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Mechanisms of Cascade Reactions in the Syntheses of Camptothecin-Family Alkaloids: Intramolecular [4+ + 2] Reactions of *N*-Arylimidates and Alkynes

Yong Liang, Xing Jiang, and Zhi-Xiang Yu*

Beijing National Laboratory for Molecular Sciences (BNLMS), Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, Peking University, Beijing 100871, China

yuzx@pku.edu.cn

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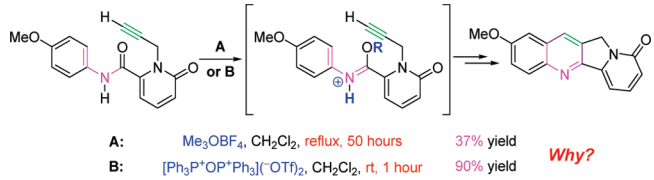
ABSTRACT



The key steps of cascade reactions employed in the syntheses of camptothecin-family alkaloids by Fortunak and Yao are intramolecular aza-Diels−Alder (IADA) reactions between in situ generated *N*-arylimidates and alkynes. The efficiencies of the IADA reactions are different but not well-understood. DFT calculations shown here provide insights into these two IADA reactions and well-rationalize why hexaphenyloxodiphosphonium triflate (Hendrickson reagent) as an amide-activating reagent is superior to trimethyloxonium fluoroborate.

The potent anticancer activities and clinical applications of camptothecin-family alkaloids have attracted considerable interests worldwide.[1] Since the isolation of camptothecin (**1**, Figure 1) from the Chinese tree *Camptotheca acuminate* in 1966,[2] the syntheses of camptothecin and its analogues have been intensively investigated by many research groups.[3,4] Among them, one of the most efficient strategies is to construct the B and C rings of camptothecin-family alkaloids by using a cascade reaction from an *N*-arylamide, which is proposed to occur via three consecutive processes (Scheme 1): (a) in situ formation of an *N*-arylimidate through activation of the corresponding amide, (b) intramolecular aza-Diels−Alder (IADA) reaction between the *N*-arylimidate and the alkyne, and (c) aromatization to the quinoline. This strategy was first applied by Fortunak and co-workers to a formal synthesis of (±)-10-methoxycamptothecin and an asymmetric synthesis of anticancer drug topotecan (**2**, Figure

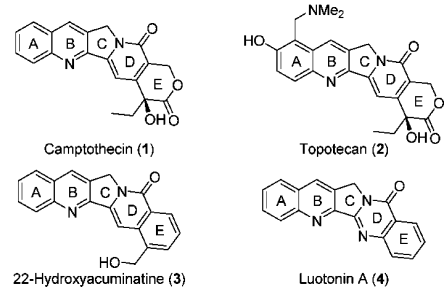


Figure 1. Camptothecin-family alkaloids.

(1) Thomas, C. T.; Rahier, N. J.; Hecht, S. M. *Bioorg. Med. Chem.* **2004**, *12*, 1585.
(2) Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; McPhail, A. T.; Sim, G. A. *J. Am. Chem. Soc.* **1966**, *88*, 3888.
(3) For a review, see: Du, W. *Tetrahedron* **2003**, *59*, 8649.
(4) For selected recent examples, see: (a) Servais, A.; Azzouz, M.; Lopes, D.; Courillon, C.; Malacria, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 576. (b) Chavan, S. P.; Pathak, A. B.; Kalkote, U. R. *Synlett* **2007**, 2635. (c) Liu, G.-S.; Dong, Q.-L.; Yao, Y.-S.; Yao, Z.-J. *Org. Lett.* **2008**, *10*, 5393. (d) Pin, F.; Comesse, S.; Sanselme, M.; Daich, A. *J. Org. Chem.* **2008**, *73*, 1975. (e) Ju, Y.; Liu, F.; Li, C. *Org. Lett.* **2009**, *11*, 3582.

