Detection of weak hydrogen bonds to fluoro and nitro groups

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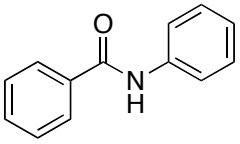
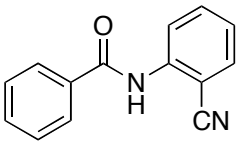
Supporting Information

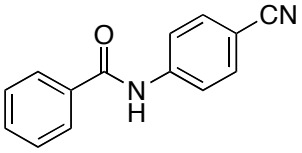
General Procedures. Proton NMR spectra were recorded on a Bruker 400 spectrometer, using $CDCl_3$ unless otherwise indicated. Proton chemical shifts are reported in ppm (δ) relative to internal tetramethylsilane (TMS, δ 0.0 ppm), or with the solvent reference relative to TMS employed as an internal standard ($CDCl_3$, δ 7.27 ppm). Data are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m)], coupling constant [Hz], integration). Carbon NMR spectra were recorded on either a Varian or a Bruker 400 MHz spectrometer with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ 77.23 ppm). Spectra for synthetic characterization were recorded at ambient temperature, while all kinetic analyses were performed at 22˚C. Flash column chromatography was performed using Silica Gel 60Å (32-63 micron). Synthetic yields are not optimized.



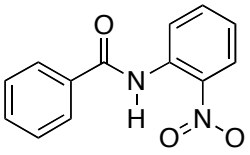
***N*-phenylbenzamide (1)** Benzoyl chloride (300 mg, 2.13 mmol) was dissolved in 20 mL dichloromethane along with aniline (200 mg, 2.13 mmol) and triethylamine (237mg, 2.35 mmol). After stirring for four hours the reaction mixture was washed with 10% HCl, sat $NaHCO_3$, dried over Na_2SO_4 and evaporated to dryness under reduced pressure to yield 405 mg (96%) of a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.88 (m, 3H), 7.65 (d, *J* = 7.6 Hz, 2H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.49 (t, *J* = 7.0 Hz, 2H), 7.358 (t, *J* = 7.5 Hz, 2H), 7.17 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR δ 166.0, 138.1, 135.2, 132.0, 129.3, 129.0, 127.2, 124.8, 120.4; HRMS (MALDI) calcd. for [$C_{13}H_{11}NO$ - M+H] requires *m/z* 198.09134, observed 198.09139.



***N*-(2-cyanophenyl)benzamide (2)** Benzoyl chloride (300 mg, 2.13 mmol) was dissolved in 20 mL dichloromethane, followed by 2-aminobenzonitrile (240 mg, 2.03 mmol) and triethylamine (215 mg, 2.13 mmol). After the reaction was stirred overnight, the solution was washed with 10% HCl, sat. $NaHCO_3$, and dried with Na_2SO_4. After removing the organic solvents under reduced pressure, the remaining orange solid was purified using flash chromatography (silica, dichloromethane) to yield 404 mg white solid (89%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.63 (d, *J* = 8.4 Hz, 1H), 8.40 (br, 1H), 7.95 (d, *J* = 7.1 Hz, 2H), 7.69-7.60 (m, 3H), 7.55 (t, *J* = 7.7 Hz, 2H), 7.23 (t, *J* = 7.7 Hz, 1H); ^{13}C NMR δ 165.7, 140.9, 134.6, 133.9, 132.9, 132.4, 129.4, 127.4, 124.5, 121.3, 116.7, 102.3; HRMS (EI) calcd. for [$C_{14}H_{11}N_2O$ - M+H] requires *m/z* 223.0871, observed 223.0870. Characterization matched the literature values.[1]

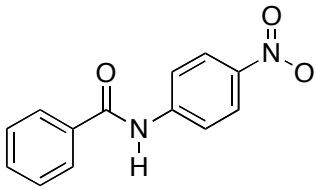


***N*-(4-cyanophenyl)benzamide (3)** Benzoyl chloride (300 mg, 2.13 mmol) was dissolved in 20 mL dichloromethane, followed by 4-aminobenzonitrile (240 mg, 2.03 mmol) and triethylamine (215 mg, 2.13 mmol). After the reaction was stirred overnight, the solution was washed with 10% HCl, sat. $NaHCO_3$, and dried with Na_2SO_4. After removing the organic solvents under reduced pressure, the remaining orange solid was purified using flash chromatography (silica, dichloromethane) to yield 421 mg white solid (93%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97 (br, 1H), 7.88 (d, *J* = 7.0 Hz, 2H), 7.80 (d, *J* = 8.8 Hz, 2H) , 7.68 (d, *J* = 8.8 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.53 (t, *J* = 7.4 Hz, 2H); ^{13}C NMR δ 166.2, 142.3, 134.3, 133.6, 132.8, 129.2, 1274, 120.2, 119.1, 107.6; HRMS (EI) calcd. for [$C_{14}H_{11}N_2O$ - M+H] requires *m/z* 223.0871, observed 223.0869. Characterization matched the literature values.[2]

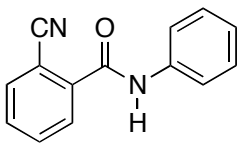


***N*-(2-nitrophenyl)benzamide (4)** Benzoyl chloride (200 mg, 1.42 mmol) was dissolved in 10 mL dichloromethane along with 2-nitroaniline (196 mg, 1.42 mmol) and triethylamine

(143mg, 1.42 mmol). The solution was refluxed for four hours, and then the reaction mixture was washed with 10% HCl, sat $NaHCO_3$. The organic layer was dried over Na_2SO_4 and evaporated to dryness under reduced pressure to yield 295 mg (86%) of a yellow solid, which was further purified using flash chromatography (silica, 10% EtOAc/hexanes) to a yield yellow solid. The solid was recrystallized from dichloromethane/hexanes yielding yellow needle-like crystals. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.35 (br, 1H), 9.00 (dd, *J* = 8.6, 1.2 Hz, 1H), 8.27 (dd, *J* = 8.4, 1.6 Hz, 2H), 7.98 (m, 2H), 7.70 (dt, *J* = 15.7, 1.6 Hz, 1H), 7.60 (m, 1H), 7.53 (m, 1H), 7.21 (dt, *J* = 15.7, 1.3 Hz, 1H); ^{13}C NMR δ 165.9, 136.4, 135.5, 134.2, 132.9, 129.2, 127.5, 126.1, 123.5, 122.3. HRMS (EI) calcd. for [$C_{13}H_9N_2O_3$ - M+H] requires *m/z* 243.0770, observed 243.0772. Characterization matched the literature values.[3]

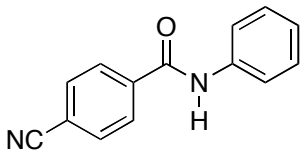


***N*-(4-nitrophenyl)benzamide (5)** Benzoyl chloride (336 mg, 2.39 mmol) was dissolved in 30 mL dichloromethane along with *para*-nitroaniline (330 mg, 2.39 mmol) and triethylamine (241mg, 2.39 mmol). After stirring for four hours the reaction mixture was washed with 10% HCl, sat $NaHCO_3$, dried over Na_2SO_4 and evaporated to dryness under reduced pressure to yield 354 mg (61%) of a yellow solid, which was further purified using flash chromatography (silica, dichloromethane) to yield off-white crystals. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.27 (d, *J* = 8.0 Hz, 2H), 8.10 (br, 1H), 7.89 (d, *J* = 8.2 Hz, 2H), 7.85 (d, *J* = 8.2 Hz, 2H), 7.62 (t, *J* = 7.0 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR δ 166.4, 145.6, 142.5, 134.3, 132.2, 128.6, 128.0, 124.8, 119.9. HRMS (EI) calcd. for [$C_{13}H_{11}N_2O_3$ - M+H] requires *m/z* 234.0770, observed 243.0766. Characterization matched the literature values.[3]

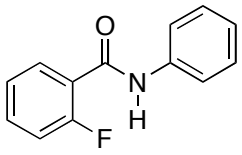


***N*-(2-cyanophenyl)benzamide (6)** Aniline (200 mg, 2.02 mmol) was dissolved in 50 mL dichloromethane along with 2-cyanobenzoic acid (300 mg, 2.03 mmol) and EDCI (400 mg, 2.09 mmol). After stirring overnight the reaction mixture was washed with 10% HCl, sat $NaHCO_3$, dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The

residue was purified using flash chromatography (silica, dichloromethane) to yield 360 mg (80%) of a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.93 (br & d, 2H, Ar & NH), 7.82 (d, *J* = 7.8 Hz, 1H), 7.73 (t, *J* = 7.8 Hz, 1H), 7.65 (m, 3H), 7.40 (t, *J* = 7.8 Hz, 2H), 7.20 (t, *J* = 7.8 Hz, 1H); ^{13}C NMR δ 165.4, 138.9, 137.4, 136.6, 134.5, 133.3, 131.7, 129.4, 129.1, 125.6120.7, 117.7. HRMS (EI) calcd. for [$C_{14}H_{11}N_2O$ - M+H] requires *m/z* 223.0871, observed 223.0873.

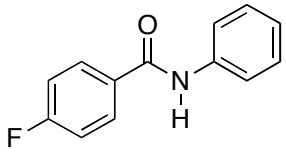


***N*-(4-cyanophenyl)benzamide (6)** Aniline (200 mg, 2.02 mmol) was dissolved in 50 mL dichloromethane along with 4-cyanobenzoic acid (300 mg, 2.03 mmol) and EDCI (400 mg, 2.09 mmol). After stirring overnight the reaction mixture was washed with 10% HCl, sat $NaHCO_3$, dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The resulting solid was purified using flash chromatography (silica, dichloromethane to yield a white solid (402 mg, 90%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.50 (br, 1H), 8.06 (t, *J* = 8.2 Hz 2H), 7.99 (t, *J* = 8.2 Hz, 2H), 7.73 (d, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.09 (t, *J* = 7.59 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 165.2, 140.0, 139.7, 133.5, 129.7, 129.5, 125.1, 121.4, 119.3, 114.8. HRMS (EI) calcd. for [$C_{14}H_{11}N_2O$ - M+H] requires *m/z* 223.0871, observed 223.0868. Characterization matched the literature values.[4]

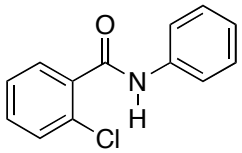


***N*-(2-fluorophenyl)benzamide (8)** Aniline (500 mg, 5.38 mmol) was dissolved in 50 mL dichloromethane along with 2-fluorobenzoic acid (755 mg, 5.38 mmol) and EDCI (1134mg, 5.92 mmol). After stirring overnight the reaction mixture was washed with 10% HCl, sat $NaHCO_3$, dried over Na_2SO_4 and evaporated to dryness under reduced pressure leaving a white solid (923 mg, 80%). This was purified using flash chromatography (silica, dichloromethane), and finally recrystallized using dichloromethane/hexanes. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.44 (br-d, *J* = 14.1, 1H), 8.19 (dt, *J* = 8.0, 1.9 Hz, 1H), 7.67 (d, *J* = 7.7 Hz, 2H), 7.53 (m, 1H), 7.39 (t, *J* = 7.6 Hz,

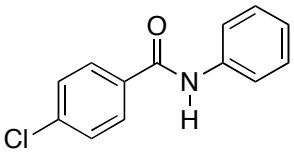
2H), 7.33 (dt, *J* = 7.6, 1.0 Hz, 1H), 7.17 (m, 2H); ^{13}C NMR δ 161.4, 160.3 (d, *J* = 246.7 Hz), 137.7, 133.6 (d, *J* = 9.6 Hz), 132.1 (d, *J* = 2.2 Hz), 129.1, 125.0 (d, *J* = 3.7 Hz), 124.7, 121.5(d, *J* = 9.6 Hz), 120.5, 116.1 (d, *J* = 24.3 Hz). HRMS (EI) calcd. for [$C_{13}H_{11}NOF$ - M+H] requires *m/z* 216.0825, observed 216.0824. Characterization matched the literature values.[5]



