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Quantifying Asymmetry in Concerted Reactions: Solvents Effect on a Diels−Alder Cycloaddition

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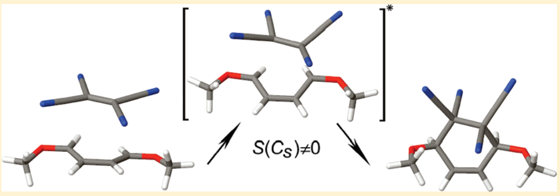
Supporting Information



ABSTRACT: We propose the notion that if *asymmetry* characterizes a concerted reaction, a quantitative treatment in terms of continuous symmetry can bridge the gap between the Woodward−Hoffmann (WH) rules, originally formulated for symmetry-idealized unsubstituted reactants, and the fact that these rules hold for a much wider scope of reactions. Instead of focusing on symmetry conservation along the minimum energy path, we suggest that the distortion with respect to the original expected symmetry must attain a certain minimal value, not necessarily zero. To demonstrate this approach we studied the effect of solvents on the symmetry and reactivity of the classical [4 + 2] Diels−Alder cycloaddition of (*E*,*E*)-1,4-dimethoxy-1,3-butadiene with tetracyanoethylene, revealing the predictive value of this approach. Calculations of the enthalpy of activation and the charge separation at the transition state (TS) predict increased reactivity with the polarity of the solvent. The symmetry measure is in excellent correlation with the enthalpy of activation and the charge separation at the TS, indicating the higher reactivity of the more symmetric case, thus quantifying the main teaching of the WH rules. The advantages of using a global structural parameter that takes into account *all* geometrical parameters, i.e., the symmetry measure, over specific ones (e.g., asynchronicity) are discussed.

INTRODUCTION

The original Woodward−Hoffmann (WH) rules[1] were formulated for concerted pericyclic reactions in terms of strict symmetry demands. For the Diels−Alder (DA) reaction, this implies that the two new bonds are formed in a synchronous manner, preserving a mirror symmetry that bisects the co-aligned olefin and diene. However, this ideal situation is rarely realized either because the olefin and diene do not approach each other in an ideally symmetric manner, or because the solvent induces symmetry distortions, or because substituents scramble that symmetry. WH related to that issue,[1−3] for instance, "A slight perturbation, say substitution by a methyl group, *may destroy total symmetry*, but cannot be expected to change dramatically the mechanism of a reaction."[1] We propose a more realistic way of addressing such situations: while WH regard the addition of a methyl as a potential for destruction of total symmetry, we suggest that substitution retains some of the original symmetry, where the word "some" relates to quantification of the degree of symmetry content. Such an approach allows one to establish quantitative relations between the degree of distortion from the ideal symmetry and reactivity.

Asymmetry of nuclei geometry in cycloadditions has been evaluated through a parameter termed "asynchronicity", defined as the difference between the lengths of the new forming bonds at the transition state (TS).[2−4] Its use to describe asymmetry is based on the assumption that distortion of the nuclei geometry is intimately related to a distortion of the reacting π orbitals. Yet these specific bond-length changes are only part of a multitude of structural changes that take place in the whole reacting molecules; practically *all* bond lengths and bond angles vary, and *all* are therefore relevant to the reaction analysis and can influence the symmetry of the orbitals. As the WH approach focuses on symmetry as the leading structural feature, we propose that a *symmetry measure* that takes into account all bond lengths and angles is inherently suitable for analyzing symmetry deviations in reactions governed by the WH rules. A measure of symmetry, the Continuous Symmetry Measure (CSM)[5−7] and the related measures of chirality[8] and of shape,[9−12] which were developed in recent years, have been applied successfully in many symmetry-related studies.[13−16] The measure spans from zero−the molecule is symmetric−to higher values for distorted symmetries (up to 100 in extreme cases). Examples of its use include correlations between tetrahedral symmetry measures and the allowedness of d-d spectral transitions[17] or between NMR chemical shifts[18,19] and more. The CSM method has also been applied to study chemical reactions.[20,21] Thus, in a recent study we applied the CSM to follow the reaction path of the *cis*−*trans* isomerization of diazene and its isotopomers[22] and developed the concept of *symmetry profile* of a reaction, a plot that shows the changes in symmetry along the intrinsic reaction coordinate (IRC).

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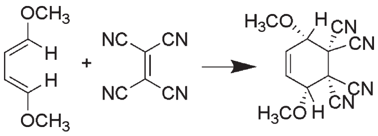
Scheme 1



