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FEATURE ARTICLE

Quantum Mechanical Methods and the Interpretation and Prediction of Pericyclic Reaction Mechanisms

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The computational study of pericyclic reactions, an important general class of organic reactions, now provides information about the transition structures of these processes with chemical accuracy, as judged by comparisons with experimental data, such as activation energies, substituent effects on rates, and kinetic isotope effects. This article introduces the methods used to study these reactions and describes how computational results have contributed to the understanding of transition states and mechanisms of the electrocyclic ring openings of cyclobutenes, Diels−Alder cycloaddition reactions, and [3,3]-sigmatropic shifts such as the Cope rearrangement.

Introduction

The study of organic reaction mechanisms has long been a province of physical organic chemistry.[1] Ingenious experimental techniques have been devised to elucidate the steps in complex organic transformations in the condensed phase. Subtle spectroscopic techniques reveal details about timing of bonding changes in transition states and properties of extremely short-lived reaction intermediates in chemical reactions.[2] The ever-increasing resolution and precision of experiments in physical chemistry have led to new ultrafast methods to observe some extremely reactive compounds such as organic diradicals[3] and even transition states themselves![4] However, the interpretation of such experiments relies heavily on quantum mechanical calculations, because frequently only a mass or single absorption of the transient is available.

Numerical quantum mechanical calculations also provide a direct tool for the understanding of systems that are too complex to be observed directly. The potential of quantum mechanical methods in chemistry was recognized soon after the formulation of the Schrödinger equation,[5] as were the mathematical problems associated with the application of these equations to systems of chemical interest.[6] To use these methods to obtain a detailed view of transition-state geometries, and therefore to understand and to predict the mechanisms of organic chemical reactions, numerous approximations had to be made. These approximations and the lack of accuracy of the calculations gave rise to intense debates about the validity of the different mechanistic models that were deduced from the calculations.[7] The refinement of the computational methods used, together with the rapid increase in computer performance over the past two decades, has contributed to the increased reliability of quantum mechanical tools for the study of organic reaction mechanisms.

The structural information obtained by computation of possible intermediates and transition states provides powerful assistance for the interpretation of experimental results, since such data are rarely available from experiment. Quantum mechanical calculations help us to understand and, ultimately, predict organic reactivity. The analysis of the combined experimental and theoretical data allows an understanding of how substituent effects and stereochemical requirements influence the intrinsic reaction barriers of a given reaction. The relative rates calculated for different pathways of the parent and substituted compounds also allow rational planning of the best method to prepare a desired substance.

The goal of this article is to show how quantum mechanical methods have been used to analyze and to predict rates and mechanisms of pericyclic reactions, an important class of organic processes. After a brief review of the methods most frequently used in organic chemistry, we will describe how certain information obtained by computations has proven useful for investigations of reaction mechanisms. Three reactions for which computations have given important mechanistic insights will be presented: the electrocyclic ring opening of cyclobutenes, the [4 + 2]-cycloaddition reactions of ethylene and butadiene (Diels−Alder reaction), and the [3,3]-sigmatropic shift reaction of 1,5-hexadiene (Cope rearrangement). The theoretical data and how they have revealed the mechanisms of these three reactions will be discussed. The current state-of-the-art of quantum mechanical calculations for the determination of organic reaction mechanisms will be illustrated for these three examples. Finally, we will show how old puzzles have been solved and new phenomena have been predicted.

Computational Methods

The most frequently used methods for quantum mechanical studies of organic reaction mechanisms are Hartree−Fock molecular orbital methods, Møller−Plesset and configuration interaction corrections for electron correlation, and, more recently, multiconfiguration self-consistent-field (MCSCF) and density functional theory (DFT) methods.[8,9]

Despite the neglect of correlation energy, Hartree−Fock theory has proven to be very useful in the exploration of organic mechanisms. With the implementation of direct SCF algo-

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rithms, calculations of systems with up to 30 non-hydrogen atoms are now routine. In some cases, computations on molecules consisting of several hundred non-hydrogen atoms have been performed.[10] Using sophisticated integral evaluation schemes, most modern programs scale as roughly $n^{2.7}$, where n is the number of basis functions, making the study of larger systems possible. Although RHF calculations have been applied successfully to a wide variety of systems, there are systematic errors that can cause problems. Electron correlation is neglected, and since the correlation energy is generally larger in transition states than in reactants, the calculated activation energies are too high when compared with the experimental values. The restricted Hartree–Fock method is, therefore, unsuitable for the calculation of absolute activation energies. Nevertheless, relative activation energies of reactions with different substituents or stereochemically different transition states can be calculated quite accurately, since these involve similar bonding and thus similar correlation energy changes from reactants to transition structures. However, the direct comparison of different reaction pathways involving closed-shell and diradicaloid pathways cannot give reliable results, because correlation energies are different for these types of species.

