Molecular Association Mediated by Nitrogen–Chlorine Donor–Acceptor Interactions

Kui Xu, Douglas M. Ho, and Robert A. Pascal, Jr.*

Department of Chemistry, Princeton University, Princeton, New Jersey 08544

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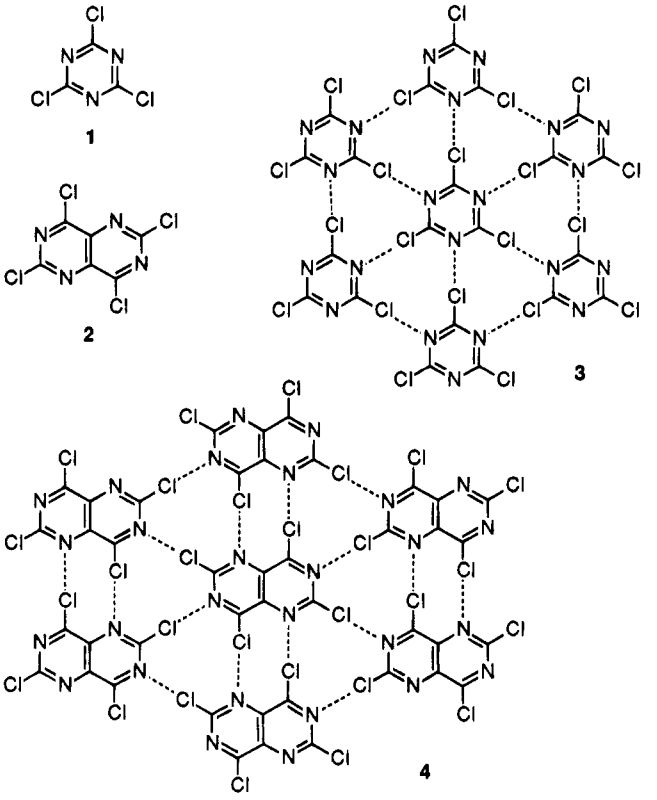
3,5-Bis(2-pyridylethynyl)-4-chloronitrobenzene (**5**) and 3,5-bis[[3-(4-(*tert*-butylbenzyl)oxy)-2-pyridyl]-ethynyl]-4-chloronitrobenzene (**13**) were synthesized as potential tridentate ligands, via nitrogen–chlorine donor–acceptor interactions, of 2,6-dichloropyridine and related compounds. Compound **5** was also synthesized in ^{15}N-labeled form, and its association with 2,6-dichloropyridine, 2,6-dibromopyridine, 2,4,6-trichloropyrimidine, and 1,3-dichlorobenzene was examined by means of ^{15}N NMR titration experiments. The first three compounds were weakly associated with **5** (K_{assoc} = 0.2–0.3 M^{-1}) in toluene solution and induced significant upfield shifts in its ^{15}N NMR resonances, but 1,3-dichlorobenzene, which cannot fit satisfactorily into the proposed "cleft" of compound **5**, had little effect. The X-ray structure of **5** and the proposed structures of its complexes are discussed.

Introduction

Short nitrogen–halogen intermolecular contacts are frequently observed in the crystal structures of organic compounds, and these close contacts are thought to reflect weakly attractive donor–acceptor interactions.[1] An approximately linear arrangement of atoms appears to be the preferred geometry for the approach of nitrogen nucleophiles to halogen–carbon groups in the solid state, and this directional preference has been used to rationalize and, to a more limited degree, to design the structures of certain organic solids.[2–8] We recently observed that the "azaaromatic chlorides", molecules containing several N=C–Cl subunits on their peripheries (e.g. **1** and **2**), are particularly prone to form such interactions in the solid state, and the crystal structures of these compounds very often take the form of planar arrays stitched together by networks of N···Cl interactions (e.g. **3** and **4**).[8].

The importance of nitrogen–halogen donor–acceptor interactions in the solid state is well established, but are these forces strong enough to influence significantly molecular associations in solution? On the basis of ab initio calculations, we have estimated that each of these weak interactions is worth on the order of 1–1.5 kcal/mol in the gas phase,[8] which, although stronger than a simple van der Waals interaction, is much weaker than a hydrogen bond. Furthermore, in solution studies of molecular association, one must contend with competition from the solvent itself, and even ordinary, nonspecific van der Waals interactions between solute and solvent may overwhelm any specific nitrogen–halogen interactions between solute molecules. In this paper we report the design and synthesis of a host–guest system based on nitrogen–chlorine donor–acceptor interactions, and the results of NMR studies which indicate that the host and guest are weakly associated in solution, apparently through specific N···Cl interactions.



