Aromatic Dienophiles. 1. A Theoretical Study of an Inverse-Electron Demand Diels−Alder Reaction between 2-Aminopyrrole and 1,3,5-Triazine

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This study is devoted to a detailed theoretical study of an inverse-electron demand Diels−Alder reaction (IDA) with 1,3,5-triazine as the diene and 2-aminopyrrole $\mathbf{1A}_\alpha$ as the dienophile, which is a key step in a cascade reaction for the one-pot synthesis of purine analogues. Geometries were optimized with the B3LYP/6-31G* method and energies were evaluated with the MP2/6-311++G** method. This IDA reaction occurs through a stepwise mechanism, where the first step corresponds to the nucleophilic attack of 2-aminopyrrole to triazine to form a zwitterionic intermediate, which is in equilibrium with a neutral intermediate through a hydrogen transfer process, followed by a rate-determining ring-closure step. It is shown that the B3LYP method significantly overestimates the activation energy, whereas the MP2 method offers a reasonable activation barrier of 27.9 kcal/mol in the gas phase. The solvation effect has been studied by the PCM model. In DMSO, the calculated activation energy of the IDA reaction is decreased to 24.0 kcal/mol with a strong endothermicity of 17.4 kcal/mol due to the energy penalty of transforming two aromatic reactants into a nonaromatic IDA adduct. The possible stepwise [2+2] pathway is ruled out based on its higher activation and reaction energies than those of the [4+2] pathway. By comparing the IDA reactions of triazine to 2-aminopyrrole and pyrrole, we address two crucial roles of the α-amino substituent in lowering activation and reaction energies and controlling the reaction regiochemistry.

Introduction

The Diels−Alder (DA) reaction constitutes one of the most frequently employed methods for the construction of six-membered ring systems.[1−3] The commonly utilized DA reaction is the normal DA reaction,[2] in which the dominating orbital interaction (corresponding to the lowest HOMO−LUMO energy separation) is between $HOMO_{diene}$ and $LUMO_{dienophile}$. In contrast, the inverse-electron demand Diels−Alder (IDA) reaction is controlled mainly by the interaction of $HOMO_{dienophile}$ and $LUMO_{diene}$ and it requires an electron-rich dienophile and an electron-poor diene. The chemistry of IDA has been the subject of recent intensive investigation[4] and is widely used in the synthesis of heterocyclic compounds and carbohydrates as well as their related highly functionalized natural products.[5,6]

It is well established that azadienes are effective aromatic dienes to participate in IDA reactions.[1c,7,8] For example, Boger's group synthesized pyrimidines by utilizing an IDA reaction involving 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine as the diene and in situ generated

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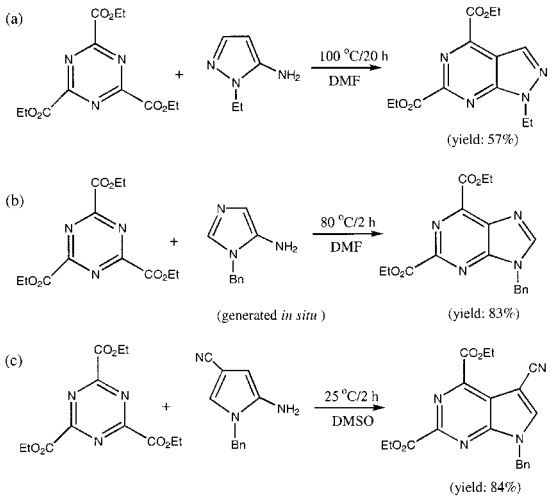
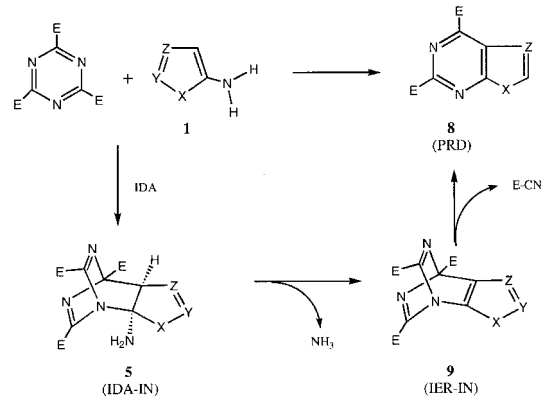
Scheme 1



Scheme 2

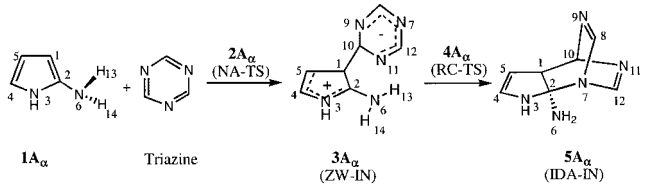


diaminoethene as the dienophile.[8] Recently, Dang and co-workers expanded this reaction by introducing aromatic heterocycles as dienophiles for the efficient synthesis of purines and purine nucleosides as well as their analogues (Scheme 1).[9a−c]

Mechanistically, these reactions are supposed to occur by a cascade reaction via an **IER** pathway,[10] where the first step involves an IDA reaction between 1,3,5-triazines (unless otherwise mentioned, triazine means 1,3,5-triazine in what follows) acting as dienes and amino-substituted five-membered heteroaromatics as dienophiles, followed by elimination of ammonia to form the intermediate (IER−IN) **5** and retro-Diels−Alder (RDA) reaction to produce the final product (PRD) **8** (see Scheme 2).

In addition to the intriguing cascade reaction mechanism, the other fascinating features are the IDA reactions that engage aromatic dienophiles. Indeed, five-membered heteroaromatic molecules, such as furan, pyrrole, thiophene, and oxazole derivatives, have been widely used as dienes in DA reactions despite the fact that harsh reaction conditions (high pressures and temperatures) or catalysts are often required and the adducts are susceptible to RDA reactions.[11] DA reactions involving aromatics as the dienophiles, nevertheless, are scarce, and usually require active dienes, such as azadienes, quinones and their derivatives.[9,12] Although the IDA chemistry has been the focus of intensive experimental and theoretical investigations,[4,13] a theoretical study of a Diels−Alder reaction involving aromatic dienophiles has not, to the best of our knowledge, been reported yet. A theoretical study of the model reactions depicted in Scheme 2 between heteroaromatic amines as the dienophiles and triazine as the diene is of fundamental importance in understanding this process and the characteristic features of aromatic dienophiles as well.

