Energetics of an $n \rightarrow \pi^*$ Interaction that Impacts Protein Structure

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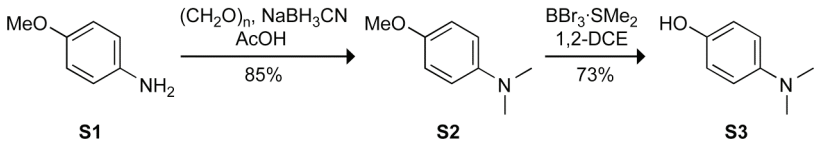
General Experimental. Commercial chemicals were of reagent grade or better and were used without further purification. Anhydrous CH_2Cl_2 was obtained from a CYCLE-TAINER solvent delivery system (Baker), and anhydrous 1,2-dichloroethane was obtained by distillation from CaH_2. In all reactions involving anhydrous solvents, glassware was either oven- or flame-dried. Flash chromatography was performed with columns of silica gel 60, 230–400 mesh (Silicycle), or with a Flashmaster Solo instrument (Argonaut). The term "concentrated under reduced pressure" refers to the removal of solvents and other volatile materials using a rotary evaporator at water aspirator pressure (<20 torr) while maintaining the water-bath temperature below 40 °C.

NMR spectra were acquired with a Bruker AC+ 300 spectrometer (^{1}H, 300 MHz; ^{13}C, 75.4 MHz) at the Magnetic Resonance Facility in the Department of Chemistry or a Bruker DMX-400 Avance spectrometer (^{1}H, 400 MHz; ^{13}C, 100.6 MHz) at the NMR Facility at Madison (NMRFAM). NMR spectra were obtained on samples dissolved in $CDCl_3$ unless indicated otherwise. Compounds containing the N-formyl-L-prolyl moiety exist as mixtures of *Z* and *E* isomers that do not interconvert on the NMR time scale. Accordingly, these compounds exhibit two sets of NMR signals. In ^{13}C data, signals that clearly arise from the minor *E* isomer are listed within parentheses.

Mass spectrometry was performed with either a Micromass LCT (electrospray ionization, ESI) or a Micromass AutoSpec (electron impact ionization, EI) mass spectrometer in the Mass Spectrometry Facility in the Department of Chemistry.

Scheme S1



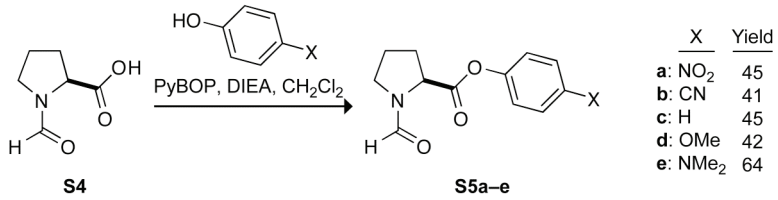
S1 **S2** **S3**

(4-Methoxy-phenyl)-dimethyl-amine (S2). To a purple solution of 4-methoxyaniline (**S1**) (1.02 g, 8.28 mmol) in glacial acetic acid (50 mL) under Ar(g) was added paraformaldehyde (2.44 g, 81.3 mmol) and sodium cyanoborohydride (2.46 g, 39.1 mmol). The addition of sodium cyanoborohydride caused vigorous bubbling. After stirring overnight, the reaction mixture was poured into a water/ice mixture (~100 mL) containing NaOH (40 g). The addition was exothermic, and more ice was added bring the total volume of the quench mixture to ~300 mL. This mixture, which had a pH of 14, was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$(s), filtered, and concentrated under reduced pressure to a purple solid. Flash chromatography (1:1 ether/hexanes) provided **S2** as a colorless solid (1.06 g, 7.01 mmol, 85%). ^{1}H NMR δ (300 MHz): 2.86 (s, 6H), 3.76 (s, 3H), 6.71–6.88 (m, 4H); ^{13}C NMR δ (75.4 MHz): 41.9, 55.7, 114.6, 114.9, 145.6, 152.1; HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_9H_{13}NO$, 151.0997; found, 151.0999.

4-Dimethylamino-phenol (S3). To a solution of **S2** (0.87 g, 5.5 mmol) in dry 1,2-dichloroethane (90 mL), was added boron tribromide·dimethyl sulfide complex (8.5 g, 27 mmol), causing a red suspension to form. The red color faded rather quickly to brown, and the mixture was heated to reflux overnight. After cooling the mixture in an ice bath, 5% w/v $KHSO_4$(aq) (50 mL) was added, causing much brown precipitate to form. This mixture was washed with CH_2Cl_2 (3 × 25 mL), and then saturated $NaHCO_3$(aq) (80 mL) was added raising the pH to 8 and changing the color of the mixture to red. The aqueous mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers, which had a light reddish color, were

dried over $MgSO_4$(s), filtered, and concentrated under reduced pressure to provide **S3** (0.55 g, 4.0 mmol, 73%) as a nearly colorless solid with a slight reddish tint. ^{1}H NMR δ (CD_3OD, 300 MHz): 2.77 (s, 6H), 4.89 (s, 1H), 6.70–6.73 (m, 2H), 6.75–6.81 (m, 2H); ^{13}C NMR δ (CD_3OD, 75.4 MHz): 43.2, 116.6, 118.0, 146.3, 151.6; HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_8H_{11}NO$, 137.0841; found, 137.0837.

Scheme S2



X	Yield
a: NO_2	45
b: CN	41
c: H	45
d: OMe	42
e: NMe_2	64

2-(4-Nitro-benzoyl)-pyrrolidine-1-carbaldehyde (S5a). N-Formyl-L-proline (**S4**) was prepared as described previously.[1] To a solution of **S4** (0.30 g, 2.1 mmol) in dry CH_2Cl_2 (30 mL) under Ar(g), was added 4-nitrophenol (0.31 g, 2.2 mmol), DIEA (0.7 mL, 4 mmol), and PyBOP (1.09 g, 2.1 mmol). After stirring overnight, the reaction mixture was washed with brine (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL), and all of the organic layers were combined and washed with 2 N HCl(aq) (3 × 25 mL), saturated $NaHCO_3$(aq) (3 × 25 mL), brine (25 mL), and water (25 mL). The organic layer was dried over $MgSO_4$(s), filtered, and concentrated under reduced pressure to a yellow oil. Flash chromatography (EtOAc) afforded **S5a** as a colorless oil (0.25 g, 0.95 mmol, 45%). ^{1}H NMR δ (400 MHz): 2.00–2.52 (m, 4H), 3.59–3.80 (m, 2H), 4.63–4.74 (m, 1H), 7.30–7.34 (m, 2H), 8.24–8.32 (m, 2H), 8.36 and 8.40 (s, 1H); ^{13}C NMR δ (100.6 MHz): 24.3 (22.8), 29.4 (29.8), 46.3 (44.1), 56.8 (58.7), 122.3 (122.0), 125.2 (125.3), 145.4, 155.2, 160.9 (161.4), 169.5; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{12}H_{13}N_2O_5$, 265.0824; found, 265.0833.

