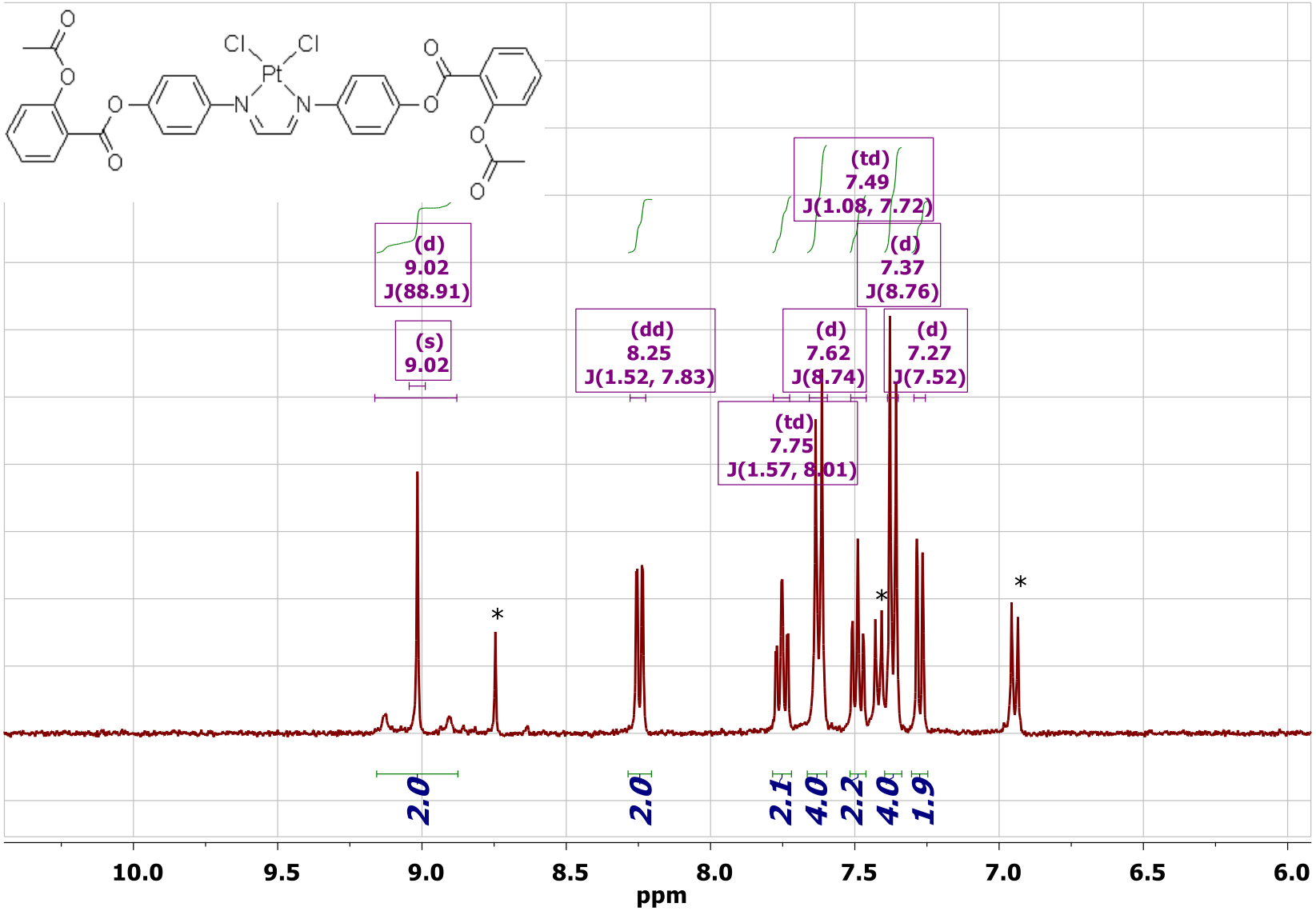


Figure S27. ^{1}H NMR spectrum (401 MHz, CD_3CN) in the 6-10 ppm region of [$PtCl_2$\{κ^2*N*-(HCN(4-C_6H_4OCO-asp))$_2$\}], **7** (in admixture with **4**; related signals are marked with asterisk *).



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