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Clarification of the Mechanism of the Cascade Reactions between Amino-Substituted Heterocycles and 1,3,5-Triazines

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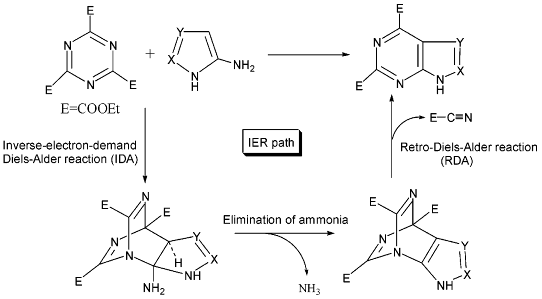

The mechanisms of the cascade reactions of amino-substituted imidazoles, pyrroles, and pyrazoles with 1,3,5-triazines have been studied using first principle MP2/6-311++G**//B3LYP/6-31G* calculations in both the gas phase and solution. Calculations indicate that these cascade reactions start with stepwise inverse-electron demand Diels−Alder (IDA) reactions, followed by elimination of ammonia from the IDA adducts, and retro Diels−Alder (RDA) reactions (referred as to the IER path). An alternative IRE path involving a reaction sequence of IDA, RDA, and elimination of ammonia is ruled out since the RDA transition states in this pathway are higher in energy than the reactants by as much as 50 kcal/mol. The preference of the IER over the IRE path is discussed.

1. Introduction

1,3,5-Triazines (unless otherwise mentioned, triazine is used to represent 1,3,5-triazine) serve as electron-deficient aza-dienes in various inverse-electron demand Diels−Alder (IDA) reactions, which are useful tools for the synthesis of numerous heterocycles.[1−3] For example, Boger and co-workers reported the development and applications of triazine IDA reactions generating pyrimidines and related natural products.[4] Recently, Dang and co-workers expanded this methodology by introducing aromatic heterocycles as dienophiles in the triazine IDA reactions.[5] The newly developed IDA cascade reactions efficiently produce purine and its analogues and other heterocycles, which are sometimes tedious to synthesize by traditional methods (Scheme 1). Two reaction pathways were proposed to describe these cascade reactions (Scheme 2). The first pathway, termed the IER pathway in Scheme 2, entails the initial IDA reaction between 1,3,5-triazines and amino-substituted, five-membered heteroaromatics, followed by elimination of ammonia to form the intermediate IER−INs, and final retro Diels−Alder (RDA) reaction to generate products **8A−C**. An alternative pathway, referred to as the IRE

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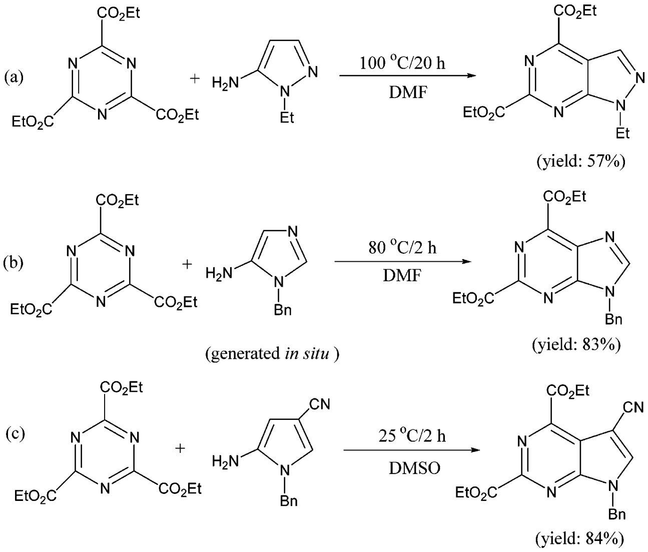
SCHEME 1



pathway in Scheme 2, consists of initial IDA reactions, subsequent RDA reactions, and a final step involving elimination of ammonia. The potential intermediates shown in Scheme 2 are probably too reactive to be isolated experimentally, and therefore there is no evidence to support one or the other pathways. Consequently, this study was undertaken, using theoretical calculations to delineate the energetically favored mechanism of these IDA cascade reactions.

The present study used first principle calculations to clarify which pathway is preferred.[6] Three model reactions, which include reactions I (**1A** + triazine), II (**1B** + triazine), and III (**1C** + triazine), as shown in Scheme 2, were chosen for the current investigation. Herein, results of the theoretical studies regarding the reaction pathways for these IDA cascade reactions are detailed.

2. Computational Methodology

All calculations were carried out with the GAUSSIAN 98 program.[7] The stationary points were fully optimized with the B3LYP/6-31G* method[8] except for **3A−C**, which were optimized with the B3LYP/6-31+G* method. Frequency calculations at the same level were performed to characterize each species as a minimum or transition structure. The energy of each species was reevaluated by the MP2/6-311++G** method[9] on the DFT structure. The reported gas-phase relative energies with respect to the reactants are all referred to as ΔE_0(MP2/6-311++G**), which include unscaled zero-point energy (ZPE) corrections computed by the DFT method.

