Supporting Information

for

Elemental Step Thermodynamics of Various Analogues of Indazolium Alkaloids to Obtain Hydride in Acetonitrile

Nan-Ping Lei,* Yan-Hua Fu, and Xiao-Qing Zhu*

The State Key Laboratory of Elemento-Organic Chemistry, Department of Chemistry, Collaborative Innovation Center of Chemical Science and Engineering, Nankai University, Tianjin 300071, China

Table of Contents:

SI-1. General Methods

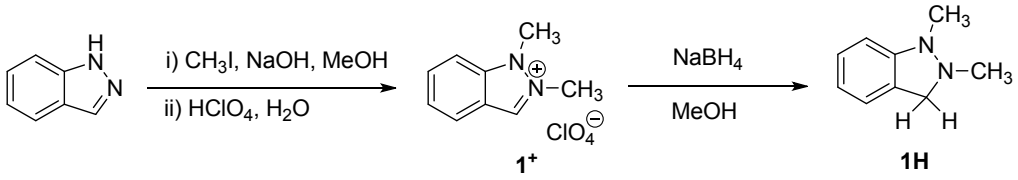
Solvents and reagents were obtained from commercial sources and used as received. HNMR spectra were recorded in CD_3CN, $CDCl_3$ or DMSO on 400 MHz NMR spectrometer. The Chemical shift (δ) were described in parts per million (ppm) downfield from tetramethylsilane (TMS, 0.00 ppm) as an internal standard.

All reagents were of commercial quality from freshly opened containers or were purified according to the standard methods before use. 1*H*-indazole was bought from Alfa Company. Reagent grade acetonitrile was refluxed over $KMnO_4$ and K_2CO_3 for several hours and was doubly distilled over P_2O_5 under argon before use. Anhydrous THF was distilled over sodium before use.[S1] Commercial tetrabutylammonium hexafluorophosphate (n-Bu_4NPF_6, Aldrich) was recrystallized from CH_2Cl_2/ether and was vacuum-dried at 110 ^oC overnight before the preparation of supporting electrolyte solution.

Acetonitrile containing 0.1 M n-Bu_4NPF_6 was used as the solvent in electrochemical measuremetns. The ferrocenium/ferrocene redox couple (Fc^+/Fc) was used as an internal reference for all measurements. All electrochemical measurements were performed under dry nitrogen atmosphere using a sweeping rate of 0.1 V/s, unless otherwise specified, the concentration of each sample was 10^{-3} M.

SI-2. Synthetic Routes of Indazolium Analogues (X^+) and Their Conjugated Amines (XH)

SI-2-1. Synthetic Routes of 1^+ and 1H [S2, S3]



1,2-dimethyl-*1H*-indazol-2-ium perchlorate (1^+): To a solution of 1*H*-indazole (1.2 g, 10 mmol) in methanol was added NaOH (0.40 g, 10 mmol) and CH_3I (3.1 ml, 50 mmol), the mixture was allowed to reflux overnight, after cooling to room temperature, the precipitate was collected by filtration and washed by ethanol to give the iodide salt as yellow solid. The iodide salt was suspended in a dilute solution of $HClO_4$, and stirred overnight at room temperature to yield perchlorate salt as a precipitate. The perchlorate salt was collected by filtration and recrystallized from ethanol to give 1.3 g of 1,2-dimethyl-*1H*-indazol-2-ium perchlorate (**1^+**) as white solid.

$1^+ClO_4^-$：

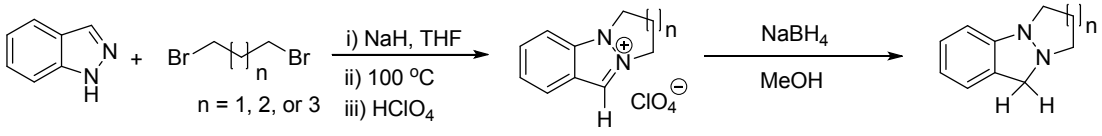
^{1}H NMR (DMSO, 400 M): δ 9.25 (s, 1H), 8.12 (d, 1H), 8.04 (d, 1H), 7.88 (t, 1H), 7.62 (t, 1H), 4.44 (s, 3H), 4.31 (s, 3H); ESI-MS/M-99 = 147.1; Anal. Calcd for $C_9H_{11}N_2O_4Cl$: C, 43.83; H, 4.51; N, 11.36. Found: C, 43.81; H, 4.50; N, 11.34.

1,2-dimethyl-2,3-dihydro-*1H*-indazole (1H): Under an inert atmosphere, $NaBH_4$ (0.38 g, 10 mmol) was added batchwise to a solution of **1^+** (1.2 g, 5 mmol) in methanol (30 ml) at 0 °C. After stirring for two additional hours at room temperature, the mixture was quickly quenched by water, exacted with ethyl acetate twice, and the combined organic phase was dried and evaporated under vacuum. The residue was quickly applied to a flash chromatography to give 0.38 g of 1,2-dimethyl-2,3-dihydro-*1H*-indazole (**1H**) as semi-solid, which was kept under an inert atmosphere and stored in the fridge before use.

1H：

^{1}HNMR (CD_3CN, 400 M): δ 7.26 (t, 1H), 7.19 (d, 2H), 6.95 (t, 1H), 6.65 (d, 1H), 4.61 (d, 1H), 4.34 (d, 1H), 3.04 (s, 3H), 2.91 (s, 3H); ESI-MS/M+1 = 149.0; Anal. Calcd for $C_9H_{12}N_2$: C, 72.94; H, 8.16; N, 18.90. Found: C, 72.92; H, 8.14; N, 18.91.

SI-2-2. Synthetic Routes of 2^+-4^+ and 2H-4H [S2,S4]



2^+ : n = 1
3^+ : n = 2
4^+ : n = 3

2H : n = 1
3H : n = 2
4H : n = 3

2,3-dihydro-*1H*-pyrazolo[1,2-*a*]indazol-10-ium perchlorate (2^+): To a mixture of 1*H*-indazole (1.2 g, 10 mmol), 1,3-dibromopropane (5.0 g) and THF (30 ml) was added NaH (40% in mineral oil, 1 g) and then stirred at room temperature overnight. The reaction was quenched by water and extracted by EA for three times. The organic phased were combined, dried over Na_2SO_4 and evaporated under vacuum. The residue was heated at 100 ^oC overnight. After cooling, the resulting solid was suspended in a dilute solution of $HClO_4$ and stirred overnight at room temperature to yield perchlorate salt as a precipitate. The precipitate was collected by filtration and recrystallized from ethanol to give 1.0 g of 2,3-dihydro-*1H*-pyrazolo[1,2-*a*]indazol -10-ium perchlorate ($\mathbf{2}^+$) as white solid. $\mathbf{3}^+$-$\mathbf{4}^+$ were synthesized accordingly.

$2^+ClO_4^-$:

^{1}HNMR (CD_3CN, 400 M): δ 8.73 (s, 1H), 8.06 (d, 1H), 7.86 (t, 1H), 7.77 (d, 1H), 7.53 (t, 1H), 4.79 (t, 2H), 4.66 (t, 2H), 3.08 (m, 2H); ESI-MS/M-99 = 159.2; ^{13}C NMR (DMSO, 100 M): δ 135.64, 132.68, 127.12, 125.17, 124.42, 123.27, 111.67, 50.5, 46.87, 27.30; Anal. Calcd for $C_{10}H_{11}N_2O_4Cl$: C, 46.43; H, 4.29; N, 10.83. Found: C, 46.42; H, 4.30; N, 10.82.

6,7,8,9-tetrahydropyridazino[1,2-*a*]indazol-10-ium perchlorate (3^+): ^{1}HNMR (CD_3CN, 400 M): δ 8.71 (s, 1H), 8.07 (d, 1H), 7.89 (t, 1H), 7.77 (d, 1H), 7.56 (t, 1H), 4.73 (t, 2H), 4.56 (t, 2H), 2.26 (m, 4H); ESI-MS/M-99 = 173.1; ^{13}CNMR (DMSO, 100 M): δ 140.37, 133.15, 133.06, 125.71, 123.40, 119.40, 111.12, 50.81, 47.05, 19.80, 19.41; Anal. Calcd for $C_{11}H_{13}N_2O_4Cl$: C, 48.45; H, 4.81; N, 10.27. Found: C, 48.44; H, 4.80; N, 10.27.

7,8,9,10-tetrahydro-*6H*-[1,2]diazepino[1,2-*a*]indazol-11-ium perchlorate (4^+): ^{1}HNMR (CD_3CN, 400 M): δ 8.72 (s, 1H), 8.06 (d, 1H), 7.89 (t, 1H), 7.78 (m, 2H), 4.74 (t, 2H), 4.62 (t, 2H), 2.00 (m, 6H); ESI-MS/M-99 = 187.2; Anal. Calcd for $C_{12}H_{15}N_2O_4Cl$: C, 50.27; H, 5.27; N, 9.77. Found: C, 50.25; H, 5.26; N, 9.76.

Syntheses of 2H-4H

Under an inert atmosphere, $NaBH_4$ (0.38 g, 10 mmol) was added batchwise to a solution of $\mathbf{2}^+$ (0.52 g, 2 mmol) in MeOH (20 ml) at 0 ^oC. After stirring for two additional hours at room temperature, the mixture was quickly quenched by water, exacted with ethyl acetate twice, and the combined organic phase was dried and evaporated under vacuum. The residue was quickly applied to a flash chromatography to give 0.20 g of 1,2,3,9-tetrahydropyrazolo[1,2-*a*]indazole (**2H**) as a white solid, which was kept under an inert atmosphere and stored in the fridge before use. **3H-4H** were synthesized accordingly.

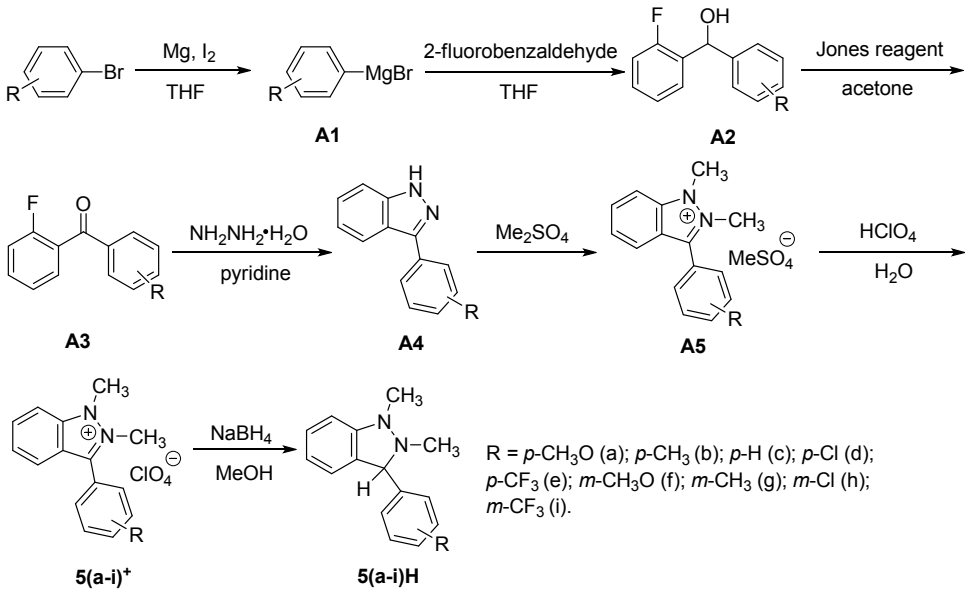
2H: ^{1}HNMR (CD_3CN, 400 M): δ 7.23 (m, 2H), 7.03 (t, 1H), 6.80 (d, 1H), 4.64 (dd, 2H), 3.70 (m, 2H), 3.46 (m, 1H), 3.05 (m, 1H), 2.17 (m, 1H), 2.02 (m, 1H); ESI-MS/M+1 = 161.1; ^{13}C NMR ($CDCl_3$, 100 M):
δ 149.58, 129.23, 123.41, 123.28, 123.02, 110.70, 65.16, 58.82, 50.68, 25.05; Anal. Calcd for $C_{10}H_{12}N_2$: C, 74.97; H, 7.55; N, 17.48. Found: C, 74.96; H, 7.56; N, 17.47.

3H: ^{1}HNMR (CD_3CN, 400 M): δ 7.22 (m, 2H), 6.90 (t, 1H), 6.61 (d, 1H), 4.38 (d, 1H), 4.10 (d, 2H), 3.92 (m, 1H), 3.82 (m, 1H), 3.14 (m, 1H), 2.93 (m, 1H), 2.43 (m, 1H), 1.57 (m, 3H); ESI-MS/M+1 = 175.1; Anal. Calcd for $C_{11}H_{14}N_2$: C, 75.82; H, 8.10; N, 16.08. Found: C, 75.81; H, 8.11; N, 16.09.

4H: ^{1}HNMR (CD_3CN, 400 M): δ 7.13 (m, 2H), 6.80 (t, 1H), 6.52 (d, 1H), 4.72 (d, 1H), 4.47 (d,

2H), 3.74 (m, 2H), 3.38 (m, 2H), 2.14 (m, 1H), 1.95 (m, 5H); ESI-MS/M+1 = 189.1; ^{13}C NMR (DMSO, 100 M):
δ 151.48, 128.10, 127.60, 122.64, 120.64, 110.78, 60.58, 59.89, 56.31, 29.23, 28.66, 25.02; Anal. Calcd for $C_{12}H_{16}N_2$: C, 76.55; H, 8.57; N, 14.88. Found: C, 76.56; H, 8.58; N, 14.87.

SI-2-3. Synthetic Routes of 5^+ and 5H [S2,S5]



Preparation of substituted phenylmagnesium bromides (A1)

Under an inert atmosphere, magnesium chips (20 mmol) and a small amount of appropriate bromobenzene (0.25 mmol) were suspended in anhydrous THF (40 ml) and heated to reflux, and the solution turned dark red after several drops of iodine were added. Once the reaction was initiated, the color of the solution turned colorless, at which point, the left bromobenzene (10 mmol) in THF (10 ml) were added dropwise, and the resulting mixture was allowed to reflux for an additional hour. The gray solution of corresponding phenylmagnesium bromide was used directly in next step.

Preparation of (2-fluorophenyl)(phenyl)methanols (A2)

Into a solution of 2-fluorobenzaldehyde (10 mmol) in anhydrous THF (40 ml) with an inert atmosphere at 0 ^{o}C, the appropriate **A1** solution (12 mmol) was added dropwise. The mixture was stirred at room temperature for three hours. The reaction was quenched by chilled solution of NH_4Cl, exacted with ethyl acetate twice, and the combined organic phase was dried and evaporated under vacuum. The residue was applied to silica gel column chromatography (PE : EA = 2 : 1) to give the title compound as colorless oil.

Preparation of (2-fluorophenyl)(phenyl)methanones (A3)

Into a solution of appropriate (2-fluorophenyl)(phenyl)methanol (8 mmol) in acetone (30 ml) at 0 ^{o}C, Jones reagent was added dropwise (16 mmol). The mixture was stirred for one additional hour. The reaction was quenched by chilled solution of Na_2SO_3, exacted with ethyl acetate twice, and the combined organic phase was dried and evaporated under vacuum. The residue was applied to

silica gel column chromatography (PE : EA = 10 : 1) to give the title compound as white solid or colorless oil.

Preparation of substituted 3-phenyl-*1H*-indazoles (A4)

To a solution of appropriate (2-fluorophenyl)(phenyl)methanone (5 mmol) and DMAP (5 mmol) in pyridine (30 ml) was added hydrazine monohydrate (50 mmmol). The mixture was stirred at 110 ^{o}C overnight. After pyridine was evaporated in vacuo, the residue was applied to silica gel column chromatography (PE : EA = 5 : 1) to give the title compound as white or light yellow solid.

Preparation of substituted 1,2-dimethyl-3-phenyl-*1H*-indazol-2-ium methyl sulfates (A5)

The appropriate 3-phenyl-1H-indazole (3 mmol) was dissolved in dimethyl sulfate (20 ml). The mixture was stirred at 130 ^{o}C overnight. After cooling down to room temperature, dimethyl sulfate (highly toxic) was carefully evaporated in vacuo, and the residue was used in next step.

Preparation of substituted 1,2-dimethyl-3-phenyl-*1H*-indazol-2-ium perchlorates (5(a-i)$^{+}$)

The appropriate 1,2-dimethyl-3-phenyl-*1H*-indazol-2-ium methyl sulfate was suspended in a dilute solution of $HClO_4$, and stirred overnight at room temperature to yield perchlorate salt as a precipitate. The perchlorate salt was collected by filtration and recrystallized from ethanol to give the title compound as white solid.

3-(4-methoxyphenyl)-1,2-dimethyl-*1H*-indazol-2-ium perchlorate (5a^{+}): ^{1}HNMR ($CDCl_3$, 400 M): δ 7.78 (m, 4H), 7.67 (m, 1H), 7.46 (d, 1H), 7.19 (m, 2H), 4.62 (d, 6H), 3.94 (s, 3H); ESI-MS/-99 = 253.3.

1,2-dimethyl-3-(p-tolyl)-*1H*-indazol-2-ium perchlorate (5b^{+}): ^{1}HNMR ($CDCl_3$, 400 M): δ 7.77 (m, 3H), 7.66 (m, 2H), 7.48 (m, 3H), 4.64 (d, 6H), 2.51 (s, 3H); ESI-MS/M-99 = 237.2.

1,2-dimethyl-3-phenyl-*1H*-indazol-2-ium perchlorate (5c^{+}): ^{1}HNMR (DMSO, 400 M): δ 8.11 (m, 1H), 7.89 (m, 7H), 7.55 (m, 1H), 4.38 (s, 3H), 4.26 (s, 3H); ESI-MS/M-99 = 223.8; ^{13}C NMR (DMSO, 100 M):
δ 142.67, 139.82, 133.62, 132.05, 130.65, 130.19, 125.89, 125.27, 122.54, 119.04, 111.65, 36.33, 34.17; Anal. Calcd for $C_{15}H_{15}N_2O_4Cl$: C, 55.82; H, 4.68; N, 8.68. Found: C, 55.81; H, 4.69; N, 8.67.

3-(4-chlorophenyl)-1,2-dimethyl-*1H*-indazol-2-ium perchlorate (5d^{+}): ^{1}HNMR ($CDCl_3$, 400 M): δ 7.82 (m, 3H), 7.68 (m, 4H), 7.50 (m, 1H), 4.60 (brs, 6H); ESI-MS/M-99 = 257.1.

1,2-dimethyl-3-(4-(trifluoromethyl)phenyl)-*1H*-indazol-2-ium perchlorate (5e^{+}): ^{1}HNMR (CD_3CN, 400 M): δ 8.04 (m, 2H), 7.85 (m, 5H), 7.50 (m, 1H), 4.28 (s, 3H), 4.17 (s, 3H); ESI-MS/M-99 = 291.2.

3-(3-methoxyphenyl)-1,2-dimethyl-*1H*-indazol-2-ium perchlorate (5f^{+}): ^{1}HNMR (CD_3CN, 400 M): δ 7.86 (m, 3H), 7.65 (m, 1H), 7.52 (m, 1H), 7.26 (m, 3H), 4.25 (s, 3H), 4.19 (s, 3H), 3.90 (s, 3H); ESI-MS/M-99 = 253.0.

1,2-dimethyl-3-(m-tolyl)-*1H*-indazol-2-ium perchlorate (5g^{+}): ^{1}HNMR (CDCl3, 400 M): δ 7.85 (m, 2H), 7.54 (m, 3H), 7.42 (m, 3H), 4.68 (s, 3H), 4.49 (s, 3H), 2.24 (s, 3H); ESI-MS/M-99 = 237.3.

3-(3-chlorophenyl)-1,2-dimethyl-*1H*-indazol-2-ium perchlorate (5h^{+}): ^{1}HNMR (CD_3CN, 400

M): δ 7.92 (m, 1H), 7.82 (m, 2H), 7.73 (m, 3H), 7.65 (s, 1H), 7.53 (m, 1H), 4.27 (s, 3H), 4.18 (s, 3H); ESI-MS/M-99 = 257.2.

1,2-dimethyl-3-(3-(trifluoromethyl)phenyl)-*1H*-indazol-2-ium perchlorate (5i$^+$): ^{1}HNMR (CD_3CN, 400 M): δ 8.07 (m, 1H), 7.93 (m, 4H), 7.83 (m, 2H), 7.55 (m, 1H), 4.27 (s, 3H), 4.16 (s, 3H); ESI-MS/M-99 = 291.3.

Preparation of substituted 1,2-dimethyl-3-phenyl-2,3-dihydro-*1H*-indazoles (5(a-i)H)

Under an inert atmosphere, $NaBH_4$ (10 mmol) was added batchwise to a solution of appropriate **5**$^+$ (2 mmol) in MeOH (20 ml) at 0 ^{o}C. After stirring for two additional hours at room temperature, the mixture was quickly quenched by water, exacted with ethyl acetate twice, and the combined organic phase was dried and evaporated under vacuum. The residue was quickly applied to silica gel column flash chromatography to give the title compound as white solid.