2-(4-Cyano-benzoyl)-pyrrolidine-1-carbaldehyde (S5b). To a solution of **S4** (0.20 g, 1.4 mmol) in dry CH_2Cl_2 under Ar(g), was added 4-cyanophenol (0.17 g, 1.4 mmol), DIEA (0.5 mL, 3 mmol), and PyBOP (0.73 g, 1.4 mmol). After stirring overnight, the reaction mixture was washed with brine (20 mL), 2 N HCl(aq) (2 × 20 mL), saturated $NaHCO_3$(aq) (2 × 20 mL), brine (20 mL), and water (20 mL). The organic layer was dried over $MgSO_4$(s), filtered, and concentrated under reduced pressure to a colorless oil. Flashmaster purification (5 g silica, 1:1 hexanes/EtOAc followed by 100% EtOAc) afforded **S5b** as a colorless glass (0.14 g, 0.57 mmol, 41%). ^{1}H NMR δ (400 MHz): 1.99–2.50 (m, 4H), 3.58–3.78 (m, 2H), 4.61–4.71 (m, 1H), 7.25–7.30 (m, 2H), 7.67–7.74 (m, 2H), 8.35 and 8.39 (s, 1H); ^{13}C NMR δ (100.6 MHz): 24.3 (22.9), 29.4 (29.8), 46.3 (44.1), 56.8 (58.7), 110.0, 118.1, 122.6 (122.3), 133.7 (133.8), 153.8, 160.9 (161.4), 169.6; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{13}H_{12}N_2O_3Na$, 267.0746; found, 267.0757.

2-Benzoyl-pyrrolidine-1-carbaldehyde (S5c). To a solution of **S4** (0.10g, 0.70 mmol) in dry CH_2Cl_2 under Ar(g), was added phenol (0.067 g, 0.71 mmol), DIEA (0.24 mL 1.4 mmol), and PyBOP (0.37 g, 0.71 mmol). After stirring for 7 h, the reaction mixture was washed with brine (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and all of the organic layers were combined and washed with 2 N HCl(aq) (3 × 15 mL), saturated $NaHCO_3$(aq) (3 × 15 mL), and brine (2 × 15 mL). The organic layer was dried with $MgSO_4$(s), filtered, and

[1] Hinderaker, M. P.; Raines, R. T. *Protein Sci.* **2003**, *12*, 1188–1194.

concentrated under reduced pressure to a yellow oil. Flash chromatography (EtOAc) afforded **S5c** as a colorless oil (0.068g, 0.31 mmol, 45%). ^{1}H NMR δ (400 MHz): 1.95–2.47 (m, 4H), 3.59–3.76 (m, 2H), 4.64–4.68 (m, 1H), 7.08–7.14 (m, 2H), 7.20–7.28 (m, 1H), 7.34–7.42 (m, 2H), 8.34 and 8.38 (s, 1H); ^{13}C NMR δ (100.6 MHz): 24.1 (22.8), 29.4 (29.8), 46.3 (44.0), 56.6 (58.8), 121.3 (121.0), 125.9 (126.3), 129.3 (129.5), 150.5 (150.2), 160.8 (161.5), 170.2; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{12}H_{13}NO_3Na$, 242.0793; found, 242.0791.

2-(4-Methoxy-benzoyl)-pyrrolidine-1-carbaldehyde (S5d). To a solution of **S4** (0.20 g, 1.4 mmol) in dry CH_2Cl_2 under Ar(g), was added 4-methoxyphenol (0.17 g, 1.4 mmol), DIEA (0.5 mL, 3 mmol), and PyBOP (0.73 g, 1.4 mmol). After stirring overnight, the reaction mixture was washed with brine (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and all of the organic layers were combined and washed with 2 N aqueous HCl (2 × 20 mL), saturated $NaHCO_3$(aq) (2 × 20 mL), brine (20 mL), and water (20 mL). The organic layer was dried over $MgSO_4$(s), filtered, and concentrated under reduced pressure to a colorless oil. Flashmater purification (5 g silica, 1:2 hexanes/EtOAc) afforded **S5d** as a colorless oil (0.25 g, 1.0 mmol, 42%). ^{1}H NMR δ (400 MHz): 1.95–2.46 (m, 4H), 3.60–3.77 (m, 2H), 3.79 and 3.80 (s, 3H), 4.61–4.66 (m, 1H), 6.85–6.91 (m, 2H), 6.99–7.06 (m, 2H), 8.35 and 8.38 (s, 1H); ^{13}C NMR δ (100.6 MHz): 24.1 (22.9), 29.5 (29.8), 46.3 (44.0), 55.6, 56.6 (58.8), 114.4 (114.5), 122.1 (121.8), 144.0, 157.3 (157.5), 160.8 (161.5), 170.6; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{13}H_{15}NO_4Na$, 272.0899; found, 272.0891.

2-(4-Dimethylamino-benzoyl)-pyrrolidine-1-carbaldehyde (S5e). To a solution of 4-dimethyamino-phenol (0.21g, 1.5 mmol) in dry CH_2Cl_2 (30 mL) under Ar(g), was added **S4** (0.23 g, 1.6 mmol), DIEA (0.56 mL), and PyBOP (0.83 g, 1.6 mmol). After stirring overnight, the reaction mixture was washed with brine (25 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL), and all of the organic layers were combined and washed with saturated $NaHCO_3$(aq) (3 × 25 mL) and brine (2 × 25 mL). The organic layer was dried over $MgSO_4$(s), filtered, and concentrated under reduced pressure to an orange oil. Flash chromatography (EtOAc) and subsequent Flashmaster purification (5 g silica, 4:1 hexanes/EtOAc followed by 1:4 hexanes/EtOAc) afforded **S5e** as a colorless oil (0.25 g, 0.95 mmol, 64%). ^{1}H NMR δ (400 MHz): 1.94–2.45 (m, 4H), 2.93 and 2.94 (s, 6H), 3.60–3.76 (m, 2H), 4.61–4.66 (m, 1H), 6.68–6.73 (m, 2H), 6.93–7.01 (m, 2H), 8.34 and 8.37 (s, 1H); ^{13}C NMR δ (100.6 MHz): 24.1 (22.9), 29.5 (29.8), 41.0 (40.8), 46.3 (44.0), 56.6 (58.8), 113.1 (112.9), 121.6 (121.2), 141.5 (141.0), 148.7 (148.9), 160.8 (161.5), 170.8; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{14}H_{19}N_2O_3$, 263.1395; found 263.1389.

Determination of trans/cis Ratios. Samples were prepared by dissolving an N-formyl-L-proline phenylester (**S5a**–**e**; 20–25 mg) in $CDCl_3$ (0.7–0.8 mL). ^{1}H NMR spectra were acquired by performing 16 scans on each sample in a 400 MHz field at 25 °C. Three spectra were acquired for each sample, and the average $K_{trans/cis}$ value was obtained by using *NUTS–NMR Utility Transform Software* (Acorn). Small amounts of the hydrolysis products were observed in the spectra of the *p*-nitrophenyl and *p*-cyanophenyl esters, but did not affect the results.

Computational Methods. Density functional theory (DFT) was used to determine the energy difference between the trans and cis conformation of each N-formyl-L-proline phenylester included in this study. In these calculations, the pyrrolidine ring is in the C_γ-exo conformation.

All calculations were performed with the Gaussian 98 package[2] using the three parameter hybrid functional of Becke[3,4] together with the correlation functional of Lee, Yang, and Parr[5] (B3LYP) and the 6-31+G(d) basis set. Following geometry optimization, vibrational frequencies were determined to ensure that each species was located at a minimum on the potential energy surface. All energies were corrected for zero-point vibrational energy. Orbital energies were determined with natural bond order (NBO) analysis,[6] and orbital interaction energies were determined by second-order perturbation theory using NBO. All energies and vibrational frequencies reported herein are unscaled.