Nonspecific solute−solvent interactions were simulated using a polarization continuum model (PCM)[10] in DMSO (ϵ = 46.7). To save computation time without sacrificing accuracy, we calculated the solvent stabilization energies (SSE) at the MP2/6-31G* level, and these SSEs then were used to correct the MP2/6-311++G** energy as follows:

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

$$\Delta E_0(\mathrm{DMSO}) = \Delta E_0(\mathrm{MP2/6\text{-}311{+}{+}G^{**}}) + \mathrm{SSE}$$

It has been demonstrated previously that this method gives solvent effect corrections that are very similar to those obtained by the MP2(PCM)/6-311++G**.[11] The calculated Cartesian coordinates (B3LYP/6-31G*), total energies, and entropy and enthalpy corrections of the structures involved in the discussion are given in Supporting Information.

3. Results and Discussion

DFT geometries of the key species involved in the IDA and RDA reactions of both the IRE and IER paths are given in Figures 1−3. Absolute energies and other thermodynamic parameters for all stationary species involved are summarized in Table S1 (Supporting Information).

3.1. IDA Reactions. To better understand the nature of the IDA reactions, the [4 + 2] cycloaddition step was investigated by frontier molecular orbital theory, and the reaction profiles are shown in Figure 4. The HOMO and LUMO energies for **1A−C** and triazine indicate that the Diels−Alder reactions leading to IDA-IN **5A−C** can be classified as IDA reactions according to Sustmman's

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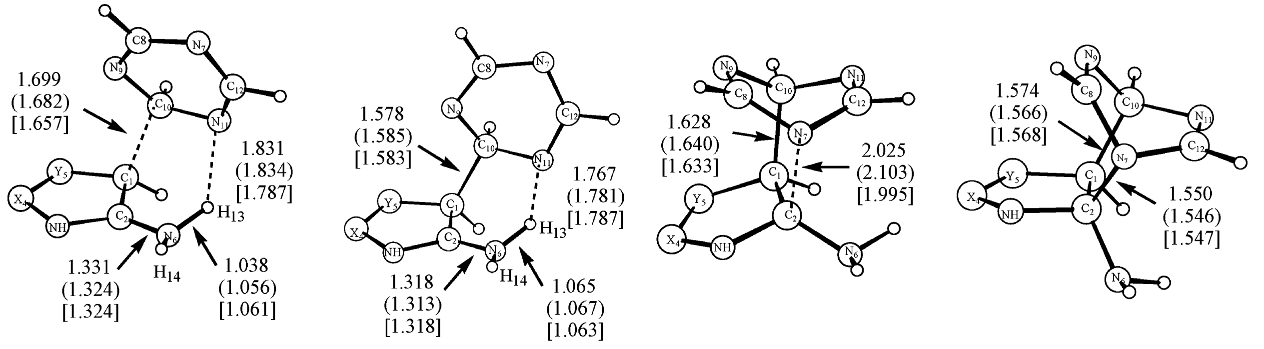


NA-TS
2A: X=Y=CH
(**2B**: X=CH, Y=N)
[**2C**: X=Y=N]

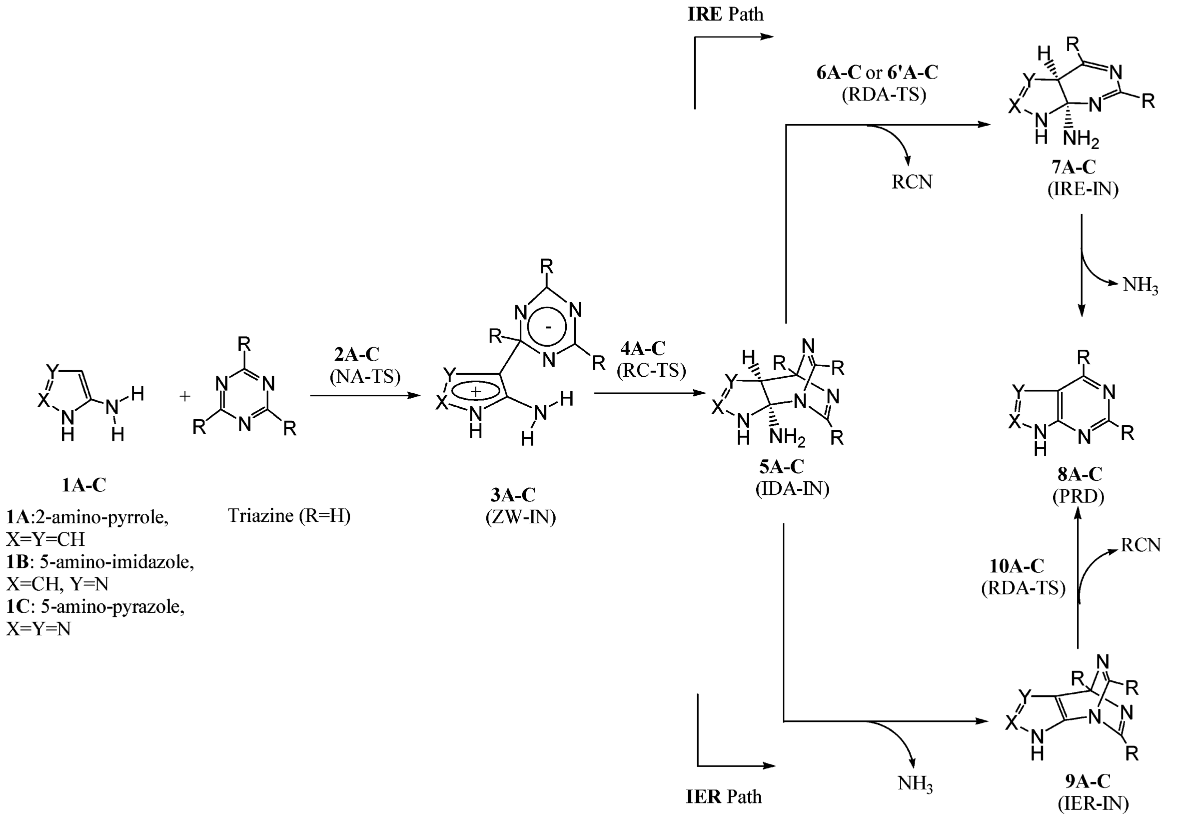
ZW-IN
3A: X=Y=CH
(**3B**: X=CH, Y=N)
[**3C**: X=Y=N]

