Modulating Accidental Fermi Resonance: What a Difference a Neutron Makes

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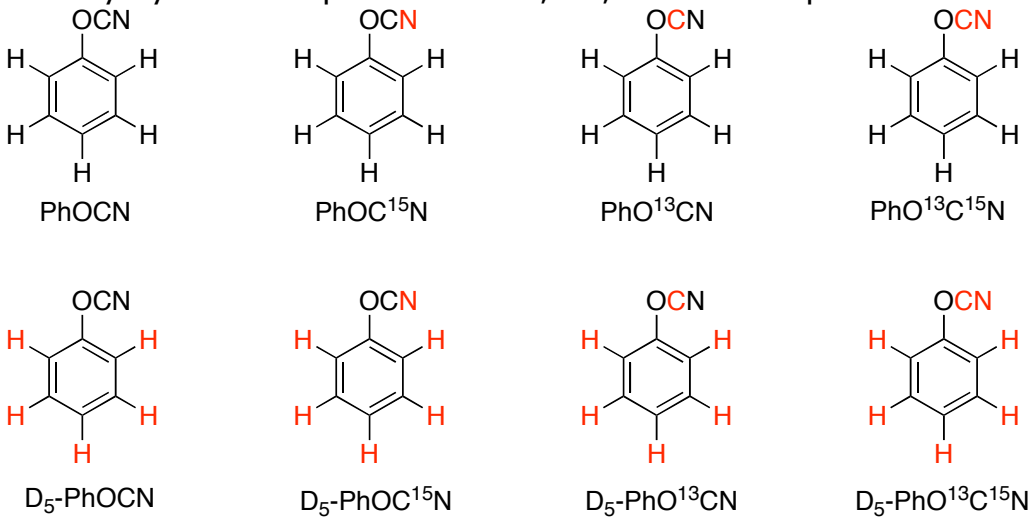
Supporting Information

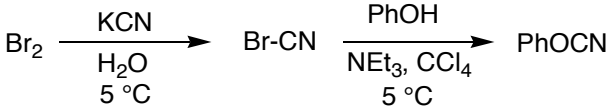
1. Synthetic Chemistry

Eight isotopomers of phenyl cyanate were prepared (Chart 1) using Martin and Bauer's *Organic Synthesis* procedure (Scheme 1) and the appropriately labeled phenol and potassium cyanide isotopomers.[1]

Chart 1: Phenyl cyanate isotopomers with ^{2}H, ^{13}C, and ^{15}N isotopes denoted in red.

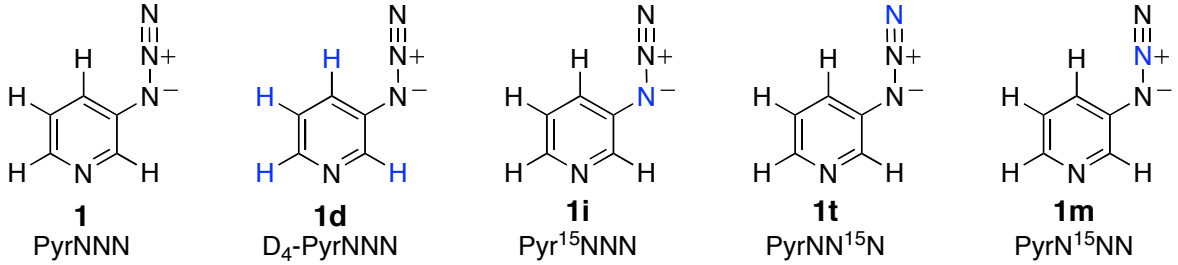


Scheme 1

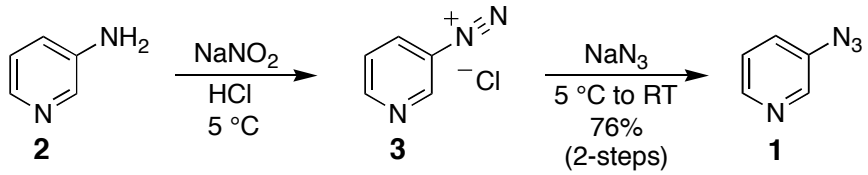


Six isotopomers of 3-azidopyridine (**1**) were synthesized (Chart 2). The unlabeled azide was prepared by Sawanishi's method which involved converting 3-aminopyridine to diazonium salt **3** with nitrous acid followed by substitution with azide (Scheme 2).[2]

Chart 2: 3-Azidopyridine isotopomers with ^{2}H and ^{15}N isotopes denoted in blue.

