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Aromaticity and Aminopyrroles: Desmotropy and Solution Tautomerism of 1*H*-Pyrrol-3-aminium and 1*H*-Pyrrol-3(2*H*)-iminium Cation: A Stable σ-Complex

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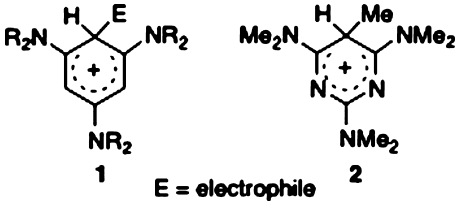
Supporting Information

ABSTRACT: Protonation of 3-aminopyrrole at C-2 gave the σ-complex 1*H*-pyrrol-3(2*H*)-iminium cation, whereas protonation at the exoamino group gave its 1*H*-pyrrol-3-aminium tautomer. Both tautomers were isolated as their respective tetrakis(pentafluorophenyl)borate salt, an example of desmotropy. In solution, the NH_3-tautomer was favored in hydrogen-bonding solvents and the CH_2-tautomer in CH_2Cl_2. A combination of effects on the aromaticity of the aminopyrrole ring increased the relative stability of the σ-complexes (conjugate acids) such that they can be readily observed or isolated.

INTRODUCTION

Cationic σ-complexes (Wheland intermediates[1]) are the pivotal intermediates in electrophilic aromatic substitution reactions,[2] one of the most important classes of reactions in organic chemistry. Many studies have appeared in which they have been isolated and characterized.[3] Of particular interest, to this study, are the examples illustrated in Chart 1. The groups of

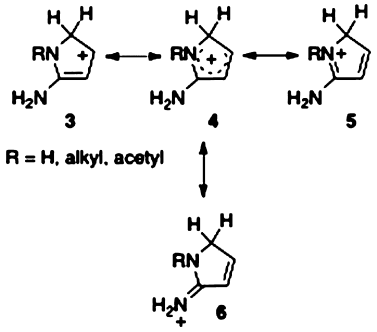
Chart 1. Examples of Stable Amino σ-Complexes



Effenberger[4] and Demeter[5] have isolated σ-complexes of 1,3,5-tris(dialkylamino)benzenes **1** and 2,4,6-triaminopyrimidines **2**, respectively. Recently, Forlani isolated the first Meisenheimer–Wheland complexes with the cationic σ-complexes derived from 1,3,5-tris(dialkylamino)benzenes.[6,7]

The simplest electrophilic aromatic substitution reaction is hydrogen or hydrogen isotope exchange,[2b] and the σ-complex formed is the conjugate acid of the aromatic or heteroaromatic compound undergoing exchange. Previously in our work,[8] and that of others,[9] the isolated conjugate acids of 2-aminopyrroles, resulting from C-protonation of the pyrrole ring, have been figured as localized structures such as iminium (**6**)[8,9e,f] and amidinium[9a] ions or as an analogue[9c,d] of **5** and not as delocalized structures as is the general practice for cationic σ-complexes (Chart 2). The delocalized structure of **4**, in Chart 2, has been rotated to emphasize the analogy of **4** with σ-complexes **1** and **2**. It can therefore be seen that the conjugate acids of 2-aminopyrrole and 1-substituted-2-aminopyrroles,

Chart 2. Resonance Structures of 1*H*-Pyrrol-2(5*H*)-iminium Cations



isolated as their tetraphenylborate salts, are previously unrecognized stable σ-complexes.[8] It should also be noted that stable salts of ring substituted 2-aminopyrroles have also been isolated.[9a−d]

As part of our study of the chemistry of aminopyrroles, we turned our attention to the isolation of the tetraphenylborate salt of 3-aminopyrrole. With this salt in hand, it could be used to generate the unstable 3-aminopyrrole in situ. With the analogous 2-aminopyrrole salts in situ, generation of 2-aminopyrroles led to reactions and intermediates not previously reported in more highly substituted 2-aminopyrroles.[10] It might be expected that similar novel results might be expected for simple 3-aminopyrroles. Not unexpectedly, the tetraphenylborate salt of 3-aminopyrrole was isolable and when treated with Et_3N gave 3-aminopyrrole. What was unexpected was the isolation of *two* salts: a species corresponding to protonation on carbon (a σ-complex analogous to **4**) and the aromatic tautomer from protonation of the amino group, the first

