Secondary Orbital Interactions Enhance the Reactivity of Alkynes in Diels–Alder Cycloadditions

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Supporting Information

ABSTRACT: We have investigated the inverse electron-demand Diels–Alder reactions of trans-cyclooctene (TCO) and eno-bicycle[6.1.0]nonyne (BCN) with a 1,2,4,5-tetrazine, a cyclopentadienone, and an ortho-benzoquinone. Tetrazines react significantly faster with TCO compared to BCN because the highest occupied molecular orbital (HOMO) of TCO is significantly higher in energy than the HOMO of BCN and there is less distortion of the tetrazine. Despite the different HOMO energies, TCO and BCN have similar reactivities toward cyclopentadienones, while BCN is significantly more reactive than TCO in the cycloaddition with ortho-benzoquinone. We find that the higher reactivity of BCN compared to TCO with ortho-benzoquinone is due to secondary orbital interactions of the BCN HOMO-1 with the diene LUMO.

The Diels–Alder (DA) reaction is a powerful synthetic tool that generates six-membered rings with remarkable regioselectivity and stereoselectivity.1 Using Frontier Molecular Orbital (FMO) theory, generalizations about the shapes and energies of the highest occupied (HOMO) and lowest unoccupied (LUMO) molecular orbitals can be applied to understand the reactivity, regioselectivity, and stereoselectivity of Diels–Alder reactions.2 Distortion energies are an additional factor that play an important role in DA cycloadditions.3,4 For example, cyclopentadiene and cycloheptadiene have similar FMO shapes and energies, but significantly different reactivities. The reactivities of these cyclic dienes are related to the energy required to geometrically deform the diene into the transition state geometry.5

Recently, Diels–Alder reactions have attracted attention as a tool for in vitro and in vivo labeling.6,7 These cycloadditions are bioorthogonal and require highly reactive and selective dienes and dienophiles that do not cross-react with biological nucleophiles. Few reactions satisfy these criteria, and the development of new bioorthogonal reactions is an active area of research.8–10 Scheme 1 shows the experimental second-order rate constants (M⁻¹ s⁻¹) for the Diels–Alder Reactions of 1, 2Ethyl, and 3 with TCO and BCN, and the Relative Rates of TCO and BCN with Each Diene. 11–15

Supporting Information

Scheme 1. Second-Order Rate Constants (M⁻¹ s⁻¹) for the Diels–Alder Reactions of 1, 2Ethyl, and 3 with TCO and BCN, and the Relative Rates of TCO and BCN with Each Diene

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these bioorthogonal reactions range from 12 to 18 kcal/mol. In agreement with experimental results, the computed rate constants predict that 1 will react 440 times faster with TCO than BCN*, that 2Methyl has similar reactivity toward TCO and BCN*, and that 3 will react with BCN* 440 times faster than with TCO. These results are in reasonable agreement with the experimental results described earlier. Calculations using the implicit solvent model SMD show the same trends as obtained in gas phase and are provided in the Supporting Information.

1, 2Methyl, and 3 are highly electron-deficient dienes that react with the electron-rich dienophiles TCO and BCN* through an inverse electron-demand DA mechanism. The primary orbital interactions involve the HOMO of TCO or BCN* interacting with the LUMO of 1, 2Methyl or 3. The HOMOs of TCO and BCN* and the LUMOs of 1–3 are shown in Figure 2. The HOMO energies of TCO and BCN* are −9.0 and −9.6 eV, respectively. With a higher lying HOMO, the strength of the primary FMO interactions with TCO are more favorable than with BCN*, and the primary FMO interactions predict that TCO should be more reactive than BCN* in inverse electron-demand Diels–Alder reactions.

To understand the origin of the differences in the Diels–Alder reactivities of TCO and BCN* toward 1, 2Methyl, and 3, we performed a distortion/interaction analysis.3 Within this analysis the energy of the system along the reaction coordinate gets dissected into two contributing factors. The distortion energy $\Delta E_{\text{dist}}$ is the energy required to geometrically deform the ground state geometries of the reactants. The interaction energy $\Delta E_{\text{int}}$ represents the energy of the interactions that occur between the distorted reactants. These include the orbital, electrostatic, and steric interactions. The distortion/interaction analysis was performed along the IRC defined by the distance of the shortest forming carbon–carbon bond from

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**Scheme 2. Structures Used in the Computational Study**

| TCO | BCN* | 1 | 2Methyl | 3 |
|-----|------|---|---------|---|

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**Figure 1.** Transition state structures, Gibbs activation free energies, and predicted relative reaction rates for the Diels–Alder reactions of 1, 2Methyl, and 3 with TCO and BCN*. Bond lengths are reported in Å and energies are reported in kcal/mol.