RC-TS
4A: X=Y=CH
(**4B**: X=CH, Y=N)
[**4C**: X=Y=N]

IDA-IN
5A: X=Y=CH
(**5B**: X=CH, Y=N)
[**5C**:X=Y=N]

FIGURE 1. B3LYP/6-31G* geometries of NA-TSs (**2A**–**C**), ZW–INs (**3A**–**C**, B3LYP/6-31+G*), RC-TSs (**4A**–**C**), and IDA-INs (**5A**–**C**). Distances in Å.

SCHEME 2



definition.[12,13] Early theoretical studies of the IDA reaction step between **1A** and triazine indicate that they are stepwise processes,[11] and current investigations of reactions II and III reveal that the IDA step is also stepwise.[14] Therefore, the IDA reactions between **1B**,**1C** and triazine entail the nucleophilic attack on the triazine carbon by the C_1 atom of **1B**,**1C** leading to zwitterionic intermediates **3B**,**3C**, which are subsequently cyclized to furnish IDA adduct **5B**,**5C** (Figure 1). The computed charge transfer (CHELPG[15] charge) from dienophiles to triazine is 0.55, 0.52, and 0.48 e in **3A**–**C**, respectively. The stepwise mechanism can be attributed to the nucleophilic character of C_1 of **1A**–**C** (see the CHELPG charge distribution of the aromatic dienophiles in Scheme 3). On the other hand, hydrogen-bonding interactions of $N_{11}\cdots H_{13}$ in NA-TSs and ZW-INs, as evidenced by the

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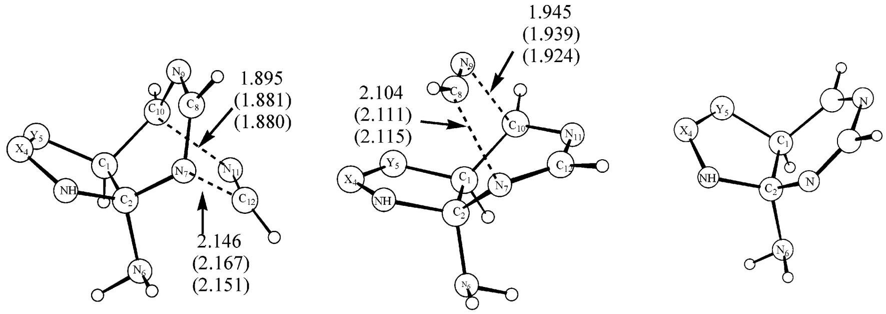
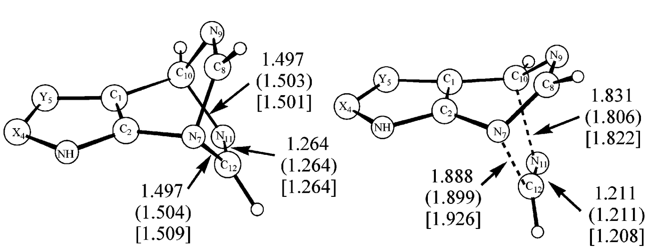


RDA-TS
6A: X=Y=CH
(**6B**: X=CH, Y=N)
[**6C**: X=Y=N]

RDA-TS
6′A: X=Y=CH
(**6′B**: X=CH, Y=N)
[**6′C**: X=Y=N]

IRE-IN
7A: X=Y=CH
(**7B**: X=CH, Y=N)
[**7C**: X=Y=N]

FIGURE 2. B3LYP/6-31G* geometries of RDA-TSs (**6A**−**C** and **6′A**−**C**) and **7A**−**C**. Distances in Å.



