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A new C–C bond formation model based on the quantum chemical topology of electron density†

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ELF topological analyses of bonding changes in non-polar, polar and ionic organic reactions involving the participation of C=C(X) double bonds make it possible to establish a unified model for C–C bond formation. This model is characterised by a C-to-C coupling of two *pseudoradical* centers generated at the most significant atoms of the reacting molecules. The global electron density transfer process that takes place along polar and ionic reactions favours the creation of these *pseudoradical* centers at the most nucleophilic/electrophilic centers of the reacting molecules, decreasing activation energies. The proposed reactivity model based on the topological analysis of the changes in electron density throughout a reaction makes it possible to reject the frontier molecular orbital reactivity model based on the analysis of molecular orbitals.

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Establishing organic molecular mechanisms based on quantum chemistry calculations and the transition state theory

From the advance of numerical computation at the end of the 20th century, computational quantum chemistry (CQC) has been greatly accepted by organic chemists due to its practicability in the study of reaction mechanisms involving actual molecules with 50–70 atoms. CQC enables the localisation and characterisation of the reagents, products, transition state structures (TS) and intermediates involved in organic reactions, thus making the study of molecular mechanisms of organic reactions possible. The comparison of computed activation parameters obtained from the transition state theory (TST)[1–3] with those experimentally obtained by kinetic experiments allows performing an analysis of available computational models. Feasible competitive reaction channels can be theoretically studied, and thus, explain experimental outcomes.

Two appealing data are first obtained through CQC in a straightforward manner: (i) total electronic energies; and (ii) molecular geometries. Although electronic energies associated with the stationary points involved in a chemical reaction are very dependent on the computational level, geometries are less dependent on it. Thus, while *ab initio* Hartee–Fock (HF) calculations[4] widely used along the two last decades of the 20th century allowed the obtention of good TS geometries, that theoretical level yielded very high activation energies overestimating TS energies. Consequently, very time-consuming post-HF energy calculations[4] were performed related to HF optimised geometries. The development of the density functional theory (DFT)[5] at the end of the 20th century, whose calculations provided activation energies closer to experimental values, allowed the standardisation of DFT computations in the study of organic reactions. Thus, several DFT functionals such as B3LYP,[6,7] MPWB1K[8] and more recently M06-2X,[9] which provide accurate energies, have been developed, allowing the study of organic reaction with a computational demand similar to HF calculations.

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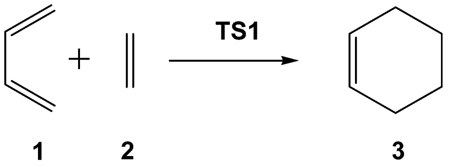
Luis R. Domingo obtained his PhD in Organic Chemistry in 1987. In 1990 he became an Associate Professor, and in 2010 obtained his current position of Full Professor at the Department of Organic Chemistry of the University of Valencia. In 1995 he came up with his first studies in the field of Theoretical Organic Chemistry. So far, he has published more than 220 theoretical studies in different fields of Organic Chemistry. His research interest comprises the study of molecular mechanisms of cycloaddition reactions, the study of organocatalysis, and the application of the DFT reactivity indices in Organic Chemistry. He says: while the distribution of the electron density is responsible for the molecular shape and physical properties, the capability for changes in electron density is responsible for the reactivity.

First, I would like to comment on some data obtained from CQC. Organic reactions involving the formation of new C–C single bonds are the most significant ones within the arsenal of the reactions in organic synthesis since they enable the construction of complex molecules. Among the diverse possibilities of creating a new C–C single bond, those involving the participation of C=C(X) double bonds are the most significant methods. Diels–Alder (DA) reactions,[10] which enable the creation of six-membered carbocyclic structures, are the most studied organic reactions due to their significance both from an experimental and theoretical point of view. Given the high potential of these reactions, the DA reaction between butadiene **1** and ethylene **2**, presented in all textbooks as the prototype, but not experimentally performed in the laboratory, has been the most studied one (see Scheme 1).