Results and Discussion

Design and Synthesis of the Host. If the cyanuric chloride crystal structure (**3**) is taken as a guide, then the tridentate host **5** should possess a nearly ideal geometry for complexation of 2,6-dichloropyridine (**6**) and related molecules via nitrogen–chlorine interactions (eq 1). Indeed, when the complex **7** was modeled by AM1 calculations[9] (which overestimate the strength of N···Cl interactions but provide reasonable geometries) with full

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(1) Bent, H. A. *Chem. Rev.* **1968**, *68*, 587–648.
(2) Britton, D. *Persp. Str. Chem.* **1967**, *1*, 109–171.
(3) Ramasubbu, N.; Parthasarathy, R.; Murray-Rust, P. *J. Am. Chem. Soc.* **1986**, *108*, 4308–4314.
(4) Desiraju, G. R.; Harlow, R. L. *J. Am. Chem. Soc.* **1989**, *111*, 6757–6764.
(5) Pascal, R. A., Jr.; Ho, D. M. *Tetrahedron Lett.* **1992**, *33*, 4707–4708.
(6) Reddy, D. S.; Panneerselvam, K.; Pilati, T.; Desiraju, G. R. *J. Chem. Soc., Chem. Commun.* **1993**, 661–662.
(7) Reddy, D. S.; Goud, B. S.; Panneerselvam, K.; Desiraju, G. R. *J. Chem. Soc., Chem. Commun.* **1993**, 663–664.
(8) Xu, K.; Ho, D. M.; Pascal, R. A., Jr. *J. Am. Chem. Soc.* **1994**, *116*, 105–110.
(9) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902–3909.

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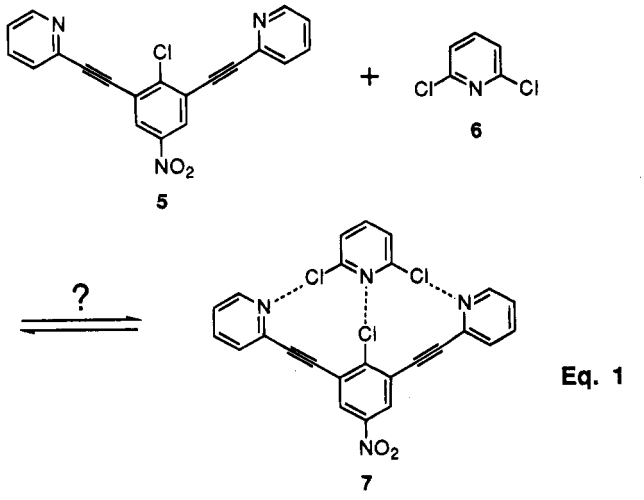
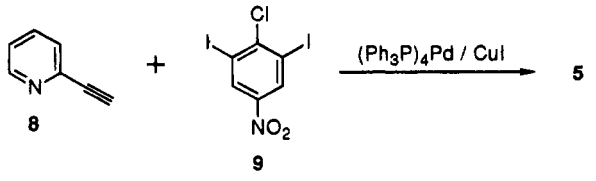
geometry optimization, the two independent N···Cl distances were found to be 3.06 Å (center) and 3.13 Å (side), with N···Cl–C angles of 180° and 169.7°, respectively. (In cyanuric chloride, the crystallographically independent distances and angles are 3.10 and 3.13 Å, and 180° and 172.3°, respectively.[8]) Furthermore, a frequency calculation showed the strictly planar C_{2v} structure to be a potential energy minimum. Compound **5** was thus a reasonable candidate for use in examining the effects of nitrogen-chlorine interactions in solution.



The synthesis of **5** was relatively straightforward. 2-Ethynylpyridine (**8**) and 3,5-diiodo-4-chloronitrobenzene (**9**) were prepared by literature procedures,[10,11] and a palladium-catalyzed coupling of the two, using tetrakis(triphenylphosphine)palladium(0) and cuprous iodide as catalysts, gave the desired product. However, we note that when the coupling reaction was carried out with bis(triphenylphosphine)palladium(II) chloride, compound **5** was not obtained; instead, a diketone resulting from hydration (with unknown regiochemistry) of the triple bonds in **5** was observed.



The X-ray crystal structure of compound **5** (Figure 1) provided some concern. In the solid state, compound **5** was found to be a disordered mixture of its *trans,trans* and *cis,trans* conformers with little, if any, of the *cis,cis* conformer required for proper complexation of the proposed guest. AM1 calculations were consistent with this result. In the absence of a guest, *trans,trans*-**5** was found to be the ground state, *cis,trans*-**5** was only 0.03 kcal/mol higher in energy, and *cis,cis*-**5** was calculated to be 0.25 kcal/mol higher.

The accuracy of these small calculated differences in energy is doubtful, but clearly all three conformations will be populated in solution. Since a compound existing predominantly as the *cis,cis* isomer need not pay so large an entropic penalty for binding of the guest, a closely related molecule with a conformational bias in favor of the *cis,cis* isomer was sought. Compound **13** is such a molecule. Due to the pendant (4-*tert*-butylbenzyl)oxy groups, it can only adopt the *cis,cis* conformation, and its synthesis, illustrated below, is entirely analogous to that of **5**. Several attempts were made to grow crystals of **13** satisfactory for X-ray analysis, in order to verify its conformation, but none were successful.