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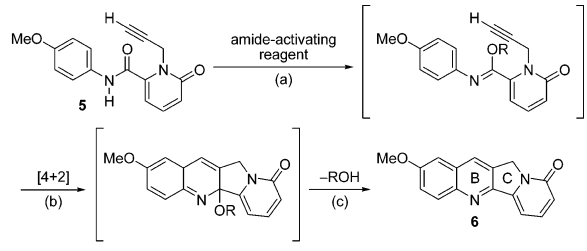
1).[5] However, Fortunak's method has several limitations related to reaction yields, side reactions, and the scope of the reaction.[5a] Recently, Yao and co-workers reported an improvement of this strategy and successfully achieved total syntheses of camptothecin, 22-hydroxyacuminatine, and luotonin A (**1**, **3**, and **4**, Figure 1) under mild conditions with significant increases of reaction yields.[6] The main difference of these two methods is the amide-activating reagents used. In Fortunak's method, trimethyloxonium fluoroborate was employed as the activating reagent, whereas hexaphenyloxodiphosphonium triflate (Hendrickson reagent[7]) was used in Yao's method. As shown in Scheme 1, for substrate **5**, with Me_3OBF_4, after refluxing in CH_2Cl_2 for 50 h, the expected product **6** was obtained in 37% yield.[5a,6a,8] However, the identical reaction with Hendrickson reagent can complete at room temperature in just 1 h with a greatly improved yield of 90%.[6a]

Scheme 1

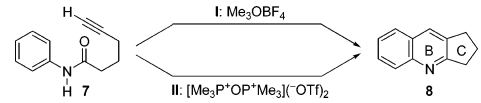


	amide-activating reagent	reaction conditions	yield
Fortunak's method:	Me_3OBF_4	CH_2Cl_2, reflux, 50 hours	37%
Yao's method:	$[Ph_3P^+OP^+Ph_3](^-OTf)_2$	CH_2Cl_2, rt, 1 hour	90%

To probe the mechanisms of the cascade reactions utilized in the construction of the B and C rings of camptothecin and its analogues, with an emphasis on understanding why different activating reagents lead to so dramatically different experimental results, DFT calculations at the B3LYP/6-31G(d) level of theory were performed on two model systems, **I** and **II** (Scheme 2).[9] Solvent effects were computed using the CPCM model[10] in CH_2Cl_2. All discussed energies below are Gibbs free energies in solution, ΔG_{sol}. The relative enthalpies in solution (ΔH_{sol}) and gas phase (ΔH_{gas}) are also given.

In model system **I**, trimethyloxonium (**9**) acts as the amide-activating reagent to initiate the cascade reaction (Figure 2).

Scheme 2. Computed Model Systems



Calculations show that the first step of the cascade reaction corresponds to methylation of the carbonyl group of amide **7** by Me_3OBF_4 to give N-protonated *O*-methylimidate **10**. This is exergonic by 10.5 kcal/mol, requiring an activation free energy of 22.1 kcal/mol. In this nucleophilic substitution transition structure **TS1**, the forming and breaking C−O bond distances are 2.03 and 1.87 Å, respectively (Figure 3). The subsequent step is an intramolecular aza-Diels−Alder reaction,[11] in which the alkyne moiety serves as a dienophile and the cationic *N*-phenylimidate moiety serves as an azadiene by using the C═N bond and the C═C bond in the

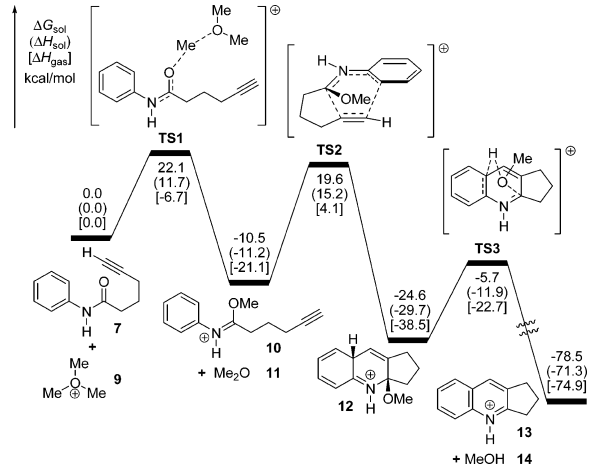
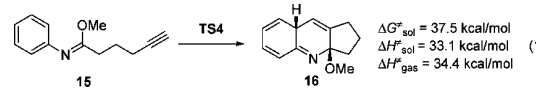


Figure 2. DFT computed energy surface for the cascade reactions triggered by trimethyloxonium.

phenyl ring. This reaction can be named as a [4$^+$ + 2] reaction[12] because the azadiene is positively charged. In the originally proposed mechanism, the neutral azadiene was regarded to take part in [4 + 2] reaction with alkyne.[5a] However, calculations show that the IADA reaction of **15** is highly energy-demanding with an activation free energy of 37.5 kcal/mol (eq 1).