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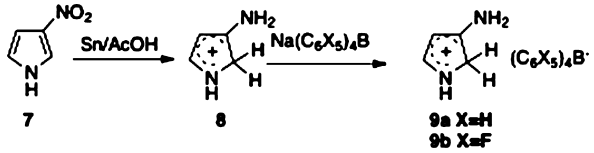
example of desmotropy[11] in pyrrole chemistry. Further, in solution both tautomerized with the tautomeric ratio contingent on the nature of the solvent.[12] A proposal is made to explain why the σ-complexes of aminopyrroles are stable enough to be observed and isolated.

RESULTS AND DISCUSSION

To our best knowledge, the parent 3-aminopyrrole has not been reported,[13] and the only simple 3-aminopyrroles (without further substitution on the ring) reported to date were the 1-trityl derivative[14] as the imino tautomer and the picrate of 1-phenyl-3-aminopyrrole.[15] Reduction of nitropyrroles has been used in the synthesis of aminopyrroles.[13,16] Recently, Gribble reported that reduction of 3-nitropyrrole[17] with Sn/acetic acid, in the presence of an imide, gave a 3-imido derivative, presumably by the trapping of the 3-aminopyrrole.[18] Similarly bipyrroles were obtained under Paal–Knorr conditions.[19] This suggested the possibility that the conjugate acid of 3-aminopyrrole was formed during the reduction of 3-nitropyrrole with Sn/acetic acid and therefore could be isolated as the tetraphenylborate salt, in a manner analogous to that of 2-aminopyrrole and 1-substituted 2-aminopyrroles.[8]

Reduction of 3-nitropyrrole (**7**) with Sn/acetic acid was over in 2–2.5 h (no starting material was detectable by TLC) (Scheme 1). The reaction mixture was filtered, through Celite,

Scheme 1. Isolation of 1*H*-Pyrrol-3(2*H*)-iminium Salts

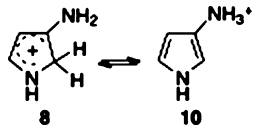


directly into an aqueous solution of sodium tetraphenylborate; the tetraphenylborate salt **9a** precipitated out and was isolated in 96–100% yield. Based on results to be discussed below, the structure of the precipitated salt was the σ-complex **9a** from protonation on carbon. In the discussion below the σ-complex will be referred to as the CH_2-tautomer **8**, whereas NH_3-tautomer **10** will be used for the aromatic tautomer.

In a similar fashion, the perfluoro salt **9b** was isolated in 78–96% yield and used in all of the ^{1}H NMR spectral studies to avoid any overlap of the desired signals with the phenyl signals. Previous ^{1}H NMR studies on more substituted 3-amino derivatives have reported that the site of protonation (C2 vs NH_2) depended on the medium.[20] When the ^{1}H NMR of **9b** was taken, in THF-d_8, two species were present; one of them contained a CH_2 group as demonstrated by DEPT-135 C-13 NMR and the other a NH_3^+ group (^{1}H NMR), results indicative of a tautomeric equilibrium between **8** (CH_2-tautomer) and **10** (NH_3-tautomer) (Scheme 2). Under these conditions, the ratio of **8** to **10** was 13:87.

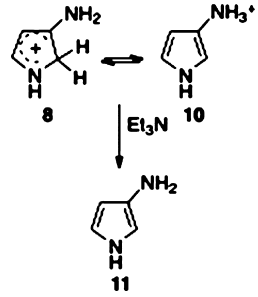
That **8** and **10** were tautomers was confirmed when Et_3N-d_{15} was added to the tautomeric mixture and only 3-aminopyrrole

Scheme 2. Tautomeric Equilibrium



(**11**) (Scheme 3 and Figure 2d) was observed. When D_2O (to identify the amino protons) or H_2O was added to the

Scheme 3. Formation of 3-Aminopyrrole (11)



tautomeric mixture, almost all of the CH_2-tautomer **8** was converted to **10** (7% of **8** was left).

