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Electronic and Steric Effects on the Mechanism of the Inverse Electron Demand Diels−Alder Reaction of 2-Aminopyrroles with 1,3,5-Triazines: Identification of Five Intermediates by ^{1}H, ^{13}C, ^{15}N, and ^{19}F NMR Spectroscopy

Michael De Rosa* and David Arnold

Department of Chemistry, Penn State Brandywine, 25 Yearsley Mill Road, Media, Pennsylvania 19063

mxd19@psu.edu

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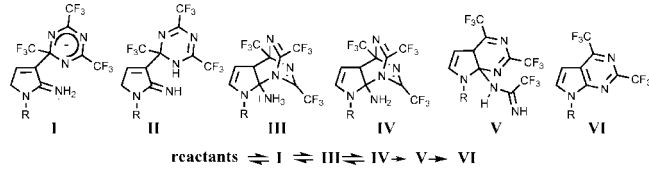

The inverse electron demand Diels−Alder (IEDDA) reaction of 1-*tert*-butyl-2-aminopyrrole with 2,4,6-tris(trifluoromethyl)-1,3,5-triazine in THF-d_8 to give a pyrrolo[2,3-*d*]pyrimidine was studied by ^{1}H, ^{13}C, ^{15}N, and ^{19}F NMR spectroscopy, and five intermediates were identified. A zwitterion was the first intermediate detected, and it cyclized to a tricyclic adduct and its conjugate acid. It also gave a neutral imine via a proton switch. The tricyclic adduct underwent a retro-Diels−Alder reaction, but the expected CF_3CN was not detected. NMR indicated that the amino group of the 2-aminopyrrole was bonded to the CF_3CN to form a trifluoroacetoamidinium ion. The products of the retro-Diels−Alder reaction reacted rapidly with each other to give the final intermediate observed. Acid-catalyzed loss of an amidine gave the final aromatic product. This is the first study in which *direct* experimental evidence for the order of the steps in the IEDDA cascade reaction of 1,3,5-triazines with amino-containing dienophiles has been obtained. This study and analogous 1,3-dipolar cycloaddition reactions, in which zwitterions have been detected or proposed, have two factors in common: electronic effects that stabilize the zwitterions and steric effects that inhibit their cyclization.

1. Introduction

In 1949, Bachmann and Deno proposed the inverse electron demand Diels−Alder reaction (IEDDA), in which the diene is electron poor and the dienophile is electron rich.[1,2] Since the first initial experimental reports,[2] the IEDDA reaction has been used extensively in the synthesis of heterocyclic systems and natural products.[3] Dang and co-workers have investigated the IEDDA reaction of amino-substituted heterocycles with 1,3,5-triazines as a route to purines and their analogues.[4] As part of this study, the reaction of 4-cyano-2-aminopyrroles with 1,3,5-triazines was found to give pyrrolo[2,3-*d*]pyrimidines.[5] On the basis of theoretical studies, a cascade mechanism was proposed, in which the initial IEDDA cycloadduct first eliminates ammonia and then undergoes a retro-Diels−Alder reaction to give the final product (Scheme 1).[6,7] This mechanism has been termed the IER path.[7] Another pathway (IRE), in which the retro-Diels−Alder step occurs before the loss of ammonia, was discounted on the basis of these theoretical calculations. It was noted that the actual pathway might be a function of the reactants and/or the reaction conditions.

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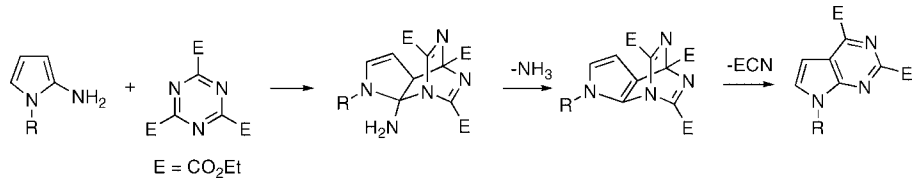
SCHEME 1



Recently, simple 2-aminopyrroles,[8,9] without further substitution on the ring, have become available as their tetraphenylborate salts.[10] Addition of base (triethylamine) generates the free 2-aminopyrrole in situ, which can then be used as a reactant. Using this method, the cycloaddition reactions of simple 2-aminopyrroles have been studied. The attempted Diels−Alder reaction with dimethyl acetylenedicarboxylate (DMAD) gave Michael addition products instead of cycloadducts.[11] IEDDA reactions of simple 2-aminopyrroles with a variety of 1,3,5-triazines were studied, and cycloaddition occurred only when the 1,3,5-triazine contained strong electron-withdrawing substituents.[12] During this study, it was observed that starting material disappeared without the concomitant formation of product. This suggested the possibility that one or more intermediates were being formed. It should also be noted that, in a recent study of the IEDDA reaction of 5-substituted 2-aminopyrroles with 2,4,6-tris(trifluoromethyl)-1,3,5-triazine, a zwitterion intermediate was observed by ^{1}H and ^{19}F NMR spectroscopy, the first such intermediate detected in IEDDA reactions of pyrroles or 2-aminopyrroles.[13a]

Studies have appeared in which an intermediate has been observed in an IEDDA reaction. Zwitterions,[13a,14] bicyclic intermediates,[15] dihydro products,[16] intermediates containing amino groups,[17] and other types of neutral intermediates[18] have been detected or isolated. Dihydro intermediates can be aromatized by oxidation, and those containing an amino function can lose ammonia or an amine to give the final aromatic cycloadduct. This study is unique in the study of IEDDA cascade reactions in that NMR evidence will be presented for the presence of *five species*–four of them are sequential intermediates before the formation of the final cycloadduct, and the other is a cul-de-sac. Evidence is presented that electronic and steric effects are responsible for this cycloaddition taking a nonconcerted pathway and for the role that tautomeric equilibria play in the intermediates observed.

2. Results and Discussion

Reaction of 1-*tert*-butyl-2-aminopyrrole **2** (generated from the tetraphenylborate salt with triethylamine) with 2,4,6-tris(trifluoromethyl)-1,3,5-triazine **3** in THF-d_8 was followed by ^{1}H NMR spectroscopy.[19] Figure 1 illustrates the changes that occurred in the *tert*-butyl region of the ^{1}H NMR spectrum. At least three *tert*-butyl groups can clearly be seen to appear and then disappear as the final product is formed. The *tert*-butyl signals in Figure 1 are bracketed by the multiplets of the triethylamine used to generate the 2-aminopyrrole. Proton NMR spectroscopy indicated that all of the intermediates still contained an *exo*-nitrogen functional group, thus ruling out the IER mechanism (Scheme 1) in which ammonia is lost in the penultimate step of the cascade.[7] A series of multinuclear (^{1}H, ^{13}C, ^{15}N, and ^{19}F) NMR experiments were carried out to identify the observed intermediates and to confirm that the reaction followed the alternative IRE pathway.[7] These experiments brought to light an additional two species present in the reaction that were not clearly resolved in Figure 1.