**Figure 2.** HOMOs of TCO and BCN*, HOMO-1 of BCN*, and LUMOs of 1, 2Methyl, and 3 generated with isovalue of 0.04. Molecular orbital energies are provided in electron volts (eV).
The results of the distortion/interaction analysis are shown in Figure 3. For the Diels–Alder reactions of TCO and BCN*, with 1, both the distortion and interaction energies are more favorable for the reaction with TCO. For reactions with diene $2_{\text{Methyl}}$, the distortion energies favor the reaction with TCO, but are offset by the interaction energies, which are more stabilizing with BCN*. This results in similar reactivities of TCO and BCN* toward $2_{\text{Methyl}}$. For the cycloaddition of TCO and BCN* with 3, the distortion energies along the IRC are nearly identical and the higher reactivity of BCN* toward 3 can be attributed to the more favorable interaction energies. Secondary orbital interactions are known to influence the reactivity and stereoselectivity of Diels–Alder reactions. The BCN* HOMO-1 is the nonreacting, out-of-plane π-bond and is nearly degenerate to the HOMO (Figure 2). Secondary orbital interactions involving overlap of the HOMO-1 of BCN* with the LUMOs of 1, $2_{\text{Methyl}}$ and 3 are illustrated in Figure 4 with a schematic orbital diagram. The $2_{\text{Methyl}}$-BCN* transition state is stabilized by secondary orbital interactions associated with the orbital overlap of the endo facing lobe of the HOMO-1 in BCN* with the LUMO of $2_{\text{Methyl}}$ at the C3 and C4 carbons, and between the exo facing lobe of the BCN* HOMO-1 with the C1 carbonyl carbon in the LUMO of $2_{\text{Methyl}}$. These secondary orbital interactions are also present in the transition state 3-BCN*, in addition to an interaction involving the overlap of the exo facing lobe of the BCN* HOMO-1 with the additional carbonyl carbon in the LUMO of 3. Although the HOMO-1 of BCN* is not a frontier molecular orbital, overlap of the BCN* HOMO-1 with the LUMOs of $2_{\text{Methyl}}$ and 3 at the transition state is significantly stabilizing and has an important effect on the Diels–Alder reactivities.

The LUMO density at the nitrogen atoms in 1 is significantly smaller compared to the carbon atoms in the LUMOs of $2_{\text{Methyl}}$ and 3, and the in-phase interaction of the BCN* HOMO-1 with the LUMO density across the N–N bond in 1 is counteracted by an out-of-phase interaction with the LUMO density across the opposite N–N bond. Because of the mismatched symmetry of the BCN* HOMO-1 and the LUMO of 1, the secondary orbital interactions result in no stabilization, and the relative strengths of the primary orbital interactions dictate reactivity, resulting in a less reactive BCN compared to TCO in tetrazene cycloadditions.

We have studied the inverse electron-demand Diels–Alder reactions of BCN and TCO toward 1, $2_{\text{Methyl}}$, and 3 and rationalize why BCN, despite having a lower HOMO energy compared to TCO, shows similar reactivity toward $2_{\text{Methyl}}$ and is even more reactive than TCO toward 3. Secondary orbital interactions between the HOMO-1 of alkynes and the LUMOs of dienes like $2_{\text{Methyl}}$ and 3 significantly stabilize the transition state and promote reactivity. The stabilization from the secondary orbital interactions in the DA reactions of $2_{\text{Methyl}}$ with BCN results in the similar reactivities of BCN and TCO. The additional carbonyl group in 3 further strengthens the secondary orbital interactions between the HOMO-1 of BCN and the LUMO of 3. This additional stabilization results in 3 being more reactive toward BCN than TCO. Diels–Alder reactions of alkynes play an important role in bioorthogonal chemistry, and secondary orbital interactions of the alkyne HOMO-1 should be considered in the development of new bioorthogonal reactions.
REFERENCES

(1) Nicolau, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. The Diels-Alder Reaction in Total Synthesis. Angew. Chem., Int. Ed. 2002, 41 (10), 1668–1698.

(2) Houk, K. N. Frontier Molecular Orbital Theory of Cycloaddition Reactions. Acc. Chem. Res. 1975, 8 (11), 361–369.

(3) Bickelhaupt, F. M.; Houk, K. N. Analyzing Reaction Rates with the Distortion/Interaction-Activation Strain Model. Angew. Chem., Int. Ed. 2017, 56 (34), 10070–10086.

(4) Liu, F.; Liang, Y.; Houk, K. N. Bioorthogonal Cycloadditions: Computational Analysis with the Distortion/Interaction Model and Predictions of Reactivities. Acc. Chem. Res. 2017, 50 (9), 2297–2308.

