Pergamon

Tetrahedron Vol. 51, No. 26, pp. 7161-7172, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00381-9

Establishing a Cationic AAA-DDD Hydrogen Bonding Complex

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Abstract: The synthesis of a cationic donor-donor-donor (DDD) hydrogen bonding receptor is described. The binding of this receptor with an acceptor-acceptor-acceptor (AAA) guest is found to have a binding constant above 5 x 10^5 M^{-1}. To prove that the isotherm from which this binding constant is determined is not due to proton transfer from the receptor to the guest, non-aqueous titrations on a variety of pyridine-like structures were performed.

Introduction

In the formation of hydrogen bonded complexes, Jorgensen has suggested that secondary hydrogen bond interactions can contribute significantly to complex stability.[1] For systems containing three hydrogen bonds, the pattern acceptor, acceptor, acceptor - donor, donor, donor (AAA-DDD) is believed to result in the most stable complexes. Zimmerman[2] provided the first experimental evidence for this when he reported the binding of 2,8-diphenyl-1,9,10-anthyridine (**1**)[3] with a neutral DDD host **2** (Figure 1A). The association constant of that complex was greater than 1 x 10^5 M^{-1}, a number significantly larger than those for similar AAD-DDA and ADA-DAD complexes.[4] Herein, we describe the development and stability of a protonated system analogous (Figure 1B) to the one reported by Zimmerman. We report that the combination of cooperative secondary interactions with a cationic charge leads to exceptionally strong binding. Such design considerations will likely prove useful in developing stable self-assembled systems based upon non-covalent interactions.

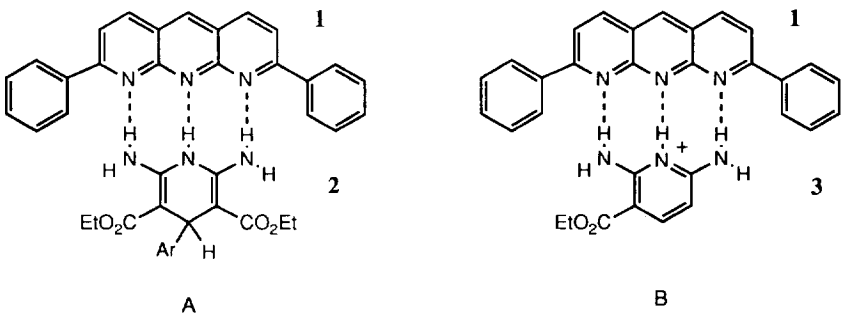


Figure 1. (A) The AAA-DDD hydrogen bond complex developed by Zimmerman. (Compound **1** with **2**) (B) The cationic AAA-DDD hydrogen bond complex described herein. (Compound **1** with **3**)

The "host", or DDD molecule, used in these studies was ethyl 2,6-diaminonicotinium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (**3**). The term "host" is used loosely, being simply defined as a molecule that possesses convergent bonding ability.[5] Originally, the anion employed was the tetraphenylborate anion, but solubility concerns required it to be changed to the tetrakis(3,5-bis(trifluoromethyl)phenyl)borate anion. The 3-carboxyethyl group in **3** was required to increase solubility and also to increase the acidity of the 2 and 6 amino groups. Complexation of host **3** with **1** (Figure 1B) was expected to produce a very large, if not the largest association constant yet determined for a three hydrogen-bond complex due to the cationic nature and the AAA-DDD pattern of the hydrogen bonds.

Results and Discussion

The synthesis of ethyl 2,6-diaminonicotinium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (**3**) is shown in Scheme 1. Enediamine **4** was prepared using the procedure reported by Collins.[6] The first step involved a conjugate addition of **4** to acrylonitrile which proceeded in excellent yields (92%). Next a base catalyzed intramolecular cyclization was performed which produced **6** in modest yields (51%). Compound **6** was oxidized with DDQ to give modest yields of **7**. The host **3** was then formed by protonation with HCl followed by metathesis with **9**. Compound **9**, sodium tetrakis(3,5-bis(trifluoro-methyl)phenyl)borate, was synthesized following the procedure reported by Nishida and coworkers.[7a]

Initially, complexation was studied by ^{1}H NMR in $CDCl_3$. Titration of **3** with **1** (or **1** with **3**) gave an isotherm that reached saturation at one equivalent (Figure 2). The lack of curvature in the binding isotherm indicated exceptionally strong association, greater than 3 x 10^4 M^{-1}. Ideally association constants are measured in the concentration range corresponding to 1/K. As the needed concentrations of host and guest were below the detection limit of ^{1}H NMR spectroscopy, another technique was required. UV-vis absorption and fluorescence spectroscopy was then employed.

