Electronic Supplementary Information

Understanding the conformational behaviour of Ac-Ala-NHMe in different media. A joint NMR and DFT study.

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Table S1: Compound **1** conformer relative energies (ΔE) in kcal mol^{-1} and corresponding populations (%P) obtained at the B3LYP-D3/aug-cc-pVDZ level for the isolated compounds and by using the IEF-PCM implicit solvent model with dichloromethane, acetone, acetonitrile, DMSO, methanol and water dielectric constants.

	1a		**1b**		**1c**		**1d**		**1e**		**1f**		**1g**		**1h**		**1i**		**1j**		**1k**		**1l**	
	ΔE	%P	ΔE	%P	ΔE	%P	ΔE	%P	ΔE	%P	ΔE	%P	ΔE	%P	ΔE	%P	ΔE	%P	ΔE	%P	ΔE	%P	ΔE	%P
Isolated	0.00	90.2	1.61	6.0	1.99	3.1	3.33	0.3	3.63	0.2	3.87	0.1	4.36	0.1	5.22	0.0	6.32	0.0	---	0.0	6.39	0.0	8.35	0.0
CH_2Cl_2	0.00	60.5	0.77	16.4	1.52	4.6	0.99	11.4	2.71	0.6	2.07	1.8	3.84	0.1	2.99	0.4	3.46	0,2	1.60	4.0	4.72	0.0	5.28	0.0
Acetone	0.00	49.5	0.69	15.5	1.50	3.9	0.48	22.0	2.67	0.5	1.86	2.1	3.40	0.2	2.48	0.8	3.05	0.3	1.34	5.1	4.52	0.0	4.92	0.0
Acetonitrile	0.00	44.5	0.66	14.6	1.49	3.6	0.28	27.5	2.65	0.5	1.79	2.2	3.30	0.2	2.28	0.9	2.91	0.3	1.23	5.6	4.45	0.0	4.79	0.0
DMSO	0.00	42.8	0.65	14.3	1.49	3.4	0.22	29.6	2.65	0.5	1.77	2.2	3.27	0.2	2.21	1.0	2.86	0.3	1.19	5.8	4.43	0.0	4.75	0.0
Methanol	0.00	45.2	0.66	14.7	1.49	3.6	0.31	26.7	2.65	0.5	1.80	2.2	3.32	0.2	2.31	0.9	2.93	0.3	1.24	5.5	4.46	0.0	4.81	0.0
Water	0.00	40.3	0.64	13.7	1.49	3.3	0.13	32.4	2.65	0.5	1.74	2.1	3.23	0.2	2.12	1.1	2.79	0.4	1.13	5.9	4.40	0.0	4.70	0.0

Table S2: Compound **1** conformer relative energies (ΔH) in kcal mol^{-1} and corresponding populations (%P) obtained at the B3LYP-D3/aug-cc-pVDZ level for the isolated compounds and by using the IEF-PCM implicit solvent model with dichloromethane, acetone, acetonitrile, DMSO, methanol and water dielectric constants.

	1a		**1b**		**1c**		**1d**		**1e**		**1f**		**1g**		**1h**		**1i**		**1j**		**1k**		**1l**	
	ΔH	%P	ΔH	%P	ΔH	%P	ΔH	%P	ΔH	%P	ΔH	%P	ΔH	%P	ΔH	%P	ΔH	%P	ΔH	%P	ΔH	%P	ΔH	%P
Isolated	0.00	88.5	1.41	8.2	2.13	2.4	3.17	0.4	3.57	0.2	3.84	0.1	4.45	0.0	5.05	0.0	6.13	0.0	---	0.0	6.36	0.0	8.25	0.0
CH_2Cl_2	0.00	57.3	0.63	19.9	1.71	3.2	0.91	12.3	2.63	0.7	2.06	1.8	3.91	0.1	2.84	0.5	3.41	0.2	1.56	4.1	4.75	0.0	5.38	0.0
Acetone	0.00	46.9	0.55	18.4	1.68	2.7	0.44	22.4	2.59	0.6	1.85	2.0	3.45	0.1	2.36	0.9	3.02	0.3	1.26	5.6	4.56	0.0	5.03	0.0
Acetonitrile	0.00	42.2	0.53	17.3	1.67	2.5	0.25	27.7	2.58	0.5	1.78	2.1	3.37	0.1	2.17	1.1	2.88	0.3	1.23	6.0	4.49	0.0	4.90	0.0
DMSO	0.00	40.6	0.52	16.9	1.67	2.4	0.19	29.7	2.58	0.5	1.76	2.1	3.34	0.1	2.11	1.2	2.83	0.3	1.13	6.1	4.46	0.0	4.86	0.0
Methanol	0.00	42.9	0.53	17.5	1.67	2.6	0.27	27.0	2.58	0.5	1.79	2.1	3.38	0.1	2.20	1.0	2.90	0.3	1.17	5.9	4.50	0.0	4.92	0.0
Water	0.00	38.4	0.51	16.3	1.66	2.3	0.10	32.4	2.58	0.5	1.73	2.1	3.30	0.1	2.02	1.3	2.77	0.4	1.08	6.2	4.43	0.0	4.80	0.0

Table S3: Compound **1** conformer relative energies (ΔG) in kcal mol^{-1} and corresponding populations (%P) obtained at the B3LYP-D3/aug-cc-pVDZ level for the isolated compounds and by using the IEF-PCM implicit solvent model with dichloromethane, acetone, acetonitrile, DMSO, methanol and water dielectric constants.

	1a		**1b**		**1c**		**1d**		**1e**		**1f**		**1g**		**1h**		**1i**		**1j**		**1k**		**1l**	
	ΔG	%P	ΔG	%P	ΔG	%P	ΔG	%P	ΔG	%P	ΔG	%P	ΔG	%P	ΔG	%P	ΔG	%P	ΔG	%P	ΔG	%P	ΔG	%P
Isolated	0.00	64.7	0.44	30.7	2.23	1.5	1.86	2.8	3.92	0.1	3.80	0.1	4.30	0.0	4.47	0.0	5.76	0.0	---	0.0	5.94	0.0	9.06	0.0
CH_2Cl_2	0.48	22.4	0.00	50.7	2.68	0.6	0.64	17.3	3.02	0.3	2.64	0.6	3.04	0.3	2.99	0.3	3.48	0.1	1.14	7.4	5.65	0.0	6.62	0.0
Acetone	0.52	17.0	0.00	41.0	2.64	0.5	0.40	20.8	2.98	0.3	2.39	0.7	3.61	0.1	2.39	0.7	3.17	0.2	0.46	18.7	5.41	0.0	6.20	0.0
Acetonitrile	0.50	17.3	0.00	40.4	2.59	0.5	0.24	26.8	2.95	0.3	2.26	0.9	3.63	0.1	2.23	0.9	3.03	0.2	0.69	12.6	5.30	0.0	6.02	0.0
DMSO	0.49	17.1	0.00	39.0	2.58	0.5	0.18	28.8	2.94	0.3	2.22	0.9	3.61	0.1	2.17	1.0	2.98	0.3	0.70	12.0	5.26	0.0	5.96	0.0
Methanol	0.51	17.3	0.00	40.7	2.60	0.5	0.26	26.1	2.96	0.3	2.28	0.9	3.64	0.1	2.25	0.9	3.05	0.2	0.68	13.0	5.31	0.0	6.04	0.0
Water	0.48	16.4	0.00	36.8	2.55	0.5	0.08	32.0	2.93	0.3	2.16	1.0	3.59	0.1	2.08	1.1	2.91	0.3	0.68	11.6	5.20	0.0	5.88	0.0

Table S4: Compound **2** conformer relative energies (ΔE) in kcal mol^{-1} and corresponding populations (%P) obtained at the B3LYP-D3/aug-cc-pVDZ level for the isolated compounds and by using the IEF-PCM implicit solvent model with dichloromethane, acetone, acetonitrile, DMSO, methanol and water dielectric constants.

	2a		**2b**		**2c**		**2d**		**2e**		**2f**		**2g**		**2h**		**2i**		**2j**		**2k**		**2l**	
	ΔE	%P	ΔE	%P	ΔE	%P	ΔE	%P	ΔE	%P	ΔE	%P	ΔE	%P	ΔE	%P	ΔE	%P	ΔE	%P	ΔE	%P	ΔE	%P
Isolated	1.06	14.3	0.00	85.7	4.97	0.0	5.58	0.0	6.80	0.0	6.68	0.0	6.43	0.0	7.91	0.0	7.08	0.0	6.12	0.0	6.75	0.0	9.12	0.0
CH_2Cl_2	1.50	7.3	0.00	91.3	2.78	0.8	4.16	0.1	5.49	0.0	4.00	0.1	3.47	0.3	6.10	0.0	6.65	0.0	4.32	0.1	5.43	0.0	6.66	0.0
Acetone	1.42	8.1	0.00	89.2	2.44	1.4	3.93	0.1	5.18	0.0	3.36	0.3	2.84	0.7	5.62	0.0	6.52	0.0	4.11	0.1	5.22	0.0	6.26	0.0
Acetonitrile	1.07	13.6	0.00	83.0	2.32	1.7	3.85	0.1	5.06	0.0	3.11	0.4	2.60	1.0	5.43	0.0	6.47	0.0	4.04	0.1	5.14	0.0	6.11	0.0
DMSO	1.04	14.1	0.00	82.2	2.28	1.8	3.82	0.1	5.01	0.0	3.02	0.5	2.52	1.2	5.36	0.0	6.45	0.0	4.02	0.1	5.11	0.0	6.07	0.0
Methanol	1.08	13.4	0.00	83.3	2.33	1.6	3.86	0.1	5.07	0.0	3.14	0.4	2.64	1.0	5.45	0.0	6.48	0.0	4.05	0.1	5.15	0.0	6.13	0.0
Water	1.01	14.8	0.00	81.0	2.22	1.9	3.79	0.1	4.96	0.0	2.91	0.6	2.42	1.4	5.27	0.0	6.43	0.0	3.98	0.1	5.08	0.0	6.00	0.0

Table S5: Compound **2** conformer relative energies (ΔH) in kcal mol^{-1} and corresponding populations (%P) obtained at the B3LYP-D3/aug-cc-pVDZ level for the isolated compounds and by using the IEF-PCM implicit solvent model with dichloromethane, acetone, acetonitrile, DMSO, methanol and water dielectric constants.

	2a		**2b**		**2c**		**2d**		**2e**		**2f**		**2g**		**2h**		**2i**		**2j**		**2k**		**2l**	
	ΔH	%P	ΔH	%P	ΔH	%P	ΔH	%P	ΔH	%P	ΔH	%P	ΔH	%P	ΔH	%P	ΔH	%P	ΔH	%P	ΔH	%P	ΔH	%P
Isolated	1.28	10.3	0.00	89.7	4.90	0.0	5.63	0.0	6.88	0.0	6.42	0.0	6.33	0.0	7.92	0.0	7.38	0.0	6.17	0.0	6.87	0.0	9.36	0.0
CH_2Cl_2	1.61	6.1	0.00	92.6	2.82	0.8	4.23	0.1	5.59	0.0	3.94	0.1	3.51	0.2	6.20	0.0	6.91	0.0	4.48	0.0	5.53	0.0	7.01	0.0
Acetone	1.59	6.2	0.00	91.2	2.48	1.4	4.03	0.1	5.29	0.0	3.33	0.3	2.92	0.7	5.72	0.0	6.79	0.0	4.29	0.1	5.31	0.0	6.63	0.0
Acetonitrile	1.17	11.8	0.00	85.1	2.36	1.6	3.95	0.1	5.17	0.0	3.10	0.5	2.69	0.9	5.54	0.0	6.74	0.0	4.23	0.1	5.22	0.0	6.48	0.0
DMSO	1.14	12.3	0.00	84.3	2.32	1.7	3.93	0.1	5.13	0.0	3.02	0.5	2.62	1.0	5.48	0.0	6.72	0.0	4.20	0.1	5.20	0.0	6.44	0.0
Methanol	1.18	11.6	0.00	85.4	2.37	1.5	3.96	0.1	5.18	0.0	3.13	0.4	2.72	0.9	5.56	0.0	6.74	0.0	4.23	0.1	5.24	0.0	6.50	0.0
Water	1.10	12.9	0.00	83.2	2.26	1.8	3.90	0.1	5.07	0.0	2.92	0.6	2.52	1.2	5.39	0.0	6.70	0.0	4.18	0.1	5.16	0.0	6.37	0.0

Table S6: Compound **2** conformer relative energies (ΔG) in kcal mol^{-1} and corresponding populations (%P) obtained at the B3LYP-D3/aug-cc-pVDZ level for the isolated compounds and by using the IEF-PCM implicit solvent model with dichloromethane, acetone, acetonitrile, DMSO, methanol and water dielectric constants.