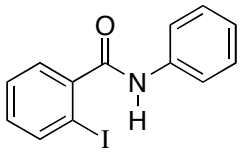
***N*-(4-fluorophenyl)benzamide (9)** Aniline (200 mg, 2.15 mmol) was dissolved in 30 mL dichloromethane along with 4-fluorobenzoic acid (271 mg, 1.93 mmol) and EDCI (452mg, 2.36 mmol). After stirring overnight the reaction mixture was washed with 10% HCl, sat $NaHCO_3$, dried over Na_2SO_4 and evaporated to dryness under reduced pressure leaving a white solid (281 mg, 68%), which was recrystallized using dichloromethane/hexanes. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.89 (m, 2H), 7.75 (br, 1H), 7.62 (d, *J* = 7.6 Hz, 2H), 7.39 (t, *J* = 7.9 Hz, 2H), 7.18 (m, 3H); ^{13}C NMR δ 165.2 (d, *J* = 251.3 Hz), 164.9, 138.0, 133.0 (d, *J* = 8.8 Hz), 129.7 (d, *J* = 8.8 Hz), 129.4, 125.0, 120.5, 116.1 (d, *J* = 21.9 Hz). HRMS (EI) calcd. for [$C_{13}H_{11}NOF$ - M+H] requires *m/z* 216.0825, observed 216.0821. Characterization matched the literature values.[6]



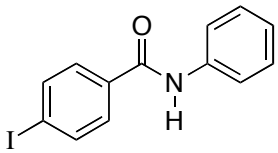
***N*-(2-chlorophenyl)benzamide (10)** Aniline (260 mg, 2.79 mmol) was dissolved in 50 mL dichloromethane along with 2-chlorobenzoic acid (394 mg, 2.52 mmol) and EDCI (562mg, 2.93 mmol). After stirring overnight the reaction mixture was washed with 10% HCl, sat $NaHCO_3$, dried over Na_2SO_4 and evaporated to dryness under reduced pressure leaving a white solid (240 mg, 41%). This was purified using flash chromatography (silica, dichloromethane), and finally recrystallized using dichloromethane/hexanes. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.11 (br, 1H), 7.63 (m, 3H), 7.41-7.28 (m, 5H, 7.15 (t, *J* = 7.4 Hz, 2H), ^{13}C NMR δ 164.7, 137.6, 135.2, 131.6, 130.6, 130.3, 130.1, 129.1, 127.2, 124.8, 120.2. HRMS (EI) calcd. for [$C_{13}H_{11}NOCl$ - M+H] requires *m/z* 232.0529, observed 232.0530. Characterization matched the literature values.[5]



***N*-(4-chlorophenyl)benzamide (11)** Aniline (260 mg, 2.79 mmol) was dissolved in 50 mL dichloromethane along with 4-chlorobenzoic acid (394 mg, 2.52 mmol) and EDCI (562mg, 2.93 mmol). After stirring overnight the reaction mixture was washed with 10% HCl, sat $NaHCO_3$, dried over Na_2SO_4 and evaporated to dryness under reduced pressure leaving a white solid (324 mg, 56%). This was purified using flash chromatography (silica, dichloromethane), and finally recrystallized using dichloromethane/hexanes. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82 (d, *J* = 8.6 Hz, 3H, Ar + NH), 7.64 (d, *J* = 7.8 Hz, 2H), 7.46 (d, *J* = 8.6 Hz, 2H), 7.38 (t, *J* = 7.8 Hz, 2H), 7.17 (t, *J* = 7.4 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 165.5, 140.0, 137.4, 134.6, 131.9, 130.6, 129.6, 129.4, 128.4, 124.8, 121.5. HRMS (EI) calcd. for [$C_{13}H_{11}NOCl$ - M+H] requires *m/z* 232.0529, observed 232.0528. Characterization matched the literature values.[5]



***N*-(2-iodophenyl)benzamide (12)** Aniline (127 mg, 1.36 mmol) was dissolved in 30 mL dichloromethane along with 2-iodobenzoic acid (299 mg, 1.20 mmol) and EDCI (289mg, 1.51 mmol). After stirring overnight the reaction mixture was washed with 10% HCl, sat $NaHCO_3$, dried over Na_2SO_4 and evaporated to dryness under reduced pressure leaving a clear oil (44 mg, 18%), which was subjected to recrystallization using dichloromethane/hexanes to yield a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.91 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.64 (d, *J* = 7.4 Hz, 2H), 7.52 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.49 (br, 1H), 7.43 (dt, *J* = 7.6, 0.9 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 2H), (t, *J* = 7.4 Hz, 1H), 7.15 (dt, *J* = 7.6, 1.5 Hz, 1H); ^{13}C NMR δ 167.5, 142.3, 140.3, 137.7, 131.8, 129.4, 128.8, 128.6, 125.2, 120.3, 92.6. HRMS (EI) calcd. for [$C_{13}H_{11}NOI$ - M+H] requires *m/z* 323.9885, observed 323.9883. Characterization matched the literature values.[7]



***N*-(4-iodophenyl)benzamide (13)** Aniline (200 mg, 2.15 mmol) was dissolved in 30 mL dichloromethane along with 4-iodobenzoic acid (479 mg, 1.93 mmol) and EDCI (452mg, 2.36 mmol). After stirring overnight the reaction mixture was washed with 10%

HCl, sat $NaHCO_3$, dried over Na_2SO_4 and evaporated to dryness under reduced pressure leaving a white solid (487 mg, 78%), which was recrystallized using dichloromethane/hexanes. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.85 (d, *J* = 8.4 Hz, 2H), 7.75 (br, 1H), 7.61 (m, 4H), 7.38 (d, *J* = 7.8 Hz, 2H), 7.17 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 164.9, 139.0, 137.3, 134.3, 129.7, 128.7, 123.9, 120.4, 99.3. HRMS (EI) calcd. for [$C_{13}H_{11}NOI$ - M+H] requires *m/z* 323.9885, observed 323.9881. Characterization matched the literature values.[8]

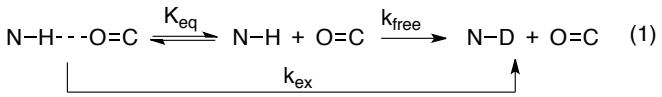
General procedure for H/D exchange:

All H/D exchange kinetics were performed in 1% $CD_3OD/CDCl_3$ and at 22˚C. An initial NMR spectrum was acquired with 990 μL of an analyte solution with a concentration of 5.0505 mM in $CDCl_3$. Immediately prior to use, the deutero-chloroform was passed through a small plug of neutral alumina to remove any acidic impurities and used then immediately. To this was added 10 μL of CD_3OD marking time = 0, and resulting in a final substrate concentration of 5 mM, which was well below the concentrations where any evidence of aggregation has been observed. The added methanol created a 1% methanol:chloroform solution, with the final methanol concentration of 247 mM, which ensured pseudo-first-order kinetics. For a typical experiment, spectra were acquired starting at 3 minutes, then every 1 minute until 10 minutes, every 5 minutes through 100 minutes, at 120, 150 and 200 minutes, and then every 50 minutes thereafter until the disappearance of the proton signal into the baseline. To minimize variability, a constant baseline correction was applied, and integration ranges for exchanging protons were user-defined and self-consistent within each experiment. A distinct non-exchanging signal was used as an internal integration reference.

Pseudo-first-order kinetic analyses were determined from the fit of a non-linear least squares fit to the graph of $A_t = A_o*\exp(-kt)$. Analyses are the average of at least two runs acquired on non-successive days, with different solvents to ensure reproducibility. Rather than estimate the values at extended time, curve fits were performed using data that was <90% exchanged. The y-intercept is taken as the calculated value at time zero, and this value is used to normalize the final data to a range from 100-0% hydrogen remaining. Errors for individual rate constant were determined through a least-squares regression analysis for each kinetic analysis. Errors for average rate constants were reported as the larger value of the following two conditions: the standard deviation of the error values for the multiple trials, or the propagation of error from individual rate constant determinations [$e_{ave} = (SQRT(e_x^2 + e_y^2))/2$]. There tended to be greater variability between kinetic experiments, but occasionally the propagated errors were larger. Average half-lives were reported from conversion of average rate constants [$t_{½} = \ln(2) / k$]. Errors in

the average half-lives were determined from the larger of two values: the average rate constant errors or the propagation of errors from raw data [$e_{half\text{-}life} = t_{½} * e_k / k$]. All errors are rounded up. Rate values for 1% $CD_3OD/CDCl_3$ were considered acceptable if the propagation of errors reflected less than 20% of the reported values. Rates were found to be dependent on solvent and substrate purity. Fresh ampules of methanol-d_4 were opened weekly, and chloroform-d was purified by passing through neutral alumina. Artificial increases in the H/D exchange rate were observed when impurities were present.

Bonds strengths were calculated using the method of Englander.[9] The overall rate of exchange for the presumed hydrogen bonding derivative (k_{ex}) is dependent on both the inherent rate of exchange of the amide functional group itself and the perturbations resulting from hydrogen bonding, as shown in Equation 1 below. The exchange rates of the para-derivatives are used as the best possible control for the inherent rate of exchange (k_{free}) in the absence of hydrogen bonding. The equilibrium constant can be calculated in the relationship between these values as described in Equation 2.

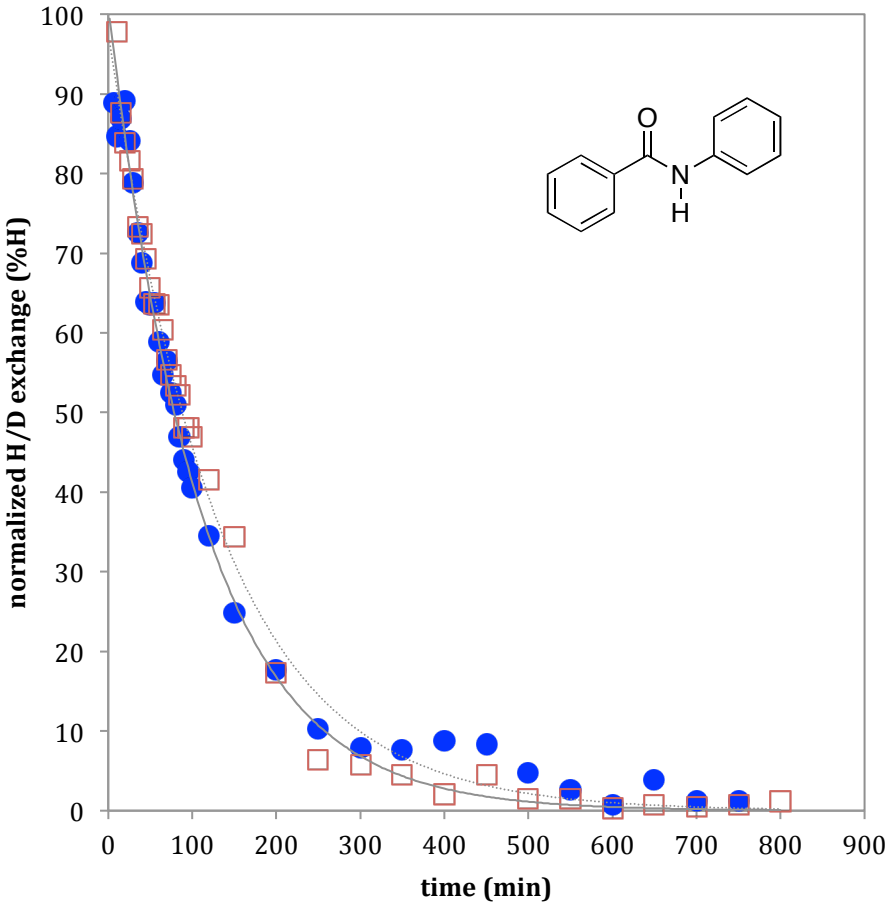


(1)

$$K_{eq} = \frac{k_{op}}{k_{cl}} = \frac{k_{ex}}{k_{free}} \qquad (2)$$

Chemical shift data for pure $CDCl_3$ was obtained from the time = 0 minutes acquisition and reflects a concentration of 5.05 mM. The change in chemical shift data was typically obtained from time = 3 minutes and reflects the final concentration of 5.00 mM.

Figure S15. H/D exchange for *N*-phenylbenzamide (**1**).