To simplify the ^{1}H NMR spectra obtained, the tetrakis(pentafluorophenyl)borate salt **1b** was also synthesized, and Et_3N-d_{15} was used as the base to generate **2**. Protons observed by ^{1}H NMR spectroscopy could, therefore, only have come from the 2-aminopyrrole **2**. COSY spectra were used to establish the coupling patterns. When the reaction was carried out with perfluoro salt **1b**, changes in the chemical shifts of the *tert*-butyl groups occurred, and another *tert*-butyl group (intermediate), a shoulder when **1a** was used (Figure 1), could then be resolved.

Reactions were also followed by COSY (0 and 25 °C), ^{13}C (DEPT-135 at 25 °C), and ^{19}F NMR (25 and −30 °C) spectroscopy. ^{15}N-enriched 2-aminopyrrole **2** (90% at the amino group) was prepared,[8] and the fate of the *exo*-amino group was then followed by ^{15}N NMR (25 °C) spectroscopy. The results in Figure 2 were used to select the optimal time to observe a particular intermediate or set of intermediates. As a check, a ^{1}H NMR spectrum was taken

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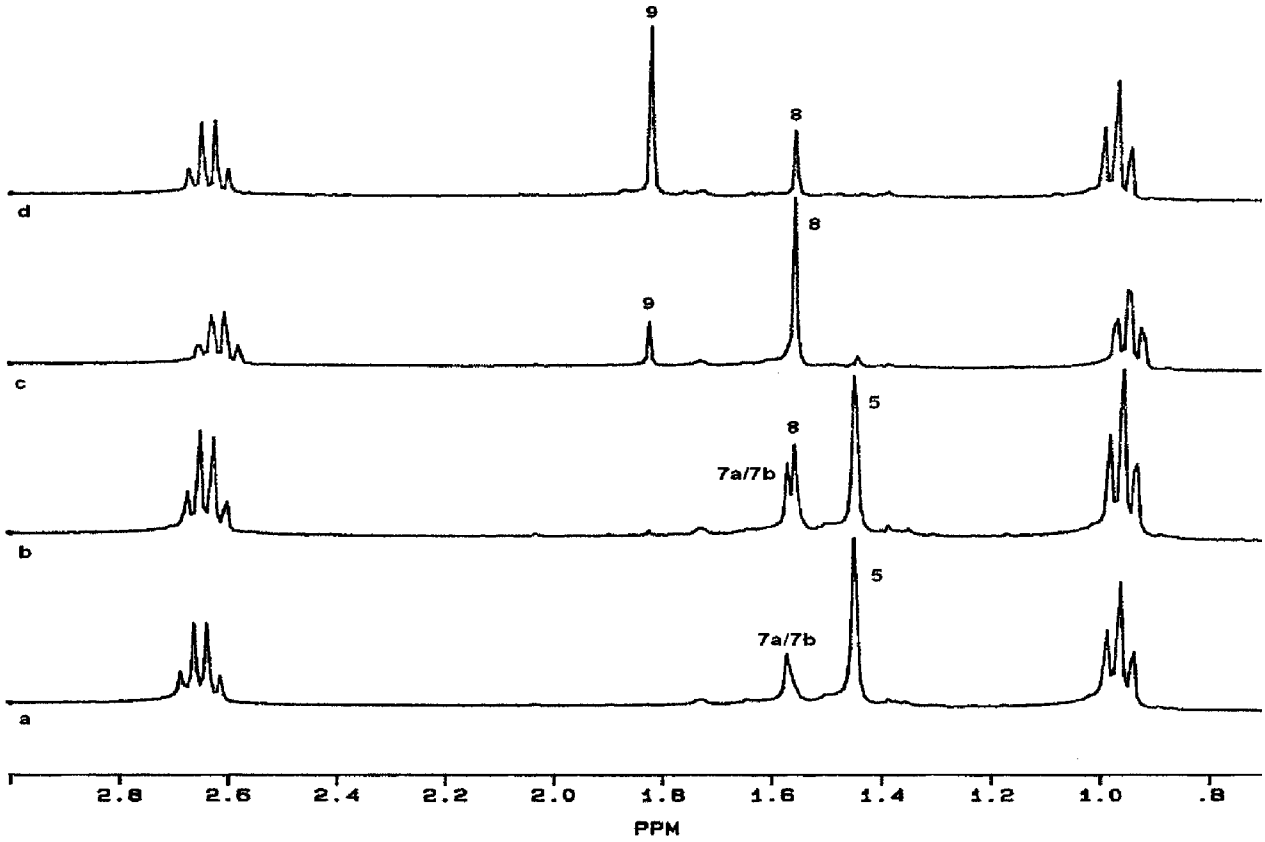


FIGURE 1. ^{1}H NMR study of the reaction of 1-*tert*-butyl-2-aminopyrrole **2** with 2,4,6-tris(trifluoromethyl)-1,3,5-triazine in THF-d_8 containing triethylamine: (a) 10 min, (b) 1 h, (c) 26.5 h, (d) 5 days.

