Supporting Information for

^{15}N Hyperpolarization of Imidazole-$^{15}N_2$ for Magnetic Resonance pH Sensing Via SABRE-SHEATH

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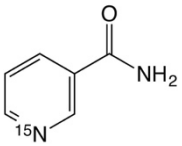
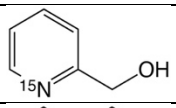
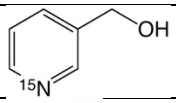
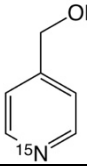
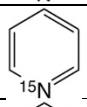
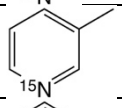
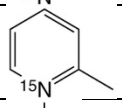
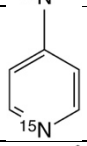
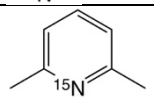
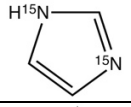
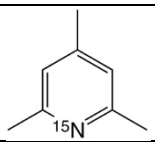
Table S1. Summary of experimentally determined pKa values and the differences between ^{15}N isotropic chemical shifts of protonated and unprotonated forms ($\Delta\delta_{15N}$) of N-heterocycles.

Compound Name	Structure	pKa	$\Delta\delta_{15N}$ (ppm)	Source
Nicotinamide-^{15}N		4.14±0.02	94	Jiang et al. 2015[1]
2-hydroxymethyl-pyridine-^{15}N		4.81±0.01	96±1	this work
3-hydroxymethyl-pyridine-^{15}N		4.95±0.02	96±1	this work
4-hydroxymethyl-pyridine-^{15}N		5.24±0.01	96±1	this work
Pyridine-^{15}N		5.28±0.02 5.17±0.07	93±1 94	this work Ref. # [1]
3-picoline-^{15}N		5.48±0.02	97±1	this work
2-picoline-^{15}N		5.94±0.02 6.02±0.05	94±1 94	this work Ref. # [1]
4-picoline-^{15}N		5.80±0.02	96±1	this work
2,6-lutidine-^{15}N		6.60±0.02 6.77	90	Ref. # [1] Ref. # [2]
Imidazole-$^{15}N_2$		6.95±0.03 7.10±0.02	30±1 31	this work Ref. # [3]
2,4,6-collidine-^{15}N		7.65 ±0.05	88	Ref. # [1]

The data was experimentally obtained in this work unless otherwise noted.