	2a		**2b**		**2c**		**2d**		**2e**		**2f**		**2g**		**2h**		**2i**		**2j**		**2k**		**2l**	
	ΔG	%P	ΔG	%P	ΔG	%P	ΔG	%P	ΔG	%P	ΔG	%P	ΔG	%P	ΔG	%P	ΔG	%P	ΔG	%P	ΔG	%P	ΔG	%P
Isolated	0.74	22.3	0.00	77.3	5.36	0.0	6.03	0.0	6.93	0.0	6.19	0.0	6.14	0.0	7.83	0.0	6.97	0.0	6.21	0.0	7.67	0.0	10.22	0.0
CH_2Cl_2	0.64	25.1	0.00	74.4	3.39	0.2	4.22	0.1	5.37	0.0	4.39	0.0	3.64	0.2	6.42	0.0	7.23	0.0	5.16	0.0	6.05	0.0	7.98	0.0
Acetone	0.70	23.2	0.00	75.7	3.06	0.4	3.93	0.1	5.12	0.0	3.78	0.1	3.13	0.4	5.67	0.0	7.16	0.0	5.00	0.0	5.80	0.0	7.54	0.0
Acetonitrile	0.63	25.4	0.00	73.2	2.92	0.5	4.04	0.1	4.98	0.0	3.57	0.2	2.94	0.5	5.44	0.0	7.16	0.0	4.95	0.0	5.71	0.0	7.42	0.0
DMSO	0.61	25.8	0.00	72.7	2.87	0.6	4.06	0.1	4.92	0.0	3.49	0.2	2.85	0.6	5.36	0.0	7.16	0.0	4.92	0.0	5.67	0.0	7.38	0.0
Methanol	0.64	25.0	0.00	73.7	2.94	0.5	4.03	0.1	5.00	0.0	3.60	0.2	2.96	0.5	5.47	0.0	7.16	0.0	4.96	0.0	5.72	0.0	7.44	0.0
Water	0.61	25.7	0.00	72.6	2.80	0.6	4.08	0.1	4.84	0.0	3.40	0.2	2.76	0.7	5.27	0.0	7.16	0.0	4.89	0.0	5.63	0.0	7.34	0.0

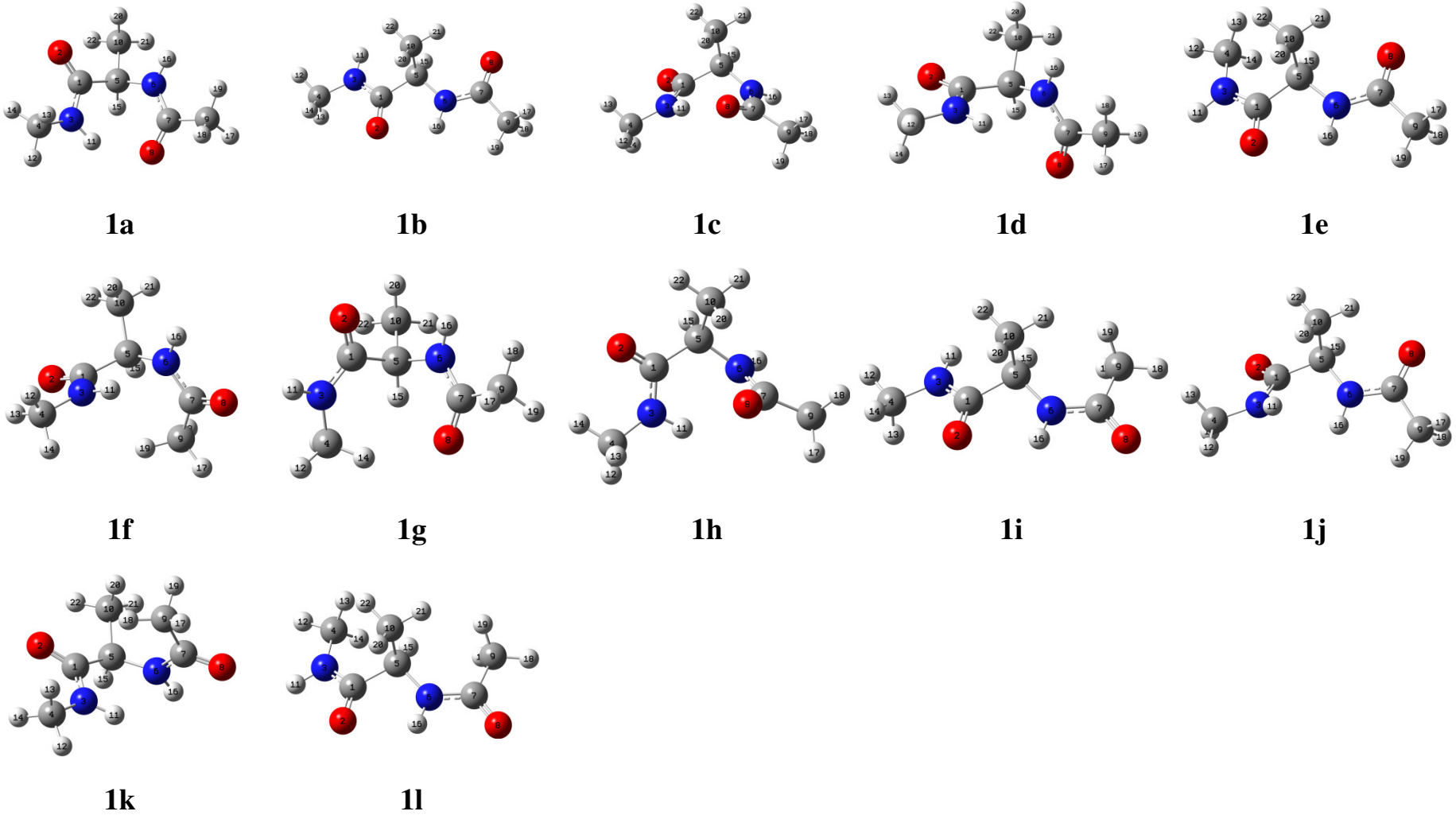


Figure S1: Geometrical representations of Ac-Ala-NHMe conformers obtained at the B3LYP-D3/aug-cc-pVDZ level.

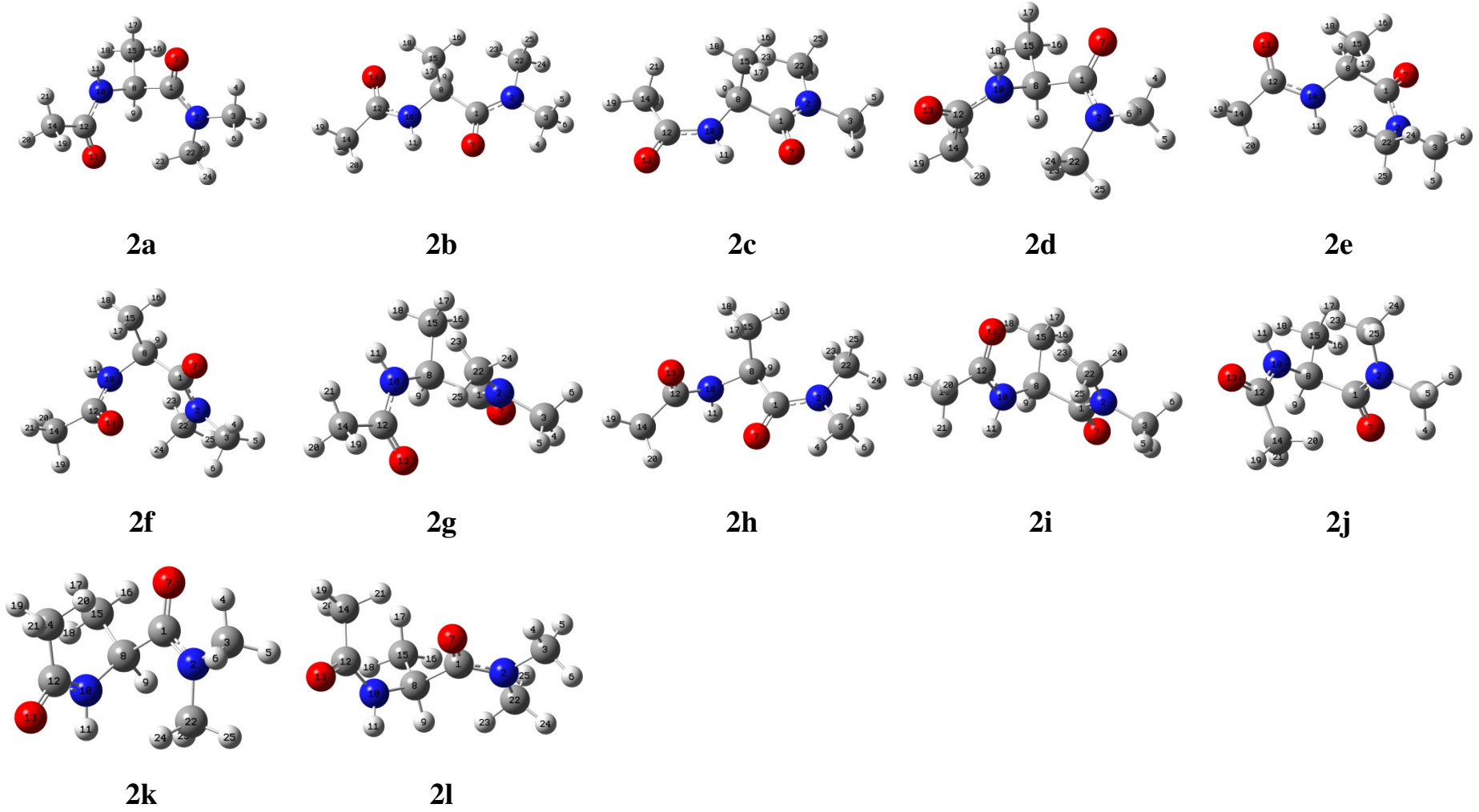
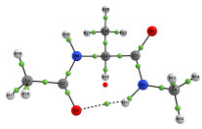
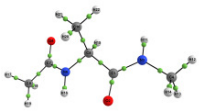
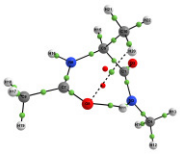
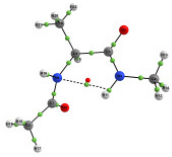
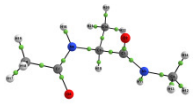
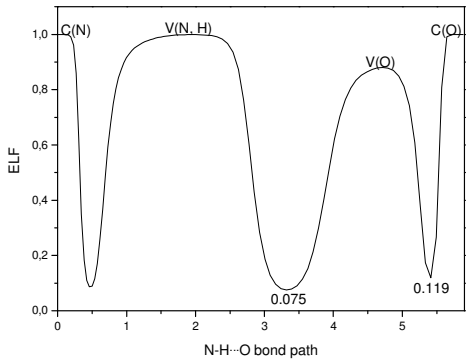
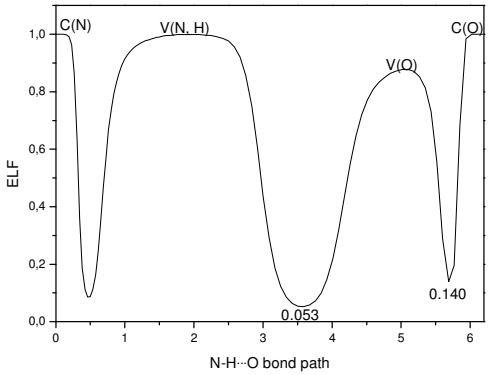
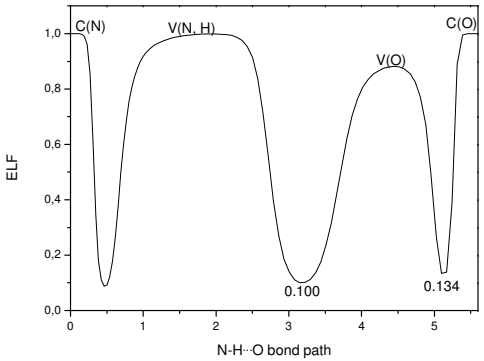


Figure S2: Geometrical representations of Ac-Ala-N(Me)$_2$ conformers obtained at the B3LYP-D3/aug-cc-pVDZ level.