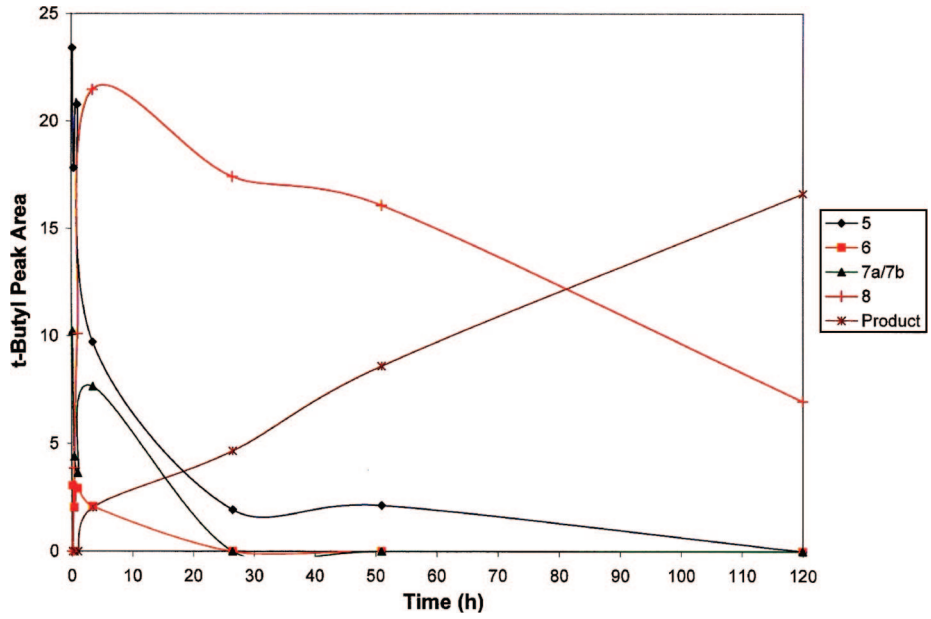


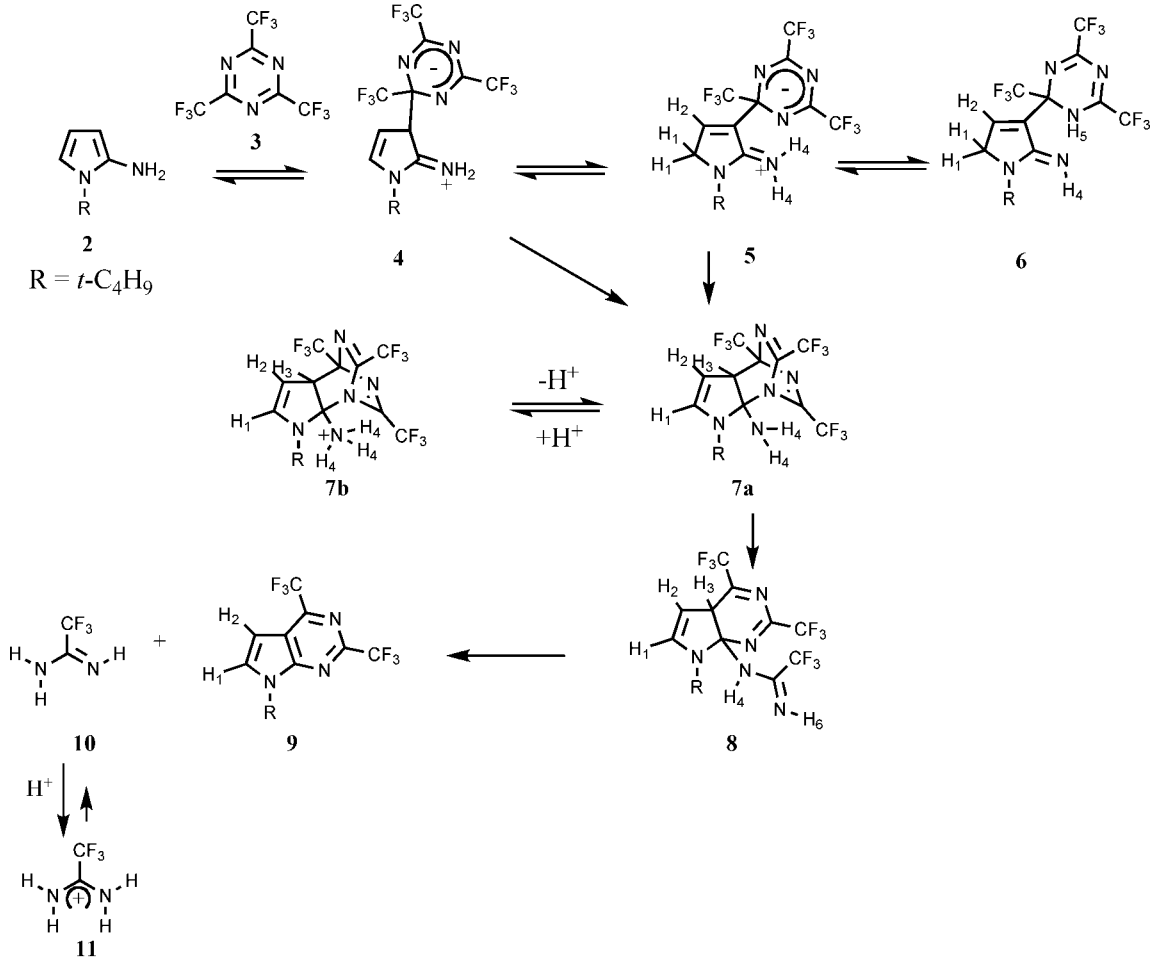
FIGURE 2. ^{1}H NMR study of the change in the concentrations of intermediates (*tert*-butyl ratio) with time.

before and after the heteronuclear NMR experiment was performed, a procedure that ensured that the set of ^{1}H, ^{13}C, ^{15}N, and ^{19}F NMR spectra obtained was of the same intermediate or mixture of intermediates. These multinuclear NMR studies helped to establish the structures of the intermediates. Changing the nucleus, observed by NMR spectroscopy, also changed the NMR time scale. As a result, it was found that one of the *tert*-butyl groups observed (Figure 1) by ^{1}H NMR was actually a rapidly equilibrating pair of intermediates.

Changes in the relative rate and the number of intermediates observed depended on the number of equivalents of base added to generate the 2-aminopyrrole **2**. Spectra were obtained when 1 equiv (100% Et_3N) and 0.5 equiv (50% Et_3N) of base was present. Under the latter conditions, the reaction was faster, and only two of the intermediates (**5** and **8**) in Scheme 2 were detectable.

These NMR studies demonstrated that at least five species were present. Tables 1–3 summarize the ^{1}H, ^{13}C, ^{15}N, and ^{19}F

SCHEME 2



data obtained in these studies. NMR spectra, summarized in Tables 1−3 and discussed below, can be found in the Supporting Information. On the basis of these results, Scheme 2 is proposed for the IEDDA cascade leading to the pyrrolo[2,3-*d*]pyrimidine **9**. NMR evidence for each of the species in this scheme and also for the rate-determining step when 100% Et_3N was used is discussed below.

2.A. Zwitterion 4. When the reaction was carried out using 1 equiv of Et_3N, the starting material **2** was consumed within the first 15 min (^1H NMR). Reaction of C3 of the neutral 2-aminopyrrole **2** with a ring carbon of the neutral electrophile **3** must initially give a zwitterion.[6,20] Zwitterion **4** would be the expected product of this reaction (Scheme 3) and is analogous to a Meisenheimer intermediate formed during nucleophilic aromatic substitution.[13b] There was no direct evidence for zwitterion **4**. Analogous zwitterions have been proposed as the initial intermediate in Diels−Alder,[21] inverse electron demand Diels−Alder,[7,13a] and Michael addition[21] reactions of pyrroles. Evidence for the equilibria involving **4** is presented below.

2.B. Zwitterion 5. After 10 min (100% Et_3N), the concentration of **5** was ca. 64%. Relative concentrations were calculated from the ratio of the *tert*-butyl of **5** to that of the total area of all the *tert*-butyl groups observed by ^1H NMR at that point in time. Similarly, the relative concentrations of the other intermediates discussed below were calculated in the same manner. The concentration of **5** slowly decreased to ca. 8% after 24 h. Zwitterion **5** was fully characterized by ^1H, DEPT-135 (CH_2 peak was negative), ^{19}F (two CF_3 groups in a ratio of 2:1), and ^{15}N NMR. In the ^{15}N NMR spectra, splitting between ^{15}N and two nonequivalent H_4 protons was observed in the later stages of the reaction. The two protons on the $=NH_2^+$ group in the conjugate acids of 2-aminopyrroles have also been reported to be nonequivalent.[8,10] Coupling between ^{15}N and ^1H was also observed in the ^1H NMR spectra (Table 1). COSY spectra demonstrated coupling between H_1, H_2, and H_4 at 0 °C (using perfluoro **1b** and 100% Et_3N). Both H_1 and H_4 exchanged with D_2O.