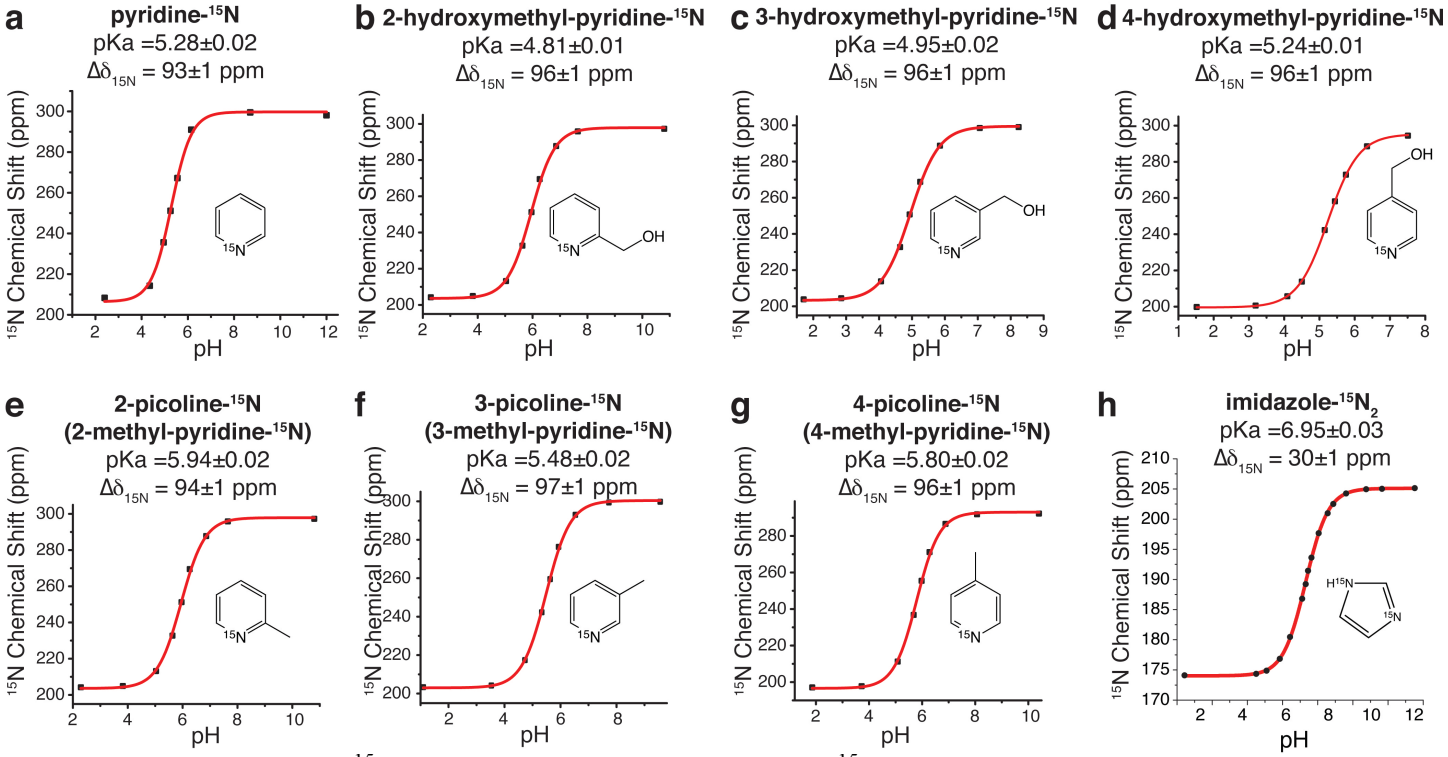


Figure S1. Dependence of ^{15}N isotropic chemical shift on pH in ^{15}N-heterocycles in ~20% aqueous solutions of natural abundance (a) pyridine, (b) 2-hydroxymethyl-pyridine, (c) 3-hydroxymethyl-pyridine, (d) 4-hydroxymethyl-pyridine, (e) 2-picoline, (f) 3-picoline, (g) 4-picoline, and (h) imidazole. All measurements are performed at 9.4 T.

