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Is It [4 + 2] or [2 + 4]? A New Look at Lewis Acid Catalyzed Diels−Alder Reactions

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Apart from its synthetic usefulness, the mechanistic aspects of the Diels−Alder reaction continue to be an endless source of surprises. After the well-known and long-lived discussion about the concertedness of this kind of cycloaddition,[1] a less general, yet interesting mechanistic question has been raised by Yamabe, Dai, and Minato (henceforth YDM),[2] concerning the Lewis acid catalyzed Diels−Alder reactions between butadiene and acrolein. Following the former work carried out by Birney and Houk (henceforth BH),[3] YDM studied this reaction by considering only the *s-cis* conformation of acrolein, coordinated to BF_3 and $AlCl_3$, using a splicing 6-31G* and 3-21G basis set (the latter for the Lewis acid moiety). In the case of the *s-cis* conformation of the BF_3 complex, these authors found an *endo* transition structure (TS), whose geometry and vibrational analysis corresponded better with a hetero-Diels−Alder reaction. In fact, an intrinsic reaction coordinate (IRC) calculation showed that this transition structure leads to the corresponding [2 + 4] dihydropyrane adduct. In the case of the $AlCl_3$ complex, the fate of the *endo s-cis* TS depends on the basis set used, leading to a "normal" [4 + 2] cyclohexene adduct at the 3-21G level and to a [2 + 4] adduct at the 6-31G* and 3−21G level. The conclusion reached by YDM is that the BF_3 catalyzed reaction follows in fact a "[2 + 4] → Cope" pathway (although Claisen would be a more adequate denomination for the rearrangement described), whereas the $AlCl_3$ catalyzed reaction presents a borderline mechanism.

Both in the BH and in the YDM works, the flatness of the potential energy surface is invoked to account for the particular behavior of the *endo s-cis* TS. BH located a family of structures almost isoenergetic in the ridge separating reactants from products, whose main structural differences lie on a slight twisting of the butadiene plane relative to acrolein. Some of these structures seem "pro-[4 + 2]" and others "pro-[2 + 4]". This flatness may gives rise to two distinct reaction channels starting from the same reactants. YDM also invoke the flatness of the potential energy surface to explain the method-dependent reaction pathway observed in the case of the $AlCl_3$ catalyzed reaction. However, the extreme sensitivity of the system to the theoretical level used prompted us to investigate whether these results have a physical meaning or could be an artifact of the method used. All the calculations were carried out using the Gaussian 94 program,[4] running on a Silicon Graphics Power Challenge computer.

First of all, we considered the effect of using a mixed basis set. The description of the acrolein and the Lewis acid with basis sets of different sizes could give rise to a distortion in the calculation of the charge transfer. Therefore, we located the *endo s-cis* TS of the BF_3 catalyzed reaction using the Schlegel's algorithm[5] with a full 6-31G* basis set. Although the same trends pointed out by YDM are also observed, there are significant differences in the calculated distances between the atoms involved in the bond formation. Thus, the C_5-C_6 distance is 1.936 Å (1.971 in the YDM work), the C_1-C_2 distance is 3.179 Å (3.263Å, YDM), and the C_4-O distance is 2.807 Å (2.739 Å, YDM). Also, the normal coordinates analysis of the imaginary frequency (575.7i cm^{-1}) shows that there is a bonding movement between both C_1-C_2 and C_4-O, unlike that described by YDM, although the vector component of the last atom pair is somewhat greater (0.036 against 0.045). As can be seen, even a small modification in the calculation method leads to non-negligible changes in the TS. In this case, the use of a full 6-31G* basis set slightly moves the TS toward the [4 + 2] cycloaddition.

Next, we considered the effect of the electron correlation. As pointed out by Houk *et al.*,[6] for transition structures of pericyclic reactions of molecules with heteroatoms, not only the use of the 6-31G* basis set is necessary, but also MP2/6-31G* calculations are recommended. A MP2/6-31G* search, starting from the RHF/6-31G* TS was carried out, leading to the structure shown in Figure 1.[7] There are noteworthy differences between this TS and that located at the RHF level. First of all, the C_1-C_2 distance is considerably reduced from 3.179 to 2.805 Å, and it becomes shorter than the C_4-O distance, which passes from 2.807 to 2.827 Å. Also, the C_5-C_6 distance increases from 1.936 to 2.209 Å. These changes suggest a change in the reaction path. The frequency analysis confirms that this is a true transition structure, and the graphic representation of the imaginary frequency (287.2i cm^{-1}, Figure 1) clearly shows that there is a bonding movement between atoms C_1 and C_2, whereas this is not the case for atoms C_4 and O (the relative vector components are 0.149 and 0.023, respectively).