3-(4-methoxyphenyl)-1,2-dimethyl-2,3-dihydro-*1H*-indazole (5aH): ^{1}HNMR (CD_3CN, 400 M): δ 7.21 (d, 2H), 7.07 (t, 1H), 6.76 (d, 2H), 6.60 (m, 3H), 4.61 (s, 1H), 3.70 (s, 3H), 2.79 (s, 3H), 2.47 (s, 3H); ESI-MS/M+1 = 255.2.

1,2-dimethyl-3-(p-tolyl)-2,3-dihydro-*1H*-indazole (5bH): ^{1}HNMR (CD_3CN, 400 M): δ 7.19 (d, 2H), 7.06 (m, 3H), 6.60 (m, 2H), 4.63 (s, 1H), 2.79 (s, 3H), 2.48 (s, 3H), 2.26 (s, 3H); ESI-MS/M+1 = 239.1.

1,2-dimethyl-3-phenyl-2,3-dihydro-*1H*-indazole (5cH): ^{1}HNMR (CD_3CN, 400 M): δ 7.34 (m, 3H), 7.13 (t, 3H), 6.69 (m, 3H), 4.76 (s, 1H), 2.89 (s, 3H), 2.58 (s, 3H); ESI-MS/M+1 = 225.3; ^{13}C NMR ($CDCl_3$, 100 M):
δ 150.88, 141.43, 131.23, 128.87, 128.58, 128.24, 127.91, 123.12, 121.09, 109.99, 77.35, 42.06, 41.33; Anal. Calcd for $C_{15}H_{16}N_2$: C, 80.32; H, 7.19; N, 12.49. Found: C, 80.31; H, 7.17; N, 12.48.

3-(4-chlorophenyl)-1,2-dimethyl-2,3-dihydro-*1H*-indazole (5dH): ^{1}HNMR (CD_3CN, 400 M): δ 7.43 (brs, 4H), 7.17 (t, 1H), 6.73 (m, 3H), 4.81 (s, 1H), 2.92 (s, 3H), 2.61 (s, 3H); ESI-MS/M+1 = 259.2.

1,2-dimethyl-3-(4-(trifluoromethyl)phenyl)-2,3-dihydro-*1H*-indazole (5eH): ^{1}HNMR (CD_3CN, 400 M): δ 7.73 (d, 2H), 7.64 (d, 2H), 7.18 (t, 1H), 6.76 (m, 3H), 4.92 (s, 1H), 2.94 (s, 3H), 2.63 (s, 3H); ESI-MS/M+1 = 293.1.

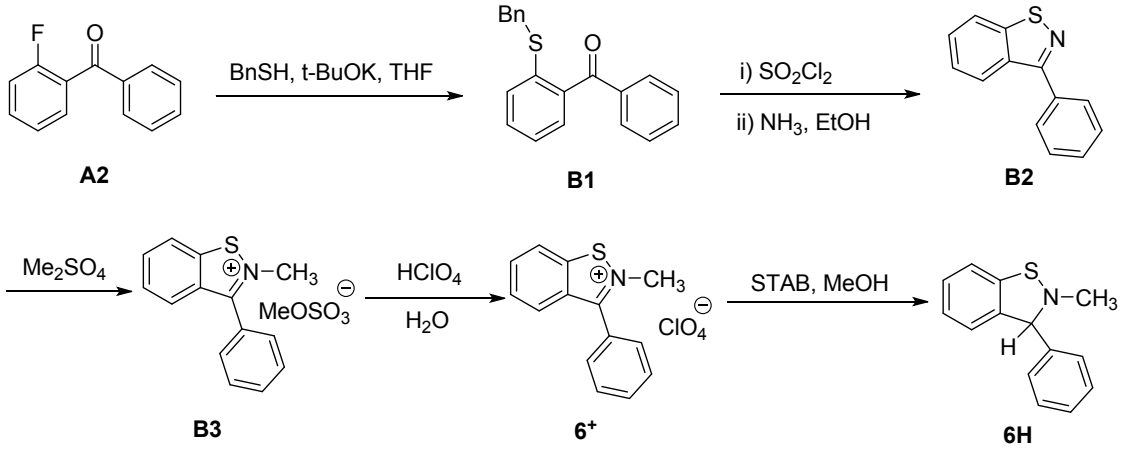
3-(3-methoxyphenyl)-1,2-dimethyl-2,3-dihydro-*1H*-indazole (5fH): ^{1}HNMR (CD_3CN, 400 M): δ 7.42 (s, 1H), 7.20 (m, 4H), 6.68 (m, 3H), 7.05 (s, 1H), 4.92 (s, 1H), 3.71 (s, 3H), 2.64 (s, 3H), 2.41 (s, 3H); ESI-MS/M+1 = 255.2.

1,2-dimethyl-3-(m-tolyl)-2,3-dihydro-*1H*-indazole (5gH): ^{1}HNMR (CD_3CN, 400 M): δ 7.11 (m, 5H), 6.62 (m, 3H), 4.63 (s, 1H), 2.79 (s, 3H), 2.48 (s, 3H), 2.08 (s, 3H); ESI-MS/M+1 = 238.9.

3-(3-chlorophenyl)-1,2-dimethyl-2,3-dihydro-*1H*-indazole (5hH): ^{1}HNMR (CD_3CN, 400 M): δ 7.53 (4H), 7.27 (t, 1H), 6.79 (m, 3H), 4.83 (s, 1H), 2.95 (s, 3H), 2.64 (s, 3H); ESI-MS/M+1 = 259.2.

1,2-dimethyl-3-(3-(trifluoromethyl)phenyl)-2,3-dihydro-*1H*-indazole (5iH): ^{1}HNMR (DMSO, 400 M): δ 8.19 (m, 4H), 7.74 (m, 1H), 7.28 (m, 3H), 5.46 (s, 1H), 3.47 (s, 3H), 3.16 (s, 3H); ESI-MS/M+1 = 293.1.

SI-2-4. Synthetic Routes of 6^+ and 6H [S2,S6]



Preparation of (2-(benzylthio)phenyl)(phenyl)methanone (B1)

Phenylmethanethiol (10 mmol) and potassium tert-butylate (6 mmol) in THF (20 ml) was stirred at room temperature for 12 hours. To the mixture was added a solution of (2-fluorophenyl)(phenyl) methanone (10 mmol) in THF, and stirred at reflux temperature for 5 hours. The mixture was quenched by chilled water and exacted with ethyl acetate twice, and the combined organic phase was dried and evaporated under vacuum. The residue was applied to silica gel column chromatography (PE : EA = 10 : 1) to give (2-(benzylthio)phenyl)(phenyl)methanone as light yellow solid.

Preparation of 3-phenylbenzo[*d*]isothiazole (B2)

(2-(benzylthio)phenyl)(phenyl)methanone (8 mmol) was dissolved in $SOCl_2$ (20 ml) and stirred at reflux temperature for 3 hours. After $SOCl_2$ was removed in vacuo, the residue was dissolved in ethanol. NH_3 (g) was bubbled into the solution for 12 h at 0 ^oC. The solvent was then evaporated under vacuum, and the residue was applied to silica gel column chromatography (PE : EA = 5 : 1) to 3-phenylbenzo[*d*]isothiazole as light yellow solid.

Preparation of 2-methyl-3-phenylbenzo[*d*]isothiazol-2-ium methyl sulfate (B3)

2-methyl-3-phenylbenzo[*d*]isothiazol-2-ium methyl sulfate (5 mmol) was dissolved in dimethyl sulfate (20 ml). The mixture was stirred at 130 ^oC overnight. After cooling down to room temperature, dimethyl sulfate (highly toxic) was carefully evaporated in vacuo, and the residue was directly used in next step.

Preparation of 2-methyl-3-phenylbenzo[*d*]isothiazol-2-ium perchlorate (6^+)

2-methyl-3-phenylbenzo[*d*]isothiazol-2-ium methyl sulfate was suspended in a dilute solution of $HClO_4$, and stirred overnight at room temperature to yield perchlorate salt as a precipitate. The perchlorate salt was collected by filtration and recrystallized from ethanol to give the title compound as a white solid.

$6^+ClO_4^-$:

^{1}HNMR (CD_3CN, 400 M): δ 8.38 (d, 1H), 8.04 (m, 2H), 7.78 (m, 6H), 4.16 (s, 3H); ESI-MS/M-99 = 226.2; Anal. Calcd for $C_{14}H_{12}N_2O_4SCl$: C, 51.62; H, 3.71; N, 4.30. Found: C, 51.60; H,

3.70; N, 4.31.

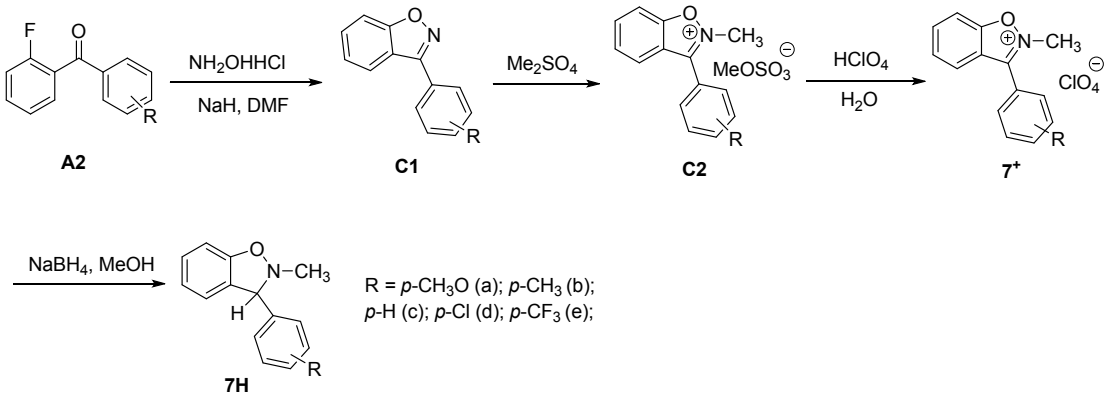
Preparation of substituted 2-methyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole (6H)

Under an inert atmosphere, STAB (6 mmol) was added batchwise to a solution of 2-methyl-3-phenylbenzo[d]isothiazol-2-ium perchlorate (5 mmol) in MeOH (15 ml) at 0 °C. After stirring for 30 min at 0 °C, the mixture was quickly quenched by cold water, exacted with ethyl acetate, and dried over Na_2SO_4 and evaporated under vacuum. The residue was quickly applied to a flash chromatography to give the title compound as yellowish solid, which was stored in fridge under an inert atmosphere.

6H:

^{1}HNMR (CD_3CN, 400 M): δ 7.25 (m, 5H), 7.12 (m, 2H), 6.78 (m, 2H), 4.98 (s, 1H), 2.85 (s, 3H); ESI-MS/M-99 = 228.0; Anal. Calcd for $C_{14}H_{13}NS$: C, 73.97; H, 5.76; N, 6.16. Found: C, 73.96; H, 5.78; N, 6.15.

SI-2-5. Synthetic Routes of 7^+ and 7H [S2,S6]



Preparation of 3-phenylbenzo[*d*]isoxazole (C1)

Into a mixture of appropriate (2-fluorophenyl)(phenyl)methanol (10 mmol) and Hydroxylamine hydrochloride (10 mmol) in DMF (20 ml) was added Sodium hydride (25 mmol) at 0 °C. After stirring at the same temperature for 30 min, the reaction was quenched by chilled water, exacted with ethyl acetate twice, and the combined organic phase was dried and evaporated under vacuum. The residue was applied to silica gel column chromatography (PE : EA = 5 : 1) to give the title compound as white solid.

Preparation of 2-methyl-3-phenylbenzo[*d*]isoxazol-2-ium methyl sulfate (C2)

Appropriate 3-phenylbenzo[*d*]isoxazole (8 mmol) was dissolved in dimethyl sulfate (20 ml). The mixture was stirred at 130 °C overnight. After cooling down to room temperature, dimethyl sulfate (highly toxic) was carefully evaporated in vacuo, and the residue was directly used in next step.

Preparation of 2-methyl-3-phenylbenzo[*d*]isoxazol-2-ium perchlorate (7^+)

Appropriate 2-methyl-3-phenylbenzo[*d*]isoxazol-2-ium methyl sulfate was suspended in a dilute solution of $HClO_4$, and stirred overnight at room temperature to yield its perchlorate salt as a precipitate. The perchlorate salt was collected by filtration and recrystallized from ethanol to give the title compound as white solid.

3-(4-methoxyphenyl)-2-methylbenzo[*d*]isoxazol-2-ium perchlorate (7a$^+$): ^{1}HNMR (CD_3CN, 400 M): δ 8.15 (m, 2H), 7.92 (m, 3H), 7.79 (m, 1H), 7.36 (m, 1H), 4.45 (s, 3H), 4.00 (s, 3H); ESI-MS/M-99 = 240.3.

2-methyl-3-(p-tolyl)benzo[*d*]isoxazol-2-ium perchlorate (7b$^+$): ^{1}HNMR (CD_3CN, 400 M): δ 8.20 (m, 2H), 8.13 (m, 1H), 7.84 (m, 3H), 7.68 (m, 2H), 4.45 (s, 3H), 2.58 (s, 3H); ESI-MS/M-99 = 223.9.

2-methyl-3-phenylbenzo[*d*]isoxazol-2-ium perchlorate (7c$^+$): ^{1}HNMR (CD_3CN, 400 M): δ 8.22 (m, 1H), 8.20 (m, 1H), 8.11 (m, 1H), 7.92 (m, 3H), 7.84 (m, 3H), 4.46 (s, 3H); ESI-MS/M-99 = 210.2; ^{13}C NMR (DMSO, 100 M): δ 159.23, 155.45, 137.81, 134.30, 130.83, 130.47, 128.69, 125.59, 121.95, 119.91, 110.97, 40.83; Anal. Calcd for $C_{14}H_{12}NO_5Cl$: C, 54.29; H, 3.91; N, 4.52. Found: C, 54.28; H, 3.90; N, 4.51.

3-(4-chlorophenyl)-2-methylbenzo[*d*]isoxazol-2-ium perchlorate (7d$^+$): ^{1}HNMR (CD_3CN, 400 M): δ 8.10 (m, 1H), 7.99 (m, 1H), 7.88 (m, 1H), 7.75 (m, 5H), 4.34 (s, 3H); ESI-MS/M-99 = 244.3.

2-methyl-3-(4-(trifluoromethyl)phenyl)benzo[*d*]isoxazol-2-ium perchlorate (7e$^+$): ^{1}HNMR (CD_3CN, 400 M): δ 8.05 (m, 7H), 7.75 (m, 1H), 4.35 (s, 3H); ESI-MS/M-99 = 277.9.

Preparation of substituted 2-methyl-3-phenyl-2,3-dihydrobenzo[*d*]isoxazole (7H)

Under an inert atmosphere, $NaBH_4$ (6 mmol) was added batchwise to a solution of appropriate 2-methyl-3-phenylbenzo[*d*]isoxazol-2-ium perchlorate (4 mmol) in MeOH (20 ml) at 0 ^{o}C. After stirring for 30 min at 0 ^{o}C, the mixture was quenched by water, exacted with ethyl acetate, and dried over Na_2SO_4 and evaporated under vacuum. The residue was applied to silica gel column chromatography to give 0.5 g title compound as white solid.

3-(4-methoxyphenyl)-2-methyl-2,3-dihydrobenzo[*d*]isoxazole (7aH): ^{1}HNMR (CD_3CN, 400 M): δ 7.23 (m, 3H), 7.01 (m, 1H), 6.91 (m, 3H), 6.84 (m, 1H), 5.16 (s, 1H), 3.77 (s, 3H), 2.89 (s, 3H); ESI-MS/M+1 = 242.2.

2-methyl-3-(p-tolyl)-2,3-dihydrobenzo[*d*]isoxazole (7bH): ^{1}HNMR (CD_3CN, 400 M): δ 7.19 (m, 5H), 7.03 (m, 1H), 6.90 (m, 1H), 6.83 (m, 1H), 5.17 (s, 1H), 2.89 (s, 3H), 2.31 (s, 3H); ESI-MS/M+1 = 226.3.

2-methyl-3-phenyl-2,3-dihydrobenzo[*d*]isoxazole (7cH): ^{1}HNMR (CD_3CN, 400 M): δ 7.35 (m, 5H), 7.22 (m, 1H), 7.06 (m, 1H), 6.91 (m, 1H), 6.85 (m, 1H), 5.22 (s, 1H), 2.91 (s, 3H); ESI-MS/M+1 = 211.9; Anal. Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.58; H, 6.18; N, 6.62.

3-(4-chlorophenyl)-2-methyl-2,3-dihydrobenzo[*d*]isoxazole (7dH): ^{1}HNMR (CD_3CN, 400 M): δ 7.36 (m, 4H), 7.23 (m, 1H), 7.09 (m, 1H), 6.93 (m, 1H), 6.85 (m, 1H), 5.23 (s, 1H), 2.90 (s, 3H); ESI-MS/M+1 = 246.2.

2-methyl-3-(4-(trifluoromethyl)phenyl)-2,3-dihydrobenzo[*d*]isoxazole (7eH): ^{1}HNMR (CD_3 CN, 400 M): δ 7.66 (m, 4H), 7.24 (m, 1H), 7.13 (m, 1H), 6.94 (m, 1H), 6.88 (m, 1H), 5.33 (s, 1H), 2.93 (s, 3H); ESI-MS/M+1 = 280.3.

SI-3. References

S1 B. S. Furniss, A. J. Hannaford, P. W. Smith, A. R. Tatchell, *Vogel's textbook of pratical organic chemistry*, 5th ed, **1989**, Lasercomp Times New Roman.

S2 R. J. Steffan, E. Matelan, M. A. Ashwell, W. J. Moore, W. R. Solvibile, T E. rybulski, C. C. Chadwick, S. Chippari, T. Kenney, A. Eckert, L. Marcucci, J. C. Keith, Z. Xu, L. Mosyak, D. C. Harnish, *J. Med. Chem.* **2004**, *47*, 6435.

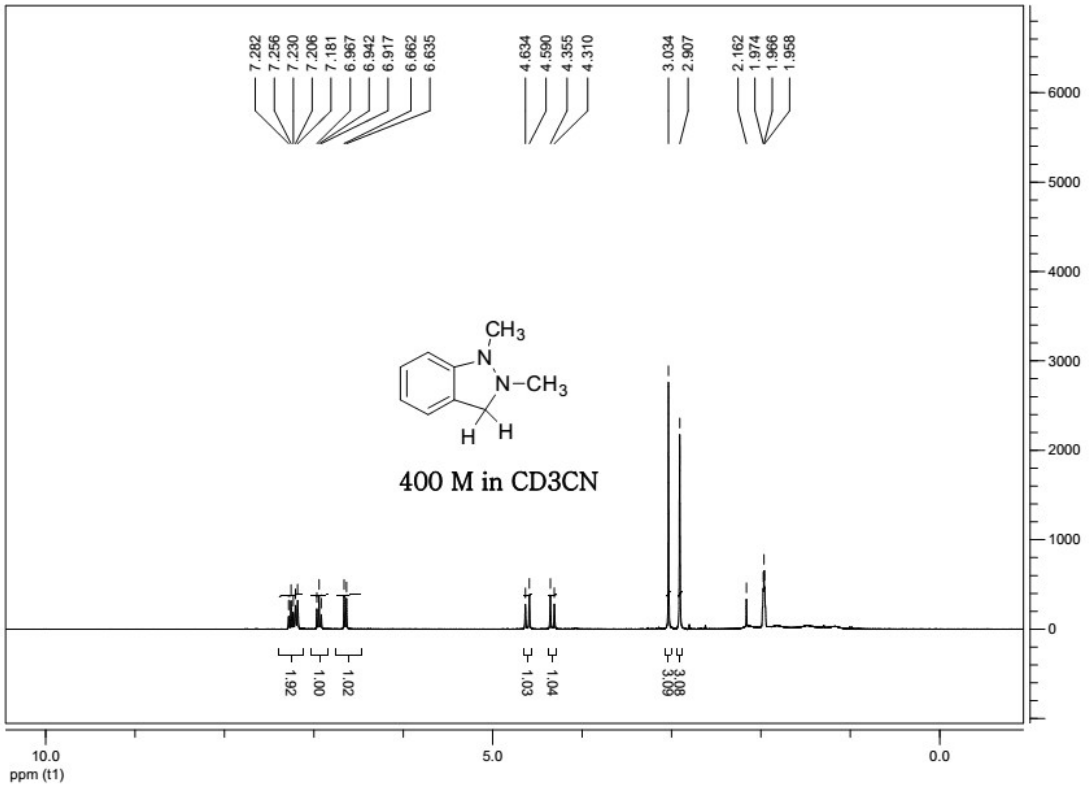
S3 A. Schmidt, B. Snovydovych, T. Habeck, P. Dröttboom, M. Gjikaj, A. Adam, *Eur. J. Org. Chem.* **2007**, 4909-4916.