The specific reaction that we selected in order to demonstrate the quantitative symmetry analysis and the correlations it provides, is the classical [4 + 2] cycloaddition of (*E*,*E*)-1,4-dimethoxy-1,3-butadiene (DMB) with tetracyanoethylene (TCNE), representing over 50 years of studies of cycloaddition reactions involving cyano-substituted ethylenes.[23−26] These studies have shown that DMB is a useful donor in DA reactions[24] and that substitution of ethylene by cyano groups dramatically increases the rate of various cycloaddition reactions, for instance, with cyclopentadiene or with 9,10-dimethylantracene.[26] Symmetry deviations in these reactions are due to two main effects: the substituents effects and the more subtle solvent effects, on which we selected to concentrate in this report. Solvent effects on hetero-DA reactions have been extensively reported in the literature,[27] showing, in general, linear correlations between various reaction properties (e.g., rate constants, *endo*/*exo* selectivity) and solvent characteristic parameters such as the acceptor number,[28] H-bond acidity,[29] and density.[30] Kiselev et al.[31−33] exemplified such solvent effects on the molar volume and the enthalpy of solution for several cycloaddition reactions involving TCNE. An interesting theoretical study by Yamabe et al.[2] showed that the DMB + TCNE reaction proceeds through an asymmetric TS if the reaction is carried out in methylene chloride, even though both the diene and the dienophile are substituted symmetrically. Such symmetry distortion does not occur when TCNE is replaced with (*E*,*E*)-1,2-dicyanoethylene or when TCNE reacts with unsubstituted butadiene. Asymmetry in cycloadditions of symmetrically substituted reactants is not uncommon, and Bachrach and White[3] attributed it to strain relief that tends to distort the structure by orbital interactions and mixing, an argument used also by Yamabe et al.[2]

Here we use the CSM approach as an analysis tool in order to explore the effect of solvents on the energy and stereochemistry of the concerted [4 + 2] DMB + TCNE cycloaddition (Scheme 1). We use this specific example in order to convey the following view: If asymmetry characterizes a concerted reaction, treatment in terms of continuous symmetry seems to be a natural way to bridge the gap between rules that were formulated originally for symmetry-idealized unsubstituted reactants and the fact that these rules hold for a much wider scope of reactions; instead of saying the system must retain symmetry, one can say that the CSM value with respect to the original expected symmetry must attain a certain minimal value, that is not necessarily zero.

COMPUTATIONAL METHODS

Quantum-Mechanical Calculations. These were performed with the Gaussian 09[34] suites of computational programs. All reactants, products, and transition states (TSs) were optimized at the modified Perdew−Wang 1-parameter model for kinetics (MPW1K) level, a hybrid density functional method developed by Truhlar and co-workers[35] with the 6-31G(d,p) basis set. The choice of the method and basis set follows the recommendations of Lynch et al.[35] and in particular those of Jones et al.,[26] who showed that compared with experimental results the MPW1K method outperforms both the B3LYP[36−38] and the BPW91[39,40] methods in reproducing the substitution effect on the activation barrier for other cycloaddition reactions involving TCNE. All optimization were followed by vibrational frequency calculations to verify that they are either minima or saddle points on the potential energy surface. The effect of solvent was explored with the polarizable continuum model (PCM) using the integral equation formalism variant (IEFPCM)[41−43] in which a set of overlapping spheres represents the solute cavity. The following 10 solvents were used: heptane, benzene, toluene, dibutylether, chloroform, acetic acid, dichloromethane, 1-pentanol, acetone, and ethanol. These solvents were chosen to sample a range of dielectric constants from ca. 2 for heptane to ca. 24 for ethanol. The full energy profile of the reaction along the minimum energy path between reactants and product was calculated using the intrinsic reaction coordinate (IRC)[44,45] method. All IRC calculations were verified by repeating them with a smaller step size.

A C_s-symmetry constrained geometry for the transition state was also computed in the gas phase. As reported previously by Yamabe et al.,[2] it was found to be a second-order saddle point. The nature of this point did not change even when very tight convergence criteria were applied or when other combinations of functionals and basis sets were used. Furthermore, using polar solvents, the nature of the C_s-symmetry constrained geometry became a third-order saddle point leading us to the conclusion that the true TS is indeed asymmetric.

To rule out a possible biradical mechanism stability, calculations of the wave function were performed on the transition state for all solvents and the gas phase. These calculations determine if the resulting structure is a local minimum, by allowing the wave function to become open-shell or reducing the symmetry of the orbitals if necessary.[46] Following the recommendations of Jones et al.,[26] transition states were also calculated using the Hartree−Fock[47] (HF) method with the 6-31G(d) basis set. However, these results showed instability of the wave function that was not corrected by using the unrestricted-HF (UHF) method. We believe this instability is due to the lack of electron correlation terms in the HF method that are crucial for the specific reaction. Since UHF calculations are known to be unreliable in the determination of activation bariers,[48] we continued our study based on the MPW1K/6-31G(d,p) results assuming the reaction is concerted in all solvents.

CSM Calculations. These calculations are based on finding the minimal distance between a given structure and the nearest structure that has the desired symmetry point group.[5−7,9,10] The algorithm is based on searching for structures with the desired symmetry and then selecting the one that has the minimal distance from the original structure, according to eq 1:

$$S(G) = 100 \times \min \frac{\sum_{k=1}^{N} |\mathbf{Q}_k - \mathbf{P}_k|^2}{\sum_{k=1}^{N} |\mathbf{Q}_k - \mathbf{Q}_0|^2} \qquad (1)$$

Here G is the desired symmetry point group. The original structure has N vertices with coordinates $\{\mathbf{Q}_k, k = 1, 2, ..., N\}$, $\mathbf{Q}_0$ being their center of mass. $\{\mathbf{P}_k, k = 1, 2, ..., N\}$ are the coordinates of the nearest structure with G symmetry. The denominator in eq 1 is a mean square size normalization factor, which is introduced to avoid size effects. The CSM defined in eq 1 is independent of the position, orientation, and size of the original structure. As mentioned above, the bounds of $S(G)$ are between 0 and 100. If a structure has the desired G-symmetry, then $S(G) = 0$ and the symmetry measure increases as it departs from G-symmetry.