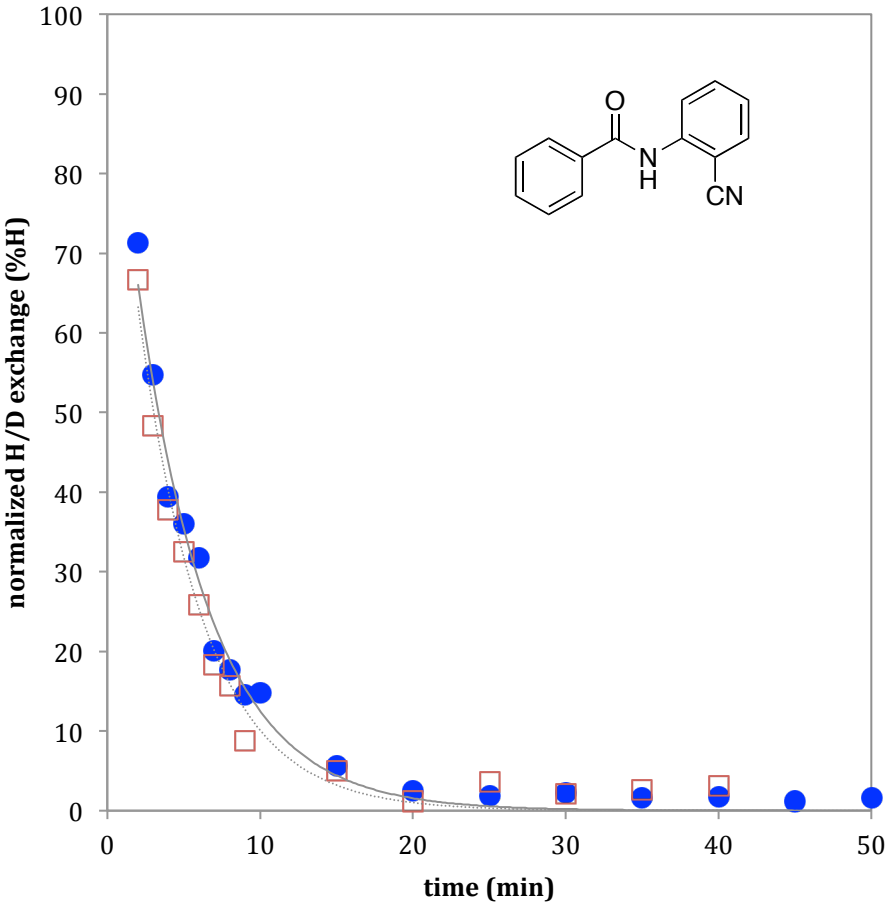


$k_1 = 0.0088 \pm 0.0002$
$k_2 = 0.0080 \pm 0.0003$

$k = 0.0084 \pm 0.006$

$t_{½} = 83 \pm 6$

Figure S15. H/D exchange for *N*-(2-cyanophenyl)benzamide (**2**).

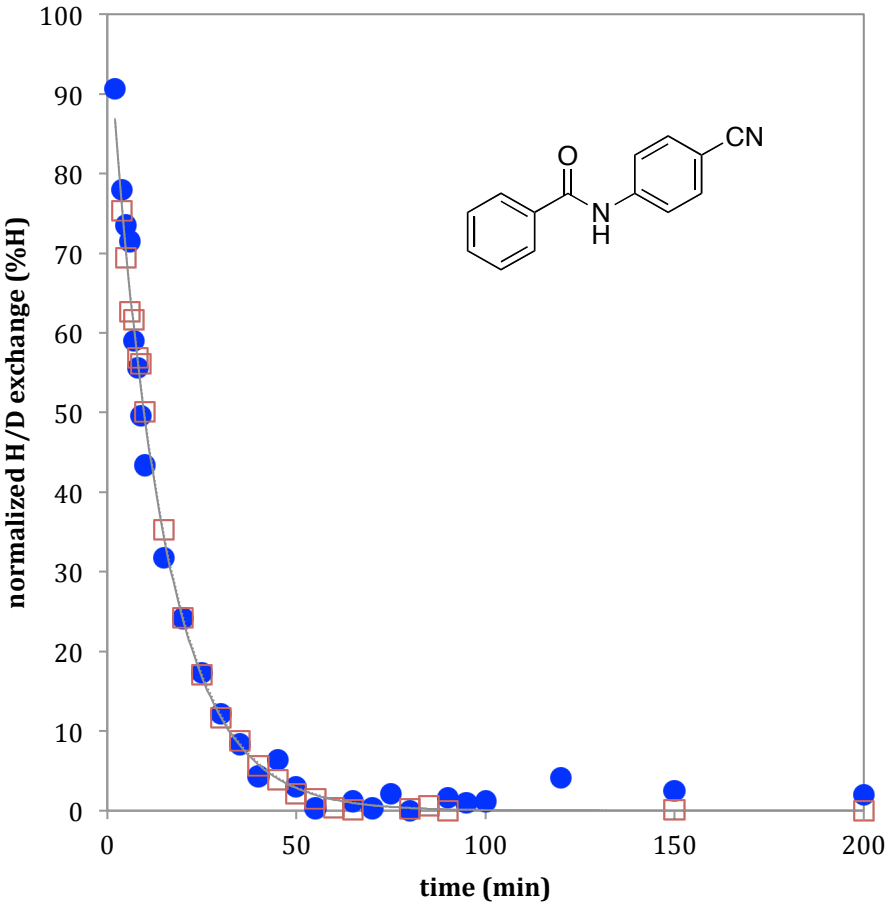


$k_1 = 0.21 \pm 0.01$
$k_2 = 0.23 \pm 0.02$

$k = 0.22 \pm 0.02$

$t_{½} = 3.2 \pm 0.3$

Figure S15. H/D exchange for *N*-(4-cyanophenyl)benzamide (**3**).

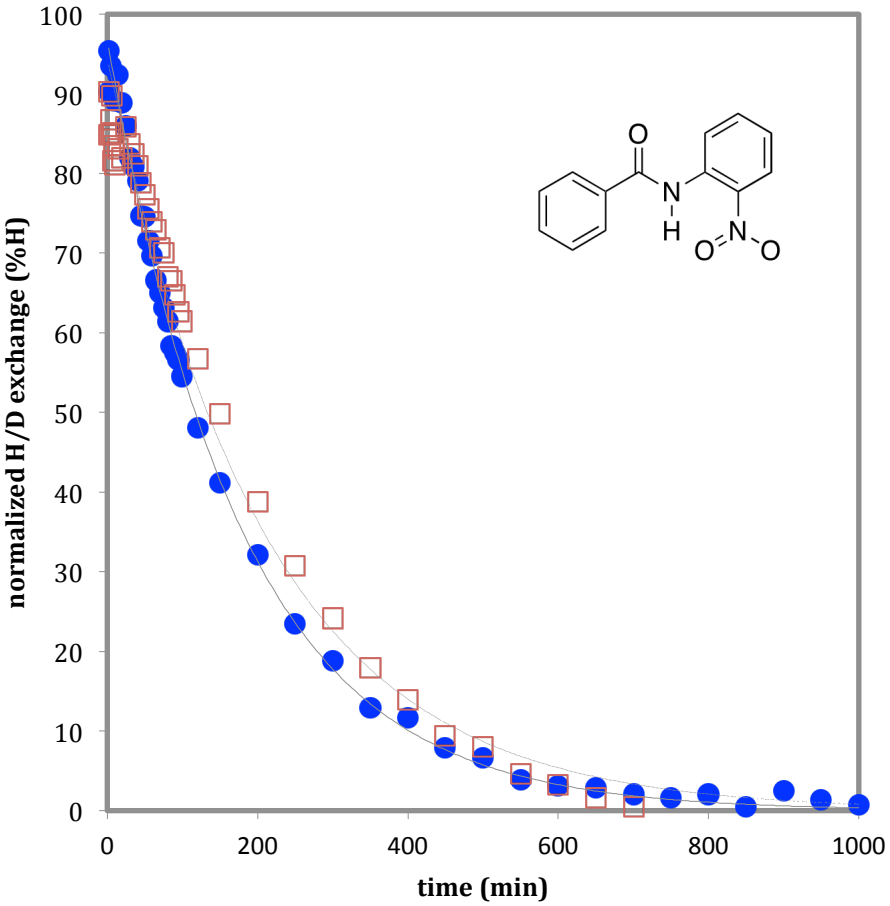


$k_1 = 0.071 \pm 0.002$
$k_2 = 0.070 \pm 0.001$

$k = 0.076 \pm 0.002$

$t_{½} = 9.8 \pm 0.1$

Figure S15. H/D exchange for *N*-(2-nitrophenyl)benzamide (**4**).

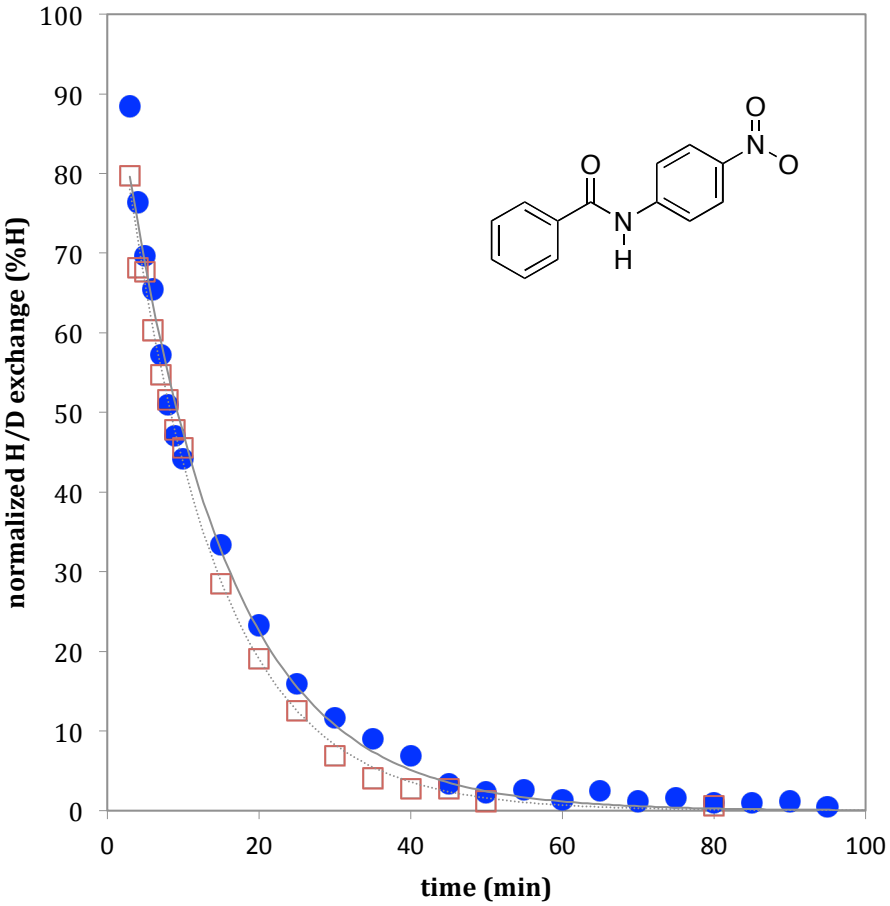


$k_1 = 0.0050 \pm 0.0001$
$k_2 = 0.0056 \pm 0.0001$

$k = 0.0053 \pm 0.0004$

$t_{½} = 130 \pm 10$

Figure S15. H/D exchange for *N*-(4-nitrophenyl)benzamide (**5**).

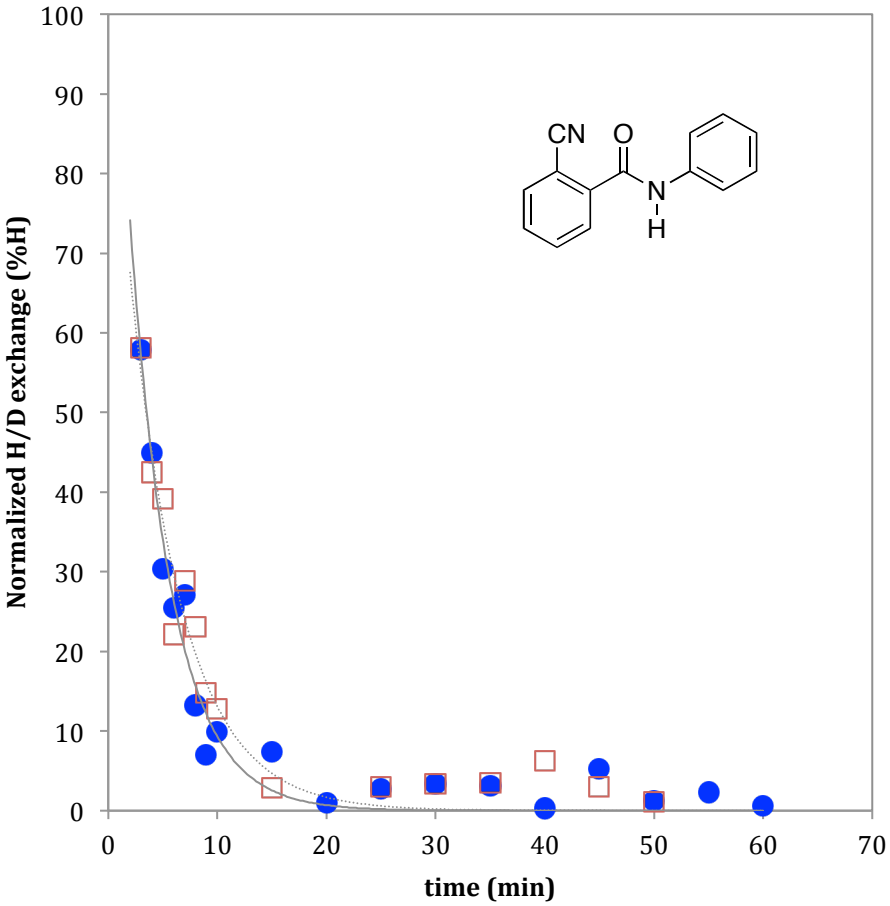


$k_1 = 0.083 \pm 0.002$
$k_2 = 0.073 \pm 0.003$

$k = 0.078 \pm 0.007$

$t_{½} = 8.9 \pm 0.8$

Figure S1. H/D exchange for 2-cyano-*N*-phenylbenzamide (**6**).