Table S7: QTAIM molecular graphs of compound **1** most stable conformers obtained from B3LYP-D3/aug-cc-pVDZ optimisations. Electron density (ρ), Laplacian of the electron density ($\nabla^2\rho$) and ellipticity values (ε, au) in the N-H···O (**1a**-**1c**) and N-H···N (**1d**) intramolecular hydrogen bond (IHB) bond critical point (BCP) are indicated for each case.

	1a	**1b**	**1c**	**1d**	**1j**
					
ρ	**0.022**	**---**	**0.029**	**0.017**	**---**
$\nabla\rho$	**+0.065**	**---**	**+0.095**	**+0.065**	**---**
ε	**0.035**	**---**	**0.038**	**1.261**	**---**

	1a	1b	1c
			
CVBI	+0.044	+0.087	+0.034

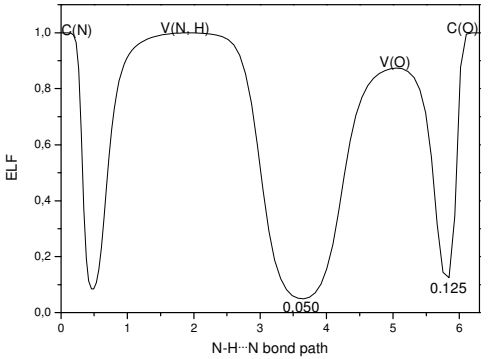
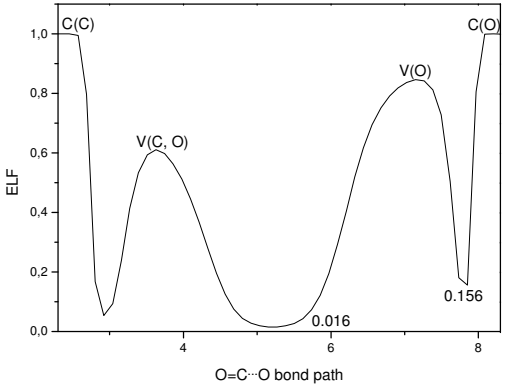
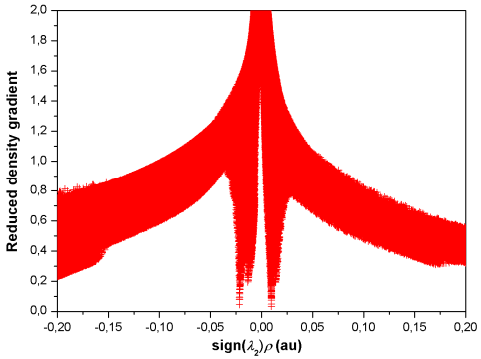
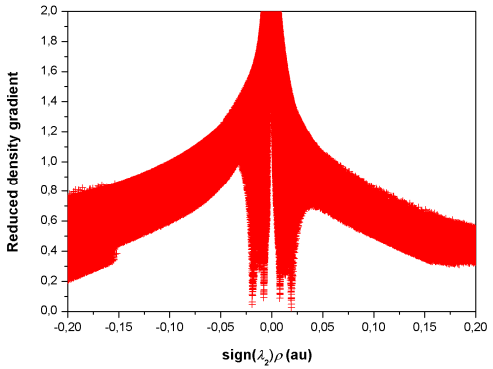
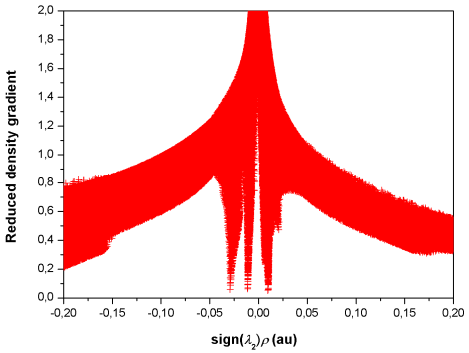
	1d	1j
		
CVBI	+0.075	+0.140

Figure S3: Graphs of ELF value along the bond path of the IHBs for the most stable conformers of compound **1**. The graph for compound **1j** measures ELF values on the C=O···C bond path. Core valence bifurcation index (CVBI) values (au) for each case obtained from those graphs are also indicated.

	1a	1b	1c
			
$sign(\lambda_2)\rho$	-0.022	-0.019	-0.029

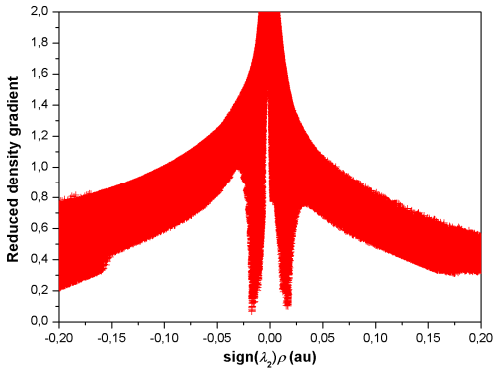
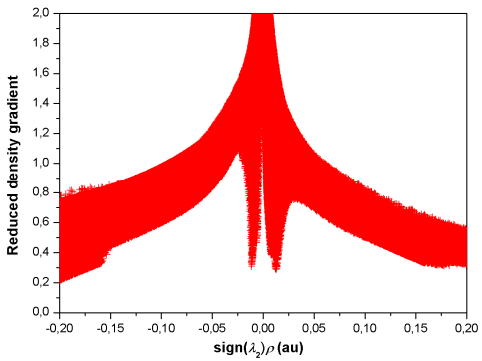
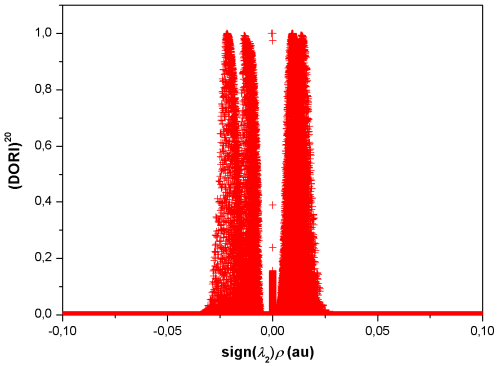
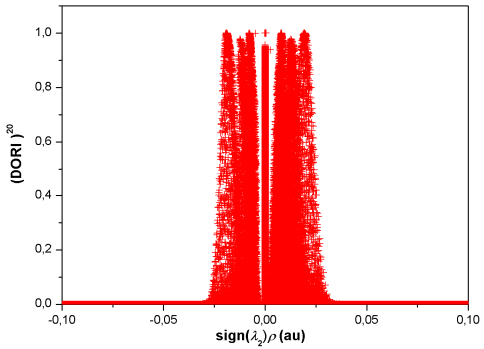
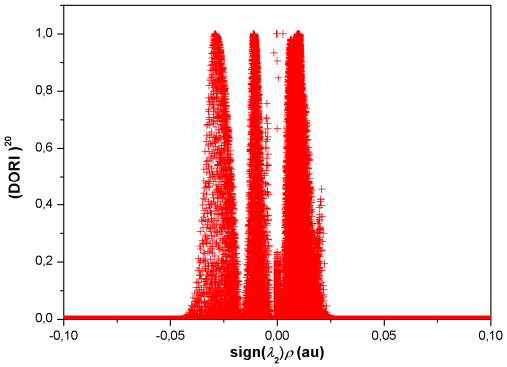
	1d	1j
		
$sign(\lambda_2)\rho$	-0.017	-0.006

Figure S4: Graph of the RDG *vs* sign(λ_2)ρ for the main conformers of compound **1**. Values of sign(λ_2)ρ (au) corresponding to IHBs peaks in the (RDG) *vs* sign(λ_2)ρ graphs are given for each case.

	1a	1b	1c
			
$sign(\lambda_2)\rho$	-0.022	-0.019	-0.029

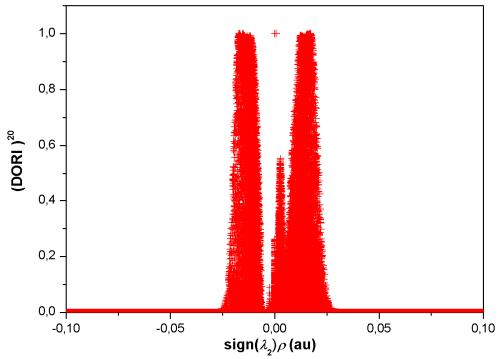
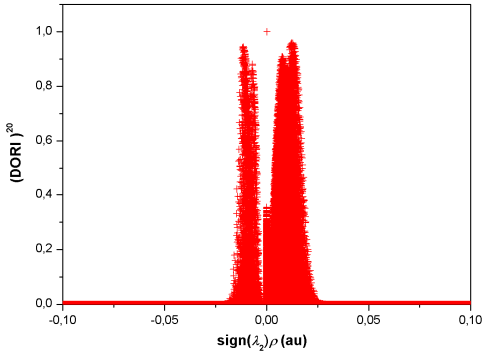
	1d	1j
		
$sign(\lambda_2)\rho$	-0.017	-0.006

Figure S5:. DORI vs sign(λ_2)ρ graphs for the most stable conformers of compound **1**. DORI values were multiplied by 10^{20} in order to obtain sharper DORI peaks.

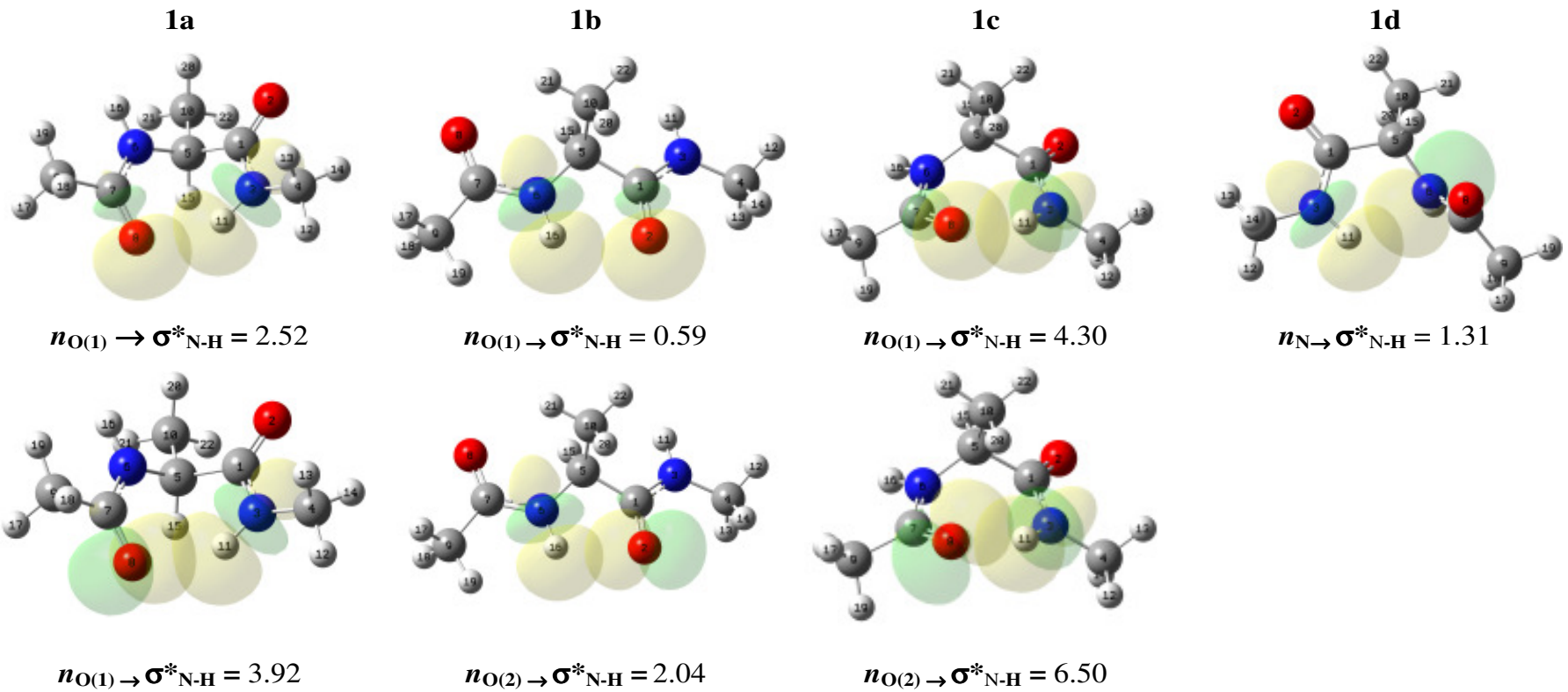
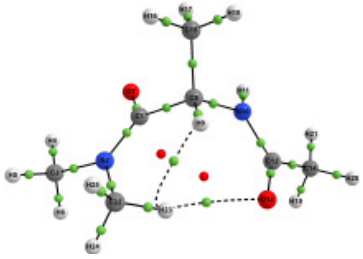
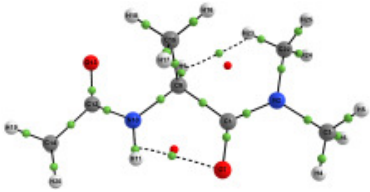


Figure S6: NBO plots of $n \rightarrow \sigma^*_{NH}$ interactions for main conformers of **1.** Figures were obtained at the B3LYP-D3/aug-cc-pVDZ level with an isovalue of 0.04 au. $n \rightarrow \sigma^*_{NH}$ energy values are given in kcal mol^{-1}.