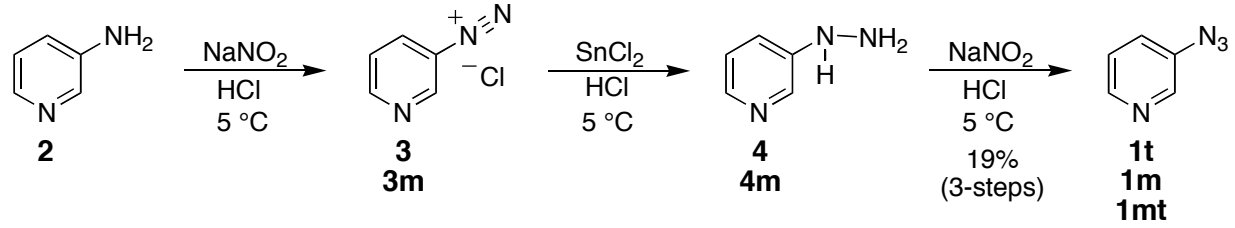


Scheme 2



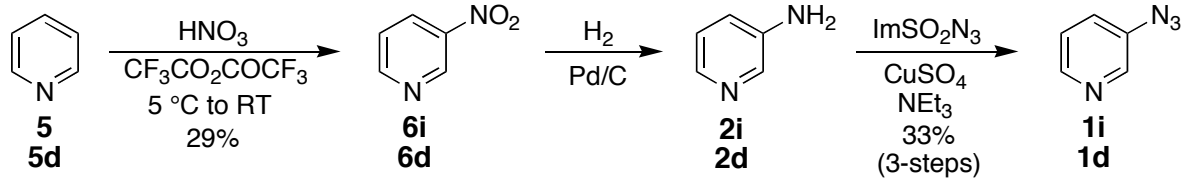
Three of the isotopomers were prepared by the novel route shown in Scheme 3. Diazonium salt **3** was prepared as above and use of N-15 labeled sodium nitrite allowed preparation of diazonium ion **3m** which contained an N-15 atom at the position which will eventually become the middle nitrogen atom of the azide. Reduction of the diazonium salts with tin(II) chloride gave hydrazines **4** and **4m**.[3] Treatment of **4** with N-15 labeled sodium nitrite in acid gave terminally labeled azide **1t**, whereas the same reaction starting with **4m** yielded the doubly-labeled azide **1mt**.[4] Likewise, treatment of **4m** with unlabeled sodium nitrite in acid provided the middle labeled azide **1m**. Yields for the three-step sequence were typically 19%.

Scheme 3



The internally labeled 3-azidopyridine **1i** and perdeutero 3-azidopyridine **1d** were prepared by the three-step route shown in Scheme 4. Nitration of pyridine (pyridine-d_5) using N-15 labeled nitric acid (unlabeled nitric acid) under Katritzky's conditions yielded N-15 labeled **6i** (deutero **6d**).[5] Hydrogenation of the nitro compounds provided the appropriately labeled 3-aminopyridines **2i** and **2d**. Copper(II)-catalyzed diazotransfer using imidazole-1-sulfonyl azide hydrochloride provided the desired azides **1i** and **1d** in ~33% overall yield for the three step synthesis.[6] All the isotopomers of **1** were purified by flash chromatography and were a single spot when analyzed by TLC and all isotopomers co-spotted with each other. The ^{1}H NMR spectrum matched the literature values.[2]

Scheme 4



General

All reagents were ACS reagent quality, purchased from Aldrich, TCI, or Alfa and used without further purification unless otherwise noted. Phenol-d_6 (99 atom% ^{2}H enrichment), ^{13}C labeled potassium cyanide (99 atom% ^{13}C enrichment), ^{13}C, ^{15}N labeled potassium cyanide (99 atom% ^{13}C, ^{15}N enrichment), and sodium nitrite (99.3 atom% ^{15}N enrichment) were obtained from ICON Isotopes. ^{15}N labeled potassium cyanide (98+ atom% ^{15}N enrichment) and ^{15}N labeled nitric acid (98+ atom% ^{15}N enrichment, 40% w/w) were obtained from Cambridge Isotope Laboratories. Pyridine-d_6 (99.5 atom% ^{2}H enrichment) was obtained from Aldrich. All aqueous solutions were prepared with 18 MΩ-cm water.

