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Computational Exploration of Concerted and Zwitterionic Mechanisms of Diels–Alder Reactions between 1,2,3-Triazines and Enamines and Acceleration by Hydrogen-Bonding Solvents

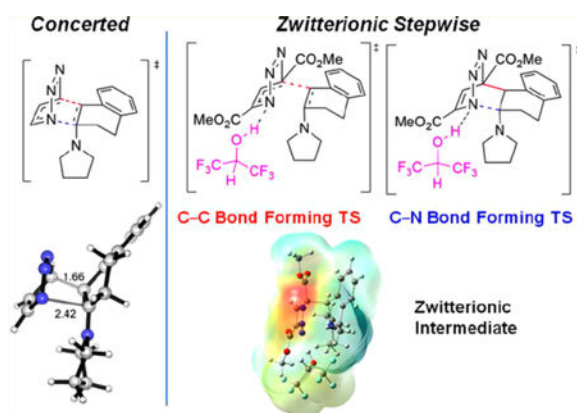
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Abstract

The mechanisms of Diels–Alder reactions between 1,2,3-triazines and enamines have been explored with density functional theory computations. The focus of this work is on the origins of the different reactivities and mechanisms induced by substituents and by hexafluoroisopropanol (HFIP) solvent. These inverse electron-demand Diels–Alder reactions of triazines have wide applications in bioorthogonal chemistry and natural product synthesis. Both concerted and stepwise cycloadditions are predicted, depending on the nature of substituents and solvents. The nature of zwitterionic intermediates and the mechanism by which HFIP accelerates cycloadditions with enamines are characterized. Our results show the delicate nature of the concerted versus stepwise mechanism of inverse electron-demand Diels–Alder reactions of 1,2,3-triazines, and that these mechanisms can be altered by electron-withdrawing substituents and hydrogen-bonding solvents.

Graphical abstract



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Notes

The authors declare no competing financial interest.

INTRODUCTION

The inverse electron-demand Diels–Alder reactions of heterocyclic azadienes are powerful approaches to construct six-membered heterocycles.¹ These reactions have wide applications in bioorthogonal chemistry² and natural product synthesis.³ Both Ess and Bickelhaupt and our group have systematically investigated the cycloadditions of benzene and ten different azabenzenes (pyridine, three diazines, three triazines, and three tetrazines) with the ethylene dienophile (Scheme 1a).⁴ Each nitrogen substitution causes higher Diels–Alder reactivity of azapolyenes due to more favorable orbital interactions and lower distortion energies.^{4b} Through these computational studies, we now have a better understanding of their intrinsic reactivities, especially on roles played by the number and position of the heteroatoms. While these simple reactions are all predicted to proceed via a concerted mechanism, substituents and solvents could change the mechanism and have various effects on their reactivity. For example, electron-withdrawing substituents on the C-5 position of 1,2,3-triazine have been found to increase its reactivity in inverse-electron demand Diels–Alder reactions.^{5b}

Recently, the cycloadditions of a 1,2,3-triazine⁵ with an enamine was used as a key step in the concise total synthesis of the natural product methoxatin⁶ by the Boger group (Scheme 1b and 1c). It was discovered that non-nucleophilic fluorinated alcohol solvents, such as hexafluoroisopropanol (HFIP), accelerate these cycloadditions. The reaction of 1,2,3-triazine **1a** with enamine **2** has a low yield in CHCl₃ (Scheme 2), but has a much higher yield with HFIP as the solvent. Similarly, for the reaction of 1,2,3-triazine **1b** with enamine **2**, the use of HFIP as the solvent provides the cycloadduct **3b** in good yield (86%). Typically, common Lewis acid catalysts are ineffective for inverse-electron demand Diels–Alder reaction because of the nonproductive consumption of the electron-rich dienophiles.⁷ Hydrogen-bond donation by HFIP appears to accelerate the reaction without destroying the enamine. Solvent-acceleration of inverse electron-demand Diels–Alder reactions with electron-deficient heterocyclic azadienes could be attributed to many factors, such as hydrogen-bonding and polarity of the solvent.⁸ We have used density functional theory (DFT) to explore the mechanisms of cycloadditions between several 1,2,3-triazines and enamines in different solvents.

COMPUTATIONAL DETAILS

All density functional theory (DFT) calculations were performed using Gaussian 09.⁹ Geometry optimizations and frequency calculations were performed at the M06–2X¹⁰/6–31G(d) ¹¹ level of theory. Normal mode vibrational analysis confirmed that optimized structures are minima or transition structures. Single-point energies were computed on the optimized geometries with the conductor-like polarizable continuum model (CPCM)¹² using chloroform ($\epsilon = 4.7$) or HFIP ($\epsilon = 16.7$) as solvent at the M06–2X/6–311+G(d,p) level of theory. An explicit HFIP was also included. Geometry optimizations and subsequent frequency calculations using M06–2X/6–311+G(d,p) with solvent produce qualitatively the same result, and were not carried out for all reactions.¹³ The frontier molecular orbitals (FMOs) and their energies were computed at the HF/6–311+G(d,p) level using the M06–2X/6–31G(d)-optimized geometries. All 3D renderings of stationary points were generated using CYLview.¹⁴

RESULTS AND DISCUSSION

Uncatalyzed Diels–Alder Reaction.

We first studied the uncatalyzed Diels–Alder reaction of parent 1,2,3-triazine **1a** with enamine **2**. Figure 1 shows the free energy profiles for the *endo* and *exo* pathways and the corresponding energetics of the reaction in CHCl₃, while Figure 2 shows the transition structures. Both **endo-TS1** and **exo-TS1** are highly asynchronous concerted transition structures, each with a shorter forming C–C bond at 1.6–1.7 Å and a longer forming C–N bond at 2.3–2.4 Å. We showed earlier that C–C bond formation is always preferred over C–N bond formation in polyazine cycloadditions.^{4b} The barriers for the Diels–Alder step through *endo* and *exo* pathways are 32.0 and 33.1 kcal/mol, respectively. The Diels–Alder adducts **endo-1** and **exo-1** are only about 7 kcal/mol more stable than **endo-TS1** and **exo-TS1**, respectively, but the subsequent release of N₂ is very exergonic, and has only low barriers (1.3 kcal/mol via **exo-TS2** and 2.2 kcal/mol via **endo-TS2**). We earlier explored the rapid dynamics of N₂ loss from similar intermediates.¹⁵ The low barrier implies a lifetime of a few 100 fs at most. The subsequent elimination of amine that leads to the aromatized compound **3a** has a barrier of 38.0 kcal/mol (Figure S2). With the assistance of HFIP, the barrier is decreased to 24.4 kcal/mol (Figure S2).

The two electron-withdrawing groups (–CO₂Et) at the 4- and 6-positions of 1,2,3-triazine **1b** were modeled as CO₂Me groups computationally. Figure 3 shows the free energy profiles for the *endo* and *exo* pathways of the Diels–Alder reaction of 1,2,3-triazine **1c** with enamine **2**, and Figure 4 shows transition structures and intermediates. Unlike the concerted Diels–Alder reaction of 1,2,3-triazine **1a** with enamine **2**, this reaction of 1,2,3-triazine **1c** with enamine **2** undergoes a stepwise mechanism, forming the C–C bond first. The optimized transition structures for the first steps of *endo* and *exo* pathways have forming C–C bonds of ~1.8 Å, while the C–N distances are ~2.9 Å in **TS3s**. Shallow intermediates **endo-3** and **exo-3** are located on the potential energy surface for both the *endo* and the *exo* pathways, and they have comparable energies to the C–C bond forming transition structures **endo-TS3** and **exo-TS3**. The forming C–C bonds are ~1.6 Å and the forming C–N bonds are ~2.3 Å in both second transition structures, **endo-TS4** and **exo-TS4**. Interestingly, the C–N bond forming transition structures **endo-TS4** and **exo-TS4** are very similar to the concerted transition structures **endo-TS1** and **exo-TS1**. The second barrier is only ~5 kcal/mol, and is the rate-determining step. Transition structure **exo-TS4** is slightly favored over **endo-TS4**. The subsequent release of N₂ is very exergonic, and the transition structures are lower in energy (22.5 kcal/mol for **exo-TS5** and 26.0 kcal/mol for **endo-TS5**) than those of the second Diels–Alder step.

