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Charge redistribution in the SpnF-catalyzed Diels–Alder reaction

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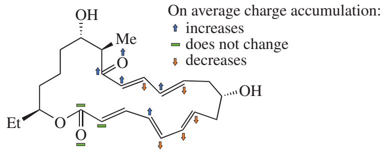
Investigation of charge delocalization (redistribution) in a SpnF-catalyzed reaction that proceeds through overlapping Diels–Alder and bis-pericyclic mechanisms has shown that it is better represented as a nonpolar cycloaddition rather than a cationic rearrangement.



Specific charge redistribution upon transition from substrate to transition state

Spinosin A is an effective green insecticide,[1] whose biosynthesis involves a transannular Diels–Alder-like cyclization catalyzed by the SpnF enzyme.[2] It is remarkable since it was the first discovered natural enzyme catalyzing solely the cycloaddition step, which is unlikely to proceed in a classic enzymatic way, *i.e.*, *via* splitting a reaction into several ones with smaller barriers.[3]

Several routes for the above cyclization were proposed and studied by quantum-chemical[3–6] and kinetic isotope effect[7] approaches. Hess Jr. and Smentek have studied[8] the cyclization of truncated **1** without five aliphatic ring atoms by DFT and MP2 calculations. They have examined NPA[8] charges rearrangement and concluded, that SpnF catalyzes a concerted, highly asynchronous Diels–Alder reaction by folding the substrate into the proper conformation and lowering its activation energy by stabilization of the highly polarized TS structure.[4] Gordeev and Ananikov have investigated[3] influence of substitutions, Mulliken charge delocalization,[9] hydrogen bonding and molecular contraction on the activation energy of the title reaction. They concluded that charge delocalization is insignificant and the main role of SpnF consists in contraction of the substrate. Finally, Patel *et al.* have shown[5] by means of DFT molecular dynamics that the title reaction can proceed through a bis-pericyclic TS (BPC), which can eventually either directly lead to **2**, or to [6+4] cyclization product, which undergoes the Cope rearrangement resulting in product **2** (Figure 1). This path cannot be well described within the transition state theory, which assumes a one-to-one relationship between TSs and products. Thus, it was proposed[5] that the enzyme controls the reaction *via* 'nonstatistical dynamical effects'.

More recently, we studied[6] this reaction by means of an exhaustive search for all possible transition state conformations of the four proposed transition state types: Diels–Alder[2] (DA), bis-pericyclic[5] (BPC), biradical[7] (BR) and alternative Diels–Alder[6] (altDA) (Figure 1). We found that only DA and BPC transition states have satisfactorily low reaction barriers. While DA transition states are more numerous, BPC transition states tend to have lower energies, and the application of the Curtin–Hammett principle[10] shows that this reaction mostly (83–91%,

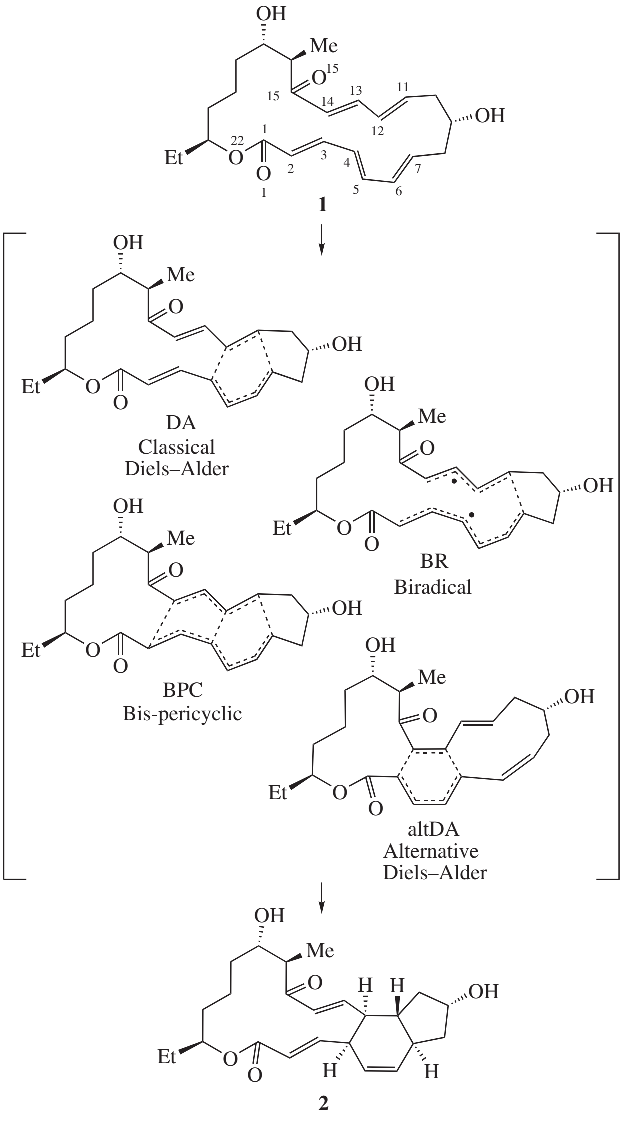


Figure 1 The SpnF-catalyzed reaction.[6]