But the initial ratio of the two tautomers depended on how the salt was isolated: The ^{1}H NMR (THF-d_8) of the salt, precipitated from H_2O/acetic acid (precipitated salt), was richer in the CH_2-tautomer **8** and slowly equilibrated over a 2–3 h period to the same ammonium NH_3-tautomer **10**-rich mixture obtained (in 10 min) from a sample of the salt that had been washed with $NaHCO_3$ (to remove traces of acetic acid) and recrystallized from DCM/hexanes (base washed salt). It should be noted that salt **9b** recrystallized from DCM/hexanes, but not washed with $NaHCO_3$, was richer in the CH_2 tautomer.[21] The differences observed in the initial tautomeric ratio, and time to reach equilibrium, suggested that the precipitated and base washed salts were not identical.

To determine the structures of the two isolated solids a sample of each salt was added to THF-d_8 that had been cooled to −70 °C and its ^{1}H NMR taken at −70 °C; the ^{1}H NMR spectrum of the precipitated salt had a peak at δ 4.74 ppm diagnostic for the CH_2 group of the CH_2-tautomer **8**, whereas no such signal was present in the base-washed salt but a NH_3^+ signal was evident (Figure 1). Therefore, the precipitated salt was the σ-complex (CH_2-tautomer **8**), and the base-washed salt was the NH_3-tautomer **10**. Tautomerization was evident on warming the two solutions to 25 °C, and after 1 h essentially the same mixture was obtained from both samples (Figure 1).[22] Desmotropy is when the two tautomers can be separated. Only a limited number of examples of this phenomenon have been reported.[11] The ^{1}H NMR results, illustrated in Figure 1, demonstrated that desmotropy was observed in this study; to our best knowledge, this is the first example in pyrrole chemistry and the first example involving charged species.[11]

A study was carried out starting with **9b** (base washed salt) to determine the effect of solvent (Table 1) on the tautomeric ratio (K_T = **8**/**10**). The NH_3-tautomer was used because it reached equilibrium faster than the CH_2 tautomer where a C–H bond would have to be broken for tautomerization to take place. In CD_2Cl_2 (Figure 2a), ^{1}H NMR indicated that essentially only the CH_2-tautomer **8** was present (K_T = 99), in contrast, in DMF-d_7 and DMSO-d_6 (Figure 2c) essentially only the NH_3-tautomer **9** was present (K_T = 0.01), whereas in CD_3CN (Figure 2b) K_T = 1.4. The results in Table 1 indicated that the NH_3-tautomer **10** was favored in hydrogen-bonding solvents, and hydrogen-bond acceptor solvents in particular. The less polar CH_2-tautomer was favored in CD_2Cl_2. Interestingly, the K_T ratio in CD_3CN would indicate that in