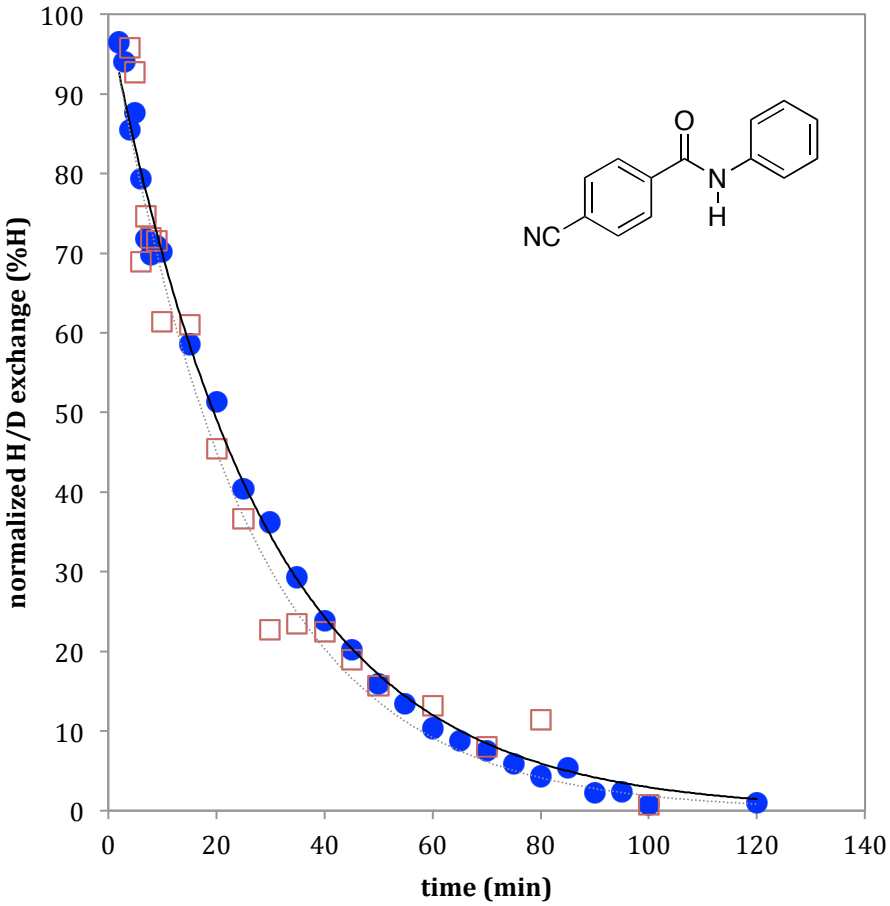


$k_1 = 0.21 \pm 0.05$
$k_2 = 0.20 \pm 0.03$

$k_{ave} = 0.21 \pm 0.002$

$t_{½\ ave} = 3.4 \pm 0.8$

Figure S1. H/D exchange for 4-cyano-*N*-phenylbenzamide (**7**).

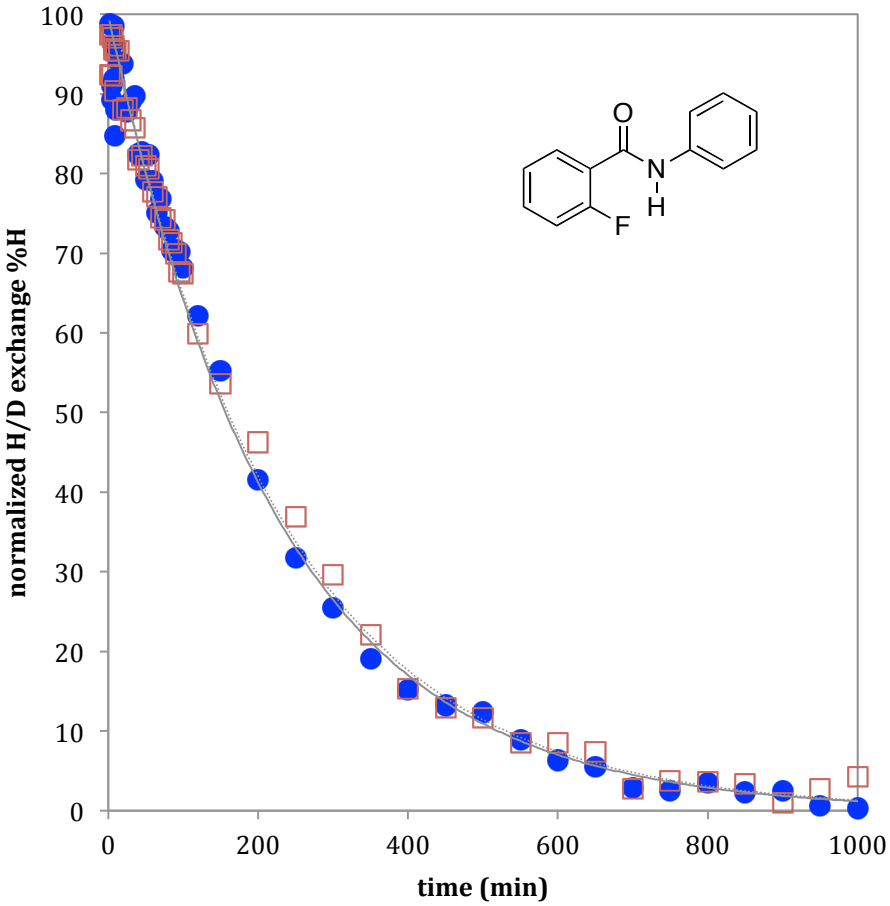


$k_1 = 0.036 \pm 0.001$
$k_2 = 0.040 \pm 0.002$

$k_{ave} = 0.038 \pm 0.003$

$t_{½\ ave} = 18 \pm 2$

Figure S1. H/D exchange for 4-fluoro-*N*-phenylbenzamide (**8**).

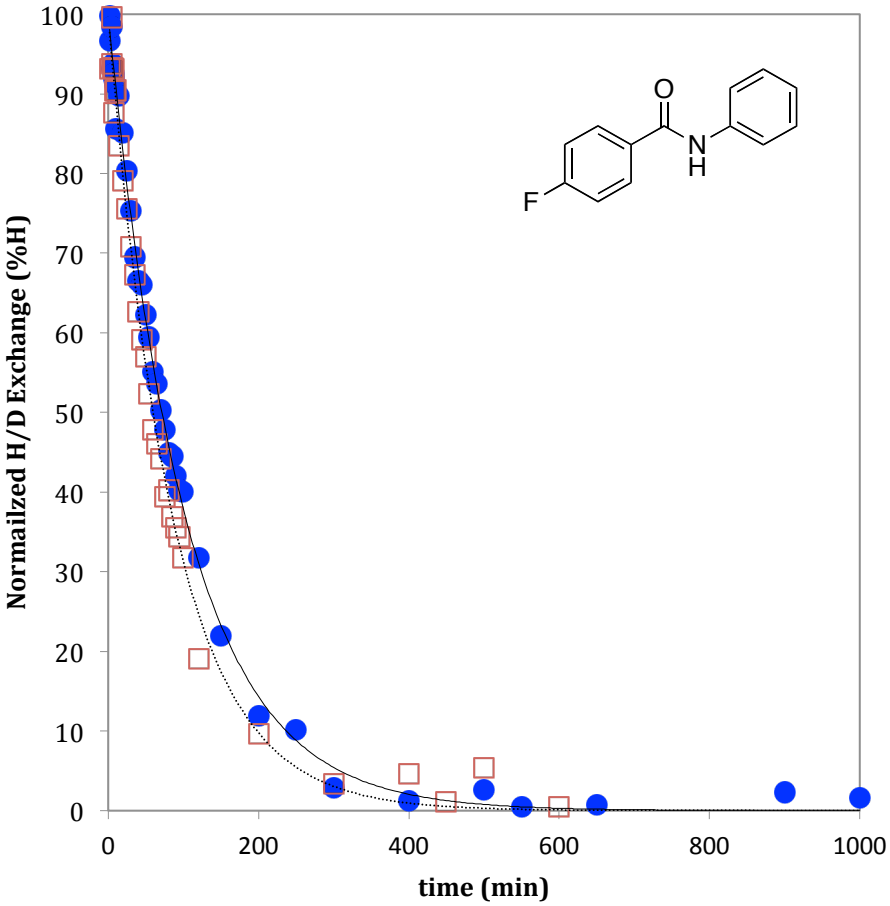


$k_1 = 0.0044 \pm 0.0001$
$k_2 = 0.0043 \pm 0.0001$

$k_{ave} = 0.0044 \pm 0.0001$

$t_{½\ ave} = 158 \pm 3$

Figure S1. H/D exchange for 4-fluoro-*N*-phenylbenzamide (**9**).

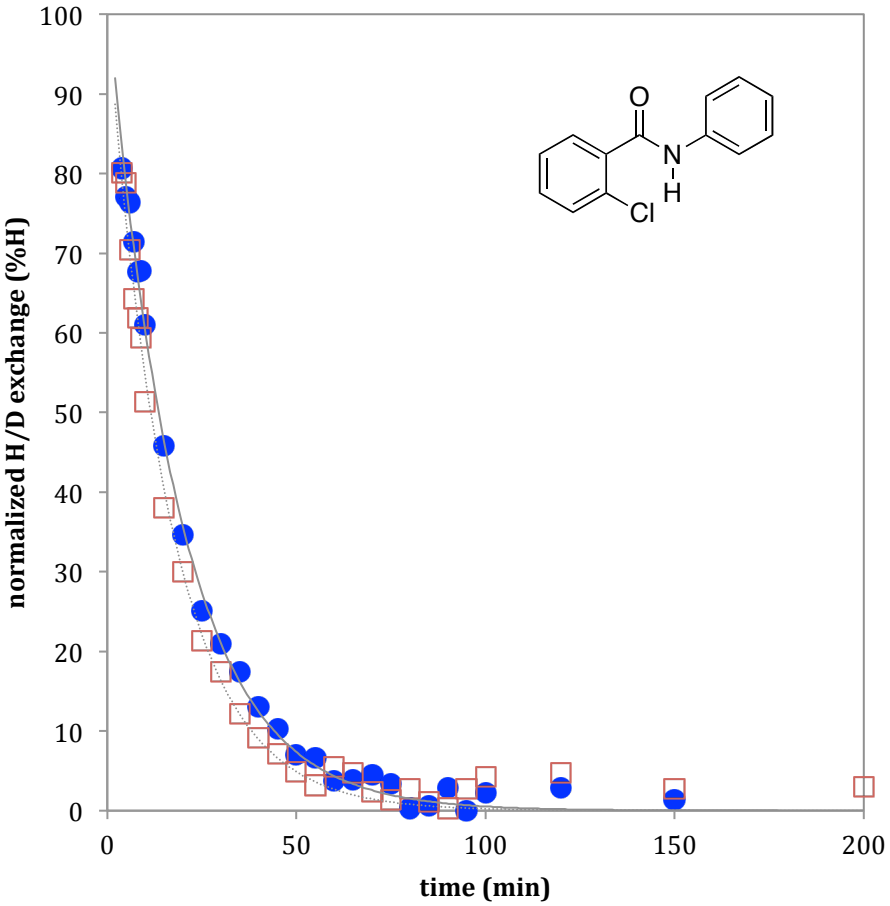


$k_1 = 0.0090 \pm 0.0001$
$k_2 = 0.0120 \pm 0.0001$

$k_{ave} = 0.010 \pm 0.002$

$t_{½\ ave} = 70 \pm 10$

Figure S1. H/D exchange for 2-chloro-*N*-phenylbenzamide (**10**).

