



Homopyrrole and homofuran as masked 1,5-dipoles in metal-free (5+2) cycloadditions with dienophiles: a DFT study



Pei-Jun Cai, Fu-Qiang Shi, Yi Wang, Xin Li, Zhi-Xiang Yu*

College of Chemistry, Peking University, Beijing 100871, China

ARTICLE INFO

Article history:

Received 6 April 2013

Received in revised form 22 May 2013

Accepted 28 May 2013

Available online 6 June 2013

ABSTRACT

Metal-free (5+2) cycloadditions of homopyrrole and homofuran with dienophiles of *N*-phenylmaleimide, dimethyl acetylenedicarboxylate (DMAD), and maleic anhydride have been investigated by DFT calculations at the (U)B3LYP/6-31+G(d) level. Homopyrrole and homofuran act as 4-electron 1,5-dipoles in these (5+2) reactions. These 1,5-dipoles can exist only in the transition states and undergo competitive concerted or stepwise (5+2) cycloadditions. The (5+2) cycloadditions of homopyrrole with dienophiles are stepwise involving generation of diradical intermediates, and its concerted pathways are disfavored marginally. In contrast, the (5+2) cycloaddition of homofuran with maleic anhydride occurs in a concerted fashion, which is preferred over the stepwise diradical pathway slightly. The distortion energies from homopyrrole and homofuran to their respective 1,5-dipoles in the transition states are not high and this is the main reason why homopyrrole and homofuran can undergo metal-free (5+2) cycloadditions with dienophiles.

© 2013 Published by Elsevier Ltd.

1. Introduction

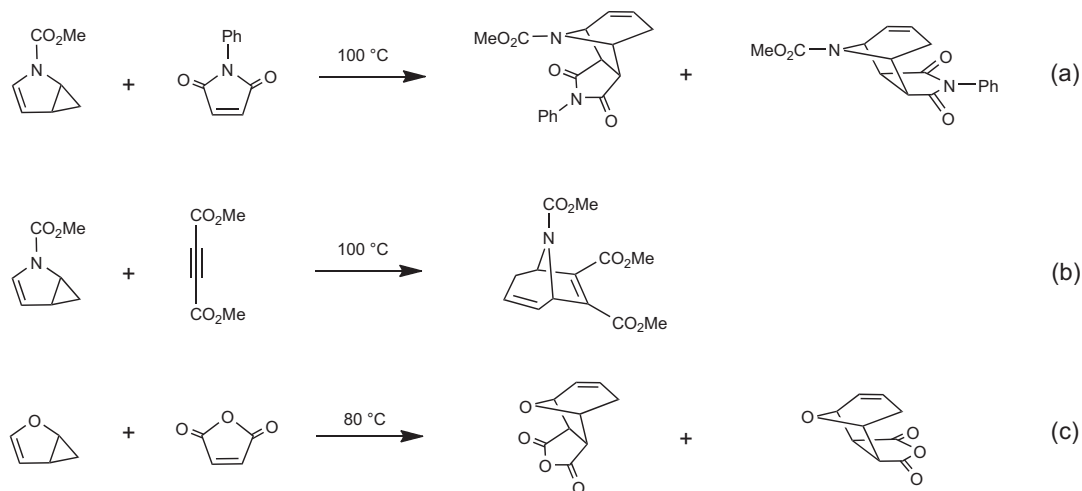
The ($m+n$) cycloadditions (m and n are referred to the atom numbers that are finally embedded in the formed cyclic rings) provide very efficient methods to construct various-sized cyclic compounds through formation of two (or more) new bonds and multiple stereogenic centers in a single synthetic operation.^{1–5} One prominent and widely applied cycloaddition reaction is the Diels–Alder (D–A) reaction for the synthesis of six-membered rings.² Seven-membered cyclic rings are also widely found in natural products. Inspired by the power of D–A reaction, synthetic chemists have been developing homo-D–A cycloadditions to achieve efficient synthesis of seven-membered cyclic compounds. For instance, if the dienophile of the original D–A reaction is replaced by an allyl cation, a (4+3) cycloaddition can be realized between a diene and the in situ generated allyl cation.³ The second variant of the D–A reaction is to replace the diene of the original D–A reaction by a pentadienyl cation,^{4,5} providing a (5+2) cycloaddition process to construct seven-membered rings. The (5+2) homolog D–A reaction could also occur between vinylcyclopropanes (VCPs) and dienophiles. Sarel and Breuer reported such a reaction. Unfortunately this reaction cannot be reproduced by other groups.⁶ Later it was found that only very special VCPs can take part in the

(5+2) cycloadditions with dienophiles. For example, in 1971, Fowler reported the (5+2) cycloadditions of *N*-methoxycarbonyl-2,3-homopyrrole with dimethyl acetylenedicarboxylate (DMAD), as well as with *N*-phenylmaleimide (Scheme 1a and b).⁷ A similar reaction was also reported by Herges and Ugi, who demonstrated that reaction of homofuran with maleic anhydride generated *endo*- and *exo*-(5+2) cycloadducts with a ratio of 1:1 (Scheme 1c).⁸