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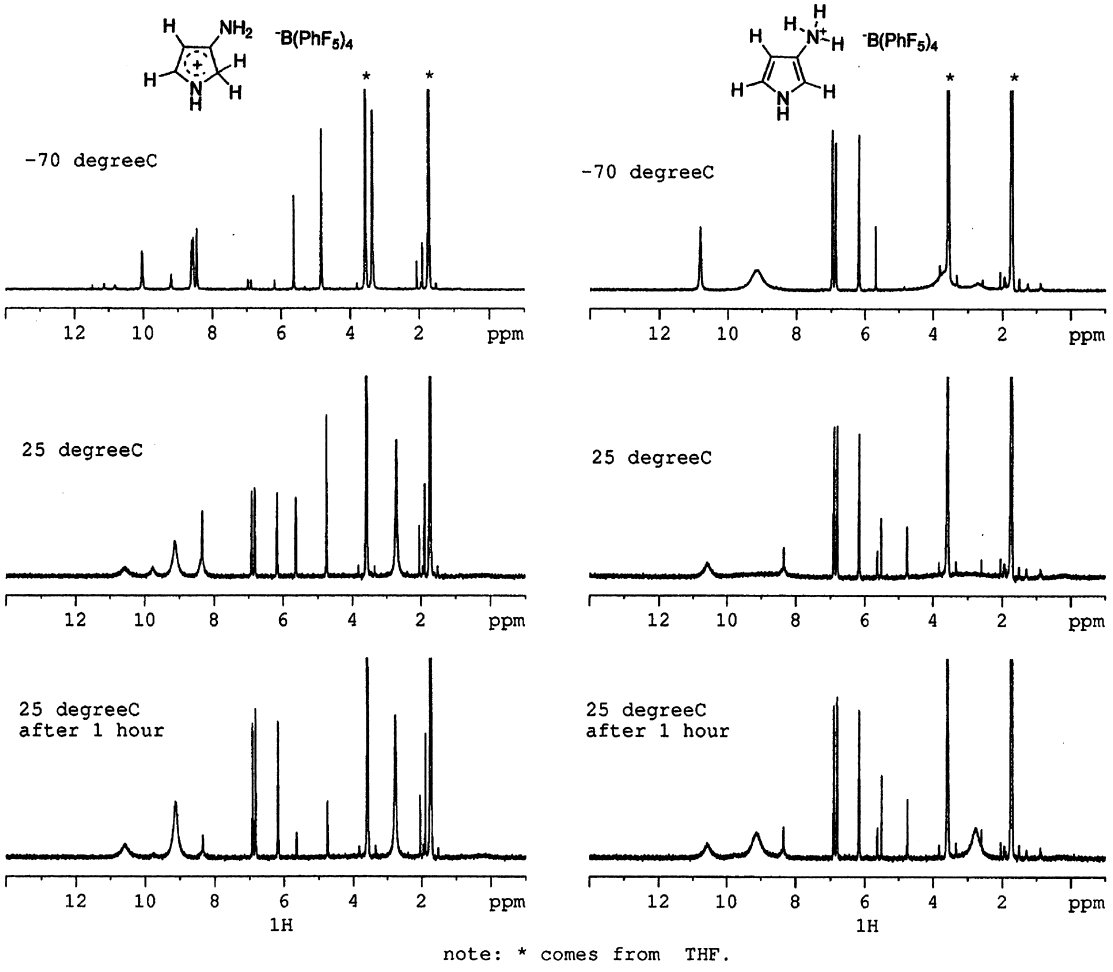

Figure 1. Low-temperature ^{1}H NMR study of salt **9b**.

Table 1. ^{1}H NMR Tautomerism Study of 9b (Base Washed) in Different Solvents at Equilibrium[a]

entry	solvent	% NH_2	% NH_3	K_T (NH_2/NH_3)
1	CD_2Cl_2	>99	<1	99
2	CD_3CN	58	42	1.2
3	THF-d_8	13	87	0.1
4	MeOD	2	98	0.02
5	DMF-d_7	1	99	0.01
6	DMSO-d_6	<1	>99	0.01

[a]NMRs taken at 25 °C, and solutions were 0.063 M.

this solvent both tautomers apparently have about the same energy.

In deuteroacetone, the solution turned brown with a third species present (^{1}H NMR). Addition of Et_3N-d_{15} converted all of the species present to 3-aminopyrrole (**11**). It seemed unlikely that this new species was another tautomer and was most likely an intermediate formed from the reaction of 3-aminopyrrole (**11**) with deuteroacetone. For this reason, the K_T value in deuteroacetone was not included in Table 1. When base (Et_3N-d_{15}) was added to the conjugate acid(s), only one tautomer, 3-aminopyrrole, was observed in all solvents studied.[23] The results are in accord with theoretical calculations that predicted that this was the most stable tautomer.[24]

The only theoretical study that has appeared was on the tautomeric conjugate acids of 2-aminopyrroles.[25] Ring protonation (CH_2-tautomer) was favored in accord with experimental results,[8] but protonation at the exocyclic amino group was predicted when the following three conditions were present simultaneously: the presence of electron-withdrawing substituents, polar solvents, and negatively charged cosolutes. This study indicated that it was not only the polarity of the solvent that was important but also its hydrogen-bonding ability that determined which was the dominant tautomer. The other two factors were not addressed in this study.