All reactions were stirred with a magnetic stir bar and conducted under a dry argon atmosphere if so noted. Reactions not at ambient temperature were heated in an oil bath. Analytical thin layer chromatography (TLC) was performed on 0.2 mm silica plastic coated sheets (Selecto Scientific) with F_{254} indicator. Flash column chromatography was performed on 230-400 mesh silica gel.

NMR spectra were obtained at the following frequencies: ^{1}H (500 MHz) and ^{13}C (125 MHz). Chemical shifts are reported in parts per million (ppm) and coupling constants are reported in hertz (Hz). ^{1}H NMR spectra in $CDCl_3$ were referenced to tetramethylsilane (TMS = 0.0 ppm) as an internal standard. ^{13}C NMR spectra taken in $CDCl_3$ were referenced to the solvent peak at 77.0 ppm. IR spectra for characterization purposes were obtained as ATR spectra of a thin film and the absorptions are reported in cm^{-1}.

Abbrevations: ATR (attenuated total reflectance); brine (saturated aqueous sodium chloride); EtOAc (ethyl acetate); Et_2O (diethyl ether); FC (flash column chromatography using silica gel); MeOH (methanol); PE (low boiling petroleum ether); water (deionized water).

3-azidopyridine (1). Unlabeled 3-azidopyridine was synthesized using Sawanishi's method[2] to give a 76% yield of **1** as a yellow oil. The NMR spectra matched the literature values:[2,7] ^{1}H NMR ($CDCl_3$) δ 8.40 (dd, J^3 = 4.7, J^4 = 1.4, 1H), 8.37 (d, J^4 = 2.4), 7.35 (m, 1H), 7.30 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 145.84, 141.13, 136.87, 125.67, 123.92; IR 3047.5 (w), 2431.9 (w), 2133.4 (s), 2096.9 (s), 1572.6 (m), 1475.2 (m), 1421.4 (m), 1304.8 (s), 1238.5 (m), 1190.2 (w), 1140.6 (w), 1103.2 (w), 1019.7 (m), 934.4 (w), 800.7 (m), 703.1 (s).

^{15}N labeled 3-Pyridylhydrazine (4m). A solution of 3-aminopyridine (228.1 mg, 2.42 mmol) in 6M HCl (2.52 mL) was cooled in an ice bath and then a solution of ^{15}N labeled $NaNO_2$ (172.9 mg, 2.47 mmol) in water (1.40 mL) was added dropwise. The mixture was stirred in an ice bath for 30 min and then a solution of $SnCl_2$•$2H_2O$ (1.3982 g, 6.20 mmol) in 6M HCl (1.40 mL) was added and stirring was continued for 3h in an ice bath. The yellow mixture was made basic (pH 14) with 40% aqueous KOH, and the mixture was extracted with EtOAc (8x). The combined organic layers were dried with Na_2SO_4 and concentrated to give 266.6 mg brown liquid (100% crude yield). The impure ^{15}N terminal labeled 3-pyridylhydrazine was used in the next step without further purification.

3-Pyridylhydrazine (4). 4 was made by the same way as **4m**, except that $NaNO_2$ was used instead of $Na^{15}NO_2$.

^{15}N terminal and middle labeled 3-azidopyridine (1mt). A solution of crude **4m** (266.6 mg) in 6M HCl (2.04 mL) was cooled in an ice bath and then a solution of ^{15}N labeled $NaNO_2$ (143.1 mg, 2.04 mmol) in water (0.56 mL) was added dropwise and the cold mixture was

allowed to slowly warm to ambient temperature and stirred for 24 h. The reaction mixture was made alkaline with Na_2CO_3 and extracted with CH_2Cl_2 (3x). The combined organic layers were dried with Na_2SO_4 and concentrated. The residue was purified by FC (20% EtOAc/PE) to give 54.7 mg (19%, 2 steps) of **2mt** as a yellow oil. TLC analysis showed that this material was a single spot that co-spotted with an authentic sample of **1**: IR 2113.8 (w), 2042.8 (s), 1577.6 (w), 1475.6 (m), 1422.1 (m), 1298.9 (m), 1238.5 (w), 1190.4 (w), 1136.5 (w), 1122.7 (w), 1101.4 (w), 1020.4 (w), 937.9 (w), 802.6 (w), 762.9 (w), 704.2 (m).