We have characterized the zwitterionic intermediates, **endo-3** and **exo-3**. The charge separations on the triazine and enamine fragments, are 0.68 and 0.72 in the *endo* and *exo* species, respectively. The electrostatic potential (ESP) maps of **endo-3** and **exo-3**, in Figure 4, show the charge separation graphically.

Compared with the reaction of concerted Diels–Alder reaction of 1,2,3-triazine **1a** with enamine **2**, the Diels–Alder reaction of 1,2,3-triazine **1c** with enamine **2** undergoes a

stepwise mechanism, with the C–N bond forming as the rate-limiting step. The overall barrier is lowered by 5.0 kcal/mol (27.0 kcal/mol vs 32.0 kcal/mol) by the two ester substituents. This is in agreement with the higher reactivity of 1,2,3-triazine **1b** found in the experiment.⁶

Solvent-Catalyzed Diels–Alder Reaction.

We next explored the reaction of triazine and the diester-substituted triazine in HFIP. One explicit HFIP molecule was included. The energies and structures for the parent triazine are shown in Figures 5 and 6. The hydrogen-bonding of one molecule of HFIP solvent with the N-1 of 1,2,3-triazine **1a** leads to complex **1a-HFIP**. This association process is 5.1 kcal/mol endergonic but 8.1 kcal/mol exothermic (**1a** + **HFIP** → **1a-HFIP**, $\Delta G = 5.1$ kcal/mol, $\Delta H = -8.1$ kcal/mol) when we use the normal standard state for gas-phase reactions (1 atm, 298.15K). Single-point energies with solvation were computed on the M06–2X/6–31G(d)-optimized structures in the gas phase. Correcting for 1 M standard state for solution-phase reactions, and the 9.5 M concentration of pure HFIP solvent,¹⁶ the ΔG becomes 1.9 kcal/mol. In addition, computed entropies of association in solution using harmonic assumption are frequently too negative.¹⁷ Considering all these factors, we believe the association process to form the complex **1a-HFIP** is favorable in solution, and we have set the complex energy to zero.

Figure 5 shows the free energy profiles for the *endo* and *exo* pathways of the reaction. The HFIP-catalyzed Diels–Alder reaction of the parent triazine now proceeds via a stepwise mechanism very similar to the reaction of the substituent-activated triazine. As shown in Figure 6, the forming C–C bond is ~1.9 Å and the C–N distance is ~3.0 Å in both *endo*-TS6 and *exo*-TS6, and ~1.6 Å and ~2.1 Å in both *endo*-TS7 and *exo*-TS7, the second step of the reaction. The zwitterionic intermediates *endo*-6 and *exo*-6 are located on the potential energy surface for both the *endo* and the *exo* pathways, and they are ~3 kcal/mol more stable than *endo*-TS6 and *exo*-TS6. The barrier of reaction (the second step) is lowered by 4.5 kcal/mol versus the single TS for the uncatalyzed one. The hydrogen-bonding distance between H of HFIP and N1 of triazine **1a** in zwitterionic intermediates *endo*-6 and *exo*-6 are shorter than in either complex **1a-HFIP** (1.85 Å for H···N distance) or transition structures that forming C–C and C–N bonds. The barriers for forming the C–N bond are once again higher than that for forming the C–C bond. Transition structure *exo*-TS7 is very close to *endo*-TS7 in free energy. The subsequent release of N₂ is rapid as always.

The hydrogen-bonding of one molecule of HFIP solvent with the N1 of the activated 4,6-dicarbomethoxy 1,2,3-triazine **1c** leads to complex **1c-HFIP**. Figure 7 shows the free energy profiles for the *endo* and *exo* pathways of the reaction, while Figure 8 shows transition structures and intermediates. The Diels–Alder reaction of **1c** with enamine **2** undergoes stepwise mechanism in either CHCl₃ or HFIP. The profile in Figure 7 is like the previous stepwise profile. The HFIP stabilizes the first transition state by 9 kcal/mol and the zwitterionic intermediate by 11 kcal/mol. The hydrogen-bonding distance between H of HFIP and N1 of triazine **1c** in zwitterionic intermediates *endo*-9 and *exo*-9 (~1.6 Å for H···N distance) are shorter than in both complex **1c-HFIP** (2.06 Å for H···N distance) and in transition structures that forming C–C and C–N bonds. The charge separation has increased

to 0.82 in the favored intermediate **exo-9**, and the ESP map in Figure 8 reflects the close association of negative and positive regions of the intermediate. The subsequent step of N₂ release now becomes the rate-limiting step, although it is still very facile. HFIP has lowered the rate-determining step by 6 kcal/mol, for an approximately 10⁴ acceleration.

Because there are other hydrogen bond acceptors in **1c** besides N1, we have also explored the possibility of HFIP binding to N2, N3, -CO₂Me of C4, and -CO₂Me of C6 of 1,2,3-triazine **1c** (Figure 9). We also explored hydrogen-bonding to the nitrogen of the enamine, but that destabilize the transition state. The HFIP binding to N2, -CO₂Me of C4, and -CO₂Me of C6 of 1,2,3-triazine **1c** is less favorable compared to binding to N1 of 1,2,3-triazine **1c**. It is worth noting that transition structure for forming the C–C bond, **endo-TS9C**, with HFIP hydrogen bonding to N3 of 1,2,3-triazine **1c**, is slightly favored over **endo-TS9** by 0.7 kcal/mol. The hydrogen-bonding interaction with N3 of 1,2,3-triazine **1c** is preferred. For the transition structure for forming the C–N bond, **endo-TS10C**, with HFIP hydrogen bonding to N3 of 1,2,3-triazine **1c**, is disfavored by 3.1 kcal/mol compared to **endo-TS10**. There may be two or more HFIP molecules hydrogen bonding to the triazine, but it is difficult to evaluate the entropy change with association reaction involving multiple molecules. Because of the polarity of transition states and intermediates, we have also reoptimized them in HFIP solvent (see Figure S1 in Supporting Information). Only minor changes were observed.

FMO Analysis of the Triazine Diels–Alder Reactions.

Figure 10a shows the computed HOMO of enamine **2**, the lowest vacant π orbitals (LUMO +1) of triazines **1a** and **1c** and HFIP-complexed triazines **1a-HFIP** and **1c-HFIP**. For all the four LUMO+1 vacant orbitals of triazines, there are two nodes in the triazine ring in each of them. Hydrogen bonding to an HFIP molecule lowers the energy of the LUMO+1 orbital by 0.33 eV (**1a-HFIP**). With two electron-withdrawing ester substituents at 4- and 6-positions, the energy of the LUMO+1 vacant orbital lowers by 0.60 eV (**1c**). The LUMO +1 vacant orbital of the HFIP-complexed complex **1c-HFIP** is further decreased to an energy of 0.85 eV.

A plot of the highest Diels–Alder reaction barrier versus the HOMO–LUMO gap is shown in Figure 10b. There is a very good correlation between the barrier and the HOMO–LUMO gap, and the HFIP-complexed triazine **1c-HFIP** is most reactive due to its lower energy of LUMO+1 compared to that of **1a**, **1c** and **1a-HFIP**.

CONCLUSION

We have explored the mechanisms of Diels–Alder reactions between 1,2,3-triazines and enamine using DFT computations and investigated the origins of the different reactivities induced by substituents or the HFIP solvent. While the Diels–Alder reaction of unsubstituted 1,2,3-triazine and the enamine undergo a concerted mechanism, either electron-withdrawing groups or the strongly hydrogen-bonding solvent stabilize zwitterionic intermediates and lead to stepwise mechanisms. Our results imply the subtle nature of the concerted versus stepwise mechanism of inverse electron-demand Diels–Alder reactions of 1,2,3-triazines, which could be altered by electron-withdrawing substituents and hydrogen-bonding

solvents. Systematic studies of the full suite of heterocyclic azadienes are underway in our research group and will be reported in due course. With a more complete picture of the mechanisms of these reactions, we envision that the power of tuning substituents and solvents could be the power of tuning substituents and solvents could be the power of tuning substituents and solvents could be harnessed more efficiently by experimentalists, to develop new variants and to discover new applications of inverse electron-demand Diels–Alder reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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REFERENCES