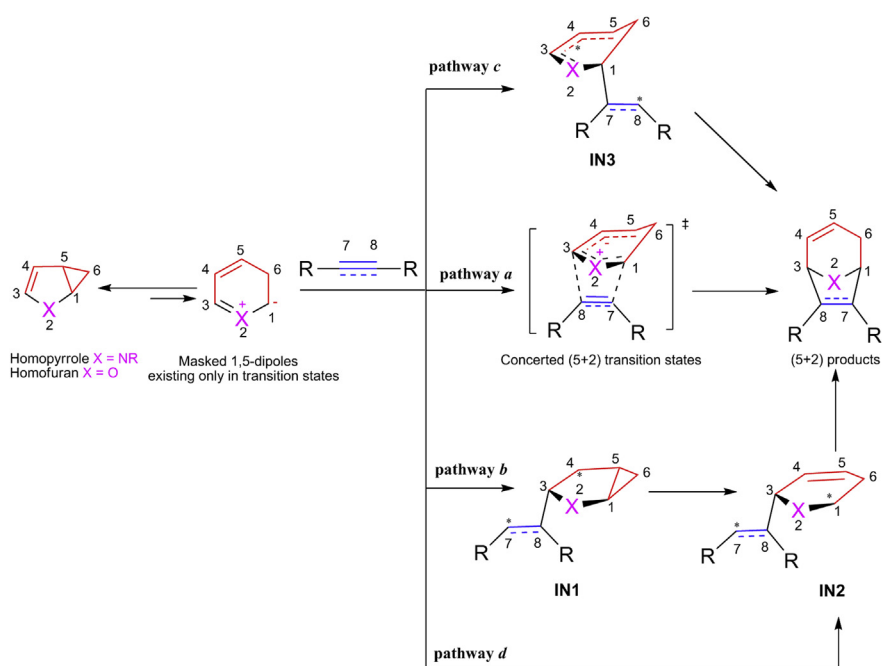
The general protocol for (5+2) cycloaddition between VCPs and 2π components, such as alkenes, alkynes, and allenes, intra- and/or intermolecularly, can be realized by using Rh(I) catalysts, as pioneered by Wender and co-workers.⁹ Later, Trost and co-workers demonstrated that an intramolecular (5+2) reaction between VCPs and alkynes can also be catalyzed by a Ru-complex. Ni and Fe catalysts can also be used as the catalysts for the (5+2) reaction between VCPs and alkyne. Recently, Yu, Tang, and Zhang further developed other different (5+2) reactions.¹⁰

The metal-catalyzed (5+2) cycloadditions between VCPs and alkenes/alkynes/allenes occur through a series of elementary reactions of oxidative addition (CP opening), alkene/alkyne/allene insertion, and reductive elimination, as supported by the computational studies by Houk, Wender, and Yu.¹¹ However, no mechanistic study of metal-free (5+2) reactions listed in Scheme 1 has been reported. We are very curious to know the following questions. Are these (5+2) reactions concerted (pathway *a*) or stepwise (involving zwitterionic or diradical intermediates **IN1**, **IN2**, pathway *b*) (Scheme 2)? In pathway *a*, the homopyrrole and homofuran

* Corresponding author. E-mail address: yuzx@pku.edu.cn (Z.-X. Yu).



Scheme 1. Selected metal-free (5+2) cycloadditions.



Scheme 2. Proposed concerted and stepwise pathways of the (5+2) reactions (atom labeling is also given here).

can be regarded as masked 1,5-dipoles, which then undergo concerted (5+2) cycloadditions. The reactions between dienophiles and the masked 1,5-dipoles could also take place stepwise via pathway c, which starts from formation of the C1–C7 bond (intermediate **IN3**), followed by ring closure to give the final cycloadducts. Dienophile can also directly attack C3 atom of the 1,5-dipole via pathway d to give **IN2** (not involving generation of **IN1**) and then (5+2) cycloadduct. Which pathway is the favored for the (5+2) cycloadditions? We also wanted to answer why these (5+2) reactions can take place without the aid of transition-metal catalysts. In addition, how to rationalize the *exo*- and *endo*-selectivity in reactions a and c (Scheme 1)? Understanding these questions in these metal-free (5+2) cycloadditions is highly required for the future design of other metal-free (5+2) and high-order (*m+n*) cycloadditions for the synthesis of medium-sized ring compounds. Therefore, DFT calculations have been undertaken to explore the energy surfaces of these metal-free (5+2) cycloadditions listed in Scheme 1.

2. Computational method

All calculations were performed with the Gaussian 03 program.¹² Geometries were optimized by either the B3LYP/6-31+G(d) (for closed-shell species) or UB3LYP/6-31+G(d) (for open-shell singlet diradicals)¹³ which has been proved to be suitable for studying D–A reactions and other pericyclic reactions with competitive concerted or stepwise pathways.¹⁴ Frequency calculations at the same level were carried out to confirm each stationary point to be either a minimum or a transition structure. For diradical species, the YJH spin-projection scheme has been used to reduce the spin contaminations.¹⁵ The reported energies are the zero-point energy-corrected electronic energies ($\Delta E_{0-\text{gas}}$) and Gibbs free energies computed at 298 K (ΔG_{gas}), both in the gas phase. The computed energies in CCl_4 solvent using PCM method¹⁶ were also given ($\Delta E_{0-\text{CCl}_4}$).¹⁷ Unless specified, all discussed energies are the zero-point energy-corrected electronic energies in the gas phase. We must point out that, even though M06 and M06-2X are better

than B3LYP to consider dispersion energy, in the present system, we found M06, M06-2X gave similar results for the (5+2) cycloaddition of homofuran and maleic anhydride (see the [Supplementary data](#), calculations were performed with the Gaussian 09 program).¹⁸ It was found that M06, M06-2X are not good for diradical species.¹⁹ Consequently, the (U)B3LYP functional is a good choice to study the present metal-free (5+2) cycloadditions.

3. Results and discussions

3.1. (5+2) Reaction of *N*-methoxycarbonyl-2,3-homopyrrole with *N*-phenylmaleimide

The (5+2) cycloaddition between *N*-methoxycarbonyl-2,3-homopyrrole and *N*-phenylmaleimide has been studied by modeling the reaction of *N*-methoxycarbonyl-2,3-homopyrrole (**1**) and *N*-hydrogen-maleimide (**2**). DFT calculations of all four pathways *a*–*d* indicated that the stepwise pathway *c* involving diradical intermediates is the most favored (Figs. 1–3 for the computed energy surfaces and structures). For the *endo* route in pathway *c* (*c-endo* pathway), the reaction starts from the formation of the C1–C7 bond, generating diradical intermediate **4a**. In the C–C bond forming transition state **TS3a**, homopyrrole becomes a planar structure and the C1–C5 bond has been cleaved. Homopyrrole in the transition state can be regarded as a 4-electron 1,5-dipole (or vinylazomethine ylide, and it can also be envisioned as a 1,3-dipole). This 1,5-dipole can only ‘exist’ in the transition state. Optimization of such 1,5-dipole structure taken from **TS3a** always led directly to the homopyrrole structure **1**. This 1,5-dipole, ‘existing only in the transition state’, can undergo concerted (5+2) reaction with dienophile (Fig. 3), however, this is not favored compared to the stepwise pathway *c* (Fig. 1). Generation of the diradical intermediate in *c-endo* pathway

requires an activation energy of 18.7 kcal/mol, which is lower than the concerted (5+2) pathway (via transition state **TS7a**) by about 3.0 kcal/mol. Generation of the diradical intermediate is endothermic by 5.4 kcal/mol. The ring-closure step to give the final (5+2) cycloadduct is easy, with an activation energy of 1.9 kcal/mol only. The (5+2) reaction via *c-endo* pathway is exothermic by 34.4 kcal/mol.