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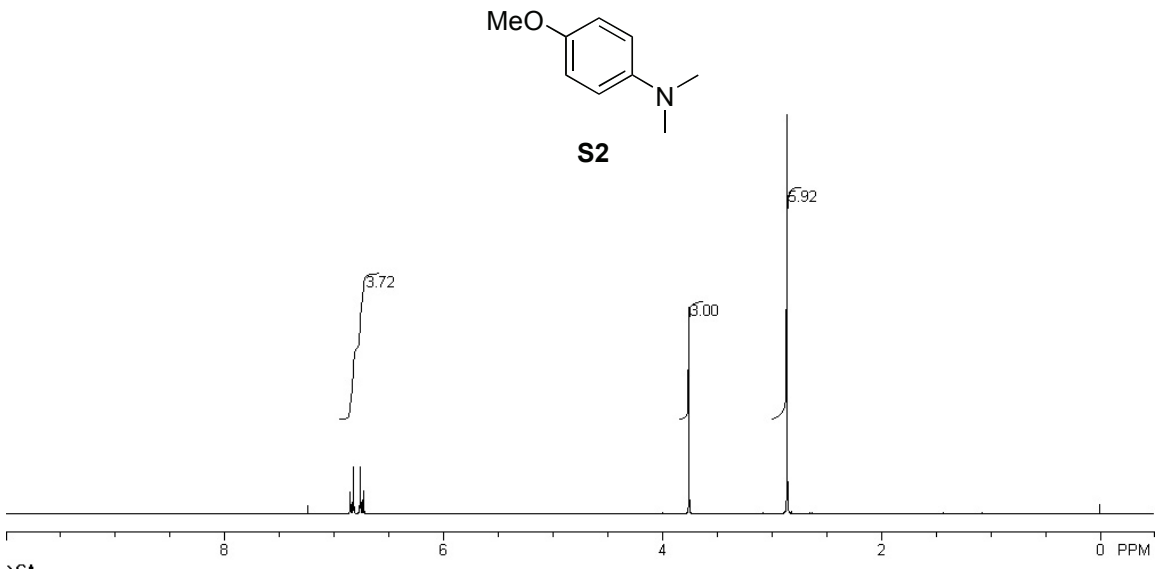
[4] Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652.

[5] Lee, C. T.; Yang, W. T.; Parr, R. G. *Phys. Rev. B–Condens. Matter* **1988**, *37*, 785–789.