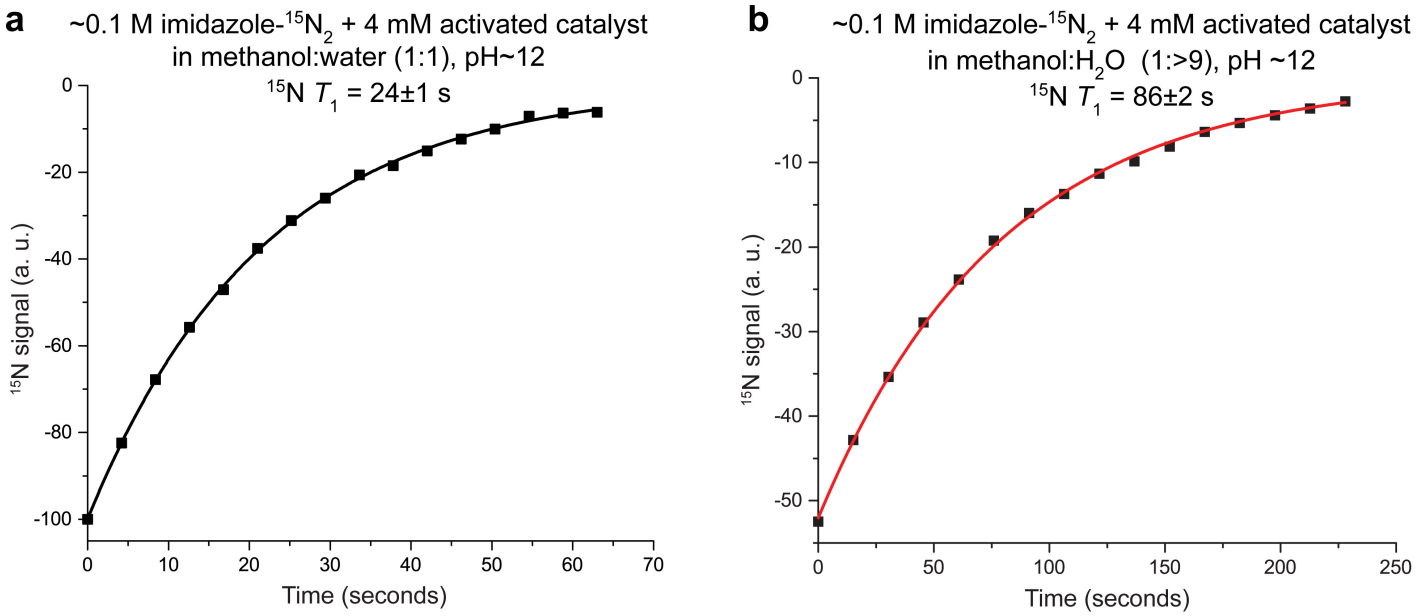


Figure S2. ^{15}N T_1 measurements of hyperpolarized imidazole-$^{15}N_2$ in methanol and aqueous medium. The measurements are performed at 9.4 T using small angle excitation pulses in the presence of the SABRE catalyst, and the data is analyzed using the approach described earlier.[4] a) ^{15}N T_1 decay of hyperpolarized imidazole-$^{15}N_2$ in methanol:water (~1:1) mixture at pH of ~ 12, b) ^{15}N T_1 decay of hyperpolarized imidazole-$^{15}N_2$ in methanol:water (~1:>9) mixture at pH of ~ 12.