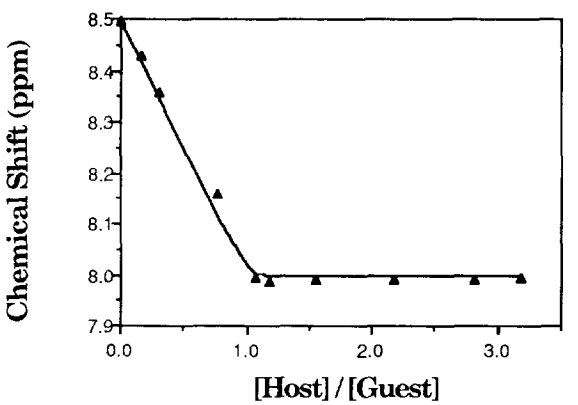
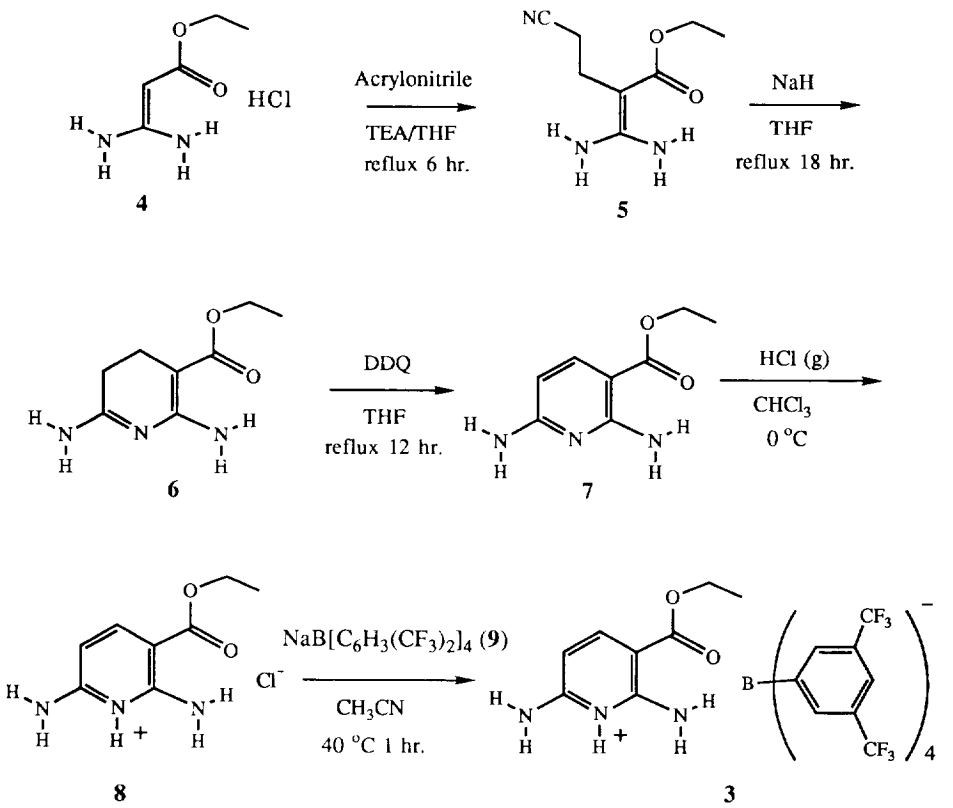


Figure 2. ^{1}H NMR binding isotherm of the ortho protons on the phenyl rings of 2,8-diphenyl-1,9,10-anthyridine (**1**) upon the addition of **3** to a 6.4 x 10^{-4} M solution of **1** in $CDCl_3$.

Scheme 1



The host **3** and host/guest complex 3:1 were both fluorescent, and upon addition of **1** to **3** the total fluorescence increased. The fluorescence spectra, however, indicated excited state proton transfer as has been seen in similar systems.[7b] Due to this complication in the interpretation of a binding isotherm, absorption spectroscopy was employed.

Addition of **3** to **1** in CH_2Cl_2 resulted in significant perturbations of the 2,8-diphenyl-1,9,10-anthyridine (**1**) absorption spectrum (Figure 3). The most pronounced changes were the appearance of new absorptions between 425 nm and 485 nm, and decreases in absorbances at wavelengths 245, 286, 387, and 405 nm. The increase in absorbance around 334 nm was due to the increasing concentration of **3**. The appearance of multiple spectral crossings instead of precise isosbestic points is misleading. The set of absorption spectra up to the addition of 1 equivalent of host contained isosbestic points at 272.9 nm 304.4 nm, 359.2 nm, and 409.4 nm. The absorption spectra after the addition of 1 equivalent of host (**3**) contained a distinct isosbestic point at 417.2 nm. The new absorptions between 425 nm and 485 nm occurred in the region of the UV-Vis spectrum where neither the host (**3**) nor the guest (**1**) absorb light ($\varepsilon_H = \varepsilon_G = 0$); thus, the new absorption indicates a new chromophore in the system.[8]