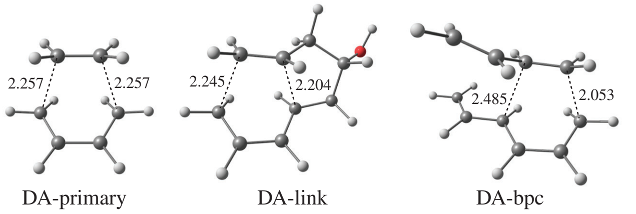


Figure 2 Optimized geometries [M06-2X/6-31+G(d) PCM(H_2O)] of the three reference systems. Lengths of forming bonds are given in Å.

depending on the DFT functional used) proceeds through BPC transition states.

To distinguish the BPC transition states from the DA ones, we used the Quantum Theory of Atoms in Molecules (QTAIM),[11] which allowed us to detect forming bond paths between atoms C^2 and C^{14} in some TSs, which were further classified as BPC ones (see ref. 6 for details). In addition to bond paths, the QTAIM theory provides atomic charges $q(\Omega)$, which are defined as the space integrals of electron density over respective atomic basins. They have been widely used for studying various electronic effects[12,13] and justified the recent discovery of the first supramolecular stereoelectronic effect.[14]

Charge polarization (redistribution) is known to play a significant role in enzymatic catalysis[15] and to accelerate bond formation in the Diels–Alder reaction.[16] In ref. 2, it was proposed, that the title reaction can proceed either as a pericyclic Diels–Alder reaction, or as a cationic rearrangement with a significant charge redistribution in the TS. Previous assessments of this conundrum using different methods led to the opposite conclusions.[3,4] Here, we studied QTAIM atomic charges redistribution upon a transition from **1** to corresponding DA or BPC TSs. We also compared them to QTAIM charge redistributions taking place in three reference systems: (1) the simplest Diels–Alder reaction between butadiene and ethylene (DA-primary), (2) the title reaction truncated to the diene and ene connected with a three-atomic link (DA-link) and (3) the simplest bis-pericyclic reaction between hexatriene and butadiene (DA-bpc) (Figure 2).

All geometries were used as obtained in our previous work, *i.e.*, optimized at M06-2X[17]/6-31+G(d)[18] level of theory with PCM[19](H_2O) solvation model. The same level of theory was used to optimize the reference systems; the initial structure guesses for them were obtained with our recent methodology.[20] For QTAIM charge redistribution analysis, we used both M06-2X and B3LYP[21] electron densities calculated on the M06-2X structures. B3LYP was chosen as a widely accepted standard for electron density studies,[22] which was also shown to produce accurate electron densities.[23,24] The QTAIM analysis was performed in the AIMAll[25] program package using default settings.

The results of M06-2x and B3LYP electron density analyses are almost identical (Figure 3) presumably because of the relatively small and stiff basis set; thus, we used M06-2x values below. Due to the known QTAIM difficulties with weak bonding in ring systems[26] and the absence of a sharp border between DA and BPC transition states,[6] the attribution of TSs to one of them is ambiguous; therefore, we will not consider them separately in the following discussion. The found changes of atomic charges from substrate to TS [denoted as $\Delta q(\Omega)$] are presented in Figure 3 by violin plots showing the distributions of $\Delta q(\Omega)$ for the title reaction and by points showing the values for corresponding atoms in the three reference structures. The positive direction in Figure 3 corresponds to a gain in electron population by a given atom in TS.

As follows from Figure 3, the O^1 atom has a highly conservative nearly-zero charge redistribution, while other atoms show a broad range of $\Delta q(\Omega)$ values. Note that atoms C^2, C^4, C^7, C^{11}, C^{12} and C^{14} have wide distributions of $\Delta q(\Omega)$ because they participate in forming bonds; therefore, the environment of an atom varies sharply between different TSs. The carbonyl atoms C^1 and C^{15} show even wider distributions probably resulting from their high involvement in π-conjugation, which changes differently in transition states depending on their type. Overall, atoms C^1, O^1 and C^2 have no preferred direction of charge flow, and atoms C^3, C^5, C^6, C^7, C^{11} and C^{13} usually lose electrons upon transition to TS and the rest atoms generally gain them.