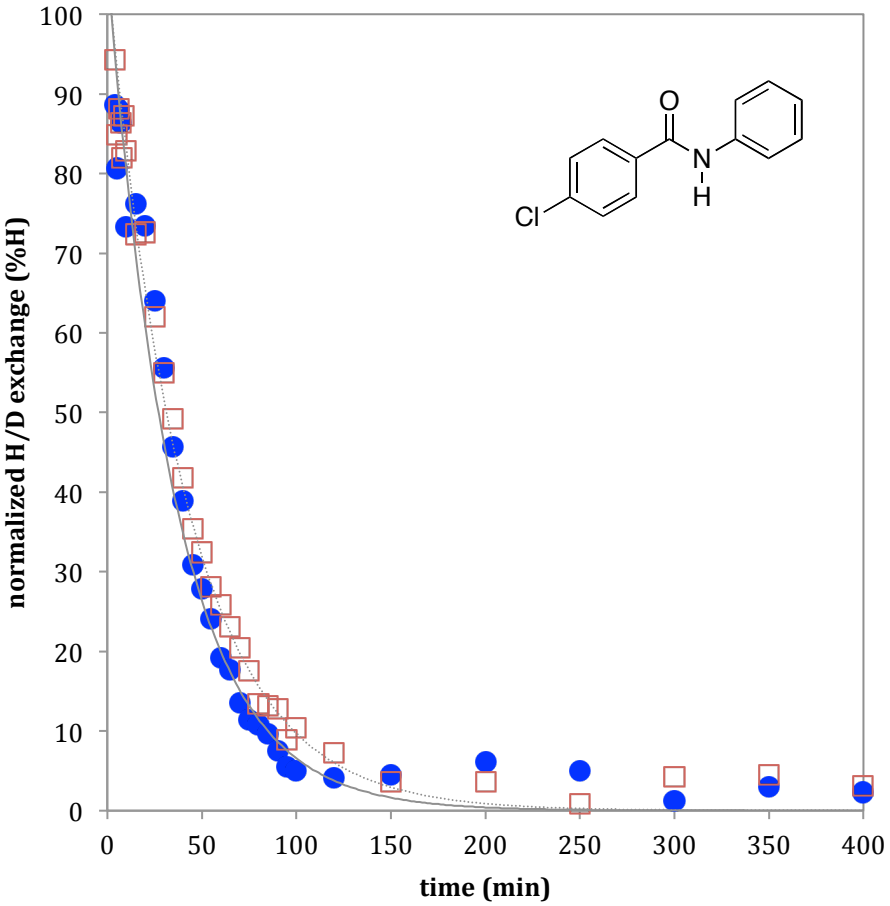


$k_1 = 0.053 \pm 0.001$
$k_2 = 0.060 \pm 0.001$

$k_{ave} = 0.056 \pm 0.005$

$t_{½\ ave} = 12 \pm 1$

Figure S1. H/D exchange for 4-chloro-*N*-phenylbenzamide (**11**).

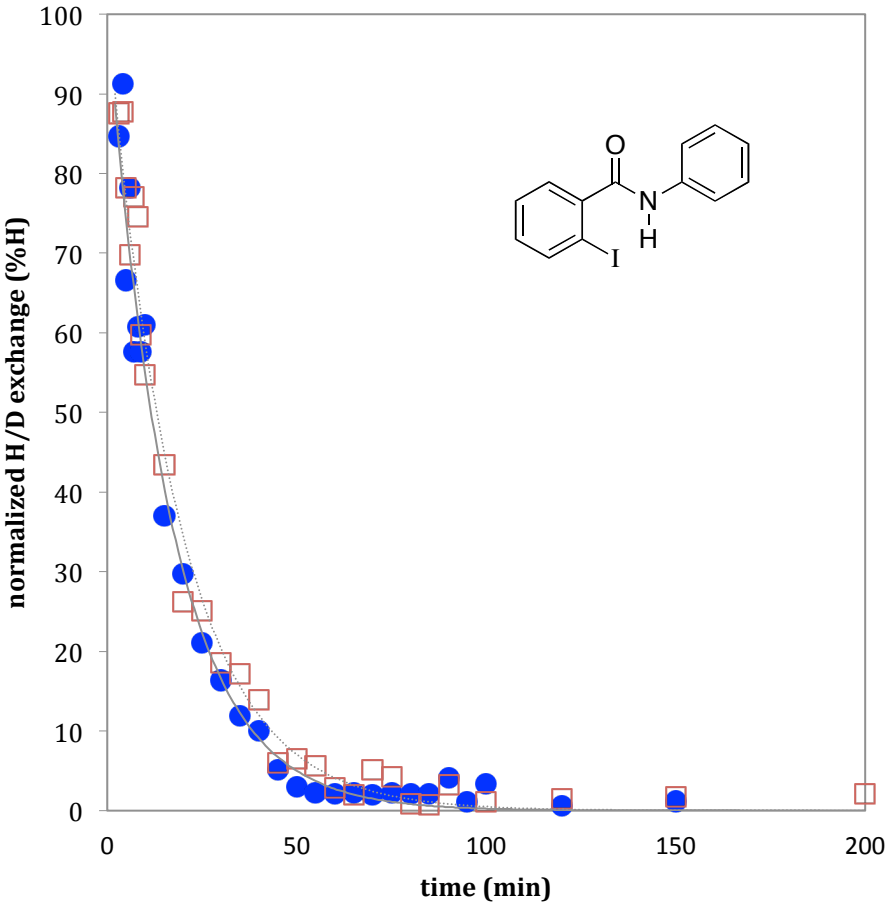


$k_1 = 0.025 \pm 0.001$
$k_2 = 0.028 \pm 0.001$

$k_{ave} = 0.026 \pm 0.002$

$t_{½\ ave} = 26 \pm 2$

Figure S1. H/D exchange for 2-iodo-*N*-phenylbenzamide (**12**).

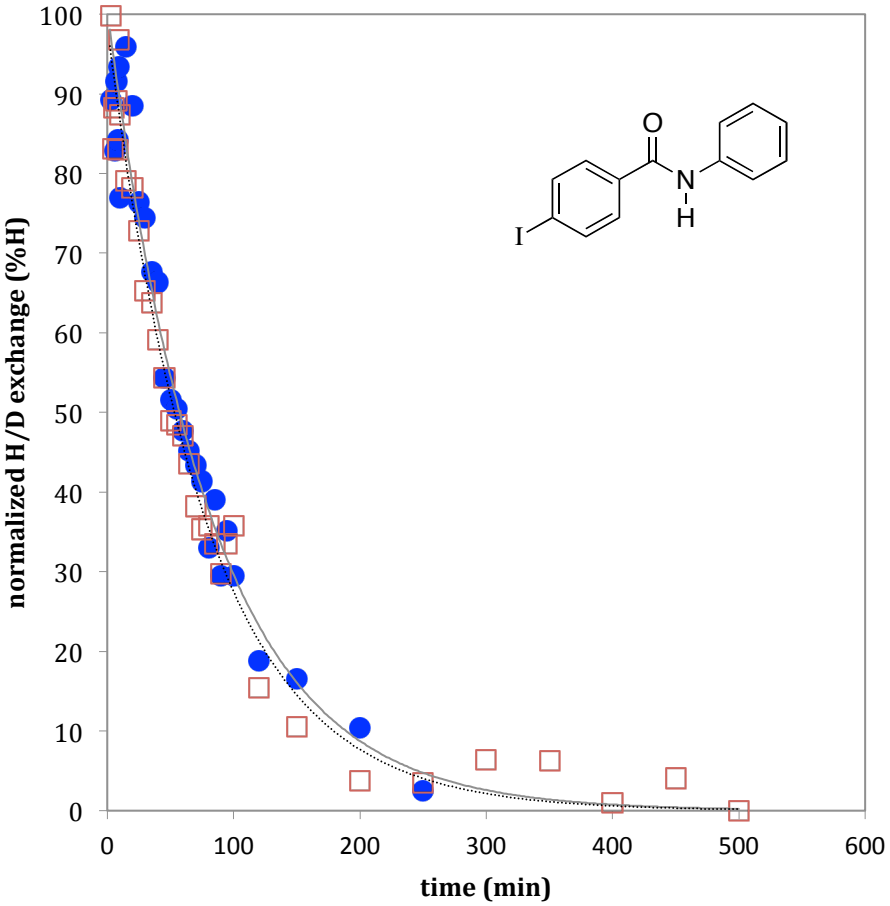


$k_1 = 0.060 \pm 0.002$
$k_2 = 0.053 \pm 0.002$

$k_{ave} = 0.056 \pm 0.005$

$t_{½\ ave} = 12 \pm 1$

Figure S1. H/D exchange for 4-iodo-*N*-phenylbenzamide (**13**).



$k_1 = 0.0121 \pm 0.0006$
$k_2 = 0.0130 \pm 0.0005$

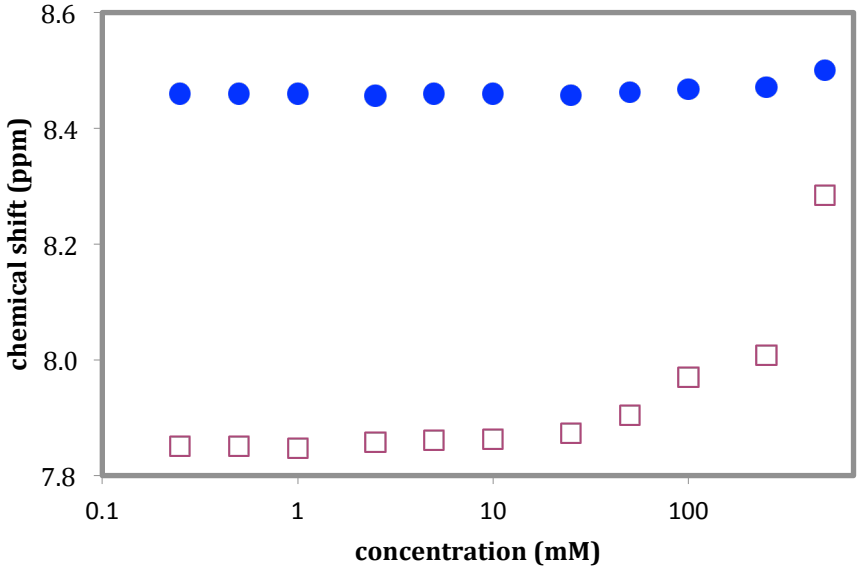
$k_{ave} = 0.013 \pm 0.001$

$t_{½\ ave} = 55 \pm 3$

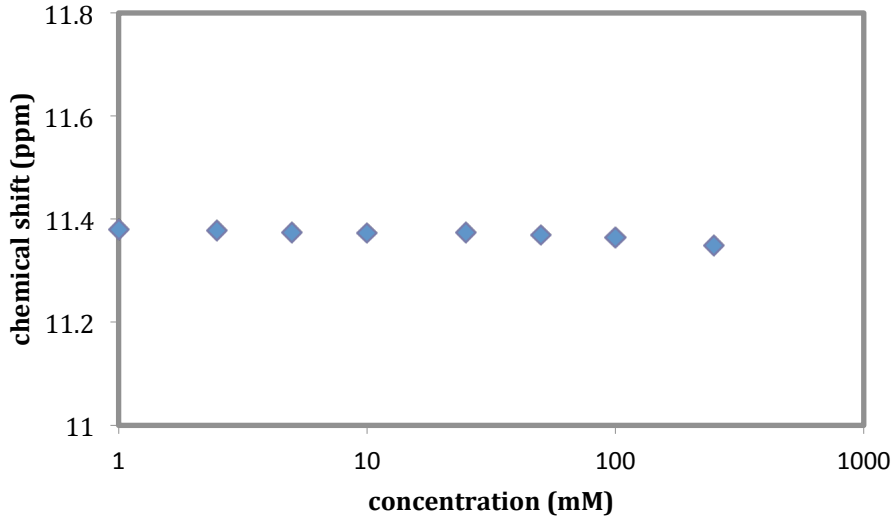
General procedure for determination of chemical shift change with concentration.

An initial NMR spectra was acquired with 400 μL of an analyte solution of known concentration, for example 500 mM in $CDCl_3$. To this was added 400 μL of $CDCl_3$ to achieve a concentration of 250 mM. Transfer of 160 μL to a new NMR tube and dilution with 240 μL $CDCl_3$ resulted in a 100 mM solution. Similar dilution patterns were repeated through concentrations of 50, 25, 10, 5, 2.5, 1, 0.5, 0.25 mM, until the NMR signals were no longer visible.