(19) Reactions were run with 2-aminopyrrole **2** and 1,3,5-triazine **3** in a ratio of 1:1. One of the bottles of **3** had the incorrect density on the label, and, as a result, in some reactions 1.5 equiv of **3** was used. No difference in the number of reaction intermediates was observed under these conditions. There was an additional product **12** (see Supporting Information for spectral data) observed by NMR, which was attributed to the reaction of **3** with triethylamine.

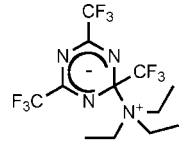


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TABLE 1. Multinuclear Chemical Shift Data for the Reaction of ^{15}N-Labeled 2-Aminopyrrole with a 1,3,5-Triazine (100% Et_3N)

	^{1}H NMR (δ)[a]						^{13}C NMR (δ)[b]				^{15}N NMR (δ)[c]	^{19}F NMR(δ)[d]
species	H_1	H_2	H_3	H_4	*t*-Bu	other	C_1	C_2	C_3	*t*-Bu		
1a[e]	3.81 (s, 2H)	5.92 (d, 1H, J_{H2-H3} = 5.4 Hz)	6.51 (d, 1H, J_{H3-H2} = 5.7 Hz)	7.35 (br d, 1H, J_{N-H} = 91.8 Hz) 7.99 (br d, 1H, J_{N-H} = 93.0 Hz)	1.28						86.07 (t, J_{N-H} = 92.7 Hz)	
2	6.36 (br s, 1H)	5.35 (br s, 1H)	5.70 (br s, 1H)	3.42 (br d, 2H, J_{N-H} = 70.2 Hz)	1.59						28.23 (s)	
3												−72.59 (s)
5	4.21 (s, 2H)[f]	not observed[g]		7.98 (br d, 1H, J_{N-H} = 92.4 Hz)[f] 9.99 (br d, 1H, J_{N-H} = 92.4 Hz)[f]	1.42		56.28	146.08		26.01	92.56 (t, J_{N-H} = 91.1 Hz)	−75.16 (s, 6F), −85.61 (s, 3F)[h]
6	4.16 (q, 2H, J_{H1-H2} = 11.7 Hz)	6.62 (s, 1H)		8.90 (br s, 1H)	1.49	H_5 (1.64 s, 1H)						−85.50 (s,3F), −80.72 (s,3F), −73.66(s,3F)[h]
7a	6.40 (d, 1H, J_{H1-H2} = 3.3 Hz)	5.90 (d, 1H, J_{H2-H1} = 3.3 Hz)	3.52 (s, 1H)	6.25 (br s)	1.57		117.82	99.47	29.17	28.89	34.21 (s)	−73.80 (br s, 6F), −82.34 (br s, 3F)[h]
7b	6.40 (d, 1H, J_{H1-H2} = 3.3 Hz)	5.90 (d, 1H, J_{H2-H1} = 3.3 Hz)	3.52 (s, 1H)	6.25 (br s)	1.57		118.05	99.74	29.22	30.90	58.62 (s)	−73.80 (br s, 6F), −82.34 (br s, 3F)[h]
8	6.56 (d, 1H, J_{H1-H2} = 3.0 Hz)	5.94 (br s, 1H)	3.24 (s, 1H)	4.77 (d, 1H, J_{N-H} = 72.0 Hz)	1.56	H_6 (8.72 br s, 1H)	114.34	101.63	36.19	29.02	59.78 (d, J_{N-H} = 71.8 Hz)	−82.78 (s,3F), −81.04 (s,3F), −73.31 (s,3F)[f]
9	7.91 (d, 1H, J_{H1-H2} = 4.2 Hz)	not observed[g]			1.81							−67.13 (s, 3F), −68.95 (d, 3F, J_{H-F} = 2.5 Hz)
10	not observed					NH: 5.80 (4H, br s)						
11												−76.56 (s, 3F)
CF_3CN[j]	not observed											−56.29 (s, 3F)

[a] 300 MHz. [b] 75 MHz DEPT-135. [c] 30.4 MHz. [d] 282 MHz. [e] Proton NMR of $B(C_6H_5)_4^-$: δ 7.35 (br s, 8H), 6.92 (br t, 8H), 6.78 (br t, 4H). [f] Exchanges with D_2O. [g] Signal buried under $B(C_6H_5)_4^-$ peaks. [h] No change at −0 °C. [i] Peaks broaden at −30 °C. [j] Authentic sample.

Previously, it has been shown that the formation of a zwitterion from the IEDDA reaction of 5-subtituted 2-aminopyrroles with 1,3,5-triazine **3** was reversible.[13a] In this study,[13a] reversion of the zwitterion to starting materials occurred upon attempted chromatographic isolation of the intermediate. Evidence for the reversible formation of zwitterions has also been reported in IEDDA reactions of 1,2,4-triazines and 1,2,4,5-tetrazines.[14] In these studies, the zwitterions isolated at low temperature gave the starting azadiene when the temperature was raised. On the basis of an analogy with these results,[13,14] it is proposed that, in this study, the formation of zwitterions **4** and **5** was reversible with respect to starting materials.

Coupling between H_1, H_2,, and H_4 and deuterium exchange were evidence for the equilibrium proposed in Scheme 2 between **4** and **5**. Another result of this equilibrium was that the H_1 protons (CH_2 group) appeared as a singlet in the ^{1}H NMR. Partial or complete collapse of the CH_2 group has been observed in the conjugate acids of 2-aminopyrroles that contain the $=NH_2^+$ group.[8,10] This result has been attributed to exchange.

Zwitterions **4** and **5** are tautomers. The pyrrole moieties in **4** and **5** correspond to protonation of the 2-aminopyrrole on C3 and C5, respectively. Theoretical calculations on the conjugate acids of 2-aminopyrroles indicated that the imino tautomer derived from protonation at C5 was the most stable under all conditions studied.[22] This was attributed to greater charge delocalization in the imino tautomer resulting from C5 protonation. On the basis of this difference in the stability, it is not surprising that zwitterion **4** was not detected. In another study of the reaction of a 5-substituted 2-aminopyrrole with a 1,3,5-triazine, the only tautomer observed was a 1*H*-pyrrole with a NH_3^+ group.[13a] Calculations have indicated that the position of the equilibrium (dominant tautomer) is a function of structure, solvent, and counterion.[22]

2.C. Imine 6 (Cul-de-Sac). Imine **6** was detected in the 100% Et_3N reaction (with perfluoro salt **1b**) but was not observed in the 50% Et_3N reaction. It reached its highest concentration (ca. 8%) within the first 10 min of the reaction and became undetectable after 24 h. Characterization of this intermediate was hindered by its low concentration. In the ^{1}H NMR spectra, protons H_1, H_2, and H_4 were in a ratio of 2:1:1, respectively. The chemical shift (δ = 8.90 ppm) of H_4 was comparable (δ = 8.78 ppm) to that of the similar proton (H_5) in **8**, an intermediate whose proposed structure was consistent with all of the NMR data (see below). At 0 °C, the COSY spectrum showed coupling between H_1 and H_2. No ^{15}N−^{1}H splitting for H_4 was observed, and there was not enough **6** present in solution to observe it by DEPT-135. Absence of ^{15}N−^{1}H coupling would be a consequence of the equilibrium between **5** and **6** (Scheme 2). The signal for H_1 appeared as an AB quartet in the ^{1}H NMR spectra, evidence for the presence of a CH_2 group and that the two hydrogens were not equivalent. Intermediate **6** is the first reported example of an imino tautomer of a 2-aminopyrrole that does not contain a substituent on the *exo*-amino group.[23,24]

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(24) Tautomerism in secondary 2-aminopyrroles has been observed. De Rosa, M.; Arnold, D.; O'Hare, B. *Tetrahedron Lett.* **2008**, DOI: 10.1016/j.tetlet.2008.10.100.