(5) Levandowski, B. J.; Houk, K. N. Theoretical Analysis of Reactivity Patterns in Diels-Alder Reactions of Cyclopentadiene, Cyclohexadiene, and Cycloheptadiene with Symmetrical and Unsymmetrical Dienophiles. J. Org. Chem. 2015, 80 (7), 3530–3537.

(6) Oliveira, B. L.; Guo, Z.; Bernardes, G. J. L. Inverse Electron Demand Diels-Alder Reactions in Chemical Biology. Chem. Soc. Rev. 2017, 46 (16), 4895–4950.

(7) Wu, H.; Devaraj, N. K. Inverse Electron-Demand Diels-Alder Bioorthogonal Reactions. Top. Curr. Chem. 2016, 374 (1), 3.

(8) Row, R. D.; Prescher, J. A. Constructing New Bioorthogonal Reagents and Reactions. Acc. Chem. Res. 2018, 51 (5), 1073–1081.

(9) Devaraj, N. K. The Future of Bioorthogonal Chemistry. ACS Cent. Sci. 2018, 4 (8), 952–959.

(10) Albada, B. Orthogonal, Dual Protein Labelling by Tandem Cycloadditions. J. Am. Chem. Soc. 2014, 136 (23), 7338–7341.

(11) Blackman, M. L.; Royzen, M.; Fox, J. M. Tetrazine Ligation: Fast Bioconjugation Based on Inverse-Electron-Demand Diels-Alder Reactivity. J. Am. Chem. Soc. 2008, 130 (41), 13518–13519.

(12) Wang, D.; Chen, W.; Zheng, Y.; Dai, C.; Wang, K.; Ke, B.; Wang, B. 3,6-Substituted-1,2,4,5-Tetrazines: Tuning Reaction Rates for Staged Labeling Applications. Org. Biomol. Chem. 2014, 12 (23), 3950–3955.

(13) Chen, W.; Wang, D.; Dai, C.; Hamelberg, D.; Wang, B. Clicking 1,2,4,5-Tetrazine and Cyclooctynes with Tunable Reaction Rates. Chem. Commun. 2012, 48 (12), 1736–1738.

(14) Liu, F.; Liang, Y.; Houk, K. N. Theoretical Elucidation of the Origins of Substituent and Strain Effects on the Rates of Diels–Alder Reactions of 1,2,4,5-Tetrazines. J. Am. Chem. Soc. 2014, 136 (32), 11483–11493.

(15) Bruins, J. J.; Blanco-Ania, D.; van der Doef, V.; van Delft, F. L.; Albada, B. Orthogonal, Dual Protein Labelling by Tandem Cycloaddition of Strained Alkenes and Alkynes to Ortho-Quinones and Azides. Chem. Commun. 2018, 54 (53), 7338–7341.

(16) Zhao, Y.; Truhlar, D. G. The M06 Suite of Density Functionals for Main Group Thermochemistry, Thermochemical Kinetics, Noncovalent Interactions, Excited States, and Transition Elements: Two New Functionals and Systematic Testing of Four M06-Class Functionals and 12 Other Functionals. Theor. Chem. Acc. 2008, 120 (1–3), 215–241.

(17) Wannere, C. S.; Paul, A.; Herges, R.; Houk, K. N.; Schaefer, H. F., 3rd; von Ragué Schleyer, P. The Existence of Secondary Orbital Interactions. J. Comput. Chem. 2007, 28 (1), 344–361.

(18) Levandowski, B. J.; Houk, K. N. Hyperconjugative, Secondary Orbital, Electrostatic, and Steric Effects on the Reactivities and Endo and Exo Stereoselectivities of Cyclopropene Diels-Alder Reactions. J. Am. Chem. Soc. 2016, 138 (51), 16731–16736.

(19) Levandowski, B. J.; Hamlin, T. A.; Bickelhaupt, F. M.; Houk, K. N. Role of Orbital Interactions and Activation Strain (Distortion Energies) on Reactivities in the Normal and Inverse Electron-Demand Cycloadditions of Strained and Unstrained Cycloalkenes. J. Org. Chem. 2017, 82 (16), 8668–8675.

(20) Levandowski, B. J.; Hamlin, T. A.; Helgeson, R. C.; Bickelhaupt, F. M.; Houk, K. N. Origins of the Endo and Exo Selectivities in Cyclopropenone, Iminocyclopropene, and Triafulvene Diels-Alder Cycloadditions. J. Org. Chem. 2018, 83 (6), 3164–3170.

(21) Lemal, D. M.; Sang, D.; Ramanathan, S. O-Fluoranil: Stereochromy and Mechanism of Its Diels-Alder Reactions. J. Org. Chem. 2009, 74 (20), 7804–7811.