- (1). (a) Boger DL Tetrahedron 1983, 39, 2869.(b) Boger DL Chem. Rev 1986, 86, 781.(c) Boger DL Chemtracts: Org. Chem 1996, 9, 149.(d) Rooshenas P; Hof K; Schreiner PR; Williams CM Eur. J. Org. Chem 2011, 2011, 983.(e) Foster RAA; Willis MC Chem. Soc. Rev 2013, 42, 63. [PubMed: 23079670]
- (2). For recent reviews and perspectives, see: (a) Devaraj NK; Weissleder R Acc. Chem. Res 2011, 44, 816. [PubMed: 21627112] (b) Schmidt MJ; Summerer D ChemBioChem 2012, 13, 1553. [PubMed: 22753121] (c) Knall A-C; Slugovc C Chem. Soc. Rev 2013, 42, 5131. [PubMed: 23563107] (d) Carroll L; Evans HL; Aboagye EO; Spivey AC Org. Biomol. Chem 2013, 11, 5772. [PubMed: 23907155] (e) Debets MF; van Hest JCM; Rutjes FP J. T. Org. Biomol. Chem 2013, 11, 6439.(f) Lang K; Chin JW ACS Chem. Biol 2014, 9, 16. [PubMed: 24432752] (g) Patterson DM; Nazarova LA; Prescher JA ACS Chem. Biol 2014, 9, 592. [PubMed: 24437719] (h) Liu F; Liang Y; Houk KN Acc. Chem. Res 2017, 50, 2297. [PubMed: 28876890]
- (3). (a) Boger DL; Wolkenberg SE J. Org. Chem 2000, 65, 9120. [PubMed: 11149859] (b) Boger DL; Hong JJ Am. Chem. Soc 2001, 123, 8515.(c) Hamasaki A; Zimpleman JM; Hwang I; Boger DL J. Am. Chem. Soc 2005, 127, 10767. [PubMed: 16045367] (d) Oakdale JS; Boger DL Org. Lett 2010, 12, 1132. [PubMed: 20148525] (e) Fu L; Gribble GW Tetrahedron Lett 2010, 51, 537.
- (4). (a) Talbot A; Devarajan D; Gustafson SJ; Fernández I; Bickelhaupt FM; Ess DH J. Org. Chem 2015, 80, 548. [PubMed: 25490250] (b) Yang Y-F; Liang Y; Liu F; Houk KN J. Am. Chem. Soc 2016, 138, 1660. [PubMed: 26804318]
- (5). (a) Anderson ED; Boger DL Org. Lett 2011, 13, 2492. [PubMed: 21488676] (b) Anderson ED; Boger DL J. Am. Chem. Soc 2011, 133, 12285. [PubMed: 21736324] (c) Anderson ED; Duerfeldt AS; Zhu K; Glinkerman CM; Boger DL Org. Lett 2014, 16, 5084. [PubMed: 25222918] (d) Duerfeldt AS; Boger DL J. Am. Chem. Soc 2014, 136, 2119. [PubMed: 24410439] (e) Glinkerman CM; Boger DL Org. Lett 2015, 17, 4002. [PubMed: 26172042] (f) Lee K; Poudel YB; Glinkerman CM; Boger DL Tetrahedron 2015, 71, 5897. [PubMed: 26273113]
- (6). Glinkerman CM; Boger DL J. Am. Chem. Soc 2016, 138, 12408. [PubMed: 27571404]
- (7). (a) Boger DL; Panek JS J. Am. Chem. Soc 1985, 107, 5745.(b) Kessler SN; Neuburger M; Wegner HA J. Am. Chem. Soc 2012, 134, 17885. [PubMed: 23066957] (c) Yu P; Li W; Houk KN J. Org. Chem 2017, 82, 6398. [PubMed: 28510451]
- (8). (a) Wijnen JW; Zavarise S; Engberts JBFN; Charton M J. Org. Chem 1996, 61, 2001.(b) Yang K; Dang Q; Cai P-J; Gao Y; Yu Z-X; Bai XJ Org. Chem 2017, 82, 2336.

- (9). Frisch MJ; Trucks GW; Schlegel HB; Scuseria GE; Robb MA; Cheeseman JR; Scalmani G; Barone V; Mennucci B; Petersson GA; Nakatsuji H; Caricato M; Li X; Hratchian HP; Izmaylov AF; Bloino J; Zheng G; Sonnenberg JL; Hada M; Ehara M; Toyota K; Fukuda R; Hasegawa J; Ishida M; Nakajima T; Honda Y; Kitao O; Nakai H; Vreven T; Montgomery JA, Jr.; Peralta JE; Ogliaro F; Bearpark M; Heyd JJ; Brothers E; Kudin KN; Staroverov VN; Keith T; Kobayashi R; Normand J; Raghavachari K; Rendell A; Burant JC; Iyengar SS; Tomasi J; Cossi M; Rega N; Millam JM; Klene M; Knox JE; Cross JB; Bakken V; Adamo C; Jaramillo J; Gomperts R; Stratmann RE; Yazyev O; Austin AJ; Cammi R; Pomelli C; Ochterski JW; Martin RL; Morokuma K; Zakrzewski VG; Voth GA; Salvador P; Dannenberg JJ; Dapprich S; Daniels AD; Farkas O; Foresman JB; Ortiz JV; Cioslowski J; Fox DJ Gaussian 09, revision D.01; Gaussian Inc.: Wallingford, CT, 2013.
- (10). (a) Zhao Y; Truhlar DG Theor. Chem. Acc 2008, 120, 215.(b) Zhao Y; Truhlar DG Acc. Chem. Res 2008, 41, 157. [PubMed: 18186612]
- (11). (a) Ditchfield R; Hehre WJ; Pople JA J. Chem. Phys 1971, 54, 724.(b) Hehre WJ; Ditchfield R; Pople JA J. Chem. Phys 1972, 56, 2257.(c) Hariharan PC; Pople JA Theor. Chim. Acta 1973, 28, 213.
- (12). (a) Barone V; Cossi M J. Phys. Chem. A 1998, 102, 1995.(b) Cossi M; Rega N; Scalmani G; Barone VJ. Comput. Chem 2003, 24, 669. [PubMed: 12666158] (c) Takano Y; Houk KN J. Chem. Theory Comput 2005, 1, 70. [PubMed: 26641117]
- (13). The optimized geometries are similar to those optimized in the gas phase. The energies vary by only about 1 kcal/mol. See Supporting Information for details (Figure S1).
- (14). Legault CY CYLview, 1.0b; Université de Sherbrooke: Quebec, Canada, 2009; <http://www.cylview.org>.
- (15). Törk L; Jiménez-Osés G; Doubleday C; Liu F; Houk KN J. Am. Chem. Soc 2015, 137, 4749. [PubMed: 25726899]
- (16). The free-energy change of 1 mol of an ideal gas from 1 atm (24.46 L/mol, standard state) to 1 M (1 mol/L, standard state) is $RT \ln(24.46) = 1.89$ kcal/mol at $T = 298.15$ K. The density of HFIP is 1.6 g/cm^3 . The concentration of HFIP is 9.5 mol/L. The free-energy change from 1 M (1 mol/L, standard state) to 9.5 M is $RT \ln(9.5) = 1.33$ kcal/mol at $T = 298.15$ K (R is the gas constant).
- (17). (a) Wertz DH J. Am. Chem. Soc 1980, 102, 5316.(b) Leung BO; Reid DL; Armstrong DA; Rauk AJ. Phys. Chem. A 2004, 108, 2720.(c) Plata RE; Singleton DA J. Am. Chem. Soc 2015, 137, 3811. [PubMed: 25714789]