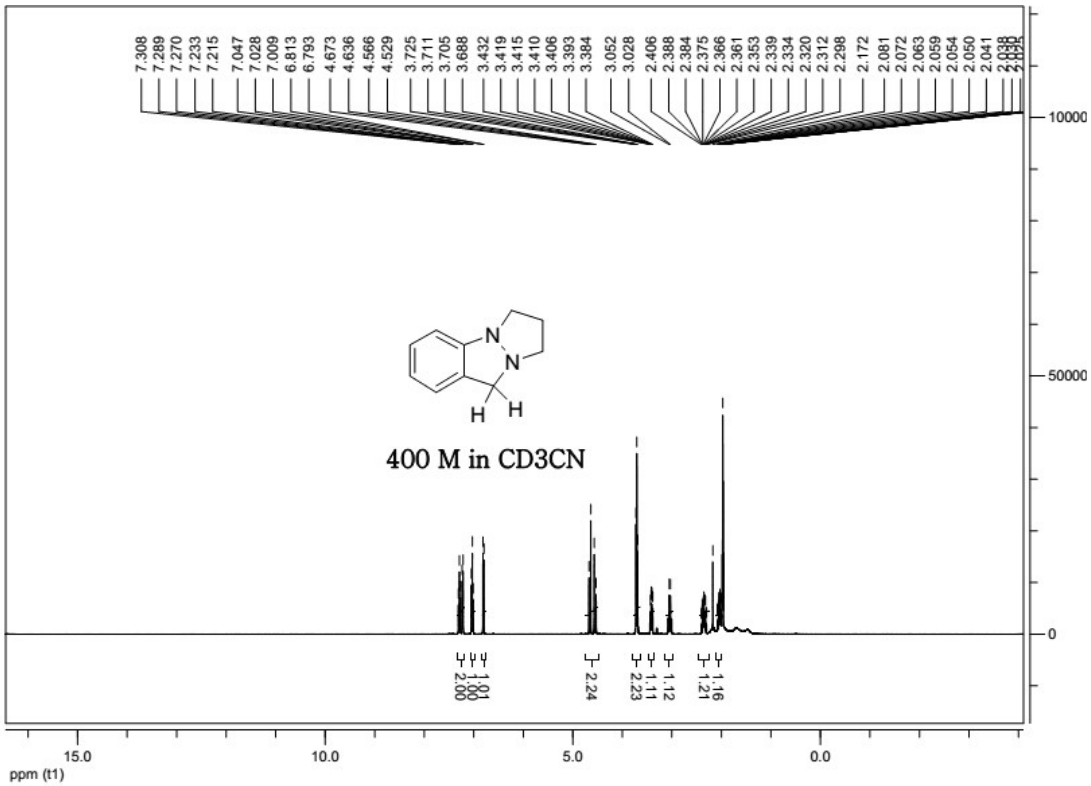
S4 J. Yang, P. Gharagozloo, *Syn. Commun.*, **2005**, *35(3)*, 409-415.

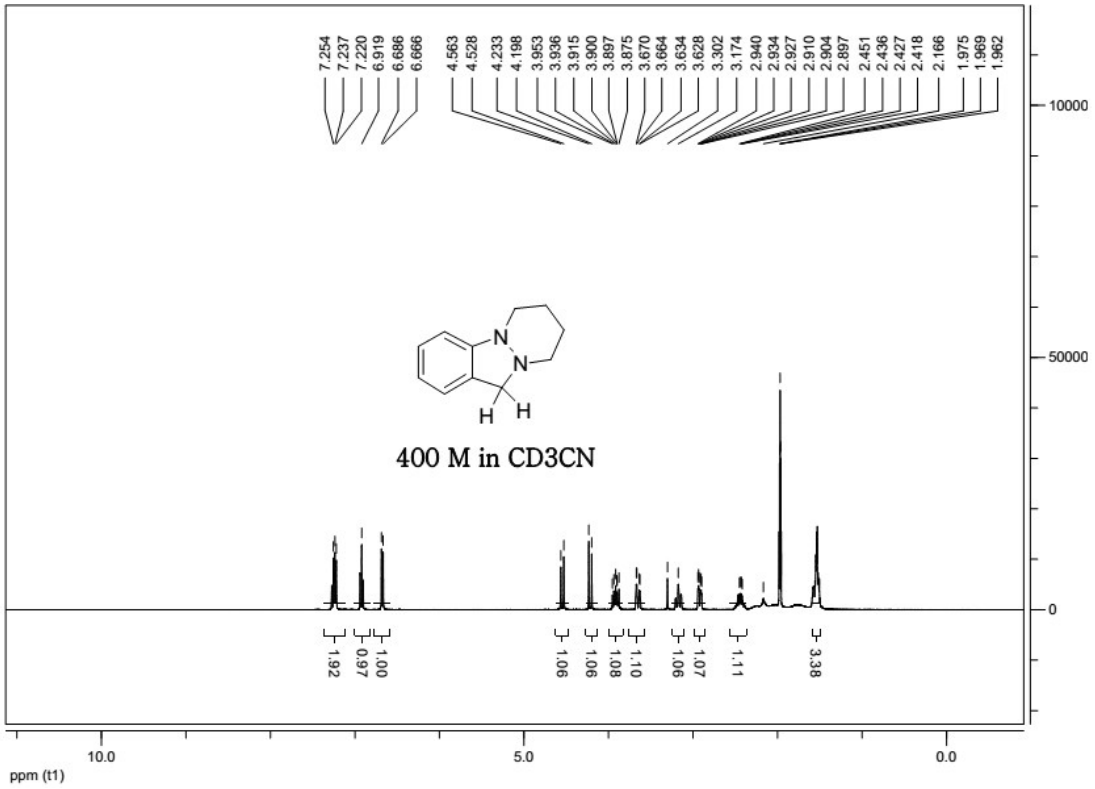
S5 Z. N. Timofeeva, M. V. Petrova, M. Z. Girshovich, A. V. El'tsov, *Zhurnal Obshchei Khimii*, **1969**, *39*, 54-59.

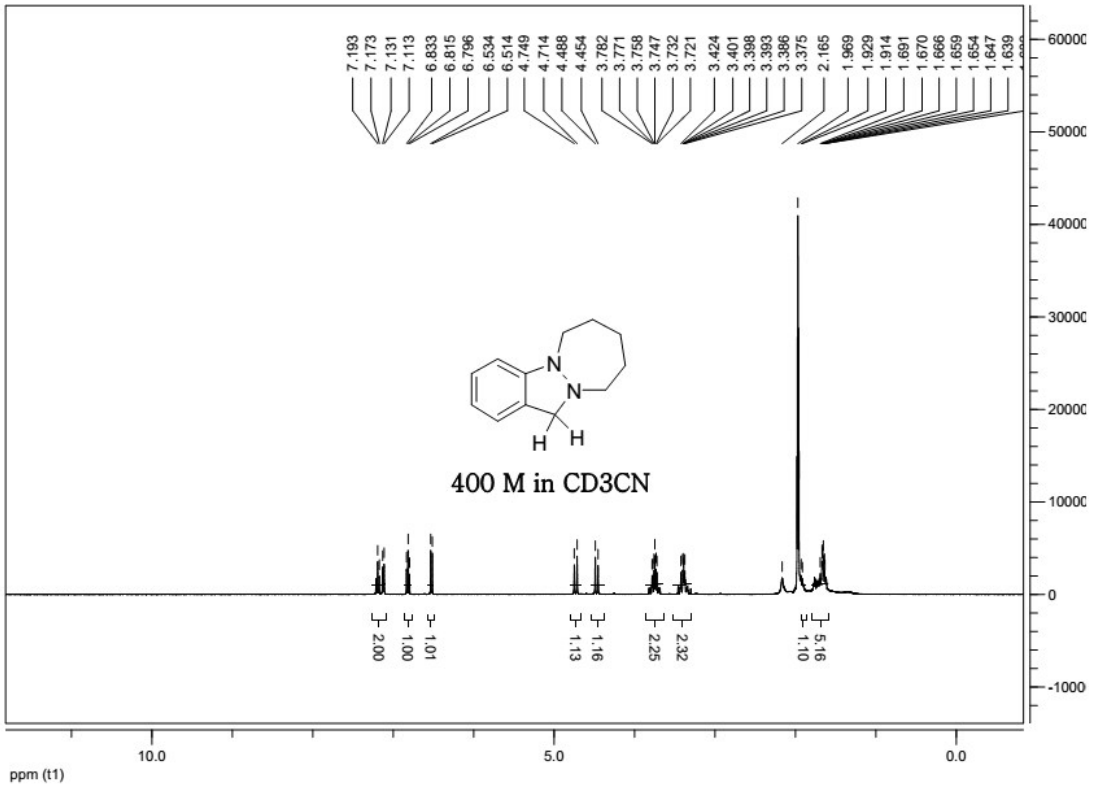
S6 T. Kitamura, M Todaka, I. Shin-machi, Y. Fujiwara, *Heterocycl. Commun.* **1998**, *4(3)*, 205-208.

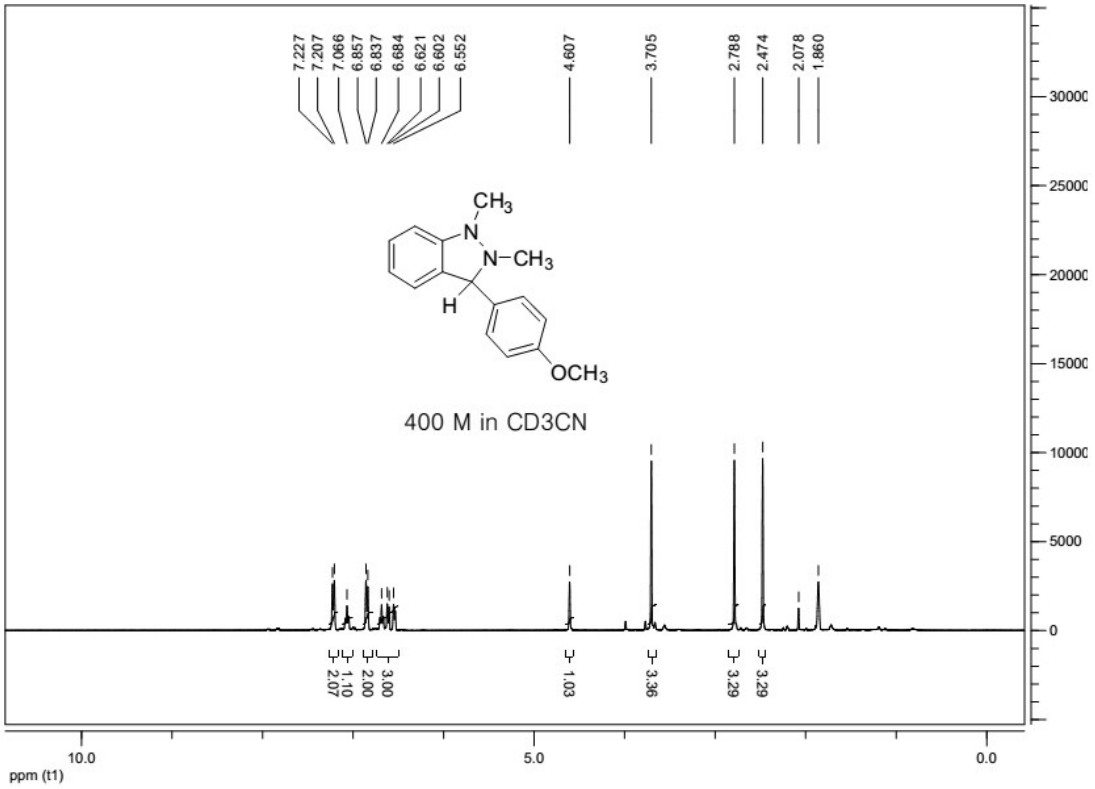
SI-4. Copies of the Typical ^{1}H NMR, ^{13}C NMR Spectra of X^{+} and XH

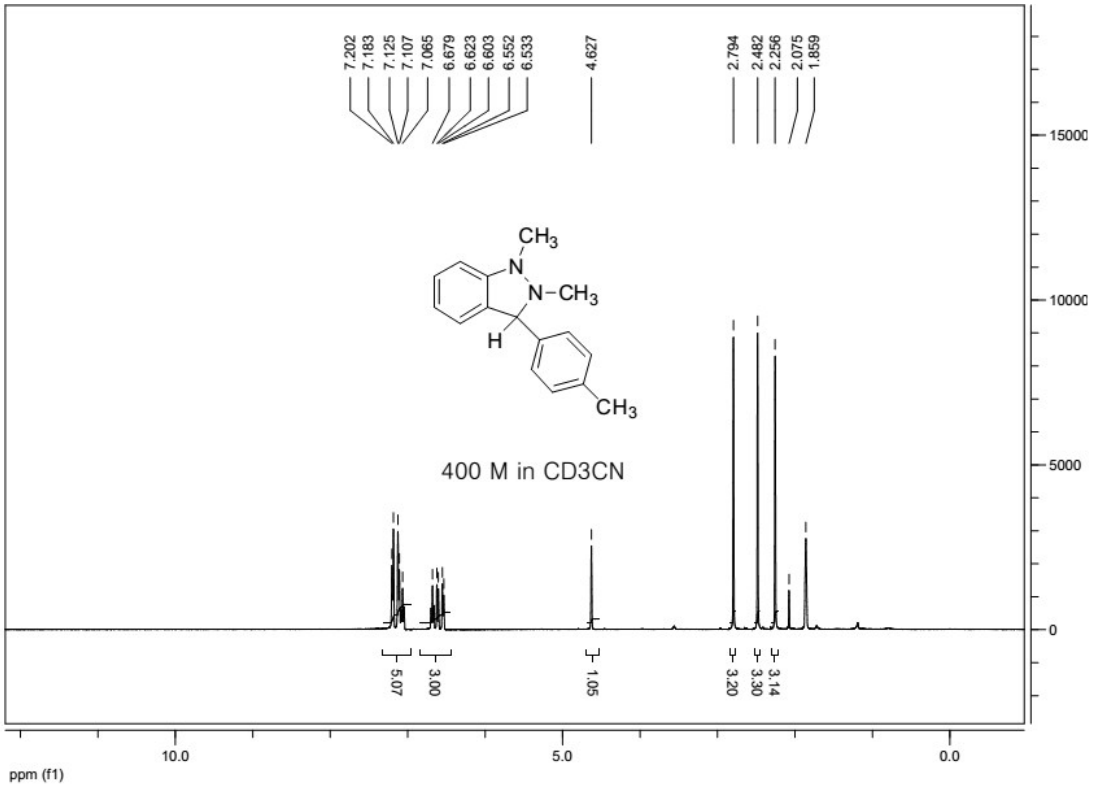


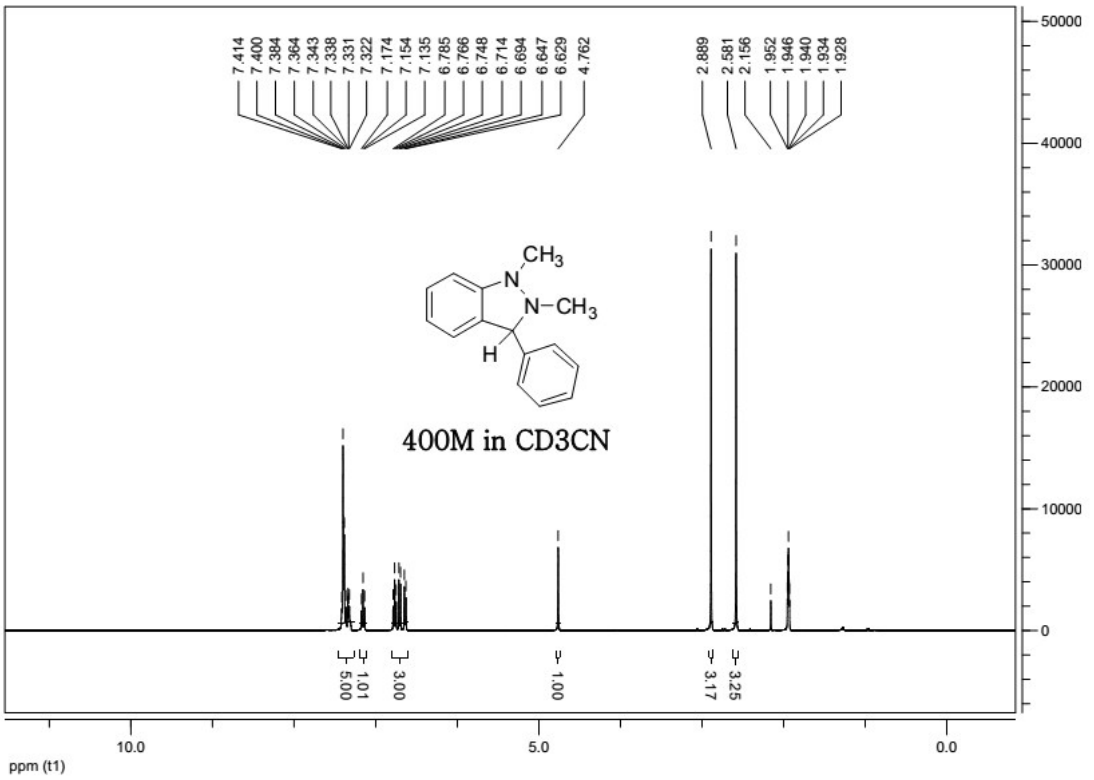


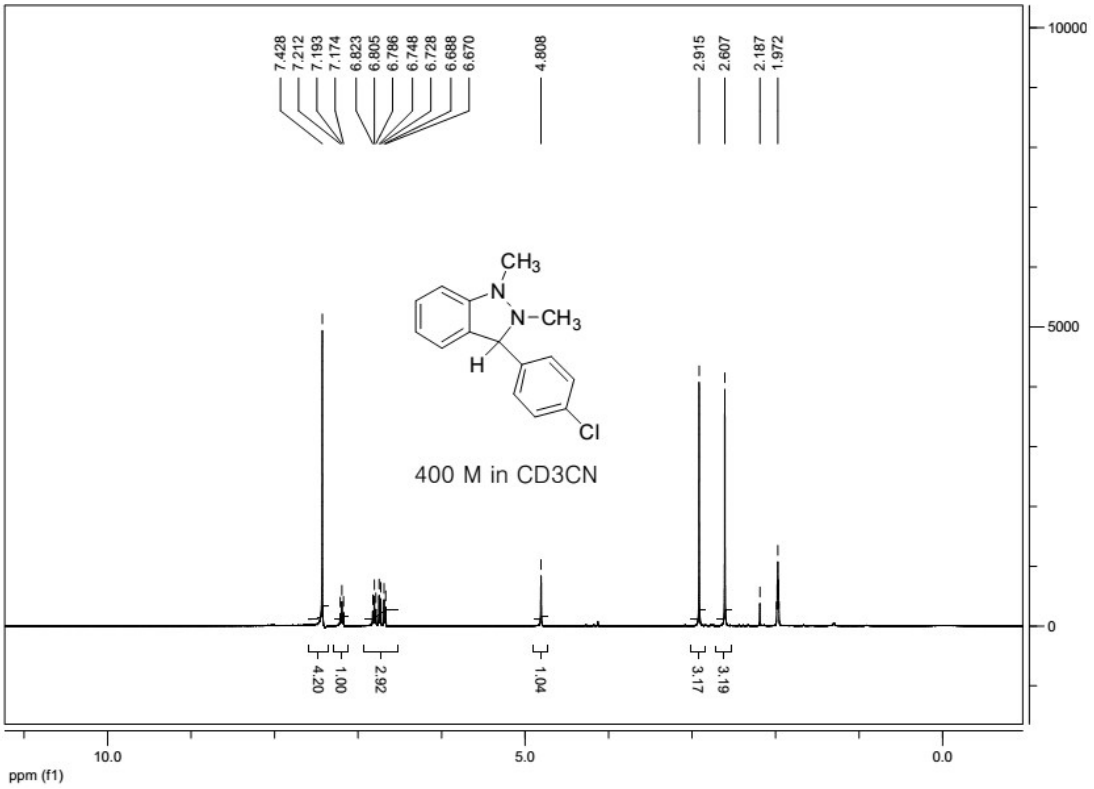

7.254
7.237
7.220
6.919
6.686
6.666
4.563
4.528
4.233
4.198
3.953
3.936
3.915
3.900
3.897
3.875
3.670
3.664
3.634
3.628
3.302
3.174
2.940
2.934
2.927
2.910
2.904
2.897
2.451
2.436
2.427
2.418
2.166
1.975
1.969
1.962
10000
50000
0
N
N
H
H
400 M in CD3CN
1.92
0.97
1.00
1.06
1.06
1.08
1.10
1.06
1.07
1.11
3.38
10.0
5.0
0.0
ppm (t1)