[6] Glendening, E. D.; Badenhoop, J. K.; Reed, A. E.; Carpenter, J. E.; Bohmann, J. A.; Morales, C. M.; Weinhold F. *NBO 5.0*; Theoretical Chemistry Institute, University of Wisconsin–Madison: Madison, WI, 2001; http://www.chem.wisc.edu/~nbo5.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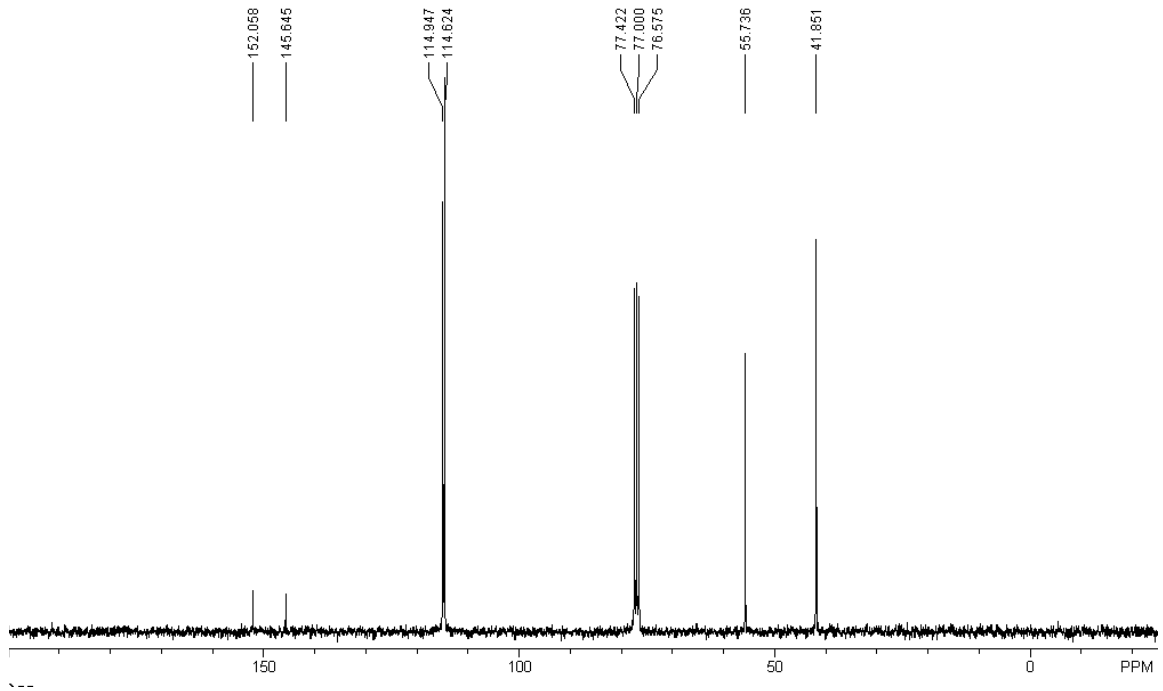
S2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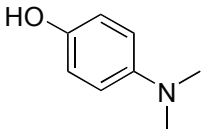
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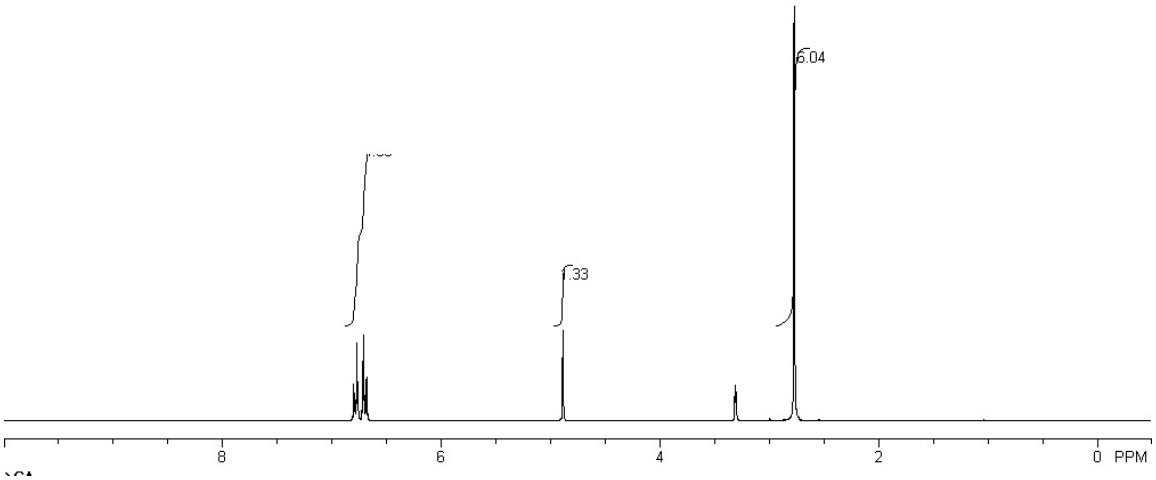
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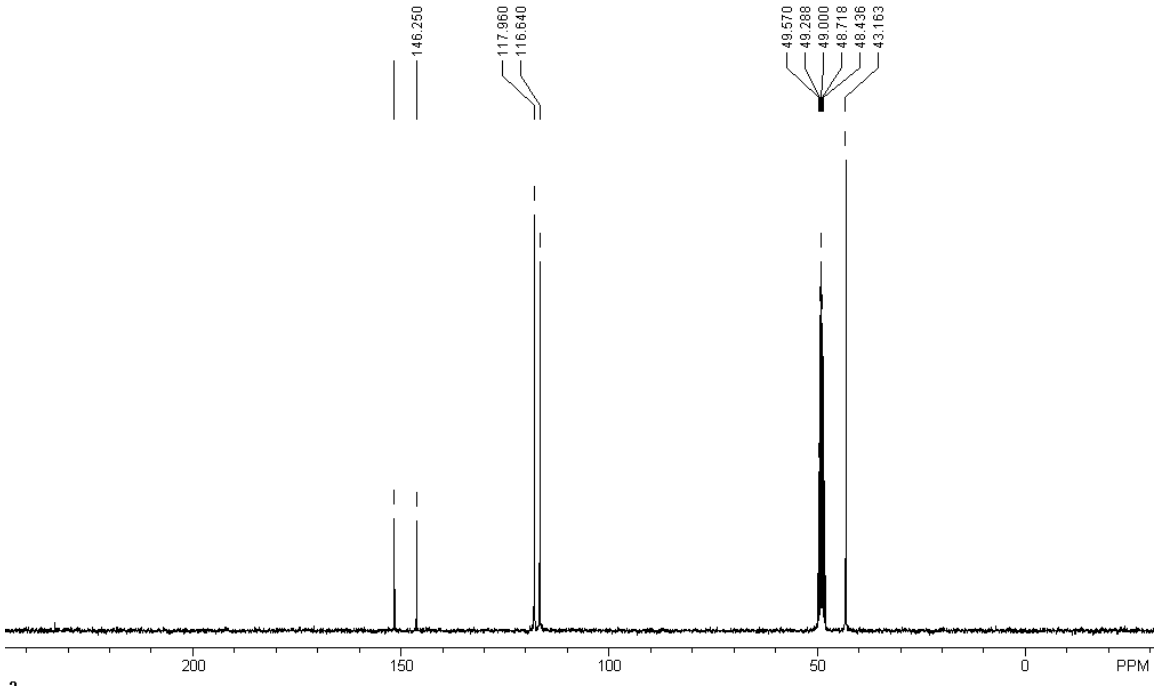
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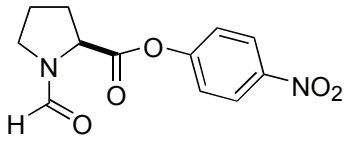
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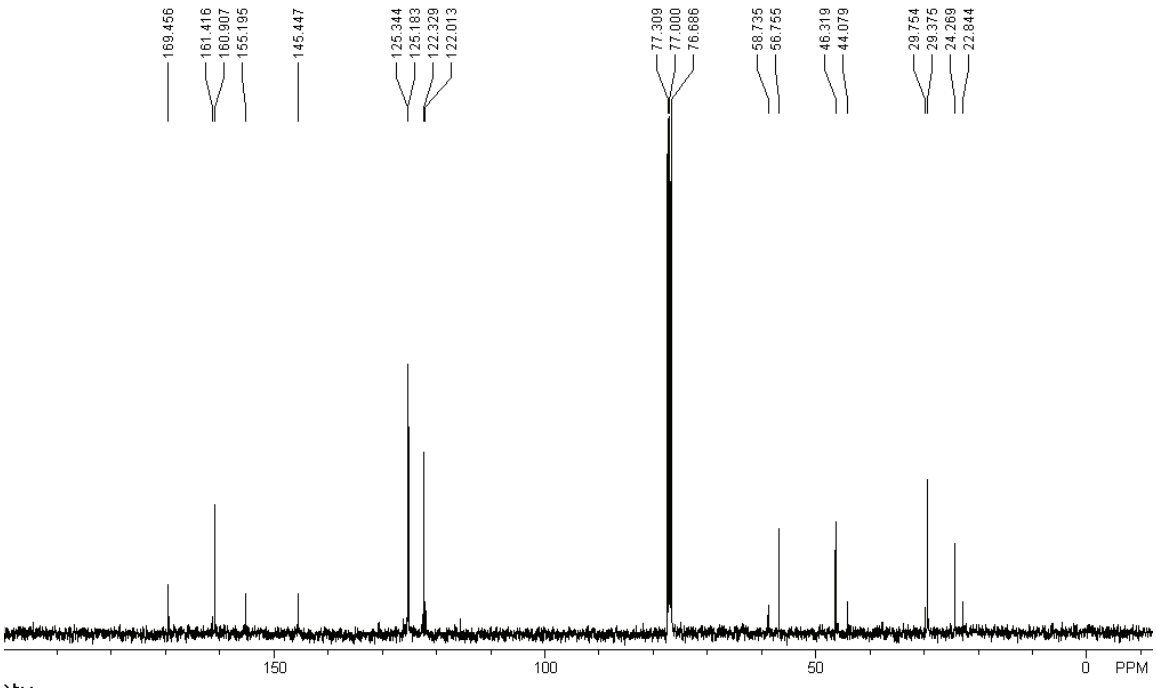
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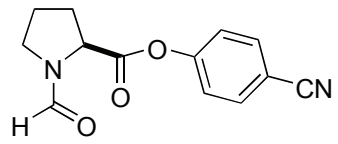