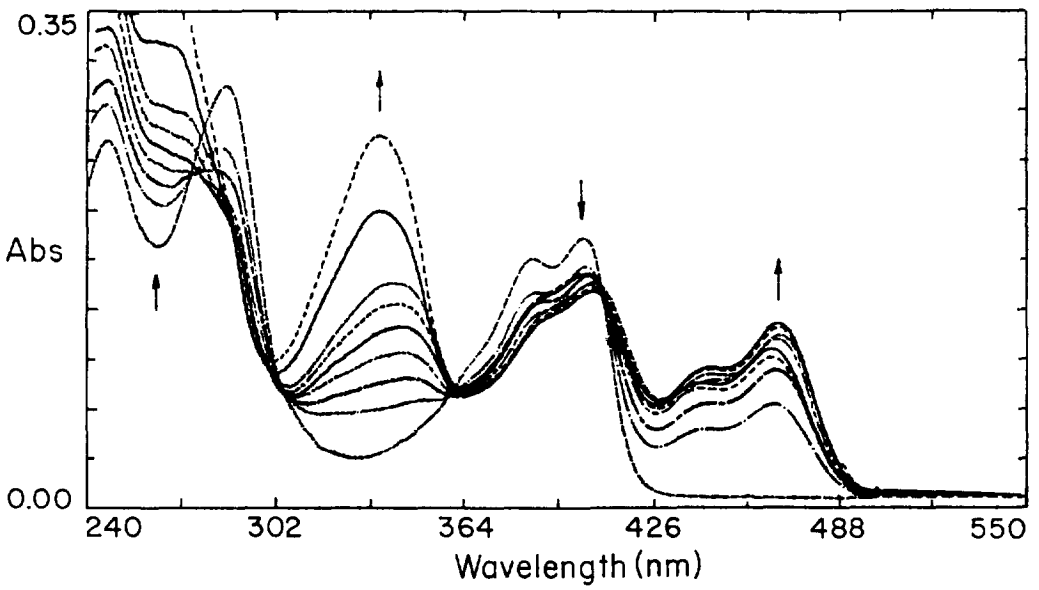


Figure 3. Absorption spectra as the host **3** is added to 2,8-diphenyl-1,9,10-anthyridine **1** in CH_2Cl_2. The appearance of multiple spectral crossings is misleading: two sets of spectra are present each containing isosbestic point(s).

Binding isotherms were made by plotting the absorbances at 466 nm and 417.2 nm against host-guest ratio. The two binding isotherms are shown in Figures 4 and 5. The isotherm based on absorbance at 466 nm indicates multiple equilibria. The inflection point in the binding isotherm (Figure 4) corresponds to the point where the first set of absorption spectra with isosbestic points at 272.9 nm 304.4 nm, 359.2 nm, and 409.4 nm ends, and the second set with an isosbestic point at 417.2 nm begins. The second binding isotherm is based on the absorbance at 417.2 nm. By monitoring the absorbance at the wavelength of the isosbestic point of the second data set, a binding isotherm free of any perturbation from a third spectral state was obtained. The third spectral state is likely due to a host-host-guest complex, which may involve two hosts each binding to a peripheral pyridine of **1**. The host-host-guest complex is indistinguishable from a host-guest complex because at this particular wavelength $\varepsilon_{HG} = \varepsilon_{HHG}$. This isotherm (Figure 5) more accurately represents the disappearance of non-complexed 2,8-diphenyl-1,9,10-anthyridine (**1**) due to complexation with **3**. Again, the lack of curvature makes the accurate determination of an association constant impossible and suggests that an extremely strong association was present. A lower limit for the association constant of 5×10^5 M^{-1} could be assigned from the inverse of the concentration of host **3** at which 1/2 saturation was observed.

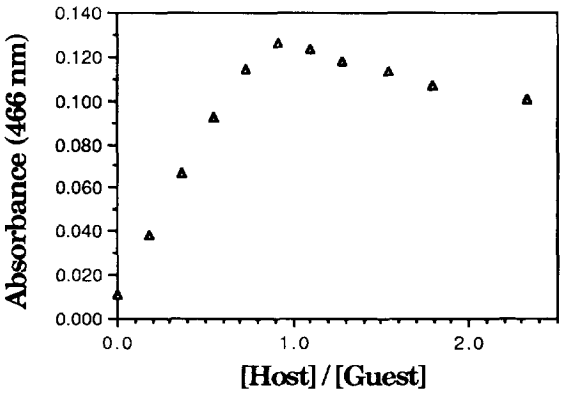


Figure 4. Absorbance binding isotherm for the addition of the host **3** to a 5.9 x 10^{-6} M solution of 2,8-diphenyl-1,9,10-anthyridine (**1**) in CH_2Cl_2. The wavelength monitored was 466 nm, and the shape of the isotherm indicates multiple equilibria.