In order to confirm that this TS leads to the [4 + 2] cyclohexene adduct, a mass-weighted Cartesian coordinates IRC calculation was carried out, using the method of González and Schlegel.[8] The variation of the total energy as well as the three critical bond distances are shown in Figure 2. As can be seen, the IRC shows the concertedness and asynchronicity of the reaction. The C_5-C_6 bond is formed first, and, when this formation is almost completed, the C_1-C_2 bond progresses rapidly toward the adduct final value (1.532 Å). The C_4-O distance decreases slowly at the first stages of the reaction path and then increases until its final value (3.646 Å), due to the conformational change of the cyclohexene ring and the rotation of the formyl group in the product. The small variation of the C_4-O distance throughout most of the reaction path highlights the strong attracting interaction existing between these two atoms.

The question remains if the flatness of the potential energy surface would lead to the existence of several structures of almost identical energy. In order to test this possibility, we performed a TS search starting from a very different initial structure, namely the TS of the noncatalyzed reaction, located

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[1] (a) For a recent review, see: Houk, K. N.; González, J.; Li, Y. *Acc. Chem. Res.* **1995**, *28*, 81. (b) Goldstein, E.; Beno, B.; Houk, K. N. *J. Am. Chem. Soc.* **1996**, *118*, 6036.

[2] Yamabe, S.; Dai, T.; Minato, T. *J. Am. Chem. Soc.* **1995**, *117*, 10994.

[3] Birney, D. M.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 4127.

[4] Gaussian 94, Revision B.1, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andrés, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; González, C.; Pople, J. A. Gaussian, Inc.: Pittsburgh, PA, 1995.

[5] Schlegel, H. B. *J. Comput. Chem.* **1982**, *3*, 214.

[6] Houk, K. N.; Li, Y.; Evanseck, J. D. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 682.

[7] As a referee noted, it should be ensured that the *endo s-cis* TS is the lowest in energy, with regard to the three other possibilities: *endo s-trans*, *exo s-cis*, and *exo s-trans*. In fact, all the previous calculations on this or similar reactions indicate that this is the case, although correlation energy has not been considered to date. In this respect, during the revision of this paper we were able to locate the *endo s-trans* TS at the MP2/6-31G* level, and we found that it is 3.4 kcal·mol^{-1} above the corresponding *endo s-cis* TS.

[8] (a) González, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154. (b) González, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523.

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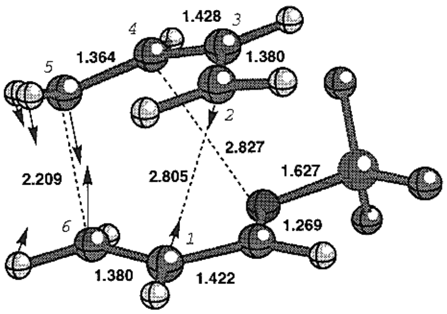

Figure 1. MP2/6-31G* *endo s-cis* transition structure of the reaction between butadiene and BF_3 coordinated acrolein. The arrows represent the normal mode associated to the imaginary frequency.

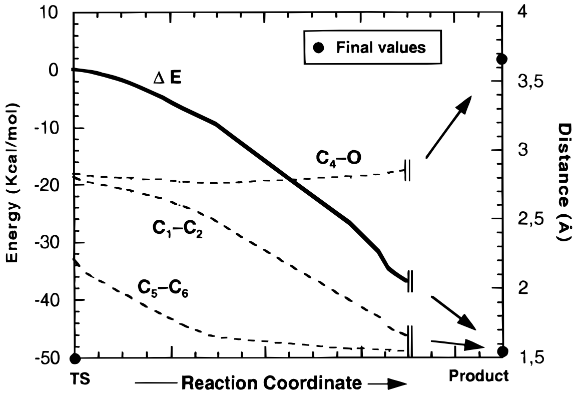

Figure 2. Variation of the relative energy and the C_1–C_2, C_5–C_6, and C_4–O distances along the minimum energy reaction path connecting the transition structure with the product.