RESULTS AND DISCUSSION

Symmetry Profiles and Energy Profiles. The TS for the concerted [4 + 2] DMB + TCNE cycloaddition in the gas phase is shown in Figure 1. For unsubstituted reactants, the WH rules predict conservation of symmetry with respect to a plane that bisects the bonds 1−2 and 9−10, perpendicular to the molecular plane. Figure 1 shows that in our case reflection symmetry does not exist for the TS of this reaction. In fact, as seen in Figure 2a, *this symmetry is never reached along the whole process* either for the gas phase (Figure 2a, left scale) or in solvents (Figure 2b; results for heptane and ethanol are shown representing the two extreme solvents in our study, all calculated at the MPW1K/6-31G(d,p) level). Figure 2 offers several observations: (i) The *symmetry profiles* of the reaction[22] reveal that the symmetry distortion is fairly constant from the initial alignment of the reactants, through the TS up to an IRC value of about 10 Bohr·amu$^{1/2}$. (ii) Beyond that value, where the product begins to assume its final shape, the distortion becomes even more pronounced due to the repulsion between the cyano groups. (iii) Symmetry changes and energy changes along the reaction coordinate follow roughly the same trends (Figure 2a); energy increases with increase in asymmetry, and decreases as the intermediates are closer to reflection symmetry. Similarly, (iv) The decrease in energy associated with the transition from the gas phase to heptane and to ethanol (which is in accordance with other studies involving cycloaddition of TCNE[31]) is paralleled by an increase in symmetry along the whole path (Figure 2b). Observations (iii) and (iv) are in line with the general teaching of WH that the more energy-favored reactions will be those that obey the symmetry rules in a stricter way; here we show it quantitatively. (v) In passing we note that this [4 + 2] reaction is chiral all along its path; we address this interesting issue in a separate report.

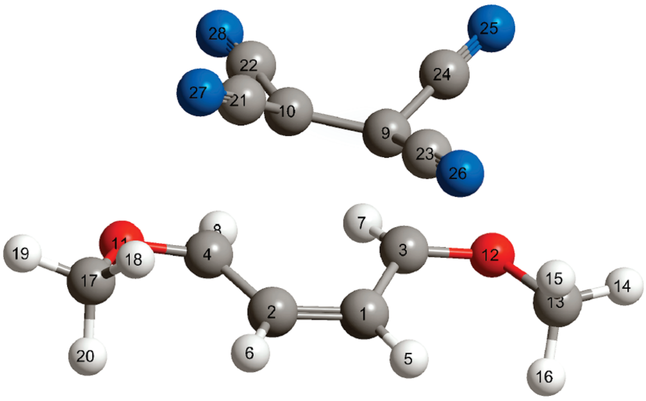


Figure 1. Transition state (TS) geometry calculated at the MPW1K/6-31G(d,p) level.

Next, let us follow the geometrical changes that hide behind the symmetry profile of Figure 2. The main observation (see the snapshots in Figure 2a) is that the out-of-plane twist of the cyano groups is the most notable contributor to the symmetry non-conservation along the IRC. At first, the two molecules get closer to each other in a way that slightly increases the distortion (TCNE loses its planarity). After the TS is reached, the new C−C bonds are created with a slight decrease in $S(C_s)$ (increase in symmetry) until a minimum point is achieved. At this point, the two new C−C bond lengths are almost at their final minimal values. After that point, the methoxy groups approach each other in an out-of-plane motion, the hydrogen atoms around the terminal carbon atoms rotate freely, and the cyano groups twist apart from each other, increasing the dihedral angle ($N_{28}-C_{10}-C_9-N_{26}$) from a value of 144.9° (gas phase) at the minimum point along the symmetry profile to a value of 171.5° (177.5° for the optimized product), with a steep increase in $S(C_s)$. We return below (the text that accompanies Figure 7) to further analysis of the structural changes that are associated with the symmetry changes, focusing there on the solvent effects on the TS and on various substructures.

We tested for possible sensitivity of these observations on the choice of the basis set by repeating the IRC calculation with the 6-31G(d) basis set for the gas phase. The results were a parallel energy profile predicting a change of 0.15 kcal/mol in the activation energy and 0.34 kcal/mol in the reaction energy and a symmetry profile identical to the one in Figure 2a. We thus continue our discussion based on the calculations at the MPW1K/6-31G(d,p) level.