Therefore, the neutral [4 + 2] pathway is not feasible. In contrast, a N-protonated azadiene is easier to participate in

(5) (a) Fortunak, J. M. D.; Mastrocola, A. R.; Mellinger, M.; Sisti, N. J.; Wood, J. L.; Zhuang, Z.-P. *Tetrahedron Lett.* **1996**, *37*, 5679. (b) Fortunak, J. M. D.; Kitteringham, J.; Mastrocola, A. R.; Mellinger, M.; Sisti, N. J.; Wood, J. L.; Zhuang, Z.-P. *Tetrahedron Lett.* **1996**, *37*, 5683.

(6) (a) Zhou, H.-B.; Liu, G.-S.; Yao, Z.-J. *Org. Lett.* **2007**, *9*, 2003. (b) Zhou, H.-B.; Liu, G.-S.; Yao, Z.-J. *J. Org. Chem.* **2007**, *72*, 6270.

(7) (a) Hendrickson, J. B.; Schwartzman, S. M. *Tetrahedron Lett.* **1975**, *16*, 277. (b) Hendrickson, J. B.; Hussoin, M. S. *J. Org. Chem.* **1989**, *54*, 1144. (c) You, S.-L.; Razavi, H.; Kelly, J. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 83.

(8) Zhou, H.-B. Thesis Dissertation, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 2007.

(9) Frisch, M. J.; *Gaussian 03*, revision C. 02; Gaussian, Inc.: Wallingford, CT, 2004. For details, see the Supporting Information.

(10) (a) Cossi, M.; Rega, N.; Scalmani, G.; Barone, V. *J. Comput. Chem.* **2003**, *24*, 669. (b) Takano, Y.; Houk, K. N. *J. Chem. Theory Comput.* **2005**, *1*, 70.

(11) For a recent review, see: Kouznetsov, V. V. *Tetrahedron* **2009**, *65*, 2721.

(12) Beck, K.; Hoffman, P.; Hünig, S. *Chem.—Eur. J.* **1997**, *3*, 1588.

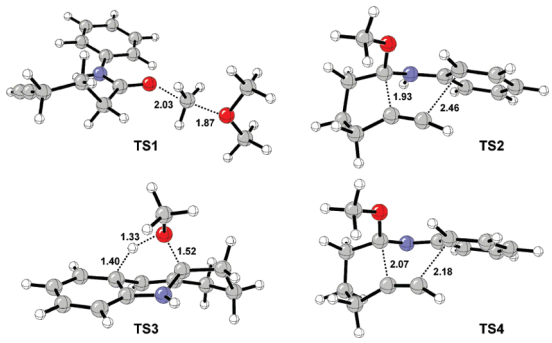


Figure 3. Transition state structures in model system **I**.

the [4+ + 2] reaction with an activation free energy of 30.1 kcal/mol. In **TS2**, two forming C−C bond distances are quite different (1.93 versus 2.46 Å, Figure 3), indicating that this proton-promoted aza-Diels−Alder reaction occurs in a concerted but highly asynchronous fashion.[13,14] This was further supported by IRC calculations.[15] Once the [4+ + 2] adduct **12** is generated, the followed elimination of methanol to form N-protonated quinoline derivative **13** is exergonic by 53.9 kcal/mol, requiring an activation free energy of 18.9 kcal/mol. The aromatization transition structure **TS3** has a bridge-like geometry, in which the breaking C−O and C−H bond distances and the forming O−H bond distance are 1.52, 1.40, and 1.33 Å, respectively (Figure 3). Reviewing the whole energy surface of this cascade reaction triggered by trimethyloxonium, we found that the rate-determining step is the proton-promoted IADA reaction. The other two steps, the amide activation and elimination−aromatization, are relatively facile. In Fortunak's experiment, the *O*-methylimidate intermediate can be observed by ^{1}H NMR spectroscopy at 20 °C, and the subsequent reaction has to take place at a relatively high temperature for a long reaction time.[5a] These phenomena can be well-rationalized by present computational results, which demonstrate that the *O*-methylimidate is about 10 kcal/mol more stable than starting materials, and the subsequent [4+ + 2] reaction is not easy with an energy barrier of about 30 kcal/mol.