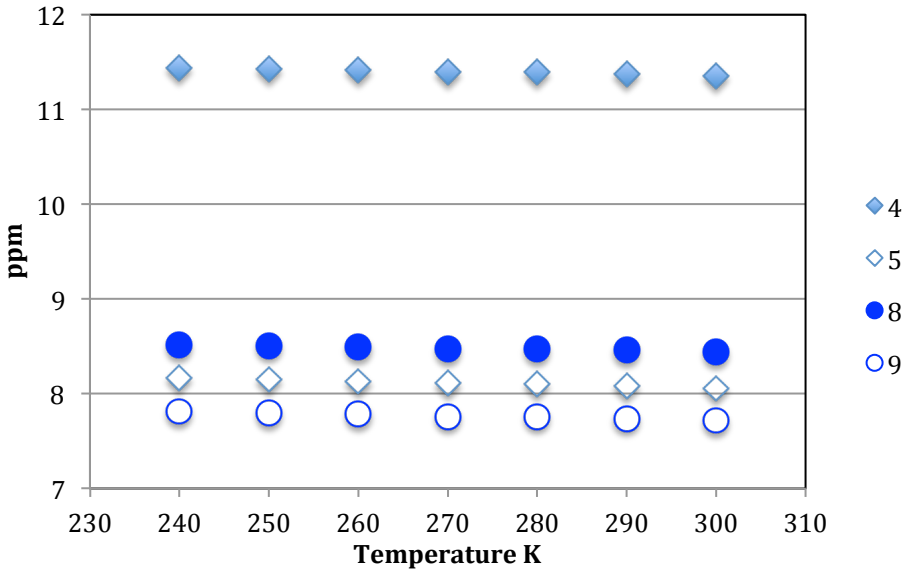
Change in chemical shift for ortho-fluoro derivative (**8**) and ortho chloro (**10**).



Change in chemical shift for ortho-nitro derivative (**4**)



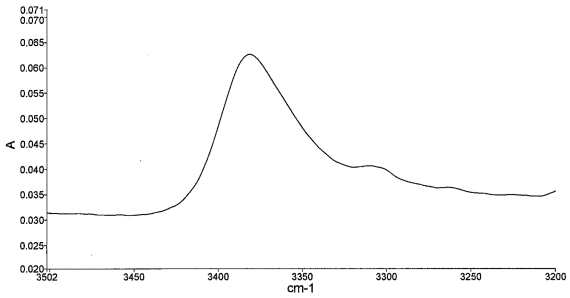
Change in chemical shift with variable temperature for ortho-nitro derivative (**4**), para nitro (**5**). ortho-fluoro derivative (**8**) and para fluoro (**9**).



Δppm (240-300K) for each derivative:	ortho-nitro derivative (**4**)	0.077
	para nitro (**5**).	0.092
	ortho-fluoro derivative (**8**)	0.087
	para fluoro (**9**)	0.107

Infrared spectra for ortho-nitro derivative (**4**), para nitro (**5**). ortho-fluoro derivative (**8**) and para fluoro (**9**).

4



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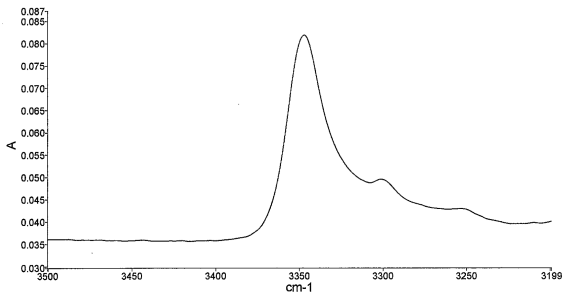
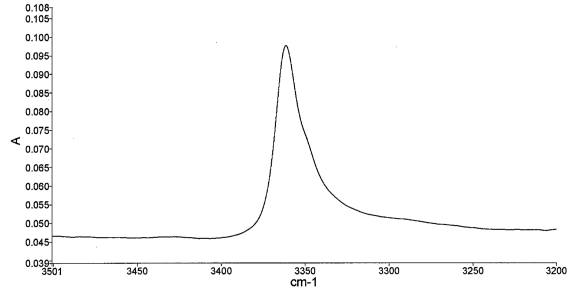


8



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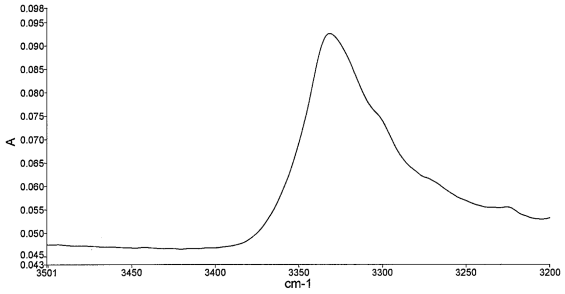
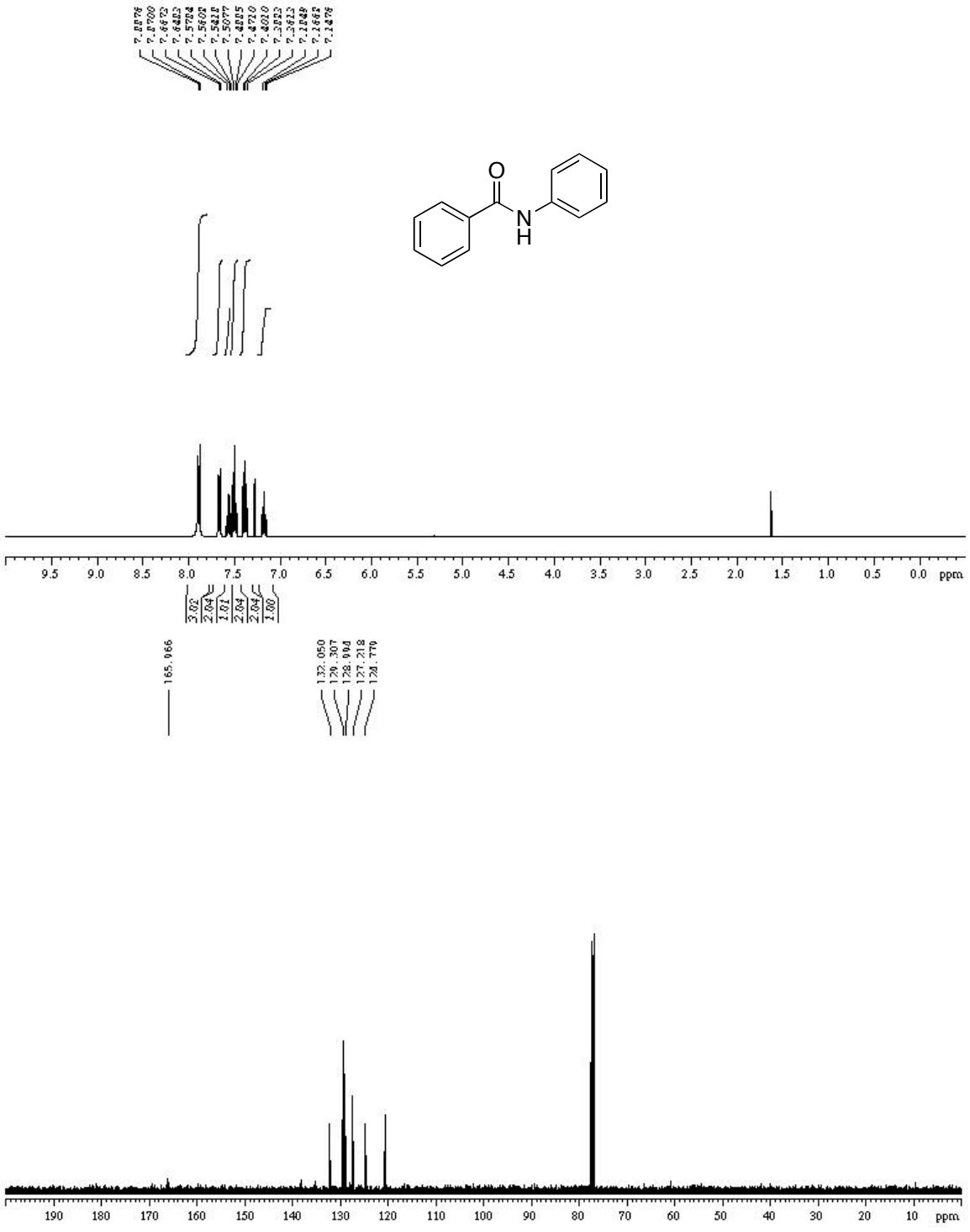
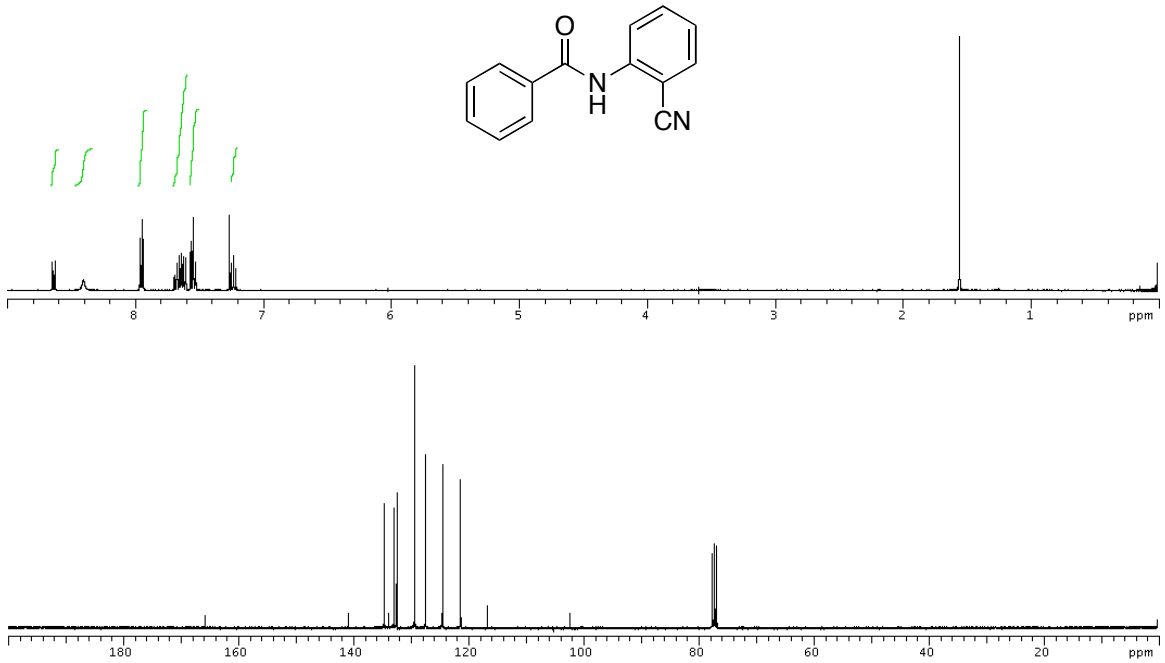


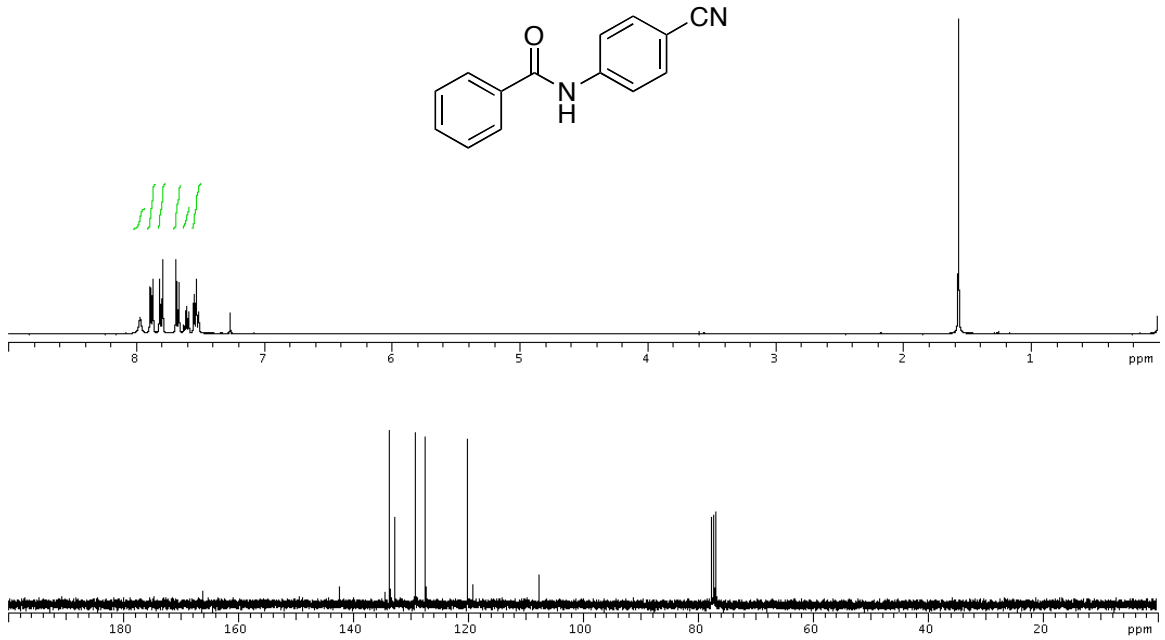
N-phenylbenzamide (4)