The stability of the isolated σ-complexes of 1,3,5-tris(dialkylamino)benzenes[4] **1** and 2,4,6-triaminopyrimidines[5c] **2** has been attributed to the stabilizing effect of the three electron-donating amino groups present in these compounds. Since the first[9e] conjugate acids of 2-aminopyrroles were detected by ^{1}H NMR in 1968, a relatively large number of aminopyrrole salts have been isolated, including examples in which an electron-withdrawing group (CN or CO_2R) was present. It is proposed that other factors may be playing a role in the relative ease of detection and isolation not only of the σ-complex (**9**) of 3-aminopyrrole but also that of 2-aminopyrroles σ-complexes.

Electrophilic aromatic substitution occurs because the loss of a proton (or other leaving group) is faster (lower activation energy) than the reaction of the σ-complex with a nucleophile to give an addition product with the resulting loss of aromatic stabilization: the tendency to retain structure.[26] If this difference in activation energy narrows then one of the

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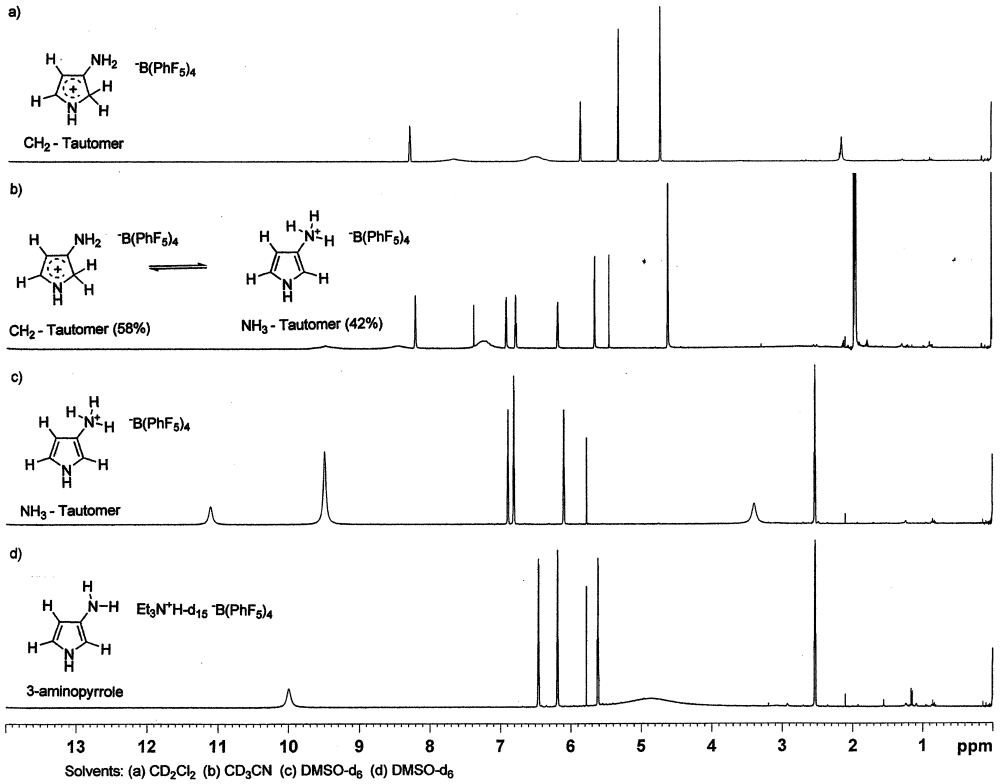

Figure 2. Effect of solvent on tautomeric equilibrium and 3-aminopyrrole.

following could occur: other reactions (addition) could become competitive, the lifetime[3c] of the σ-complex could be increased such that it could be observed or trapped, or the reaction could become reversible. There are three ways in which the difference in activation energy, between these competing possibilities, could narrow: the stability of ground state could decrease (less aromatic as measured by aromatic stabilization energy[27]) with little or no change in the transition state (intermediate), stabilization of the transition state (intermediate) could decrease with little or no change in the ground state, or a combination of these two effects.