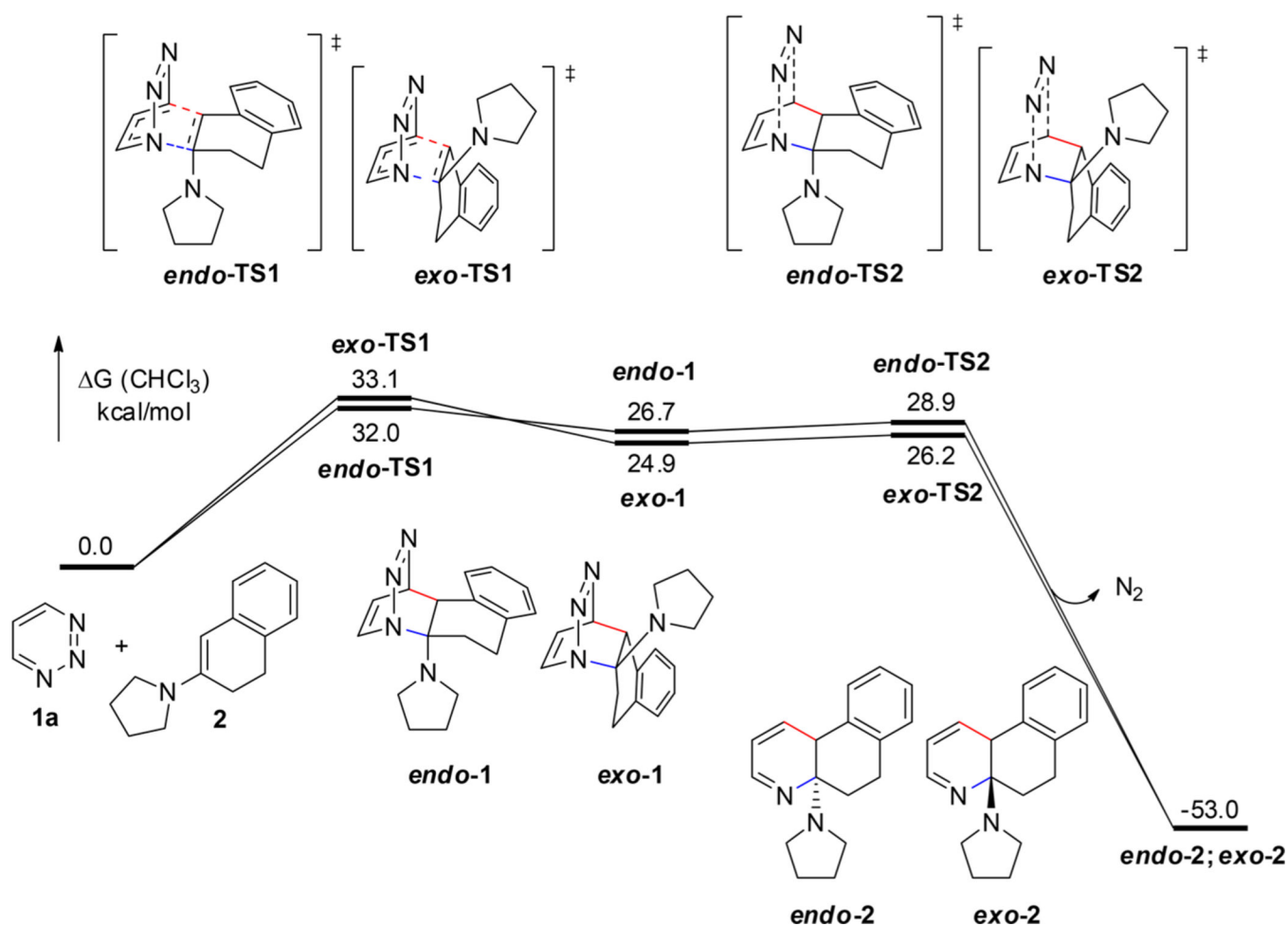


Figure 1. Gibbs free energy profiles for the *endo* and *exo* pathways of the reaction of 1,2,3-triazine **1a** with enamine **2** in CHCl_3 . Energies are in kcal/mol.

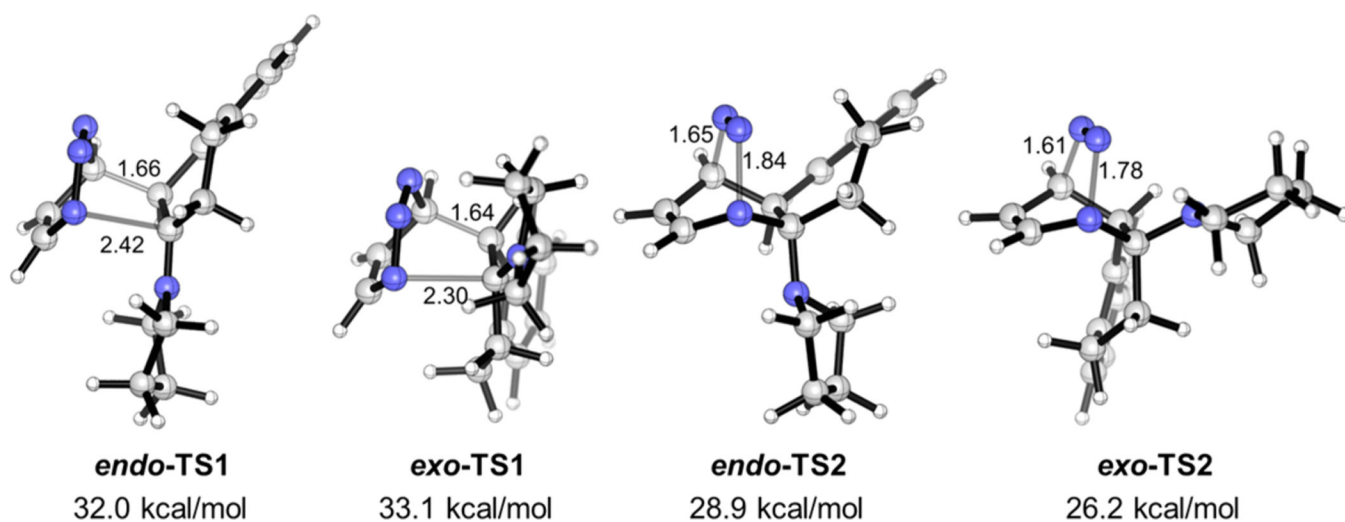


Figure 2.
Optimized transition structures of *endo* and *exo* pathways of the reaction of 1,2,3-triazine 1a with enamine 2. Distances are in Å.

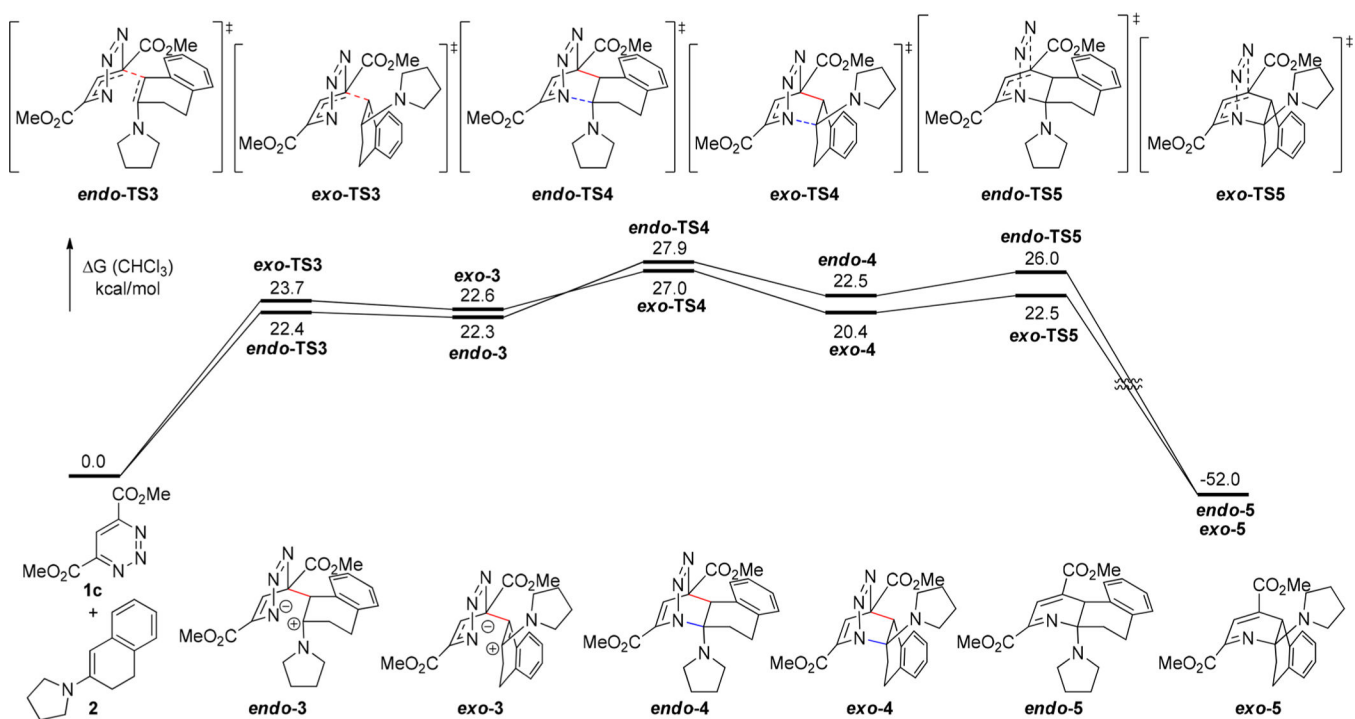


Figure 3. Gibbs free energy profiles for the *endo* and *exo* pathways of the reaction of 1,2,3-triazine **1c** with enamine **2** in solvent CHCl_3 . Energies are in kcal/mol.