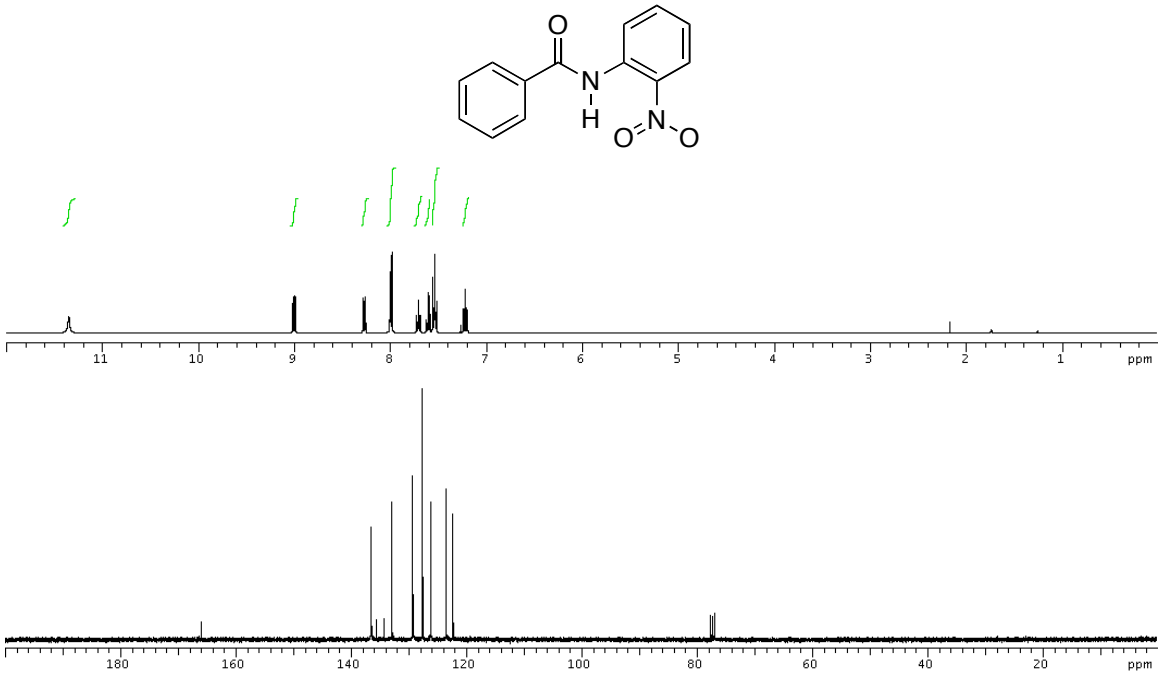
N-(2-cyanophenyl)benzamide (2)



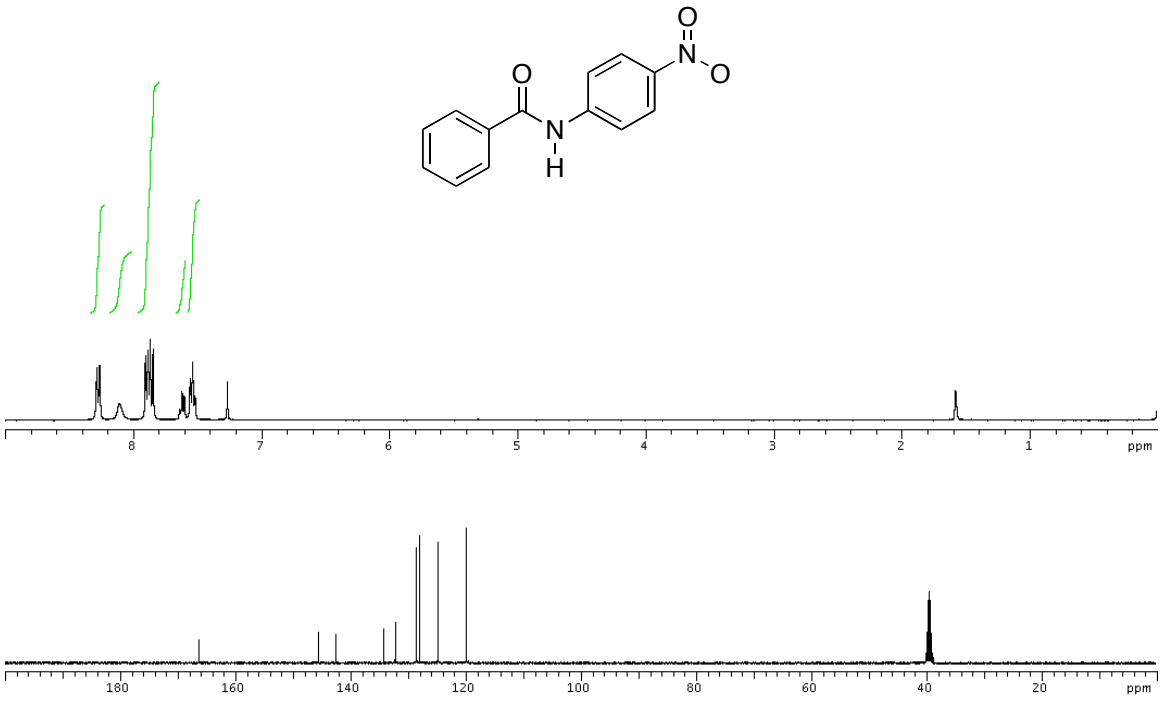
N-(4-cyanophenyl)benzamide (3)



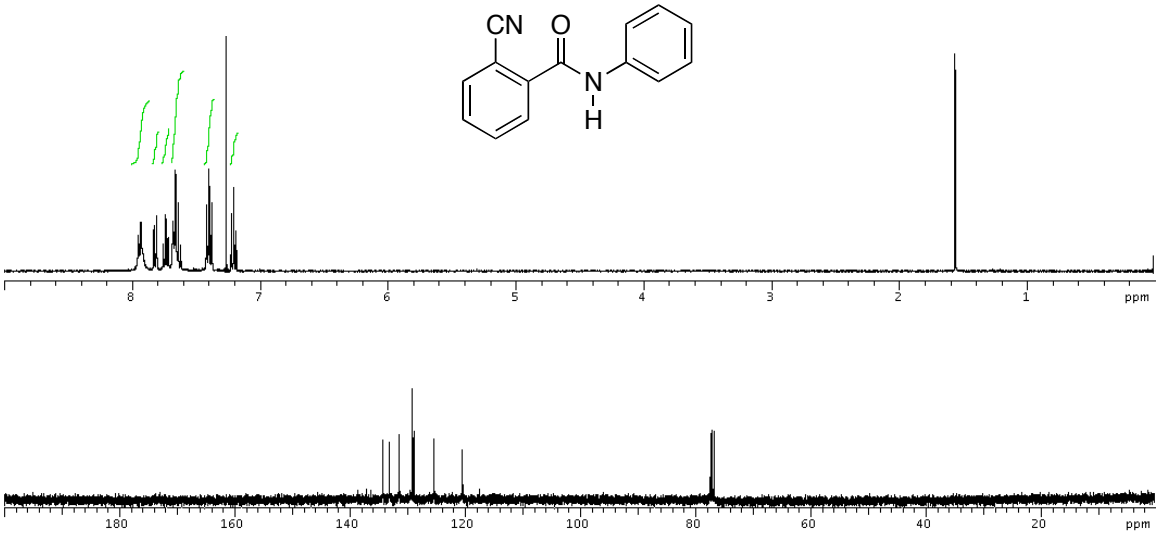
N-(2-nitrophenyl)benzamide (4)



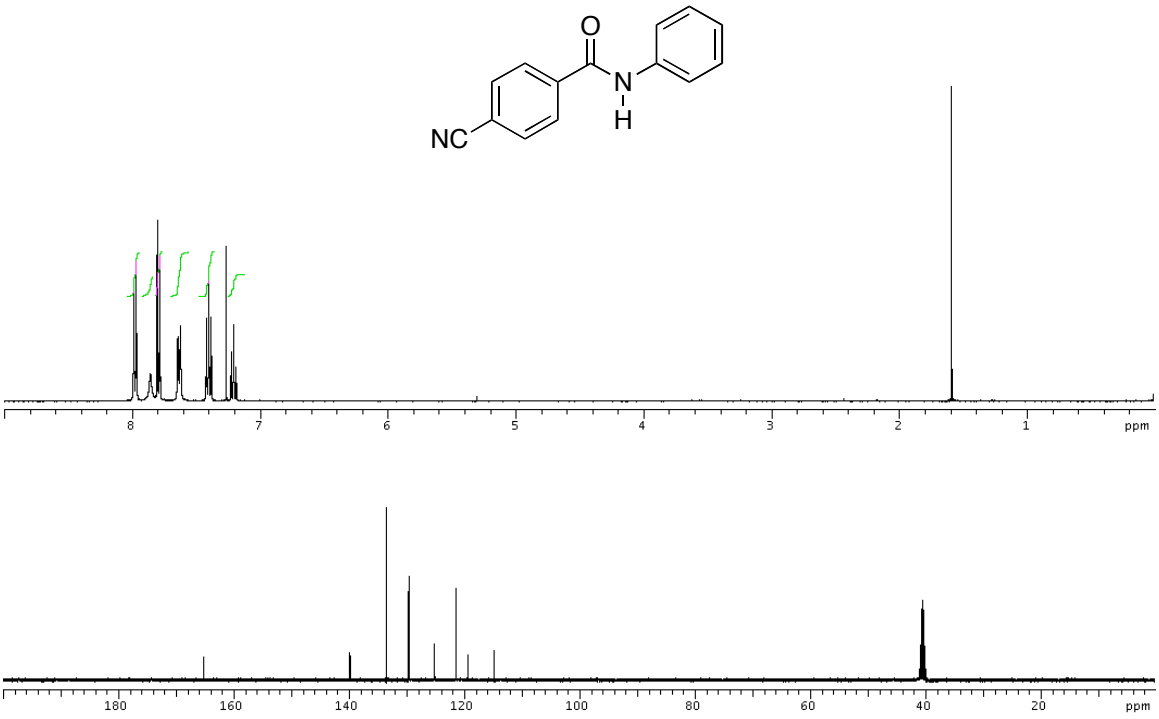
N-(4-nitrophenyl)benzamide (5)



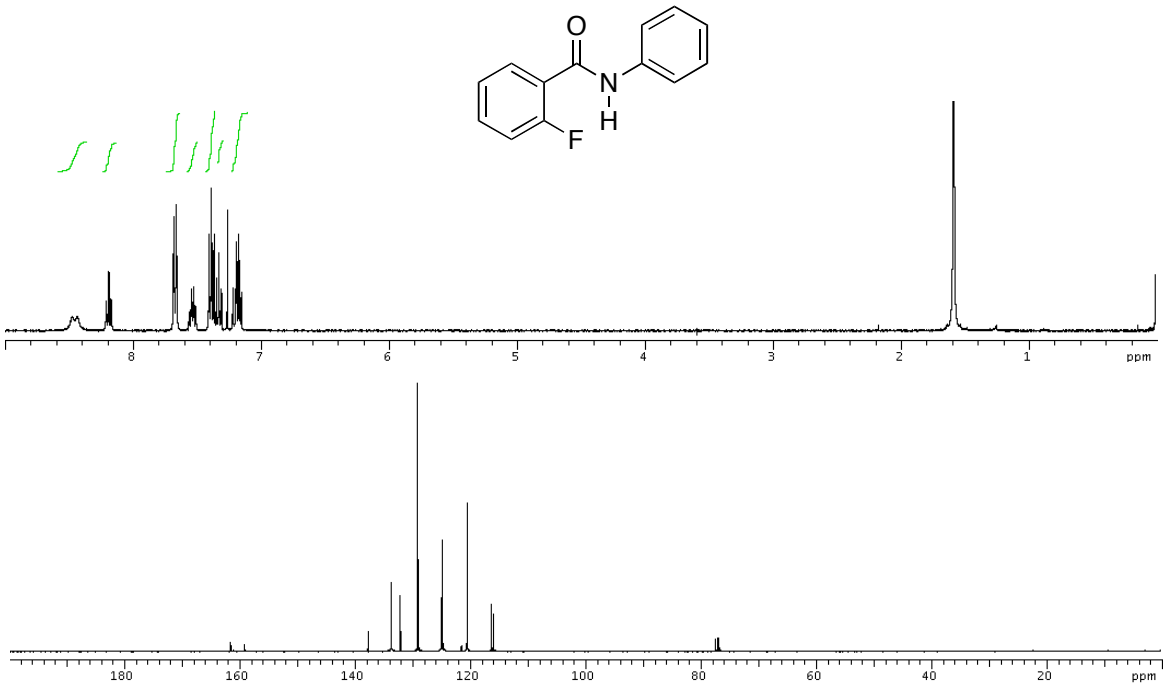
2-cyano-*N*-phenyl-benzamide (6)