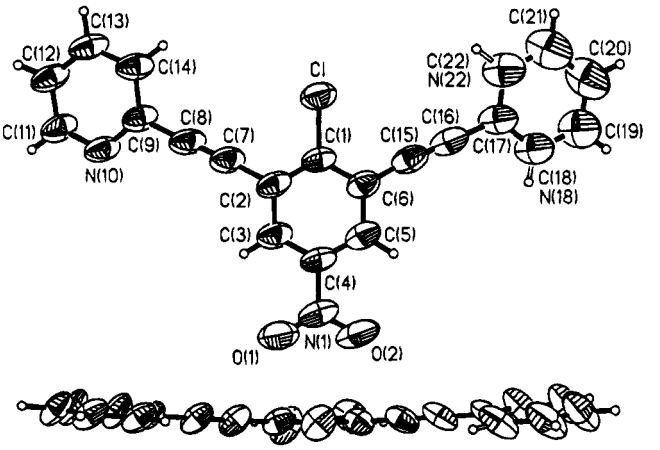
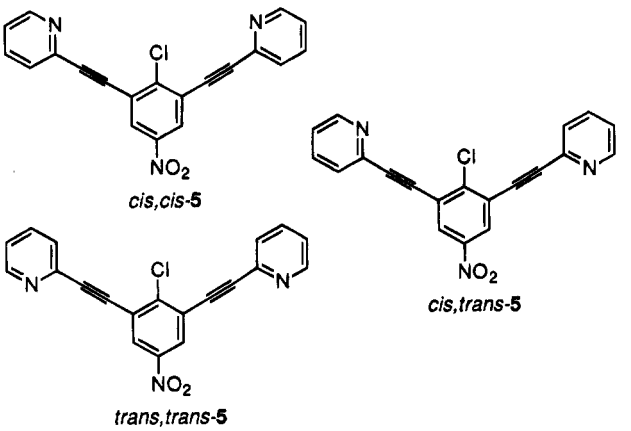
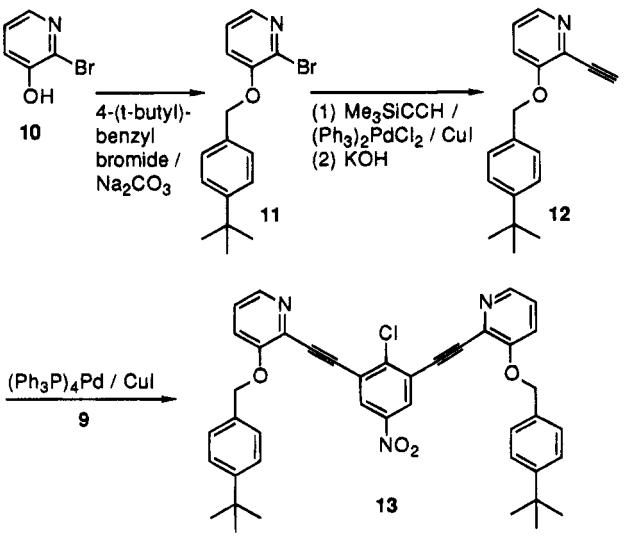


Figure 1. Two views of the X-ray structure of compound **5**. Thermal ellipsoids are drawn at the 50% probability level.



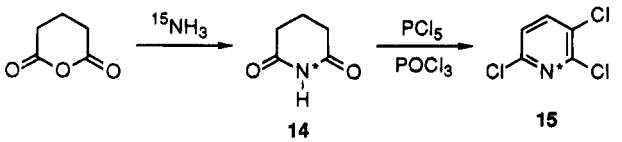


NMR Studies of Complexation with ^{15}N-Labeled Guests and Hosts. Nitrogen–halogen interactions are relatively weak, and the contact distance is generally

(10) Arotsky, J.; Darby, A. C.; Hamilton, J. B. A. *J. Chem. Soc., Perkin Trans. II* **1973**, 595–599.
(11) Sakamoto, T.; Shiraiwa, M.; Kondo, Y.; Yamanaka, H. *Synthesis* **1983**, 312–314.

greater than 3 Å. For this reason, we wished to employ a method that would provide the most nearly direct evidence of the approach of a nitrogen atom of one molecule to the halogen of another. One would expect the approach of the large electron cloud of a halogen atom to result in the magnetic shielding of an ^{15}N nucleus and thus produce an upfield shift of its NMR resonance. Accordingly, we chose to conduct NMR titration experiments with guests and hosts labeled with ^{15}N as probes of molecular association. Furthermore, by conducting the titrations in aromatic solvents, there should be little effect on chemical shifts upon the addition, for example, of an aromatic guest to a solution of an aromatic host, *unless* the molecules could form some specific association.

For our initial ^{15}N NMR experiments, we employed 2,3,6-trichloro[^{15}N]pyridine (**15**), which was synthesized as illustrated below. (In all structure diagrams, the presence of an ^{15}N label is indicated by "N*".) A series of trial reactions had shown that it would be easy to obtain pure **15** by this sequence, but much more difficult to isolate the 2,6-dichloro[^{15}N]pyridine which is also formed. The conversion of glutaric anhydride to [^{15}N]-glutarimide (**14**) was accomplished by bubbling [^{15}N]-ammonia into the melted anhydride at 110 °C for 15 min, followed by dehydration at 180 °C for 10 min. The yield was quite sensitive to the reaction conditions, with incomplete reaction occurring at lower temperatures and decomposition at higher. Treatment of **14** with PCl_5 and $POCl_3$ at 60 °C gave **15** in 40% overall yield.