Scheme 3



The aim of the present study is to contribute to a better understanding of the IDA reaction engaging aromatic dienophiles and to clarify the nature of the transition states, the origin of the regioselectivity and the effects of the amino substituent. We chose the reaction between 2-aminopyrrole $\mathbf{1A}_\alpha$ and triazine as a representative example of this kind of IDA process. Our work shows that the title IDA reaction follows a stepwise process, where the first step corresponds to the nucleophilic addition of electron-rich 2-aminopyrrole $\mathbf{1A}_\alpha$ to electron-deficient triazine via transition state (NA-TS) $\mathbf{2A}_\alpha$ to form a zwitterionic intermediate (ZW-IN) $\mathbf{3A}_\alpha$, followed by a ring-closure via rate-determining transition state (RC-TS) $\mathbf{4A}_\alpha$ to generate IDA adduct (IDA-IN) $\mathbf{5A}_\alpha$. This process is schematically shown in Scheme 3 together with atom labeling.[14] To address the role of the amino substituent, the parent molecule pyrrole (**1A**) has been studied as a potential dienophile as well. Simultaneously, analyses of the regioselectivity and the competitive stepwise [2+2] pathway are conducted when applicable.

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(10) Another possible pathway, referred to as the IRE pathway, which follows the sequence of inverse-electron demand Diels−Alder reaction, retro-Diels−Alder reaction to loss E−CN, and elimination of ammonia, has been ruled out since our calculations show that the RDA process in this pathway has a prohibitive activation barrier (unpublished results).

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(14) A competitive IDA reaction involves the addition of the C_4-C_5 double bond of 2-aminopyrrole to triazine. Indeed, Liao and co-workers reported this pattern of reactivity for the DA reaction between 2-methoxyfuran and pyrones.[12c] In the present situation, such a reaction would lead to the formation of an adduct that cannot participate in a further cascade reaction. A detailed study of the relative reactivities between the C_1-C_2 and C_4-C_5 double bonds of 2-amino-substituted heteroaromatics will be reported later.

Computational Details. All the calculations were performed with the GAUSSIAN 98 program.[15] The geometries were fully optimized with the density functional theory[16] at the B3LYP/6-31G* level,[17] except for ZW-IN **3A**$_\alpha$, which was optimized with the B3LYP/6-31+G* method.[18] The DFT methods have been applied to the study of many pericyclic reactions including DA reaction and Cope rearrangement.[19,20] In the DA reactions involving aromatic dienes, the DFT calculations usually yield relatively higher activation barriers due to the overestimation of the aromaticity of the reactants.[21,22] In this case, second-order or high-order Møller−Plesset (MPn) methods usually offer a more reliable estimation of the activation barrier.[22−24] Therefore, all energetics were evaluated with the MP2/6-311++G**(5d) method.[25]

Harmonic vibrational frequencies were calculated for each structure of the reaction of **1A**$_\alpha$ with triazine to confirm each structure being either a minimum (no imaginary frequency) or a transition state (one imaginary frequency).

Atomic charges were calculated by the CHELPG[26] method at the B3LYP/6-31G* level and molecular orbital energies were calculated at the HF/6-31G* level. The reported bond orders are the Wiberg bond indices[27a] calculated by means of natural bond orbital (NBO) analysis.[27b−c]

The solvation effect on the IDA reaction between **1A**$_\alpha$ and triazine has been considered with a DMSO solvent ($\epsilon = 46.7$). A polarization continuum model (PCM)[28] was used both for geometric optimization (B3LYP(PCM)/6-31G*) and energy evaluation (MP2(PCM)/6-311++G**).

Results and Discussion

This section includes two parts. The first part focuses on the IDA reaction between 2-aminopyrrole **1A**$_\alpha$ and triazine, in which geometries, energies, the solvation effect, the competitive [2+2] reaction pathway and the regiochemistry are discussed. The reaction between pyrrole **1A** and triazine is presented in the second part to provide a rationalization for the role of the amino substituent. All of the Cartesian coordinates and energies of the DFT optimized species within this context are provided in the Supporting Information. Unless otherwise noted, the energies are referred to the ΔE_0(MP2/6-311++G**) level, which includes unscaled zero-point energy (ZPE) correction.

I. IDA Reaction between 2-Aminopyrrole 1A$_\alpha$ and Triazine. The B3LYP/6-31G* structures of the stationary points of the title stepwise IDA reaction are shown in Figure 1 and their relative energies are summarized in Table 1.

Frontier Molecular Orbital (FMO) Analysis. The frontier molecular orbitals[29] of 2-aminopyrrole, triazine and pyrrole are depicted in Figure 2. Triazine adopts a D_{3h} symmetry with 2-fold degenerated HOMO and LUMO orbitals of −11.89 and 2.64 eV, respectively. The reacting conformation of 2-aminopyrrole **1A**$_\alpha$ adopts a structure with the amino lone pair nearly parallel with the pyrrole ring π orbital (see discussion on geometries) and hence the orbital energies and coefficients shown in Figure 2 are calculated on a planar C_s structure (Scheme 4). It has the HOMO and LUMO+1 energies of −6.69 and 6.17 eV, respectively (its LUMO corresponds to the σ* orbitals of the N−H bonds).