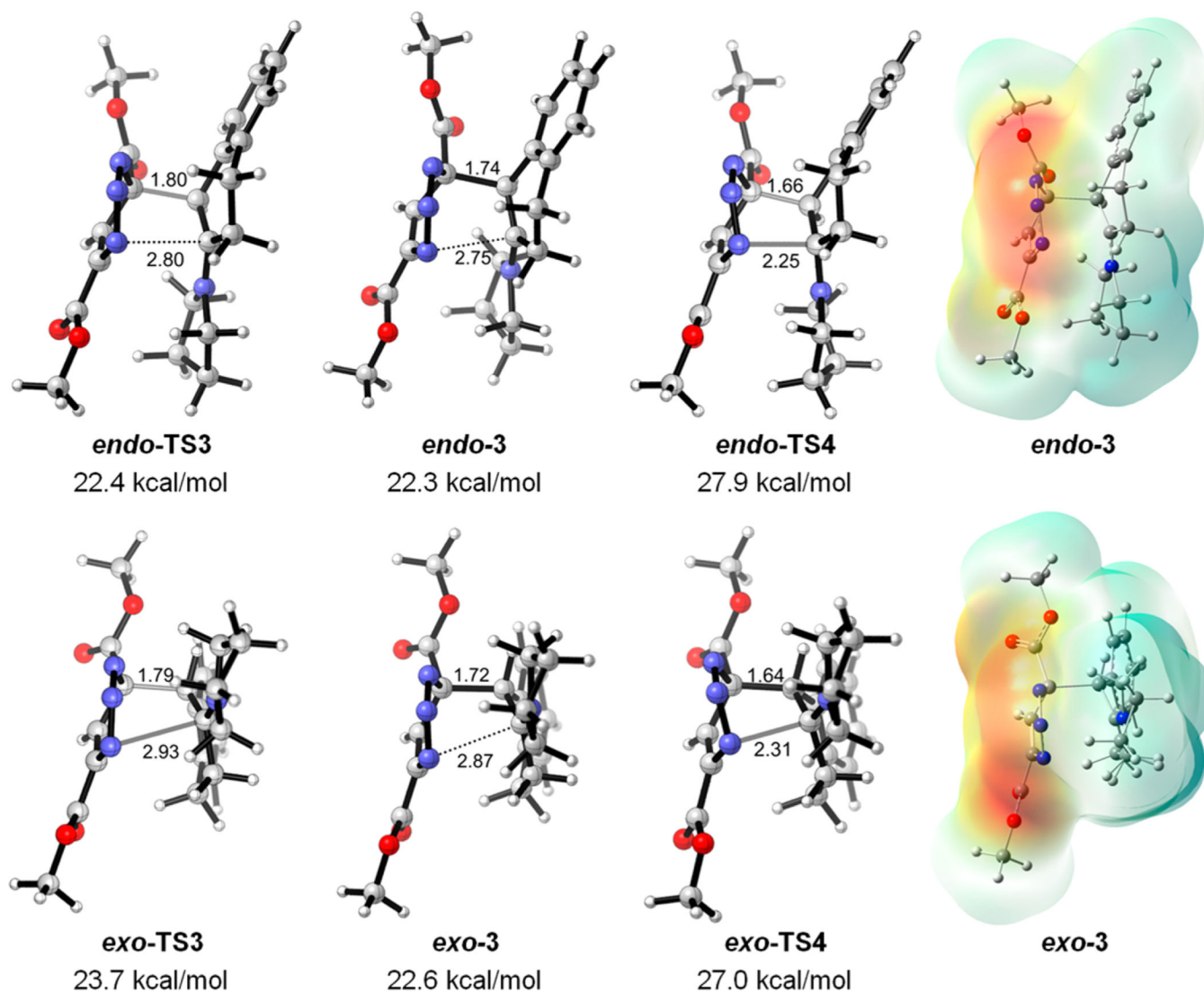


Figure 4. Optimized transition structures and intermediates of *endo* and *exo* pathways of the reaction of 1,2,3-triazine **1c** with enamine **2** and the ESP maps of *endo*-3 and *exo*-3. Distances are in Å.

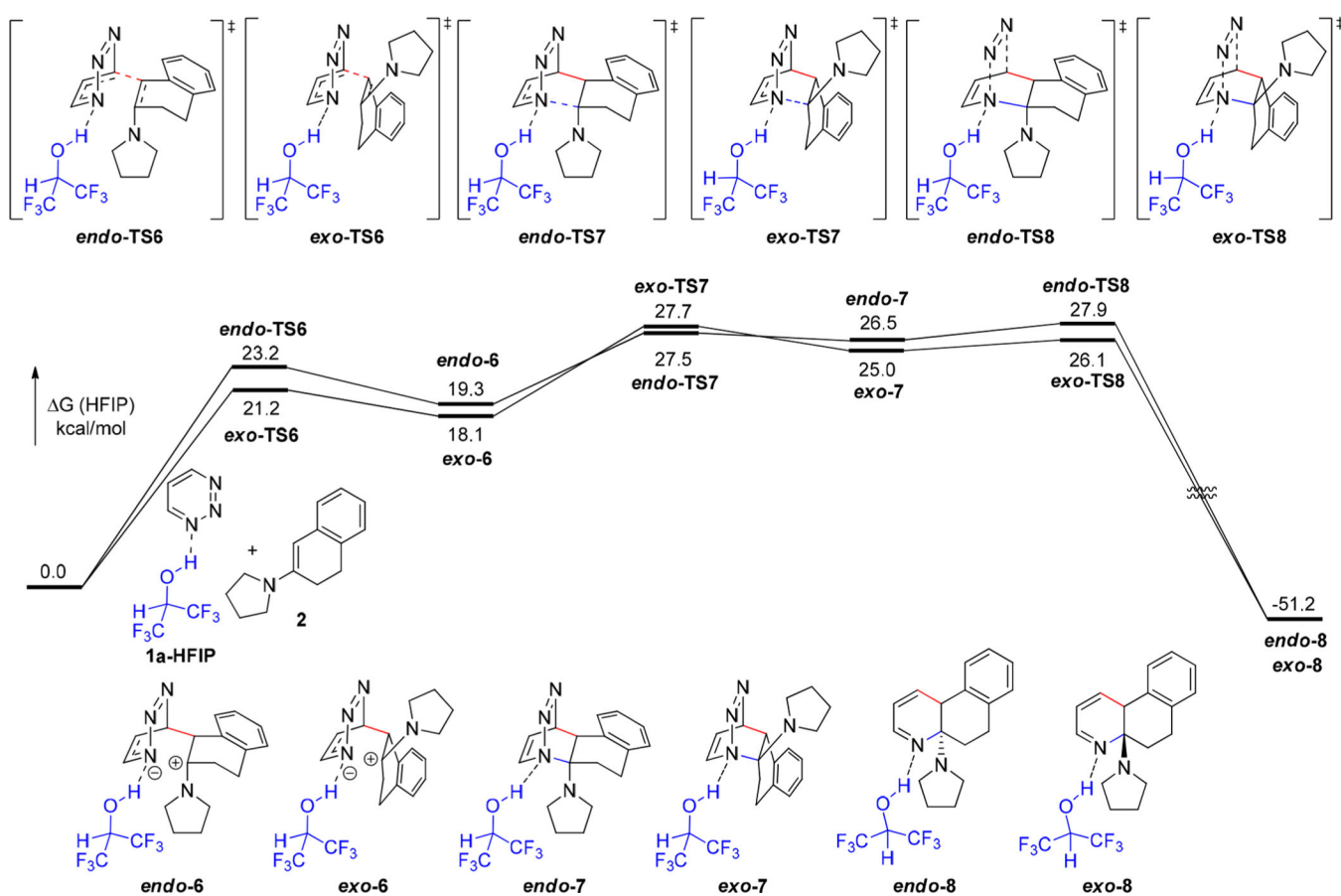


Figure 5. Gibbs free energy profiles for the *endo* and *exo* pathways of the reaction of 1,2,3-triazine **1a**-HFIP with enamine **2** in solvent HFIP. Energies are in kcal/mol.