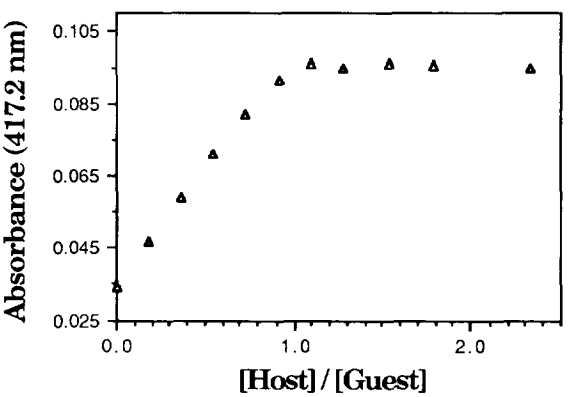


Figure 5. Absorbance binding isotherm for the addition of the host (**3**) to a 5.9 x 10^{-6} M solution of 2,8-diphenyl-1,9,10-anthyridine (**1**) in CH_2Cl_2. The absorbance was monitored at the isosbestic point of the second data set (417.2 nm).

The appearance of new absorptions upon the addition of **3** to **1** suggested the formation of a hydrogen bonded host-guest complex. However, the observed spectral changes were similar to those observed with protonation of **1** by trifluoroacetic acid. One would expect the spectral change of **1** that is caused by hydrogen bonding to a cationic donor such as **3** to be similar to the spectral change induced by an acid. The acidic proton in the host-guest complex is undoubtedly shared between the host and guest, and thus this partial protonation of **1** within the complex would cause a spectral change similar to full protonation. Irrespective of this expectation, the possibility that the spectral changes were due solely to proton transfer, and not a hydrogen bonding complex, needed to be explored.

In order to determine the origins of the spectral changes, UV-vis and non-aqueous acid base titration experiments were performed. Observations made from the interaction of **3** with pyridine and 2,6-lutidine indirectly indicated a host-guest complex as the source of the new absorptions in the titration experiment with **1**. As expected, when **3** in CH_2Cl_2 was titrated with 2,6-lutidine, the λ_{max} of the absorption spectrum of **3** shifted

from 334 nm to 321.5 nm with the addition of one equivalent of 2,6-lutidine. The λ_{max} of 321.5 nm and its extinction coefficient correspond to the λ_{max} and extinction coefficient of the free base form of the **3**. The isotherm displays very little curvature indicating quantitative transfer of the acidic proton of **3** to the strong base 2,6-lutidine (Figure 6). When **3** in CH_2Cl_2 was titrated with pyridine the same shift in λ_{max} and change in extinction coefficient were observed. In this case, unlike the 2,6-lutidine, the isotherm had a significant amount of curvature, evidence that a quantitative transfer of the acidic proton of **3** was not taking place (Figure 7). Over 60 equivalents of pyridine were needed to approach saturation. Bases weaker than pyridine would require even greater numbers of equivalents to bring about proton transfer from **3** and would result in significantly curved isotherms. 2,8-Diphenyl-1,9,10-anthyridine (**1**) was expected to be less basic than pyridine, thus the lack of curvature in Figure 5 indicated complexation rather than proton transfer.

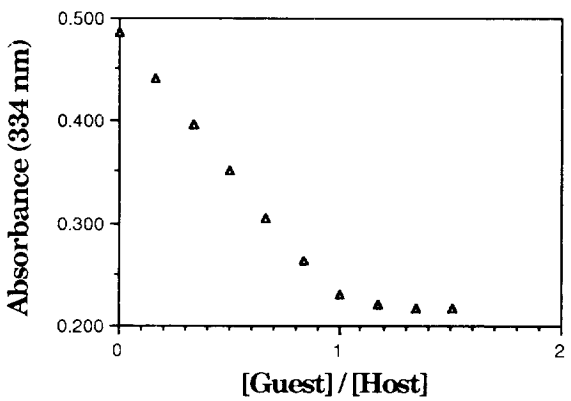


Figure 6. Absorbance isotherm for the titration of **3** with 2,6-lutidine in CH_2Cl_2. The absorbance is monitored at 334 nm. As expected, the isotherm displays very little curvature indicating quantitative transfer of the acidic proton of **3** to 2,6-lutidine.