Table S8: QTAIM molecular graphs of compound **2** most stable conformers obtained from B3LYP-D3/aug-cc-pVDZ optimisations. Electron density (ρ), Laplacian of the electron density ($\nabla^2\rho$) and ellipticity values (ε, au) in the C-H···O=C (**2a**) and C-H···O=C (**2b**) IHB bond critical point (BCP) are indicated.

	2a	**2b**
		
ρ	0.012	0.021
$\nabla\rho$	+0.034	+0.086
ε	0.136	1.760

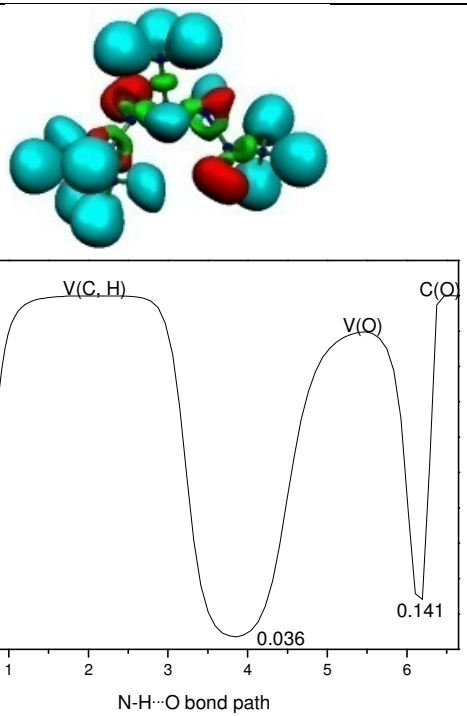
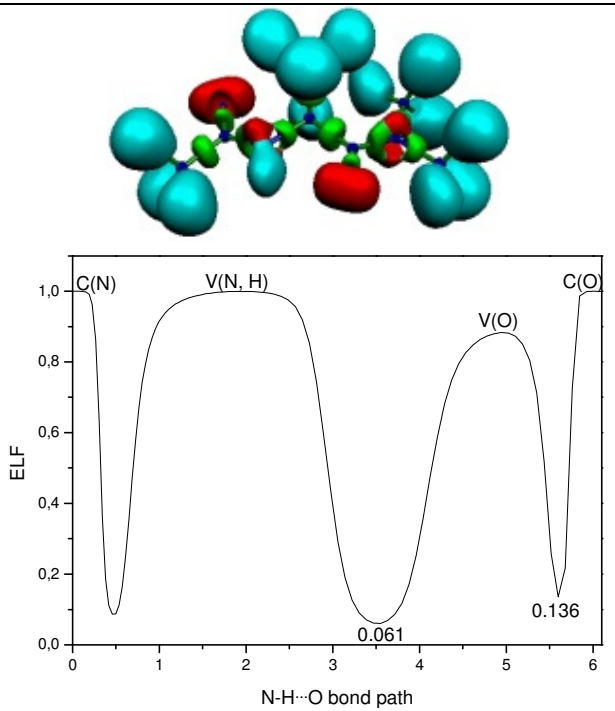
	2a	2b
		
CVBI	+0.105	+0.065

Figure S7: ELF localization domains, built with an 0.8 au isodensity value, and graphs of ELF value along the bond path of the IHBs for the most stable conformers of compound **2**. Core valence bifurcation index (CVBI) values (au) for each case obtained from those graphs are also indicated.

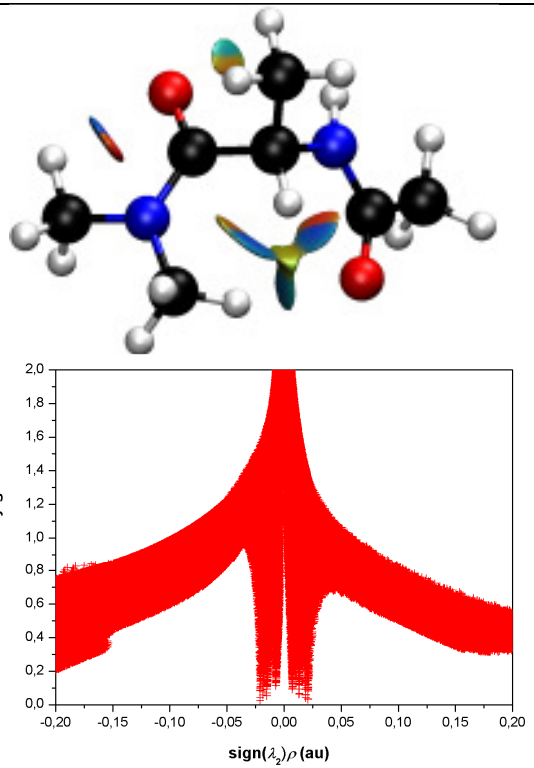
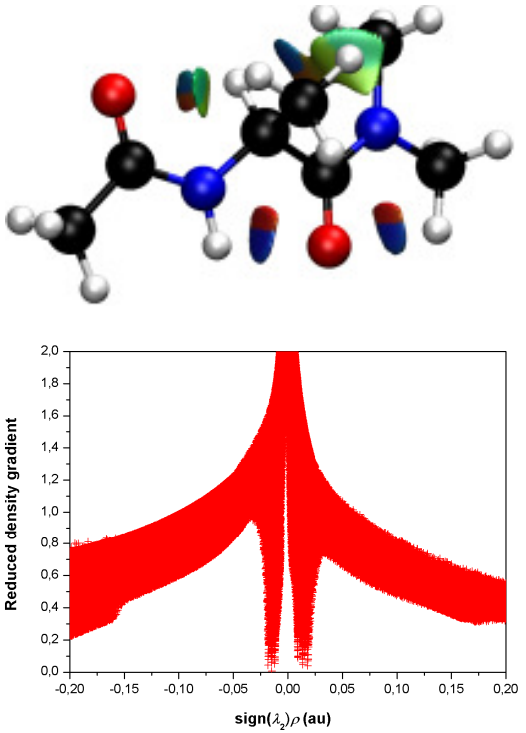
	2a	2b
		
sign(λ_2)ρ	-0.012	-0.021

Figure S8: Graph of the RDG *vs* sign(λ_2)ρ for the most stable conformers of compound **2**. Values of sign(λ_2)ρ (au) corresponding to IHBs peaks in the (RDG) *vs* sign(λ_2)ρ graphs are given for each case. NCI figures were obtained with a blue-green-red scale ranging from -0.02 < signλ_2 < 0.02 au and with a RDG cutoff of 0.5 au. Sign(λ_2)ρ values given are related to the C-H···O=C (**2a**) and N-H···O=C IHBs (**2b**).

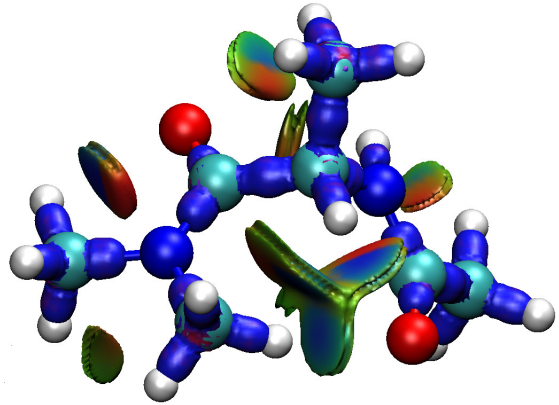
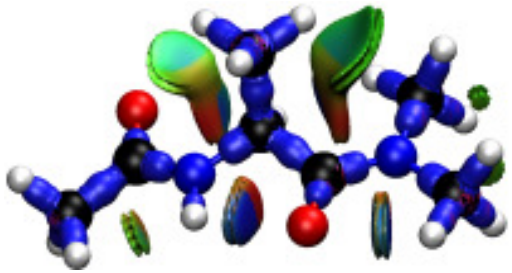
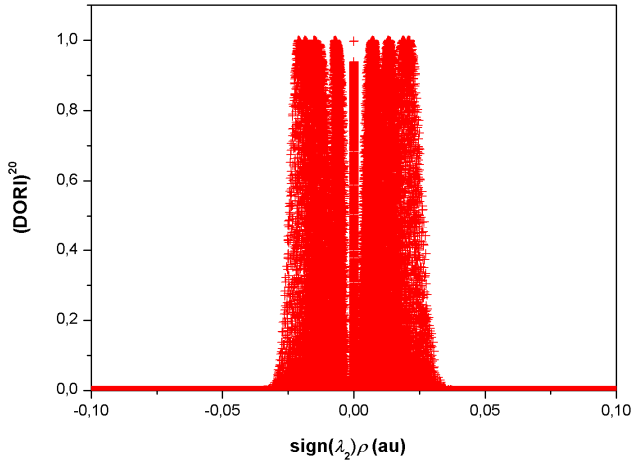
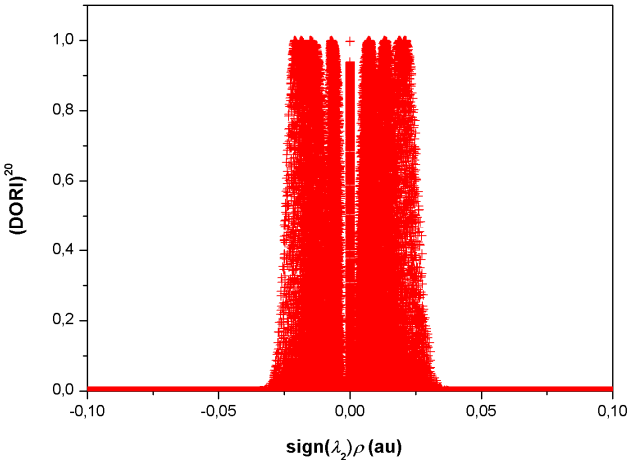
	2a	2b
		
		
sign(λ_2)ρ	-0.012	-0.021

Figure S9:. DORI vs sign(λ_2)ρ graphs for the most stable conformers of compound **1**. DORI values were multiplied by 10^{20} in order to obtain sharper DORI peaks.