Solvent Effects on the Symmetry of the Transition State, on the Activation Enthalpy, and on the Charge Separation. The content of mirror symmetry, $S(C_s)$, and the enthalpies of activation relative to a gauche conformer of DMB (Figure 3) were calculated for the gas phase and for the 10 solvents listed above. Figure 4a shows the MPW1K/6-31G(d,p) results for $S(C_s)$ at the TS as a function of the dielectric constant. As is evident from the plot, with increased polarity of the solvent, $S(C_s)$ decreases and the TS is closer to having reflection symmetry (ideally obeyed in the TS of the unsubstituted DA reaction). Remarkably, the decrease in $S(C_s)$ closely correlates with a decrease in the enthalpy of activation, (right scale of

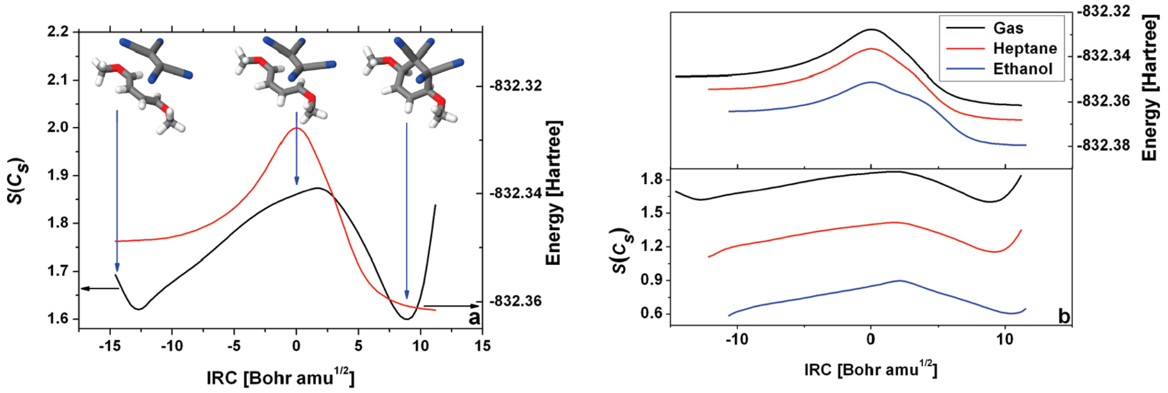


Figure 2. (a) The mirror-symmetry profile (black line, left scale) and the potential energy profile (red line, right scale) along the intrinsic reaction coordinate (IRC) of the [4 + 2] cycloaddition of (*E,E*)-1,4-dimethoxy-1,3-butadiene (DMB) with tetracyanoethylene (TCNE) for the gas phase. (b) Solvent effects on the symmetry profile (bottom) and energy profile (top).

Figure 4a; left scale in Figure 4b). It thus emerges that the symmetry measure of the TS points to the reactivity of the system: for solvents of higher polarity, the TS is less distorted and the enthalpy of activation is lower, leading one to predict faster reactions for the more polar solvents. In other words, this observation suggests that $S(C_s)$ can serve as a measure of relative reactivity. A similar correlation between the enthalpy of activation of the retro Diels–Alder reaction and the $S(C_s)$ at the TS was observed (Figure 4b, right scale).

Analysis of the effect of solvent on the amount of charge transferred from the diene to the dienophile at the TS, provides a possible explanation for this observation. Figure 5 presents the total charge on TCNE (Mulliken Population Analysis was used) as a function of $S(C_s)$ at the TS for the various solvents used in this study. It is clearly seen that increase in solvent polarity stabilizes a higher charge separation and that this stabilization is related to increase in the content of reflection symmetry. As we have seen above (snapshots of Figure 2a), the spatial orientation of the four cyano groups is the major carrier of the symmetry deviation in this reaction.

Comparison of the Symmetry Measure to the Asynchronicity of the Transition State. As mentioned in the Introduction, asynchronicity is a common descriptor of cycloaddition reaction mechanisms.[2,4,49,50] Comparison of $S(C_s)$ to this parameter is provided in Table 1 (the asynchronicity is based on the changes in the lengths of the new forming C···C bonds ($d_{9,3}$ and $d_{10,4}$, in Figure 1) and is defined as their difference). As is evident from the table, $d_{9,3}$ and $d_{10,4}$ are not equal, and the solvents affect only $d_{10,4}$ (it increases with polarity) and not $d_{9,3}$. We also recall here that the symmetry measure is based on the changes that *all* bond lengths and bond angles undergo. Figure 6 presents a comparison between $S(C_s)$ (left scale) and asynchronicity (right scale), both calculated at the TS, as a function of the dielectric constant of the solvent. It is seen that opposite trends, almost mirror imaging each other, are obtained. While $S(C_s)$ decreases with polarity (as described in the previous section), asynchronicity increases with the polarity. How can that be? It is

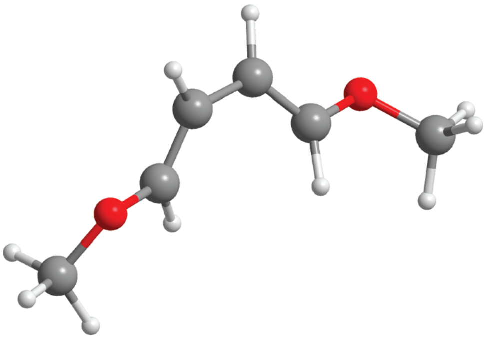


Figure 3. Gauche conformer of DMB.