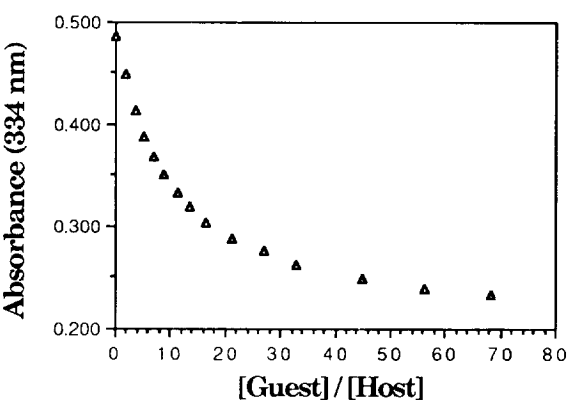


Figure 7. Absorbance isotherm for the titration of **3** with pyridine in CH_2Cl_2. The absorbance was monitored at 334 nm. The transfer of the acidic proton of the host to pyridine results in a curved isotherm.

In order to confirm complexation as being responsible for the spectral changes observed in the **3** - **1** system, the relative base strengths of **3**, **1**, pyridine, and 2,6-lutidine were determined in a non-aqueous solvent. These titrations were carried out in acetonitrile, a solvent in which these compounds were all readily soluble and for which potentiometric methods and standards are well established in the literature.[10] The relative basicities of these compounds in acetonitrile were expected to mirror their relative basicities in the low dielectric solvent dichloromethane. A computer program was employed to fit the experimental titration curves to theoretical ones based on the Henderson-Hasselbach equation.[11] The titration of the free base form of the host **3** with perchloric acid is shown in Figure 8, and the pK_as in acetonitrile for the compounds of concern are tabulated in Table 1.

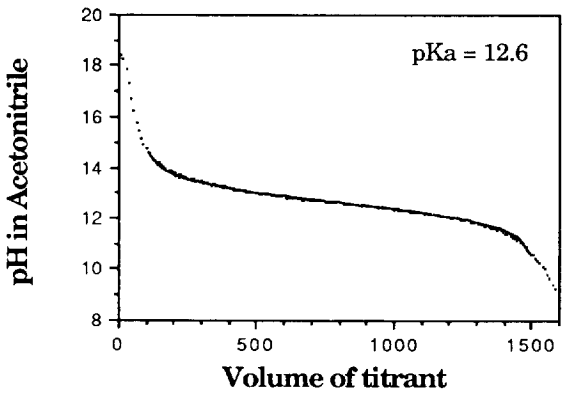


Figure 8. Titration curve of the free base form of the host (**3**) with $HClO_4$ in CH_3CN. The solid line is the theoretical curve. At start of the titration: [host **3**] = 2 x 10^{-3} M, [$HClO_4$] = 7.6 x 10^{-3} M, [$Et_4N^+ClO_4^-$] = 8.3 x 10^{-6} M.

Table 1.

Compound	pK_a of conjugate acid in acetonitrile
2,6-lutidine	14.2
Ethyl 2,6-diaminonicotinate	12.6
Pyridine	12.5
2,8-diphenyl-1,9,10-anthyridine (**1**)	12.2

Table 1. Summary of determined pK_as in acetonitrile. Ethyl 2,6-diaminonicotinate is the free base form of host **3**.

Of particular note in Table 1 is the pK_a value for the conjugate acid of 2,8-diphenyl-1,9,10-anthyridine (**1**) which was found to be lower than the pK_a of host **3** in a non-aqueous solvent. This result confirms the hypothesis that the lack of curvature in the binding isotherm of **1** with **3** (Figure 5) was due to the formation of an ionic hydrogen bonded complex. Had the observed changes in the UV-Vis spectra been due solely to proton transfer, then the binding isotherm would have shown that multiple equivalents of host were required to quantitatively protonate **1.** Although the pK_a values of **1** and **3** indicate that the complex should best be viewed as a cationic AAA-DDD structure, the pK_a values within the microenvironment of the complex likely change. Therefore, we cannot currently determine the extent to which the proton is shared by the host and guest within the complex, yielding some character of a cationic ADA-DAD complex.

Conclusions

The interaction of host **3** with 2,8-diphenyl-1,9,10-anthyridine (**1**) was studied in low dielectric media. The results from the UV-vis absorption experiments, along with the base strengths determined by the titrations in acetonitrile, confirm that the observed spectral changes were due to complex formation and not solely proton transfer. The charged character of the hydrogen bonds in this system are hypothesized to be perturbing the electronic structure of the chromophore **1** in a manner analogous to protonation. Based on the binding isotherm, an association constant greater than 5×10^5 M^{-1} was assigned to this complex.

Acknowledgements

We gratefully acknowledge financial support for this project from both the Welch Foundation and an NSF-PYI award to E.V.A.