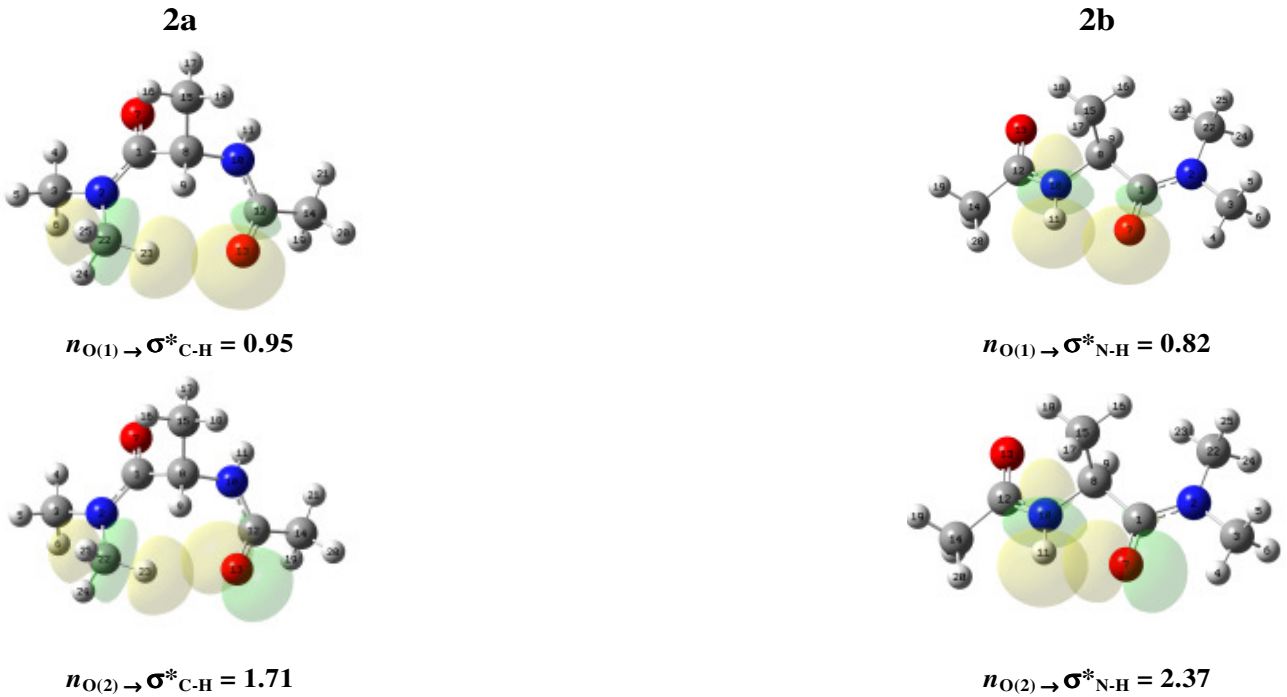
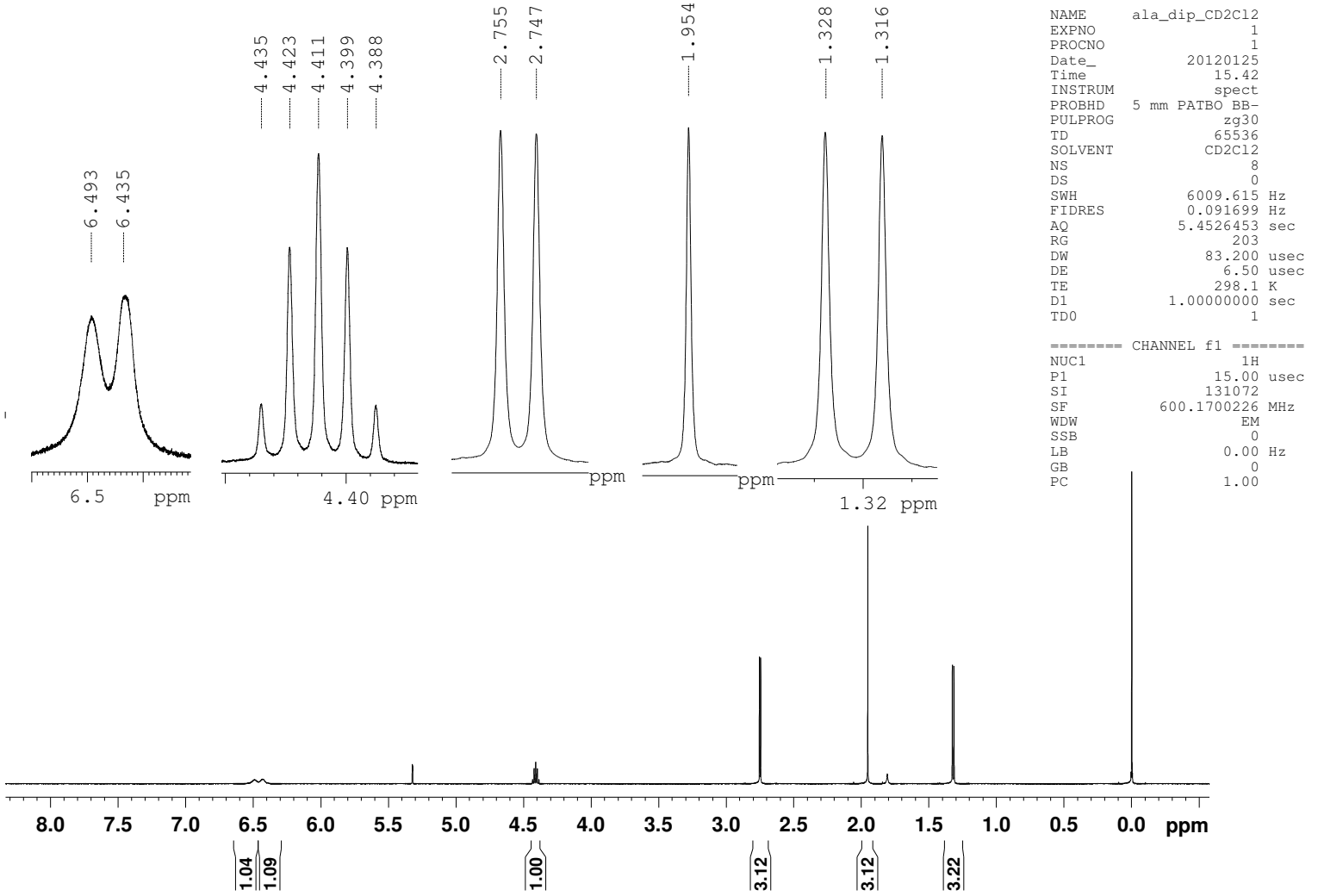
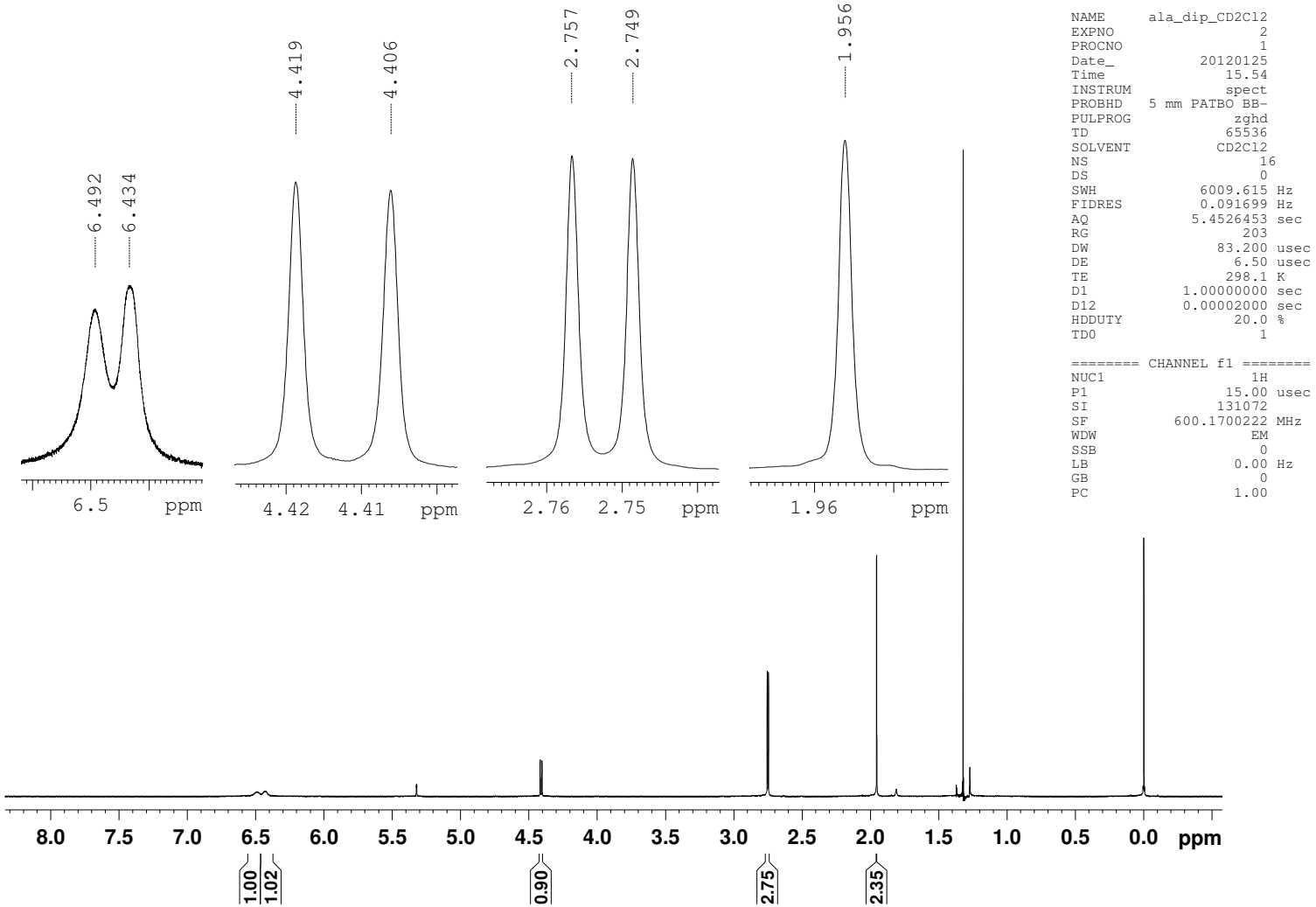


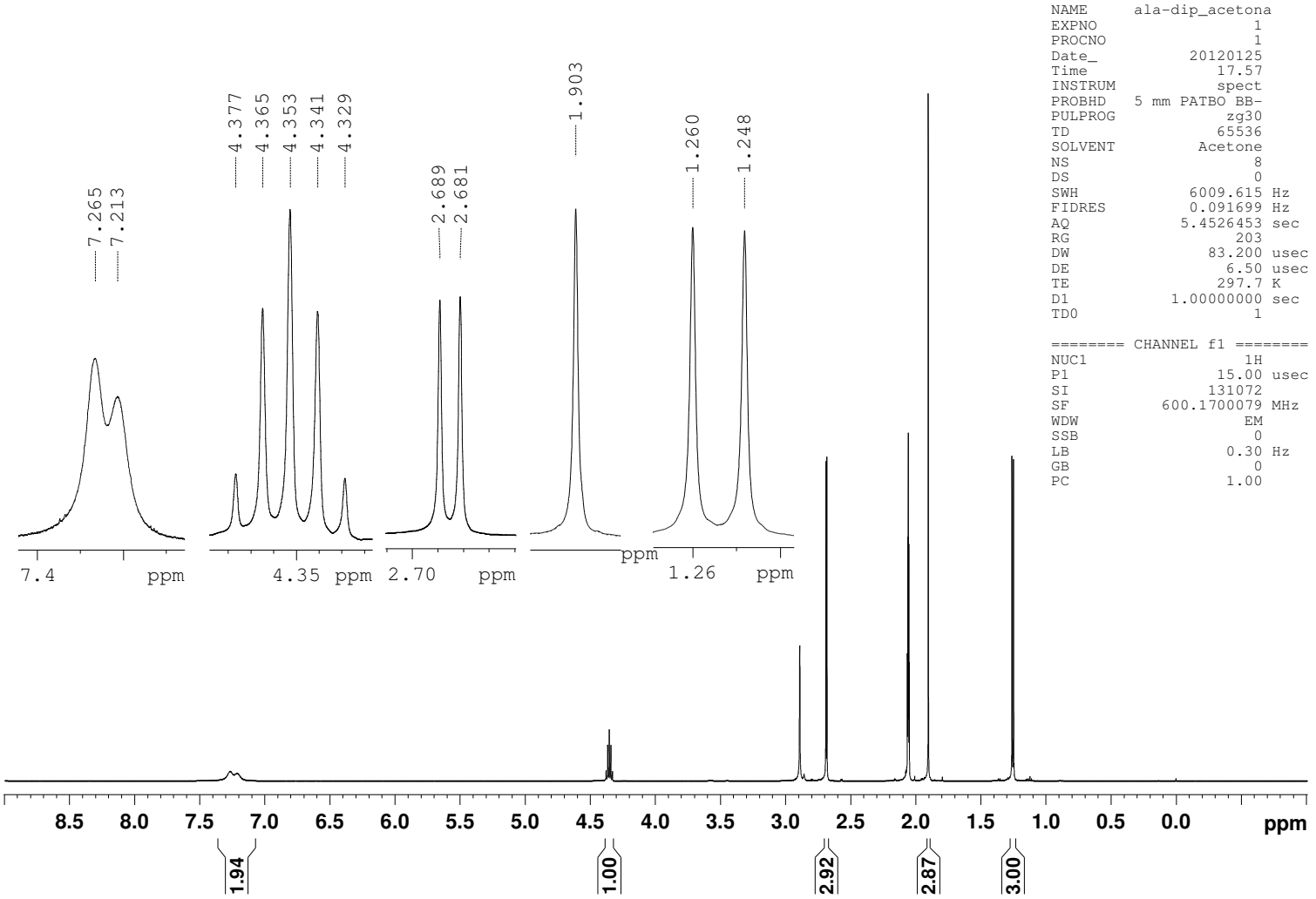
Figure S10: NBO plots of $n \rightarrow \sigma^*_{NH}$ interactions for main conformers of **1.** Figures were obtained at the B3LYP-D3/aug-cc-pVDZ level with an isovalue of 0.04 au. $n \rightarrow \sigma^*_{NH}$ energy values are given in kcal mol^{-1}.