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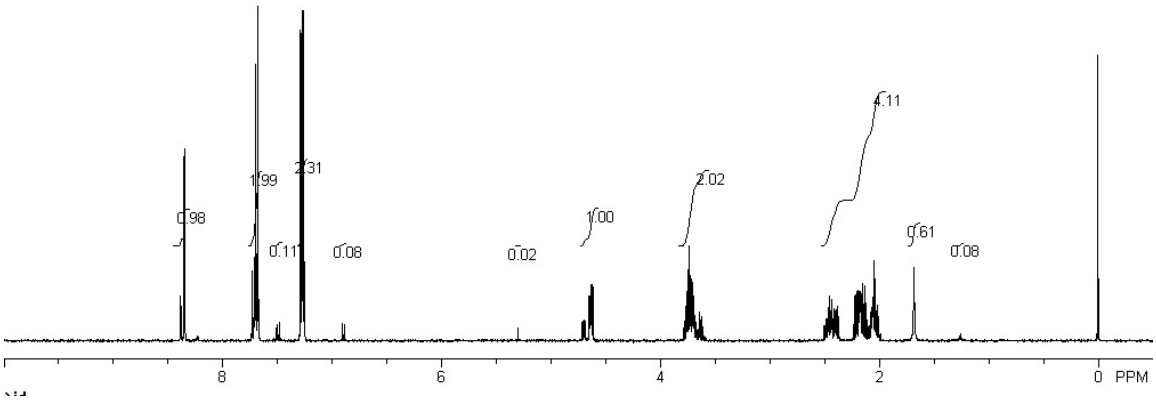
S5b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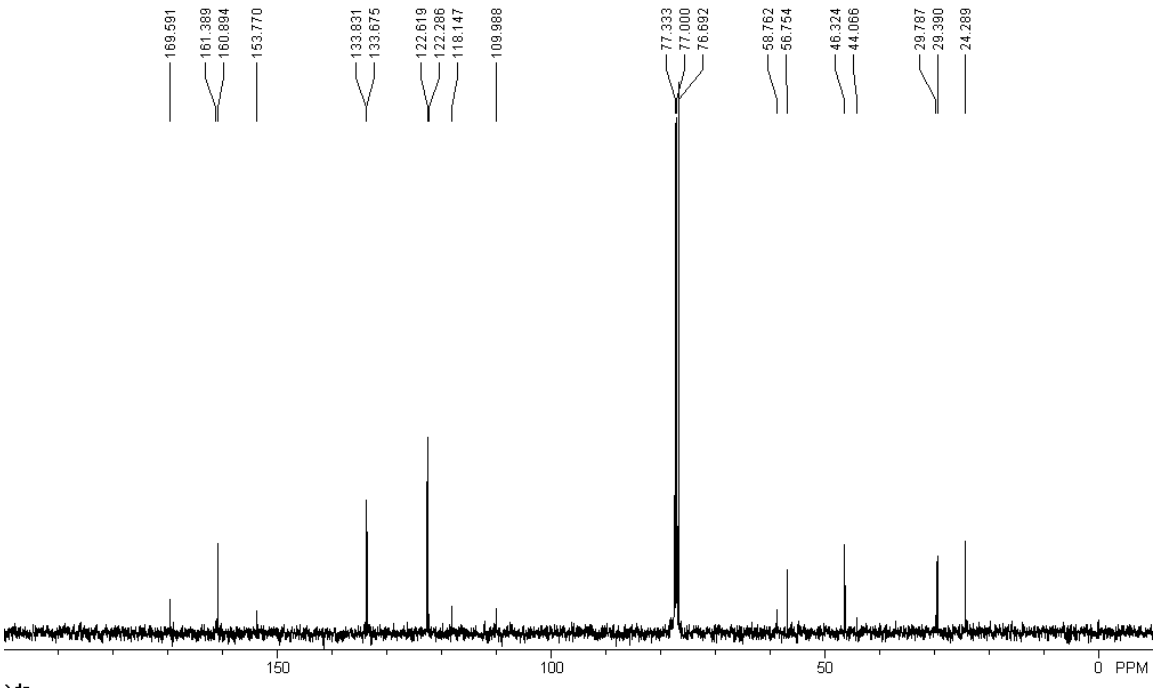
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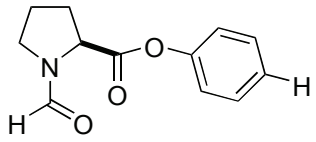
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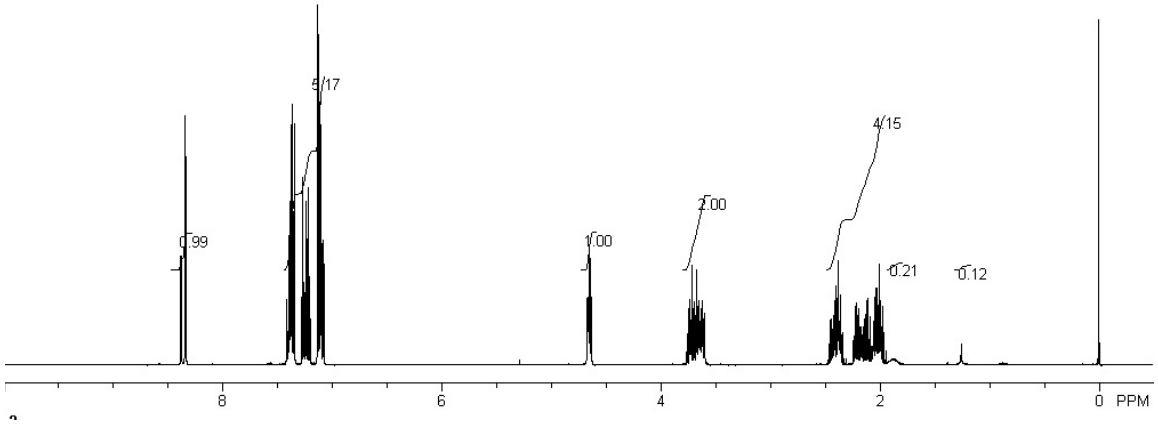
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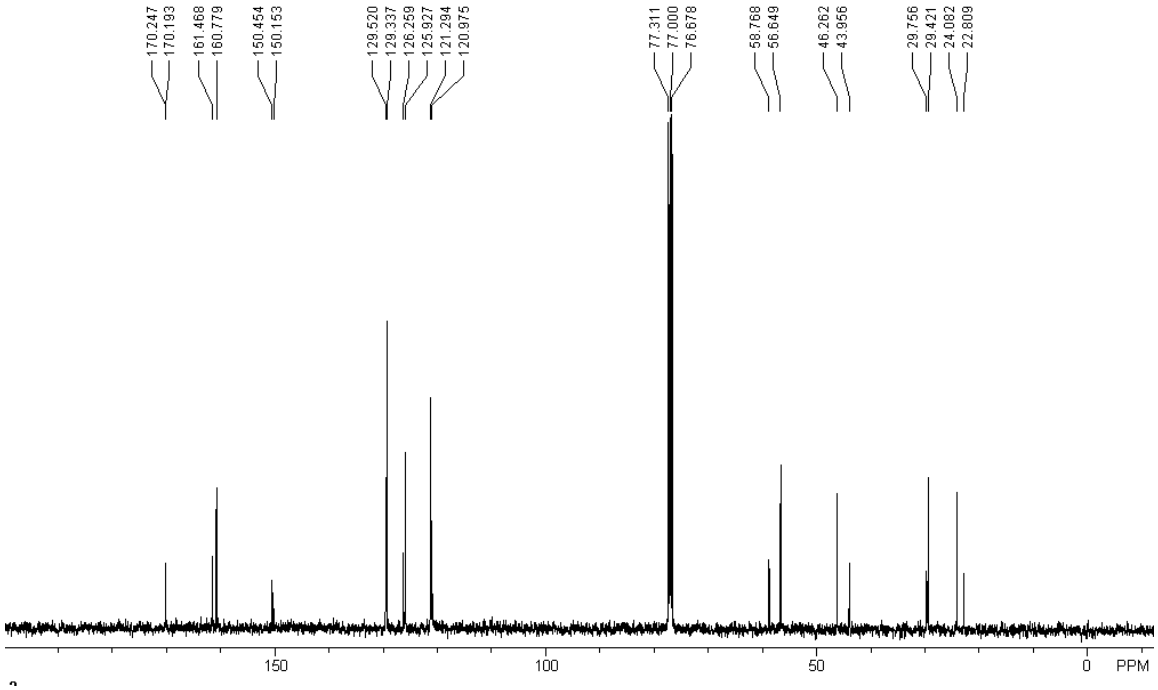
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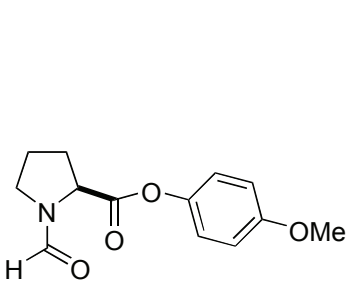
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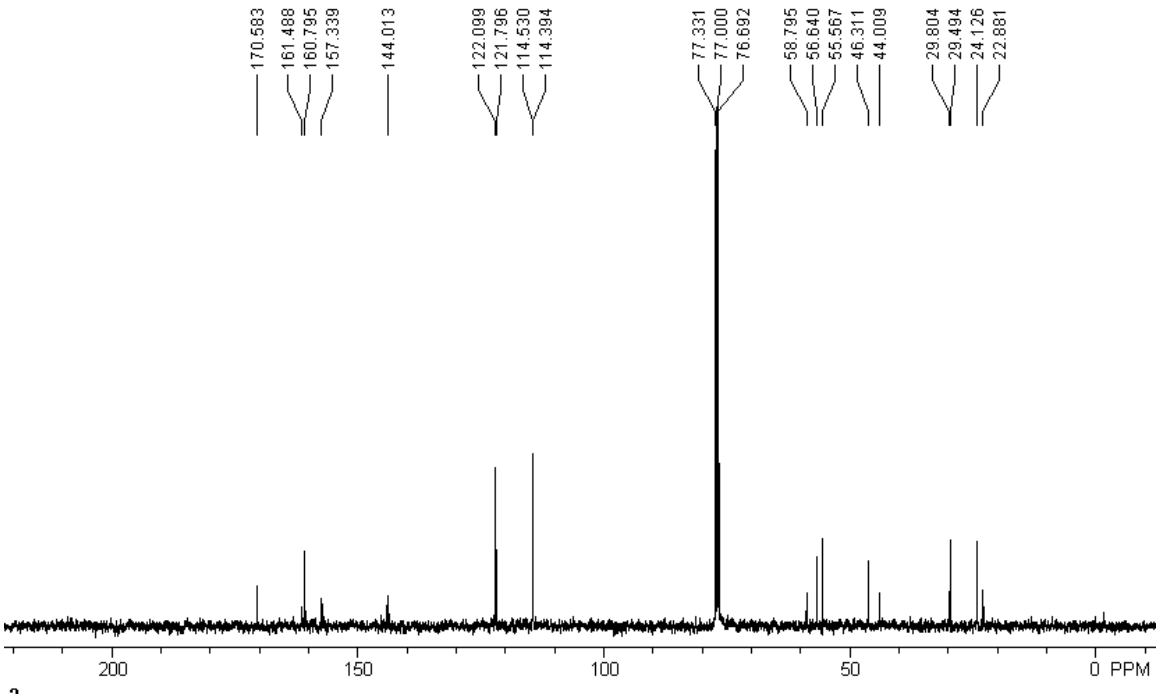
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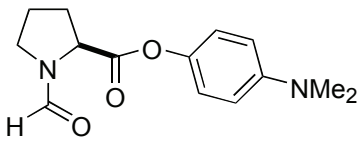
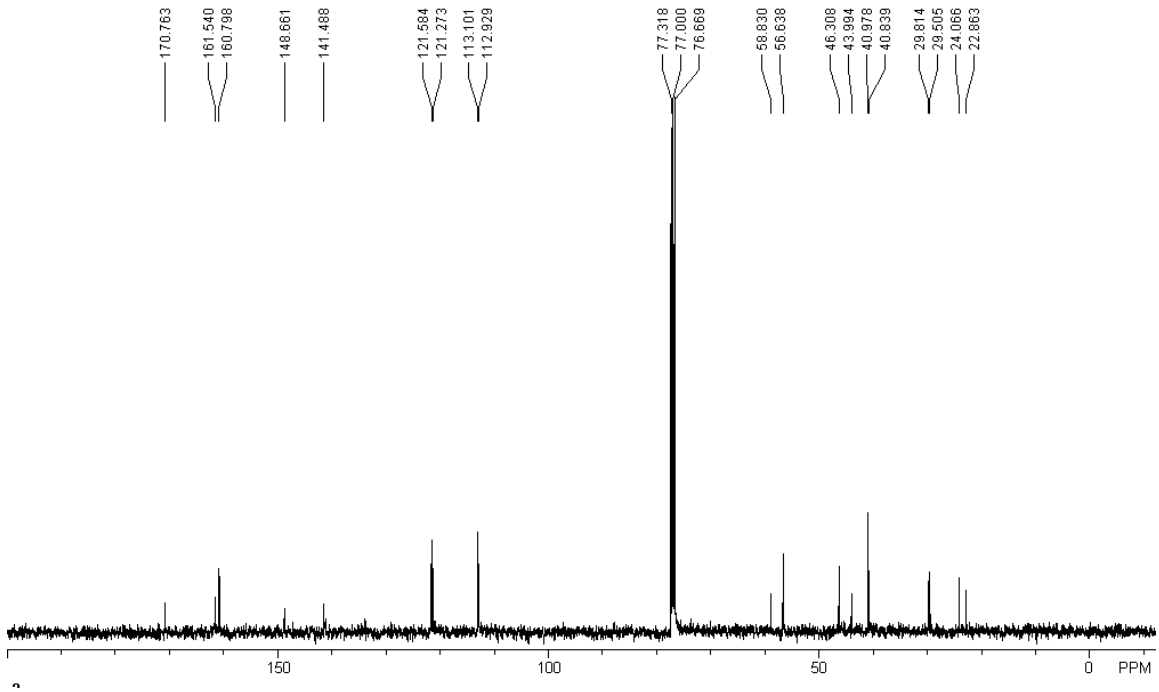
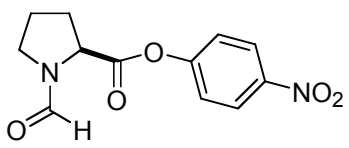