The computed energy surface for model system **II** with hexamethyloxodiphosphonium triflate as the amide-activating reagent is given in Figure 4. The computed transition state structures are shown in Figure S1 in Supporting Information. Calculations indicate that, in contrast to the exergonic formation of N-protonated *O*-methylimidate **10** (Figure 2), the formation of N-protonated *O*-trimethylphosphoniumimidate **18** is endergonic by 13.7 kcal/mol,[16] due to the existence of disfavored intramolecular repulsion between two positive charged centers (the phosphonium and the iminium moieties) in **18**. The followed IADA reaction requires an activation free energy of 23.8 kcal/mol.[17] Even though this [4+ + 2] reaction is not difficult, the overall activation free energy to reach **TS5** is still as high as 37.5 kcal/mol due to the endergonic generation of dicationic azadiene **18**. Therefore, the cascade reaction via **TS5** is impossible kinetically, considering the fact that this reaction smoothly occurs at room temperature.[6]

Further calculations show that dicationic intermediate **18** can be easily converted into another cationic intermediate, N-protonated *O*-trifluoromethylsulfonylimidate **22** (Figure 4). First, the nucleophilic addition of triflate anion **20** to **18** generates intermediate **21**, which then undergoes elimination of trimethylphosphine oxide (**19**) to form **22** with a low energy barrier. The subsequent [4+ + 2] cycloaddition of **22** via **TS7** has an energy barrier of 23.8 kcal/mol,[18] close to that for the [4+ + 2] reaction of **18**. However, because the transformation from **18** to **22** is a downhill process with 14.2 kcal/mol of exergonicity, the overall activation free energy to reach **TS7** is 23.8 kcal/mol, about 14 kcal/mol lower than the energy required from starting materials **7** and **17** to **TS5**. Aromatization of the [4+ + 2] adduct **23** via **TS8** requires a very low activation free energy and is drastically exergonic. Therefore, in this cascade reaction triggered by hexamethyloxodiphosphonium triflate, **22** instead of **18** is the reactive precursor for the rate-determining IADA reaction. Notably, the activation free energy of this step is only 23.8 kcal/mol, about 6 kcal/mol lower than that of model system **I**. Therefore, the cascade reaction of model system **II** is more efficient than that of model system **I**, and consequently, the side reactions in model system **II** could be suppressed more efficiently than those in model system **I**. This is the reason why the cascade reaction employing Hendrickson reagent occurs much faster under milder conditions with better yields as compared to the corresponding reaction using trimethyloxonium fluoroborate (Scheme 1).

To better understand the key aza-Diels−Alder reactions, we carried out frontier molecular orbital (FMO) analysis (Table 1).[19] For neutral azadienes **28** and **29**, the energy gaps of $HOMO_{28(29)}$−$LUMO_{27}$ and $HOMO_{27}$−$LUMO_{28(29)}$ are all large (about 14 eV), indicating that both inverse electron-demand and normal electron-demand aza-Diels−Alder reactions are difficult to occur. However, after protonation, the LUMO energies of cationic azadiene **30** and **31** remarkably

(13) (a) For a DFT study on the [4+ + 2] reactions between the N-protonated azadiene and olefins, see: Ding, Y.-Q.; Fang, D.-C. *J. Org. Chem.* **2003**, *68*, 4382. (b) For DFT studies on [4 + 2+] reactions of iminium cations, see: Domingo, L. R. *J. Org. Chem.* **2001**, *66*, 3211. (c) Iafe, R. G.; Houk, K. N. *J. Org. Chem.* **2008**, *73*, 2679. (d) Domingo, L. R.; Sáez, J. A. *Org. Biomol. Chem.* **2009**, *7*, 3576.

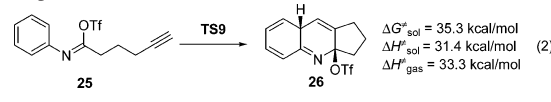
(14) Stepwise mechanisms can be ruled out by calculations. For details, see the Supporting Information. For theoretical studies on stepwise Diels−Alder reactions, see: (a) Domingo, L. R.; Oliva, M.; Andrés, J. *J. Org. Chem.* **2001**, *66*, 6151. (b) Wakayama, H.; Sakai, S. *J. Phys. Chem. A* **2007**, *111*, 13575.

(15) (a) Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154. (b) Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523.

(16) After many attempts, the nucleophilic substitution transition state for the generation of **18** could not be located. Nevertheless, this step is expected to be facile with a low activation free energy because the similar amide activation by Hendrickson reagent can smoothly occur at 0 °C for 10 min (for details, see ref 7c).