Pyrroles, and in general heteroaromatic compounds, are less aromatic than benzene.[28] Additionally, the pyrrole nitrogen (heteroatom) stabilizes the σ-complex (intermediate).[29] The combination of these two effects is reflected in the ease of protonation[30] (σ-complex formation) of pyrrole vs benzene: pyrrole[31] was substantially protonated (by ^{1}H NMR)[32] in 0.1 M acid, compared to an estimate of less than one molecule per mole of benzene in 1 M acid (lifetime of <100 ps).[33] Similar results have been observed in thiophene derivatives.[29,31] Another difference between benzene and pyrrole is the effect that substituents have on aromaticity; substituents have little effect on the aromaticity of the benzene ring.[34,35] This is not the case for pyrrole where electron-withdrawing substituents on nitrogen[36] and electron-donating substituents on carbon[37] decreased the aromaticity of the pyrrole ring (more dienic/enaminic) and for the same reason; at these positions, the substituents suppressed delocalization of the nitrogen electron pair into the pyrrole ring.

Electron-withdrawing substituents on pyrrole nitrogen have received the most attention;[38] when electron-withdrawing substituents are present pyrroles undergo Diels–Alder reactions more readily than pyrrole.[39] Less attention has been paid to ring-substituted pyrroles. It has been observed that 2-aminopyrroles behave as enamines, reacting on either carbon (Michael addition[10a] or cycloaddition[40,41]) or nitrogen[10c] (S_NAr). The enaminic character of aminothiophenes has also been ascribed to a lower aromaticity of the aminothiophene ring.[42] Calculations by Radom[37] indicated that π-electron donors such as the amino group decreased aromatic stabilization by suppressing electron donation from the pyrrole nitrogen with the effect being greatest when the substituent was on C2. The amino group of aminopyrroles therefore stabilized the cationic σ-complex via π-electron donation and the same effect destabilized the pyrrole ring. The net effect was to increase the lifetime of the σ-complex (narrow the activation energy gap as discussed above).

It is therefore proposed that a combination of effects, on the aromaticity of the aminopyrrole ring, increased the relative stability of the σ-complexes (conjugate acids) such they can be readily observed or isolated, as was the case in this study.

■ EXPERIMENTAL SECTION

General Experimental Procedures. All reactions were performed under either an atmosphere of argon or nitrogen gas. Reactions were monitored by TLC analysis, and visualization was accomplished with a 254 nm UV light. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained in THF-d_8 unless otherwise specified. Chemical shifts were reported in parts per million with the residual solvent peak or TMS used as an internal standard. ^{1}H NMR spectra were recorded at 400 MHz and are tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), number of protons, and coupling constants. ^{13}C NMR were recorded at 100 MHz using a proton-decoupled pulse sequence with a d_1 of 5 s and are tabulated by observed peak. The 3-nitropyrrole, sodium tetraphenylborate, and

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potassium tetrakis(pentafluorophenyl)borate were commercially available.