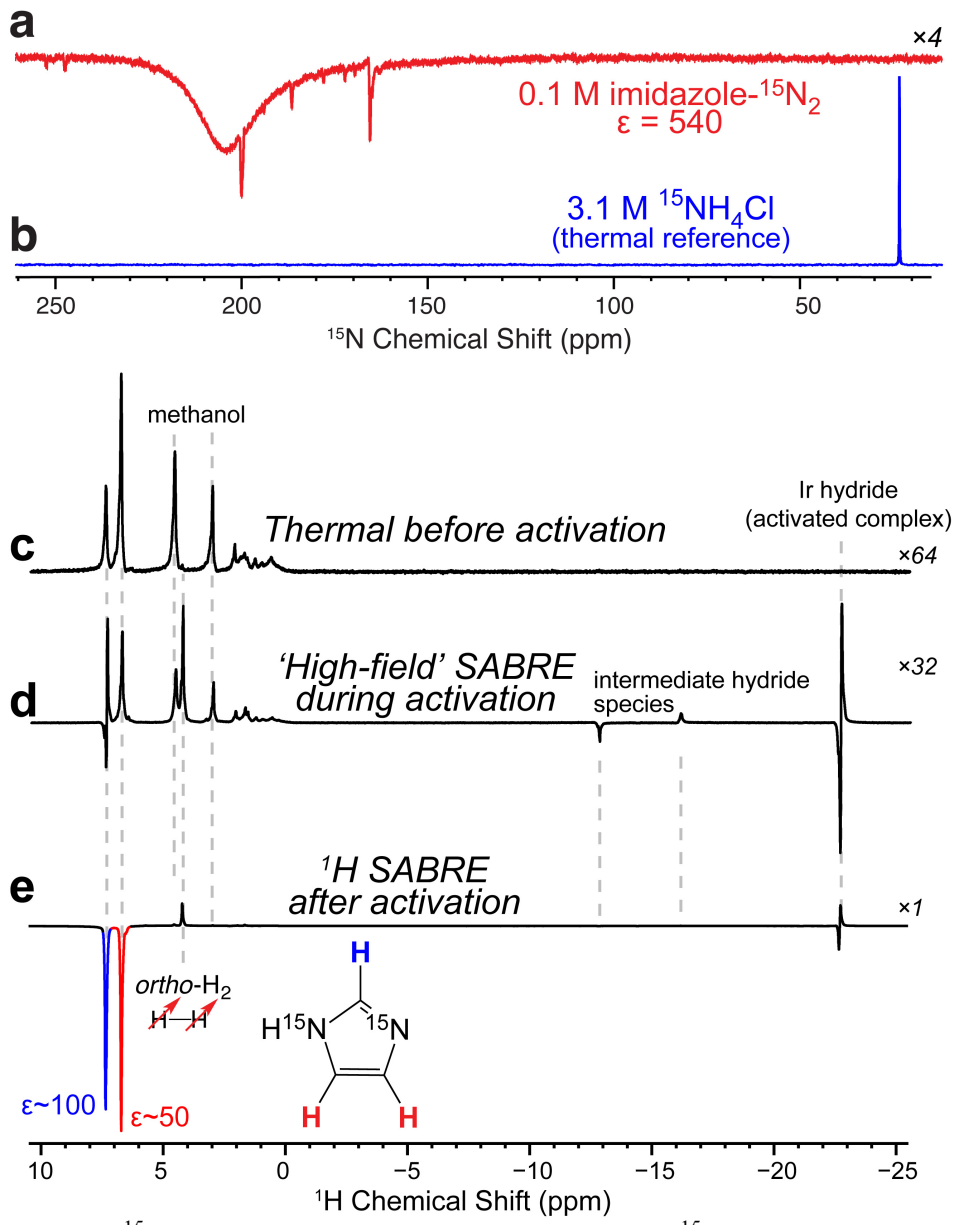


Figure S3. ^{1}H SABRE and ^{15}N SABRE-SHEATH study of imidazole-$^{15}N_2$ in methanol-d_4. a) ^{15}N spectrum of HP imidazole-$^{15}N_2$ (~0.1 M) in methanol-d_4 prepared via SABRE-SHEATH (B_T~0.5 μT, [catalyst] ~ 4 mM), b) ^{15}N spectrum of ^{15}N signal reference. c-e) ^{1}H SABRE hyperpolarization of imidazole-$^{15}N_2$. c) ^{1}H NMR spectrum of thermally polarized 100 mM imidazole-$^{15}N_2$ solution in methanol-d_4. d) *In situ* (or "high-field") SABRE ^{1}H NMR spectroscopy of imidazole-$^{15}N_2$ recorded inside 9.4 T spectrometer. The spectrum was recorded approximately 2 s after bubbling was stopped; *para*-H_2 bubbling was conducted at 9.4 T: note (i) the weak SABRE signal enhancement of one of the imidazole protons manifested as the signal with negative (emissive) phase—consistent with the previously described 'high-field' SABRE effect[5]; and (ii) upfield signals from intermediate hydride species formed transiently during the catalyst activation process.[6] The weaker-than-normal high-field SABRE signal may result in part from the dispersive (rather than purely absorptive) nature of the hyperpolarized hydride signal (which in turn reflects a relative lack of unidirectional non-equilibrium z magnetization available to drive the high-field SABRE effect via cross-relaxation compared to that observed with unlabeled pyridine as the substrate). e) ^{1}H NMR spectrum of the conventional SABRE hyperpolarization of imidazole-$^{15}N_2$; SABRE hyperpolarization was performed in the fringe field of a 9.4 T magnet at 6±4 mT. All NMR spectra are recorded using 400 MHz (9.4 T) Bruker high-resolution NMR spectrometer. Spectra shown in S3d and S3e are recorded using 50% *para*-H_2 at ~6 atm pressure, and 30 sccm and 90 sccm flow rate of *para*-H_2 respectively gas using the setup previously described.[7-8]

1. Experimental Details

1.a. Preparation procedure for imidazole-$^{15}N_2$ solution for SABRE-SHEATH hyperpolarization in methanol-d_4 (the data is shown in Figure S3)