at the RHF/6-31G* level, to which a BF_3 molecule was coordinated. This structure corresponds to a “pure” Diels–Alder reaction, or “pro-[4 + 2]”, with the following atom distances: C_5–C_6 = 2.140 Å, C_1–C_2 = 2.591 Å, and C_4–O = 3.078 Å. The MP2/6-31G* optimization leads to the same TS previously located starting from the “pro-[2 + 4]” structure. We have interpreted this result such that the MP2 TS is unique, and no other structures close in energy exist at this level. This fact, together with the IRC result, discards the possibility of dual reaction channels, as proposed by YDM.[2]

What is the origin of the noticeable differences found between the RHF and the MP2 levels? The MP2 TS is earlier in the reaction path than the corresponding RHF TS. This is clearly shown by the C_5–C_6 distance, but it can also be illustrated by the charge transfer between the diene and the dienophile. The Mulliken population analysis of the RHF TS reveals that butadiene has transferred as much as 0.378 electrons, which are distributed over the acrolein (0.095) and the BF_3 (0.283). The Mulliken overlap population between C_1 and C_2 is 0.033, which is identical to that found between C_4 and O. This result differs from that described by BH,[3] who found an overlap of 0.031 between C_4 and O, but only of 0.018 between C_1 and C_2, for the BH_3 complex, at the RHF/3-21G level. On the other hand, in the MP2 TS, butadiene has transferred only 0.208 electrons, and acrolein 0.041, resulting in an excess of 0.249 electrons for the BF_3. It is important to note that the main effect of the global charge transfer comes from the geometry of the TS, given that the analysis of the RHF electron density of the MP2 TS leads to similar results: 0.196 electrons transferred from butadiene and 0.023 from acrolein, resulting in an excess of 0.219 electrons for BF_3. On the contrary, as previously reported,[9] the Mulliken overlap population is quite sensitive to correlation effects. Thus, the overlap between C_1 and C_2 is 0.020 with the RHF density, but 0.040 with the MP2 density, whereas for C_4 and O, it is 0.021 with the RHF density, and 0.030 with the MP2 density. As can be seen, the MP2 overlap population correctly reflects the fact that the C_1–C_2 bond is formed to a greater extent in the MP2 TS, and it is better correlated with the differences found in atom distances when the RHF and the MP2 TS are compared.

The natural population analysis, calculated by means of the NBO 3.1 program included in the Gaussian 94 package, confirms the charge transfer picture given by the Mulliken population analysis. Thus, in the RHF TS, 0.410 electrons are transferred from butadiene, which are distributed between acrolein (0.144) and BF_3 (0.266). In the MP2 TS, butadiene and acrolein transfer 0.214 and 0.031 electrons, respectively, to the BF_3. Further work is currently ongoing in order to analyze in depth the effect of the electron correlation on the changes described.

To sum up, the Diels–Alder reaction of butadiene with acrolein coordinated to BF_3 follows a concerted and asynchronous reaction mechanism, even for the *endo s-cis* TS, although the inclusion of electronic correlation corrections is essential to achieve this result. However, even at the MP2/6-31G* level, the *endo s-cis* TS has an ambiguous character, so that it would not be surprising that steric or electronic effects in related systems would lead to a preference for the [2 + 4] reaction path.

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Supporting Information Available: Cartesian coordinates (in the Gaussian 94 standard orientation) for the RHF/6-31G* and MP2/6-31G* TS and normal coordinates of the imaginary frequency of both TS (2 pages). See any current masthead page for ordering and Internet access instructions.

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[9] (a) Wiberg, K. B.; Hadad, C. M.; LePage, T. J.; Breneman, C. M.; Frisch, M. J. *J. Phys. Chem.* **1992**, *96*, 671. (b) Velders, G. J. M.; Feil, D. *J. Phys. Chem.* **1992**, *96*, 10725. (c) López, X.; Ugalde, J. M.; Cossio, F. P.; Lecea, B.; Largo, A.; Barrientos, C. *J. Phys. Chem.* **1993**, *97*, 9337.