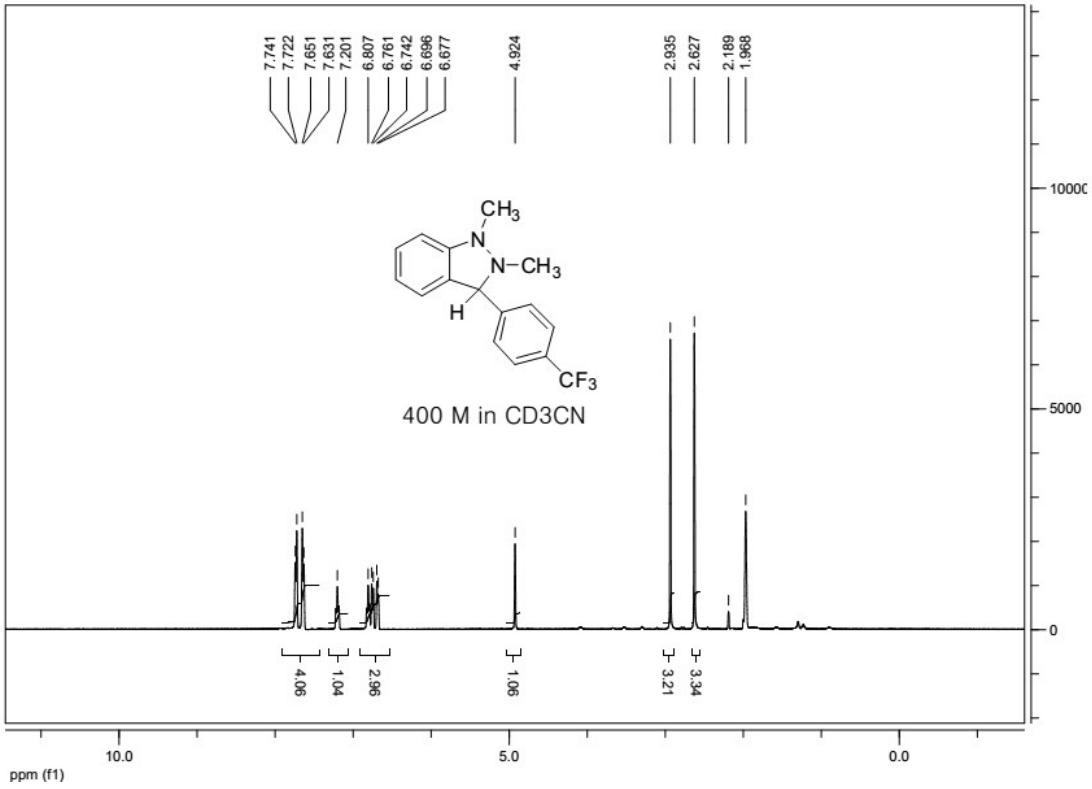

7.193
7.173
7.131
7.113
6.833
6.815
6.796
6.534
6.514
4.749
4.714
4.488
4.454
3.782
3.771
3.758
3.747
3.732
3.721
3.424
3.401
3.398
3.393
3.386
3.375
2.165
1.969
1.929
1.914
1.691
1.670
1.666
1.659
1.654
1.647
1.639
60000
50000
40000
30000
20000
10000
0
-1000
N
N
H
H
400 M in CD3CN
2.00
1.00
1.01
1.13
1.16
2.25
2.32
1.10
5.16
10.0
5.0
0.0
ppm (t1)

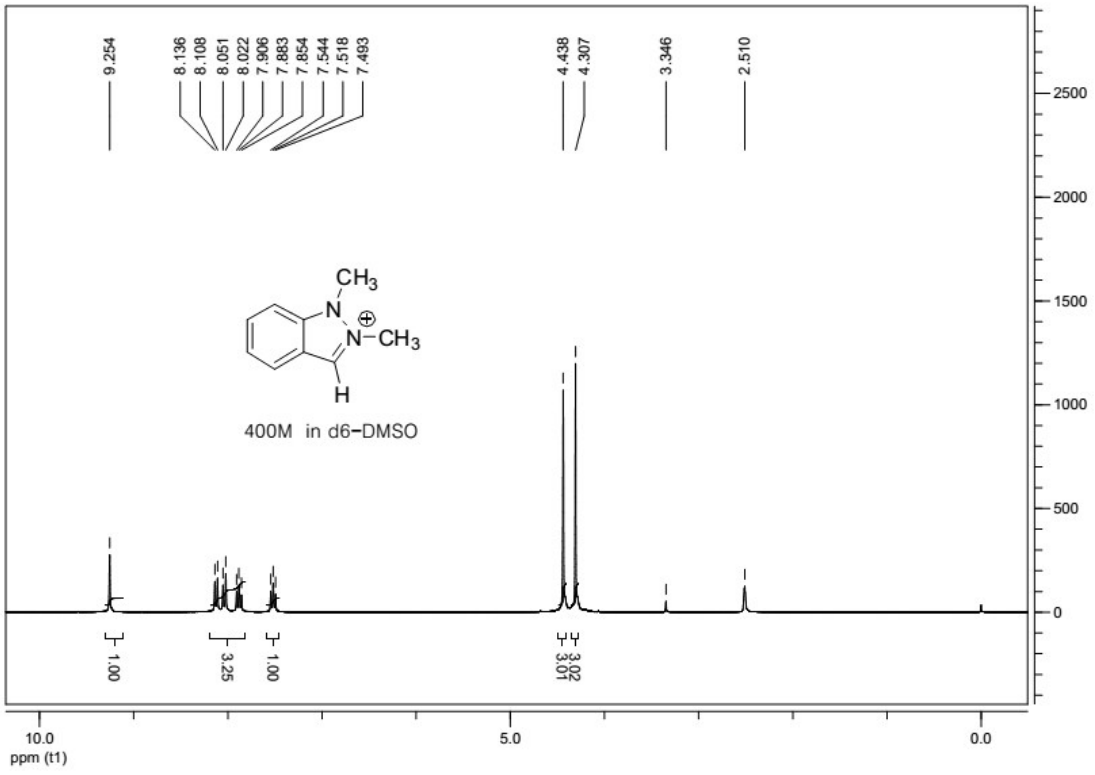

7.227
7.207
7.066
6.857
6.837
6.684
6.621
6.602
6.552
4.607
3.705
2.788
2.474
2.078
1.860
CH3
N
N−CH3
H
OCH3
400 M in CD3CN
2.07
1.10
2.00
3.00
1.03
3.36
3.29
3.29
10.0
5.0
0.0
ppm (t1)

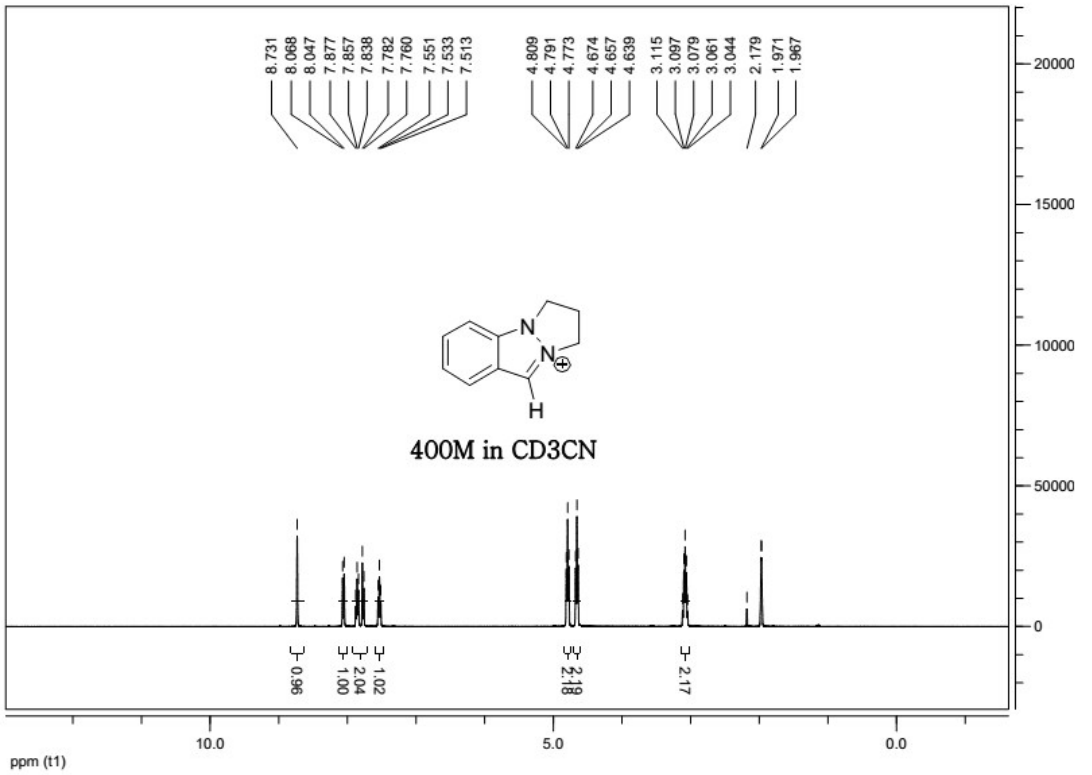

7.202
7.183
7.125
7.107
7.065
6.679
6.623
6.603
6.552
6.533
4.627
2.764
2.482
2.256
2.075
1.859
CH3
N
N−CH3
H
CH3
400 M in CD3CN
5.07
3.00
1.05
3.20
3.30
3.14
10.0
5.0
0.0
ppm (f1)

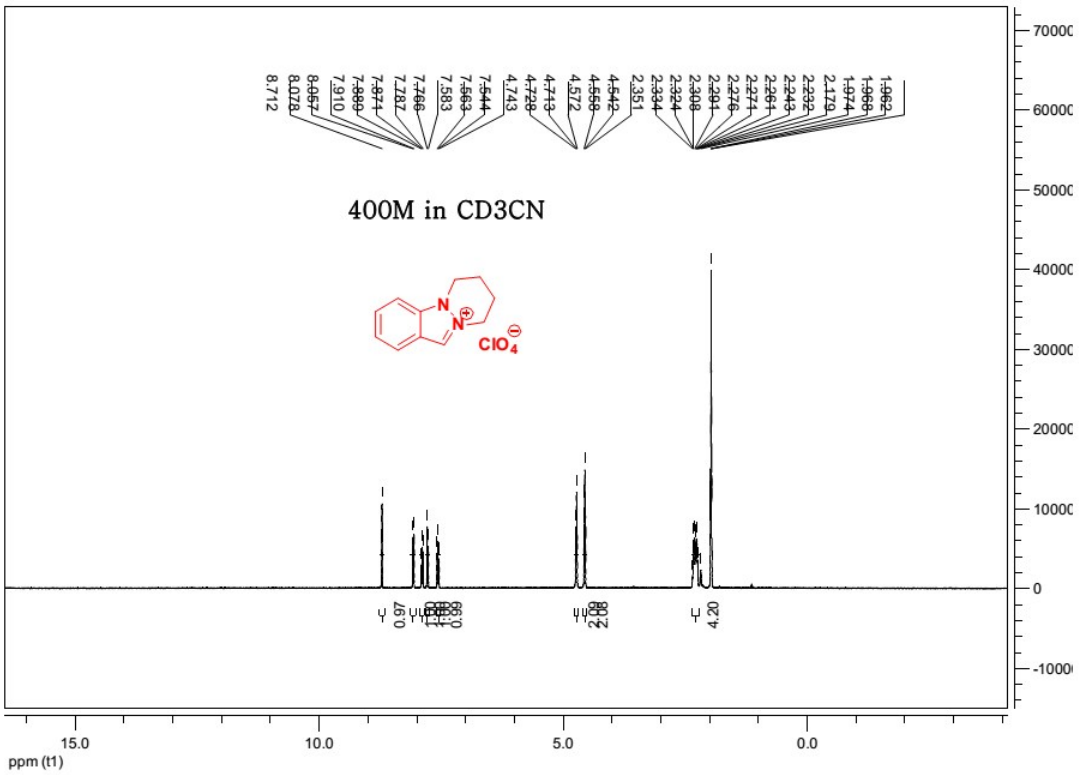

7.414
7.400
7.384
7.364
7.343
7.338
7.331
7.322
7.174
7.154
7.135
6.785
6.766
6.748
6.714
6.694
6.647
6.629
4.762
2.889
2.581
2.156
1.952
1.946
1.940
1.934
1.928
CH3
N
N−CH3
H
400M in CD3CN
5.00
1.01
3.00
1.00
3.17
3.25
50000
40000
30000
20000
10000
0
10.0
5.0
0.0
ppm (t1)

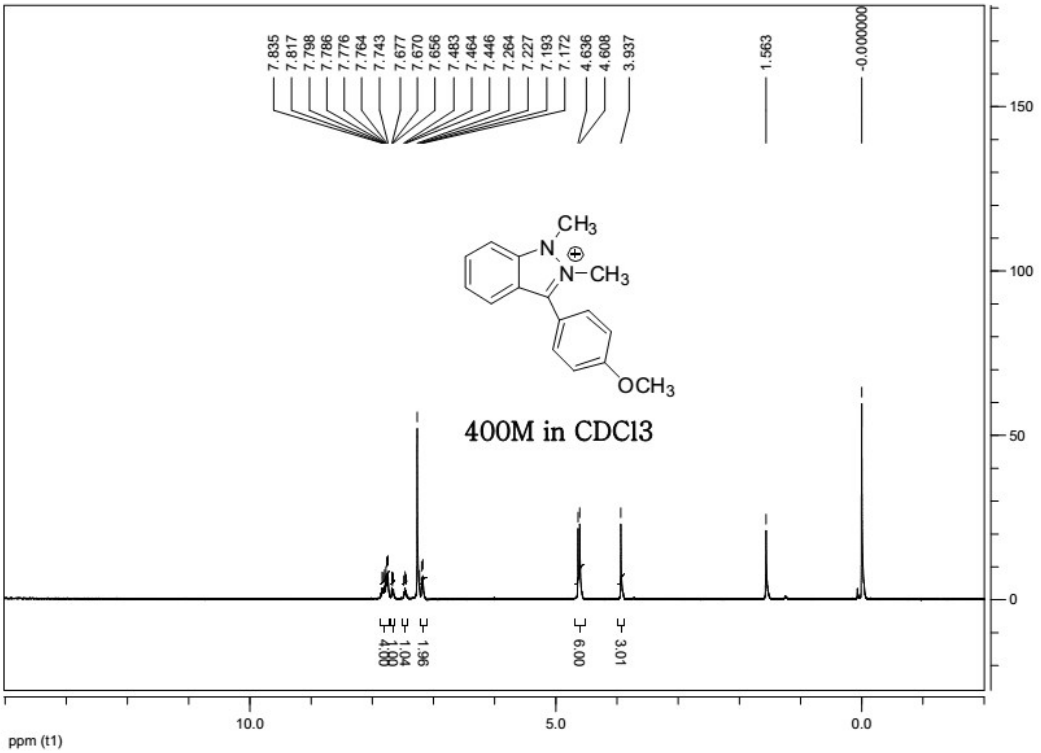

7.428
7.212
7.193
7.174
6.823
6.805
6.786
6.748
6.728
6.688
6.670
4.808
2.915
2.607
2.187
1.972
CH3
N
N−CH3
H
Cl
400 M in CD3CN
4.20
1.00
2.92
1.04
3.17
3.19
10000
5000
0
10.0
5.0
0.0
ppm (f1)

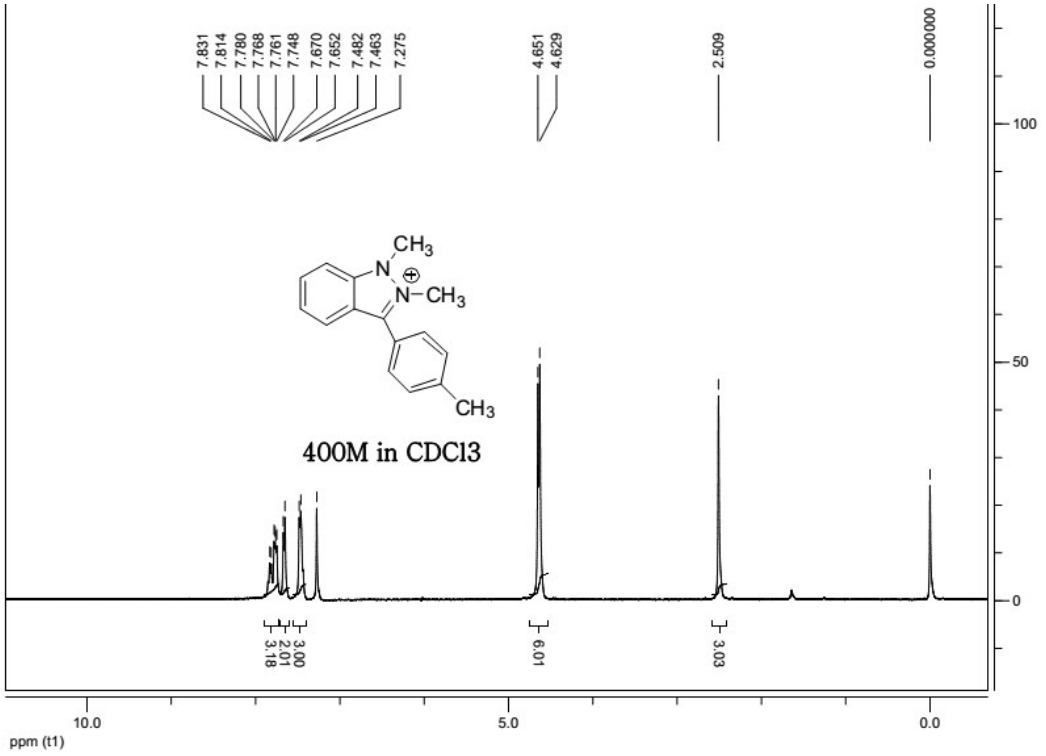

7.741
7.722
7.651
7.631
7.201
6.807
6.761
6.742
6.696
6.677
4.924
2.935
2.627
2.189
1.968
CH3
N
N−CH3
H
CF3
400 M in CD3CN
4.96
1.04
2.96
1.06
3.21
3.34
10000
5000
0
10.0
5.0
0.0
ppm (f1)

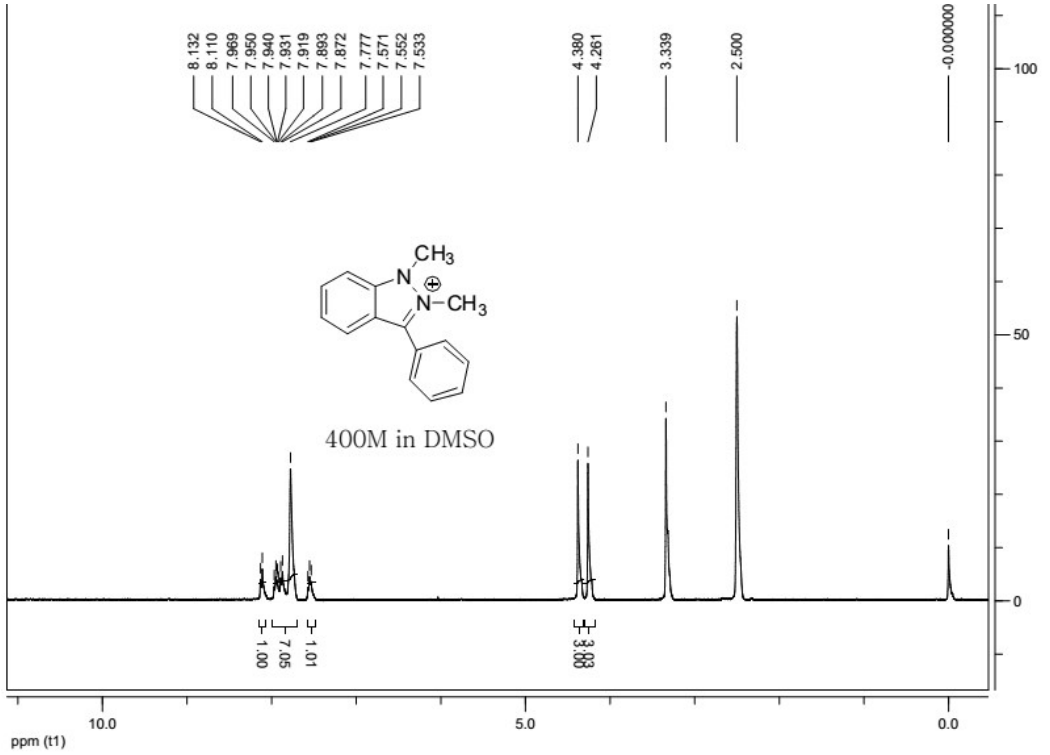

9.254
8.136
8.108
8.051
8.022
7.906
7.883
7.854
7.544
7.518
7.493
4.438
4.307
3.346
2.510
CH3
N
N−CH3
H
400M in d6−DMSO
1.00
3.25
1.00
3.02
3.01
2500
2000
1500
1000
500
0
10.0
5.0
0.0
ppm (t1)