According to symmetry principle, two pairs of frontier molecular orbital interactions between the reactants, $HOMO_{\mathbf{1A}\alpha}$ with $LUMO_{triazine}$ and $HOMO_{triazine}$ with $(LUMO+1)_{\mathbf{1A}\alpha}$, contribute to the stability of the transition state. The energy gap of the former pair is much smaller. Thus, the DA reaction is an IDA process according to Sustmann's classification.[2] The charge-transfer feature occurring during the DA reaction process further supports this assertion. The triazine moiety has a negative charge of 0.42, 0.55 and 0.33 units in the NA-TS **2A**$_\alpha$, ZW-IN **3A**$_\alpha$ and RC-TS **4A**$_\alpha$, respectively, while the dienophile unit has a positive charge of the same magnitude.[30]

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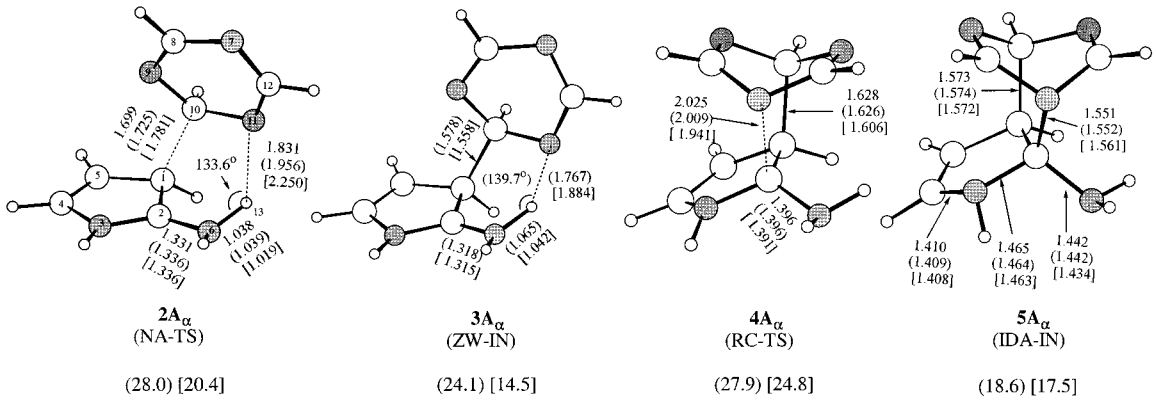


Figure 1. The relevant geometries of various stationary points involved in the IDA process of the reaction between 2-aminopyrrole **1A**$_\alpha$ and 1,3,5-triazine. Bond lengths in angstroms and angles in degrees. The geometries were optimized by B3LYP/6-31G*, B3LYP/6-31+G* (in parentheses) and B3LYP(PCM)/6-31G* (ϵ = 46 for the DMSO solution, in brackets).

Table 1. The Elative Energies (kcal/mol) of the Transition States, Intermediate, and IDA Adduct with Respect to the Reactants at Different Levels of Theories; ΔE_{ele} and ΔE_0 Represent Electronic Energy without and with ZPE Correction, Respectively, ΔG_{298} Represents Free Energy at 298 °C

	2A$_\alpha$ (NA-TS)			**3A**$_\alpha$ (ZW-IN)			**4A**$_\alpha$ (NA-TS)			**5A**$_\alpha$ (IDA-IN)		
	ΔE_{ele}	ΔE_0	ΔG_{298}	ΔE_{ele}	ΔE_0	ΔG_{298}	ΔE_{ele}	ΔE_0	ΔG_{298}	ΔE_{ele}	ΔE_0	ΔG_{298}
B3LYP/6-31G*	29.2	30.4	43.2	28.8	29.8	42.2	41.6	43.3	57.1	35.2	38.0	52.0
B3LYP/6-31+G*	30.6	31.7	44.2	29.2	30.3	42.7	43.6	45.3	58.7	37.7	40.5	54.1
MP2/6-311++G** [a]	26.8	28.0	40.8	23.0	24.1	36.5	26.2	27.9	41.7	15.8	18.6	32.7
MP2(PCM)/6-311++G** [b]	19.1	20.2	33.0	13.8	14.9	27.2	22.3	24.0	37.7	14.6	17.4	31.4
SSE[c]	−7.6	−7.6	−7.6	−9.6	−9.6	−9.6	−3.1	−3.1	−3.1	−1.1	−1.1	−1.1
ΔE(DMSO)[d]	19.2	20.4	33.2	13.4	14.5	26.9	23.1	24.8	38.6	14.7	17.5	31.6

[a] With B3LYP/6-31G* geometries. [b] With B3LYP(PCM)/6-31G* geometries. [c] The solvation stabilization energy is defined as SSE = ΔE_{ele}(MP2(PCM)/6-31G*) − ΔE_{ele}(MP2/6-31G*) [d] ΔE(DMSO) = ΔE(MP2/6-311++G**) + SSE.

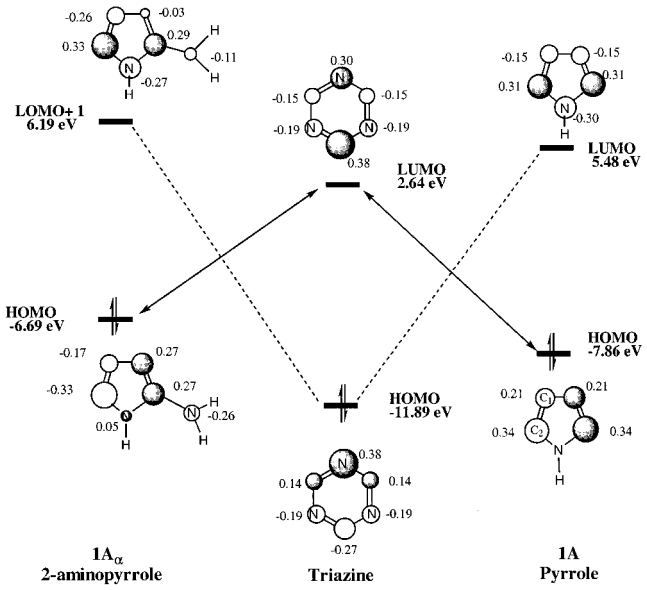
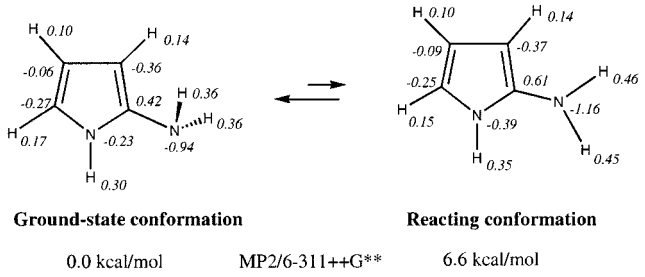


Figure 2. Frontial molecular orbitals with coefficients (2p) of 2-aminopyrrole **1A**$_\alpha$, triazine and pyrrole **1A** (**1A**$_\alpha$ is in its reacting conformation).