Experimental

^{1}H NMR Binding Studies. ^{1}H NMR binding studies were performed with a General Electric QE 300 NMR spectrometer using $CDCl_3$ that had been refluxed over P_2O_5, fractionally distilled, and stored under a dry N_2 atmosphere. All solutions were prepared in the dry box. Gastight syringes, septa, and nitrogen balloons were used to exclude water from the system when working outside of the dry box.

A ^{1}H NMR binding study consists of incremental additions of small volumes (3-20 μL) of a concentrated guest solution to a large volume (700-800 μl) of a host solution. No more than a 7% volume change was allowed. After each addition of titrant (the guest solution), the ^{1}H NMR spectrum of the system was recorded. Changes in the spectrum of the host were plotted against the concentration of the added guest. The guest concentration was known from the amount of guest solution added and the resulting volume change and/or from integration of each recorded ^{1}H NMR spectrum. The resulting curve (or isotherm) was used to determine the association constant by fitting the curve with a non-linear least squares regression program developed by Whitlock.[12]

Ultraviolet-Visible Absorption Spectroscopy. The UV-Vis absorption experiments were performed with a Beckman DU-640 spectrometer. The experiments were carried out in spectral grade dichloromethane that had been distilled from calcium hydride. A quartz cuvette capable of holding 4 mL of sample and possessing a ground glass stopper was employed in all of the binding studies.

A binding study consisted of incremental additions of small volumes (3-20 μL) of a concentrated guest solution to a large volume (4 mL) of a host solution. No more than a 2% volume change was allowed. After

each addition of guest, the spectrum was recorded and the changes in absorbance intensities were recorded. The concentration of the guest in the cuvette at each addition was calculated based on the guest's stock solution concentration. Changes in the absorbance intensity were plotted against the guest concentration to obtain the binding isotherm.

Acid-Base Titrations in Acetonitrile. Potentiometric measurements were taken with an Orion Model 720A pH meter set in the millivolt mode with an Orion glass pH electrode model 91-01 in conjunction with a silver/silver nitrate reference electrode. The reference electrode consisted of a silver metal rod that extended into a solution of 0.01 M $AgNO_3$ and 0.1 M Et_4NClO_4 in dry acetonitrile. All measurements were carried out in Omnisolve 'low water' acetonitrile with tetraethyl ammonium perchlorate (Et_4NClO_4) as the electrolyte. A calibration curve for the conversion of millivolt readings into pH values was created prior to each titration. The calibration curve was based on a 1:1 mixture of picric acid (pK_a=11)[13] with tetraethyl ammonium picrate and a 1:1 mixture of 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) with its conjugate acid with a tetraphenylborate counter ion ($DBUH^+TPB$; pK_a=23.9).[14] The heterocyclic base of interest was dissolved in dry acetonitrile and transferred via syringe into the titration cell. A syringe was filled with $HClO_4$ in acetonitrile and then placed in the infusion pump. A small diameter (i.d. <1 mm) polyethylene tube was used to transfer the titrant from the syringe mounted in the infusion pump to the titration cell. The volume of titrant added as well as the electrode potential were recorded with an IBM computer. The pK_a of the heterocyclic base in acetonitrile was determined from the resulting titration curve with the aid of a computer program.[11]

Extinction coefficients. Extinction coefficients of **1**, **3**, and **7** were determined using Beer's law from absorbance measurements made with a Beckman DU-640 spectrometer. Extinction coefficients of **1** in CH_2Cl_2 are reported here: $\varepsilon_{245.6\ nm} = 3.96 \times 10^4$; $\varepsilon_{285.0\ nm} = 4.82 \times 10^4$; $\varepsilon_{386.0\ nm} = 2.92 \times 10^4$; $\varepsilon_{402.5\ nm} = 3.19 \times 10^4$. Extinction coefficients for compounds **3** and **7** are reported below.

General Considerations. Pyridine and 2,6-lutidine were purchased from Aldrich and distilled prior to use. 2,8-diphenyl-1,9,10-anthyridine (**1**) was synthesized following the procedure reported by Caluwe and Majewicz.[3] All elemental analyses were performed by Atlantic Microlabs. The host (**1**) was synthesized in the following manner.