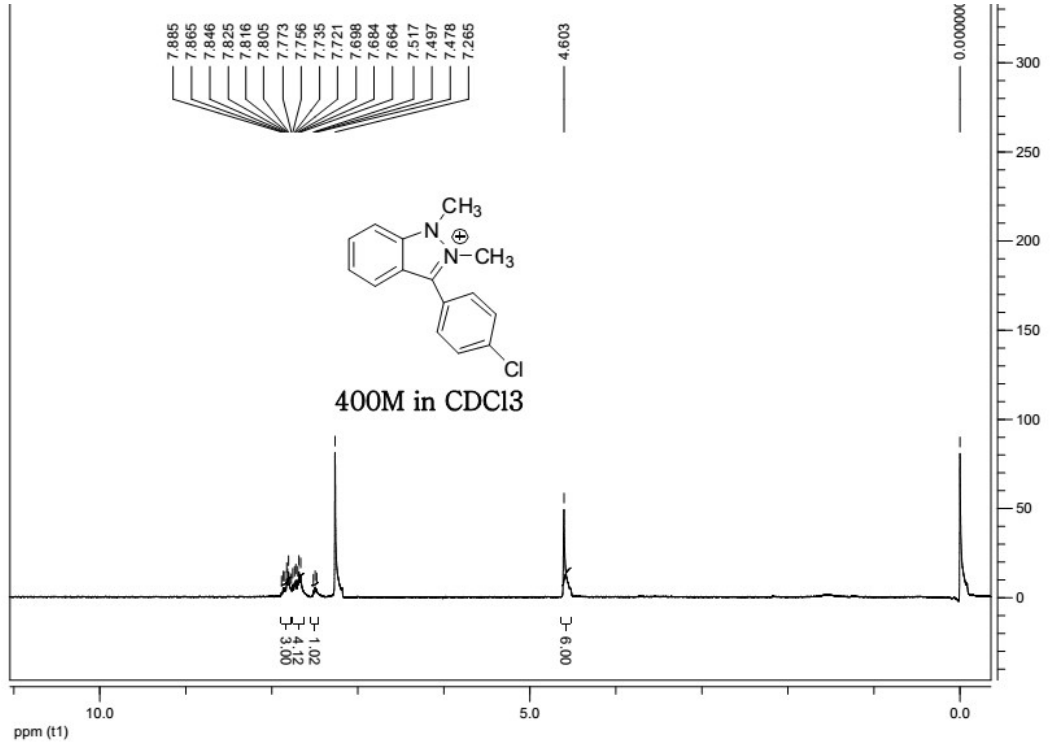

8.731
8.068
8.047
7.877
7.857
7.838
7.782
7.760
7.551
7.533
7.513
4.809
4.791
4.773
4.674
4.657
4.639
3.115
3.097
3.079
3.061
3.044
2.179
1.971
1.967
400M in CD3CN
0.96
1.00
2.04
1.02
2.18
2.18
2.17
ppm (t1)

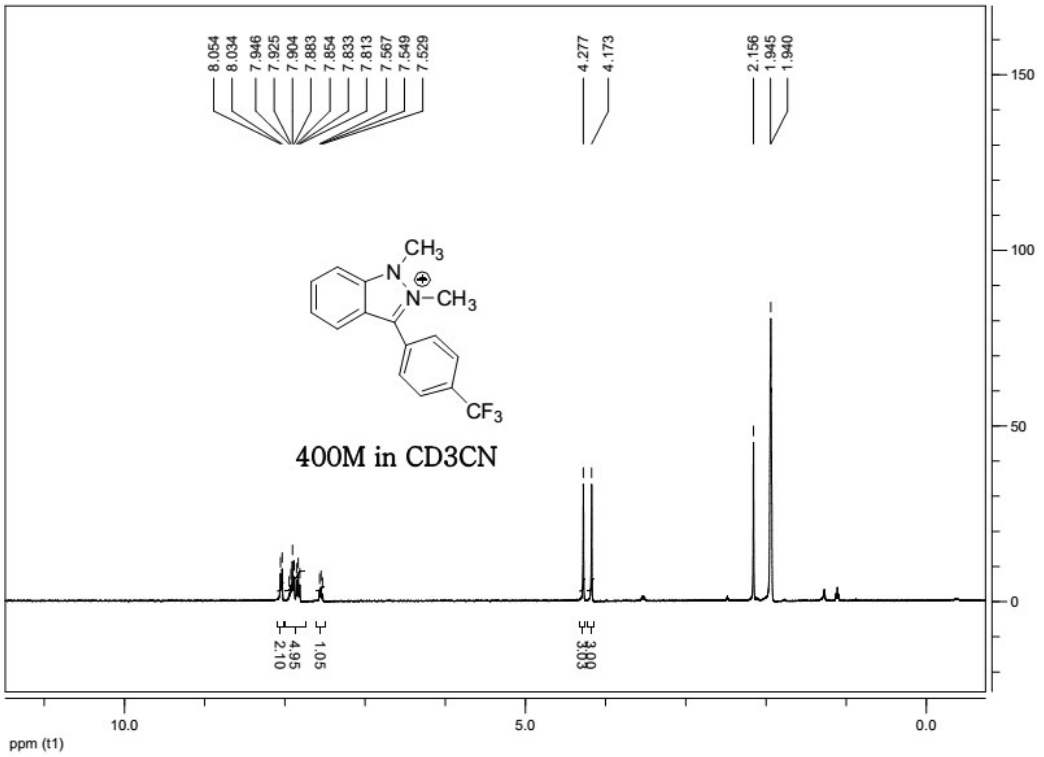

8.712
8.078
8.067
7.910
7.889
7.871
7.787
7.766
7.583
7.563
7.544
4.743
4.728
4.713
4.572
4.558
4.542
2.351
2.334
2.324
2.308
2.291
2.276
2.271
2.261
2.243
2.232
2.179
1.974
1.968
1.962
400M in CD3CN
ClO4
ppm (t1)

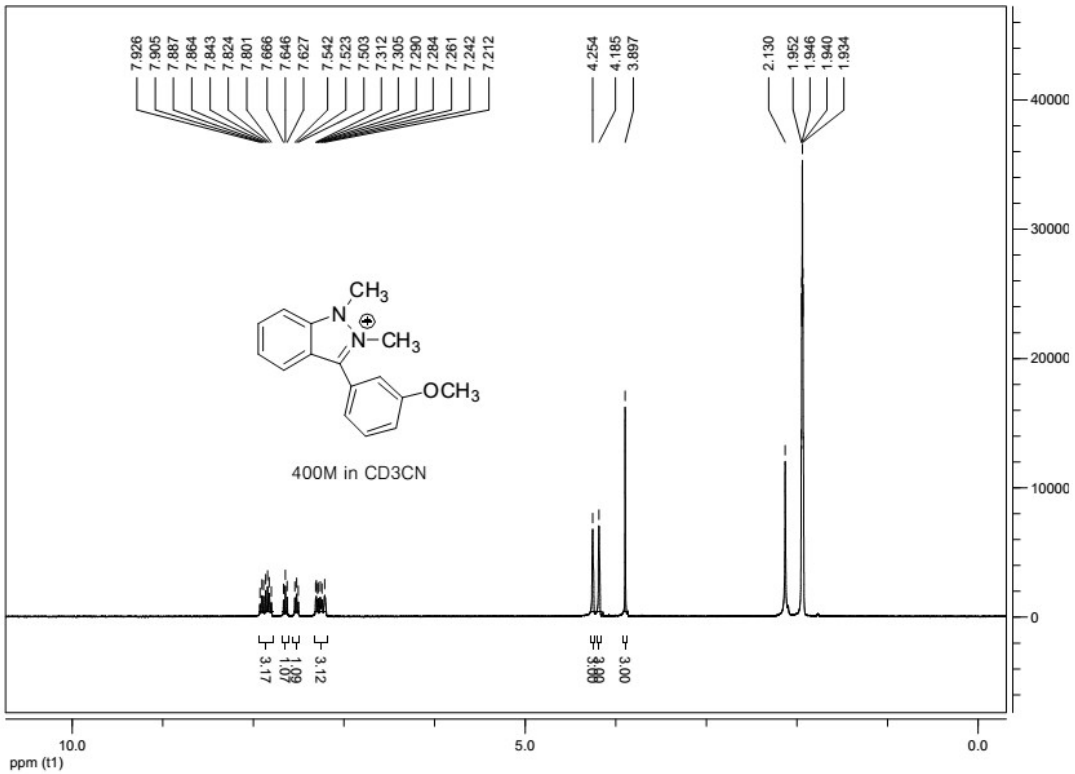

7.835
7.817
7.798
7.786
7.776
7.764
7.743
7.677
7.670
7.656
7.483
7.464
7.446
7.264
7.227
7.193
7.172
4.636
4.608
3.937
1.563
-0.000000
CH3
N
N−CH3
OCH3
400M in CDCl3
1.88
1.48
1.04
1.96
6.00
3.01
150
100
50
0
10.0
5.0
0.0
ppm (t1)

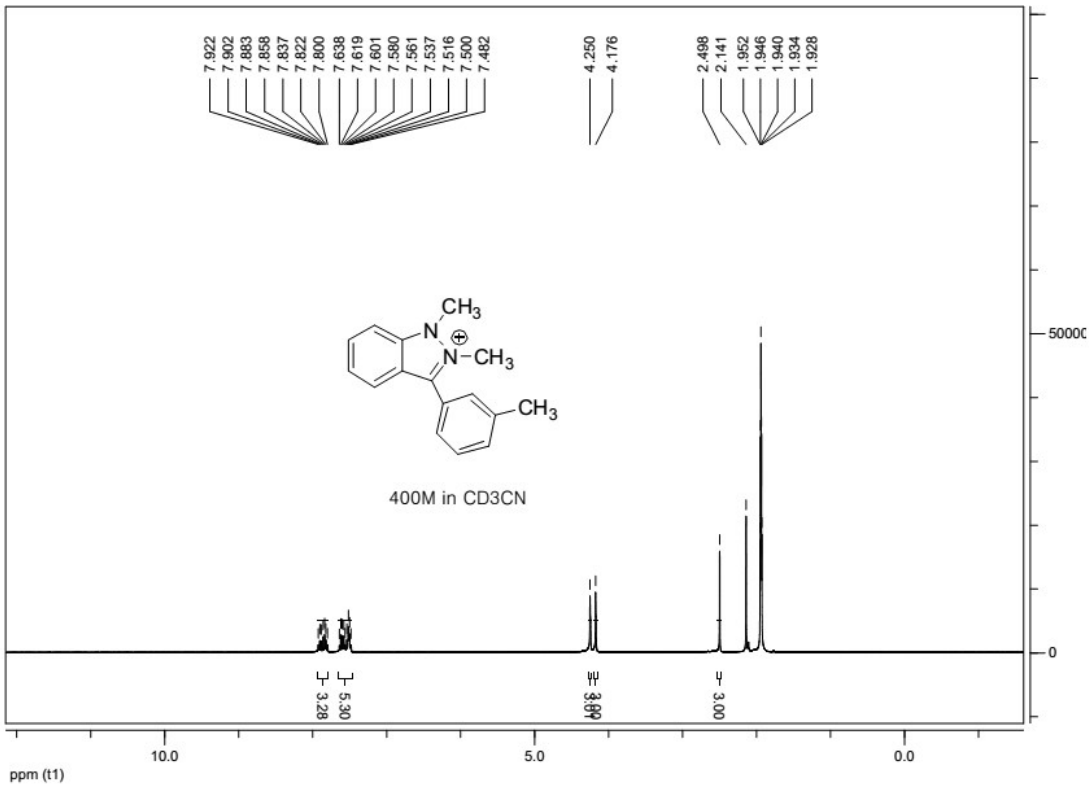

7.831
7.814
7.780
7.768
7.761
7.748
7.670
7.652
7.482
7.463
7.275
4.651
4.629
2.509
0.000000
CH3
N
N−CH3
CH3
400M in CDCl3
3.18
2.01
3.00
6.01
3.03
100
50
0
10.0
5.0
0.0
ppm (t1)

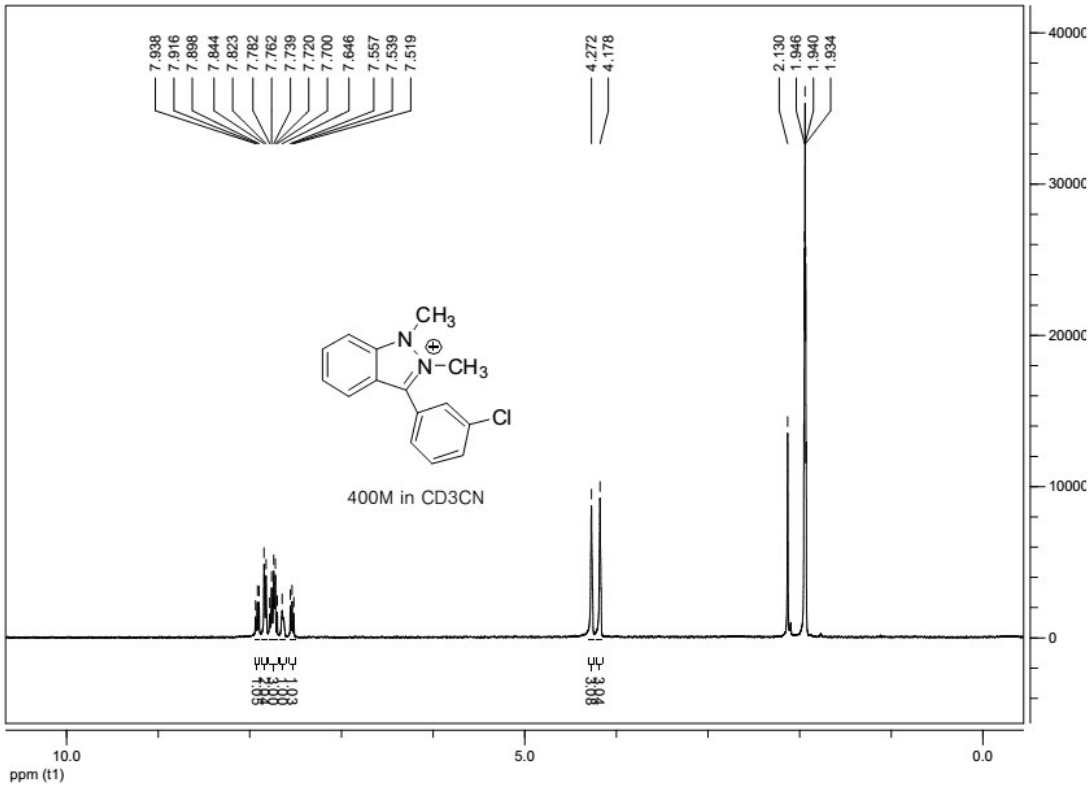

8.132
8.110
7.969
7.950
7.940
7.931
7.919
7.893
7.872
7.777
7.571
7.552
7.533
4.380
4.261
3.339
2.500
-0.000000
CH3
N
N−CH3
400M in DMSO
1.00
7.05
1.01
3.00
3.03
100
50
0
10.0
5.0
0.0
ppm (t1)

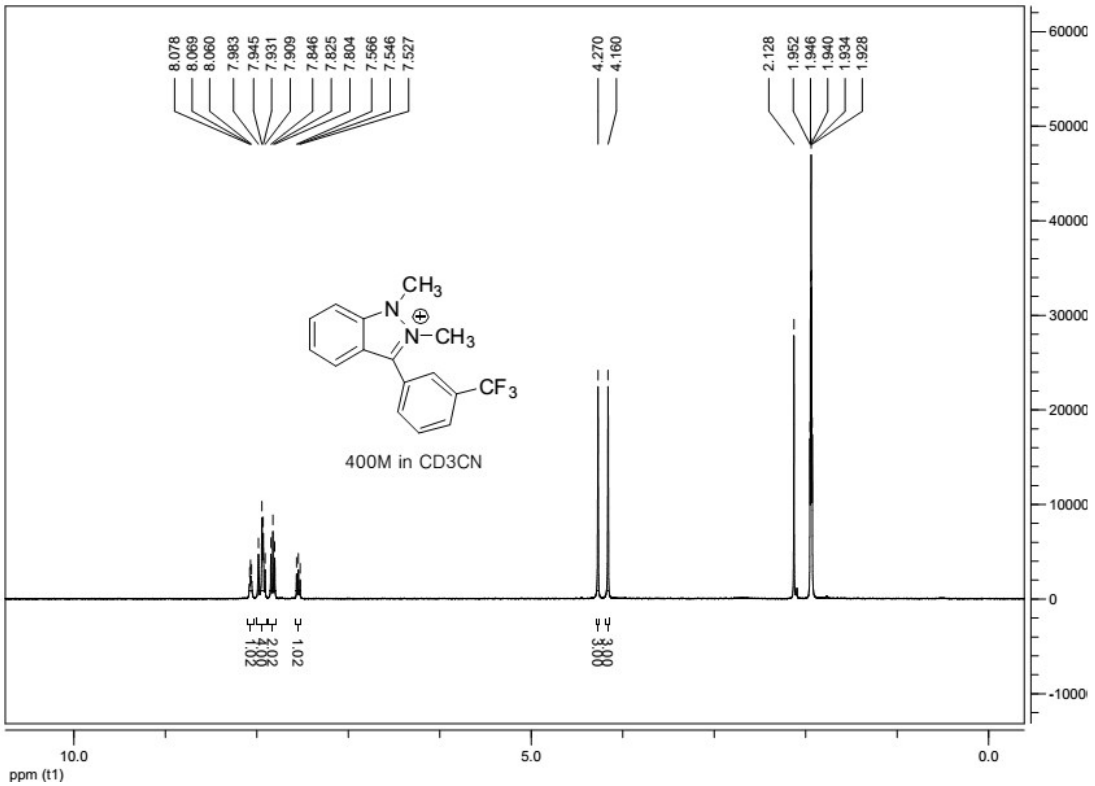

7.885
7.865
7.846
7.825
7.816
7.805
7.773
7.756
7.735
7.721
7.698
7.684
7.664
7.517
7.497
7.478
7.265
4.603
0.000000
CH3
N
N−CH3
Cl
400M in CDCl3
3.00
4.12
1.02
6.00
300
250
200
150
100
50
0
10.0
5.0
0.0
ppm (t1)

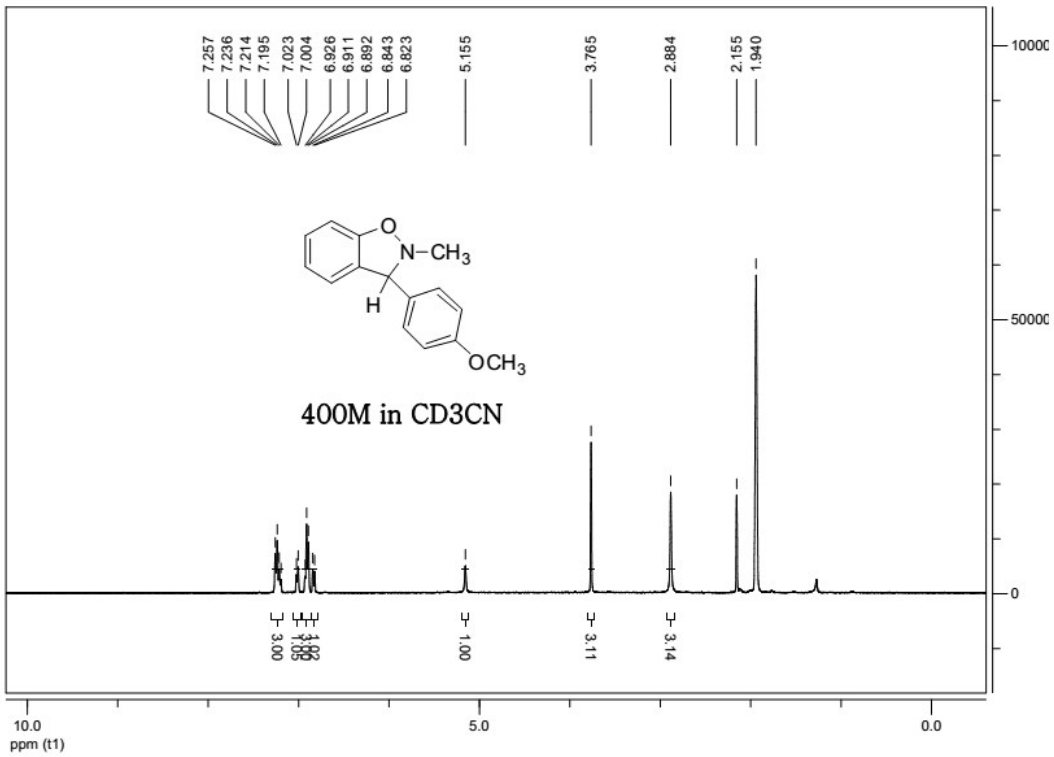

8.054
8.034
7.946
7.925
7.904
7.883
7.854
7.833
7.813
7.567
7.549
7.529
4.277
4.173
2.156
1.945
1.940
CH3
N
N−CH3
CF3
400M in CD3CN
2.10
4.95
1.05
3.00
3.03
150
100
50
0
10.0
5.0
0.0
ppm (t1)