^{15}N middle labeled 3-azidopyridine (1m). 1m was made by the same way as **1mt**, except that $NaNO_2$ was used instead of $Na^{15}NO_2$: IR 2124.5 (w), 2067.8 (s), 1669.9 (w), 1586.5 (m), 1555.4 (w), 1535.0 (w), 1475.4 (m), 1423.8 (m), 1358.9 (w), 1302.7 (m), 1238.8 (w), 1190.4 (w), 1140.3 (w), 1119.7 (w), 1102.2 (w), 1038.6 (w), 1020.5 (m), 994.5 (w), 938.0 (w), 803.8 (m), 767.2 (m), 755.5 (m), 704.5 (s).

^{15}N terminal labeled 3-azidopyridine (1t). 1t was made by the same way as **1mt**, except that **4** was used instead of **4m**: IR 3037.0 (w), 2078.7 (s), 1578.0 (m), 1475.7 (m), 1422.1 (m), 1301.1 (m), 1239.0 (w), 1190.1 (w), 1137.8 (w), 1020.4 (w), 801.2 (m), 761.6 (w), 703.7 (m).

^{15}N labeled 3-nitropyridine (6i). Trifluoroacetic anhydride (1.0 ml, 7.08 mmol) was chilled in an ice bath and pyridine (55 μL, 0.64 mmol) was added dropwise. The mixture was stirred at ice-bath temperature for 2 h followed by the dropwise addition of ^{15}N labeled 40% w/w nitric acid (178 μL, 1.39 mmol). After stirring for 10 h, the solution was slowly added to a chilled aqueous solution of $Na_2S_2O_5$ (0.1218 g, 0.64 mmol) in water (1.0 mL). After stirring at ambient temperature for 24 h, the solution was neutralized to pH 6–7 by addition of 40% aqueous KOH solution. The mixture was extracted with CH_2Cl_2 and the organic layer was dried over Na_2SO_4 and concentrated to give 68.4 mg (85% crude yield) of crude **6i**.

^{15}N labeled 3-aminopyridine (2i). A solution of crude **6i** (68.4 mg, 0.55 mmol) in ethanol (3.0 mL) was mixed with activated 10% palladium on carbon (41.6 mg). The mixture was shaken on Parr hydrogenation apparatus with a hydrogen pressure of 43 barr for 24 h. The mixture was filtered through a Celite pad and the Celite was washed with 150 mL of MeOH to give 31.9 mg crude **2i** as a yellow solid (62% crude yield). TLC analysis (12% MeOH/CH_2Cl_2) showed that this material was a single spot that co-spotted with an authentic sample of **2**.

^{15}N internal labeled 3-azidopyridine (1i). To an ice bath chilled solution of crude **2i** (31.9, 0.34 mmol) in water (0.5 mL) was added triethyl amine (0.110 mL), $CuSO_4 \bullet 5H_2O$ (7.5 mg, 0.03 mmol) and imidazole-1-sulfonyl azide hydrochloride[6] (88.2 mg, 0.42 mmol) in water (0.2 mL). The reaction was stirred at ambient temperature for 24 h. The mixture was extracted with dichloromethane (4x). The organic layers were dried with Na_2SO_4 and concentrated. The residue was purified by FC (20% EtOAc/PE) to give 25.7 mg (63% yield) of **1i** as a yellow oil. TLC analysis showed that this material was a single spot that co-spotted with an authentic sample of **1**: IR 2956.0 (m), 2921.6 (s), 2851.6 (m), 2122.1 (m), 1727.9 (m), 1463.0 (m), 1379.0 (m), 1262.2 (m), 1178.2 (w), 1121.4 (m), 1073.0 (m), 1039.2 (m), 800.7 (m), 741.7 (m), 704.1 (m).

2, 4, 5, 6-tetradeutero-3-nitropyridine (6d). 6d was made by the same procedure as **6i**, except that concentrated HNO_3 was used instead of $H^{15}NO_3$ and pyridine-d_5 was used instead of pyridine.

2, 4, 5, 6-tetradeutero-3-aminopyridine (2d). **2d** was made by the same procedure as **2i**, except that **6d** was used instead of **6i**.

2, 4, 5, 6-tetradeutero-3-azidopyridine (1d). **1d** was made by the same procedure as **1i**, except that **2d** was used instead of **2i**: IR 3349.7 (m), 3214.6 (m), 2358.0 (w) 2265.7 (w), 2123.1 (s), 2047.3 (w), 1635.3 (m), 1561.3 (m) 1551.0 (m) 1405.9 (m), 1374.6 (s), 1330.9 (s), 1260.7 (m), 1231.1 (m), 1158.6 (m), 1096.9 (w), 1064.6 (m), 1024.1 (w), 883.7 (w), 828.9 (m), 749.1 (m).