TABLE 2. ^{1}H NMR Chemical Shift Data for the Reaction of 2-Aminopyrrole (from 1b) with a 1,3,5-Triazine (100% Et_3N)

species	H_1	H_2	H_3	H_4	*t*-Bu	other
1	4.74 (s, 2H)	6.43 (d,1H, J_{H2-H3} = 5.8 Hz)	7.42 (d, 1H, J_{H3-H2} = 6.1 Hz)	7.89 (br s, 1H), 8.83 (br s, 1H)	1.56	
2						
5	4.65 (s, 2H)[a]	7.56 (s, 1H)		8.16 (br, 1H), 10.07 (br, s, 1H)	1.56	
6	4.28 (dq, 2H, J_{H1-H2} = 15 Hz, J_{H1-H2} = 0.9 Hz)[b]	6.72 (br s, 1H)		9.00 (s, 1H)	1.47	H_5 (1.61, s, 1H)
7a/7b	6.40 (d, 1H, J_{H1-H2} = 2.7 Hz)[b]	5.88 (d, 1H, J_{H2-H1} = 2.7 Hz)	3.49 (s, 1H)	7.16 (br s)	1.57	
8	6.56 (d, 1H, J_{H1-H2} = 2.7 Hz)[c,d]	5.94 (br s, 1H)	3.21 (s, 1H)	4.75 (s, 1H)	1.56	H_6 (8.69, br s, 1H)
9	8.07 (d, 1H, J_{H1-H2} = 3.0 Hz)	6.85 (m, 1H)			1.86	
10	not observed					
11						NH (5.70, 4H, br s)

[a] COSY: Strong coupling between H_1, H_2, and H_4. [b] COSY: Strong coupling between H_1 and H_2. [c] COSY: Strong coupling between H_1 and H_2 (all temperatures). Weak coupling between H_1 to H_4 and H_4 to H_3 observed at 0 °C. [d] H_4 and H_5 exchanged with D_2O.

The assignment of the H_5 proton was not obvious. Fluorine NMR showed the existence of three CF_3 groups in a ratio of 1:1:1, indicating that the six-membered ring in this intermediate was no longer symmetrically substituted. Proton transfer to the triazine ring would give an asymmetrical intermediate. Intermediate **6** can also be considered to be the Michael addition product from the reaction of **2** and **3**. An analogous adduct was reported from the reaction of **2** with DMAD via a zwitterionic intermediate.[11] Formation of **6** was considered to be a cul-de-sac since there is not an obvious mechanism for it to cyclize to either **7a** or **7b**.

2.D. Tricyclic Adducts 7a/7b. Intramolecular cyclization of **4** and/or **5** gave **7a** that was in equilibrium with its conjugate acid **7b**. This pair of intermediates was generated in highest concentration (ca. 28%) within the first 10 min of the reaction, which stayed relatively constant for the first 3.5 h of the reaction. These intermediates disappeared after ca. 24 h. Proton NMR (300 MHz) of the **7a/7b** equilibrium showed a single peak. Fluorine NMR (289 MHz) of the **7a/7b** equilibrium showed a single set of two broad peaks (ratio of 2:1), indicative of an equilibrium. These peaks broaden at −30 °C. DEPT-135 (75 MHz) showed two distinct *tert*-butyl peaks (ca. 1:1 ratio) attributed to **7a** and **7b**. ^{15}N NMR (30.4 MHz) showed two signals at δ 34.21 and 58.62 (ca. 1:1 ratio) that were assigned to the C−NH_2 and C−NH_3^+ groups of **7a** and **7b**, respectively. Coupling (COSY) between H_1 and H_2 was observed at 0 °C (100% Et_3N). When 50% Et_3N was used, intermediates **7a/7b** were undetectable either because they were formed in very low concentrations or because they were converted to **8** faster than when 100% Et_3N was used.

Changing the observed nuclei (applied magnetic field) in the NMR experiment changes the NMR time scale, which is also a function of the chemical shift difference ($\Delta\nu$) between the two equilibrating (exchanging) species.[25] In the present study, chemical shift differences changed dramatically as the nucleus, observed by NMR, was changed (Tables 1−3); this was why there was a change in the number of intermediates observed. Experimentally changing the chemical shift difference by varying the applied magnetic field is functionally equivalent to lowering the temperature. The same results would be observed; at low temperature, two signals would be expected (75 and 30.4 MHz) that would coalesce into a broad signal as the temperature increases (289 MHz), becoming a sharp singlet at higher temperature (300 MHz).[25] Using the equation[25] $\tau = \sqrt{2}/2\pi\Delta\nu$, at 75 MHz (^{13}C NMR), $\Delta\nu$ for **7a/7b** was 143 Hz (Table 1) and $\tau = 1.57 \times 10^{-3}$ s^{-1}. At 30.4 MHz (^{15}N NMR), $\Delta\nu$ = 742 Hz (Table 1) and $\tau = 3.03 \times 10^{-4}$ s^{-1}.

2.E. Retro-Diels−Alder Loss of CF_3CN. Trifluoroacetonitrile (CF_3CN) is predicted to be formed via a retro-Diels−Alder reaction either in the penultimate step (IER path) or in the last step (IRE path) of the cascade (Scheme 1).[7] There was no evidence for CF_3CN during the course of the reaction. Authentic CF_3CN had a peak at δ −56.29 (Table 1) in the ^{19}F NMR spectrum. At no point in the reaction was a signal observed at this chemical shift by ^{19}F NMR. NMR evidence (^{1}H, ^{15}N, and ^{19}F) was consistent with the trifluoroacetoamidinium **11**. When the reaction was carried out with 50% Et_3N, the amidine **10** was present and the ^{15}N signal appeared as a quartet–demonstrating ^{15}N−^{19}F coupling (J_{NF} = 3.1 Hz) in **10** (Table 3). ^{15}N NMR indicated that the amino group of 2-aminopyrrole **2** was bonded to the expected CF_3CN at the end of the reaction. Either CF_3CN was not formed directly or it reacted extremely fast with the amino group present in the initially formed heterocyclic retro-Diels−Alder product **13**. Reactions of primary and secondary amines with trifluoroacetonitrile under mild conditions have been reported[26] (e.g., CF_3CN reacted with methyl- and dimethylamine at −60 °C). Therefore, it is proposed (Scheme 4) that the products of the retro-Diels−Alder reaction (**13** and CF_3CN) reacted rapidly with each other to give **8**. As a result, the initially formed CF_3CN was not detected in the reaction mixture.