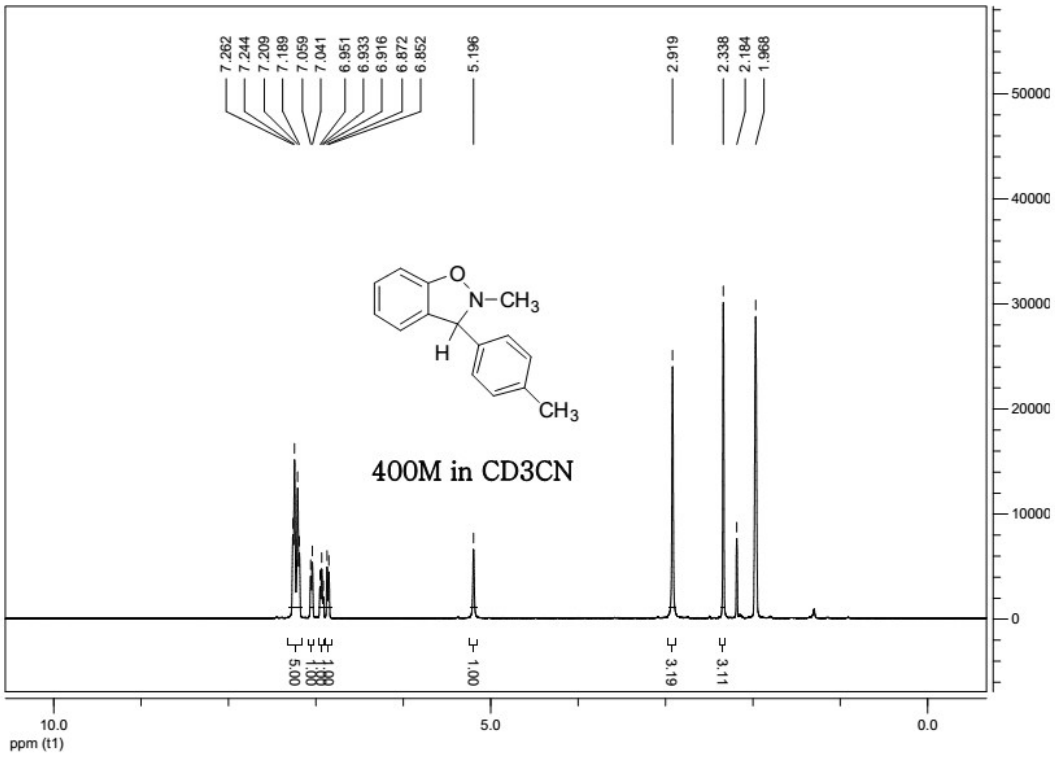

7.926
7.905
7.887
7.864
7.843
7.824
7.801
7.666
7.646
7.627
7.542
7.523
7.503
7.312
7.305
7.290
7.284
7.261
7.242
7.212
4.254
4.185
3.897
2.130
1.952
1.946
1.940
1.934
CH3
N
N−CH3
OCH3
400M in CD3CN
3.17
1.09
1.07
3.12
3.00
40000
30000
20000
10000
0
10.0
5.0
0.0
ppm (t1)

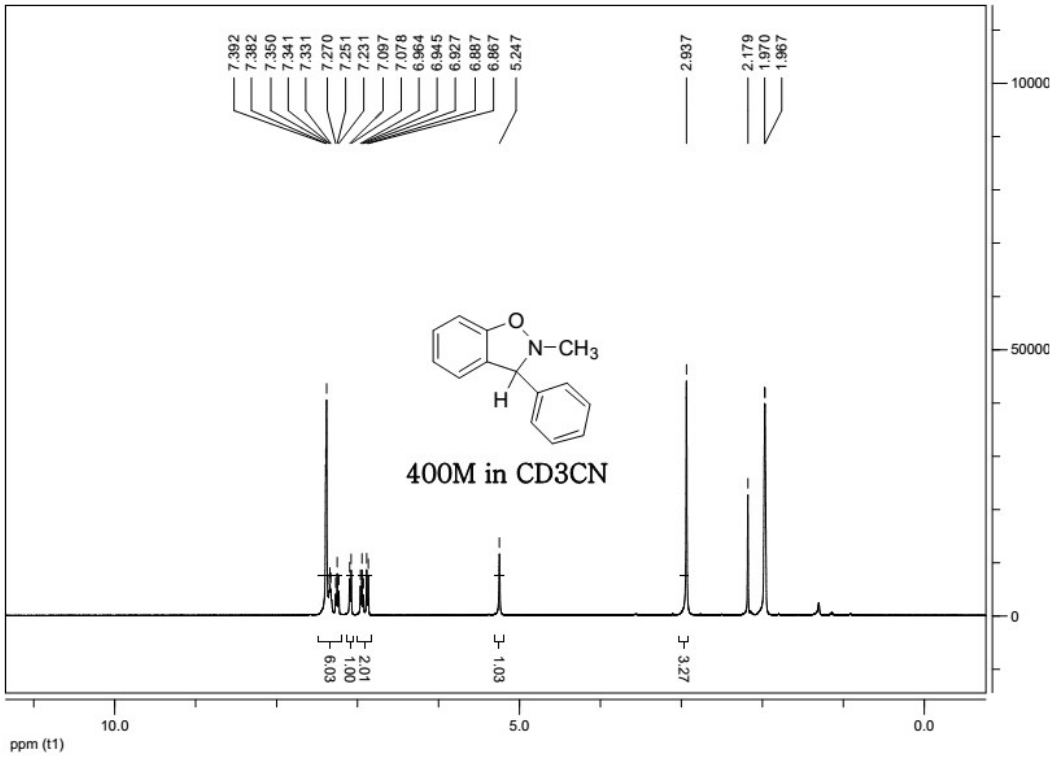

7.922
7.902
7.883
7.858
7.837
7.822
7.800
7.638
7.619
7.601
7.580
7.561
7.537
7.516
7.500
7.482
4.250
4.176
2.498
2.141
1.952
1.946
1.940
1.934
1.928
CH3
N
N−CH3
CH3
400M in CD3CN
3.28
5.30
3.00
3.00
10.0
5.0
0.0
ppm (t1)

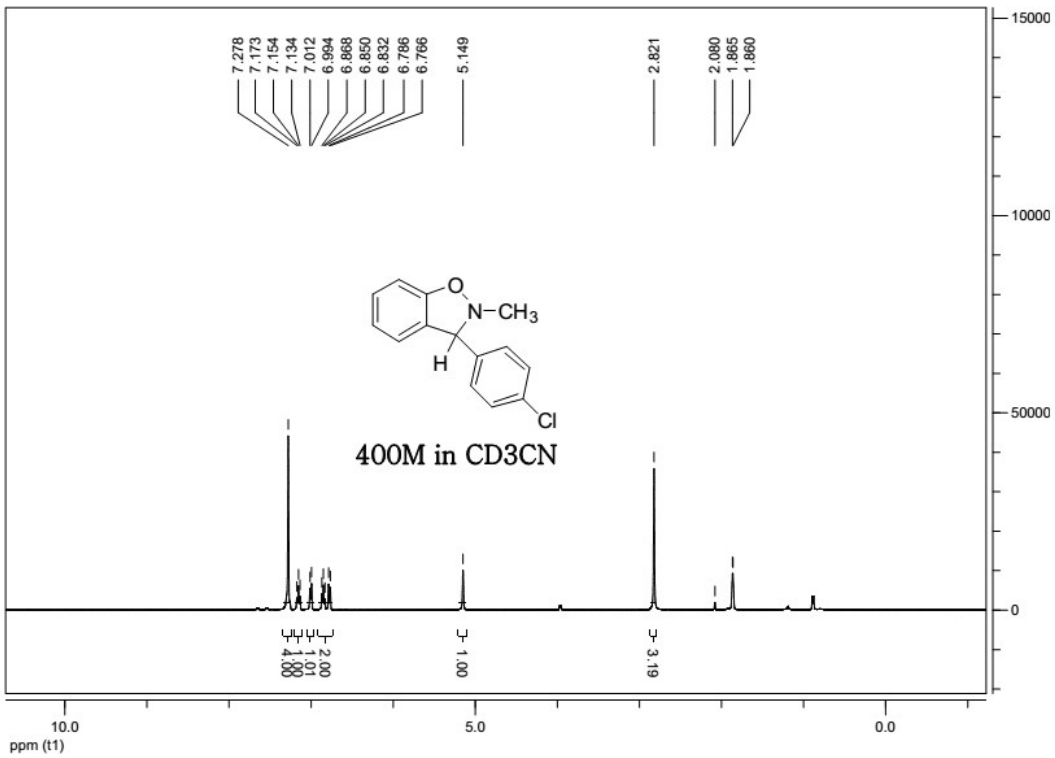

7.938
7.916
7.898
7.844
7.823
7.782
7.762
7.739
7.720
7.700
7.646
7.557
7.539
7.519
4.272
4.178
2.130
1.946
1.940
1.934
CH3
N
N−CH3
Cl
400M in CD3CN
3.08
10.0
5.0
0.0
ppm (t1)

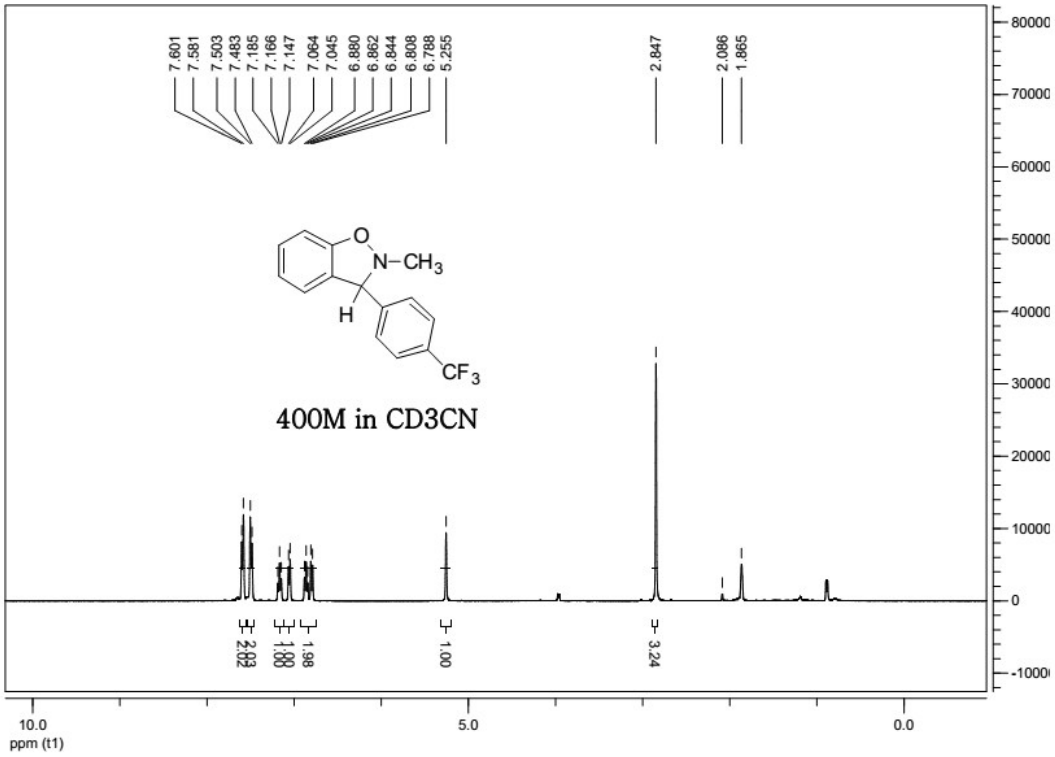

8.078
8.069
8.060
7.983
7.945
7.931
7.909
7.846
7.825
7.804
7.566
7.546
7.527
4.270
4.160
2.128
1.952
1.946
1.940
1.934
1.928
CH3
N
N−CH3
CF3
400M in CD3CN
1.02
3.00
10.0
5.0
0.0
ppm (t1)

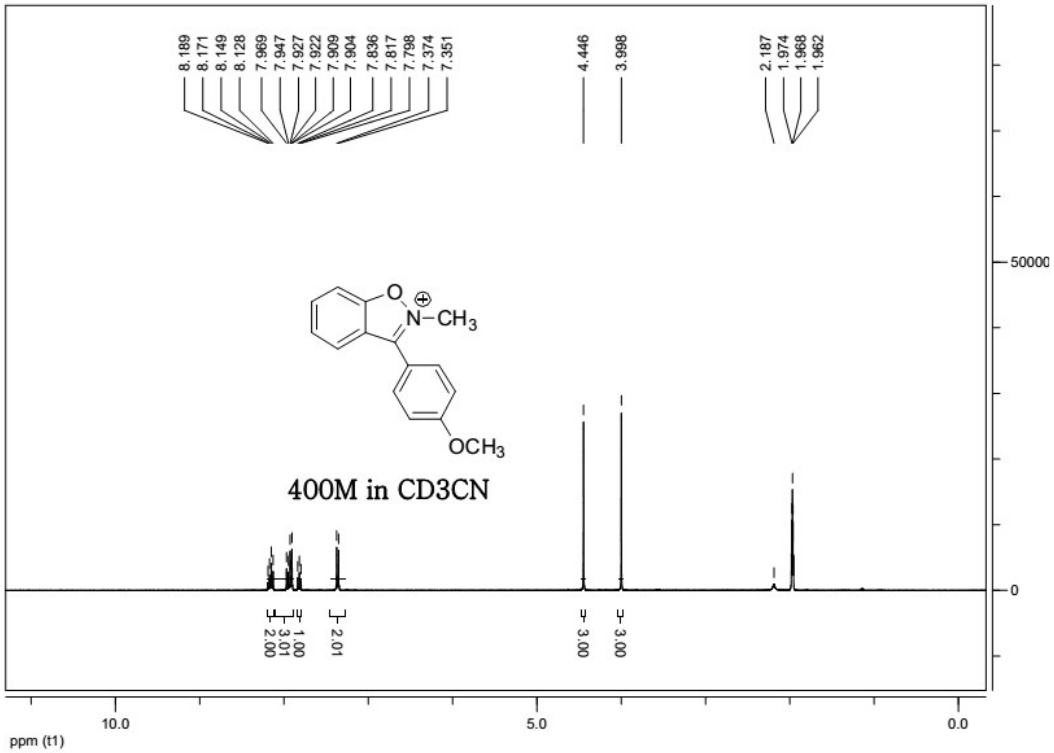

7.257
7.236
7.214
7.195
7.023
7.004
6.926
6.911
6.892
6.843
6.823
5.155
3.765
2.884
2.155
1.940
O
N−CH3
H
OCH3
400M in CD3CN
3.00
1.00
3.11
3.14
10.0
5.0
0.0
ppm (t1)

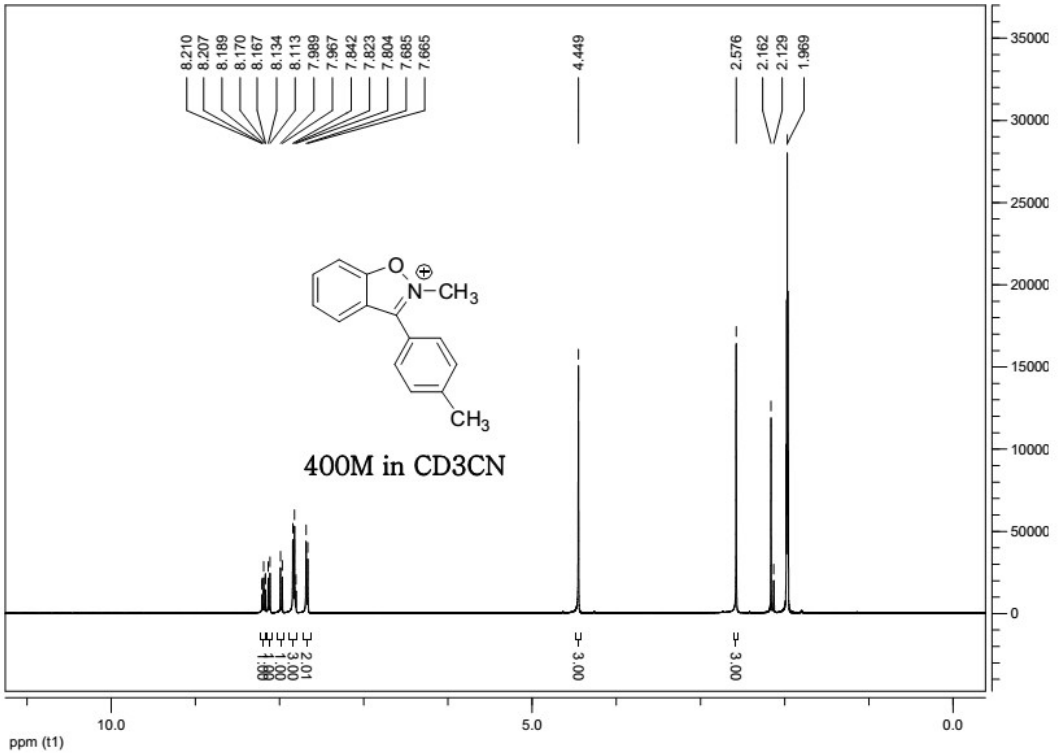

7.262
7.244
7.209
7.189
7.059
7.041
6.951
6.933
6.916
6.872
6.852
5.196
2.919
2.338
2.184
1.968
O
N−CH3
H
CH3
400M in CD3CN
5.00
1.00
3.19
3.11
10.0
5.0
0.0
ppm (t1)

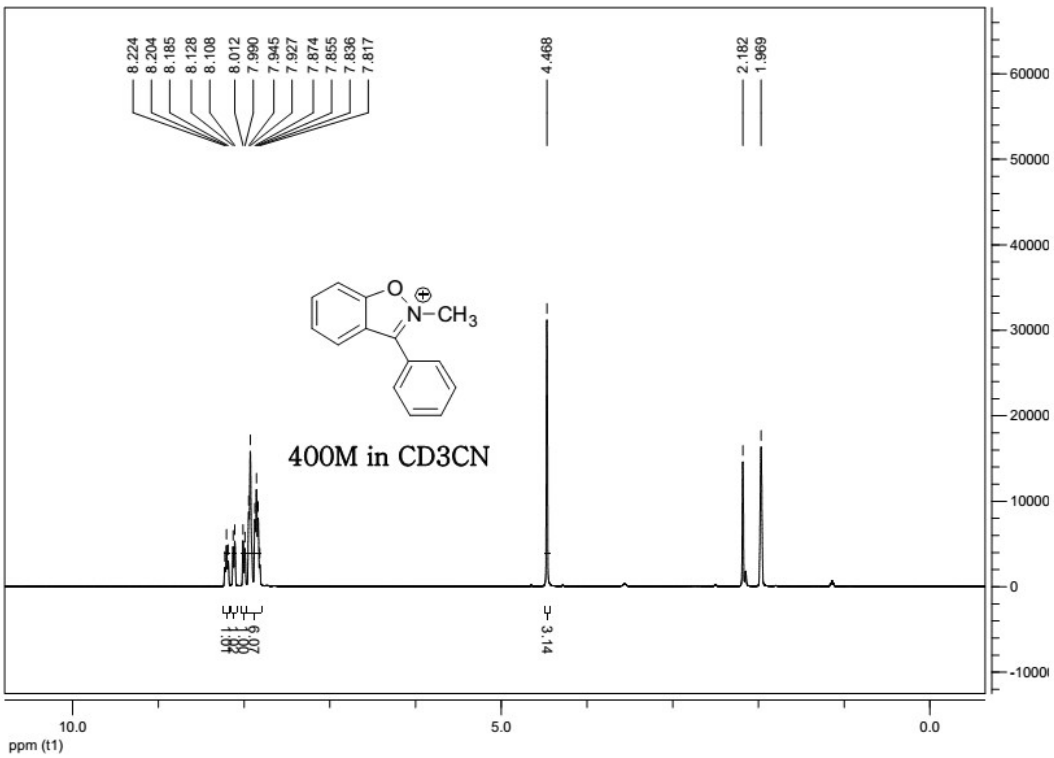

7.392
7.382
7.350
7.341
7.331
7.270
7.251
7.231
7.097
7.078
6.964
6.945
6.927
6.887
6.867
5.247
2.937
2.179
1.970
1.967
O
N−CH3
H
400M in CD3CN
6.03
1.00
2.01
1.03
3.27
10.0
5.0
0.0
ppm (t1)