The results from Hartree–Fock calculations can be systematically improved by the inclusion of electron correlation at various levels of accuracy.[11] The most economical method for this is Møller–Plesset (MP) perturbation theory,[12] with the second-order method (MP2) being the most widely used. Due to the less favorable scaling of about n^4 and the large disk requirements[13] of this and related higher-order methods, the size of the systems that can be studied is rather limited. Furthermore, it has been found for a number of systems that the MP2 method overestimates the correlation energy and thus the stabilities of radicals and transition states. Therefore, the calculated activation energies are often too low as compared to experiment. In the case of competition between closed-shell and open-shell pathways, the prediction of the lowest energy pathway may be biased. It has also been shown that the convergence of MPn methods for highly spin contaminated systems is slow, making this approach unsuitable for such species.[14]

An alternative, although computationally more demanding, approach to electron correlation is the configuration interaction (CI) method using different truncation schemes such as the CI with single and double excitations (CISD), the coupled cluster, or the quadratic CI methods.[15−17] Among the multiconfiguration methods, the complete active space SCF (CASSCF) method has been particularly valuable for the study of organic chemical reactions.[18,19] Using highly sophisticated algorithms, molecules with up to 12 non-hydrogen atoms are routinely treated.[20] Further improvements of the MCSCF method are possible by inclusion of second-order perturbation theory (CASPT2N or CAS/MP2).[21] These highly correlated methods are used generally for single-point energy calculations of structures that have been optimized at a lower level of theory.

During the past five years, density functional theory (DFT) has evolved as a computationally efficient alternative to MO-based methods,[22] and further improvements in the computational algorithms may lead to a linear scaling for these methods.[23] Although these methods are not variational, and their use for the calculation of excited states is a topic that is still under discussion,[24] the results from studies of the ground states of a variety of chemical systems are very promising.[25] The results obtained with gradient corrected, nonlocal DFT methods[26] such as the BLYP or the BP88 functionals and hybrid[27] functionals such as the Becke3LYP or the ACM method are generally at least comparable in accuracy to the ones obtained by MP2 calculations, while the computational effort is similar to Hartree–Fock calculations. The fact that the exact functionals for the Kohn–Hohenberg theorem[28] are not known has led to some concern about the application of DFT methods, in cases where no experience from other sources has been accumulated.

An additional problem in computational organic chemistry arises from the fact that basis sets which are practical for the calculation of larger organic molecules are usually not flexible enough to achieve basis set convergence.[29] The most commonly used basis sets are the split-valence basis sets developed by Pople and co-workers,[30] supplemented by additional polarization[31] and/or diffuse functions.[32] Various other basis sets for electronic structure calculations have been published[33] and are used especially for high-precision calculations. Although Hartree–Fock and MCSCF calculations with double-ζ plus polarization basis sets are generally in good agreement with the results from calculations using more extensive basis sets, many-body perturbation methods usually require larger basis sets. Methods such as Pople's G1, G2, and G2(MP2)[34] and Petersson's complete basis set (CBS) methods[35] involve a series of calculations with various basis sets and correlation energy corrections and extrapolation to energies believed to be within 2 kcal/mol of the experimental values. It has been pointed out that basis set convergence for DFT methods is generally faster than in MO-based methods.[36]

Comparison with Experimental Values

Quantum mechanical calculations provide the organic chemist with an opportunity to understand processes that cannot be observed directly, to interpret experimental findings, and to make predictions that can then be tested experimentally. The most important piece of information that connects these goals are the structures which are the key to understanding the chemical, physical, and biological properties of molecules.[37] Although structural information is available from X-ray crystallography or NMR experiments for a large number of molecules, the lack of suitable single crystals or synthetic and stability problems may still present severe limitations for structure determination with experimental methods. Furthermore, it is not yet possible to obtain accurate structural information about transition states and short-lived reactive intermediates.