1*H*-Pyrrol-3(2*H*)-iminium Tetraphenylborate (9a). A gray suspension of 3-nitropyrrole (350 mg, 3.12 mmol) and tin powder (1.85 g, 15.6 mmol, 5 equiv) in glacial AcOH (20 mL) was stirred at room temperature for 2 h under a nitrogen gas atmosphere. The thick gray reaction mixture was then diluted with distilled water (5 mL), and the resulting thin solution was pressure filtered through a plug of Celite (2 in.) into a solution of $NaBPh_4$ (4.27g, 12.5 mmol, 4 equiv) in distilled water (20 mL) with stirring. The plug of Celite was flushed with distilled water (~30 mL) until no longer golden in color. The resulting suspension was vacuum filtered. The isolated solid was washed with distilled water (35 mL) and dried in vacuo over P_2O_5 to afford **9a** as a yellow solid (1.20 g, 96%). An analytical tin analysis of **9a** (100.0 mg) was performed by Galbraith Laboratories and revealed 0.545% tin. Based on tin and ^{1}H NMR analysis the salt purity is estimated to be >90%: mp 170.6−173.7 °C dec; ^{1}H NMR (400 MHz, THF-d_8, 10 min, $^-BPh_4$ peaks) δ 7.32 (br m, 8 H), 6.88 (t, 8 H, J = 7.4 Hz), 6.74 (t, 4 H, J = 7.4 Hz); ^{1}H NMR (400 MHz, THF-d$_8$, 10 min, CH_2-tautomer, 29%) δ 8.20 and 7.46 (br s, 2 H), 7.26 (br s, 1 H), 5.09 (d, 1 H, J = 2.8 Hz), 3.56 (s, 2 H); ^{1}H NMR (400 MHz, THF-d_8, 10 min, NH_3-tautomer, 71%) δ 10.05 (br s, 1 H), 8.20 (br s, 3 H), 6.62 (dd, 1 H, J = 5.2, 2.8 Hz), 6.56 (ddd, 1 H, J = 4.4, 2.2, 0.8 Hz), 5.95 (dd, 1 H, J = 4.4, 2.8 Hz); ^{13}C NMR (100 MHz, THF-d_8, $^-BPh_4$ peaks) δ 165.0 (q, 4 C, J_{C-B} = 49 Hz), 137.0 (q, 8 C, J_{C-B} = 1.5 Hz), 126.0 (q, 8 C, J_{C-B} = 3.0 Hz), 122.1 (4 C); ^{13}C NMR (100 MHz, THF-d_8, CH_2-tautomer) δ 179.5, 169.2, 69.1, 54.7; ^{13}C NMR (100 MHz, THF-d_8, NH_3-tautomer) δ 119.9, 114.2, 112.5, 103.1.

1*H*-Pyrrol-3(2*H*)-iminium Tetrakis(pentafluorophenyl)-borate (9b). A gray suspension of 3-nitropyrrole (250 mg, 2.23 mmol) and tin powder (1.33 g, 11.2 mmol, 5 equiv) in glacial AcOH (15 mL) was stirred at room temperature for 3 h. The thick gray reaction mixture was then diluted with distilled water (3 mL), and the resulting thin solution was pressure filtered through a plug of Celite (2 in.) into a solution of $KB(PhF_5)_4$ (3.20 g, 4.46 mmol, 2 equiv) in an 8:1 mixture of distilled water/glacial AcOH (90 mL) with stirring. The plug of Celite was flushed with distilled water (~30 mL) until no longer golden in color. The resulting suspension was further slowly diluted with distilled water (20 mL), stirred at rt for 10 min, and vacuum filtered. The isolated solid was washed with distilled water (75 mL) and dried in vacuo over P_2O_5 to afford **9b** (precipitated) as a light brown solid containing ~7% AcOH (1.33 g, 78%): mp 251.7−255.8 °C dec.

A sample of **9b** (precipitated, 472 mg) was dissolved in DCM (10 mL) and filtered by vacuum filtration to remove a gray solid. The DCM filtrate was brought to a boil and then slowly diluted with hexane (10 mL). The resulting cloudy mixture was cooled to room temperature and then to −20 °C for 30 min. The suspension was vacuum filtered, and the isolated solid was washed with hexane (20 mL) and dried under high vacuum over P_2O_5 and KOH. The product **9b** (precipitated and recrystallized) was isolated as a light brown solid containing ~10% DCM and ~1% AcOH (386 mg, 82% recovery).