The possible reaction between pyrrole **1A** and triazine can also be classified as an IDA reaction from the viewpoint of FMO theory (Figure 2). However, it is expected to have a higher activation energy than the reaction of **1A**$_\alpha$ since the presence of the NH_2 group in **1A**$_\alpha$ promotes **1A**$_\alpha$'s HOMO by about 1 eV compared to that of **1A**.

(30) According to the CHELPG calculations, the negative charge in the triazine moiety is mainly on the N_9 and N_{11} atoms in **2A**$_\alpha$ and **3A**$_\alpha$ but shifts to the N_7 atom in **2A**$_\alpha$. For more detailed information, see Figure S1 of the Supporting Information.

Scheme 4



Origin of Stepwise Rather than Concerted Mechanism. There is now a consensus that the archetypal DA reaction between 1,3-butadiene and ethene is a synchronous concerted process.[3,19b,31] When some substituents are introduced, the reaction mechanism may change progressively from a synchronous concerted to an asynchronous concerted or even to a stepwise process.[32] The stepwise mechanism of the title reaction reflects this trend and can be rationalized by considering the electronic features of the two reactants.

On one hand, the pyrrole ring is electron-rich[33] and this feature is further strengthened by the presence of an electron-donating amino substituent. The amino group makes the C_1 atom more nucleophilic, which is demon-

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(32) (a) Sustmann, R.; Sicking, W. *J. Am. Chem. Soc.* **1996**, *118*, 12562. (b) Sustmann, R.; Tappanchai, S.; Bandmann, H. *J. Am. Chem. Soc.* **1996**, *118*, 12555.

(33) Gilchrist, T. L. *Heterocyclic Chemistry*; John Willey & Sons Inc.: New York, 1985.

Table 2. The Calculated C_2-N_6 Bond Lengths (BL, Å) and Wiberg Bond Orders (BO) as Well as the Dihedral Angles of $H_{13}-N_6-C_2-C_1$ and $N_6-C_2-C_1-C_5$ (in degrees) of All Stationary Points of the Title IDA Reaction between 2-aminopyrrole $1A_\alpha$ and Triazine Obtained by the B3LYP/6-31G* Method

	$1A_\alpha$ [a]	$1A_\alpha$ [b]	$2A_\alpha$ (NA-TS)	$3A_\alpha$ (ZW-IN)	$4A_\alpha$ (RC-TS)	$5A_\alpha$ (IDA-IN)
BL (C_2-N_6)	1.42	1.39	1.33	1.32	1.40	1.44
BO (C_2-N_6)	1.05	1.11	1.36	1.43	1.15	1.04
$H_{13}-N_6-C_2-C_1$	59.7	0.0	20.2	16.6	45.0	43.5
$N_6-C_2-C_1-C_5$	180.0	180.0	180.0	−177.6	131.2	133.6

[a] Ground-state conformation. [b] Reacting conformation.

strated by its relatively large negative charge than its adjacent carbon atoms (the CHELPG charges are shown in Scheme 4 in italic script). On the other hand, triazine is an electron-deficient aromatic system[33] in which the carbon atoms are electron-poor and have a strong electrophilic character. Apparently, the existence of the first transition state NA-TS **2A**$_\alpha$ is resulted from the attack of nucleophilic C_1 of the 2-aminopyrrole **1A**$_\alpha$ to one of the three electrophilic carbon atoms of triazine.

As will be discussed later, the reaction between pyrrole **1A** and triazine proceeds through an asynchronous concerted transition state. The 2-amino substituent plays a pivotal role in the stepwise mechanism, not only making the C_1 atom more nucleophilic, but also stabilizing the zwitterionic intermediate by delocalizing the positive charge developed in the pyrrole ring and allowing the existence of hydrogen bonding between H_{13} and N_{11} of the triazine (see Figure 1). In addition, the solvation effect also contributes to the stepwise mechanism through stabilizing the zwitterionic intermediate, which will be discussed later.

Geometries. The ground state of 2-aminopyrrole **1A**$_\alpha$ is in a nonplanar conformation with the NH_2 lone pair coplanar with the pyrrole ring and directing to the imido hydrogen (Scheme 4).[34] However, in the transition structures and the zwitterionic intermediate, the amino group has to rotate by about 90° to allow its lone pair to overlap with the π orbital of the pyrrole ring in order to stabilize these species through conjugation, which is demonstrated by the changes of bond length and bond order of the C_2-N_6 during the IDA process (see Table 2). Therefore, a conformation switch in the amino group is necessary upon the reaction,[4a,35] even though the dienophile's reacting conformation is less stable by about 6.6 kcal/mol than its ground-state conformation (Scheme 4).

The first transition state, NA-TS **2A**$_\alpha$, does not correspond to a supra-supra [4+2] mechanism but to the nucleophilic attack of C_1 to C_{10}, with the forming bond distance and bond order of 1.70 Å and 0.78, respectively. The distance between C_2 and N_7 is about 4.3 Å, indicating that there is no interaction between them. The NH_2 lone-pair conjugates well with the pyrrole ring. There is a strong hydrogen-bonding interaction between N_{11} and H_{13} as indicated by the short $N_{11}-H_{13}$ distance (This distance is larger in the DMSO solvent, see discussion below).