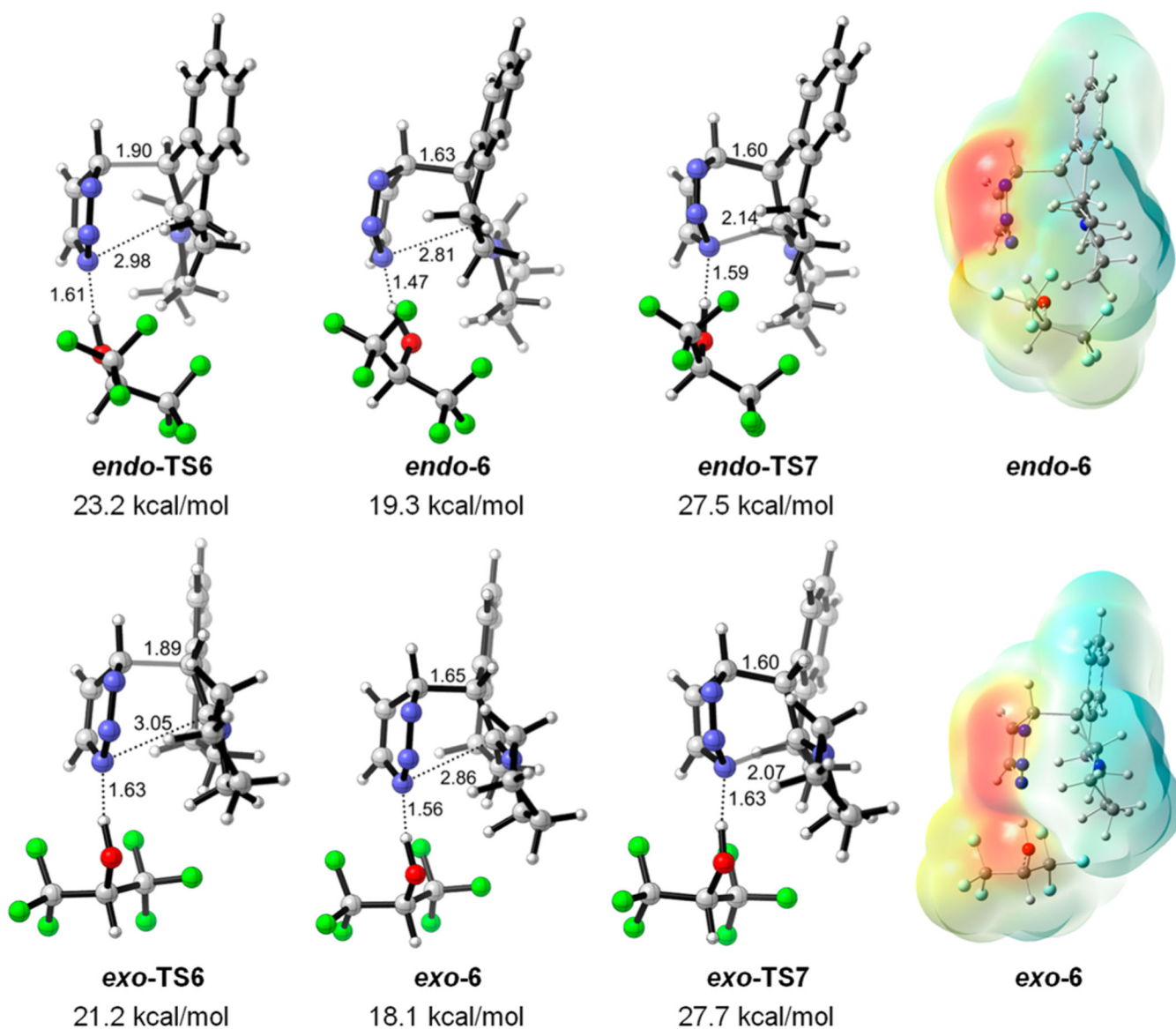


Figure 6. Optimized transition structures and intermediates of *endo* and *exo* pathways of the reaction of 1,2,3-triazine **1a** with enamine **2** in solvent HFIP and the ESP maps of **endo-6** and **exo-6**. Distances are in Å.

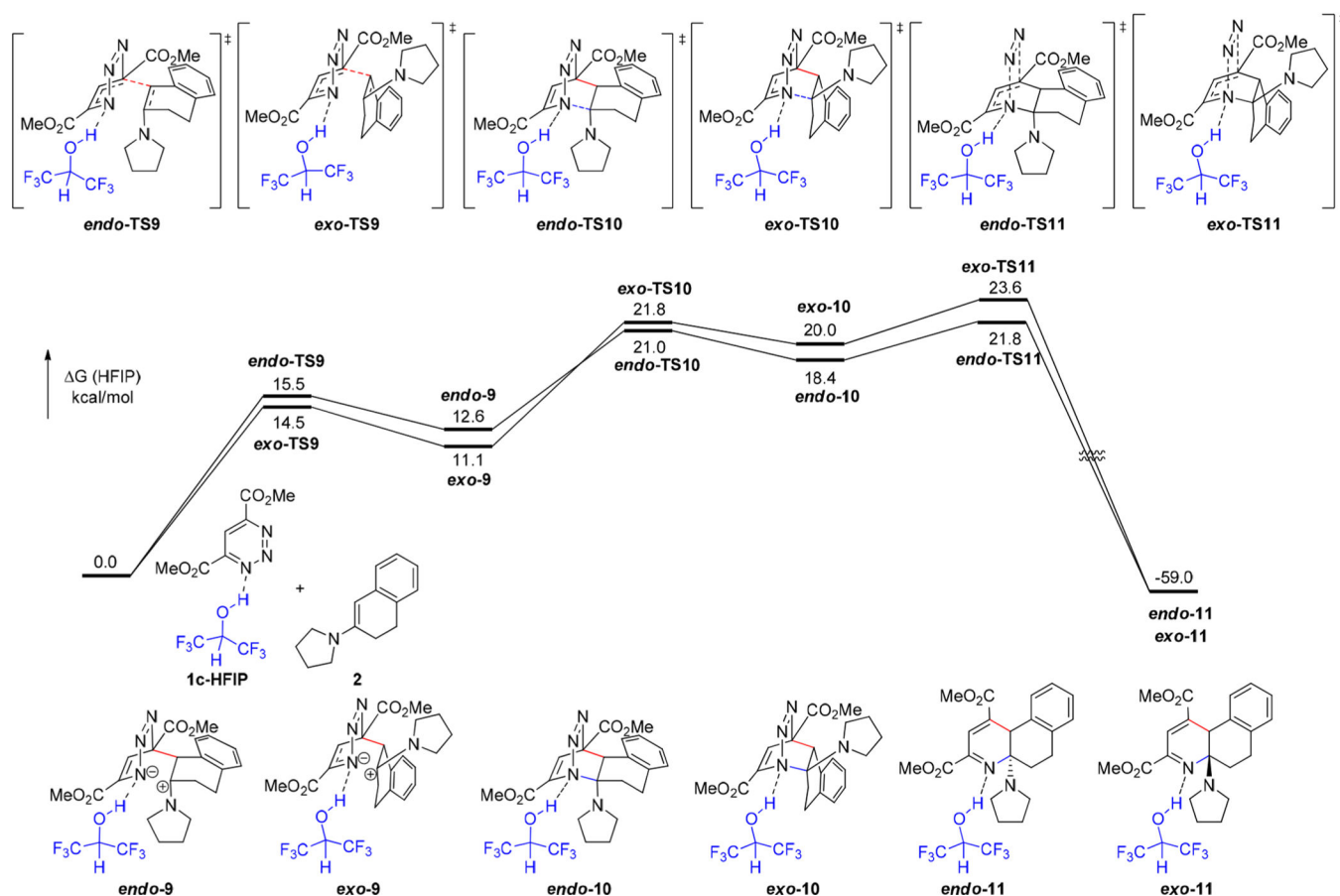


Figure 7. Gibbs free energy profiles for the *endo* and *exo* pathways of the reaction of 1,2,3-triazine **1c**-HFIP with enamine **2** in solvent HFIP. Energies are in kcal/mol.