2.F. Retro-Diels−Alder Intermediate 8. Intermediate **8** (100% Et_3N) was formed after the first 10 min of the reaction and reached its peak (ca. 73%) after 24 h, then slowly gave pyrrolo[2,3-*d*]pyrimidine **9**. Proton NMR and DEPT-135 (Table 1) were consistent with the proposed structure for **8**. The COSY spectrum for intermediate **8** (0 °C) showed coupling between H_1 and H_2, as well as between H_1 and H_4, and H_4 and H_3. Coupling between H_4 and the *exo*-nitrogen was observed by ^{1}H and ^{15}N NMR. The ^{19}F NMR (100% Et_3N) at room temperature showed three CF_3 groups in a ratio of 1:1:1. At

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TABLE 3. Multinuclear Chemical Shift Data for the Reaction of ^{15}N-Labeled 2-Aminopyrrole with a 1,3,5-Triazine (50% Et3N)

	^{1}H NMR (δ)[c]						^{15}N NMR (δ)[b]	^{19}F NMR(δ)[c]
species	H_1	H_2	H_3	H_4	*t*-Bu	other		
1a[d]	3.81 (s, 2H)	5.92 (d, 1H, J_{H2-H3} = 5.4 Hz)	6.51 (d, 1H, J_{H3-H2} = 5.7 Hz)	7.35 (br d, 1H, J_{N-H} = 91.8 Hz)[e] 7.99 (br d, 1H, J_{N-H} = 93.0 Hz)	1.29		86.07 (t, J_{N-H} = 92.7 Hz)	
2	6.36 (br s, 1H)	5.35 (br s, 1H)	5.70 (br s, 1H)	3.42 (br d, 2H, J_{N-H} = 70.2 Hz)	1.59		28.31 (s)	
3								−72.59 (s)
5	3.96 (s, 2H)[f]	7.25 (s, 1H)		7.92 (d, 1H, J_{N-H} = 92.1 Hz)[e,f] 9.80 (d, 1H, J_{N-H} = 89.7 Hz)	1.35		90.36 (s)	−75.06 (s, 6F), −85.54 (s, 3F)
6	not observed							
7a	not observed							
7b	not observed							
8	6.56 (d, 1H, J_{H1-H2} = 3.0 Hz)	5.96 (br s, 1H)	3.26 (s, 1H)	4.78 (d, 1H, J_{N-H} = 72.3 Hz)	1.57	H_6 (8.75 br s, 1H)		−82.79 (s, 3F), −81.04 (s, 3F), −73.27 (s, 3F)
9	7.91 (d, 1H, J_{H1-H2} = 4.2 Hz)	not observed[g]			1.81			−67.13 (s, 3F), −68.96 (d, 3F, J_{H-F} = 2.5 Hz)
10						9.95 (br, s), 6.0 (br, s)	244.37 (q, J_{N-F} = 3.1 Hz)	−73.09
11						5.9 (br s)	254.97 (s)	−76.58

[a] 300 MHz. [b] 30.4 MHz. [c] 282 MHz. [d] Proton NMR of $B(C_6H_5)_4^-$: δ 7.35 (br s, 8H), 6.92 (br t, 8H), 6.78 (br t, 4H). [e] H_4 hydrogens are nonequivalent. [f] Exchanged with D_2O. [g] Signal buried under $B(C_6H_5)_4^-$ peaks.

SCHEME 3

−30 °C, other small peaks became visible, suggesting that **8** was in equilibrium with at least one other unidentified intermediate. Additional evidence for an equilibrium was obtained in reactions run using 50% Et_3N. Under these conditions, the ^{19}F NMR spectrum (at room temperature) showed the same three CF_3 resonances for intermediate **8** (δ −82.79, −81.06, and −73.27) during the first half-hour of the reaction; however, the two signals at −82.79 and −81.06 became broad after 45 min. This difference, with changing the concentration of base, suggested a possible equilibrium between **8** and its conjugate acid (not observed). The role of acid will be discussed in more detail below.

2.G. The Rate-Determining Step of the Cascade. Figure 2 (100% Et_3N) illustrates the changes that occurred in the concentrations of the intermediates with time. They were obtained by plotting the ratio of the areas of the *tert*-butyl peaks and the peak of the small amount of proton containing THF, a constant present in the solvent (99.5% D), versus time. Figure 2 indicates that the disappearance of **8** was a zero-order process and that the rate-determining step could not be the formation of product **9**. On the basis of the changes that occurred in the concentrations of the intermediates (Figure 2) with time, formation of **8** was rate-determining when 100% Et_3N was present. When 5 equiv of base was present, the reaction stopped at the last intermediate, **8**. Product **9** was only formed when trifluoroacetic acid was added. These results proved that the final step, the loss of the amino group as an amidine, was acid-catalyzed. Aromatization by the loss of ammonia or an amine has been shown to be acid-catalyzed in some IEDDA reactions.[17,27] Previous theoretical calculations had not been able to determine the rate-determining step, given that not all of the activation energies could be calculated.[7]

2.H. Mechanism of the Reaction. Spectral evidence (Figures 1 and 2 and Tables 1−3) clearly demonstrated the presence of multiple intermediates in the IEDDA reaction of 1-*tert*-butyl-2-aminopyrrole **2** with 2,4,6-tris(trifluoromethyl)-1,3,5-triazine **3**. ^{15}N NMR demonstrated that the amino group was not lost until the last step of the cascade–contrary to theoretical calculations that the reaction occurred via an IRE pathway.[7] This reaction has been carried out successfully with two 2-aminopyrroles (R = methyl and *tert*-butyl) and 2,4,6-tris(trifluoromethyl)-1,3,5-triazine and 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine.[12] In the present study, no intermediates were observed when 1-methyl-2-aminopyrrole was used. The reaction of 1-methyl-2-aminopyrrole with **3** was over in <5 min, compared to 25 h for 1-*tert*-butyl-2-aminopyrrole **2** under the same conditions (including base).[12] When the reaction of 1-*tert*-butyl-2-aminopyrrole **2** with 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine in THF-d_8 was studied by ^{1}H NMR, a number of