The ZW-IN **3A**$_\alpha$ is quite similar to NA-TS **2A**$_\alpha$ except that it has a shorter C_1-C_{10} bond and a shorter $N_{11}-H_{13}$ hydrogen bond distance.

In RC-TS **4A**$_\alpha$, the forming C_2-N_7 bond length and bond order are about 2.0 Å and 0.43, respectively. Intrinsic reaction coordinate (IRC) calculations further confirm that RC-TS **4A**$_\alpha$ connects ZW-IN **3A**$_\alpha$ and IDA-IN **5A**$_\alpha$. The almost-formed C_1-C_{10} bond, which has bond length and bond order of 1.63 Å and 0.86, respectively, is slightly elongated, compared with the C_1-C_{10} bond in ZW-IN **3A**$_\alpha$.

Energetics. The energetics of the title reaction is shown in Table 1. It is apparent that the DFT calculations overestimate the activation energy, which is as high as 43.3 kcal/mol (ΔE_0(B3LYP/6-31G*)) for the rate-determining RC-TS **4A**$_\alpha$. On the contrary, the relative energy of this transition state computed by the MP2/6-31G* method is dramatically reduced to 27.7 kcal/mol, confirming the overestimation of the aromatic stabilization of the reactants by the DFT method.

Table 1 indicates that in the gas phase, NA-TS **2A**$_\alpha$ and RC-TS **4A**$_\alpha$ are close in energy. Although NA-TS **2A**$_\alpha$ is less stable than RC-TS **4A**$_\alpha$ by about 0.1 kcal/mol, the latter is 0.9 kcal/mol less stable than the former (40.8 vs 41.7 kcal/mol in terms of $\Delta \boldsymbol{G}_{298}$) when the entropy contributions are introduced. The entropies for NA-TS **2A**$_\alpha$ and RC-TS **4A**$_\alpha$ are 93.6 and 90.5 eu, respectively. The sum of the entropies of the two reactants is 140.8 eu.

The activation barrier for this IDA process is still as high as 28 kcal/mol in terms of $\Delta \boldsymbol{E}_0$. In addition, the overall IDA reaction is very endothermic (18.6 kcal/mol in terms of $\Delta \boldsymbol{E}_0$). The high activation energy and endothermicity involved in this IDA process is very understandable considering the energy penalty in transforming two aromatic reactants to a nonaromatic adduct.

It is apparent that if there were no other influencing factors, the title IDA reaction could not occur owing to the adverse endothermicity and the entropy penalty accompanying this transformation. The influencing factor in the title reaction is the coupling of the IDA reaction with two subsequent cascade reactions, namely the elimination of ammonia and the RDA reaction to form the final stable aromatic product. The cascade reaction is an entropy gaining process (from two reactants to three final products), and the RDA is a strong exothermic process that can compensate for the adverse endothermicity of the IDA reaction. Therefore, the coupling with the last two steps of the **IER** pathway (Scheme 2) is the key to the occurrence of the title IDA reaction.

Solvation Effect. The solvation effect on the reactivity and mechanism of DA reactions is well documented and has received considerable attention.[36] The solvation effect in a concerted reaction is generally small; however, a stepwise reaction can usually be accelerated in polar media due to the stabilization of the polar zwitterionic intermediate and transition states. The asymmetric 2-aminopyrrole **1A**$_\alpha$ has a dipole moment of 1.09 D, while NA-TS **2A**$_\alpha$, ZW-IN **3A**$_\alpha$, RC-TS **4A**$_\alpha$, and IDA-IN **5A**$_\alpha$ have larger dipole moments of 8.11, 9.94, 4.89 and 2.92 D, respectively. The increase in dipole moment accompanying this reaction course implies that a polar solvent should be able to accelerate the reaction.

(34) For the discussion of nonplanarity of heteroamines, see: (a) Govorun, D. N.; Danchuk, V. D.; Mishchuk, Y. R.; Kondratyuk, I. V.; Radomsjy, N. F.; Zheltovsky, N. K. *J. Mol. Struct.* **1992**, *267*, 99. (b) Hovorun, D. M.; Gorb, L.; Leszczynski, J. *Int. J. Quantum. Chem.* **1999**, *75*, 245. (c) Shishkin, O. V. *J. Mol. Struct.* **1998**, *447*, 1.

(35) Other examples of conformational switches can be found in: (a) Coxon, J. M.; Houk, K. N.; Luibrand, R. T. *J. Org. Chem.* **1995**, *60*, 418. (b) Houk, K. N.; Duh, H.-Y.; Wu, Y.-D.; Moses, S. R. *J. Am. Chem. Soc.* **1986**, *108*, 2754.

(36) For a review of methods for solvation effect modelling on the Diels−Alder reactions, see: Cativiela, C.; Garcia, J. I.; Mayoral, J. A.; Salvatella, L. *Chem. Soc. Rev.* **1996**, 209.

As shown in Figure 1, the inclusion of the DMSO solvation effect leads to a "looser" NA-TS 2$\mathbf{A}_\alpha$ as indicated by the elongation of the C_1-C_{10} bond (value in bracket) and the $N_{11}-H_{13}$ hydrogen bond distance. Other structures are influenced only very little by the solvation effect.

Energetically, the solvent significantly stabilizes the two transition states and the intermediate compared with the reactants, reducing the activation barrier of the overall IDA reaction to 24.0 kcal/mol (ΔE_0(MP2(PCM)/6-311++G**, see Table 1). The magnitudes of the solvent stabilization to NA-TS **2A**$_\alpha$, ZW-IN **3A**$_\alpha$, RC-TS **4A**$_\alpha$ and IDA-IN **5A**$_\alpha$ are about 8, 9, 4, and 1 kcal/mol relative to the reactants, respectively, matching very well with their respective polarities. Thus, the solvation effect not only promotes the stepwise mechanism, but also makes the ring-closure step as the rate-determining step.