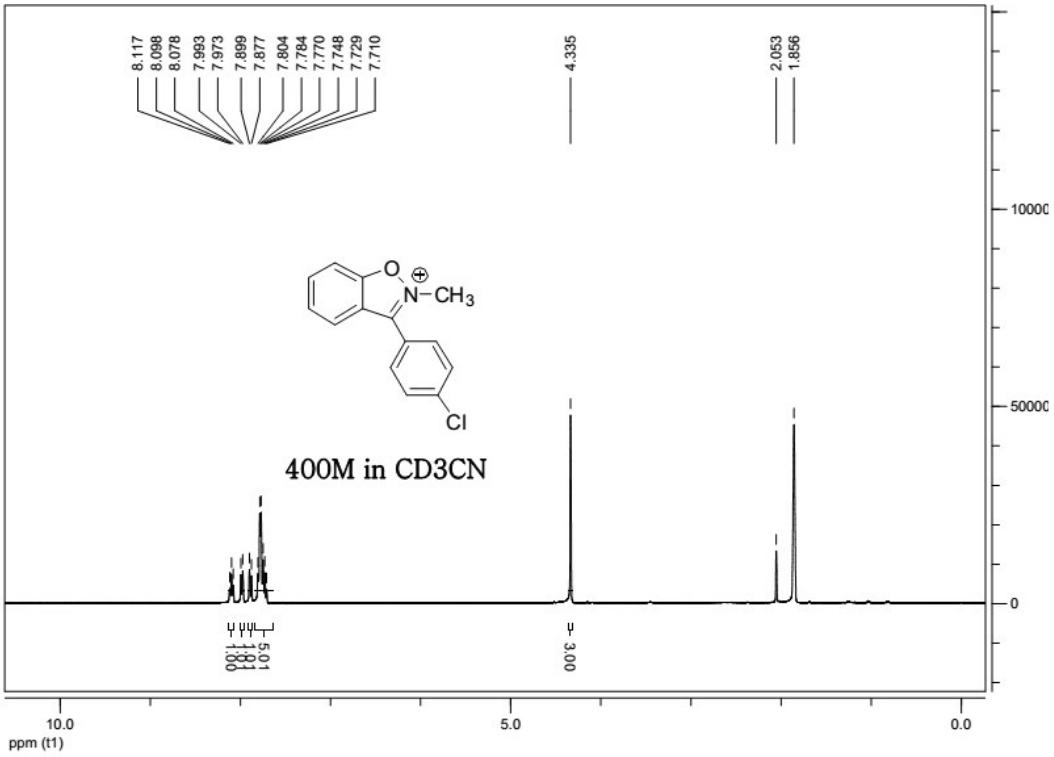

7.278
7.173
7.154
7.134
7.012
6.994
6.868
6.850
6.832
6.786
6.766
5.149
2.821
2.080
1.865
1.860
O
N−CH3
H
Cl
400M in CD3CN
4.88
1.01
2.00
1.00
3.19
10.0
5.0
0.0
ppm (t1)

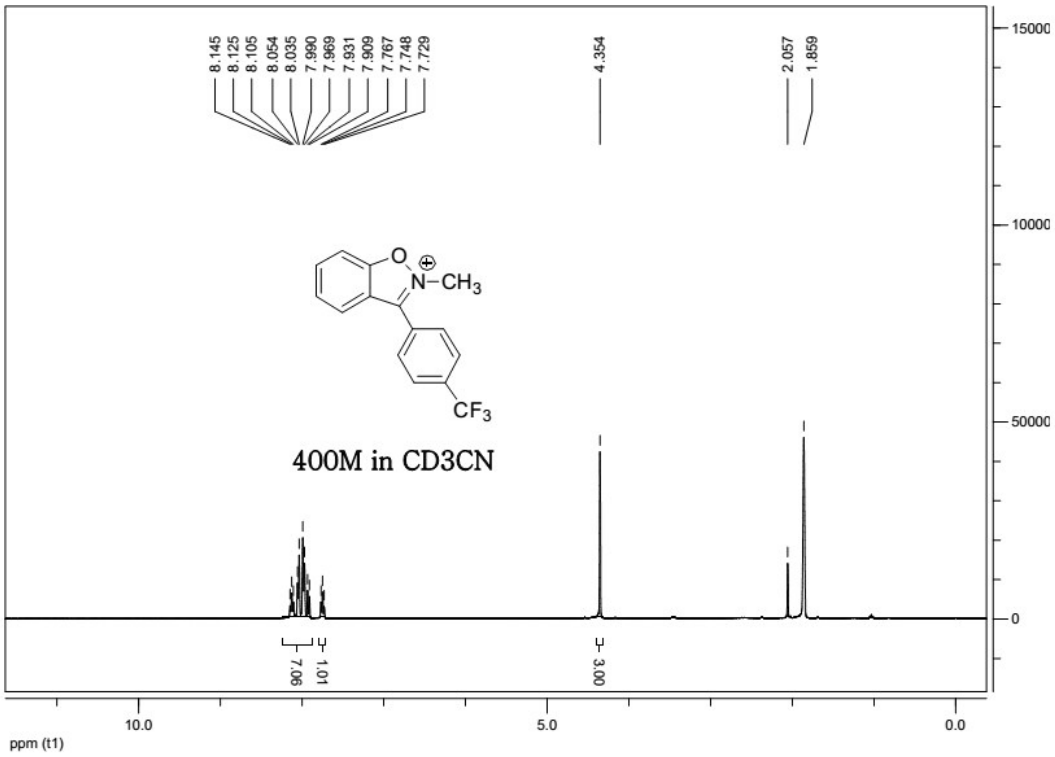

7.601
7.581
7.503
7.483
7.185
7.166
7.147
7.064
7.045
6.880
6.862
6.844
6.808
6.788
5.255
2.847
2.086
1.865
O
N−CH3
H
CF3
400M in CD3CN
2.03
1.88
1.98
1.00
3.24
10.0
5.0
0.0
ppm (t1)

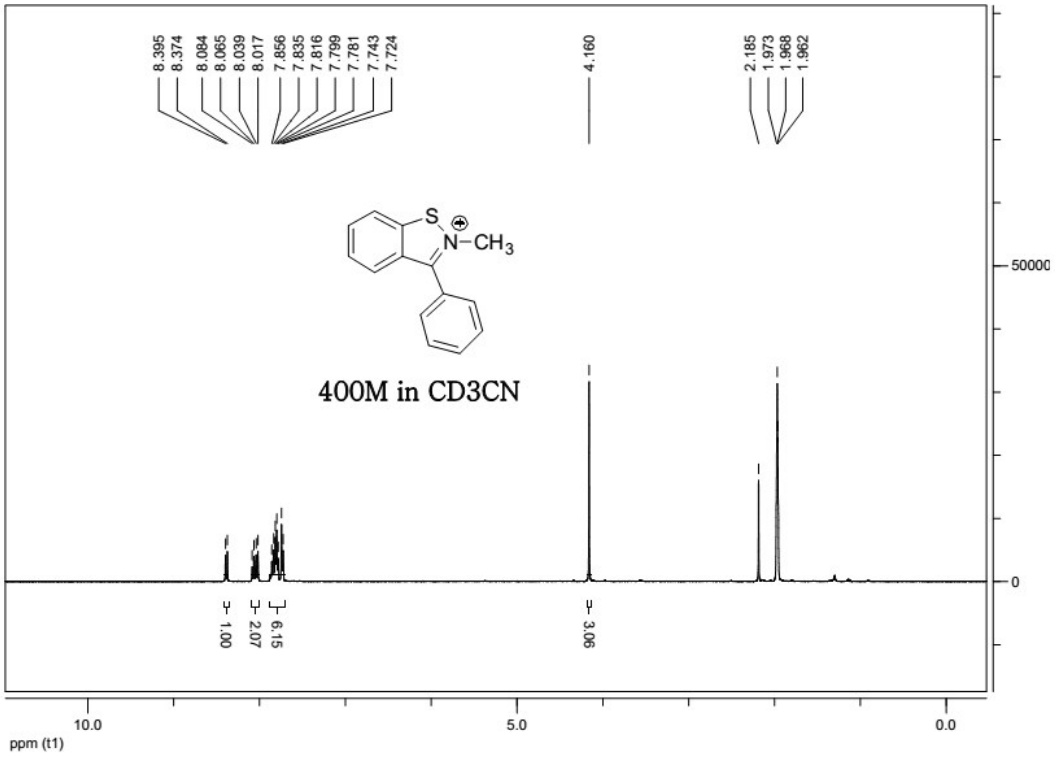

8.189
8.171
8.149
8.128
7.969
7.947
7.927
7.922
7.909
7.904
7.836
7.817
7.798
7.374
7.351
4.446
3.998
2.187
1.974
1.968
1.962
O
N⊕
CH3
OCH3
400M in CD3CN
50000
0
2.00
3.01
3.00
2.01
3.00
3.00
10.0
5.0
0.0
ppm (t1)

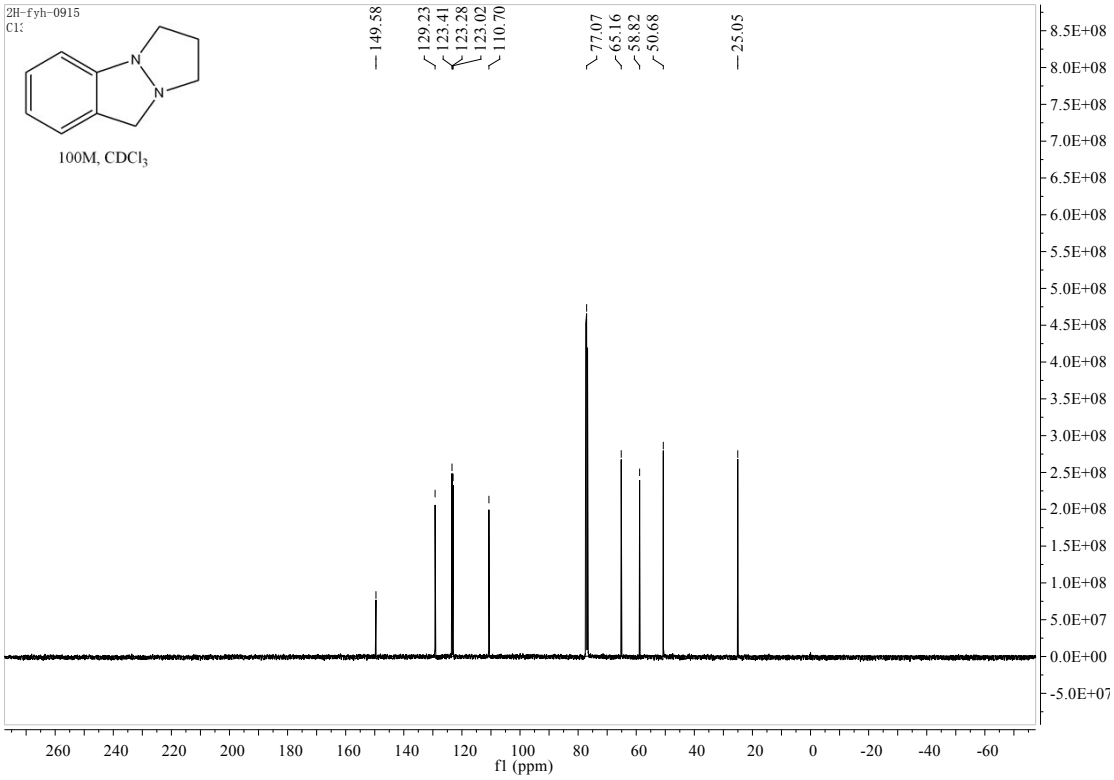

8.210
8.207
8.189
8.170
8.167
8.134
8.113
7.989
7.967
7.842
7.823
7.804
7.685
7.665
4.449
2.576
2.162
2.129
1.969
O
N⊕
CH3
CH3
400M in CD3CN
35000
30000
25000
20000
15000
10000
50000
0
3.00
3.00
2.01
10.0
5.0
0.0
ppm (t1)

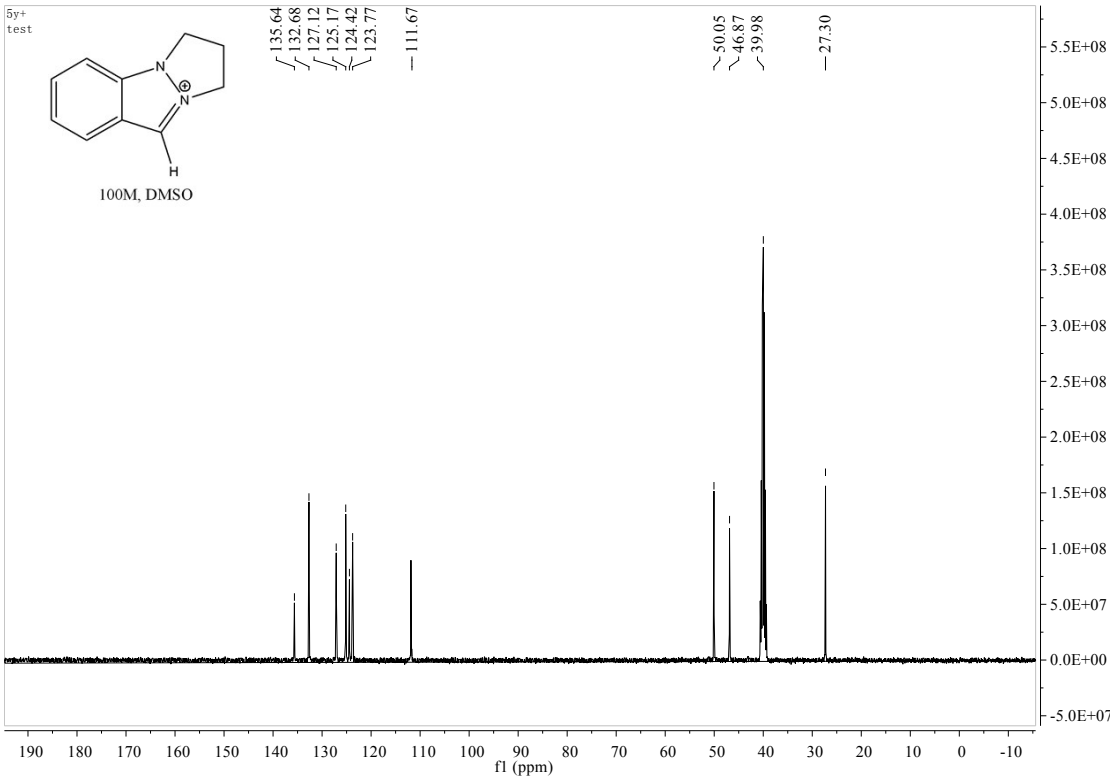

8.224
8.204
8.185
8.128
8.108
8.012
7.990
7.945
7.927
7.874
7.855
7.836
7.817
4.468
2.182
1.969
400M in CD3CN
3.14
10.0
5.0
0.0
ppm (t1)

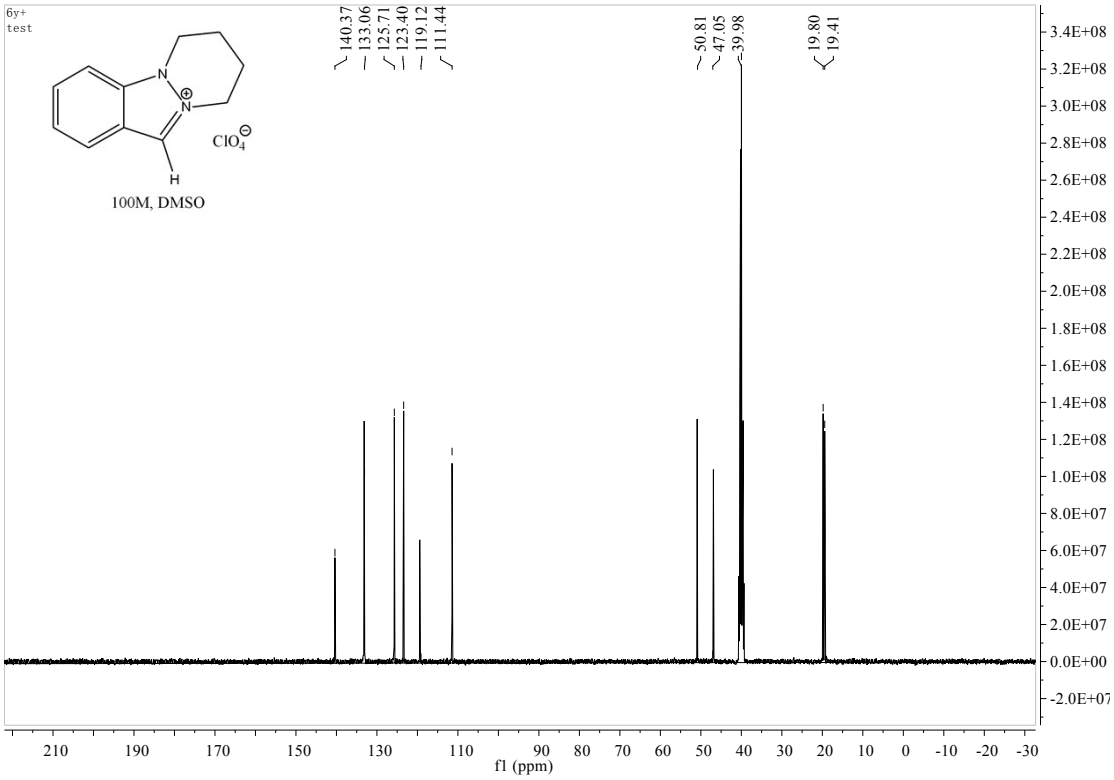

8.117
8.098
8.078
7.993
7.973
7.899
7.877
7.804
7.784
7.770
7.748
7.729
7.710
4.335
2.053
1.856
Cl
400M in CD3CN
5.01
3.00
10.0
5.0
0.0
ppm (t1)

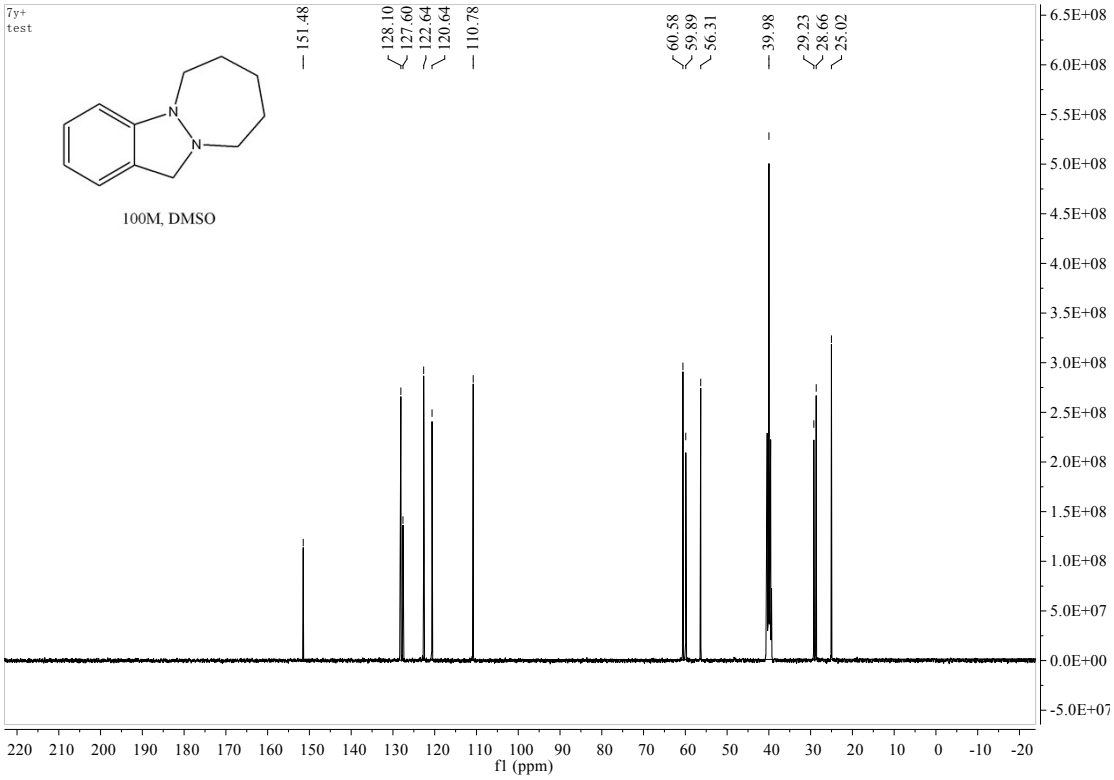

8.145
8.125
8.105
8.054
8.035
7.990
7.969
7.931
7.909
7.767
7.748
7.729
4.354
2.057
1.859
O
N−CH3
CF3
400M in CD3CN
7.06
1.01
3.00
15000
10000
50000
0
10.0
5.0
0.0
ppm (t1)