IER-IN
9A: X=Y=CH
(**9B**: X=CH, Y=N)
[**9C**: X=Y=N]

RDA-TS
10A: X=Y=CH
(**10B**: X=CH, Y=N)
[**10C**: X=Y=N]

FIGURE 3. B3LYP/6-31G* geometries of IRE-INs **9A**−**C** and RDA-TSs **10A**−**C**. Distances in Å.

short $N_{11}...H_{13}$ distances, are reasonably expected to be important to stabilize these two kinds of zwitterionic species (Figure 1).

3.2. IRE Pathway. The calculated potential energy surfaces for the IRE paths of reactions I−III are shown in Figure 5. For the IRE pathway, there are two possible RDA reaction transition states via either RDA-TS **6A**−**C** or **6′A**−**C**, which differ from each other by the relative orientation of the H−C≡N moiety with respect to the amino group (cis or trans, Figure 2). It is found that RDA-TSs **6′A**−**C** are higher in energy than RDA-TSs **6A**−**C** by 1.9, 2.0, and 1.8 kcal/mol, respectively. These differences in energies are most likely attributable to the larger steric repulsion between the H−C≡N moiety and the five-membered ring (C_1−C_2−X_3−Y_4−C_5) in **6′A**−**C** compared to that in **6A**−**C**. It becomes more clear to understand this steric effect if we consider the reverse reactions, **7** + HCN→ **5**, where the [4 + 2] addition transition structure **6′** is more crowed than transition structure **6**, as shown by the larger dihedral angle (between the five-membered ring and the plane of C_1−C_2−N_7−C_{10}) in **6′** than in **6**.

In the gas phase, the RDA reactions converting **5A**−**C** to **7A**−**C** are endothermic by 4.2, 8.3, and 6.9 kcal/mol, respectively. These transformations are not easy, requiring activation energies of 29.3, 30.1, and 28.8 kcal/mol, respectively.[16] Compared to the reactants, **6A**−**C** are higher in energy by 48.0, 45.5, and 53.2 kcal/mol, respectively. Even when solvation effects are taken into account, **6A**−**C** are still higher in energy than their corresponding reactants by about 50 kcal/mol, which is an activation barrier that is too high for the mild experimental conditions (25−100 °C, Scheme 1). Therefore, the IRE pathway is ruled out for the cascade reactions developed by Dang.[5]

3.3. IER Pathway. Alternatively, the cascade reactions can avoid the insurmountable RDA reactions of **6A**−**C** by adopting the IER path, which entails the elimination of ammonia from the IDA adducts **5A**−**C** before the RDA reactions (see Scheme 2 and Figure 6). Even though it is hard to model the details of stepwise elimination reactions in solution,[17,18] elimination of ammonia to form an aromatic pyrrole moiety in **9A**−**C** is expected to occur readily and irreversibly under thermal reaction conditions. In fact, this kind of aromatization reaction is common. One prominent example is the Fischer indole synthesis, in which the loss of ammonia in the last step is not regarded as a very difficult reaction (Scheme 4).[19,20]

It is critical to emphasize that, even though loss of ammonia in the IER path is endothermic by 10.0, 18.5, and 8.0 kcal/mol for reactions I−III, respectively, these processes are favorable in terms of free energy: at the

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(16) No stepwise retro-Diels−Alder transition states in both IRE and IER pathways can be located using both RB3LYP and UB3LYP methods.

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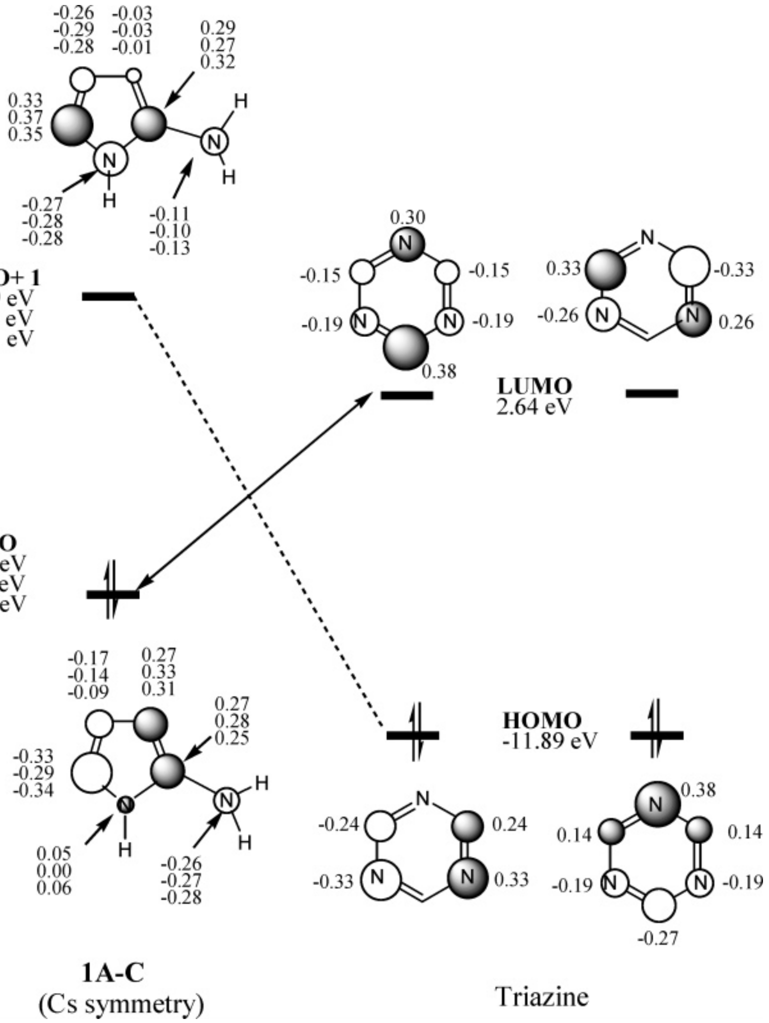
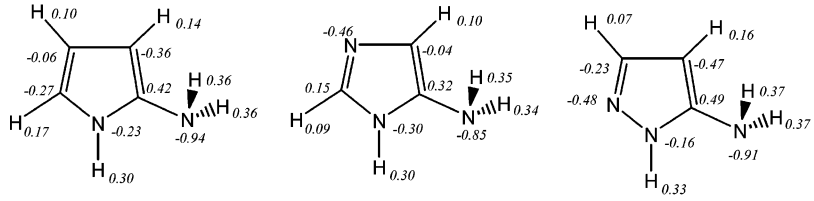