The *c-exo* pathway is very similar to the *c-endo* pathway, but is disfavored by 1.6 kcal/mol in the gas phase (this difference is increased to 1.7 kcal/mol in solution). This suggests that *endo* product is the favored one. This is consistent with the experiment.²⁰ The preference of *endo* product is due to the fact that **TS3a** is lower than **TS3b**. In **TS3a**, the dienophile is pointing away from the 1,5-dipole of homopyrrole, while in **TS3b**, the dienophile is experiencing the repulsion from homopyrrole framework. The *endo* product **6a** is less stable than *exo* product **6b** by 3.4 kcal/mol. This suggests that the preference of *c-endo* pathway of the (5+2) reaction is kinetically controlled and this preference is attributed to the steric reason in the first C–C bond formation transition states. It is interesting that, if the reaction takes place via pathway *a*, no *endo/exo* selectivity would be observed because *a-endo* and *a-exo* have very close activation energies (Fig. 3).

Pathways *b* and *d* are not favored compared with both pathways *a* and *c* by more than 9 kcal/mol (see the Supplementary data for the computed energy surfaces). Calculations found that generations of intermediate **IN1** (via pathway *b*) and **IN2** (via pathway *d*) are not favored kinetically compared to the generation of **IN3**. This is because the generated radicals or cations at C4 in **IN1** and at C1 in **IN2** are isolated species, while in **IN3**, the diradical or cation can be stabilized by conjugation via a larger conjugated system. Usually, it is hard to have the dienophile to directly attack the C1 atom of homopyrrole because this is an sp³ carbon without π orbitals. However, the easy generation of 1,5-dipole from homopyrrole

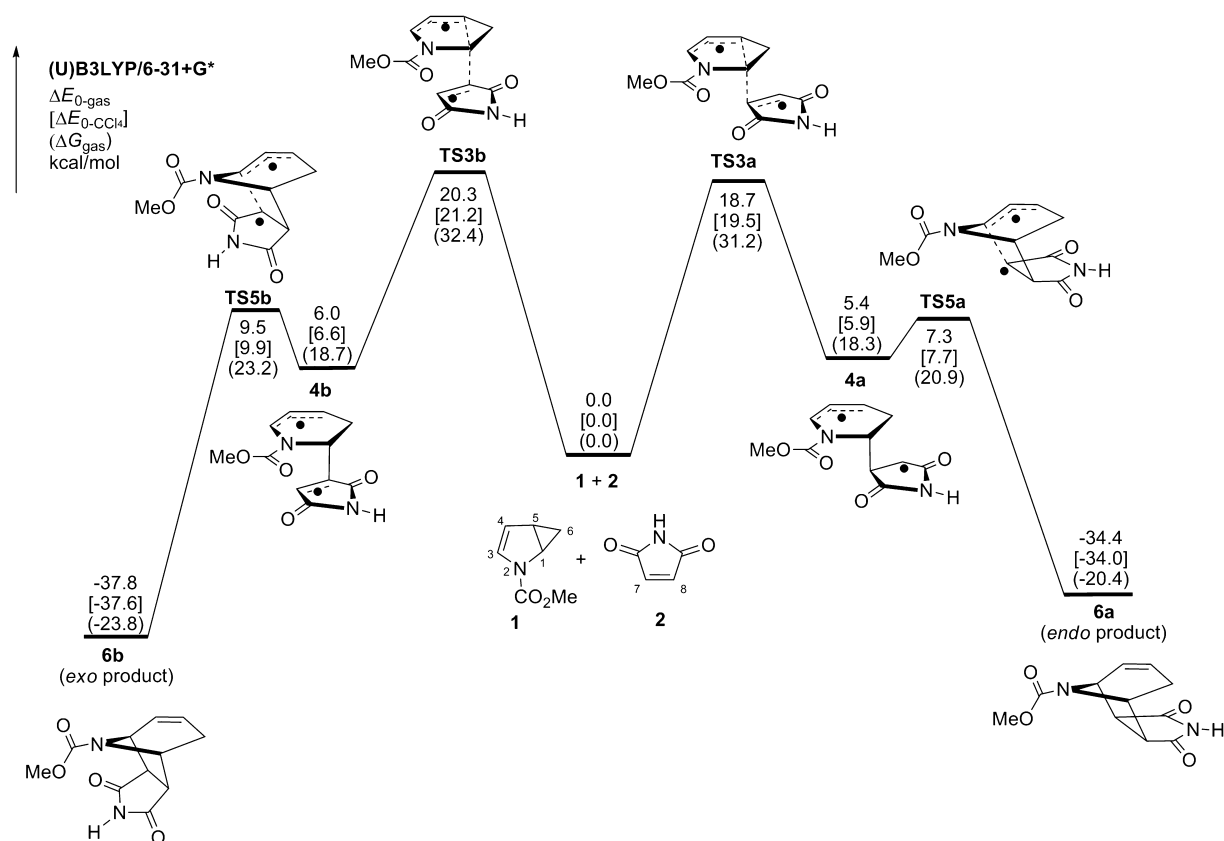


Fig. 1. The computed energy surface of (5+2) reaction between **1**+**2** (via the *c-endo* and *c-exo* pathways).