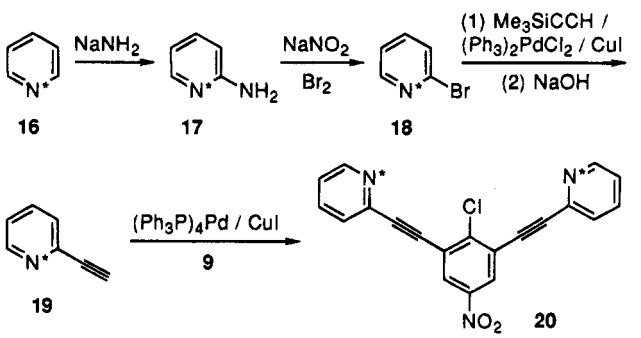
14 15

For NMR titrations, solid compound **5** was added in portions to solutions of **15** (90 mM) in toluene/toluene-d_8. The ^{15}N NMR spectra were recorded at 25 °C at concentrations of **5** ranging from 0 to 18 mM, the limit of solubility of **5**. Unfortunately, the changes in ^{15}N chemical shifts were insignificant—at most 0.03 ppm upfield (1.5 Hz at 50.7 MHz).

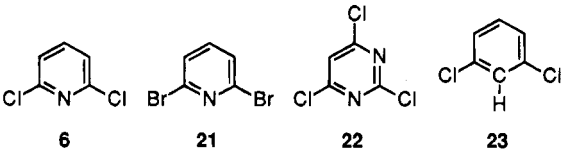
Clearly the association, if any, was very weak, and there would be no way to measure a meaningful association constant unless a much higher concentration of the titrant could be achieved. Compound **13** proved to be no more soluble than **5**, so the titration was reversed. Since simple dihalopyridines have very high solubilities in toluene, a significant result should be achieved by titrating ^{15}N-labeled **5** or **13** with unlabeled dihalopyridines.

Of the two hosts, only the synthesis of ^{15}N-labeled **5** (compound **20**) proved to be practical. [^{15}N]Pyridine (**16**) was prepared as described previously[12] and carefully dried. Amination, diazotization, and bromination under standard conditions gave 2-bromo[^{15}N]pyridine (**18**). The remainder of the synthesis was the same as that for the unlabeled host, and ultimately 190 mg of **20** was obtained from 0.76 g of **16** (11% overall yield).

The ^{15}N NMR titrations with compound **20** gave much more satisfactory results, and substantial changes in the ^{15}N chemical shifts of the pyridyl groups of host **20** were observed upon the addition of several different halogenated guests. In a typical experiment, solid 2,6-dichloropyridine (**6**) was added to a 4.4 mM solution of **20** in toluene/toluene-d_8. Carefully referenced ^{15}N NMR spectra were recorded at 25 °C at concentrations of the guest **6** ranging from 0 to 2 M. Chemical shift changes of up to 1.2 ppm upfield (60 Hz) were observed at high concentrations of the guest. For such weakly associated donor–acceptor complexes, where one component is in great excess, and the NMR chemical shift of the minor component is monitored, the analysis of Hanna and Ashbaugh[13] or Foster and Fyfe[14] is appropriate. Figure 2 illustrates the double reciprocal plot of the change in chemical shift vs the guest concentration.[13] From these data the equilibrium constant for the association reaction illustrated in eq 1 was estimated to be 0.32 ± 0.02 M^{-1}.[15] Similar experiments with 2,6-dibromopyridine (**21**) and 2,4,6-trichloropyrimidine (**22**) yielded association constants of 0.23 ± 0.09 and 0.21 ± 0.07 M^{-1}, respectively.



16 17 18 19 9 20



6 21 22 23

These are very weak association constants, but two factors argue in favor of the specific association illustrated in eq 1. First, the upfield ^{15}N chemical shift changes induced by the 2,6-*dibromo*pyridine were approximately 50% greater than those induced by the chlorinated guests at every concentration, even though the association constants did not differ significantly. This greater shielding of the ^{15}N nuclei is to be expected for interaction with bromine atoms (with larger electron clouds) than for chlorine atoms.[16] Second, and more significant, is the observation that 1,3-dichlorobenzene (**23**), which cannot fit properly into the cleft of **20** due to the presence of a methine group in place of the nitrogen of **6**, induced only much smaller chemical shift changes

(12) (a) Whaley, T. W.; Ott, D. G. *J. Labelled Compds.* **1974**, *10*, 283–286. (b) Leffler, M. T. *Org. React.* **1942**, *1*, 91–104.

(13) Hanna, M. W.; Ashbaugh, A. L. *J. Phys. Chem.* **1964**, *68*, 811–816.

(14) Foster, R.; Fyfe, C. A. *Trans. Faraday Soc.* **1965**, *61*, 1626–1631.

(15) The *y*-intercept of the double reciprocal plot (see Figure 2) is $1/\Delta_0$, where $\Delta_0 = \delta_{20\text{-}6} - \delta_{20}$, the chemical shift change in the fully complexed host, and the slope of the plot is $1/(K_{assoc} \cdot \Delta_0)$. For the complex of **6** and **20**, $\Delta_0 = 150 \pm 6$ Hz, the slope is 0.0207 ± 0.002 M Hz^{-1}, and thus $K_{assoc} = 0.32 \pm 0.02$ M^{-1}.