A sample of **9b** (precipitated, 837 mg) was dissolved in DCM (20 mL) at room temperature, vacuum filtered to remove a gray solid, washed with a saturated $NaHCO_3$ solution (1 × 20 mL), and dried (Na_2SO_4). The resulting green/black DCM filtrate was brought to a boil, and then hexane (20 mL) was added. The resulting turbid solution was cooled to room temperature and vacuum filtered. The isolated solid was washed with hexane (30 mL) and dried in vacuo over P_2O_5 to afford **9b** (based washed and recrystallized) as a light brown solid (648 mg, 77% recovery). An analytical tin analysis of **9b** (base washed and recrystallized, 97.66 mg) was performed by Galbraith Laboratories and revealed 132 ppm tin. Based on tin and ^{1}H NMR analysis the salt purity is estimated to be >90%: mp 252.8−254.5 °C dec; ^{1}H NMR (400 MHz, THF-d_8, CH_2-tautomer) δ 9.76 (br s, 1 H), 9.13 (br s, 1 H), 8.39 (br s, 1 H), 8.34 (app sextet, 1 H, J = 2.0 Hz), 5.63 (app t, 1 H, J = 2.0 Hz), 4.75−4.73 (app quintet, 2 H, J = 1.6 Hz); ^{1}H NMR (400 MHz, THF-d_8, NH_3-tautomer) δ 10.57 (br s, 1 H), 9.12 (br s, 3 H), 6.90 (dd, 1 H, J = 4.4, 2.2 Hz), 6.81 (ddd, 1 H, J = 3.2, 2.8, 2.4 Hz), 6.16 (dd, 1 H, J = 4.4, 2.8 Hz); ^{13}C NMR (100 MHz, THF-d_8, $^-B(PhF_5)_4$ peaks) δ 149.3 (dm, 8 C, J_{C-F} = 239 Hz), 139.2 (dm, 4 C, J_{C-F} = 242 Hz), 137.2 (dm, 8 C, J_{C-F} = 244 Hz), 125.4 (br m, 4 C); ^{13}C NMR (100 MHz, THF-d_8, CH_2-tautomer) δ 180.8, 196.9, 96.4, 55.3; ^{13}C NMR (100 MHz, THF-d_8, NH_3-tautomer) δ 120.2, 114.8, 112.6, 103.4.

3-Aminopyrrole (11). To a sample of **9b** (base washed and precipitated) (25.0 mg, 0.0328 mmol) in an NMR tube was added THF-d_8 followed by Et_3N-d_{15} (4.6 μL, 0.0328 mmol). The sample was shaken and the ^{1}H NMR was obtained: ^{1}H NMR (400 MHz, THF-d_8) δ 9.26 (br s, 1 H), 6.41 (br s, 1 H), 6.71 (br s, 1H), 5.64 (d, 1 H, J = 2.8 Hz); ^{13}C NMR (100 MHz, THF-d_8) δ 129.7, 117.5, 106.0, 102.1

Effect of Solvent on the Tautomerism of 9b (Table 1). A sample of **9b** (base washed and recrystallized) (25.0 mg, 0.0382 mmol) was dissolved in 0.6 mL of the reported duterated solvent, and a ^{1}H NMR (400 MHz) spectrum was taken after 10 min and 1 h at 25 °C. The tautomeric ratio was found to be consistent over the 10 min to 1 h time interval.

Desmotropy Study: Low-Temperature ^{1}H NMR of 9b (Precipitated) and 9b (Base Washed and Precipitated) in THF-d_8. Individual samples (~20 mg) of **9b** (precipitated) and **9b** (base washed and recrystallized) were dissolved in THF-d_8 (1 mL) in small vials precooled to −78 °C in a dry ice−acetone slurry. These samples were quickly pipetted into precooled NMR tubes and were left in the dry ice−acetone slurry prior to taking the ^{1}H NMR spectrum. With the NMR probe cooled to −70 °C, the NMR samples were quickly inserted and a ^{1}H NMR spectrum was taken at this temperature. The probe was warmed to 25 °C, and ^{1}H NMR spectra were taken at 25 °C and at 25 °C after 1 h.

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra (^{1}H and ^{13}C) of salts; ^{1}H NMR spectra of tautomeric mixtures (six solvents) and 3-aminopyrrole (six solvents). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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