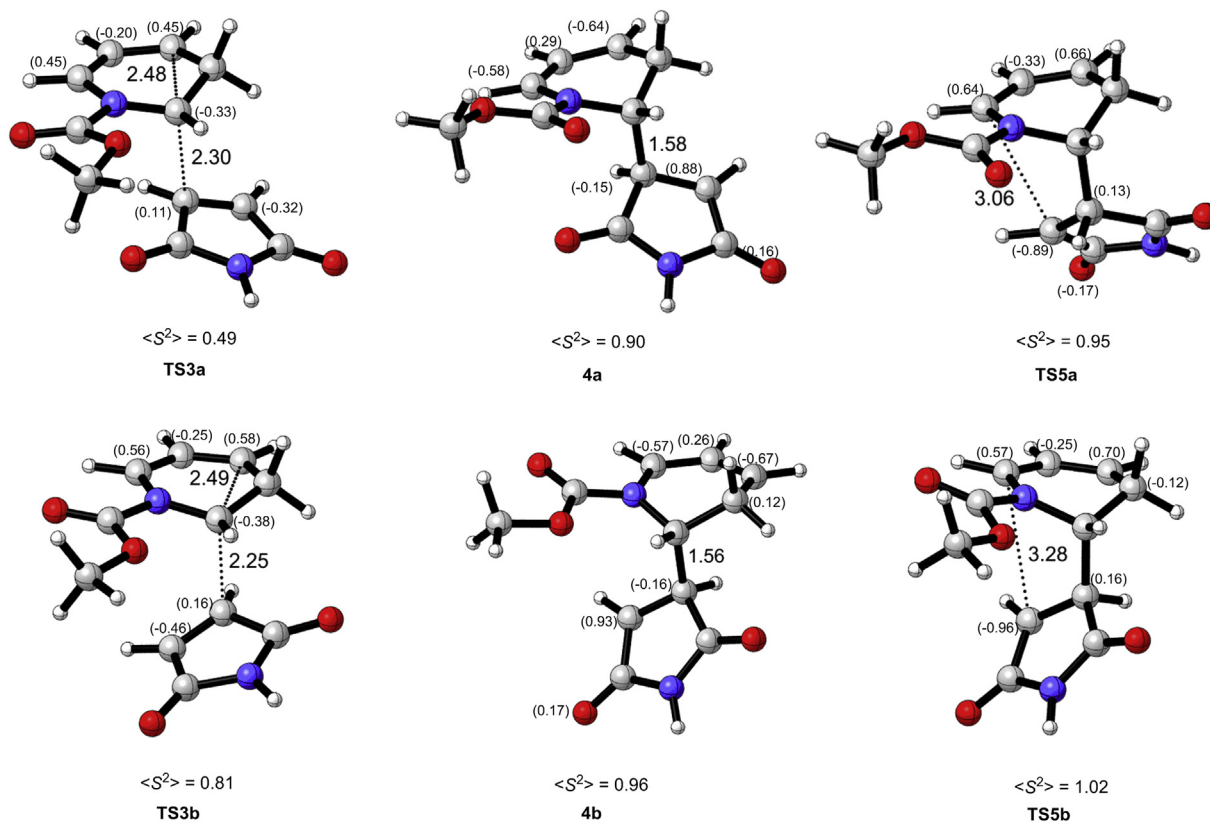


Fig. 2. The computed key transition states and intermediates in the (5+2) reaction of 1+2 (the *c-endo* and *c-exo* pathways). Distances are in Å and the values in the parentheses are the computed spin densities. The $\langle S^2 \rangle$ values are also given for the diradical species.

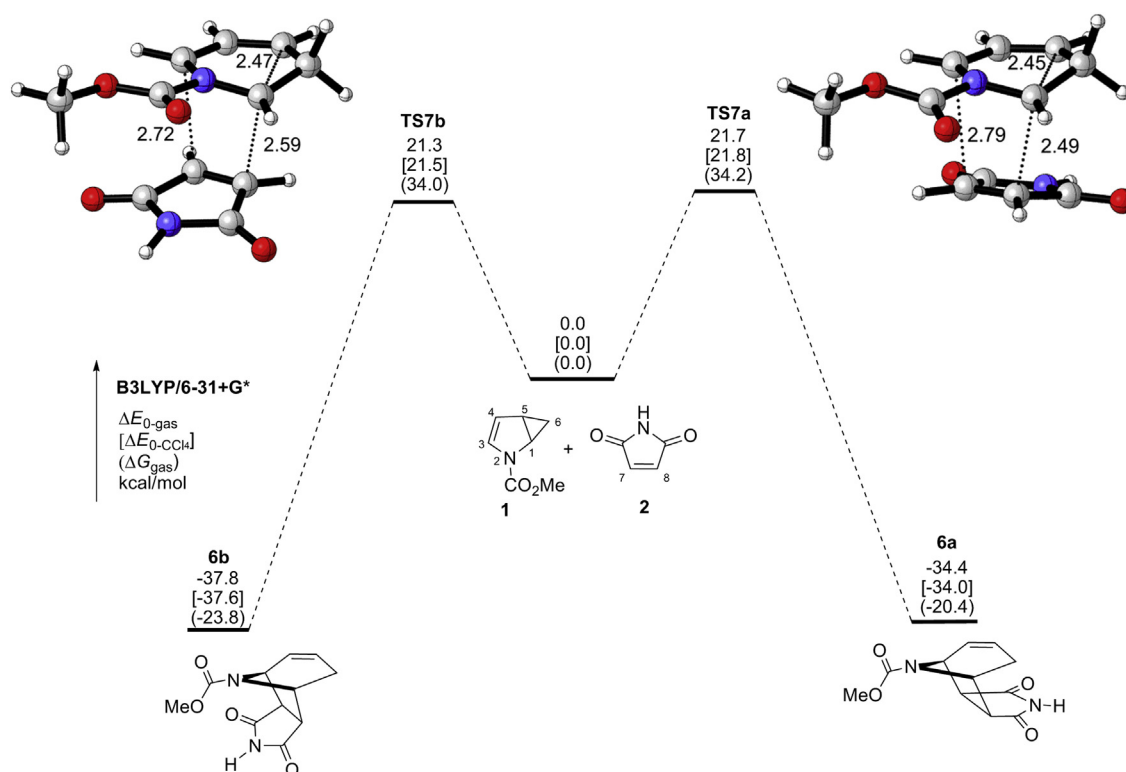


Fig. 3. The DFT computed energy surfaces of the (5+2) reaction between 1 and 2 via *a-endo* and *a-exo* pathways.

makes C1 in the transition state to become an sp^2 carbon, whose π orbital can be attacked by dienophile **2** to give (5+2) cycloadducts via pathway *c*.