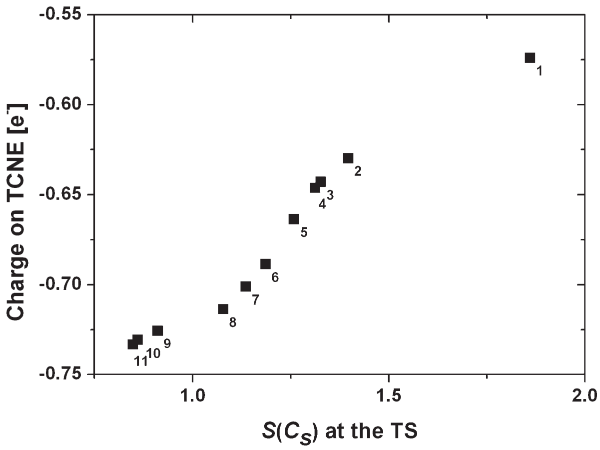


Figure 5. Charge on TCNE as a function of $S(C_s)$ at the transition state.

Table 1. Geometrical Parameters of the TS in different solvents, MPW1K/6-31G(d,p)

solvent (dielectric constant)[a]	$S(C_s)$	$d_{9,3}$ (nm)	$d_{10,4}$ (nm)	asynchronicity (nm)
gas phase (1.0000)	1.861	0.2022	0.2428	0.0406
heptane (1.9113)	1.397	0.2015	0.2465	0.0450
benzene (2.2706)	1.327	0.2014	0.2476	0.0462
toluene (2.3741)	1.313	0.2014	0.2479	0.0465
dibutylether (3.0473)	1.259	0.2014	0.2497	0.0483
chloroform (4.7113)	1.187	0.2015	0.2523	0.0508
acetic acid (6.2528)	1.137	0.2017	0.2535	0.0518
dichloromethane (8.9300)	1.079	0.2019	0.2548	0.0529
1-pentanol (15.1300)	0.911	0.2021	0.2558	0.0537
acetone (20.4930)	0.861	0.2022	0.2563	0.0541
ethanol (24.8520)	0.849	0.2023	0.2566	0.0543

[a] Dielectric constants are taken from the Gaussian user's reference.[34]

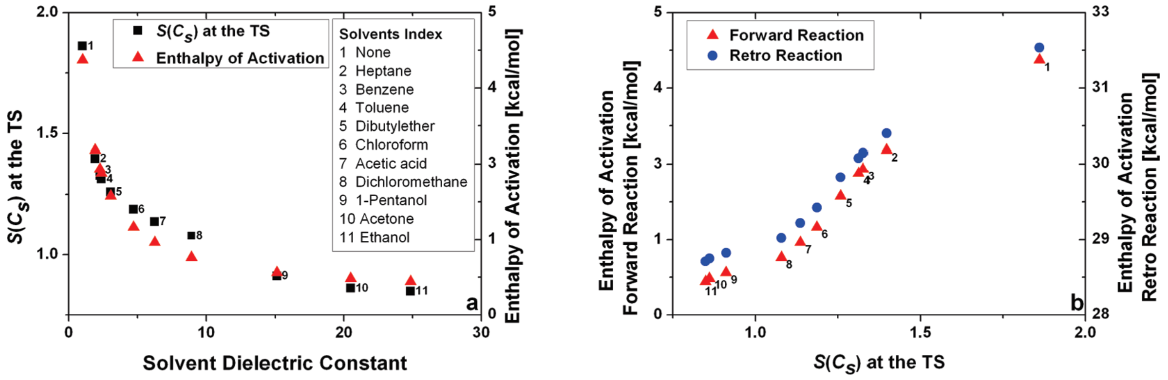


Figure 4. (a) The symmetry measure, $S(C_s)$ (left scale) and the enthalpy of activation (right scale) as a function of the dielectric constant of the solvent. (b) Enthalpy of activation of the forward and retro Diels–Alder reactions versus $S(C_s)$ at the transition state.

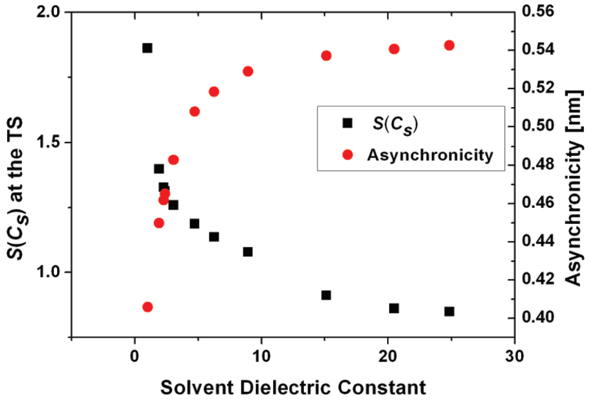


Figure 6. $S(C_s)$ at the TS (left scale) and asynchronicity of the TS (right scale) as a function of the dielectric constant of the solvent.