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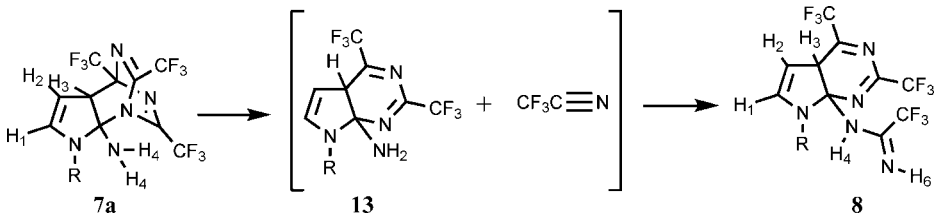
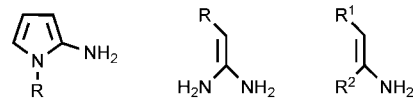
SCHEME 4



intermediates were detected. The number of overlapping multiplets from the nonequivalent ethyl groups present made it difficult to follow the course of the reaction. For this reason, the present study focused on the reaction with 2,4,6-tris(trifluoromethyl)-1,3,5-triazine **3**, with the added advantage that the reaction could also be followed by ^{19}F NMR. Ethylcyanoformate was detected as a product (^{1}H NMR) in the early part of the reaction of **2** with 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine; however, after reaching a maximum, its concentration diminished as the reaction progressed. This suggested that ethylcyanoformate was also reacting with the ethoxycarbonyl analogue of **13**. Reaction was slower because ethylcyanoformate was not as electrophilic as trifluoroacetonitrile. Another IEDDA study reported that the ethylcyanoformate generated participated in side reactions that lowered the yield of the expected product.[27b]

Possible models for the reaction under study are the IEDDA reactions of 1,3,5-triazines with 1,1-diaminoethenes[27b] (from the in situ amidine to 1,1-diaminoethene tautomerization) and enamines.[15b] As can be seen in the figure below, 2-aminopyrroles **2**, the 1,1-diaminoethenes **14**, and enamines **15** are vinylogs, and, as such, all three classes of compounds might be expected to react by the same mechanism. When a 1,1-diaminoethene or an enamine was the dienophile, the first step was a [4 + 2] cycloaddition, and no zwitterion was formed.[15b,27b] This can be contrasted with the reaction of 2-aminopyrroles, in which the formation of cycloadduct **7a/7b** was nonconcerted (Scheme 2), as predicted by theoretical calculations.[7] Once the initial cycloadduct was formed, there were differences in how the final aromatic heterocyclic product was formed. The cycloadduct from the IEDA reaction of 1,1-diaminoethenes **14** with 1,3,5-triazines has been reported to go via an IER mechanism,[27b] but from the reaction with enamines[15b] **15**, it went via the IRE path, as did the 2-aminopyrrole under study. None of the previous studies with 1,1-diaminoethenes,[27b] enamines,[15b] or 2-aminopyrroles[5,12,13a] have provided direct experimental evidence for the timing of the two events leading to the final product: loss of the amino group and the retro-Diels−Alder elimination of a nitrile. Diels−Alder reactions are



analogous to 1,3-dipolar cycloaddition reactions. Sustmann has proposed that dipolar [3 + 2] cylcoaddition reactions can be either normal electron demand (NED) or inverse electron demand (IED) reactions.[28] In 1986, Huisgen reported the first example of a two-step, 1,3-dipolar cycloaddition reaction via the formation of a zwitterion.[29] This occurred when a sterically hindered thiocarbonyl ylid (1,3-dipole) reacted with an electron-deficient dipolarophile. He found that two acceptor groups on the anionic part of the zwitterion stabilized it and promoted the two-step path.[30] Since then, a few other examples have been found.[31] Nucleophilic ketene *N*,*N*-acetals have been reported to react with electron-deficient azides via a two-step mechanism.[32] Theoretical and mechanistic studies on the 1,3-dipolar cycloaddition reactions of N-substituted azomethine ylids have found that the ability of substituents to stabilize the zwitterionic intermediates determines if the reaction will be concerted or stepwise.[33] Interestingly, Saur has presented theoretical and mechanistic evidence that the 1,3-dipolar cycloaddition reactions of electron-poor azomethine ylids with electron-rich enamines was a two-step process, with the formation of a zwitterion–a direct parallel to the reaction under study.[34] Recently, Huisgen has summarized these results as follows:[35]"A switch from concerted cycloaddition to a two-step pathway was observed when two conditions are met: a great difference in nucleophilicity and electrophilicity between the reactants and steric hindrance at least at one terminus of the 1,3-dipole."

Both of these conditions appeared to be met in the present study: the 2-aminopyrrole (dienophile) was very electron-rich and 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (diene) was very electron-deficient, and the *tert*-butyl group (on the dienophile) provided the steric driving force. In zwitterion **5**, the six-membered ring is an anionic σ-complex and the five-membered is a cationic σ-complex.[13b] Electron-withdrawing substituents are known to stabilize anionic σ-complexes (Meisenheimer complexes),[36] and electron-donating subtituents (amino groups)[37] stabilize cationic σ-complexes. In the case of 2-aminopyrroles, the conjugate acids (σ-complexes) can be isolated as stable salts.[10,38] Therefore, it can be seen that in zwitterion **5**, both electron-withdrawing and electron-donating groups stabilized the zwitterionic intermediate. As indicated above, **5**

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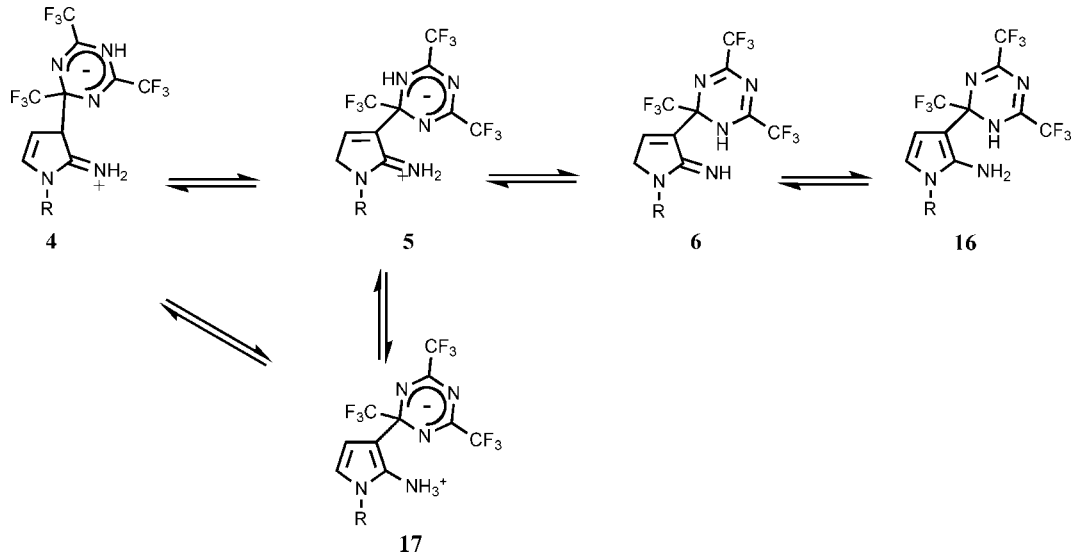
SCHEME 5



was observed instead of **4** because it was the more stable cationic σ-complex (conjugate acid of the 2-aminopyrrole).[22]