We also tested whether the solvation effect on the activation and reaction energies can be accounted for with a cheaper computational method. Consequently, the solvation effect was calculated with the MP2/6-31G* method using the B3LYP/6-31G* geometries. We define solvent stabilization energy (SSE) as

$$\mathrm{SSE} = \Delta \boldsymbol{E}_{\mathrm{ele}}(\mathrm{MP2(PCM)/6\text{-}31G^*}) - \Delta \boldsymbol{E}_{\mathrm{ele}}(\mathrm{MP2/6\text{-}31G^*})$$

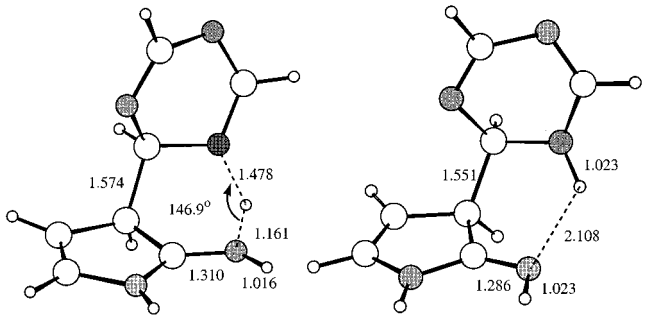
The relative energies for the species in DMSO were then computed by

$$\Delta \boldsymbol{E}_0(\mathrm{DMSO}) = \Delta \boldsymbol{E}_0(\mathrm{MP2/6\text{-}311{+}{+}G^{**}}) + \mathrm{SSE}$$

This Scheme assumes that the solvation stabilization calculated with the MP2/6-31G* method is about the same as that calculated with the MP2/6-311++G** method. A similar additive strategy has been successfully applied by Calvo-Losada and Suarez in modeling the DA reaction between furan and maleic anhydride.[22] Table 1 shows that the relative energies obtained by $\Delta \boldsymbol{E}_0$(DMSO) and $\Delta \boldsymbol{E}_0$(MP2(PCM)/6-311++G**) are close, suggesting that this additive procedure is a reasonably good model for the solvation effect.

Equilibrium Between two Intermediates. The zwitterionic intermediate is unstable and it is easily converted into a neutral intermediate (NEU−IN **3′A**$_\alpha$) by the hydrogen shift transition state **HT-TS-A**$_\alpha$, as shown in Figure 3. Although NEU−IN **3′A**$_\alpha$ is about 15.3 kcal/mol more stable than ZW-IN **3A**$_\alpha$ at the MP2/6-311++G** level, it is still about 8.8 kcal/mol less stable than the reactants. This suggests that this species is in equilibrium with ZW-IN **3A**$_\alpha$ and that it cannot be isolated but might be observed by a trapping experiment.

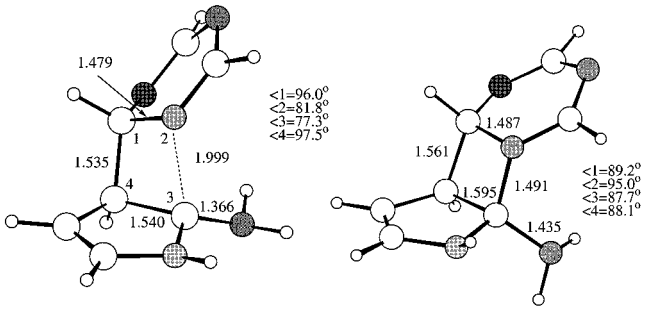
Competitive [2+2] Pathway. For some stepwise [4+2] Diels−Alder reactions, a [2+2] adduct is sometimes a concomitant product or the major product under certain reaction conditions.[38] For example, Sustmann and coworkers observed a concomitant minor [2+2] adduct along with the major [4+2] adduct in the reaction between 1,1-dimethoxyl-1,3-butadiene and β,β-dicyanoacrylate at −70 °C.[33b] Although such a [2+2] product for the current cascade reaction was not observed experimentally, a theoretical study of this possible pathway can enhance our understanding of the stepwise IDA reaction. Figure 6 shows the located [2+2] transition state and the adduct. This pathway can be excluded since its transition state is higher in energy by 8.2 kcal/mol



HT-TS-1A$_\alpha$ (22.0) [15.1]

3'A$_a$ (NEU-IN) (8.8) [8.2]

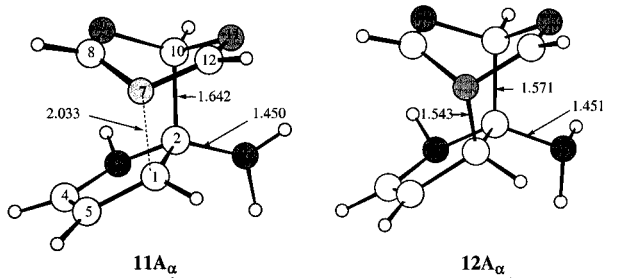
Figure 3. The B3LYP/6-31+G* optimized hydrogen transfer transition state **HT-TS-A**$_\alpha$ and the neutral intermediate NEU−IN **3′A**$_\alpha$. The energies (kcal/mol) relative to the reactants are ($\Delta \boldsymbol{E}_0$(MP2/6-311++G**)) and [$\Delta \boldsymbol{E}_0$(DMSO)]. Distances are in angstroms.



TS$^{[2+2]}$**-A**$_\alpha$ (36.1) [31.5]

IN$^{[2+2]}$**-A**$_\alpha$ (24.1) [24.6]

Figure 4. The B3LYP/6-31G* optimized transition state **TS**$^{[2+2]}$**-A**$_\alpha$ and adduct **IN**$^{[2+2]}$**-A**$_\alpha$ of the competitive [2+2] pathway for the reaction between 2-aminopyrrole **1A**$_\alpha$and triazine. The relative energies (kcal/mol) with respect to the reactants are ($\Delta \boldsymbol{E}_0$(MP2/6-311++G**)) and [$\Delta \boldsymbol{E}_0$(DMSO)]. Bond lengths are in angstroms and angles in degrees.