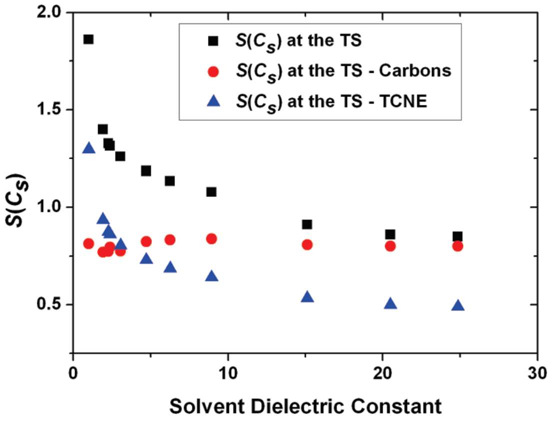


Figure 7. $S(C_s)$ at the TS for the whole structure (squares), the [4 + 2] carbon skeleton of the structure (atoms 1–4, 9, and 10) (circles), and the TCNE part of the structure (atoms 9, 10, and 21–28) (triangles).

an outcome of the fact that the distortion from the optimal symmetry is not dictated solely by the $d_{10,4}$ bond changes but by the full picture of structural changes, which we describe in the next section. We suggest that this is one of the indications (more are described below) that the CSM is a better analyzer of symmetry changes in concerted reactions. Using asynchronicity as a measure of asymmetry could have led to the false conclusion that the reactivity of this reaction increases with increased asymmetry. Indeed, based on asynchronicity/polarity correlation in the cycloaddition of cyclopenadiene with methylacrylate, Ruiz-López[4] predicted that the reaction coordinate in solution should be more asymmetric than in the gas phase, a conclusion that seems to be in need of reconsideration.

A somewhat different formula for asynchronicity was suggested by Contini et al.[51] and used later on by Legnani et al.[52] They defined asynchronicity as the difference between the ratios of the new forming bond lengths in the TS and the corresponding bond lengths in the product. In our case, this would lead to the expression $[d_{10,4}(\mathrm{TS})/d_{10,4}(\mathrm{prod}) - d_{9,3}(\mathrm{TS})/d_{9,3}(\mathrm{prod})]$. However, when applied to our data, similar results to the traditional definition of asynchronicity were obtained, both quantitatively and qualitatively (not shown here).

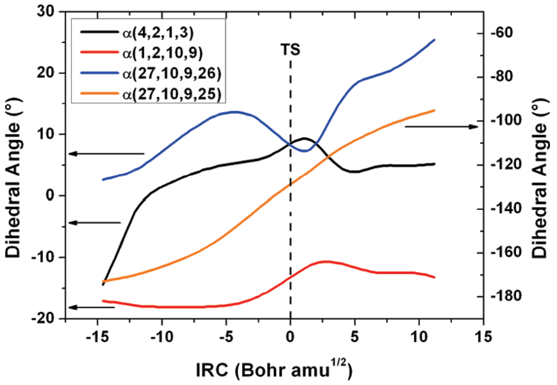


Figure 8. Changes of several dihedral angles along the IRC (see Figure 1 for atoms numbers). Black: the butadiene carbon skeleton. Red: the orientation of the ethylene skeleton relative to the butadiene skeleton. Blue: the dihedral angle between two CN groups representing the twist motion. Orange (right scale): the dihedral angle between CN groups representing the folding motion. The dashed vertical line represents the location of the TS.

Subgroup Analysis of the Symmetry at the Transition States. Let us now see the information obtained by comparing the solvent dependency of $S(C_s)$ of the full structure (Figure 7, squares) to the $S(C_s)$ values of two subgroups, the [4 + 2] carbon skeleton of the structure (atoms 1–4, 9–10 (see Figure 1), Figure 7, circles) and the TCNE part of the structure (atoms 9–10, 21–28 (see Figure 1), Figure 7, triangles). It is immediately evident that the "burden" of the symmetry distortion is mainly due to the TCNE part; its trend parallels that of the full structure, whereas the [1–4, 9–10] carbon skeleton remains practically unaffected. In other words, looking only at that carbons subgroup (as the asynchronicity measure does) may cause one to miss solvent effects on this symmetry-dictated DA reaction. Moreover, the major source of asymmetry of the TS is the substituents, while the solvents play a minor role. The asymmetry of the DMB part of the TS structure (atoms 1–8, 12–20) was also calculated (not shown) indicating a slight increase of $S(C_s)$ with polarity of the solvent, but with values which are smaller by a factor of 10 and can therefore be ignored. Thus, in accordance with the WH assumptions, the lack of perfect symmetry does not prevent the creation of the cycloadduct; the symmetry analysis contributes a quantitative aspect to that statement and to its relation to reactivity.