(16) A referee suggested that, due to the greater bulk of its bromine atoms, the guest **21** might fit less well in the cleft of **20** than guests **6** and **22**, and thus **21** might produce smaller changes in chemical shift than the chlorinated guests. However, Desiraju and Harlow (ref 4) observed that nitrogen–halogen distances in crystalline *p*-halobenzonitriles actually shorten with increasing halogen size (i.e., for N···Cl, the contact was 3.36 Å; for N···Br, 3.25 Å; and for N···I, 3.13 Å). Thus the nitrogen atoms of the host **20** should penetrate more deeply into the bromine electron clouds of **21** than into the chlorines of **6** and **22**, and due to the shorter N···Br contact distance, there should be no difficulty in accommodating the guest **21** in the cleft of the host.

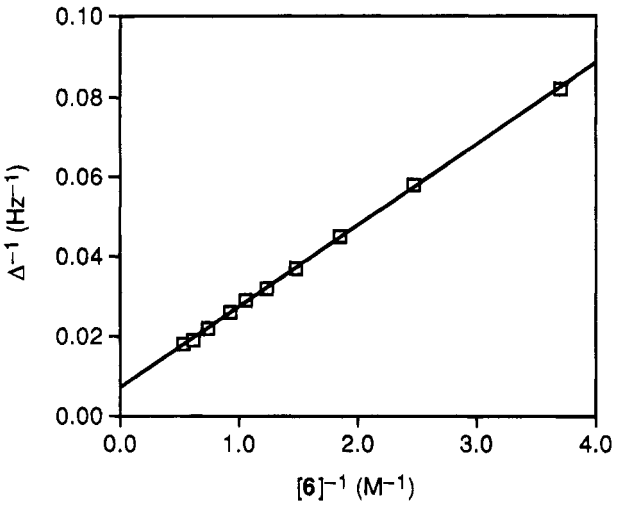


Figure 2. Double reciprocal plot of the titration of host **20** with guest **6** monitored by ^{15}N NMR spectroscopy in toluene/toluene-d_8 solution. The concentration of **20** was 4.4 mM; the concentration of **6** was varied from 0 to 2 M. Spectra were recorded at 50.7 MHz with broad-band proton decoupling; 80% nitromethane in toluene-d_8 was used as an external reference. $\Delta = \delta - \delta_{20}$, the change (in Hz) in the observed chemical shift of the ^{15}N-labeled pyridyl nitrogens of **20** from that of uncomplexed **20**. See the text for discussion.

[e.g. 7 Hz at 1 M], and the data were too scattered to permit the estimation of an association constant.

We had also wished to conduct titration experiments in hexanes or mixtures of hexanes and toluene, but the very poor solubility of the host **20** in these solvents, even at somewhat elevated temperatures, made these experiments impossible. In addition, we made numerous attempts to cocrystallize the hosts **5** and **13** with a variety of potential guests, including **1**, **6**, **15**, **21**, **22**, pentachloropyridine, 2,6-dichloropyrazine, and 2,4,5,6-tetrachloropyrimidine, but no satisfactory crystals of complexes with either host were obtained.

In conclusion, the low association constants observed in our NMR experiments indicate that large numbers of nitrogen–halogen donor–acceptor interactions will be required to form any strongly bound host–guest system where such interactions are the primary attractive force. On the other hand, nitrogen–halogen interactions may prove quite useful as a secondary directing force in molecular association, perhaps acting in conjunction with a stronger force, such as one or more hydrogen bonds, to compel a guest molecule to adopt a particular conformation or orientation when complexed with a host.

Experimental Section

3,5-Bis(2-pyridylethynyl)-4-chloronitrobenzene (5). 3,5-Diiodo-4-chloronitrobenzene[10] (7.3 g, 18 mmol), 2-ethynylpyridine[11] (3.7 g, 36 mmol), tetrakis(triphenylphosphine)palladium(0) (230 mg, 0.20 mmol), and cuprous iodide (16 mg, 0.08 mmol) were heated in a solution of triethylamine (150 mL) and benzene (50 mL) at 80 °C for 20 h under argon. The solvent was evaporated, and water and chloroform were added. After shaking, the organic layer was taken, dried over Na_2SO_4, and concentrated. The residue was chromatographed on a column of silica gel (solvents 1:1 ether–hexanes, then ether) to yield compound **5** (4.0 g, 62%). Recrystallization of this material from ethyl acetate yielded crystals suitable for X-ray analysis: mp 195–196 °C; ^1H NMR ($CDCl_3$) δ 8.66 (d, 2H, J = 4 Hz), 8.42 (s, 2H), 7.73 (ddd, 2H, J = 8, 8, 2 Hz), 7.62 (d, 2H, J = 8 Hz), 7.32 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 150.5, 145.8, 144.4, 142.1, 136.3, 127.9, 127.8, 124.7, 123.9, 96.0, 83.2; MS, m/z 359 (M^+ [^{35}Cl], 100), 313 (M – NO_2, 50), 277 (M – NO_2 – HCl, 55); exact mass 359.0434, calcd for $C_{20}H_{10}{}^{35}ClN_3O_2$ 359.0461.