The (5+2) reaction of *N*-methoxycarbonyl-2,3-homopyrrole **1** with DMAD also prefers to take place through pathway *c* and this is given in Fig. S3 of the Supplementary data.

A conclusion from the above study is that the (5+2) reactions of *N*-methoxycarbonyl-2,3-homopyrrole **1** with dienophiles favor to undergo the stepwise diradical pathway *c*, giving diradical intermediates. The concerted pathways between the existing-in-transition-state 1,5-dipole and dienophiles are disfavored.²¹ These conclusions obtained in the gas phase also hold in solution because the solvent effects on the reaction pathways are not very significantly different from those in the gas phase (see the computed (ΔE_{0-CCl_4}) in solution in Figs. 1 and 3).

3.2. (5+2) Reaction of homofuran with maleic anhydride

DFT calculations showed that the (5+2) cycloaddition between homofuran **8** and maleic anhydride **9** prefers to take place concertedly via pathway *a* to give both *endo* and *exo* (5+2) cycloadducts, while the competing diradical pathway *c* is marginally disfavored (by 1 kcal/mol) (Figs. 4 and 5). The computed activation energies for *endo* and *exo* pathways are 19.8 and 19.9 kcal/mol, respectively, suggesting that both cycloadducts are generated in the same amount. This is consistent with the experimental report.^{8,22–24} The (5+2) reaction is very exothermic by 37.3 and 40.5 kcal/mol, suggesting that this reaction is irreversible. In the concerted **TS10a** and **TS10b**, the breaking C1–C5 bonds are 2.42 and 2.43 Å, respectively, indicating that the C1–C5 bonds are completely broken (Wiberg bond index is 0.13). The concerted (5+2) reaction here suggests that homofuran in the transition state is distorted to give a distorted 1,5-dipole (vinyl oxonium ylide). Here homofuran also acts as a 1,5-dipole, ‘existing’ only in the transition state.

If the (5+2) reaction takes place via pathways *c-endo* and *c-exo*, the reaction would give *endo/exo* selectivity (Fig. 5). This is in contrast to the experiment. Therefore, this provides an evidence to support that (5+2) cycloaddition between homofuran **8** and maleic anhydride **9** prefers to take place concertedly.

Here we want to comment why (5+2) cycloaddition between homofuran **8** and maleic anhydride **9** prefers to take place concertedly (via pathways *a-endo* and *a-exo*) while the (5+2) cycloaddition between *N*-methoxycarbonyl-2,3-homopyrrole **1** and *N*-hydrogen-maleimide **2** occur via stepwise diradical pathways *c-endo* and *c-exo*. We think that the amide group in *N*-methoxycarbonyl-2,3-homopyrrole is better than oxygen in homofuran to stabilize diradical species (amide group is more electron-withdrawing than oxygen atom, also amide has additional resonance effect than oxygen to stabilize radical species).

3.3. Easy or difficult formation of ‘in-transition state’ 1,5-dipoles

The easy metal-free (5+2) reactions discussed above can be attributed to the easy generations of the 1,5-dipoles in the transition states. A distortion-interaction mode can be used to analyze these (here we only discuss the concerted pathway due to the small energy difference between the concerted and stepwise pathways).²⁵ The distortion energy for homopyrrole **1** in **TS7a** is 28.5 kcal/mol (the distortion energy of **2** in the transition state is 3.8 kcal/mol, Scheme 3). For homofuran, the distortion energy to generate the 1,5-dipole in the transition state in **TS10a** is 27.5 kcal/mol (the distortion energy of **9** is 2.5 kcal/mol). However, if bicyclo [3.1.0]hex-2-ene could undergo the (5+2) cycloadditions with dienophiles, the distortion energy of this VCP with a cleaved cyclopropane (distance between C1–C5 is 2.42 Å) is estimated to be 41.3 kcal/mol, suggesting that simple VCP is difficult to reach metal-free (5+2) cycloaddition transition states.²⁶

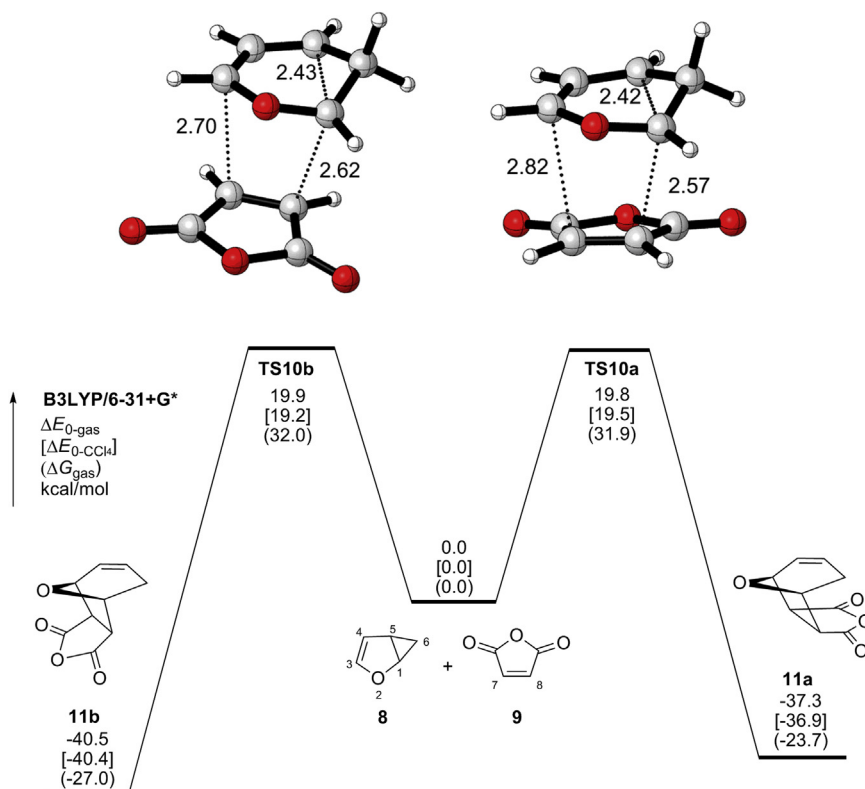


Fig. 4. The computed energy surfaces for the (5+2) reaction homofuran **8** and maleic anhydride **9** via *a-endo* and *a-exo* pathways.