The close coupling of theoretical and experimental methods is desirable in order to validate the assumptions necessarily made in practical computations on large systems. These assumptions might arise in the choice of the theoretical model, for example, by neglection of electron correlation in calculations on either large models or the actual system. Alternatively, the assumption might arise in the choice of the chemical model; for example, the chemical system of interest might be modeled using a smaller system, and solvent, counterions, or substituents might be neglected. The balance between a more advanced theoretical model versus a more realistic chemical one has to be found for each case and constitutes much of the art of computational chemistry. When such simplifications are made, it is necessary that the computational results be validated by comparisons with experimental values. This contrasts to highly accurate calculations on small systems, where the results can be highly reliable without calibration.

Whereas there are a number of experimental methods available to obtain data on stable molecules that can be compared with the results from computations, information on transition states of complex molecules is usually quite indirect. Information such as activation energies and entropies, kinetic isotope effects, and substituent and solvent effects on rates are used to deduce information about the transition states involved in a reaction. Insights into the geometrical and electronic structures of transition states can be obtained with quantum mechanical calculations, and the results can be validated by computation of experimentally accessible properties.

The starting point for most studies is the calculation of the structures of reactants and products of the reaction, including low-energy conformations. Although it is generally not possible to prove whether a given conformation corresponds to a local or a global minimum without knowledge of the complete hypersurface, only a small number of reasonable conformers is typically considered. Next, the first-order saddle point connecting the reactants and products is calculated. Although several methods for the localization of stationary points (minima and saddle points) on a multidimensional hypersurface have been developed,[38] the choices of the conformations and initial geometries of the saddle points are often guided by chemical intuition and a qualitative understanding of the mechanism under study. As with conformation searches for stable molecules, the location of a saddle point does not guarantee that this is the lowest energy transition state for the process in question. The efficiency of a geometry optimization (either to a minimum or a saddle point) depends on the choice of the coordinate system. Internal and Cartesian coordinate systems are traditionally the most frequently employed of the numerous possible coordinate systems, but recently the use of redundant internal coordinates has been found to be the most efficient for many systems.[39] For all methods, once the starting point is defined, the initial force constant matrix must be generated, either by simple force field methods or, in more complicated cases, by calculation of the second derivatives. Several quasi-Newton algorithms, such as eigenvector following routines,[40] are available for optimizing saddle points. To prove the successful location of a saddle point connecting reactants and products, intrinsic reaction coordinate (IRC) calculations may be performed.[41] This procedure follows the lowest energy path on the potential hypersurface from the located saddle point downhill to the reactants and products.

The stationary points located can be characterized by a harmonic frequency analysis, showing whether the stationary point is a minimum or a saddle point on the hypersurface. A minimum on the hypersurface has only positive frequencies, while a transition structure has exactly one imaginary frequency, proportional to the square root of the negative force constant for motion along the reaction coordinate. Second derivatives can normally be calculated analytically,[42] although only numerical methods are available for several of the highly correlated methods. The location and characterization of stationary points and the determination of geometries and activation energies can be followed by an analysis using the Mulliken[43] or CHELPG[44] methods which give information about electron distributions and bond orders.[45] In addition, many other specialized molecular properties (e.g., magnetic properties, UV and IR spectra, etc.) can be calculated and have been used for the analysis for organic reactions.

Since geometry optimizations are performed on a potential energy surface, a first-order saddle point that is calculated is related, but not equal, to the quasi-thermodynamic transition state as defined by the Eyring theory,[46] which is a Boltzmann average on the free energy surface. To distinguish these two entities, the term "transition structure" has been used to describe the saddle point on the computed potential energy surface. As shown in Figure 1, the difference (ΔG) between the calculated potential energy surface and the measured free energy surface at a given temperature T is

$$\Delta G = \Delta E + \mathrm{ZPE} + C_pT + T\Delta S + RT \qquad (1)$$

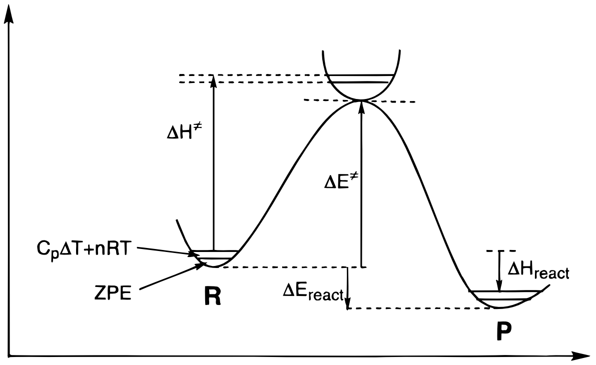

Figure 1. Schematic representation of the relationship between ΔH and ΔE along a reaction path.