It is widely known that, upon transition from sp^2 to sp^3, carbon becomes less electronegative and its electron population decreases. Charge redistribution analysis of DA-primary and DA-link showed that carbon atoms, which form new bonds, indeed, become more positive in TSs, while it is not true for both the title reaction and DA-bpc. In these, atoms C^2, C^4, C^{12} and C^{14} become more negative, whereas atoms C^7 and C^{11} lose more electrons compared to DA-primary and DA-link. This correlates with the lengths of forming bonds shown in Figure 2. Notably, the O^{15} atom always gains some electrons in transition states.

However, a positive correlation between the charge depletion of the C^5–C^6–C^7–C^{11} fragment and the relative activation free energy (Figure 4) suggests that, in agreement with the previous mechanism studied,[3] the polarization of the TS (visible as a charge redistribution) is unfavorable: TSs with higher net charge depletion on the C^5–C^6–C^7–C^{11} fragment tend to have higher

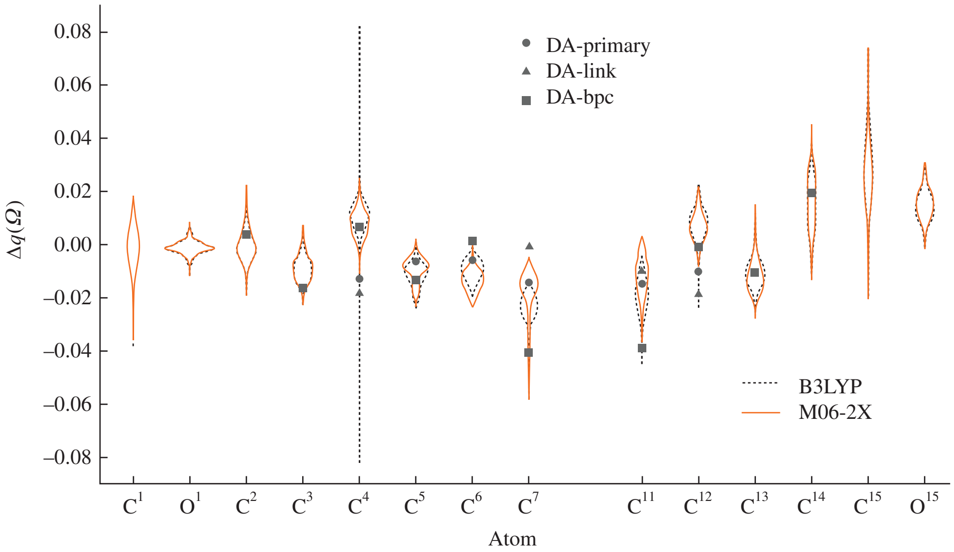


Figure 3 The violin plot of QTAIM charge redistributions [$\Delta q(\Omega) = q(\Omega)_{\mathbf{1}} - q(\Omega)_{TS}$; denotes the atomic basin].

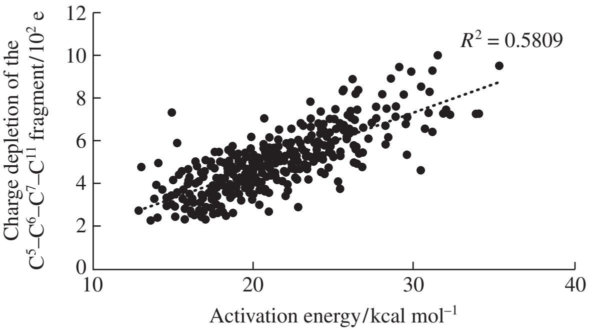


Figure 4 Charge depletion of the $C^5–C^6–C^7–C^{11}$ fragment upon transition from substrates to TSs *vs*. activation free energy.

activation energies despite the fact that calculations were performed using PCM with a water solvent, which should, in principle, favor more polar transition states. Nevertheless, a minor charge depletion in this region takes place even in TSs with the smallest barriers. A low overall correlation coefficient likely results from steric hindrance, which is present in all conformations in different proportions and significantly affects their free activation energies rather than charge redistributions.

In conclusion, we have found that the test reaction has a specific (but varying in magnitude) charge redistribution associated with it; the larger charge redistribution is, however, unfavorable and the reaction is better represented as a non-polar cycloaddition rather than a cationic rearrangement.