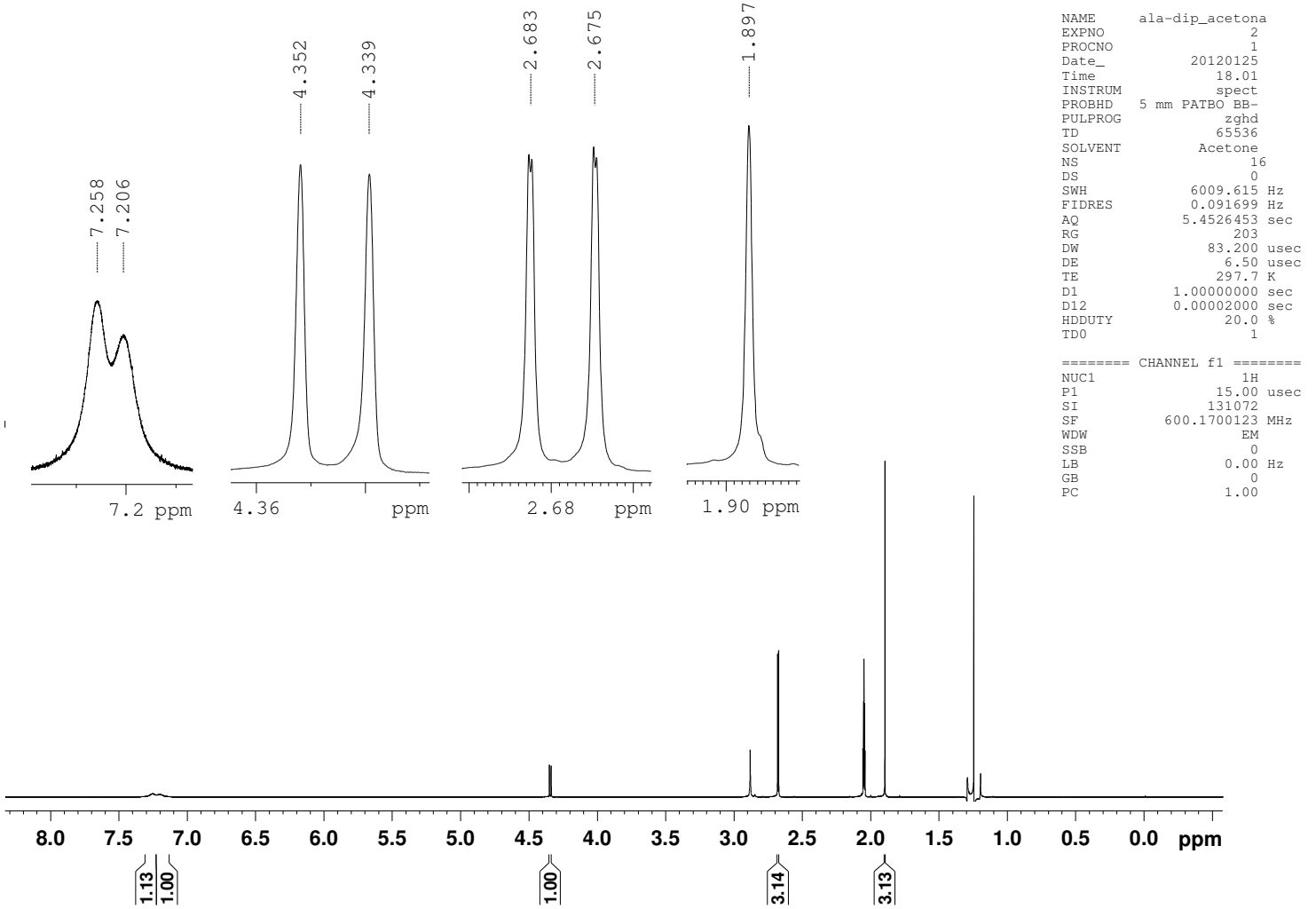
Spectrum S1: Experimental ^{1}H NMR spectrum of Ac-Ala-NHMe in CD_2Cl_2.



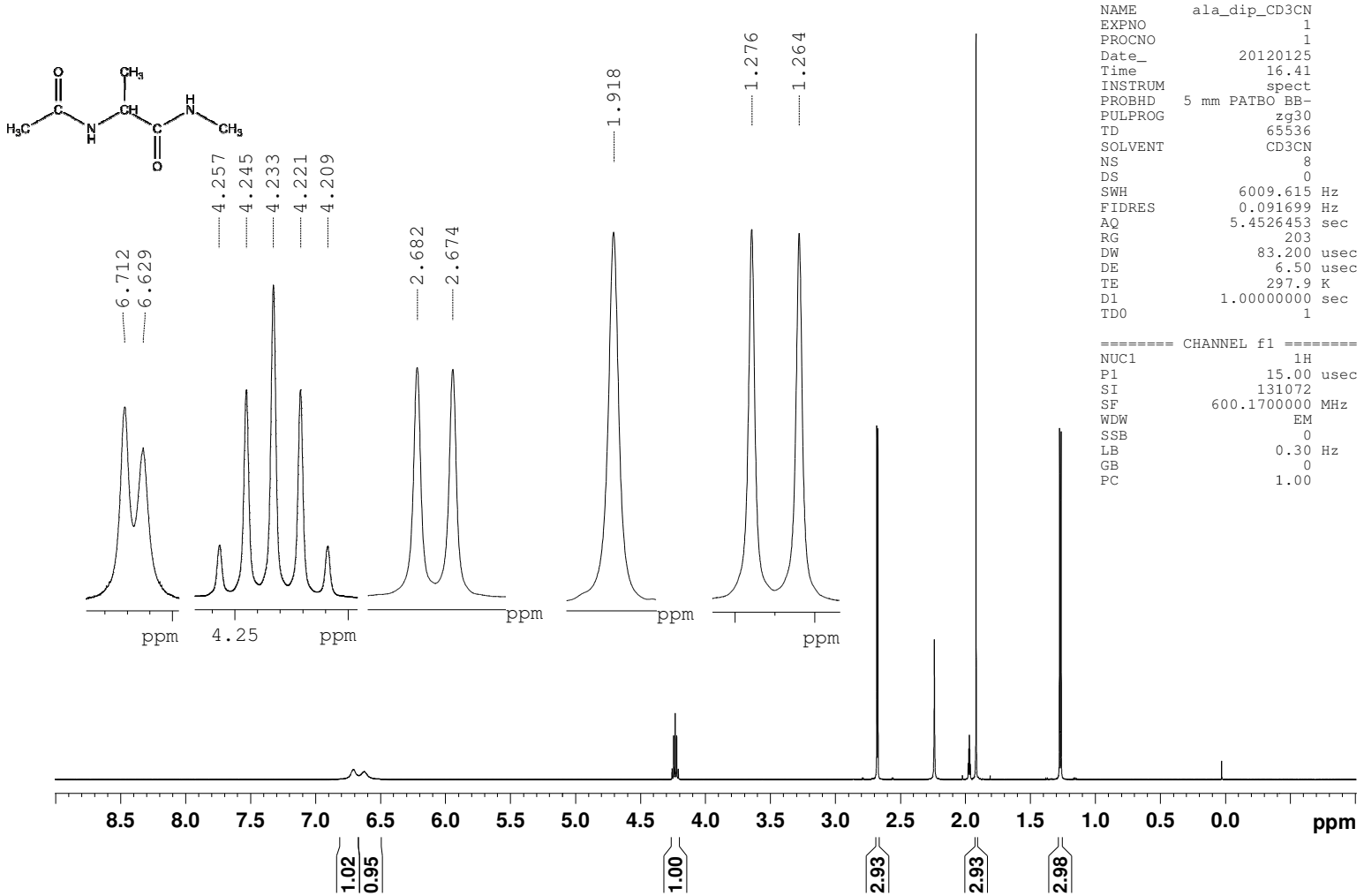
Spectrum S2: Experimental ^{1}H NMR homonuclear decoupling spectrum of Ac-Ala-NHMe in CD_2Cl_2. (irradiated CH_3 signal at ~1.3 ppm)



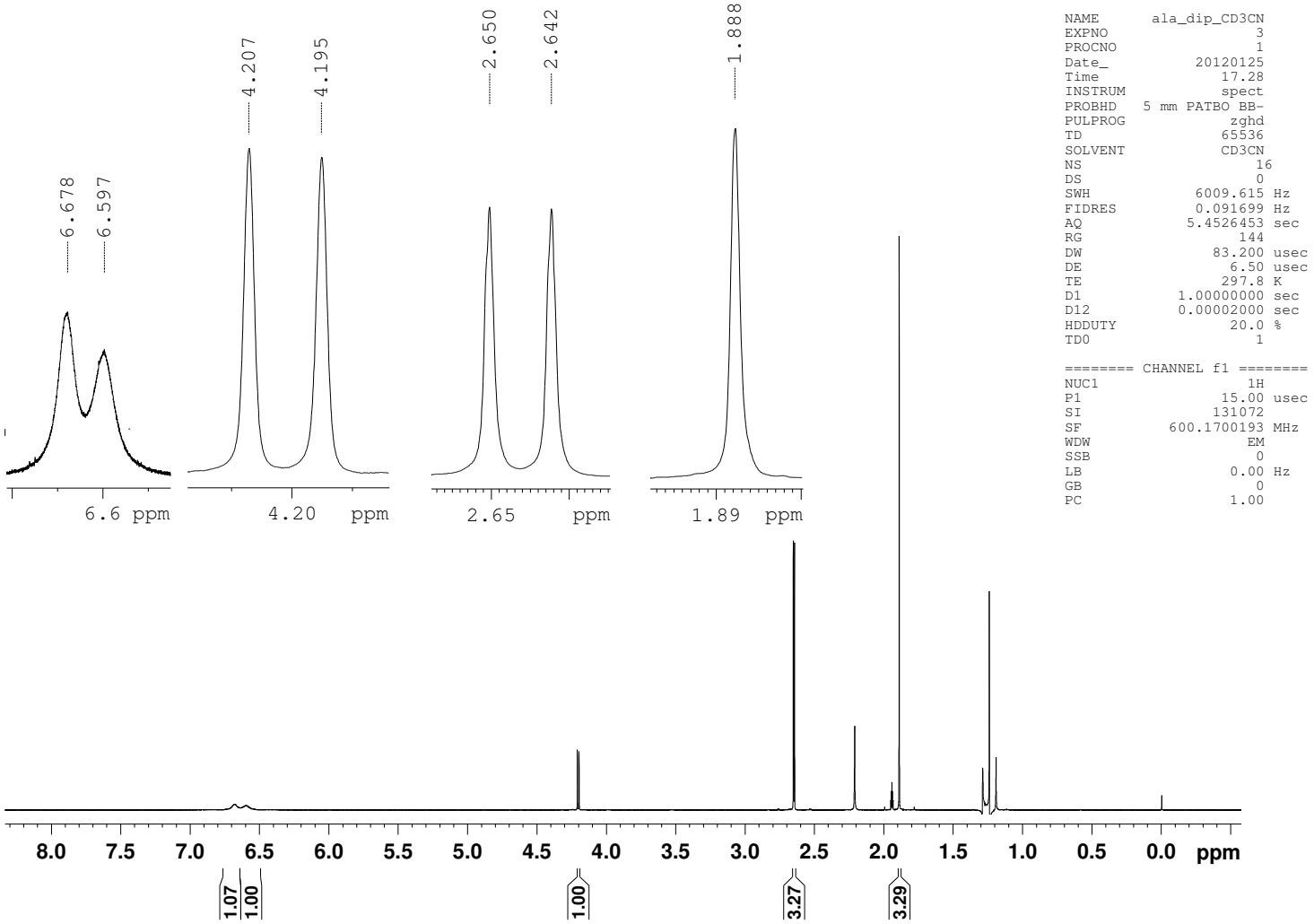
Spectrum S3: Experimental ^{1}H NMR spectrum of Ac-Ala-NHMe in acetone-d_6.