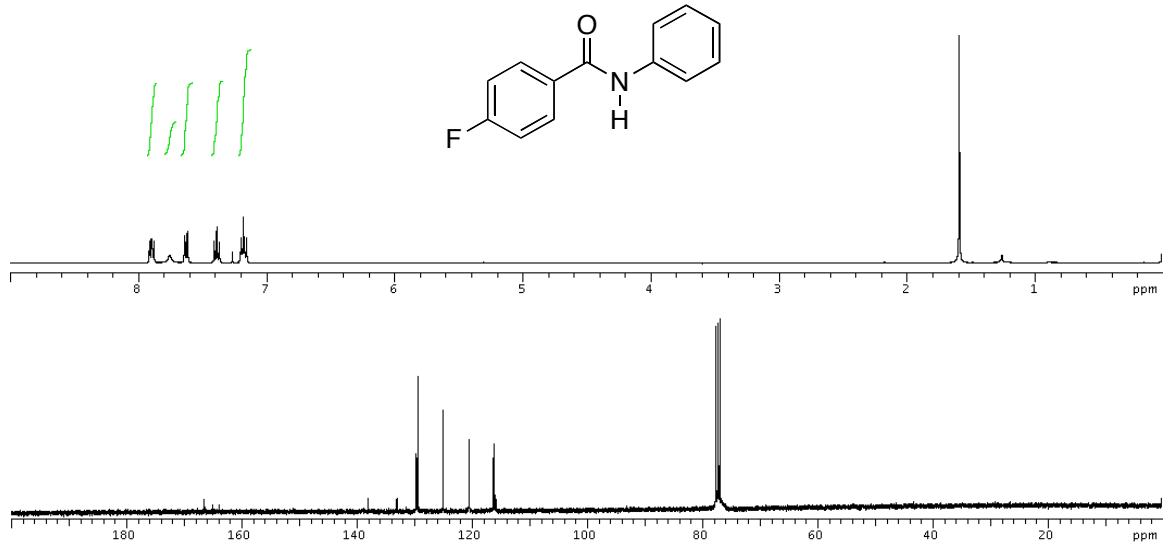
4-cyano-*N*-phenyl-benzamide (7)



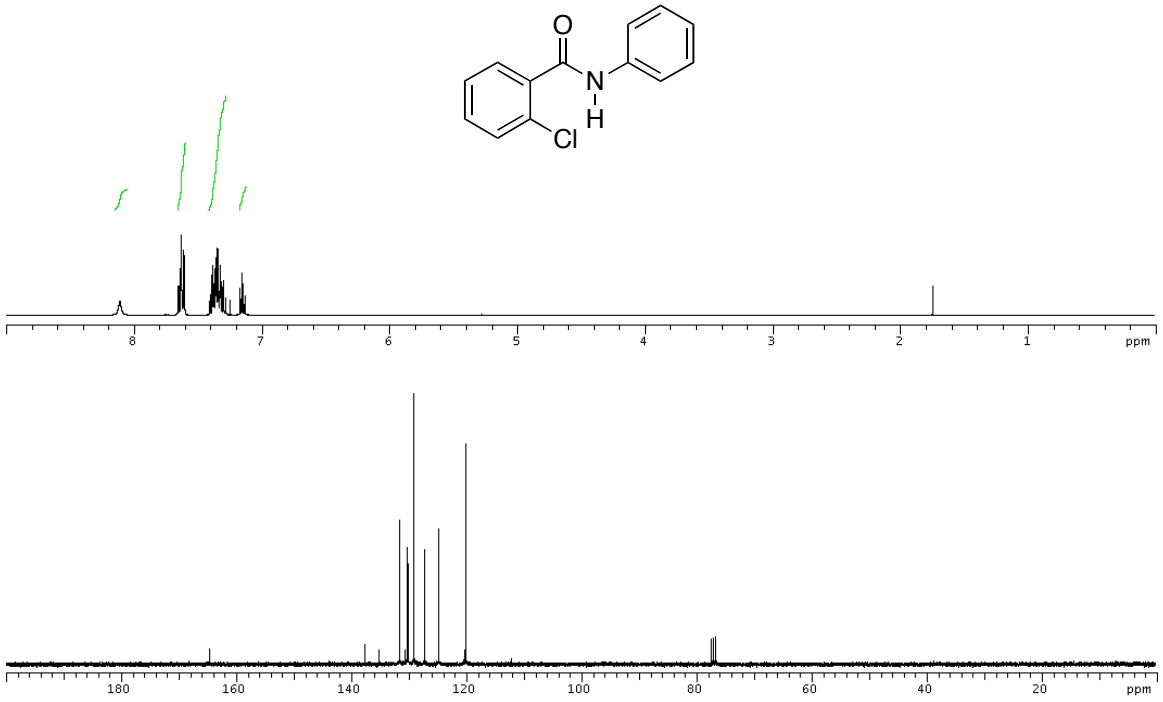
2-fluoro-*N*-phenyl-benzamide (8)



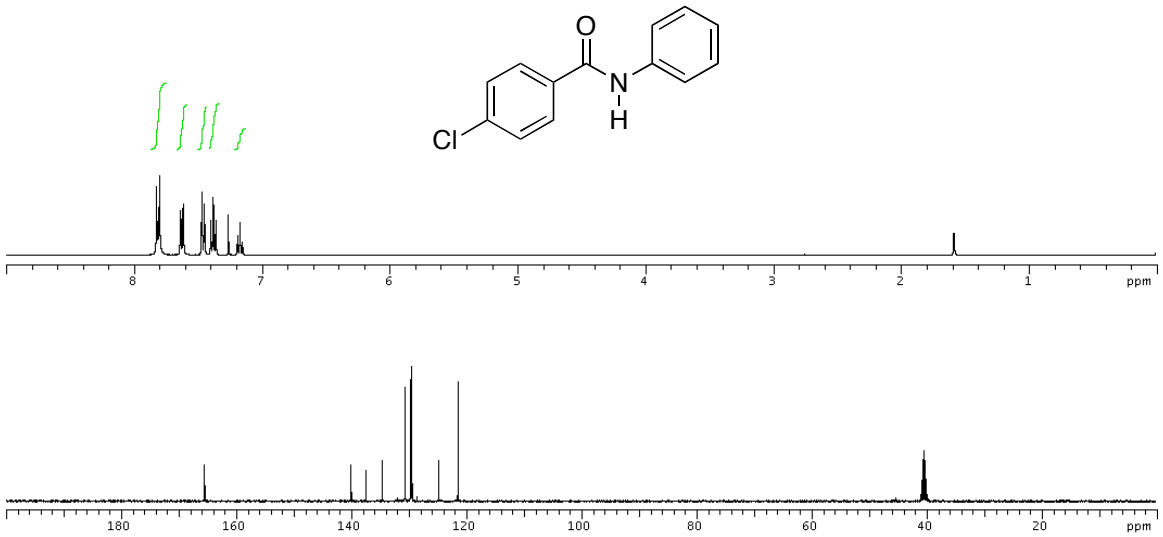
4-fluoro-*N*-phenyl-benzamide (9)



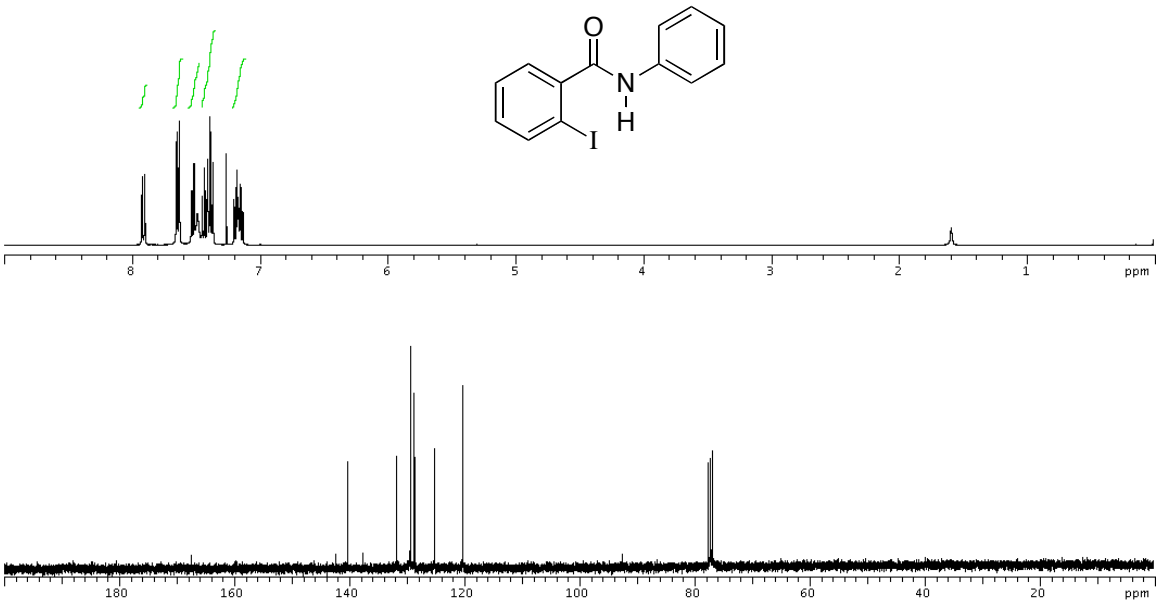
2-chloro-*N*-phenyl-benzamide (10)



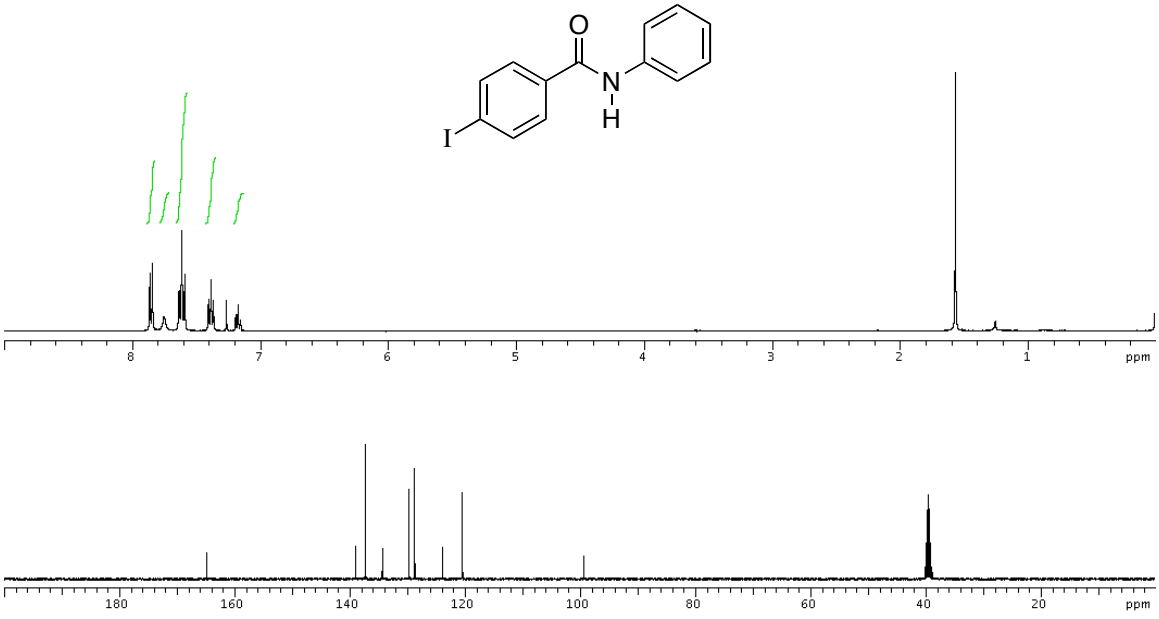
4-chloro-*N*-phenyl-benzamide (11)



2-iodo-*N*-phenyl-benzamide (10)



4-iodo-*N*-phenyl-benzamide (10)



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