N
O
O
H
O
NMe2

S5e

1.00
1.99
1.92
1.00
2.01
5.79
1.39
3.31
8
6
4
2
0 PPM

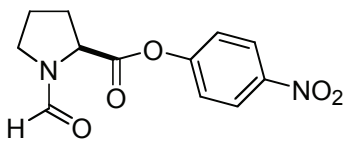

170.763
161.540
160.798
148.661
141.488
121.584
121.273
113.101
112.929
77.318
77.000
76.669
58.830
56.638
46.308
43.994
40.978
40.839
29.814
29.505
24.066
22.863
150
100
50
0 PPM

2-(4-Nitro-benzoyl)-pyrrolidine-1-carbaldehyde (S5a, cis).
Energy (Hartrees) and optimized geometry (B3LYP/6-31+G*):
E = –950.077763123 *ZPVE* = 0.236895



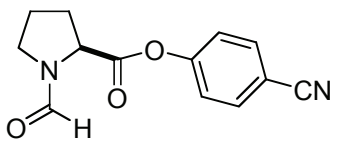
C	–0.23370	0.40500	4.80849
C	–1.75251	–0.13500	3.01737
C	–0.33823	–0.63494	2.59831
N	0.51163	–0.23272	3.71421
H	–0.13755	1.49751	4.74837
H	0.17802	0.08242	5.76763
H	–2.53801	–0.79836	2.64671
H	–1.92784	0.86487	2.60285
H	–0.34206	–1.72528	2.47315
C	0.08120	–0.00937	1.27121
C	1.84415	–0.49570	3.79103
O	2.55981	–0.19645	4.73644
H	2.23351	–1.02725	2.90168
O	0.74744	0.98180	1.12220
O	–0.47120	–0.74166	0.24689
C	–1.67222	–0.05951	4.55199
H	–1.83113	–1.05170	4.99136
H	–2.41748	0.62121	4.97450
C	–0.30053	–0.37423	–1.08517
C	0.94656	–0.03703	–1.61842
C	1.04468	0.24123	–2.97989
C	–0.09956	0.17179	–3.77539
C	–1.34498	–0.17069	–3.24757
C	–1.44198	–0.44649	–1.88685
H	1.82305	0.01663	–0.98536
H	1.99512	0.50776	–3.42649
H	–2.21217	–0.21790	–3.89515
H	–2.39151	–0.72153	–1.43927
N	0.00985	0.46451	–5.21336
O	–1.01646	0.39409	–5.89200
O	1.12045	0.76204	–5.65560

2-(4-Nitro-benzoyl)-pyrrolidine-1-carbaldehyde (S5a, trans).
Energy (Hartrees) and optimized geometry (B3LYP/6-31+G*):
E = –950.081739445 *ZPVE* = 0.237334



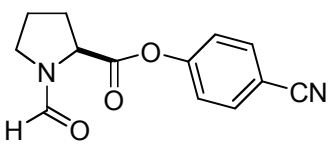
C	–0.02091	0.42915	4.90016
C	–1.85040	–0.08233	3.42314
C	–0.55169	–0.56303	2.72629
N	0.50151	–0.18486	3.67144
H	0.03229	1.52470	4.83695
H	0.55677	0.10161	5.77002
H	–2.69622	–0.73764	3.19834
H	–2.09843	0.92874	3.08080
H	–0.54522	–1.64745	2.57485
C	–0.33763	0.11246	1.37396
C	1.80573	–0.39824	3.37448
O	2.19469	–0.88391	2.31611
H	2.49831	–0.09732	4.18076
O	–0.02654	1.26498	1.21188
O	–0.62040	–0.76499	0.36073
C	–1.47738	–0.05395	4.91723
H	–1.53351	–1.06149	5.34655
H	–2.12947	0.60210	5.50161
C	–0.36292	–0.39369	–0.95550
C	0.92956	–0.04633	–1.35569
C	1.16435	0.24157	–2.69698
C	0.10463	0.16795	–3.60408
C	–1.18495	–0.18766	–3.20742
C	–1.41850	–0.47110	–1.86384
H	1.73204	–0.00865	–0.62719
H	2.15299	0.51523	–3.04537
H	–1.98092	–0.23758	–3.94055
H	–2.40687	–0.75347	–1.51586
N	0.35506	0.47033	–5.02134
O	–0.59527	0.39047	–5.80297
O	1.50037	0.78647	–5.34852