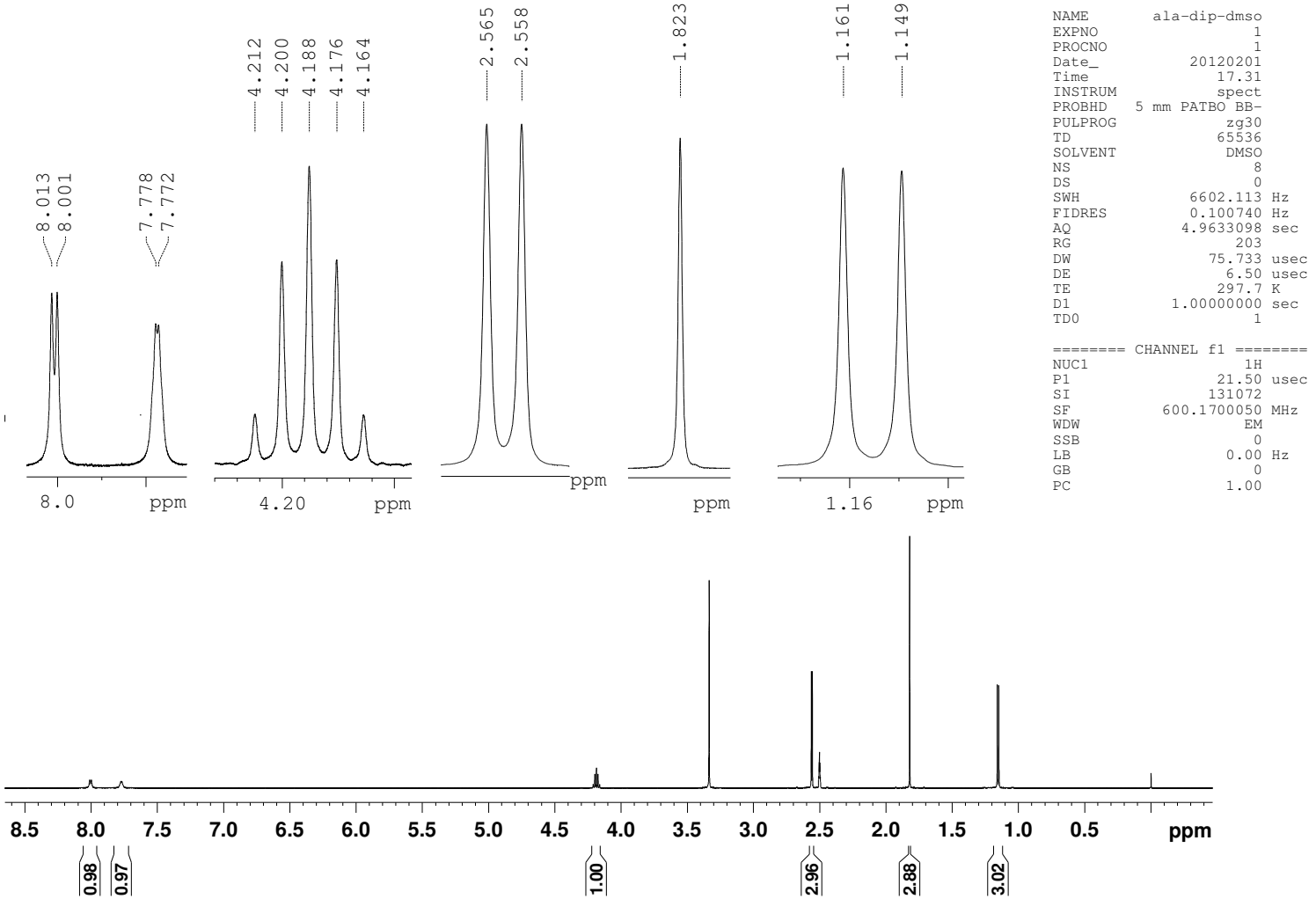
Spectrum S4: Experimental ^{1}H NMR spectrum of Ac-Ala-NHMe in acetone-d_6 (irradiated CH_3 signal at ~1.3 ppm).



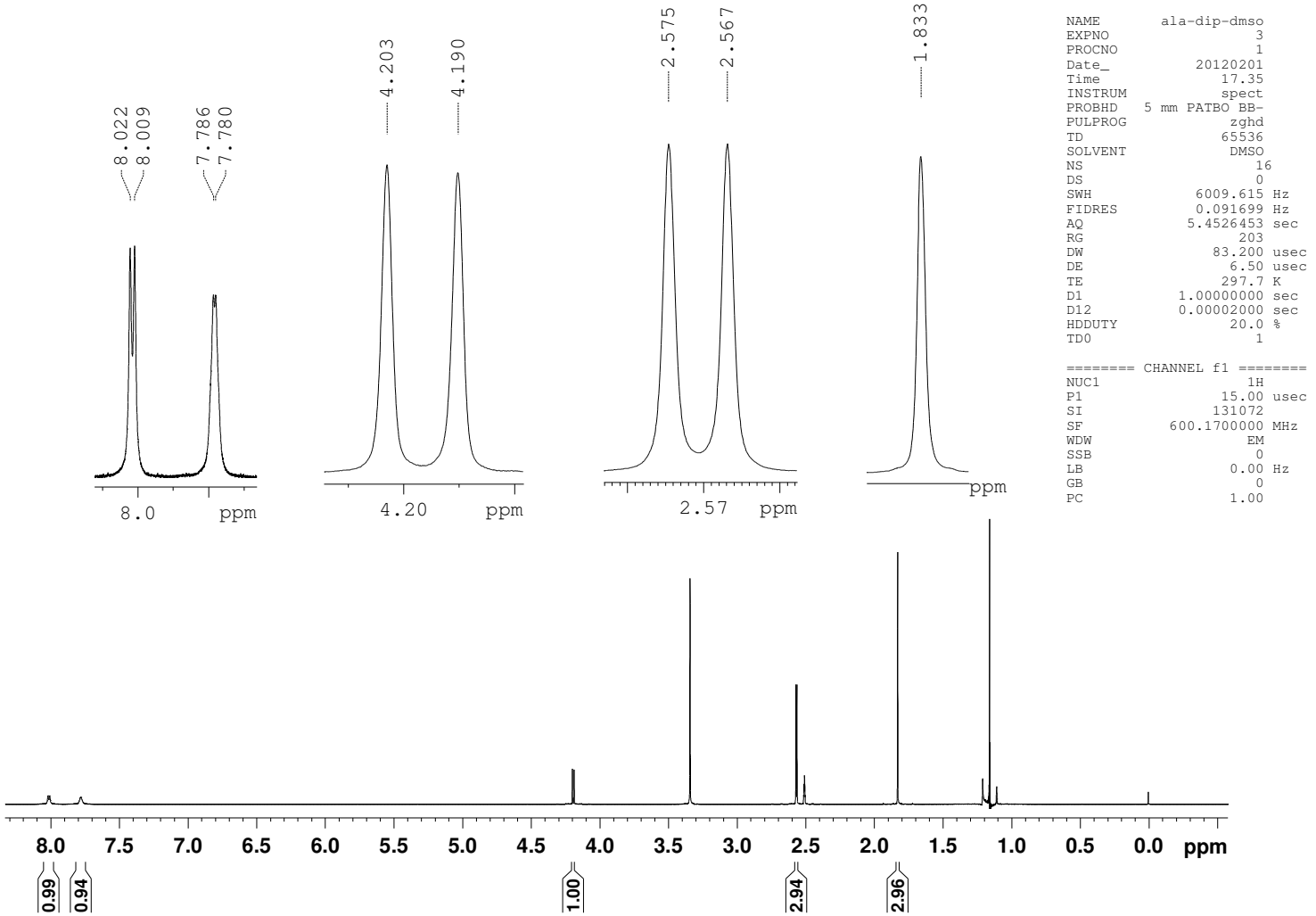
Spectrum S5: Experimental ^{1}H NMR spectrum of Ac-Ala-NHMe in CD_3CN.



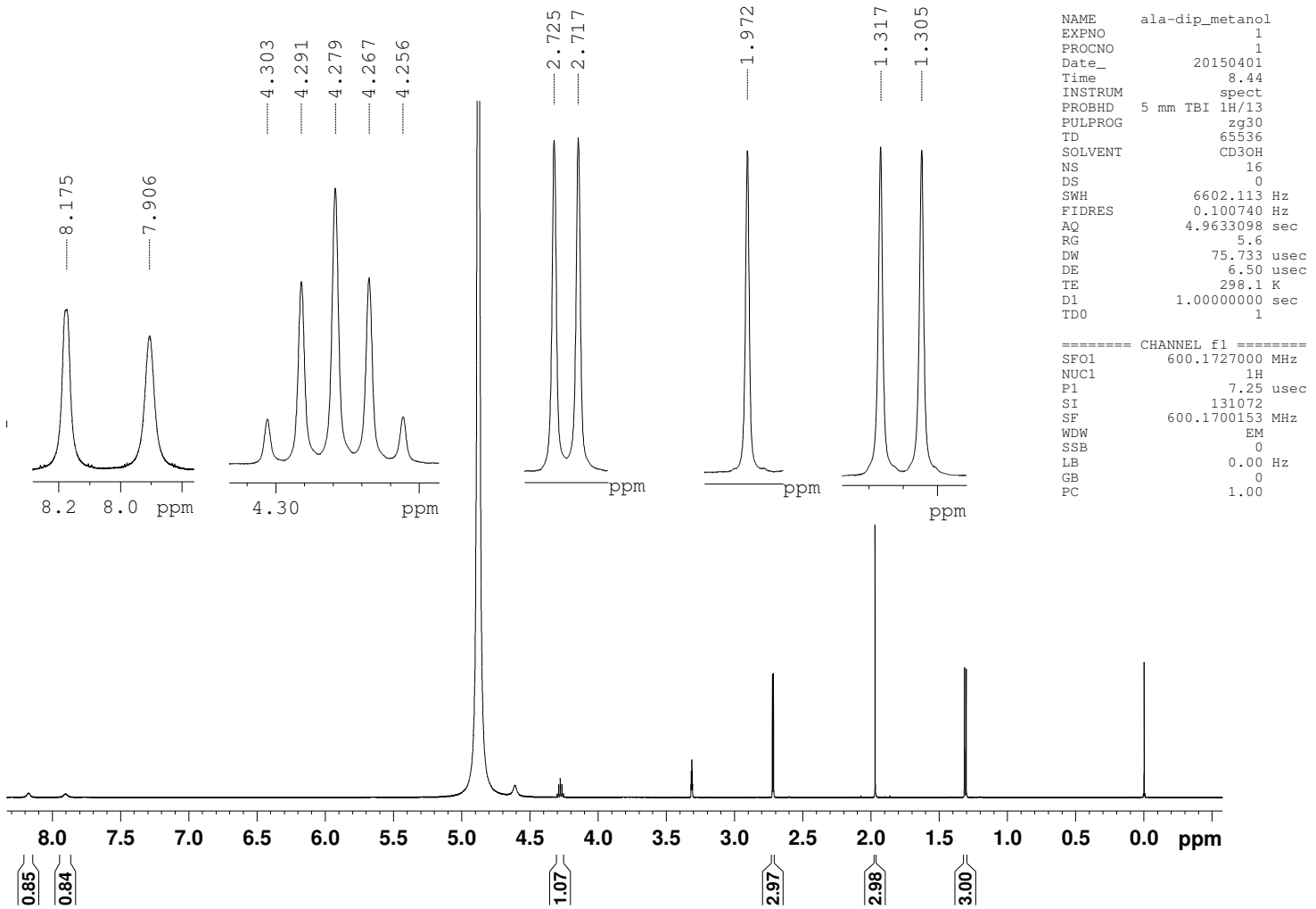
Spectrum S6: Experimental ^{1}H NMR spectrum of Ac-Ala-NHMe in CD_3CN (irradiated CH_3 signal at ~1.3 ppm).