In 1996, studying the DA reaction between butadiene **1** and ethylene **2**, Houk performed an evaluation of the emerging B3LYP calculations developed within DFT by comparing them with different *ab initio* methods (see Table 1).[11]

As can be observed, while the reaction energies, $\Delta E_{\text{reac.}}$, were found in the range of 36.0 to 49.1 kcal mol^{-1}, the activation energies, ΔE_{act}, ranged from 20.0 (MP2) to 47.4 (HF) kcal mol^{-1}. Note that the predicted B3LYP activation energy, 24.8 kcal mol^{-1}, was found to be closer to that experimentally estimated, 27.5 kcal mol^{-1}.

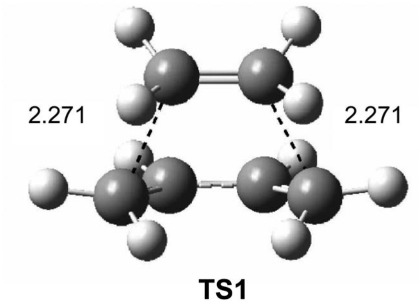
Interestingly, in spite of these wide ranges of energies, TS geometries were found not to be dependent on computational methods. Thus, in all the methods studied, the distance between the two carbons involved in the formation of the two new single bonds in the synchronous **TS1** were found to be *ca.* 2.2 Å (see Fig. 1). That is, while the energies of the stationary points involved in this DA reaction were found to be very dependent on the computational method, the geometry of **TS1**, which depends on its electronic structure, proved to be very similar.



Scheme 1 DA reaction between butadiene **1** and ethylene **2**.

Table 1 Activation and reaction energies, in kcal mol^{-1}, and C–C distances of the two forming single bonds, in Angstroms, at **TS1** obtained using different computational levels (see Scheme 1)

Method	ΔE_{act}	$\Delta E_{\text{reac.}}$	d(C–C)
RHF/6-31G*	47.4	36.0	2.201
MP2/6-31G*	20.0	45.9	2.286
MP4/6-31G*		49.1	
CASSCF/6-31G*	47.4		2.223
B3LYP/6-31G*	24.8	36.6	2.273
Experimental	27.5	38.4	



TS1

Fig. 1 B3LYP/6-31G* transition structure **TS1** associated with the DA reaction between butadiene **1** and ethylene **2**. Distances are given in Angstroms.

However, the TS geometries in different organic reactions are not invariable, being dependent on the nature of the bonds involved in the chemical process. In addition, for a given reaction, TS geometries can also be dependent on the substitution. Thus, among DA reactions both synchronous TSs, in which the two C–C single bonds are being formed at the same time, and highly asynchronous TSs, in which the two C–C single bonds are formed in two different stages of the reaction, can be found. It is noteworthy that the synchronous **TS1** given in Fig. 1 is not representative of DA reactions, asynchronous TSs being the most common ones.

Therefore, as TS geometry depends on its electronic structure, the different TSs observed are a consequence of the different degree of the evolution of the bonding changes along the reaction. It is remarkable that the TS does not present any special characteristic in bonding changes along a reaction; it only corresponds to a structure of maximum energy along the intrinsic reaction coordinates[12] (IRC).

Classification of organic reactions into non-polar, polar and ionic reactions

In order to establish the mechanism of DA reactions taking place experimentally under mild conditions, the DA reactions of cyclopentadiene (Cp, **4**) with twelve ethylenes of different electron-withdrawing substitution were studied (see Scheme 2).[13]

While for the DA reaction with ethylene **2** a synchronous TS similar to **TS1** was found, the asymmetric substitution on the ethylene yielded highly asynchronous TSs. Interestingly, while the B3LYP/6-31G* relative energies of the TSs of the studied DA reactions fluctuate from 22.0 kcal mol^{-1} for the most unfavourable reaction of Cp **4** towards methyl vinyl ether, an electron-rich ethylene, to -5.1 kcal mol^{-1} for the most favourable reaction towards an iminium cation, the strongest electron-deficient ethylene of the series, TS geometries showed in most cases a high asynchronicity in the C–C single bond formation, thus suggesting similar electronic structures. Note that in the DA reaction between Cp **4** and the iminium cation, formation of a pre-reaction complex with a relative energy of -9.6 kcal mol^{-1} makes the activation energy positive. The distance between the two carbons involved in the formation of the first C–C single