FIGURE 4. Frontier molecular orbitals of **1A−C** (C_s symmetry) and triazine. The orbital coefficients refer to the 2p part of each heavy atom. Atom numbering refers to that in Figure 1.

SCHEME 3



1A **1B** **1C**

B3LYP/6-31G* level, the computed free energy changes for the reaction of **5→9** + NH_3 in reactions I−III are reduced to 0.4, 7.4, and −2.0 kcal/mol, respectively. If we further consider the solvation effects on ammonia or ammonium ion (if the elimination is acid-catalyzed), it is expected that the entropy-driven process of elimination is irreversible and becomes more favorable in terms of free energy.

In contrast to the RDA reactions via **6A−C** in the IRE path, the RDA reactions of **9A−C** in the IER pathway via RDA-TS **10A−C** are not only exothermic but also facile (the activation/reaction energies in the gas phase for the transformation of **9A−C** to **8A−C** are 9.1/−40.9, 7.7/−43.9, and 10.6/−37.3 kcal/mol for reactions I−III, respectively, see Figure 6). The exothermic nature of the RDA reactions of **9A−C** is a result of the formation of aromatic species **8A−C**, which requires the cascade reactions to adopt the IER path instead of the IRE path. Although the overall cascade reactions are only slightly exothermic (−9.7, −9.3, and −3.9 kcal/mol for reactions I−III in the gas phase, see Figure 6), these transformations are favored entropically by converting two reactants (**1A−C** + triazine) to three products (**8A−C** + HCN + NH_3).

To compare the reactivity of **1A−C**, the rate-determining steps for these reactions need to be identified. Since

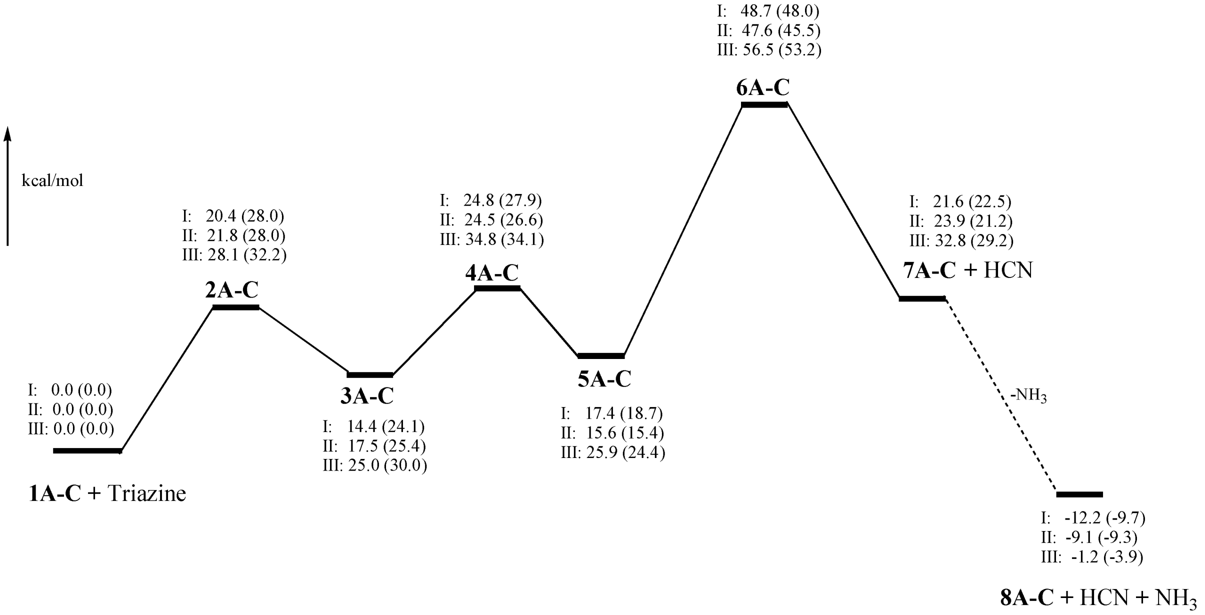


FIGURE 5. Potential energy surface of the IRE pathway for reactions I–III. The values are ΔE_0 (DMSO) and ΔE_0 (MP2/6-311++G**) (in parentheses). The dashed line represents the elimination process.