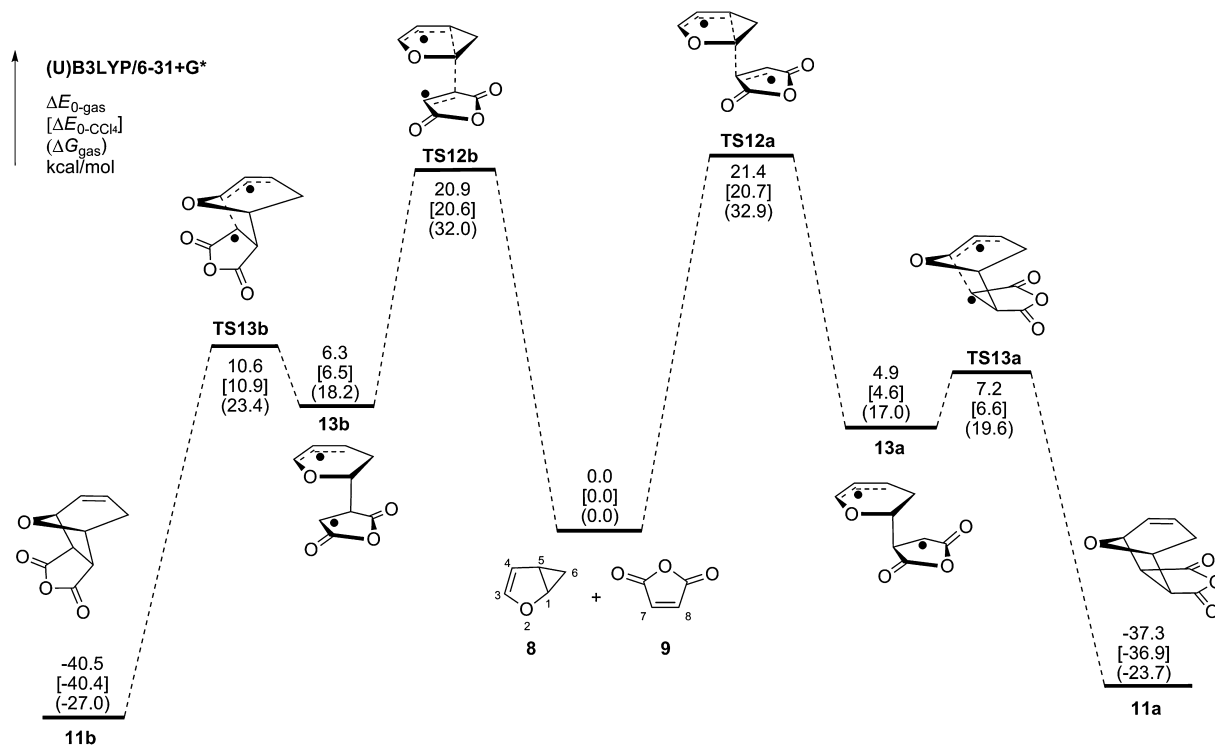
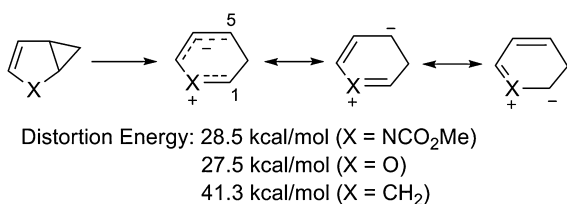


Fig. 5. The computed energy surfaces for the (5+2) reaction homofuran **8** and maleic anhydride **9** via *c-endo* and *c-exo* pathways.



Scheme 3. The distortion energies of 1,5-dipoles in transition states.

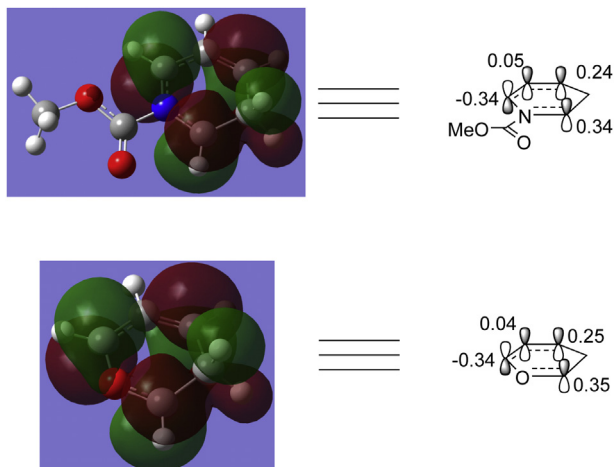


Fig. 6. The HOMOs of 1,5-dipoles for homopyrrole and homofuran computed by the HF/6-31G method (structures are taken from **TS7a** and **TS10a**, respectively). The orbital coefficients are the 2p_z parts of C atoms.

The highest occupied molecular orbitals (HOMOs) of these homopyrrole and homofuran 1,5-dipoles, existing in the transition states, are given in Fig. 6 to know the orbital shapes and their components (the geometries of these dipoles are from the concerted (5+2) transition states shown in Figs. 3 and 4). HOMOs of these dipoles show that C1 and C3 atoms (with close orbital coefficients) have similar nucleophilicities toward dienophiles and the preference of pathway *c* over pathway *d* in the (5+2) cycloadditions is due to the resonance effects discussed above.