2-(4-Cyano-benzoyl)-pyrrolidine-1-carbaldehyde (S5b, cis).
Energy (Hartrees) and optimized geometry (B3LYP/6-31+G*):
E = –837.813236017 *ZPVE* = 0.232988



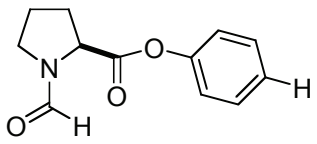
C	–0.26005	0.47421	4.38596
C	–1.74613	–0.17731	2.60487
C	–0.30588	–0.59942	2.18972
N	0.52023	–0.13296	3.29886
H	–0.22881	1.56962	4.31105
H	0.17096	0.18943	5.34861
H	–2.49219	–0.88979	2.24397
H	–1.97956	0.80539	2.17805
H	–0.24615	–1.68978	2.08013
C	0.07501	0.03069	0.85280
C	1.86642	–0.31156	3.37470
O	2.56469	0.04375	4.31396
H	2.28578	–0.82964	2.49114
O	0.68249	1.05743	0.69046
O	–0.43184	–0.74633	–0.15973
C	–1.66905	–0.07751	4.13825
H	–1.76875	–1.07161	4.59058
H	–2.45259	0.56358	4.55353
C	–0.28115	–0.37733	–1.49659
C	0.95573	–0.02142	–2.03767
C	1.04032	0.25736	–3.39955
C	–0.10192	0.17511	–4.21512
C	–1.33688	–0.19151	–3.65261
C	–1.42436	–0.46767	–2.29113
H	1.83498	0.04599	–1.40901
H	1.99346	0.53845	–3.83598
H	–2.21856	–0.25848	–4.28190
H	–2.36749	–0.75713	–1.83867
C	–0.00721	0.46039	–5.61796
N	0.06793	0.69024	–6.75644

2-(4-Cyano-benzoyl)-pyrrolidine-1-carbaldehyde (S5b, trans).
Energy (Hartrees) and optimized geometry (B3LYP/6-31+G*):
E = –837.816961514 *ZPVE* = 0.233392



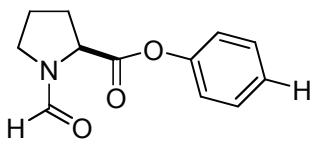
C	–0.04356	0.50246	4.49212
C	–1.83261	–0.12933	3.01268
C	–0.50486	–0.54185	2.32689
N	0.51987	–0.09638	3.27429
H	–0.05274	1.59841	4.41491
H	0.54692	0.21963	5.36906
H	–2.63816	–0.83468	2.79131
H	–2.13668	0.86195	2.65783
H	–0.43595	–1.62545	2.18567
C	–0.32245	0.13302	0.96915
C	1.83619	–0.24042	2.98940
O	2.26117	–0.71643	1.94058
H	2.50400	0.10844	3.79742
O	–0.07576	1.30066	0.80084
O	–0.54699	–0.76657	–0.03668
C	–1.47021	–0.06265	4.50820
H	–1.47118	–1.06676	4.94912
H	–2.16178	0.56188	5.08170
C	–0.30569	–0.38560	–1.35610
C	0.97311	0.00442	–1.75647
C	1.19645	0.30090	–3.09764
C	0.14768	0.19951	–4.03040
C	–1.13034	–0.20391	–3.60704
C	–1.35677	–0.49642	–2.26398
H	1.77367	0.06869	–1.02732
H	2.18336	0.60737	–3.42952
H	–1.93707	–0.28561	–4.32853
H	–2.33565	–0.81183	–1.91698
C	0.38258	0.50259	–5.41291
N	0.57109	0.74784	–6.53514

2-Benzoyl-pyrrolidine-1-carbaldehyde (S5c, cis).
Energy (Hartrees) and optimized geometry (B3LYP/6-31+G*):
E = –745.568556279 *ZPVE* = 0.23458



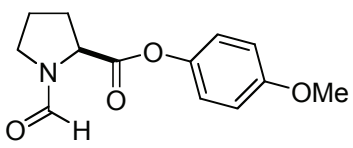
C	–2.66347	1.27912	–2.35364
C	–2.35519	1.13673	0.03076
C	–0.94280	1.22095	–0.61622
N	–1.22655	1.25450	–2.04884
H	–3.01039	0.27461	–2.63201
H	–2.84767	1.94556	–3.19968
H	–2.38529	1.64886	0.99581
H	–2.62235	0.08585	0.19476
H	–0.43182	2.13660	–0.29221
C	–0.08494	0.02801	–0.19777
C	–0.27391	1.32211	–3.01565
O	–0.50264	1.37846	–4.21692
H	0.75563	1.33236	–2.61100
O	0.06387	–0.99477	–0.81810
O	0.46089	0.28877	1.02744
C	–3.28121	1.75216	–1.03226
H	–3.25342	2.84716	–0.97456
H	–4.32154	1.43339	–0.91492
C	1.24234	–0.68376	1.67281
C	2.40558	–1.18292	1.08989
C	3.18212	–2.09117	1.81343
C	2.80107	–2.48533	3.09976
C	1.63408	–1.96761	3.66827
C	0.84647	–1.06115	2.95344
H	2.69323	–0.87613	0.09040
H	4.08864	–2.49039	1.36661
H	3.41168	–3.19129	3.65590
H	1.33306	–2.26684	4.66862
H	–0.06169	–0.64371	3.37791

2-Benzoyl-pyrrolidine-1-carbaldehyde (S5c, trans).
Energy (Hartrees) and optimized geometry (B3LYP/6-31+G*):
E = –745.570826047 *ZPVE* = 0.234819



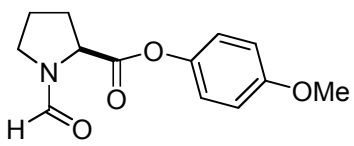
C	0.86002	–0.10689	–3.78325
C	2.24798	–0.27553	–1.82675
C	0.82173	–0.73488	–1.42109
N	0.05494	–0.60475	–2.66143
H	0.74830	0.98136	–3.88726
H	0.54870	–0.57986	–4.71985
H	3.01930	–0.83858	–1.29438
H	2.37474	0.78682	–1.58880
H	0.80707	–1.77603	–1.08312
C	0.23860	0.14064	–0.31216
C	–1.25291	–0.95518	–2.71334
O	–1.89379	–1.36740	–1.75186
H	–1.69770	–0.84158	–3.71900
O	–0.19924	1.25401	–0.46924
O	0.35015	–0.49436	0.88725
C	2.28571	–0.47677	–3.35362
H	2.49027	–1.52607	–3.59848
H	3.04547	0.14177	–3.84134
C	–0.18127	0.11594	2.03423
C	–1.55758	0.29505	2.15746
C	–2.05880	0.83212	3.34509
C	–1.19397	1.17546	4.38976
C	0.18241	0.98070	4.24655
C	0.69755	0.44794	3.06097
H	–2.21480	0.01874	1.33927
H	–3.13008	0.97937	3.45329
H	–1.59210	1.59053	5.31177
H	0.85918	1.24202	5.05581
H	1.76326	0.28526	2.92992

2-(4-Methoxy-benzoyl)-pyrrolidine-1-carbaldehyde (S5d, cis).
Energy (Hartrees) and optimized geometry (B3LYP/6-31+G*):
E = –860.094513593 *ZPVE* = 0.267245