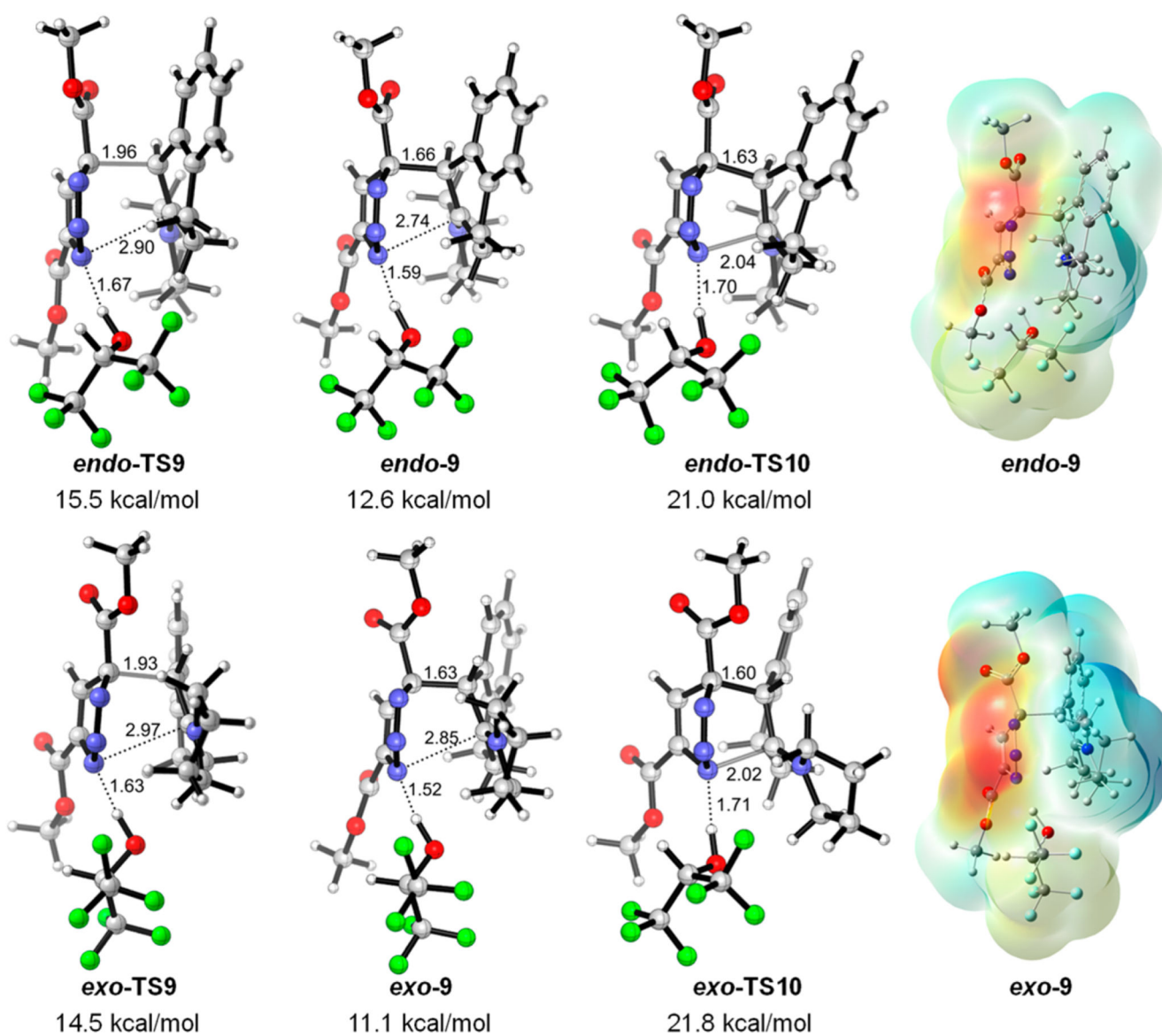


Figure 8. Optimized transition structures and intermediates of *endo* and *exo* pathways of the reaction of 1,2,3-triazine **1c** with enamine **2** in solvent HFIP and the ESP maps of **endo-9** and **exo-9**. Distances are in Å.

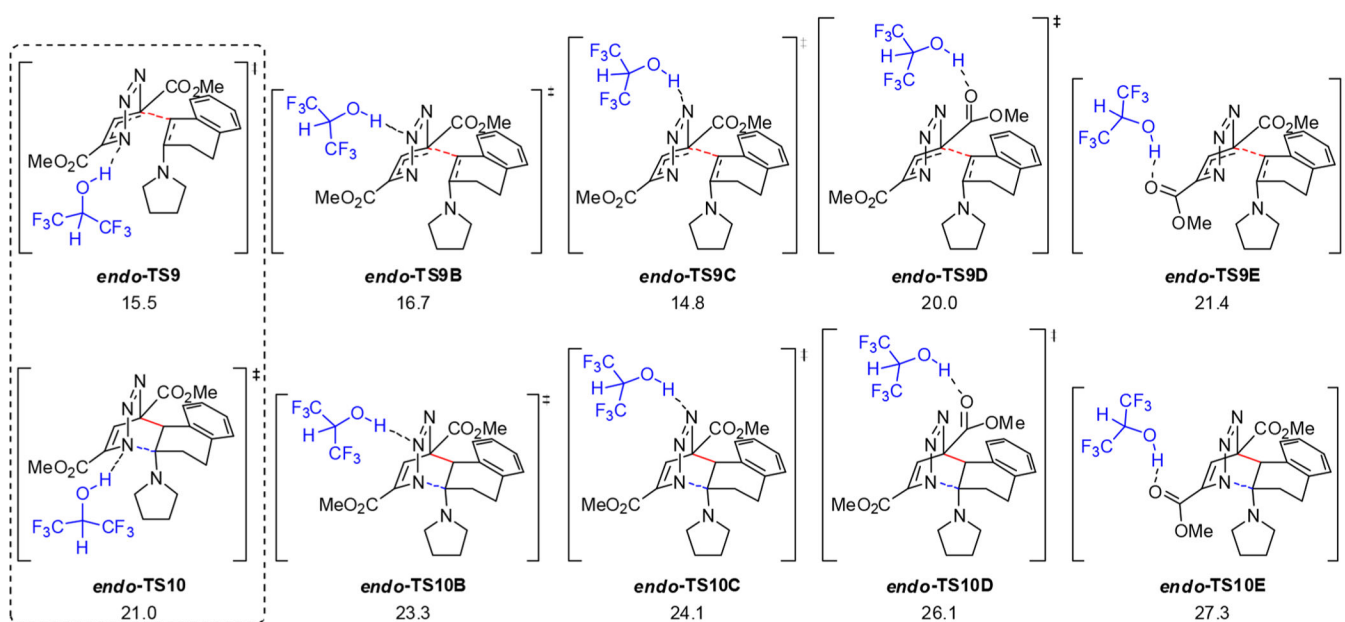


Figure 9. Transition structures of *endo* pathways of the reaction of 1,2,3-triazine **1c** with enamine **2** with one HFIP binding to different sites of **1c** in solvent HFIP. Energies are in kcal/mol.