4. Conclusion

In summary, through DFT study of the mechanism of metal-free (5+2) cycloadditions of homopyrrole and homofuran with dienophiles, we can conclude that (5+2) cycloaddition can be realized with special VCPs that are directly connected to heteroatoms, such as N, O.⁸ This is due to the easy generation of 4-electron 1,5-dipoles from homopyrrole and homofuran, which can exist in the transition states. The (5+2) cycloadditions of homopyrrole and homofuran with dienophiles can take place via either a concerted fashion (pathway *a*) or stepwise way involving diradical species (pathway *c*). Pathway *b* involving direct addition of dienophiles to the double bond of homopyrrole and homofuran is not favored compared to both pathways *a* and *c*. Pathway *d* is not favored either. The disfavored pathways *b* and *d* can be understood due to the corresponding transition states experience less resonance stabilizations compared to those in pathways *a* and *c*. Usually, the *endo/exo* selectivity will be observed if the (5+2) reaction takes place via pathway *c*, but no such selectivity can be observed if pathway *a* is favored. The present understanding will help the future development of other metal-free (5+2) and (*m*+*n*) cycloadditions. Further study of other metal-free (5+2) and (2+2) cycloadditions of vinylcyclopropanes and dienophiles are ongoing, which is aimed to know the reactivities of different dienophiles (PTAD, singlet

dioxygen, and tetracyanoethene) and the substituted vinylcyclopropanes.^{26,27}

Acknowledgements

We are indebted to generous financial support from the Natural Science Foundation of China (21072013).

Supplementary data

The DFT optimized structures and energies of all stationary points are included in the Supplementary data. Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.tet.2013.05.123>.