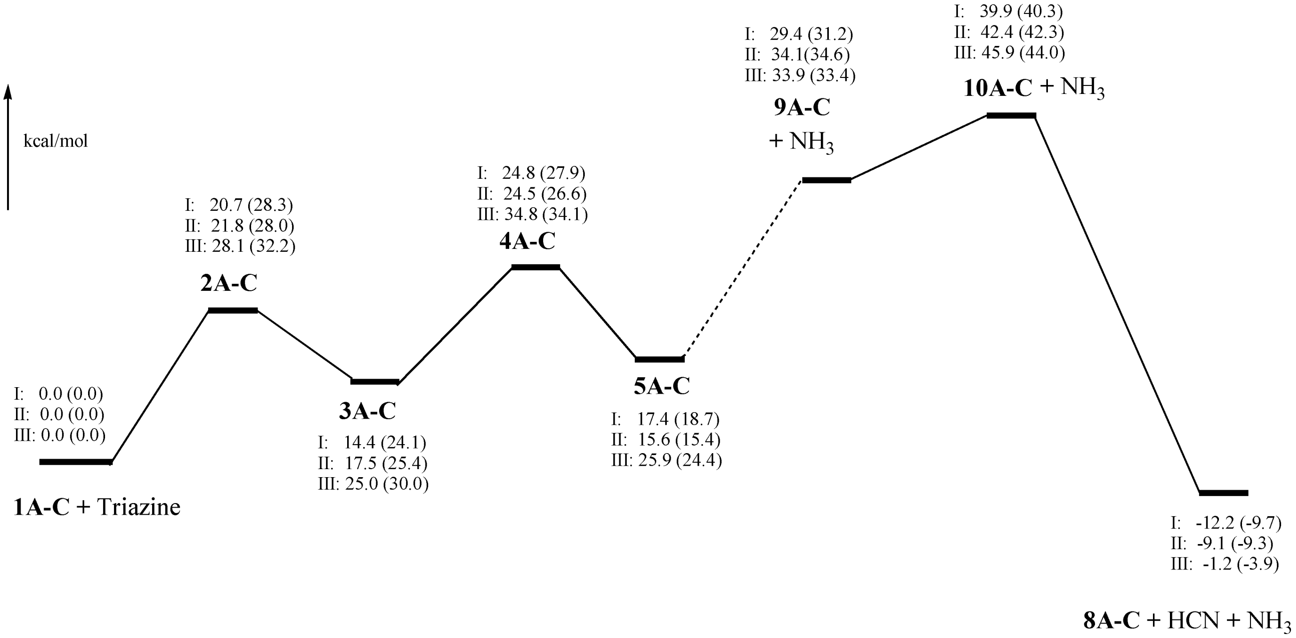


FIGURE 6. Potential energy surface of the IER pathway for reactions I–III. The values are ΔE_0 (DMSO) and ΔE_0 (MP2/6-311++G**) (in parentheses). The dashed line represents the elimination process.

the activation barriers for the ammonia elimination reactions cannot be calculated, it is not possible to define which step, the IDA reaction or the elimination of ammonia, is rate-determining.[21] However, if one assumes that the irreversible loss of ammonia is facile, then the IDA reactions should be rate-determining steps for reactions I–III (as indicated in Figure 6), and therefore the order of reactivities for these dienophiles is **1A** ≈ **1B** > **1C**, which is consistent with experimental observations.[5,21] It is important to point out that when substituents are introduced in either the diene or the dienophile, the barriers for IDA and ammonia elimination reactions may change and possibly become lower than that of the subsequent RDA reaction. Consequently, the RDA step could become rate-determining.

3.4. Origin of the Preference for the IER Path instead of the IRE Path. The above analysis clearly demonstrates that the IRE pathway can be ruled out due to the higher activation energies of the RDA steps in reactions I–III. Another topic that warrants more discussion is why the difference in activation energies for the

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[21] We prefer the IDA reaction to be the rate-determining step on the basis of the following arguments: The elimination of ammonia could be accelerated by acidic reaction conditions. Experimentally,[5] it has been found that addition of acids in some reactions has little effect on the reaction rate, suggesting that the elimination of ammonia is not rate-determining.