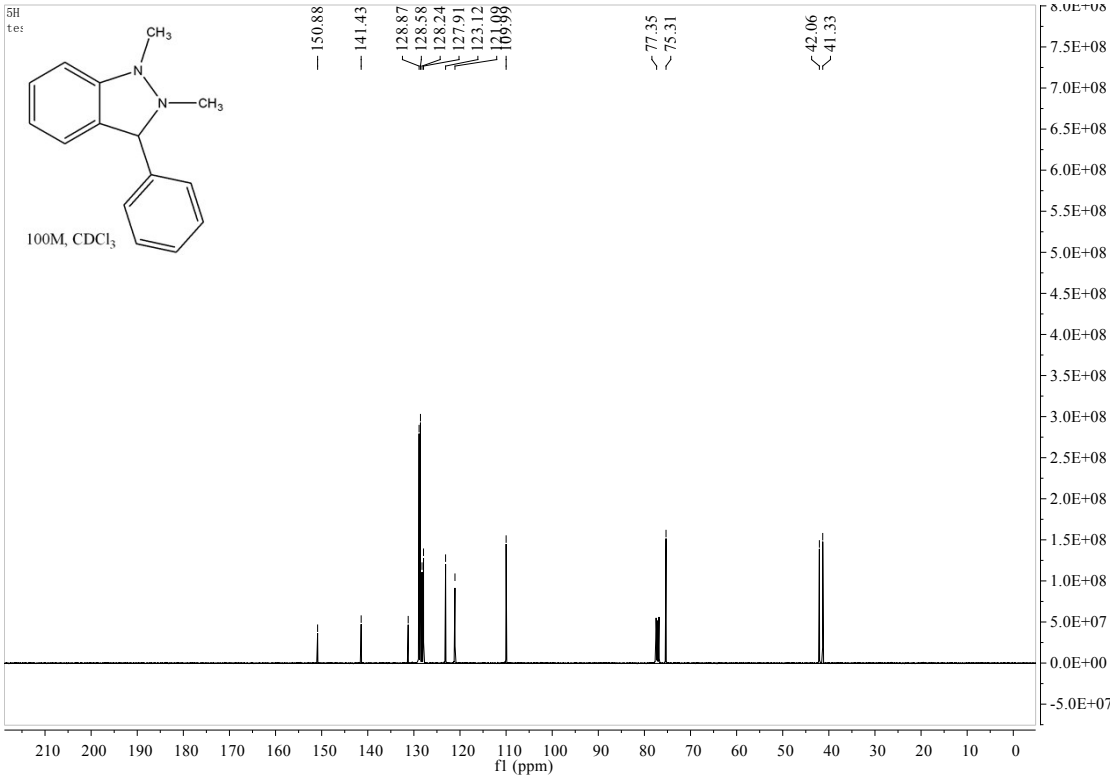

8.395
8.374
8.084
8.065
8.039
8.017
7.856
7.835
7.816
7.799
7.781
7.743
7.724
4.160
2.185
1.973
1.968
1.962
S
N−CH3
400M in CD3CN
1.00
2.07
6.15
3.06
50000
0
10.0
5.0
0.0
ppm (t1)

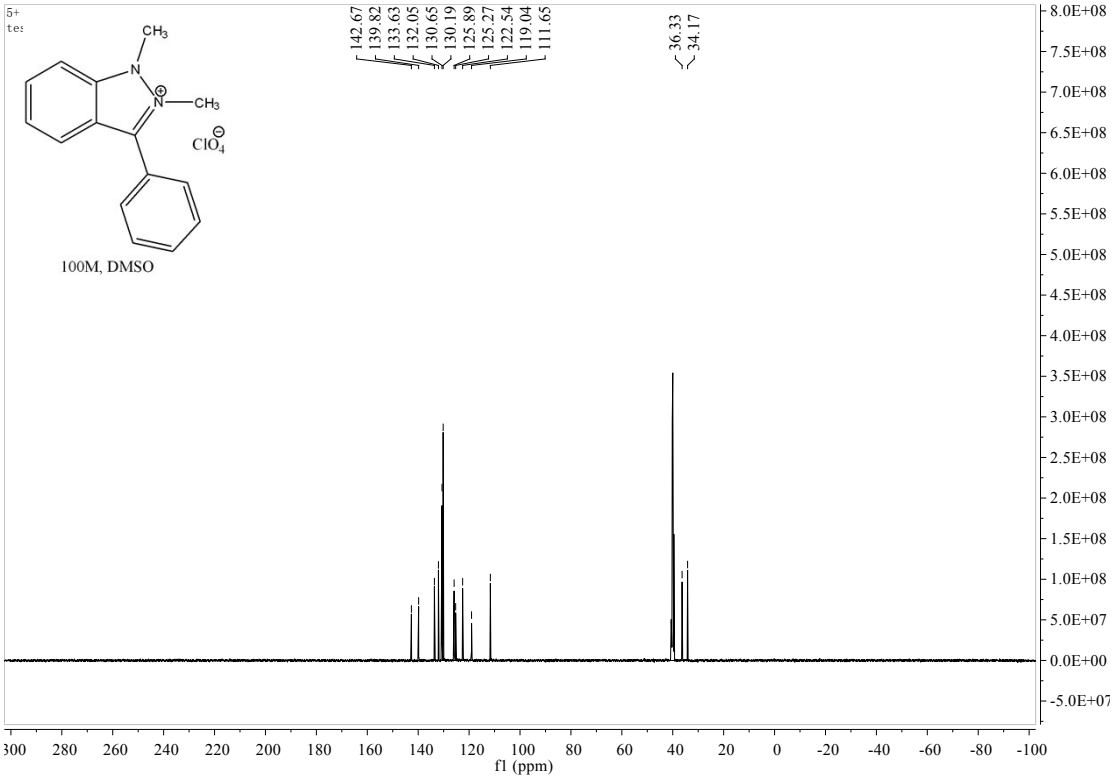

2H-fyh-0915
C13
149.58
129.23
123.41
123.28
123.02
110.70
77.07
65.16
58.82
50.68
25.05
100M, CDCl3
f1 (ppm)

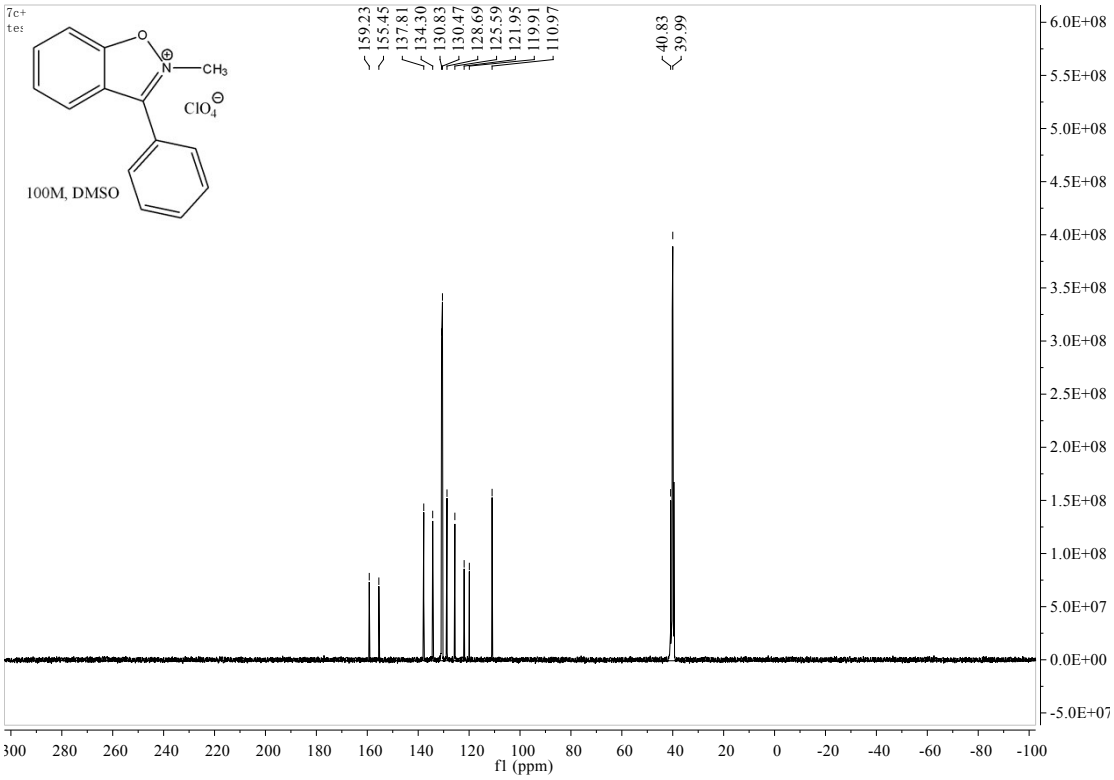

5y+
test
135.64
132.68
127.12
125.17
124.42
123.77
111.67
50.05
46.87
39.98
27.30
100M, DMSO
f1 (ppm)


6y+
test
140.37
133.06
125.71
123.40
119.12
111.44
50.81
47.05
39.98
19.80
19.41
100M, DMSO
f1 (ppm)


7y+
test
151.48
128.10
127.60
122.64
120.64
110.78
60.58
59.89
56.31
39.98
29.23
28.66
25.02
100M, DMSO
f1 (ppm)


5H
tes
CH3
N
N
CH3
100M, CDCl3
150.88
141.43
128.87
128.58
128.24
127.91
123.12
77.35
75.31
42.06
41.33
7.5E+08
7.0E+08
6.5E+08
6.0E+08
5.5E+08
5.0E+08
4.5E+08
4.0E+08
3.5E+08
3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
-5.0E+07
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


5+
tes
CH3
N
N
CH3
ClO4
100M, DMSO
142.67
139.82
133.63
132.05
130.65
130.19
125.89
125.27
122.54
119.04
111.65
36.33
34.17
8.0E+08
7.5E+08
7.0E+08
6.5E+08
6.0E+08
5.5E+08
5.0E+08
4.5E+08
4.0E+08
3.5E+08
3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
-5.0E+07
300 280 260 240 220 200 180 160 140 120 100 80 60 40 20 0 -20 -40 -60 -80 -100
f1 (ppm)



SI-5. Plots of $\Delta H_{HA}(X^+)$, $\Delta H_{PA}(X^{\bullet})$, $\Delta H_{HA}(X^{\bullet})$, $E(X^{+/0})$ as well as $E(XH^{+/0})$ against the Hammett substituent parameters σ_p or σ_m

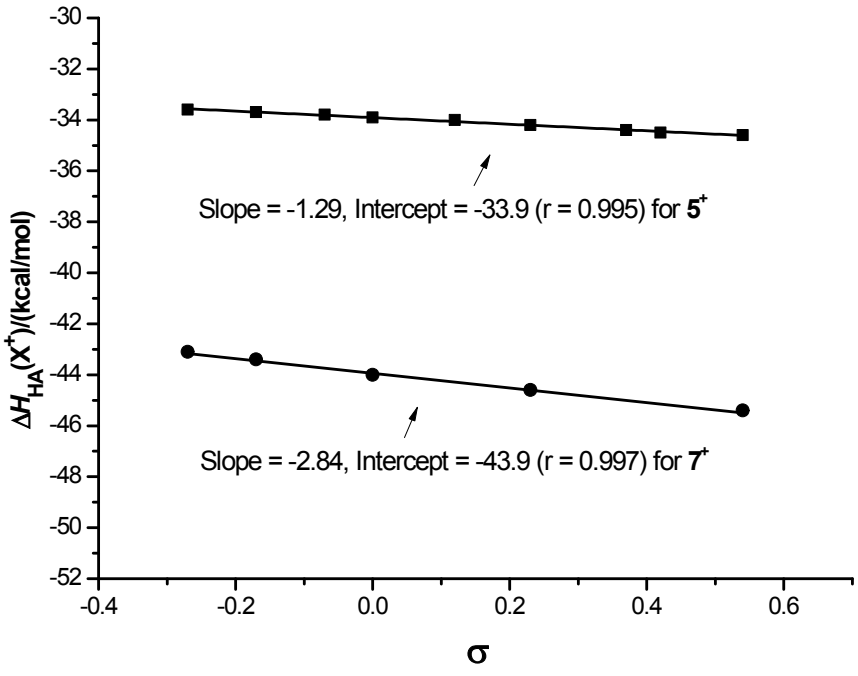


Figure S1. Plot of $\Delta H_{HA}(X^+)$ against Hammett substituent parameter (σ).

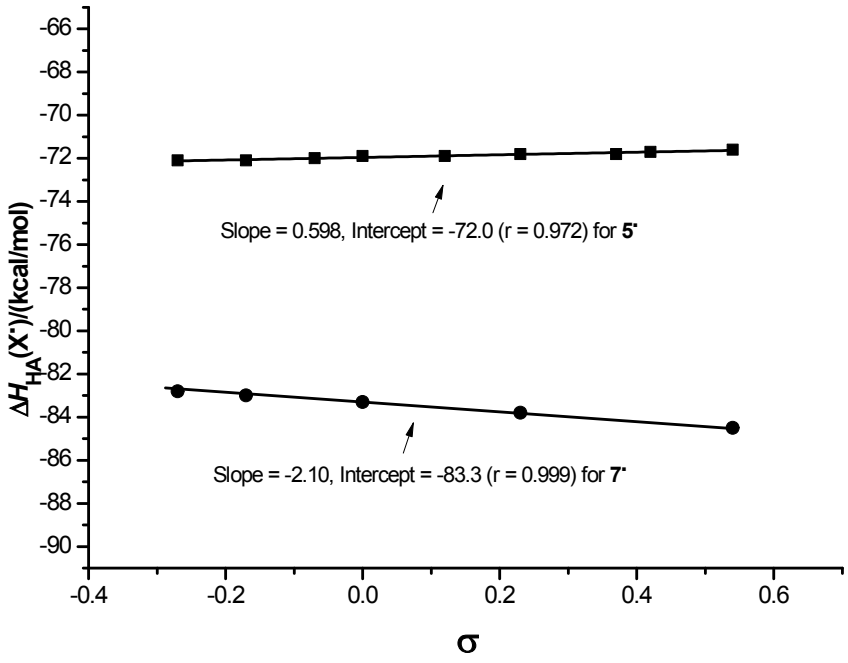


Figure S2. Plot of $\Delta H_{HA}(\mathbf{X}^{\bullet})$ against Hammett substituent parameter (σ).

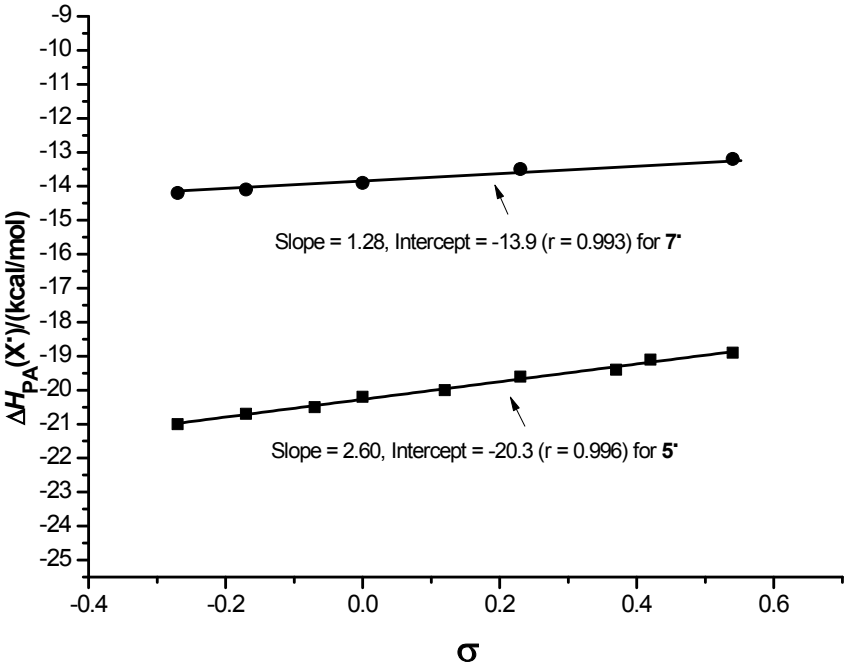


Figure S3. Plot of $\Delta H_{HP}(\mathbf{X}^{\bullet})$ against Hammett substituent parameter (σ).

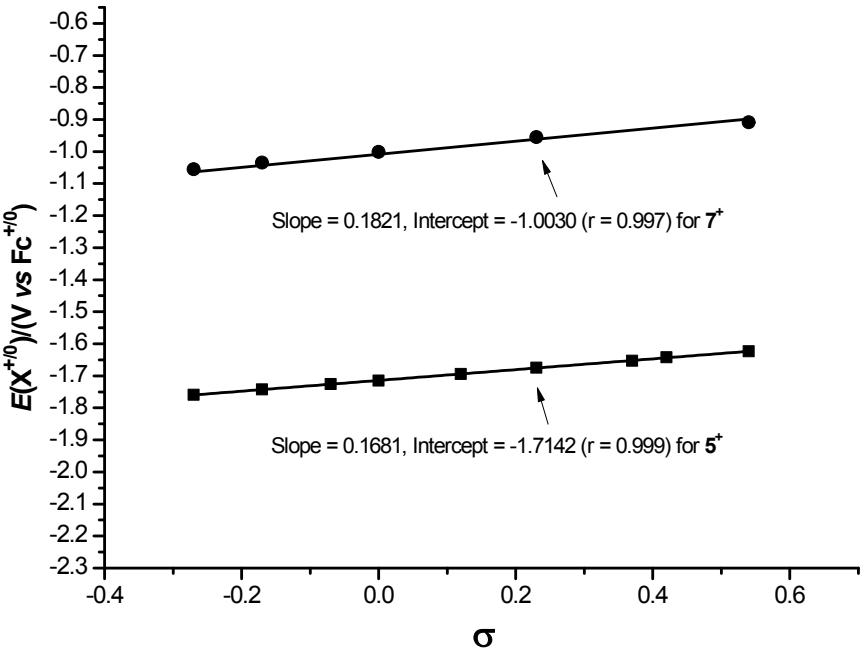


Figure S4. Plot of $E(\mathbf{X}^{+/0})$ against Hammett substituent parameter (σ).

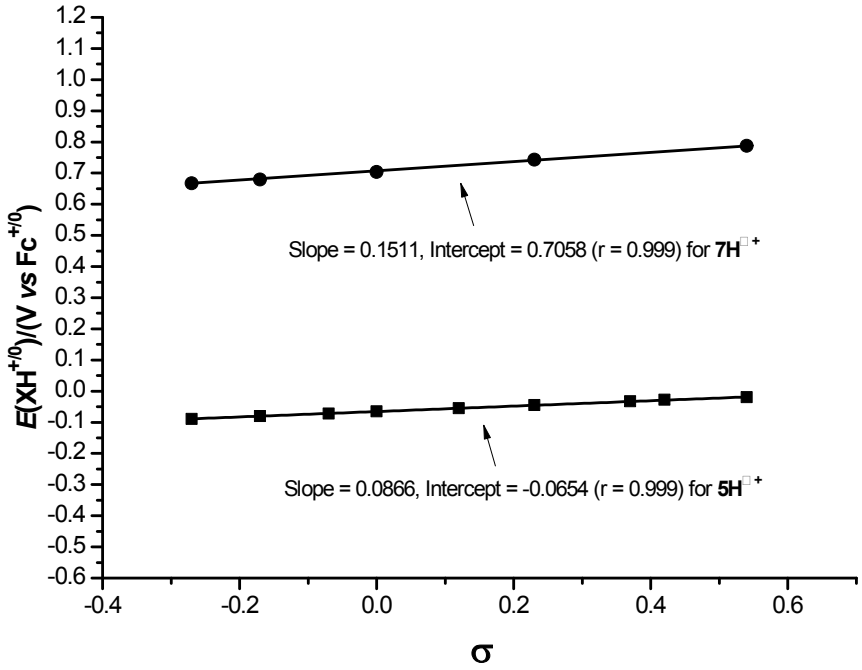


Figure S5. Plot of $E(\mathbf{XH}^{+/0})$ against Hammett substituent parameter (σ).