Non-activated Iridium catalyst prepared in the previous studies,[9] [IrCl(cod)(IMes), MW ~ 640] was dissolved in methanol-d_4 to yield ~4 mM final catalyst concentration, and imidazole-$^{15}N_2$ was added to yield ~0.1 M final concentration. The solution was transferred using a glass pipet into a medium-walled NMR (5 mm medium wall precision (3.43 mm ID), NMR Sample Tube 9 in. long, Wilmad glass P/N 503-PS-9) tube equipped with the Teflon tube (0.25 in. OD, 3/16 in. ID) extension, which was approximately 7 cm long. The tube was attached to the previously described setup[6] through a wye push-to-connect adapter.[6] The sample was activated by running hydrogen or parahydrogen (*para*-H_2) at ~30 sccm flow rate at ~6 atm *para*-H_2 (50% *para*-fraction) pressure for >20 min with a flow rate controlled by the mass flow controller (Sierra Instruments, Monterey, CA, model number C100L-DD-OV1-SV1-PV2-V1-S0-C0).

1.b. Preparation procedure for imidazole-$^{15}N_2$ solution for SABRE-SHEATH hyperpolarization in methanol-water mixtures

A medium-walled NMR (5 mm medium wall precision (3.43 mm ID), NMR Sample Tube 9 in. long, Wilmad glass P/N 503-PS-9) tube equipped with the Teflon tube (0.3 in. OD, 3/16 in. ID) extension, which was approximately 7 cm long was flashed with Argon at least three times and kept vertical while Stock solution (0.25 mL) was added via Ranin XLS pipet. The tube was attached to the previously described setup[6] through wye push-to-connect adapter.[6] The sample was activated by running parahydrogen (*para*-H_2) at 130 sccm (for 1min) and 30sccm (for 4min) flow rate at ~6.5 atm *para*-H_2 (50% *para*- fraction) pressure with flow rate controlled by the mass flow controller (Sierra Instruments, Monterey, CA, model number C100L-DD-OV1-SV1-PV2-V1-S0-C0). The pressure was gently released and the pH buffer (pH=10, EMD Millipore Corporation, BX1642-1, 0.3mL) was added rapidly via Ranin XLS pipet. The sample was reactivated activated by running parahydrogen (*para*-H_2) at 130 sccm (for ~1 min) and 30 sccm (for ~4 min) flow rate at ~6.5 atm *para*-H_2 (50% *para*- fraction) pressure with flow rate controlled by the mass-flow controller.

1.c. ^{15}N SABRE-SHEATH hyperpolarization

Samples were warmed by temperature-equilibrated by placing them for at least 3 minutes inside 9.4 T Bruker NMR spectrometer, where sample temperature was maintained by the spectrometer. ^{15}N SABRE-SHEATH hyperpolarization procedure was conducted similarly to that described earlier.[9] The sample solution was bubbled with *para*-H_2 (*para*- fraction 50%, 130 sccm (for ~1 min) at ~6.5 atm) inside the magnetic shield for a period of ~1 min. The Earth's magnetic field was attenuated using three-layered mu-metal shield (6 in. ID & 15 in. in length, part number ZG-206, Magnetic Shield Corp., Bensenville, IL), which was degaussed before use. The magnetic field was created using a custom-built solenoid coil and a power supply (GPRS series, GW INSTEK). After stopping *para*-H_2 bubbling the sample was quickly transferred from the shield to the Earth's magnetic field followed by quenching the flow of *para*-H_2 and sample insertion in the bore of 9.4 T magnet and acquisition of the ^{15}N NMR spectrum. ^{15}N chemical shifts were referenced to external urea-$^{15}N_2$ sample calibrated to 77.6 ppm. ^{15}N peaks integrals were integrated with respect to a sample of neat pyridine-^{15}N or a solution of $^{15}NH_4Cl$ (integral value was set to 1.00).