Ethyl 2-(2-cyanoethyl)-3,3-diaminopropenoate (5). To a nitrogen purged solution of 1.1 g (6.5 mmol) of ethyl 3,3-diaminopropenoate hydrochloride[6] and 600 μL of acrylonitrile in 20 mL of dry tetrahydrofuran was added 1.0 mL of triethylamine. The solution was refluxed under nitrogen for 6 hr. Next, 20 mL of diethyl ether was added and the resulting precipitate (triethylamine hydrochloride) collected and washed with ether. The washings were combined with the THF/ether solution, which was then dried with sodium sulfate and evaporated. The solid residue was dried under vacuum for 2 days. An amorphous yellow solid was collected (1.1 g, 92%), m.p. 79-84.5 °C. This material was used without further purification. ^1H NMR ($CDCl_3$, 300 MHz): δ 6.56 (br, 2 H, NH_2), 4.43 (s, 2 H, NH_2), 4.10 (q, 2 H, J=7.1 Hz, $CO_2C\underline{H}_2CH_3$), 2.53 (t, 2 H, J=6.0 Hz, $NCC\underline{H}_2CH_2$), 2.46 (t, 2 H, J=5.8 Hz, $NCCH_2C\underline{H}_2$), 1.25 (t, 3 H, J=7.1 Hz, $CO_2CH_2C\underline{H}_3$). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 170.1, 159.6, 120.9, 73.7, 58.7, 22.3, 17.6, 14.7. HRMS (CI^+): calcd. for $C_8H_{13}N_3O_2$: 183.1009 (M^+); found: 183.1007. IR (KBr): υ CN: 2247.0 cm^{-1}.

Ethyl 2,6-diamino-4,5-dihydronicotinate (6). A solution consisting of 0.98 g (5.3 mmol) of ethyl 2-(2-cyanoethyl)-3,3-diaminopropenoate (**5**) in 25 mL of dry tetrahydrofuran was transfered with a

cannula under nitrogen to a flask containing 0.22 g (9.3 mmol) of sodium hydride. An immediate reaction was evident (bubbles, heat). The solution was refluxed under nitrogen for 18 hr. After cooling, water was added dropwise to quench the reaction. The THF and water were then evaporated until only 2 mL of solution remained. A few more mL of water were added and the solution was extracted with ethyl acetate. The ethyl acetate was dried with Na_2SO_4, evaporated, and the residue dried under vacuum to yield a light yellow solid. This was recrystallized from benzene to give 0.50 g (51%) of a white solid, m.p. 155-157 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 4.14 (q, 2 H, J=7.1 Hz, $CO_2C\underline{H}_2CH_3$), 2.49 (t, 2 H, J=8 Hz, -$C\underline{H}_2CH_2$-), 2.30 (t, 2 H, J=7 Hz, -$CH_2C\underline{H}_2$-), 1.27 (t, 3 H, J=7.1 Hz, $CO_2CH_2C\underline{H}_3$). ^{13}C {^1H} NMR ($CDCl_3$, 75 MHz): δ 169.7, 167.4, 160.5, 75.0, 58.6, 27.4, 18.9, 14.8. HRMS (CI$^+$): calcd. for $C_8H_{13}N_3O_2$: 183.1007 (M$^+$); found: 183.1007. IR(KBr): no absorption between 2200-2300 cm^{-1}.

Ethyl 2,6-diaminonicotinate (7). A solution consisting of 0.46 g (2.5 mmol) of ethyl 2,6-diamino-4,5-dihydronicotinate (**6**) and 0.68 g (3.0 mmol) of 2,3-dichloro-4,5-dicyanobenzoquinone (DDQ) in 25 mL of tetrahydrofuran was stirred for 15 min followed by refluxing for 12 hr. After the solution was cooled, the THF was evaporated. The residue was run through a 5 cm alumina plug with ethyl acetate to remove the DDHQ created and the excess DDQ. The ethyl acetate was evaporated to yield a white solid (0.46 g, 50 %). This was run through a second column (silica gel, ethyl acetate : dichloromethane, 95:5) for further purification. This could then be recrystallized from ethyl acetate : hexanes, 50:50, and recrystallized again from CH_2Cl_2 to give a white crystalline material, m.p. 104-105.5 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.90 (d, 1 H, J=7.5 Hz, aryl #4), 6.4 (br, 2 H, 6-NH_2), 5.81 (d, 1 H, J=8.7 Hz, aryl #5), 4.67 (br, s, 2 H, 2-NH_2), 4.27 (q, 2 H, J=7.2 Hz, $CO_2C\underline{H}_2CH_3$), 1.34 (t, 3 H, J=7.2 Hz, $CO_2CH_2C\underline{H}_3$). ^{13}C {^1H} NMR ($CDCl_3$, 75 MHz): δ 167.2, 160.6, 160.1, 141.7, 97.8, 96.7, 59.9, 14.4. HRMS (CI$^+$): calcd. for $C_8H_{11}N_3O_2$: 181.0844 (M$^+$); found: 181.0851. $\varepsilon_{321.5\ nm}=1.54 \times 10^4$. Analysis: calcd: C, 53.06; H, 6.12; N, 23.20; found: C, 53.08; H, 6.28; N, 23.26.