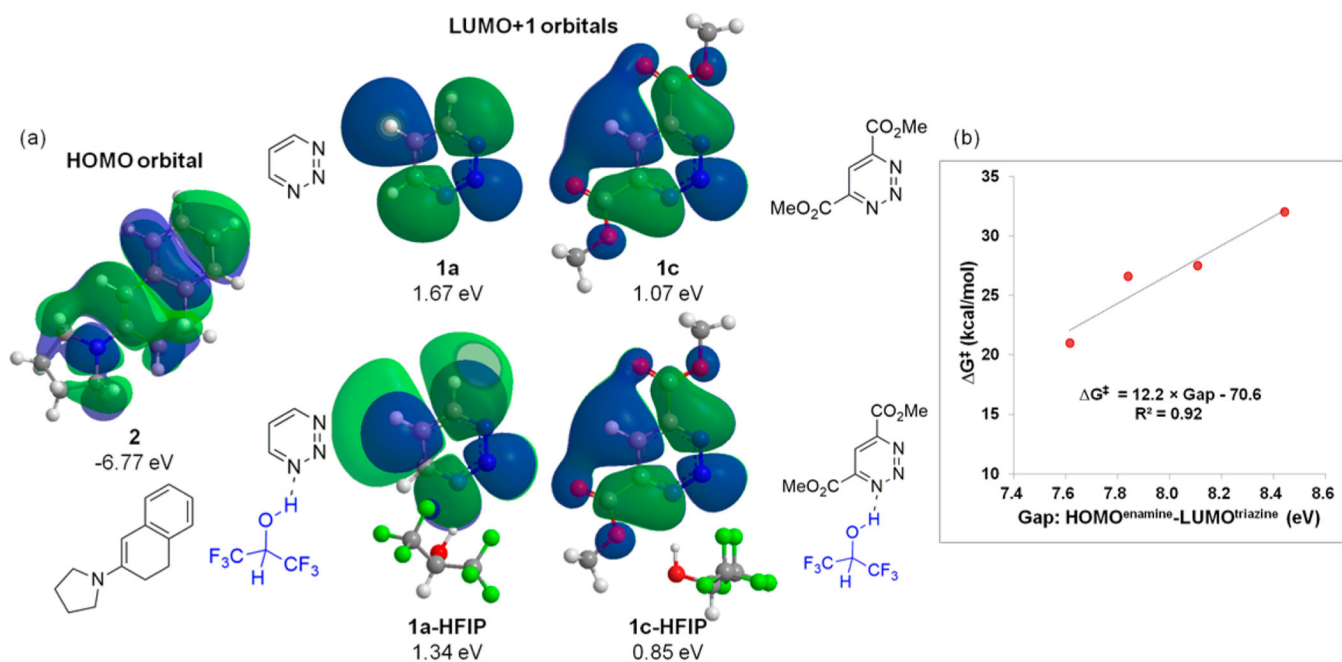
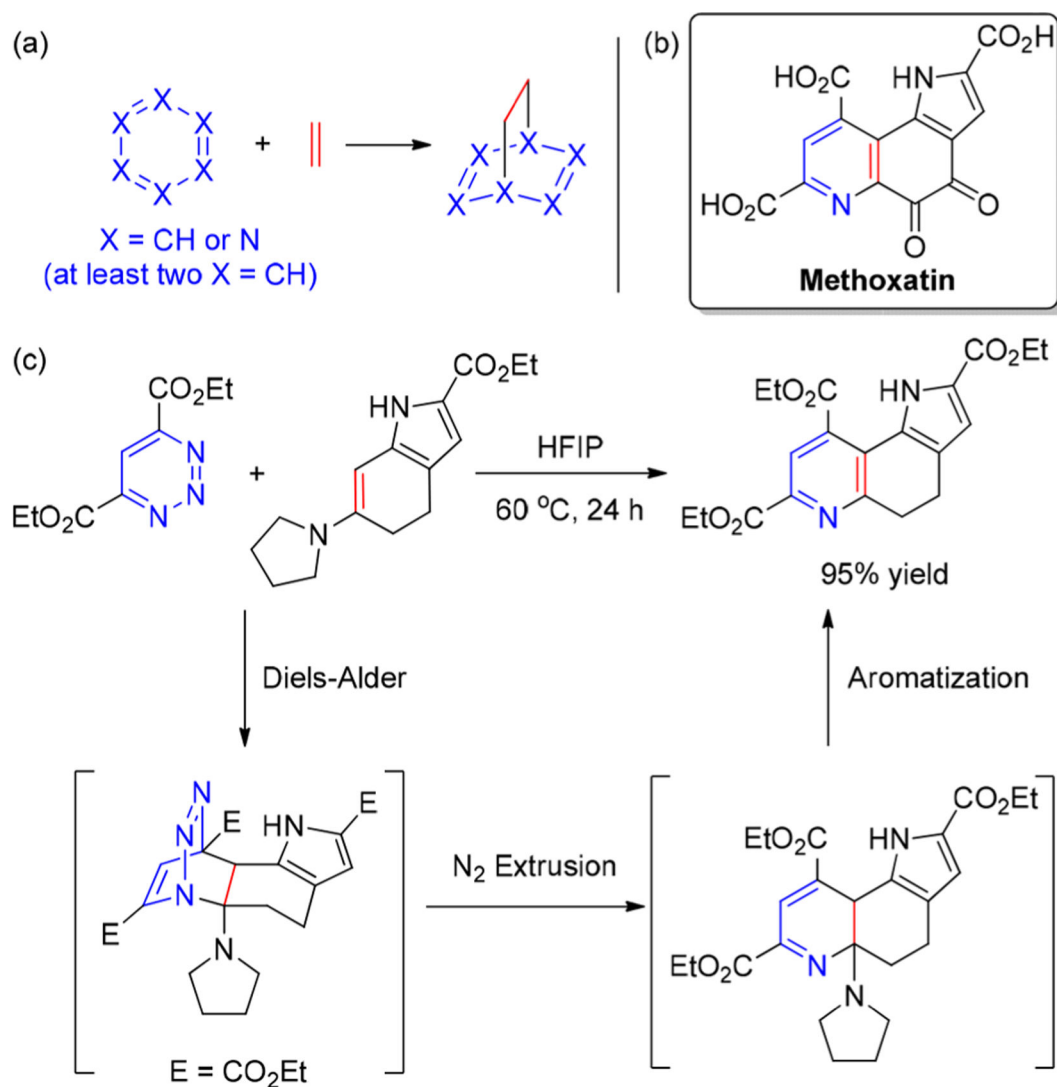


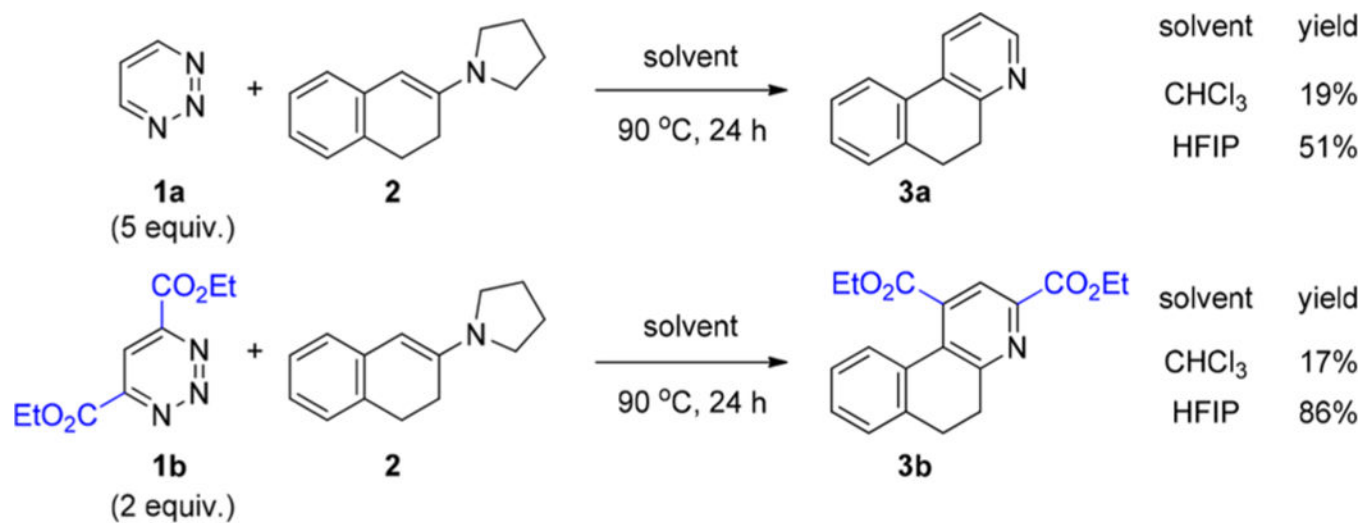
Figure 10. (a) Computed HOMO of enamine **2**, the lowest vacant LUMO+1 orbital of triazines **1a** and **1c** and HFIP-complexed triazines **1a-HFIP** and **1c-HFIP**. (b) Plot of Diels-Alder reaction barrier versus HOMO-LUMO gap (energy difference between HOMO orbital of enamine and LUMO+1 orbital of triazine).



^aSee ref 6.

Scheme 1.

(a) General Scheme of Diels–Alder Reactions of Azapolyenes, (b) Structure of Methoxatin, and (c) Diels–Alder Reactions of 1,2,3-Triazines^a



^aSee ref 6.

Scheme 2.

Cycloaddition Reactions of Enamine with Triazines in Different Solvents^a