(17) For detailed analysis using the FMO theory, see Table 1 and the Supporting Information.

(18) For comparison, the aza-Diels−Alder reaction involving neutral precursor **25** was also computed, whose activation free energy was 35.3 kcal/mol (eq 2), 11.7 kcal/mol higher than that in the reaction involving cationic precursor **22**.



(19) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361.

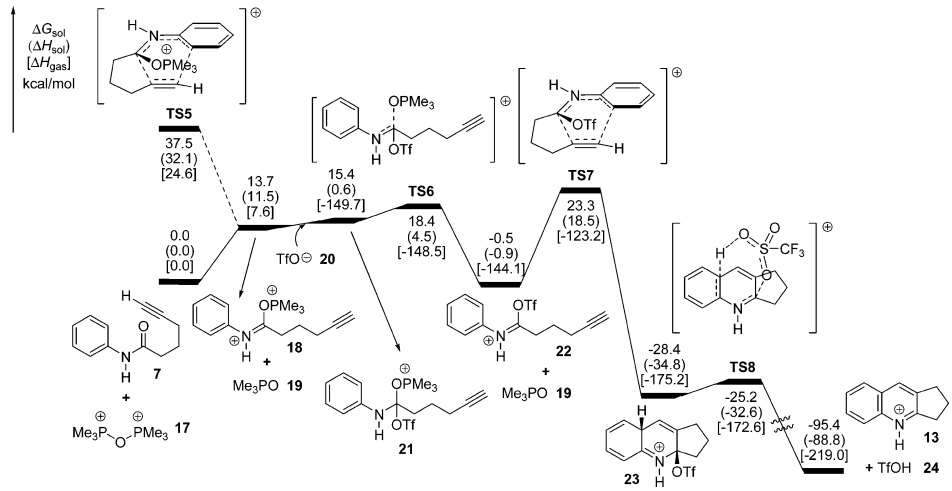
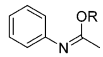
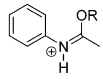


Figure 4. DFT computed energy surface for the cascade reactions triggered by hexamethyloxodiphosphonium triflate.

decrease, leading to much smaller $HOMO_{27}-LUMO_{30(31)}$ gaps (8.6 eV for **30** and 8.1 eV for **31**). Therefore, the inverse electron-demand aza-Diels−Alder reaction[20] between N-protonated *N*-phenylimidate and "electron-rich" alkyne becomes much easier. More importantly, the energy gap of $HOMO_{27}-LUMO_{31}$ is 0.5 eV lower than that of $HOMO_{27}-LUMO_{30}$, suggesting that N-protonated *O*-trifluoromethylsulfonylimidate is more reactive than N-protonated *O*-methylimidate in aza-Diels−Alder reactions.[17] This is also in agreement with the electronic effect of the substituent on the oxygen of imidate: a strong electron-withdrawing trifluoromethylsulfonyl group can further decrease the frontier molecular orbital energy of N-protonated imidate, making the electron flow from electron-rich alkyne to cationic azadiene much easier.

Table 1. FMO Analysis (HF//B3LYP/6-31G(d))[17]

structure		HOMO (eV)	LUMO (eV)
H—≡—	**27**	−10.23	6.00
	**28** R = Me	−7.84	3.72
	29 R = Tf	−8.69	2.74
	**30** R = Me	−12.35	**−1.65**
	31 R = Tf	−12.69	**−2.12**
	32 R = P^+Me_3	−15.28	−5.53

In summary, the present computational study reveals the detailed mechanisms of cascade reactions employed in the construction of the B and C rings of camptothecin and its analogues. It is found that the key IADA reaction occurs via a $[4^+ + 2]$ fashion, and the amide-activating reagents are critical to the success of cascade reactions. When Me_3OBF_4 is used as the amide-activating reagent, the azadiene is cationic *N*-phenyl *O*-methylimidate. In contrast, the use of Hendrickson reagent results in a more electron-deficient cationic *N*-phenyl *O*-trifluoromethylsulfonylimidate, which is more efficient in the rate-determining $[4^+ + 2]$ reaction, and consequently, a milder reaction condition and a higher reaction yield can be achieved.

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Supporting Information Available: Computational details and Figure S1. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) For DFT studies on inverse electron-demand Diels−Alder reactions, see: Yu, Z.-X.; Dang, Q.; Wu, Y.-D. *J. Org. Chem.* **2005**, *70*, 998, and references therein.