X-ray Crystallographic Analysis of Compound 5. A crystal of **5** measuring 0.15 mm × 0.38 mm × 0.42 mm was used for X-ray measurements. Crystal data: $C_{20}H_{10}ClN_3O_2$; monoclinic, space group $P2_1/c$; a = 13.466 (2) Å, b = 11.303 (2) Å, c = 11.479 (2) Å, β = 107.84 (2)°, V = 1663.2 (5) Å^3, Z = 4, D_{calcd} = 1.437 g/cm^3. Intensity measurements were made with 4° ≤ 2θ ≤ 50° by using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) at 235 K on a Siemens P4 diffractometer. A total of 2946 independent reflections were measured, of which 1370 were considered to be observed [$|F_o| > 3\sigma(F_o)$]. The structure was solved by heavy atom methods (Patterson) and refined with the SHELXTL PLUS software. Refinement of 235 parameters converged at $R(F)$ = 0.045, wR(F) = 0.044, with goodness-of-fit = 1.02. All of the nonhydrogen atoms were refined with anisotropic displacement coefficients, hydrogen atoms were included with a riding model [C–H = 0.96 Å, U(H) = 1.2U(C)], and the weighting scheme employed was $w^{-1} = \sigma^2(F) + 0.0006F^2$. Refinements with Atom(18) treated as 100% N and Atom(22) as 100% C gave U(eq) values for N(18) = 0.111 (2) Å^2 and C(22) = 0.082 (2) Å^2. A reverse assignment with Atom(18) treated as 100% C and Atom(22) as 100% N gave U(eq) values for C(18) = 0.080 (2) Å^2 and N(22) = 0.115 (2) Å^2. These results are consistent with rotational disordering of the pyridyl ring. Therefore, Atom(18) and Atom(22) were both treated as though containing 50% C and 50% N. Refinement of this disorder model gave the final balanced and more realistic U(eq) values of 0.095 (2) and 0.098 (2) Å^2 for Atom(18) and Atom(22), respectively.[21]

3-((4-*tert*-Butylbenzyl)oxy)-2-bromopyridine (11). 2-Bromo-3-pyridinol (5.0 g, 29 mmol), 4-*tert*-butylbenzyl bromide (13.0 g, 57 mmol), and Na_2CO_3 (6.2 g, 58 mmol) were heated in methanol (150 mL) at reflux for 17 h. Sodium metabisulfite (10.9 g, 57 mmol) was added, and the mixture was heated for another 4 h. After cooling, the mixture was poured into 1 M NaOH, and it was extracted with dichloromethane (2 × 200 mL). The combined organic layers were dried over Na_2SO_4 and concentrated, and the resulting red oil was crystallized from ethyl acetate to yield white crystals of compound **11** (8.0 g, 87%), mp 147–148 °C; ^1H NMR ($CDCl_3$) δ 7.99 (t, 1H, J = 3 Hz), 7.42 and 7.39 (AA'BB' system, 4H), 7.18 (d, 2H, J = 3 Hz), 5.15 (s, 2H), 1.33 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 151.7, 150.8, 141.0, 132.8, 132.1, 126.6, 125.2, 123.1, 120.0, 70.3, 34.2, 31.0; MS, m/z 319 (M^+ [^{79}Br], 3), 147 ($C_{11}H_{15}^+$, 100); exact mass 319.0574, calcd for $C_{16}H_{18}{}^{79}BrNO$ 319.0572

3-((4-*tert*-Butylbenzyl)oxy)-2-ethynylpyridine (12). Compound **11** (3.0 g, 9.4 mmol), (trimethylsilyl)acetylene (0.92 g, 9.4 mmol), bis(triphenylphosphine)palladium(II) chloride (130 mg, 0.19 mmol), and cuprous iodide (13 mg, 0.07 mmol) were stirred in diethylamine (40 mL) at 50 °C for 4 h under argon. The solvent was removed by rotary evaporation, and the residue was treated with a mixture of 1 M KOH (25 mL) and methanol (35 mL) for 1 h. Most of the methanol was evaporated, water (80 mL) was added, and the mixture was extracted with ether (2 × 120 mL). The combined organic layers were dried over Na_2SO_4, concentrated, and chromatographed

on silica gel (solvent 2:1 hexanes–ether) to yield compound **12** (1.2 g, 48%), mp 116.0–116.5 °C: ^{1}H NMR ($CDCl_3$) δ 8.18 (dd, 1H, J = 4, 2 Hz), 7.40 and 7.37 (AA'BB' system, 4H), 7.21 (d, 1H, J = 2 Hz), 7.18 (d, 1H, J = 4 Hz), 5.15 (s, 2H), 3.40 (s, 1H), 1.32 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 156.5, 151.1, 142.0, 132.9, 132.8, 126.7, 125.5, 124.0, 119.7, 81.5, 79.5, 70.3, 34.5, 31.2; MS, m/z 265 (M^+, 8), 147 ($C_{11}H_{15}^+$, 100); exact mass 265.1451, calcd for $C_{18}H_{19}NO$ 265.1467.