Ethyl 2,6-diaminonicotinate hydrochloride (8). A solution consisting of 0.33 g (1.82 mmol) of ethyl 2,6-diaminonicotinate (**7**) in 20 mL of $CHCl_3$ was cooled to 0 °C. Hydrogen chloride gas was bubbled through the solution for 10 min. The solution was allowed to stir at room temperature for 1 hr. The $CHCl_3$ was removed by evaporation yielding a white solid. The solid was placed under vacuum to remove the last traces of $CHCl_3$ and HCl. A white precipitate was collected (0.40 g, 95%). This was recrystallized from ethanol to give a white solid, m.p. 194-196 °C. ^1H NMR (DMSO-d_6, 300 MHz): δ 13 (br, acidic proton), 8.32 (br, s, 2 H, 6-NH_2), 8.12 (br, s, 2 H, 2-NH_2), 7.99 (d, 1 H, J=9.0 Hz, aryl #4), 6.03 (d, 1 H, J=9.0 Hz, aryl #5), 4.22 (q, 2 H, J=7.1 Hz, $C\underline{H}_2CH_3$), 1.26 (t, 3 H, J=7.1 Hz, $CH_2C\underline{H}_3$). ^{13}C {^1H} NMR (DMSO-d_6, 75 MHz): δ 164.8, 154.8, 153.2, 144.6, 97.4, 93.1, 60.3, 14.1. HRMS (CI$^+$): calcd. for $C_8H_{11}N_3O_2$ (free base form): 181.0851 (M$^+$); found: 181.0851. Analysis: calcd. (for dihydrate): C, 37.87; H, 6.36; N, 16.56; found: C, 37.24; H, 5.56; N, 16.06.

Ethyl 2,6-diaminonicotinium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (3). Sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate was prepared according to the synthesis reported by Nishida and coworkers.[7a] To a suspension of 0.22 g (0.99 mmol) of ethyl 2,6-diaminonicotinium chloride (**8**) in 10 mL of acetonitrile was added a solution of 0.83 g (0.94 mmol) of sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate in 10 mL of acetonitrile. The solution was warmed to 40 °C and stirred for 1 hr. The solution was placed in a centrifuge tube and "spun down". The acetonitrile was then decanted away

from the NaCl which had formed during the reaction. The acetonitrile was further filtered through celite 545 to remove the remaining NaCl. The acetonitrile was removed by evaporation to yield a gold/brown oil. To the oil was added 1 mL of dichloromethane. The resulting solution was placed under a vacuum. The addition of 1 mL aliquots of CH_2Cl_2 followed by "pumping off" the CH_2Cl_2 was repeated several times to facilitate the removal of acetonitrile from the product. As many as ten additions of CH_2Cl_2 may be necessary to change the collected material from a gold/brown oil to a gold/tan colored solid. The solid was quite hydroscopic. A total of 0.67 g (69% yield) of product was collected. ^1H NMR ($CDCl_3$, 300 MHz): δ 11.3 (br, 1 H, acidic proton), 8.20 (d, 1 H, J=8.9 Hz, aryl #4), 7.71 (s, 8 H, aryl #2 anion), 7.53 (s, 4 H, aryl #4 anion), 5.81 (d, 1 H, J=8.9 Hz, aryl #5), 5.30 (s, 2 H, 6-NH_2), 4.34 (q, 2 H, J=7.2 Hz, $C\underline{H}_2CH_3$), 1.36 (t, 3 H, J=7.2 Hz, $CH_2C\underline{H}_3$), $^{13}C\{^1H\}$ NMR ($CDCl_3$ 75 MHz): δ 164.4, 152.1, 148.3, 98.7, 97.5, 62.4, 13.7 (cation), 161.7 (q), 134.7, 129.0 (q), 126.3, 122.7 (anion). MS(CI^+): m/z 1044. $\varepsilon_{334\ nm}=1.93 \times 10^4$. Analysis: calcd. (for monohydrate): C, 45.17; H, 2.27; N, 3.95; found: C, 45.08; H, 2.67; N, 3.47.

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11. Mac pK_as (Joseph Smith, 1993) is a Macintosh computer application that calculates a potentiometric curve based on the Henderson-Hasselbach equation and a user-defined pK_a value. The program then displays a plot of this theoretical curve on top of the experimental titration curve. Several parameters can be changed interactively including pK_a and axis values until the calculated curve overlays and matches the experimental potentiometric curve. Mac pK_as can take either millivolts or pH units as input and can output both experimental and calculated data in a file format that is compatible with most graphing or spreadsheet

programs. It is available upon request.

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(*Received in USA* 15 *March* 1995; *accepted* 10 *May* 1995)