A steric effect was obvious when a *tert*-butyl group was present, less so with 1-methyl-2-aminopyrrole. Reactions with this 2-aminopyrrole were fast; either no intermediates were formed or they reacted very fast. Theoretical calculations carried out using the parent 2-aminopyrrole and 1,3,5-triazine as model compounds (R = H and E = H in Scheme 1) determined that the formation of the cycloadduct was nonconcerted.[7] No steric effect was present in these substrates. Reactions of 2-aminopyrroles with other electrophiles have also been reported to go via a zwitterion. With DMAD, Michael addition occurred,[11] and with 2,4,5,6-tetrachloropyrimidine, substitution by addition–elimination[20] was observed instead of the expected IEDDA reaction. These reactions were observed with both 1-methyl- and 1-*tert*-butyl-2-aminopyrrole. In the reaction with 2,4,5,6-tetrachloropyrimidine, regiochemistry was a function of the 1-substituent.[20] On the basis of these results, a nonconcerted mechanism would, therefore, be expected regardless of whether a steric effect was present in the 2-aminopyrrole or the 1,3,5-triazine. In the reaction under study, the *tert*-butyl group either stabilized the intermediates or, more likely, increased the activation energy for the cyclization of the zwitterion to the cycloadduct.[14a,b] Steric effects after the formation of the cycloadduct were also possible.[14a,b]

Added base (triethylamine) played a role in determining the number of intermediates observed in this study and the reaction rate. When 50% Et_3N was used, the reaction was faster and only intermediates **5** and **8** were detected; when 5 equiv of Et_3N was used, the reaction stopped at **8**. Apart from the initial formation of the first zwitterion **4**, the only step of the cascade that did not seem to involve an obvious proton transfer was the formation of the tricyclic intermediate **7a**. Tautomerization is subject to both general acid and base catalysis. A base and its conjugate acid can be expected to a play a role in the tautomeric equilibria discussed below.

Studies of IEDDA reactions of 2-aminopyrroles are complicated by the possible existence of multiple tautomeric equilibria, as illustrated in Scheme 5. Direct NMR evidence for **5** and **6** are presented in this study. Intermediate **17** was not observed in the present study, but an analogous species has been observed (^{1}H and ^{19}F NMR) in another IEDDA study of 2-aminopyrroles.[20] No evidence for **15** was found in this study. Solvent-dependent amino/imino tautomerism has recently been observed in secondary 2-aminopyrroles.[24] In that study, the CH_2 group, of the imino tautomer analogous to **6**, appeared as a broad multiplet, indicative of a fast tautomeric equilibrium. It is possible that in this study, this equilibrium was slow on the NMR time scale and was not observed. Any experimental or theoretical study of the IEDDA reaction of 2-aminopyrroles must explicitly consider all of the possible tautomers in Scheme 5 as potential intermediates in the reaction cascade leading to the cycloadduct.

Theoretical calculations have shown or implied[7,22] that the types of intermediates expected in the IEDDA cascade of 2-aminopyrroles are very sensitive to experimental conditions. There is experimental evidence for this. This study, using unsubstituted (on the ring) 2-aminopyrroles, provided evidence for intermediates **5** and **6**. Another study using a 2-aminopyrrole substituted at C5 by an electron-withdrawing group provided evidence for an analogue of **17**.[20] This intermediate was stable in solution and only gave the final product after the addition of acid. On the basis of this, an IER mechanism was proposed. Calculations showed that reactions of 4-cyano-2-aminopyrroles occurred via the IER mechanism.[7] Clearly, the presence or absence of substituents, their positions, and steric bulk affect the reaction, making it difficult to propose a single general mechanism for the IEDDA reaction of 2-aminopyrroles and 1,3,5-triazines. This is not surprising, given how sensitive tautomeric equilibria (Scheme 5) are to changes in structure, pH, and solvent.[23] These factors varied in this study and the two other studies of the IEDDA reaction of 2-aminopyrroles carried out to date. Another consequence of the tautomeric equilibia illustrated in Scheme 5 is that an intermediate detected in the reaction mixture might not be the ultimate intermediate leading to the next stage of the cascade, as noted above for the analogue of **17**.[20]

3. Conclusions

The IEDDA cascade reaction of a 2-aminopyrrole with a 1,3,5-triazine can be subdivided into two stages: formation of the cycloadduct **7a/7b** and its subsequent conversion to the final aromatic product **9**. The first stage was nonconcerted and a direct

consequence of electronic factors present in the starting compounds. Zwitterions have now been proposed and/or observed in the reaction of 2-aminopyrroles with three different types of electrophiles.[7,11,20] From this, it can be seen that the formation of a zwitterion would appear to be the norm rather than the exception. Observation of the intermediates (Scheme 2) was possible when a steric effect was present. Once formed, the initial zwitterion was one of five possible tautomers, a possibility that had not been considered in previous experimental or theoretical studies. Cycloadducts can then go on to the final product by two pathways.[7] In this study, NMR evidence demonstrated that it was the IRE pathway, a retro-Diels−Alder elimination of a nitrile, followed by aromatization by the loss of the amino group as an amidine. This is a novel pathway since, previously, only the acid-catalyzed elimination of ammonia or an amine had been proposed.[17,27] This is the first study in which *direct* experimental evidence for the order of the steps in the IEDDA cascade reaction of 1,3,5-triazines with amino containing dienophiles has been obtained.[5−7,12,13,15b,27b] This study and analogous 1,3-dipolar cycloaddition reactions, in which zwitterions have been detected or proposed, have two factors in common: electronic effects that stabilize the zwitterions and steric effects that inhibit their cyclization.

4. Experimental Section

Synthesis of Salt 1b: A 5 mL test tube was charged with *N*-(1-*tert*-butyl-1*H*-pyrrol-2-yl)-2-(hydroxymethyl)benzamide (0.2939 g, 1.08 mmol) and glacial acetic acid (2 mL) added.[10] The resultant reaction mixture was placed under N_2(g) and heated in a water bath to 80 °C in the dark for 2 h. After 2 h of heating, the reaction mixture was cooled to room temperature and transferred with approximately 5 mL of distilled H_2O to a 150 mL beaker containing 50 mL of distilled H_2O. Immediately, a solution of (3.10 g, 4.3 mmol) of potassium tetrakis(pentafluorophenyl)borate salt dissolved in 6.5 mL of THF was added to the aqueous solution with vigorous stirring. A white colloidal precipitate formed that was coagulated by heating the solution near boiling for approximately 15 min. The resulting solid was isolated by vacuum filtration and dried under high vacuum (0.300 g, 34%).

General Procedure for NMR Experiments: A dry NMR tube was charged with **1a/1b** (0.218 mmol, 1.0 equiv), 1.0 mL of THF-d_8, and Et_3N-d_{15} (0.5−1.0 equiv). The NMR tube was shaken, and then **3** (1.0−1.5 equiv) was added. The NMR tube was shaken again to ensure mixing, and the corresponding heteronuclear NMR experiments were performed at the specified temperatures and time intervals.

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Supporting Information Available: Multinuclear NMR spectral studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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