CONCLUSIONS

The conservation of orbital symmetry in concerted reactions has become one of the more important pillars of modern chemistry. Yet very few reactions follow the symmetry dictates in a strict way. In order for the WH and Fukui[53] approaches to embrace freely the majority of concerted reactions, namely, those who follow the desired symmetry only (very) approximately, quantification of that structural property is needed. Indeed, asynchronicity was developed for that purpose. Yet, looking at Figure 8, which depicts only few of the many molecular parameters that undergo a change during a concerted reaction (the [4 + 2] cycloaddition reaction of (*E*,*E*)-1,4-dimethoxy-1,3-butadiene with tetracyanoethylene in our case), it is clear that selection of specific parameters cannot grasp the full symmetry changes as a whole. The method of continuous symmetry measures has been applied to address this need. Symmetry, the inherent structural property of relevance to concerted reactions, is used as a global parameter (Figure 2a) to follow up the reaction and parameters that affect it. The specific example we have selected in order to demonstrate this approach has been the study of the effects of solvents on the symmetry and reactivity of a Diels–Alder reaction, revealing the predictive value of this approach. Our data for the enthalpy of activation and the charge separation at the TS predict that the reactivity increases with the polarity of the solvent. The symmetry measure is in excellent correlation with the enthalpy of activation and the charge separation at the TS, indicating the higher reactivity of the more symmetric case, thus quantifying the main teaching of the WH rules. In particular these results suggest that in concerted reactions one can find a minimal symmetry measure value that is not necessarily zero (i.e., ideally symmetric), with respect to the original expected symmetry, and that higher reactivity in such reactions is associated with lower CSM values, that is, with higher quantitative symmetry values. Finally, we draw attention to a recent study by Casanova et al., who suggested a symmetry measure of the electron density[54,55] that could be suitable to test the influence of substitution on the orbital symmetry of concerted reactions; extension of our nuclei geometry analysis to orbitals analysis by this and by related methods[56,57] is in progress.

■ ASSOCIATED CONTENT

Ⓢ **Supporting Information.** Cartesian coordinates and electronic energies for the reactants, transition structures and product in different solvents optimized at the MPW1K6/31-G(d,p) level. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed.* **1969**, *8*, 781–853.

(2) Yamabe, S.; Nishihara, Y.; Minato, T. *J. Phys. Chem. A* **2002**, *106*, 4980–4987.

(3) Bachrach, S. M.; White, P. B. *THEOCHEM* **2007**, *819*, 72–78.

(4) Ruiz-López, M. F.; Assfeld, X.; Garcia, J. I.; Mayoral, J. A.; Salvatella, L. *J. Am. Chem. Soc.* **1993**, *115*, 8780–8787.

(5) Pinsky, M.; Casanova, D.; Alemany, P.; Alvarez, S.; Avnir, D.; Dryzun, C.; Kizner, Z.; Sterkin, A. *J. Comput. Chem.* **2008**, *29*, 190–197.

(6) Pinsky, M.; Dryzun, C.; Casanova, D.; Alemany, P.; Avnir, D. *J. Comput. Chem.* **2008**, *29*, 2712–2721.

(7) Zabrodsky, H.; Peleg, S.; Avnir, D. *J. Am. Chem. Soc.* **1992**, *114*, 7843–7851.

(8) Zabrodsky, H.; Avnir, D. *J. Am. Chem. Soc.* **1995**, *117*, 462–473.

(9) Zabrodsky, H.; Peleg, S.; Avnir, D. *J. Am. Chem. Soc.* **1993**, *115*, 11656–11656.

(10) Zabrodsky, H.; Peleg, S.; Avnir, D. *J. Am. Chem. Soc.* **1993**, *115*, 8278–8289.

(11) Alvarez, S. *Dalton Trans.* **2005**, *13*, 2209–2233.

(12) Alvarez, S.; Alemany, P.; Casanova, D.; Cirera, J.; Llunell, M.; Avnir, D. *Coord. Chem. Rev.* **2005**, *249*, 1693–1708.

(13) Alvarez, S. *J. Am. Chem. Soc.* **2003**, *125*, 6795–6802.

(14) Dryzun, C.; Mastai, Y.; Shvalb, A.; Avnir, D. *J. Mater. Chem.* **2009**, *19*, 2062–2069.

(15) Katzenelson, O.; Edelstein, J.; Avnir, D. *Tetrahedron: Asymmetry* **2000**, *11*, 2695–2704.

(16) Malek, K.; Jansen, A. P. J.; Li, C.; van Santen, R. A. *J. Catal.* **2007**, *246*, 127–135.

(17) Keinan, S.; Avnir, D. *J. Chem. Soc., Dalton Trans.* **2001**, 941–947.

(18) Steinberg, A.; Karni, M.; Avnir, D. *Chem.—Eur. J.* **2006**, *12*, 8534–8538.

(19) Simons, R. S.; Galat, K. J.; Bradshaw, J. D.; Youngs, W. J.; Tessier, C. A.; Aullon, G.; Alvarez, S. *J. Organomet. Chem.* **2001**, *628*, 241–254.

(20) Llunell, M.; Alemany, P.; Bofill, J. M. *Theor. Chem. Acc.* **2008**, *121*, 279–288.