1.d. ^{1}H SABRE hyperpolarization

^{1}H SABRE-SHEATH hyperpolarization procedure was performed similarly to that described earlier.[9] Briefly, the sample tube with activated catalyst and to-be-hyperpolarized substrate is placed in the fringe field of the magnet at 6±4 mT (calibrated with gauss meter), and *para*-H_2 (*para*- fraction 50%) is bubbled for ~30 seconds using the setup described above.

1.e. Calculation of SABRE polarization enhancement factors

^{1}H SABRE enhancements (Figure S3) were calculated by comparing integral signal intensities of corresponding NMR peaks of the spectra of hyperpolarized and thermally polarized conditions.

^{15}N SABRE-SHEATH enhancements were calculated by comparing integral signal intensities of all hyperpolarized NMR peaks obtained from the hyperpolarized sample in a 5 mm medium-walled NMR tube at 100 mM concentration of imidazole-$^{15}N_2$ and referencing it to the ^{15}N NMR signal from a thermally polarized 3.1 M solution of $^{15}NH_4Cl$ in D_2O in a standard 5 mm NMR tube. All ^{15}N-containing compounds were purchased from Isotec-Sigma-Aldrich. The following formula was used for ^{15}N signal enchantments:

$$\varepsilon = (S_{HP}/S_{REF})*([REF]/[HP])*(N15N_{REF}/N15N_{HP})*(A_{REF}/A_{HP}),$$

where S_{HP} is hyperpolarized signal, S_{REF} is a signal from reference compound, [REF] and [HP] are concentrations of reference (3.1 M) and hyperpolarized (0.1 M) samples respectively, $N15N_{REF}$ and $N15N_{HP}$ are the number of ^{15}N sites per molecule in reference (1) and hyperpolarized (2) samples respectively, A_{REF} and A_{HP}, are the effective cross sections (i.e. inner area) of the NMR tubes for reference and hyperpolarized samples. (A_{REF}/A_{HP}) was calculated as $4.14^2/(3.43^2 - 1.59^2) = 1.85$, where 4.14 mm is the ID of standard NMR tube, 3.43 mm is the ID of medium wall NMR tube, and 1.59 mm is the OD of the Teflon capillary (for *para*-H_2 bubbling) inserted in the HP sample. For the data presented in Figure 2, ^{15}N signal enhancement was computed as the following: $\varepsilon = (16.8/1)*(12.5/0.1)*(1/2)*1.85 \sim 2\ 000$.

1.f. pH measurements, correlation with ^{15}N isotropic chemical shifts and pKa determination

Approximately 10-20% (by volume) solutions on N-heterocyclic compounds (Figure S1 and Table S1) were prepared in water at ^{15}N natural abundance. The solutions were buffered by the addition of HCl or/and NaOH. Their pH was measured using a glass-electrode (Metter Toledo/ pH Electrode LE407) in a glass beaker supplied with magnetic stir bar, and ~0.6 mL of each solution was transferred into a standard glass 5 mm NMR tube. Isotropic ^{15}N chemical shifts were measured once for each sample (and referenced to $(^{15}NH_4)_2SO_4$ externally). The data points collected in this fashion for each compound (at various pH values) were modeled using the Henderson–Hasselbalch equation:[1]

$$pH = pKa + log\left(\frac{\delta_{15NOBS} - \delta_{15PROTONATED}}{\delta_{15UNPROTONATED} - \delta_{15PROTONATED}}\right) \quad (1),$$

where $\boldsymbol{\delta_{15NOBS}}$ is the observed ^{15}N isotropic chemical shift, $\boldsymbol{\delta_{15PROTONATED}}$ is the ^{15}N isotropic chemical shift of protonated form (i.e. acid), $\boldsymbol{\delta_{15UNPROTONATED}}$ is the ^{15}N isotropic chemical shift of the unprotonated form (i.e. base), and *pH* is a pH value detected by the glass electrode of pH meter. Note that ($\boldsymbol{\delta_{15UNPROTONATED} - \delta_{15PROTONATED}}$) corresponds to $\boldsymbol{\Delta\delta_{15N}}$ in Table S1.

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