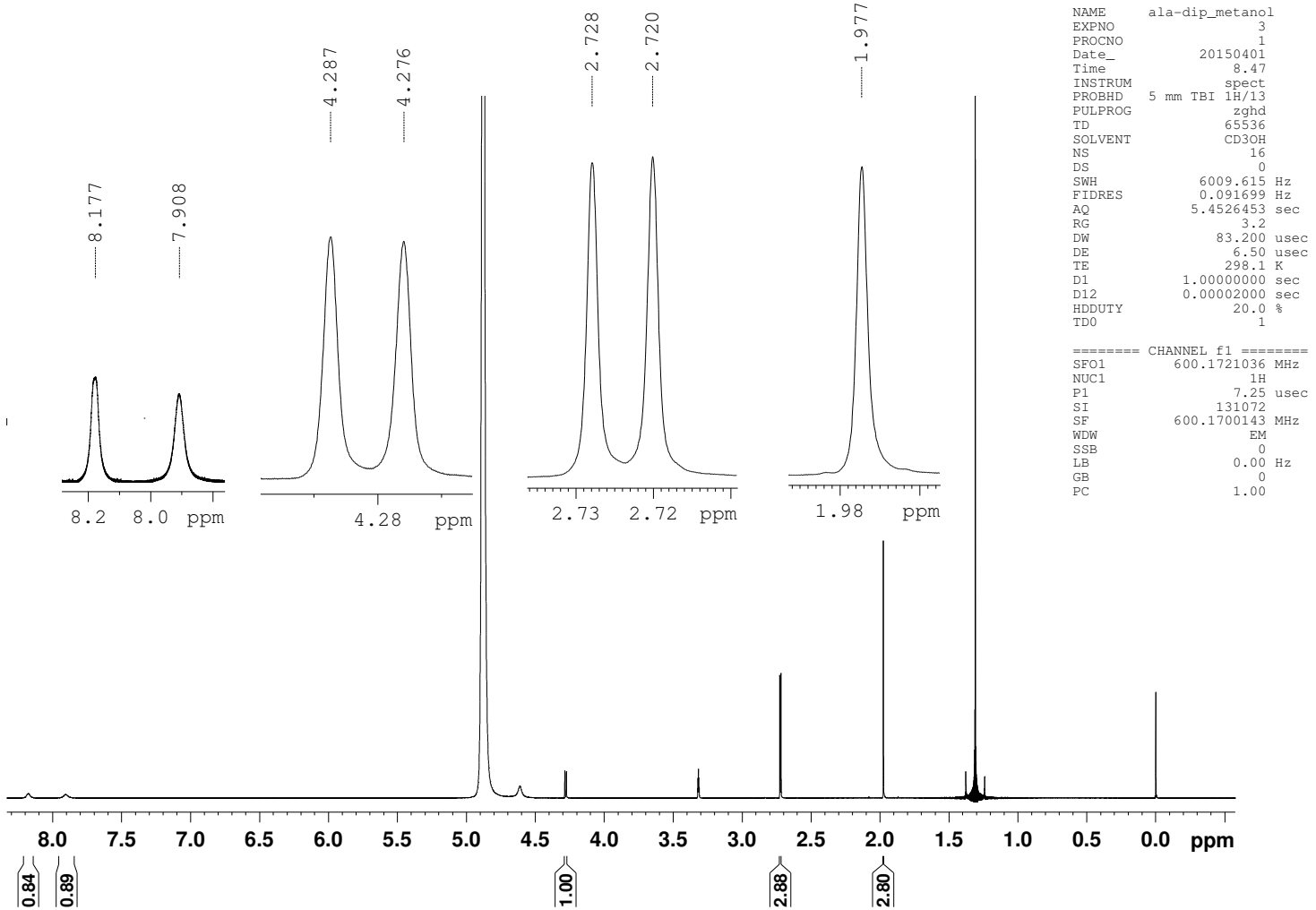
Spectrum S7: Experimental ^{1}H NMR spectrum of Ac-Ala-NHMe in DMSO-d_6.



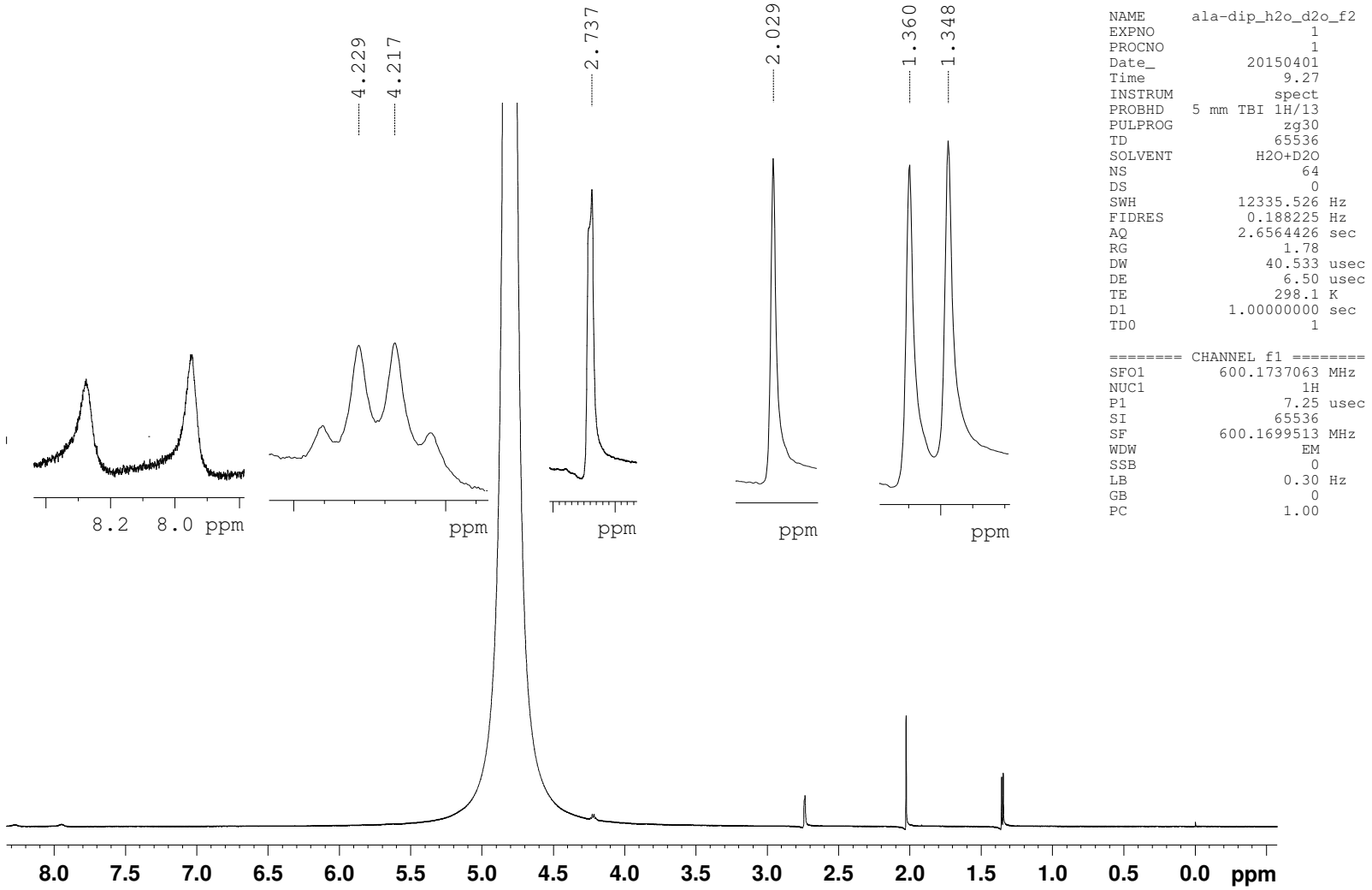
Spectrum S8: Experimental ^{1}H NMR spectrum of Ac-Ala-NHMe in DMSO-d_6 (irradiated CH_3 signal at ~1.3 ppm).



Spectrum S9: Experimental ^{1}H NMR spectrum of Ac-Ala-NHMe in CD_3OH.



Spectrum S10: Experimental ^{1}H NMR spectrum of Ac-Ala-NHMe in CD_3OH (irradiated CH_3 signal at ~1.3 ppm).

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D1                1.00000000 sec
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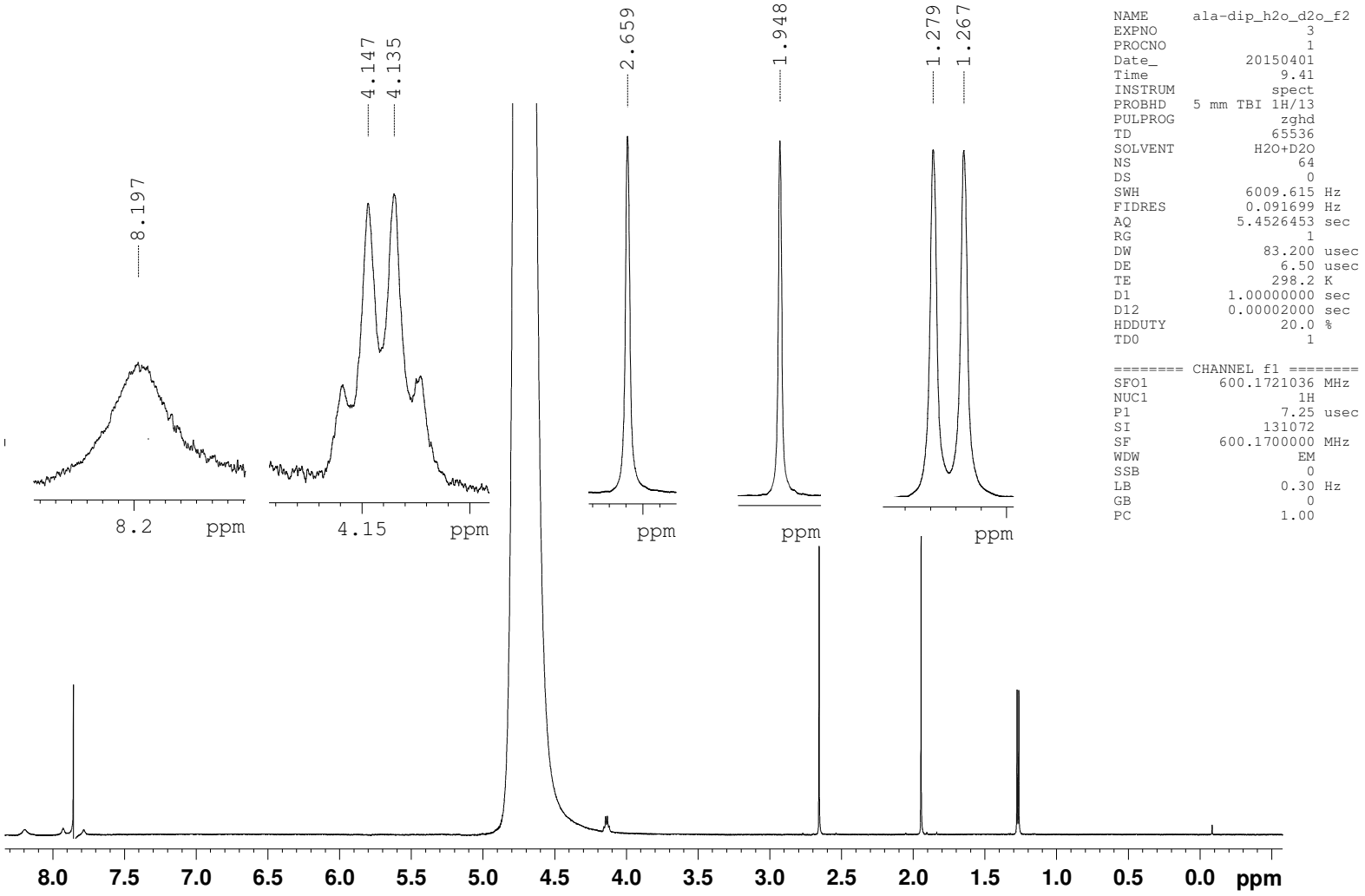
Spectrum S11: Experimental ^{1}H NMR spectrum of Ac-Ala-NHMe in H_2O, using D_2O in a insertion tube.



Spectrum S12: Experimental ^{1}H NMR homonuclear decoupling spectrum of Ac-Ala-NHMe in H_2O, using D_2O in a insertion tube (irradiated CH_3 signal at ~1.3 ppm).