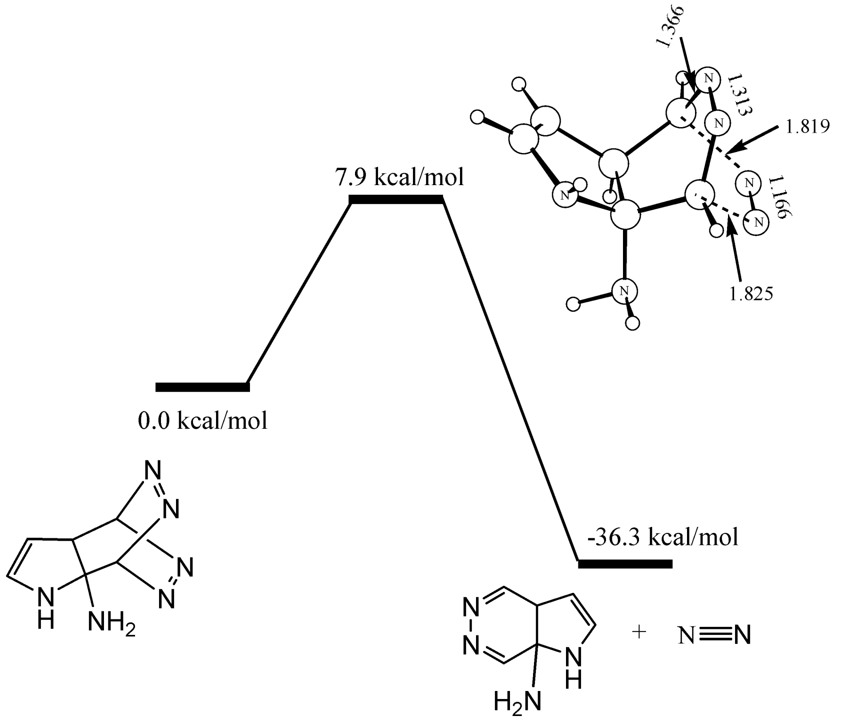

FIGURE 7. Potential surface for the RDA step of the reaction of 2-aminopyrrole and 1,2,4,5-tetrazine computed at the B3LYP/6-31G* level. Distances in Å.

RDA reactions between **5A**−**C** and **9A**−**C** is as high as 20 kcal/mol.

One reason for the different activation energies is attributed to their reaction energies: the RDA reactions in IER path are exothermic due to conversion of nonaromatic intermediates **9A**−**C** to aromatic products **8A**−**C**; in contrast, the RDA reactions in the IRE path are endothermic since the products obtained, **7A**−**C**, are nonaromatic. For similar reactions, the more exothermic process should have the lower activation energy according to the Bell−Evans−Polanyi principle.[22] Therefore, RDA reactions in the IER path require lesser activation energies because these processes are exothermic.

The transition states **6A**−**C** and **10A**−**C** are aromatic, and therefore their relative aromaticities can be used to compare relative reactivities. To compare the aromaticities of these transition states, we chose to calculate their "nuclear-independent chemical shifts" (NICSs)[23] at the center (nonweighted mean of the heavy-atom coordinates) of the ring composed of C_1, C_2, N_7, C_8, N_9, and C_{10} in **10A** and **6A**. NICS was developed by Schleyer and co-workers to evaluate the aromaticity of different species, including transition states. The calculated NICS values are −7.27 and −4.44 ppm for **10A** and **6A**, respectively, which indicates a stronger aromaticity contribution in stabilizing **10A** in the IER path compared to the IRE path (the NICS value of −7.27 ppm for **10A** is comparable to −10.2 ppm for benzene).[24]

It is well documented that many RDA reactions benefit from aromatization energy when nonaromatic Diels−Alder adducts are converted to aromatic species. For example, Jacobi and Lee successfully applied an intramolecular Diels−Alder reaction in the synthesis of stemoamide,[25] in which an intramolecular DA reaction was followed immediately by an RDA reaction that generated an aromatic intermediate (Scheme 5).

Other factors may also lead to the alteration of reaction pathways for these cascade reactions. For example, in hypothetical reactions between amino-substituted, five-membered aromatics and 1,2,4,5-tetrazine derivatives, the RDA reaction of the IRE path may result in the elimination of N≡N instead of RC≡N for triazines. This kind of RDA reaction is now significantly exothermic, and the activation energy is only 7.9 kcal/mol as shown in

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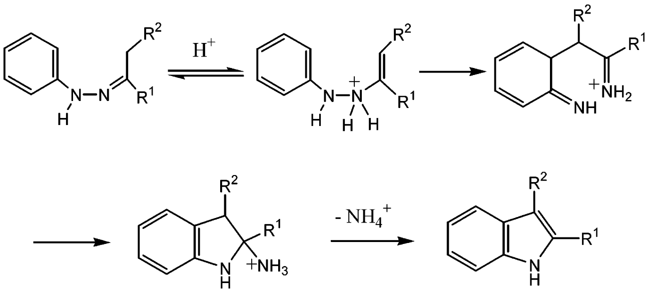
[22] The different reactivity of the aromatic heterocycles is attributed to their different aromaticity (unpublished results). For discussions of aromaticity in different heterocycles, see: (a) Katritzky, A. R.; Karelson, M.; Sild, S.; Krygowski, T. M.; Jug, K. *J. Org. Chem.* **1998**, *63*, 5228. (b) Cyranski, M.; Krygowski, T. M.; Katritzky, A. R.; Schleyer, P. v. R. *J. Org. Chem.* **2002**, *67*, 1333. For discussions of effects of product aromaticity on the lowering of barrier heights, see: (c) Birney, D, M.; Berson, J. A. *Tetrahedron* **1986**, *42*, 1561. (d) Braun, R.; Kummer, M.; Martin, H.-D.; Rubin, M. B. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1059. (e) Bertsch, A.; Grimme, W.; Reinhardt, G. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 377. (f) Bearpark, M.; Bernaidyi, F.; Olivucci, M.; Robb, M. A. *J. Am. Chem. Soc.* **1990**, *112*, 1732. (g) Bernardi, F.; Celani, P.; Olivucci, M.; Robb, M. A.; Suzzi-Valli, G. *J. Am. Chem. Soc.* **1995**, *117*, 10531. For the Bell−Evans−Polanyi principle, see: (h) Dewar, M. J. S. *The Molecular Orbital Theory for Organic Chemistry*; McGraw-Hill: New York, 1969. (i) Dewar, M. J. S. *J. Am. Chem. Soc.* **1984**, *106*, 209.