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References

1 B. L. Yano, D. M. Bond, M. N. Novilla, L. G. McFadden and M. J. Reasor, *Toxicol. Sci*., 2002, **65**, 288.
2 H. J. Kim, M. W. Ruszczycky, S. Choi, Y. Liu and H. Liu, *Nature*, 2011, **473**, 109.
3 E. G. Gordeev and V. P. Ananikov, *PLoS ONE*, 2015, **10**, e0119984.
4 B. A. Hess, Jr. and L. Smentek, *Org. Biomol. Chem*., 2012, **10**, 7503.
5 A. Patel, Z. Chen, Z. Yang, O. Gutiérrez, H. Liu, K. N. Houk and D. A. Singleton, *J. Am. Chem. Soc*., 2016, **138**, 3631.
6 M. G. Medvedev, A. A. Zeifman, F. N. Novikov, I. S. Bushmarinov, O. V. Stroganov, I. Y. Titov, G. G. Chilov and I. V. Svitanko, *J. Am. Chem. Soc*., 2017, **139**, 3942.
7 N. H. Kim, *PhD Thesis*, The University of Texas at Austin, 2013.
8 A. E. Reed, R. B. Weinstock and F. Weinhold, *J. Chem. Phys*., 1985, **83**, 735.
9 R. S. Mulliken, *J. Chem. Phys*., 1955, **23**, 1833.
10 J. I. Seeman, *J. Chem. Educ*., 1986, **63**, 42.
11 R. F. W. Bader, *Atoms in Molecules: A Quantum Theory*, Oxford University Press, Oxford, USA, 1994.
12 I. S. Bushmarinov, M. Yu. Antipin, V. R. Akhmetova, G. R. Nadyrgulova and K. A. Lyssenko, *J. Phys. Chem. A*, 2008, **112**, 5017.
13 I. S. Bushmarinov, I. V. Fedyanin, K. A. Lyssenko, V. L. Lapteva, S. A. Pisarev, V. A. Palyulin, N. S. Zefirov and M. Yu. Antipin, *J. Phys. Chem. A*, 2011, **115**, 12738.
14 M. G. Medvedev, I. S. Bushmarinov and K. A. Lyssenko, *Chem. Commun*., 2016, **52**, 6593.
15 A. Warshel, P. K. Sharma, M. Kato, Y. Xiang, H. Liu and M. H. M. Olsson, *Chem. Rev*., 2006, **106**, 3210.
16 A. C. Aragonès, N. L. Haworth, N. Darwish, S. Ciampi, N. J. Bloomfield, G. G. Wallace, I. Diez-Perez and M. L. Coote, *Nature*, 2016, **531**, 88.
17 Y. Zhao and D. G. Truhlar, *Theor. Chem. Acc*., 2007, **120**, 215.
18 W. J. Hehre, R. Ditchfield and J. A. Pople, *J. Chem. Phys*., 1972, **56**, 2257.
19 J. Tomasi, B. Mennucci and R. Cammi, *Chem. Rev*., 2005, **105**, 2999.
20 M. G. Medvedev, M. V. Panova, G. G. Chilov, I. S. Bushmarinov, F. N. Novikov, O. V. Stroganov, A. A. Zeifman and I. V. Svitanko, *Mendeleev Commun*., 2017, **27**, 224.
21 A. D. Becke, *J. Chem. Phys*., 1993, **98**, 5648.
22 C. F. Matta, *J. Comput. Chem*., 2014, **35**, 1165.
23 M. G. Medvedev, I. S. Bushmarinov, J. Sun, J. P. Perdew and K. A. Lyssenko, *Science*, 2017, **355**, 49.
24 K. R. Brorsen, Y. Yang, M. V. Pak and S. Hammes-Schiffer, *J. Phys. Chem. Lett*., 2017, **8**, 2076.
25 T. A. Keith, *AIMAll, Version 16.01.09*, TK Gristmill Software, Overland Park, KS, USA, 2015; http://aim.tkgristmill.com.
26 J. R. Lane, J. Contreras-García, J.-P. Piquemal, B. J. Miller and H. G. Kjaergaard, *J. Chem. Theory Comput*., 2013, **9**, 3263.
27 V. Sadovnichy, A. Tikhonravov, Vl. Voevodin and V. Opanasenko, in *Contemporary High Performance Computing: From Petascale toward Exascale*, ed. J. S. Vetter, CRC Press, Boca Raton, 2013, pp. 283–307.

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