3,5-Bis[[3-((4-*tert*-butylbenzyl)oxy)-2-pyridyl]ethynyl]-4-chloronitrobenzene (13). Compound **12** (200 mg, 0.75 mmol), 3,5-diiodo-4-chloro-nitrobenzene[10] (154 mg, 0.38 mmol), tetrakis(triphenylphosphine)palladium(0) (9 mg, 0.008 mmol), and cuprous iodide (1 mg, 0.005 mmol) were heated in a solution of triethylamine (6 mL) and benzene (2 mL) at 80 °C for 4 h under argon. The solvent was evaporated, and the residue was chromatographed on a column of silica gel (solvents 20:1 dichloromethane–methanol) to yield compound **13** (120 mg, 47%), mp 170 °C dec; ^{1}H NMR ($CDCl_3$) δ 8.44 (s, 2H), 8.30 (m, 2H), 7.44 (m, 8H), 7.32 (m, 4H), 5.21 (s, 4H), 1.31 (s, 18H); ^{13}C NMR ($CDCl_3$) δ 156.9, 151.5, 145.7, 144.3, 142.4, 132.8, 132.6, 127.5, 127.1, 125.7, 125.0, 124.6, 119.7, 93.0, 88.0, 70.5, 34.6, 31.3; MS, m/z 683 (M^+ [^{35}Cl], 32), 537 (M – $C_{11}H_{14}$, 6), 147 ($C_{11}H_{15}^+$, 100); exact mass 683.2560, calcd for $C_{42}H_{38}{}^{35}ClN_3O_4$ 683.2551.

[^{15}N]Glutarimide (14). Glutaric anhydride (1.00 g, 8.77 mmol) was heated to 110 °C, and [^{15}N]ammonia (1 L, 99.7 atom % ^{15}N) was bubbled into the liquid over 15 min. A dry ice condenser was used to collect the ammonia which escaped, and this material was passed through the liquid a second time. The mixture was then heated to 180 °C for 10 min, and after cooling the crude product was dissolved in acetone (200 mL). This solution was dried over Na_2SO_4, the solvent was evaporated, and the residue was recrystallized from benzene to give compound **14** (0.82 g, 82%), mp 152–154 °C [lit.[17] mp 154.5 °C (unlabeled)]: ^{1}H NMR ($CDCl_3$) δ 8.04 (br s, 1H), 2.60 (t, 4H, J = 7 Hz), 2.01 (quintet, 2H, J = 7 Hz).

2,3,6-Trichloro[^{15}N]pyridine (15). Compound **14** (100 mg, 0.88 mmol) and phosphorus pentachloride (600 mg) were mixed together, and phosphorus oxychloride (1.0 mL) was added with stirring. The reaction mixture turned golden yellow with vigorous evolution of HCl. The reaction mixture was then heated to 60 °C for 15 min. After cooling, it was poured onto ice, the resulting solid was broken up, and ammonium hydroxide solution was added until the pH was greater than 9. The mixture was extracted with dichloromethane (2 × 100 mL), and the combined organic layers were dried over Na_2SO_4, concentrated, and chromatographed on silical gel (solvent hexanes) to yield pure 2,3,6-trichloro[^{15}N]pyridine (78 mg, 49%), mp 68.5–69.5 °C [lit.[18] mp 66–67 °C (unlabeled)]: ^{1}H NMR (CD_3CN) δ 7.90 (dd, 1H, J_{HH} = 8, J_{HN} = 0.5 Hz), 7.26 (dd, 1H, J_{HH} = 8, J_{HN} = 1 Hz); ^{13}C NMR ($CDCl_3$) δ 148.2 (d, $^1J_{CN}$ = 6 Hz), 148.0 (d, $^1J_{CN}$ = 7 Hz), 140.6, 129.4 (d, $^2J_{CN}$ = 3 Hz), 123.9; ^{15}N NMR (toluene-d_8) δ –73.39; MS, m/z 182 (M^+ [$^{15}N^{35}Cl_3$], 100), 147 (M – Cl, 58), 111 (M – Cl – HCl, 31).

2-Amino[^{15}N]pyridine (17). [^{15}N]Pyridine [0.76 g, 9.5 mmol; prepared by as described previously[12] from [^{15}N]-ammonium chloride (99.7 atom % ^{15}N)] and sodium amide (0.92 g) were stirred in *N,N*-dimethylaniline (4 mL) at 118 °C for 18 h under argon. After cooling, 5% NaOH solution (5 mL) was added, followed by water (15 mL). The mixture was stirred for 15 min and then extracted with petroleum ether (10 mL) to remove the dimethylaniline. Additional solid NaOH was added to the aqueous layer, and after cooling, it was extracted with benzene (3 × 20 mL). Concentration left a yellow residue of **17** (0.59 g, 66%) which crystallized upon standing, mp 57.5–58 °C [lit.[19] mp 57.5 °C (unlabeled)]: ^{1}H NMR ($CDCl_3$) δ 8.08 (dddd, 1H, J_{HN} = 11, J_{HH} = 5 Hz, 2 Hz, 1 Hz), 7.42 (ddd, 1H, J = 8, 8, 2 Hz), 6.64 (m, 1H), 6.50 (dd, 1H, J = 8, 1 Hz), 4.38 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 158.4 (d, $^1J_{CN}$ = 6 Hz), 148.0 (d, $^1J_{CN}$ = 7 Hz), 137.6, 113.8, 108.5.