(21) Pinto, Y.; Fowler, P. W.; Mitchell, D.; Avnir, D. *J. Phys. Chem. B* **1998**, *102*, 5776–5784.

(22) Tuvi-Arad, I.; Avnir, D. *J. Math. Chem.* **2010**, *47*, 1274–1286.

(23) Sauer, J. *Chem. Ber. /Recl.* **1964**, *97*, 3183.

(24) Hiranuma, H.; Miller, S. I. *J.Org. Chem.* **1982**, *47*, 5083–5088.

(25) Wise, K. E.; Wheeler, R. A. *J. Phys. Chem. A* **1999**, *103*, 8279–8287.

(26) Jones, G. O.; Guner, V. A.; Houk, K. N. *J. Phys. Chem. A* **2006**, *110*, 1216–1224.

(27) Chiappe, C.; Malvaldi, M.; Pomelli, C. S. *Green Chem.* **2010**, *12*, 1330–1339.

(28) Desimoni, G.; Faita, G.; Pasini, D.; Righetti, P. P. *Tetrahedron* **1992**, *48*, 1667–1674.

(29) Gajewski, J. J. *J. Org. Chem.* **1992**, *57*, 5500–5506.

(30) Firestone, R. A.; Saffar, S. G. *J. Org. Chem.* **1983**, *48*, 4783–4784.

(31) Kiselev, V. D.; Konovalov, A. I.; Asano, T.; Kashaeva, E. A.; Iskhakova, G. G.; Shihab, M. S.; Medvedeva, M. D. *J. Phys. Org. Chem.* **2001**, *14*, 636–643.

(32) Kiselev, V. D.; Kashaeva, E. A.; Shihab, M. S.; Medvedeva, M. D.; Konovalov, A. I. *Russ. Chem. Bull.* **2000**, *49*, 1040–1044.

(33) Kiselev, V. D.; Kashaeva, E. A.; Bolotov, A. V.; Shakirova, I. I.; Konovalov, A. I. *Russ. Chem. Bull.* **2009**, *58*, 21–24.

(34) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; 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.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*; Gaussian, Inc.: Wallingford CT, 2009.

(35) Lynch, B. J.; Fast, P. L.; Harris, M.; Truhlar, D. G. *J. Phys. Chem. A* **2000**, *104*, 4811–4815.

(36) Lee, C. T.; Yang, W. T.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789.

(37) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652.

(38) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623–11627.

(39) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098–3100.

(40) Perdew, J. P.; Wang, Y. *Phys. Rev. B* **1992**, *45*, 13244–13249.

(41) Tomasi, J.; Mennucci, B.; Cammi, R. *Chem. Rev.* **2005**, *105*, 2999–3093.

(42) Pascual-Ahuir, J. L.; Silla, E.; Tunon, I. *J. Comput. Chem.* **1994**, *15*, 1127–1138.

(43) Cances, E.; Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3032–3041.

(44) Hratchian, H. P.; Schlegel, H. B. In *Theory and Applications of Computational Chemistry: The First 40 Years*; Dykstra, C. E., Frenking, G., Kim, K. S., Scuseria, G., Eds.; Elsevier: Amsterdam, 2005; pp 195−249.

(45) Fukui, K. *Acc. Chem. Res.* **1981**, *14*, 363–368.

(46) Bauernschmitt, R.; Ahlrichs, R. *J. Chem. Phys.* **1996**, *104*, 9047–9052.

(47) Roothaan, C. C. J. *Rev. Mod. Phys.* **1951**, *23*, 69.

(48) Goldstein, E.; Beno, B.; Houk, K. N. *J. Am. Chem. Soc.* **1996**, *118*, 6036–6043.

(49) Cayzer, T. N.; Paddon-Row, M. N.; Moran, D.; Payne, A. D.; Sherburn, M. S.; Turner, P. *J. Org. Chem.* **2005**, *70*, 5561–5570.

(50) Ess, D. H.; Houk, K. N. *J. Am. Chem. Soc.* **2008**, *130*, 10187–10198.

(51) Contini, A.; Leone, S.; Menichetti, S.; Viglianisi, C.; Trimarco, P. *J. Org. Chem.* **2006**, *71*, 5507–5514.

(52) Legnani, L.; Lunghi, C.; Albini, F. M.; Nativi, C.; Richichi, B.; Toma, L. *Eur. J. Org. Chem.* **2007**, *2007*, 3547–3554.

(53) Fukui, K. In *Topics in Current Chemistry*; Springer: Berlin/Heidelberg, 1970; pp 1−85.

(54) Casanova, D.; Alemany, P. *Phys. Chem. Chem. Phys.* **2010**, *12*, 15523–15529.

(55) Casanova, D.; Alemany, P.; Alvarez, S. *J. Comput. Chem.* **2010**, *31*, 2389–2404.

(56) Dryzun, C.; Avnir, D. *Phys. Chem. Chem. Phys.* **2009**, *11*, 9653–9666.

(57) Pinsky, M.; Danovich, D.; Avnir, D. *J. Phys. Chem. C* **2010**, *114*, 20342–20349.