2. Equilibrium FTIR Spectroscopy

Equilibrium FTIR absorbance spectra of phenyl cyanate and 3-azidopyridine were recorded on a Bruker Vertex 70 FTIR spectrometer equipped with a global source, KBr beamsplitter, and a liquid nitrogen cooled mercury cadmium telluride (MCT) detector. The spectra were the results of 512 scans recorded at a resolution of 1.0 cm^{-1}. The transmission measurements were recorded using a temperature-controlled cell consisting of calcium fluoride windows with a path length of ~100 μm. The FTIR absorbance spectra were recorded at 298 K, baseline corrected, and normalized. The concentration of the phenyl cyanate and 3-azidopyridine dissolved in THF or water was ~25 mM.

Figure S1 shows the solvent dependent frequency shift of the cyanate asymmetric stretch of $PhO^{13}CN$. The cyanate asymmetric frequency blue shifts 8.2 cm^{-1} upon going from THF to water. This shift is likely due to H-bonding interactions between the cyanate group and water molecules of the solvent.

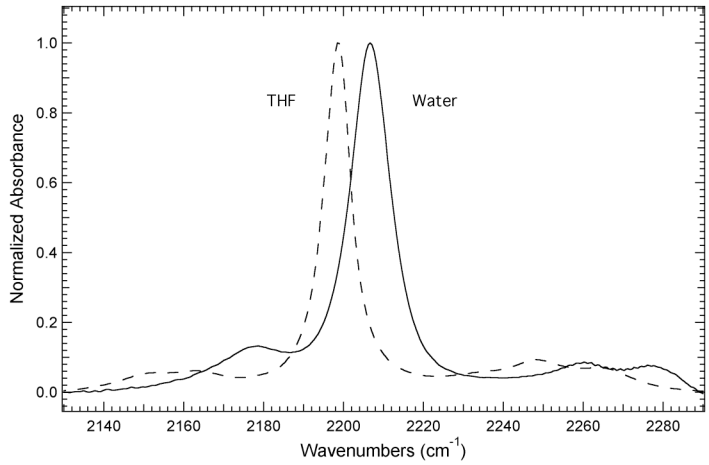


Figure S1. Normalized FTIR spectra of $PhO^{13}CN$ in THF (dashed curve) and water (solid curve) recorded at 298 K.

3. Density Functional Theory Calculations

Geometry optimizations and vibrational analyses were performed on phenyl cyanate and 3-azidopyridine in the gas phase using the quantum chemical software

package Gaussian 03 on a multiprocessor Mac Pro computer.[8] The calculations were performed using the density function theory (DFT) method, the B3PW91 density functional[9,10] and a 6-31++G(d,p) basis set.[11,12] A second-order perturbation treatment of the vibrational energy[13] was utilized to calculate the anharmonic constants x_{ij}, which were used to determine the anharmonic fundamental frequencies v_i, the overtones $[2v_i]$, and the combination bands $[v_i v_j]$ by Equations 1-3:

$$v_i = \omega_i + 2x_{ij} + \frac{1}{2}\sum_{j \neq i} x_{ij} \qquad (1)$$

$$[2v_i] = 2v_i + 2x_{ii} \qquad (2)$$

$$[v_i v_j] = v_i + v_j + x_{ij} \qquad (3)$$

where ω_i is the harmonic frequency of the ith mode. The graphical user interface GaussView 4 was used to build the structures and visualize the normal modes of vibrations.

Figures S2 and S3 show the calculated eigenvector projection of the cyanate asymmetric and azide asymmetric stretch of phenyl cyanate and 3-azidopyridine, respectively.

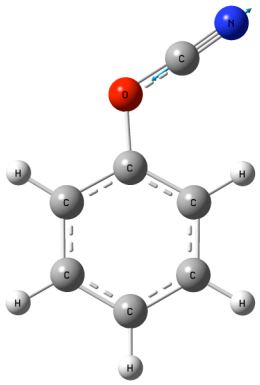


Figure S2. DFT calculated eigenvector projection for the cyanate asymmetric stretch vibration of phenyl cyanate.

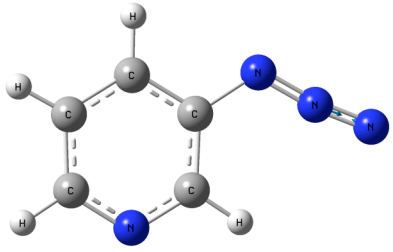


Figure S3. DFT calculated eigenvector projection for the azide asymmetric stretch vibration of 3-azidopyridine.

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