2-Bromo[^{15}N]pyridine (18). Compound **18** was prepared by the method of Craig[20] (for the unlabeled compound). Compound **17** (0.59 g, 6.2 mmol) and hydrobromic acid (48%, 3.7 mL) were mixed and cooled to –2 °C. Bromine (1.0 mL, 19 mmol) was added dropwise, and the mixture turned deep orange. Sodium nitrite (1.1 g, 16 mmol) was then added in small portions with vigorous evolution of nitrogen. After stirring for another 20 min, 30% NaOH (12 mL) was added gradually so that the temperature rose only to 10 °C. After 15 min, the mixture was extracted with ether (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, concentrated, and chromatographed on silica gel (solvent 3:1 hexanes–ether) to yield compound **18** (0.61 g, 62%): ^{1}H NMR ($CDCl_3$) δ 8.37 (dddd, 1H, J_{HN} = 12, J_{HH} = 5, 2, 1 Hz), 7.50 (m, 2H), 7.27 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 150.1 (d, $^1J_{CN}$ = 9 Hz), 142.1 (d, $^1J_{CN}$ = 3 Hz), 138.4, 128.1, 122.5; MS, m/z 158 (M^+ [$^{15}N^{79}Br$], 58), 79 (M – Br, 100).

2-Ethynyl[^{15}N]pyridine (19). Compound **19** was prepared by the method of Sakamoto et al.[11] (for the unlabeled compound). Compound **18** (0.61 g, 3.8 mmol), (trimethylsilyl)acetylene (0.53 g, 5.4 mmol), bis(triphenylphosphine)palladium(II) chloride (40 mg, 0.057 mmol), and cuprous iodide (4 mg, 0.02 mmol) were stirred in diethylamine (15 mL) at 40 °C for 5 h under argon. The solvent was removed by rotary evaporation, and the residue was treated with a mixture of 1 M NaOH (5 mL) and methanol (5 mL) for 1 h. Then 3 M HCl (3 mL) was added, and most of the methanol was evaporated. The pH was adjusted to 10 with K_2CO_3, and the mixture was extracted with ether (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, concentrated, and chromatographed on silica gel (solvent 2:1 hexanes–ether) to yield 2-ethynyl[^{15}N]pyridine (0.18 g, 45%): ^{1}H NMR ($CDCl_3$) δ 8.60 (dddd, 1H, J_{HN} = 11, J_{HH} = 5, 2, 1 Hz), 7.66 (ddd, 1H, J = 8, 8, 2 Hz), 7.48 (dd, 1H, J = 8, 1 Hz), 7.28 (m, 1H), 3.16 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 150.0 (d, $^1J_{CN}$ = 8 Hz), 142.3, 136.1, 127.4, 123.4, 87.9, 82.7 (d, $^3J_{CN}$ = 9 Hz); MS, m/z 104 (M^+, 100), 76 (M – $HC^{15}N$, 36).

3,5-Bis(2-[^{15}N]pyridylethynyl)-4-chloronitrobenzene (20). 3,5-Diiodo-4-chloronitrobenzene[10] (0.34 g, 0.83 mmol), 2-ethynyl[^{15}N]pyridine (0.18 g, 1.7 mmol), tetrakis(triphenylphosphine)palladium(0) (18 mg, 0.016 mmol), and cuprous iodide (2 mg, 0.01 mmol) were heated in a solution of triethylamine (10 mL) and benzene (4 mL) at 80 °C for 12 h under argon. The solvent was

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(21) The author has deposited atomic coordinates for structure 5 with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

evaporated, and the yellow residue was chromatographed on a column of silica gel (solvents 2:1 ether–hexanes, then ether) to yield compound **20** (0.19 g, 63%), mp 192.5–193.5 °C: ^{1}H NMR ($CDCl_3$) δ 8.69 (dd, 2H, J_{HN} = 11, J_{HH} = 4 Hz), 8.47 (s, 2H), 7.76 (ddd, 2H, J = 8, 8, 2 Hz), 7.64 (d, 2H, J = 8 Hz), 7.34 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 150.4 (d, $^1J_{CN}$ = 8 Hz), 145.8, 144.4, 142.1 (d, $^1J_{CN}$ = 3 Hz), 136.4, 127.9 (d, $^2J_{CN}$ = 5 Hz), 127.7, 124.7, 123.9, 96.0 (d, $^3J_{CN}$ = 10 Hz), 83.2 (d, $^2J_{CN}$ = 2 Hz); ^{15}N NMR (toluene-d_8) δ −56.63; MS, m/z 361 (M^+ [$^{35}Cl^{15}N_2$], 100), 315 (M − NO_2, 34), 279 (M − NO_2 − HCl, 13); exact mass 361.0402, calcd for $C_{20}H_{10}{}^{35}Cl^{14}N^{15}N_2O_2$ 361.0402.

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Supporting Information Available: ^{1}H NMR spectra of compounds **5**, **11**, **12**, **13**, **15**, **17**, **18**, and **20** and ^{13}C NMR spectra of compounds **5**, **13**, and **20** (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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