[23] (a) Schleyer, P. von R.; Maerker, C.; Dransfeld, A.; Jiao, H.; Hommes, N. J. R. v. E. *J. Am. Chem. Soc.* **1996**, *118*, 6317. (b) Manoharan, M.; Proft, F. D.; Geerlings, P. *J. Org. Chem.* **2000**, *65*, 7971.

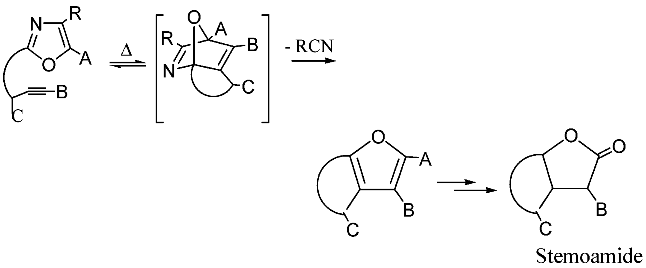
[24] Reported NICS values in this paper were computed using the keyword "NMR" in Gaussian 98. The NICS values computed here are smaller than that of the (3 + 2) transition state (see: Cossio, F. P.; Morao, I.; Jiao, H.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1999**, *121*, 6737). The different NICSs values for the (4 + 2) and (3 + 2) transition states could be attributed to their different geometries (folded vs planar transition states). For discussions of computing aromaticity, see also: (a) Alajarin, M.; Sanchez-Andrada, P.; Cossio, F. P.; Arrieta, A.; Lecea, B. *J. Org. Chem.* **2001**, *66*, 8470. (b) Schleyer, P. v. R.; Mancharan, M.; Wang, Z.-X.; Kiran, B.; Jiao, H.; Puchta, R.; Hommes, N. J. R. v. E. *Org. Lett.* **2001**, *3*, 2465.

[25] Jacobi, P. A.; Lee, K. *J. Am. Chem. Soc.* **2000**, *122*, 4295.

SCHEME 4



SCHEME 5



SCHEME 6

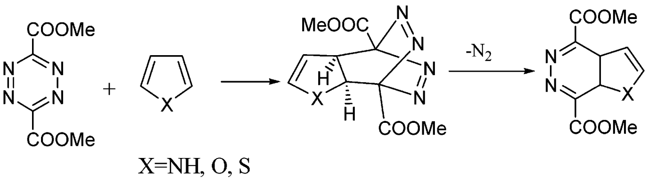


Figure 7. The reason for the higher exothermicity in the loss of N≡N than in the loss of RC≡N is due to the fact that the N≡N bond exists as a stronger bond than the C≡N bond (the bond enthalpies are 226.3 and 212.9 kcal/mol, respectively).[12] On the basis of the Bell−Evans−Polanyi principle, the RDA reaction losing N≡N is predicted to be easier than RDA reaction losing R−C≡N. In fact, the RDA reaction without aromatization has been observed previously by Seitz and Kampchen (Scheme 6).[5e,26] On the basis of these findings, we expect that both IER and IRE are competitive in the cascade reaction between amino-substituted heterodienophiles and 1,2,4,5-tetrazines. The adoption of the IER or the IRE pathways depends on whether the rate of ammonia eliminations in the IER path is faster or slower than the RDA steps of the IRE path, and therefore the substitution of the amino group may alter the reaction pathways.

4. Conclusion

Theoretical studies of three cascade reactions between triazine and **1A**−**C** at the MP2/6-311++G**//B3LYP/6-31G* level in both the gas phase and solution reveal that these reactions occur via the IER pathway, in which a stepwise IDA reaction is followed by elimination of ammonia and then RDA reactions. The alternative IRE path is ruled out because the RDA reactions require a very high activation energy that is insurmountable under the mild thermal experimental conditions. The preference of the IER pathway over the IRE pathway is attributed to the presence of the amine substituent in the aromatic dienophiles that is critical in driving the cascade reactions to completion.

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Supporting Information Available: Calculated Cartesian coordinates and total energies of the reactants, intermediates and transition states. This material is available free of charge via the Internet at http://pubs.acs.org.

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[26] Raw, S. A.; Taylor, J. K. *J. Am. Chem. Soc.* **2004**, *126*, 12260.