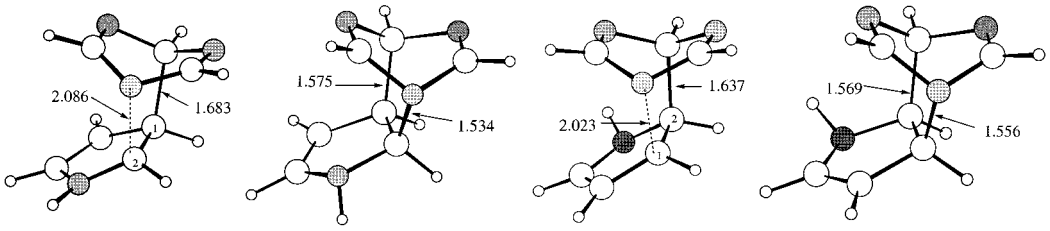
11A$_\alpha$ (RC-TS^{iso}) (31.2) [30.2]

12A$_\alpha$ (IDA-IN^{iso}) (22.1) [21.3]

Figure 5. The B3LYP/6-31G* optimized structures of transition state RC-TS^{iso} **11A**$_\alpha$ and adduct IDA-IN^{iso} **12A**$_\alpha$ of the iso path for the reaction between 2-aminopyrrole **1A**$_\alpha$ and triazine. The relative energies with respect to the reactants are (ΔE_0-(MP2/6-311++G**)) and [ΔE_0(DMSO)]. Bond lengths are in angstroms.

(37) (a) Domingo, L. R.; Arnó, M.; Andrés, J. *J. Am. Chem. Soc.* **1998**, *120*, 1617. (b) Domingo, L. R.; Picher, M. T.; Zaragozá, R. J. *J. Org. Chem.* **1998**, *63*, 9183. (c) Domingo, L. R.; Picher, M. T.; Andrés, J.; Oliva, M. *J. Org. Chem.* **1999**, *64*, 3026. (d) Domingo, L. R.; Picher, M. T.; Andrés, J. *J. Phys. Chem. A* **1999**, *103*, 11425. (e) Domingo, L. R.; Picher, M. T.; Andrés, J. *J. Org. Chem.* **2000**, *65*, 3437.

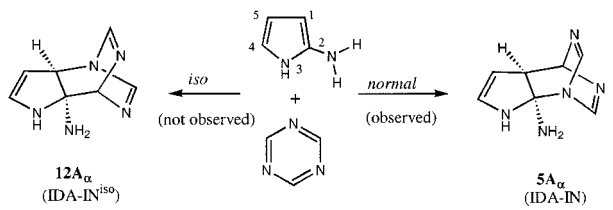
(38) Desimoni, G.; Tacconi, G. *Chem. Rev.* **1975**, *75*, 651.



19A (RC-TS) (34.1) [31.1] **20A** (IDA-IN) (24.4) [22.7] **21A** (RC-TS^{iso}) (33.1) [31.4] **22A** (IDA-IN^{iso}) (24.7) [24.2]

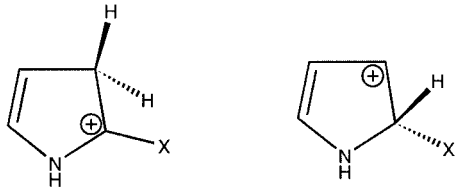
Figure 6. The transition states and adducts for the reaction between pyrrole **1A** and triazine in two competitive pathways obtained by the B3LYP/6-31G* method. The relative energies (kcal/mol) with respect to the reactants are (ΔE_0(MP2/6-311++G**)). Bond lengths are in angstroms and angles in degrees.

Scheme 5



12A$_\alpha$ (IDA-IN^{iso}) **5A**$_\alpha$ (IDA-IN)

Scheme 6



	α cation	β cation
X=NH$_2$	0.0 kcal/mol	18.2 kcal/mol
X=H	4.9 kcal/mol	0.0 kcal/mol

than the [4+2] RC-TS **4A**$_\alpha$. Furthermore, the [2+2] adduct is less stable than the [4+2] adduct IDA-IN **5A**$_\alpha$ by about 5.5 kcal/mol. Their instabilities are certainly related to the strain of their four-membered rings.

Regioselectivity. Two reaction pathways involving the C_1-C_2 double bond as dienophile are possible for the [4+2] IDA reaction (Scheme 5): the normal pathway, which has been discussed so far, yields IDA-IN **5A**$_\alpha$ and the iso pathway results the corresponding isomer IDA-IN^{iso} **12A**. Figure 5 shows the transition state and adduct of the iso pathway located by the B3LYP/6-31G* method. All careful attempts to find a nucleophilic attack transition state and the possible zwitterionic intermediate, even by using the B3LYP/6-31+G* method, were unfruitful, suggesting that the iso path is a concerted process. The transition state is asynchronous. The C_2-C_{10} bond is largely formed (1.642 Å) while the C_1-N_7 bond (2.033 Å) formation lags behind. The amino group adopts the same conformation as in the ground state of the reactant.

Our calculations indicate that the iso path is higher in activation energy than the normal path by about 3.3 kcal/mol in the gas phase and by 5.4 kcal/mol in DMSO (ΔE_0(DMSO)). The cyclic adduct (IDA-IN^{iso}) **12A**$_\alpha$ is also less stable than the IDA-IN **5A**$_\alpha$ by about 3.5 and 3.8 kcal/mol in the gas phase and DMSO solvent, respectively. These results suggest that the alternative iso pathway is unfavourable both kinetically and thermodynamically,[39] in accordance with the experimental observation.

The origin of the preference for the normal over the iso pathway is primarily attributed to the conjugation effect between the NH_2 group and the pyrrole ring in the RC-TS **4A**$_\alpha$. A direct appreciation of the relative stabilities between transition states RC-TS **4A**$_\alpha$ and RC-TS^{iso} **11A**$_\alpha$ is a comparison between the α- and *β*-cations as shown in Scheme 6. When X=NH_2, the α cation, which resembles RC-TS **4A**$_\alpha$, is estimated to be more stable than the *β* cation, which resembles RC-TS^{iso} **11A**$_\alpha$, by almost 18 kcal/mol.