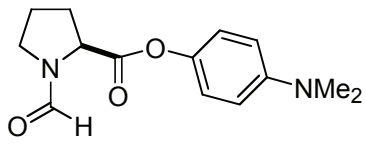
C	–0.51389	0.63698	4.49497
C	–1.95213	0.00841	2.66782
C	–0.52738	–0.52418	2.34190
N	0.27626	–0.05667	3.46914
H	–0.41019	1.72493	4.38351
H	–0.14782	0.36351	5.48750
H	–2.72698	–0.66665	2.29567
H	–2.09685	0.98651	2.19354
H	–0.53591	–1.62034	2.29008
C	–0.04630	0.00969	0.99300
C	1.60790	–0.28844	3.60665
O	2.28414	0.07367	4.56099
H	2.03909	–0.85807	2.76199
O	0.63823	0.98735	0.82007
O	–0.55095	–0.78138	0.00267
C	–1.94243	0.16486	4.19819
H	–2.12722	–0.80229	4.68158
H	–2.70145	0.86993	4.55102
C	–0.32030	–0.45133	–1.34492
C	0.96383	–0.38644	–1.87033
C	1.14080	–0.12869	–3.23426
C	0.02552	0.05626	–4.06200
C	–1.26577	–0.01947	–3.51700
C	–1.43804	–0.27192	–2.16005
H	1.82699	–0.52463	–1.22800
H	2.14836	–0.07435	–3.63007
H	–2.11960	0.12244	–4.17227
H	–2.43285	–0.33609	–1.72940
O	0.08971	0.31078	–5.40281
C	1.36860	0.39733	–6.01888
H	1.96328	1.21465	–5.59043
H	1.92026	–0.54738	–5.92610
H	1.17550	0.60281	–7.07303

2-(4-Methoxy-benzoyl)-pyrrolidine-1-carbaldehyde (S5d, trans).
Energy (Hartrees) and optimized geometry (B3LYP/6-31+G*):
E = –860.096670679 *ZPVE* = 0.267464



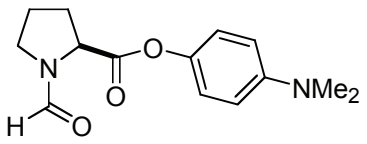
C	–3.35265	1.61178	–2.76355
C	–3.15136	1.74647	–0.37075
C	–1.71315	1.68231	–0.95150
N	–1.93127	1.61072	–2.39767
H	–3.71807	0.58472	–2.90194
H	–3.50997	2.16579	–3.69421
H	–3.19860	2.38019	0.51899
H	–3.48091	0.73948	–0.09034
H	–1.13219	2.57759	–0.70812
C	–0.95039	0.45887	–0.44277
C	–0.88820	1.57752	–3.26154
O	0.29018	1.57522	–2.91990
H	–1.19873	1.55992	–4.32247
O	–1.12769	–0.67201	–0.82602
O	–0.09153	0.82563	0.54614
C	–4.00597	2.26965	–1.54109
H	–3.92746	3.36097	–1.61661
H	–5.06421	2.00990	–1.43921
C	0.74671	–0.15107	1.11130
C	1.77893	–0.70567	0.36596
C	2.65038	–1.61985	0.96751
C	2.48036	–1.96407	2.31535
C	1.43741	–1.38769	3.05620
C	0.56935	–0.48181	2.45369
H	1.90307	–0.42981	–0.67645
H	3.45058	–2.04881	0.37523
H	1.32328	–1.66238	4.10035
H	–0.23975	–0.02841	3.01866
O	3.27611	–2.84432	2.99638
C	4.34312	–3.47347	2.29950
H	5.06991	–2.73688	1.93209
H	4.82660	–4.12804	3.02678
H	3.97151	–4.07339	1.45830

2-(4-Dimethylamino-benzoyl)-pyrrolidine-1-carbaldehyde (S5e, cis).
Energy (Hartrees) and optimized geometry (B3LYP/6-31+G*):
E = –879.53851193 *ZPVE* = 0.307854



C	–0.41496	0.57204	4.87444
C	–1.88130	–0.02336	3.05927
C	–0.46955	–0.57722	2.71508
N	0.35401	–0.12476	3.83489
H	–0.29761	1.65929	4.76932
H	–0.04191	0.28677	5.86109
H	–2.67144	–0.68239	2.69046
H	–2.01343	0.96050	2.59326
H	–0.49584	–1.67300	2.66203
C	0.00359	–0.04830	1.36125
C	1.68545	–0.36643	3.95203
O	2.37745	–0.01523	4.89958
H	2.10093	–0.93316	3.09783
O	0.69623	0.92365	1.18376
O	–0.51744	–0.83301	0.37715
C	–1.85330	0.12235	4.59038
H	–2.04684	–0.84543	5.06922
H	–2.59815	0.83582	4.95647
C	–0.29165	–0.50378	–0.97378
C	0.98798	–0.48705	–1.51944
C	1.15818	–0.23035	–2.87795
C	0.05128	0.00137	–3.73014
C	–1.23463	–0.01337	–3.13945
C	–1.39963	–0.26798	–1.77870
H	1.85461	–0.65892	–0.88973
H	2.16768	–0.21211	–3.27009
H	–2.11905	0.17148	–3.73689
H	–2.39436	–0.28299	–1.34241
N	0.22061	0.21972	–5.09424
C	–0.90661	0.69950	–5.87826
H	–1.28407	1.67568	–5.52988
H	–0.59684	0.80310	–6.92016
H	–1.73578	–0.01734	–5.85258
C	1.55797	0.46713	–5.61112
H	2.02472	1.36656	–5.17571
H	2.21648	–0.38788	–5.41875
H	1.50181	0.59886	–6.69362

2-(4-Dimethylamino-benzoyl)-pyrrolidine-1-carbaldehyde (S5e, trans).
Energy (Hartrees) and optimized geometry (B3LYP/6-31+G*):
E = –879.540149764 *ZPVE* = 0.307988



C	–3.52336	1.79461	–3.01348
C	–3.28960	1.96942	–0.62653
C	–1.85926	1.89797	–1.22829
N	–2.09722	1.81735	–2.67042
H	–3.87858	0.76077	–3.12664
H	–3.70164	2.32905	–3.95180
H	–3.32441	2.62014	0.25138
H	–3.61215	0.96760	–0.32050
H	–1.27286	2.79339	–0.99936
C	–1.09450	0.67638	–0.71718
C	–1.06790	1.81233	–3.55168
O	0.11582	1.84167	–3.23149
H	–1.39674	1.78740	–4.60716
O	–1.25709	–0.45291	–1.11272
O	–0.25732	1.04351	0.28796
C	–4.16493	2.46699	–1.79279
H	–4.09575	3.55749	–1.88733
H	–5.21968	2.20097	–1.67162
C	0.57093	0.06587	0.87103
C	1.64341	–0.46445	0.16174
C	2.49716	–1.37532	0.77914
C	2.30863	–1.76669	2.12676
C	1.20273	–1.21396	2.81389
C	0.34804	–0.3042	2.19075
H	1.80672	–0.17298	–0.87125
H	3.31822	–1.77806	0.19865
H	0.99915	–1.48581	3.84255
H	–0.49349	0.11558	2.73467
N	3.18821	–2.64848	2.75504
C	4.13375	–3.39660	1.94053
H	4.81261	–2.72059	1.4084
H	4.74439	–4.02496	2.59253
H	3.63951	–4.04423	1.19648
C	2.80672	–3.22829	4.03309
H	2.66305	–2.44797	4.78928
H	1.88035	–3.82516	3.97377
H	3.61213	–3.87728	4.38382