References and notes

- (a) Schore, N. E. *Chem. Rev.* **1988**, *88*, 1071; (b) Katritzky, A. R.; Dennis, N. *Chem. Rev.* **1989**, *89*, 827; (c) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49; (d) Bienaymé, H. *Angew. Chem., Int. Ed.* **1997**, *36*, 2670; (e) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863; (f) Varela, J. A.; Saa, C. *Chem. Rev.* **2003**, *103*, 3787; (g) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765; (h) Nájera, C.; Sansano, J. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6272.
- (a) Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167; (b) Kumar, A. *Chem. Rev.* **2001**, *101*, 1; (c) Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14179; (d) Takao, K.-i.; Munakata, R.; Tadano, K.-i. *Chem. Rev.* **2005**, *105*, 4779.
- (a) Hoffman, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1; (b) Mann, J. *Tetrahedron* **1986**, *42*, 4611; (c) Kuja, E.; Giguere, R. J. *Synth. Commun.* **1995**, *25*, 2105; (d) Harmata, M.; Carter, K. W. *Tetrahedron Lett.* **1997**, *38*, 7985.
- (a) Feldman, K. S. *Tetrahedron Lett.* **1983**, *24*, 5585; (b) Sammes, P. G.; Street, L. J. *J. Chem. Soc., Chem. Commun.* **1983**, 666; (c) Padwa, A.; Hornbuckle, S. F.; Fryxell, G. E.; Stull, P. D. *J. Org. Chem.* **1989**, *54*, 817; (d) Wender, P. A.; Lee, H. Y.; Wilhelm, R. S.; Williams, P. D. *J. Am. Chem. Soc.* **1989**, *111*, 8954.
- For recent reviews of (5+2) reactions: (a) Pellissier, H. *Adv. Synth. Catal.* **2011**, *353*, 189; (b) Ylijoki, K. E. O.; Stryker, J. M. *Chem. Rev.* **2013**, *113*, 2244.
- (a) Sarel, S.; Breuer, E. *J. Am. Chem. Soc.* **1959**, *81*, 6522; (b) Christl, M.; Brunn, E.; Lanzendorfer, F. *J. Am. Chem. Soc.* **1984**, *106*, 373; (c) Pasto, D. J.; Borchardt, J. K.; Fehlner, T. P.; Baney, H.; Schwartz, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 526; (d) Yamaoka, H.; Yamada, Y.; Ono, S.; Hanafusa, T. *Chem. Lett.* **1979**, 523.
- Fowler, F. W. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 135.
- Herges, U.; Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 594.
- (a) Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *117*, 4720; (b) Wender, P. A.; Husfeld, C. O.; Langkopf, E.; Love, J. A.; Pleuss, N. *Tetrahedron* **1998**, *54*, 7203; (c) Wender, P. A.; Sperandio, D. *J. Org. Chem.* **1998**, *63*, 4164; (d) Wender, P. A.; Husfeld, C. O.; Langkopf, E.; Love, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 1940; (e) Wender, P. A.; Riecko, R.; Fujii, M. *J. Am. Chem. Soc.* **1998**, *120*, 10976; (f) Wender, P. A.; Glorius, F.; Husfeld, C. O.; Langkopf, E.; Love, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 5348; (g) Wender, P. A.; Dyckman, A. J.; Husfeld, C. O.; Kadereit, D.; Love, J. A.; Rieck, H. *J. Am. Chem. Soc.* **1999**, *121*, 10442; (h) Wender, P. A.; Barzilay, C. M.; Dyckman, A. J. *J. Am. Chem. Soc.* **2001**, *123*, 179.
- (a) Trost, B. M.; Toste, F. D.; Shen, H. *J. Am. Chem. Soc.* **2000**, *122*, 3534; (b) Trost, B. M.; Shen, H. *Org. Lett.* **2000**, *2*, 2523; (c) Trost, B. M.; Shen, H. *Angew. Chem., Int. Ed.* **2001**, *40*, 2313; (d) Trost, B. M.; Shen, H. C.; Horne, D. B.; Toste, F. D.; Steinmetz, B. G.; Koradin, C. *Chem.—Eur. J.* **2005**, *11*, 2577; (e) Zuo, G.; Louie, J. *J. Am. Chem. Soc.* **2005**, *127*, 5798; (f) Fürstner, A.; Majima, K.; Martin, R.; Krause, H.; Kattnig, E.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 1992; (g) Inagaki, F.; Sugikubo, K.; Miyashita, Y.; Mukai, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 2206; (h) Jiao, L.; Ye, S.; Yu, Z.-X. *J. Am. Chem. Soc.* **2008**, *130*, 7178; (i) Feng, J.-J.; Zhang, J. *J. Am. Chem. Soc.* **2011**, *133*, 7304; (j) Shu, X.-Z.; Huang, S.; Shu, D.; Guzei, I. A.; Tang, W. *Angew. Chem., Int. Ed.* **2011**, *50*, 8153.
- For selected mechanistic studies of metal-catalyzed (5+2) reactions, Rh catalyst: (a) Yu, Z.-X.; Wender, P. A.; Houk, K. N. *J. Am. Chem. Soc.* **2004**, *126*, 9154; (b) Yu, Z.-X.; Cheong, P. H.-Y.; Liu, P.; Legault, C. Y.; Wender, P. A.; Houk, K. N. *J. Am. Chem. Soc.* **2008**, *130*, 2378; (c) Li, P.; Cheong, P. H.-Y.; Yu, Z.-X.; Wender, P. A.; Houk, K. N. *Angew. Chem., Int. Ed.* **2008**, *47*, 3939; (d) Liu, P.; Sirois, L. E.; Cheong, P. H.-Y.; Yu, Z.-X.; Hartung, I. V.; Rieck, H.; Wender, P. A.; Houk, K. N. *J. Am. Chem. Soc.* **2010**, *132*, 10127; (e) Xu, X.; Liu, P.; Lesser, A.; Sirois, L. E.; Wender, P. A.; Houk, K. N. *J. Am. Chem. Soc.* **2012**, *134*, 11012 Ni catalyst: (f) Hong, X.; Liu, P.; Houk, K. N. *J. Am. Chem. Soc.* **2013**, *135*, 1456 Ru catalyst: (g) Hong, X.; Trost, B. M.; Houk, K. N. *J. Am. Chem. Soc.* **2013**, *125*, 6588.
- Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, P.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Revision D.02*; Gaussian: Wallingford, CT, 2004.
- (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648; (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
- For selected references, see: (a) Goldstein, E.; Beno, B.; Houk, K. N. *J. Am. Chem. Soc.* **1996**, *118*, 6036; (b) Guner, V.; Khuong, K. S.; Leach, A. G.; Lee, P. S.; Bartberger, M. D.; Houk, K. N. *J. Phys. Chem. A* **2003**, *107*, 11445; (c) Yu, Z.-X.; Houk, K. N. *J. Am. Chem. Soc.* **2003**, *125*, 13825; (d) Yu, Z.-X.; Caramella, P.; Houk, K. N. *J. Am. Chem. Soc.* **2003**, *125*, 15420; (e) Xia, Y.; Liang, Y.; Chen, Y.; Wang, M.; Jiao, L.; Huang, F.; Liu, S.; Li, Y.; Yu, Z.-X. *J. Am. Chem. Soc.* **2007**, *129*, 3470; (f) Chen, Y.; Ye, S.; Jiao, L.; Liang, Y.; Sinha-Mahapatra, D. K.; Herndon, J. W.; Yu, Z.-X. *J. Am. Chem. Soc.* **2007**, *129*, 10773; (g) Siebert, M. R.; Osbourn, J. M.; Brummond, K. M.; Tantillo, D. J. *J. Am. Chem. Soc.* **2010**, *132*, 11952.
- Yamaguchi, K.; Jensen, F.; Dorigo, A.; Houk, K. N. *Chem. Phys. Lett.* **1988**, *149*, 537.
- (a) Barone, V.; Cossi, M. *J. Phys. Chem. A* **1998**, *102*, 1995; (b) Cossi, M.; Rega, N.; Scalmani, G.; Barone, V. *J. Comput. Chem.* **2003**, *24*, 669; (c) Takano, Y.; Houk, K. N. *J. Chem. Theory. Comput.* **2005**, *1*, 70.
- Here we only computed the reaction in CCl₄. Reaction (a) were carried out in CCl₄ while the solvents for reaction (b) and (c) were not mentioned in the original report.
- For M06, M06-2X methods, see: Zhao, Y.; Truhlar, D. G. *Acc. Chem. Res.* **2008**, *41*, 157.
- Zhao, Y.; Truhlar, D. G. *J. Phys. Chem. A* **2008**, *112*, 1095.
- In the original report, there was no indication about which cycloadducts are the major one. Calculations indicated that for (5+2) reaction a (Scheme 1), the *endo*-cycloadduct is still the favored one (see the Supplementary data for details).
- The (2+2) cycloaddition between enamine and dienophiles have been studied: Siebert, M. R.; Yudin, A. K.; Tantillo, D. J. *Org. Lett.* **2008**, *10*, 57. Here the (2+2) reaction between **1** and **2** is energetically disfavored compared to the (5+2) reaction (see the Supplementary data).
- The reported activation enthalpy for reaction c is about 14 kcal/mol, but the solvent used in the reaction was not mentioned. This difference between the DFT computed and experimentally measured activation energies could be caused by solvent effect and/or overestimation of the reaction barrier by the B3LYP method. M06, M06-2X gave similar results as B3LYP did (See Supplementary data).
- The computed activation energies by M06-2X are 20.6 and 21.4 kcal/mol, very close to those from B3LYP calculations. The computed activation energies, which are 8.7 and 9.4 kcal/mol, by MP2 are underestimated. All these energies are electronic energies without ZPE corrections in the gas phase.
- For MP2 method, see: Moller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 618.
- For discussions of distortion energies: (a) Kitaura, K.; Morokuma, K. *Int. J. Quantum Chem.* **1976**, *10*, 325; (b) Nagase, S.; Morokuma, K. *J. Am. Chem. Soc.* **1978**, *100*, 1666; (c) Ess, D. H.; Houk, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 10646; (d) Ess, D. H.; Houk, K. N. *J. Am. Chem. Soc.* **2008**, *130*, 10187; (e) Legault, C. Y.; Garcia, Y.; Merlic, C. A.; Houk, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 12664.
- Tetracyanoethylene (TCNE) can react with VCP (which does not have heteroatom directly connected to it) to give (5+2) cycloadducts, but these cycloadditions were proposed to proceed through (2+2) cycloaddition and rearrangement. See: (a) Sarel, S.; Felzenstein, A.; Yovell, J. *J. Chem. Soc., Chem. Commun.* **1973**, 859; (b) Sarel, S.; Felzenstein, A.; Yovell, J. *J. Chem. Soc., Chem. Commun.* **1974**, 753; (c) Felzenstein, A.; Sarel, S.; Yovell, J. *J. Chem. Soc., Chem. Commun.* **1975**, 918.
- Adam, W.; Griesbeck, A.; Klärner, F.-G.; Schröer, D. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 989.