The 3.5 kcal/mol greater stability for IDA-IN **5A**$_\alpha$ over IDA-IN^{iso} **12A**$_\alpha$ can be accounted for by invoking the additional hyperconjugation stabilization (or generalized anomeric stabilization)[40] of the former, which has the N_7 connected to the anomeric C_2 center, so that the three amino groups can have donor/acceptor interactions.

II. IDA Reaction Between Pyrrole (1A) and Triazine. The reaction between pyrrole **1A** and triazine is shown in Figure 6. A comparison of the reactions of triazine with 2-aminopyrrole **1A**$_\alpha$ and pyrrole **1A** demonstrates the following three major differences.

Mechanism. The IDA reaction between **1A** and triazine, whether it proceeds via the normal or iso path, is a concerted but asynchronous process. In the absence of the amino substituent, the pyrrole ring is not electron-rich enough and the nucleophilicity of the carbon atom is reduced. More importantly, the zwitterionic intermediate of the stepwise mechanism cannot be stabilized by amine conjugation and hydrogen bond formation without the amino group.

Regioselectivity. In contrast to 2-aminopyrrole **1A**$_\alpha$, which prefers the normal pathway over the iso pathway by 3.5 kcal/mol, pyrrole **1A** has a preference for the iso pathway (33.1 kcal/mol) over the normal pathway (34.1 kcal/mol) by about 1.0 kcal/mol in the gas phase.

The relative stabilities of the two transition states are once again related to the stabilities of their corresponding positively charged pyrrole rings, as can be appreciated

(39) It should be noted here that the regioselectivity in the IDA step predetermines the overall regiochemistry of the cascade reaction, given the reasonable assumption that the following eliminations of ammonia of the two competitive pathways starting form IDA-IN**5A**$_\alpha$ and IDA-IN^{sio} **12A**$_\alpha$, respectively, have similar activation barriers. It also works if the IDA reaction is the rate-determining step of the whole cascade reaction.

(40) (a) Juaristi, E.; Cuevas, G. *Tetrahedron* **1992**, *48*, 5019. (b) Salzner, U.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1993**, *115*, 10231. (c) Reed, A. E.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1987**, *109*, 7362. (d) Reed, A. E.; Schleyer, P. v. R. *J. Inorg. Chem.* **1988**, *27*, 3969. (e) Wu, Y.-D.; Kirmse, W.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 4557.

by the two limiting cases in Scheme 6. When X=H, the β cation is more stable than the α cation by 4.9 kcal/mol, in qualitative agreement with the result that the transition state RC-TS^{iso} **21A** (resembling the β cation) is more stable than the RC-TS **19A** (resembling the α cation). The energy difference between the α and β cations for the X=H case (4.9 kcal/mol) is less than that for the X=NH_2 case (18.2 kcal/mol), which is in agreement with the calculated higher regioselectivity for the 2-aminopyrrole case (3.5 kcal/mol) than that for the parent pyrrole **1A** case (1.0 kcal/mol).

Energetics. Compared to the IDA reaction between **1A**$_\alpha$ and triazine, the IDA reaction between **1A** and triazine not only has a higher activation energy, but also has a higher endothermicity. For example, the preferred iso pathway of **1A** has activation and reaction energies of 33.1 and 24.7 kcal/mol, respectively, about 5 and 6 kcal/mol higher than those of the normal pathway reaction between **1A**$_\alpha$ and triazine, respectively.

This reaction between pyrrole and triazine could not happen, even though the activation barrier of **1A** is high (33.1 kcal/mol) but not insurmountable. The major challenge comes from its high endothermicity. The endothermicity of the IDA reaction encountered by 2-aminopyrrole **1A**$_\alpha$ can be released through subsequent cascade reactions by elimination of ammonia and the RDA reaction, while the cascade reaction cannot take place for the IDA reaction between pyrrole and triazine. This is in agreement with the experimental findings that the parent pyrazole cannot react with triazine derivatives while 5-aminopyrazole can.[9a]

Conclusions

A theoretical study based on the MP2/6-311++G**//B3LYP/6-31G* calculations has been used to investigate the IDA reaction with 1,3,5-triazine as the diene and 2-aminopyrrole as the dienophile in both the gas phase and in DMSO solution. Through a comparison of the different reactivities and mechanisms, it is found that the α-amino group plays an important role in several aspects.

(1) While the reaction of pyrrole proceeds by a concerted but asynchronous process, 2-aminopyrrole reacts with triazine through a stepwise mechanism, namely the nucleophilic addition of 2-aminopyrrole to triazine forms a zwitterionic intermediate that is in equilibrium with a neutral intermediate via hydrogen transfer, followed by the rate-determining ring-closure reaction to generate the IDA adduct.[41]

(2) Reactions of **1A**$_\alpha$ and **1A** are both regioselective. While the former occurs via the normal pathway, the latter prefers the iso pathway.

(3) Due to the loss of aromaticity in both the diene and dienophile, these reactions have reasonably high activation energies. The 2-amino group reduces the activation energy by about 5 kcal/mol. In addition, polar solvents such as DMSO further stabilize the transition states.

(4) These reactions are highly endothermic. The amino group reduces the endothermicity by about 6 kcal/mol and allows the elimination of ammonia to happen, which is crucial for the further cascade reaction. On the other hand, a cascade reaction is impossible with pyrrole as the dienophile.

In addition, the possible [2+2] pathway is ruled out since it is both kinetically and thermodynamically unfavorable compared with the stepwise [4+2] normal pathway.

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Supporting Information Available: The calculated energies and the Cartesian coordinates of the reactants, intermediates, and transition states discussed in this paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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(41) The stepwise mechanism for the IDA process is shared by the other cascade reactions shown in Scheme 1 (unpublished results).