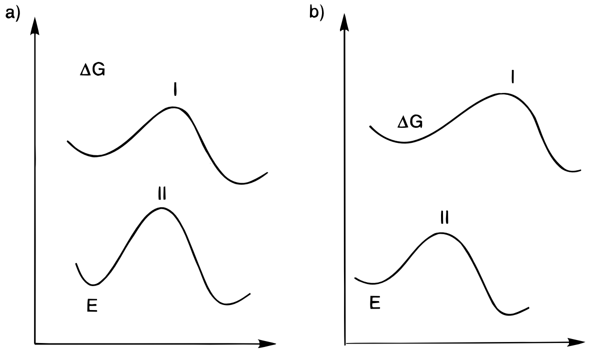

Figure 2. Relationship between transition state I and transition structure II. I and II coincide in (a), but not in (b).

To compare the experimental activation energies to the energy difference of the optimized reactants and the transition structure, corrections for the populations of the different vibronic levels, determined by the heat capacity, C_p, the zero-point energy, ZPE, and the entropy ΔS, have to be made. Among these, the difference in zero-point energies is usually the most important, because one reactant vibration becomes a translation, and many frequencies become quite low as bonds are weakened in the transition state. Since only the lowest vibronic levels are occupied at the temperatures where most organic reactions are performed, all correction terms can be obtained within the harmonic approximation with sufficient precision. The computation of entropies from vibrational frequencies, moments of inertia, and masses is straightforward for a single minimum, but the correct computation of entropies for species with multiple, thermally accessible minima requires averaging over all of these minima.

These differences between the potential energy and the free energy surface can in certain cases lead to different geometries of the stationary points. As shown in Figure 2a, the geometries of the transition state and the transition structure will be very similar if the reaction has a relatively large activation enthalpy and only small changes in entropy in the region of the hypersurface corresponding to the saddle point. In cases where the activation barrier is small or the entropy changes quickly (see Figure 2b), the average geometry of the transition state might differ from the calculated transition structure. The free energy maximum can be located with variational transition state theory, which has occasionally been applied to organic reactions.[47]

Information about the changes in vibrational frequencies during reactions may be obtained using isotopically labeled starting materials.[48] The secondary kinetic isotope effects obtained by these experiments have been important tools for the elucidation of a variety of reaction mechanisms.[49] According to a qualitative analysis by Streitweiser et al.,[50] changes in the out-of plane bending force constants are the main factor leading to secondary kinetic isotope effects (SKIE) in reactions that involve a change in hybridization at a given center. The more dramatic change of a stretching mode to a translational mode along the reaction coordinate is responsible for primary kinetic isotope effects (PKIE).[51] Both the PKIE and the SKIE reveal information about the shape of the potential surface around the transition state. If the force constants of these vibrations are known, the KIE can be analyzed quantitatively using the Bigeleisen−Mayer formalism.[52] Here, the kinetic isotope effect is expressed as the ratio of the reduced partition functions

$$\frac{k_\mathrm{H}}{k_\mathrm{D}} = \frac{\nu^\ddagger{}_\mathrm{H} \prod_1^{3n-6} \frac{u_\mathrm{H}}{u_\mathrm{D}}}{\nu^\ddagger{}_\mathrm{D} \prod_1^{3n-7} \frac{u^\ddagger{}_\mathrm{H}}{u^\ddagger{}_\mathrm{D}}} \frac{\prod_1^{3n-6} \frac{[1-\exp(-u_\mathrm{H})]}{[1-\exp(-u_\mathrm{D})]}}{\prod_1^{3n-7} \frac{[1-\exp(-u^\ddagger{}_\mathrm{H})]}{[1-\exp(-u^\ddagger{}_\mathrm{D})]}} \frac{\exp\left(\sum_1^{3n-6} \frac{u_\mathrm{H}-u_\mathrm{D}}{2}\right)}{\exp\left(\sum_1^{3n-7} \frac{\mathrm{u}^\ddagger{}_\mathrm{H}-u^\ddagger{}_\mathrm{D}}{2}\right)} = \frac{\nu^\ddagger{}_\mathrm{H}}{\nu^\ddagger{}_\mathrm{D}} \frac{(s_2/s_1)f(2/1)}{(s_2/s_1)f(2/1)^\ddagger} \tag{2}$$

with

$$u_i = \frac{h\nu_i}{kT} = 1.43879\frac{\nu_i\,[\mathrm{cm}^{-1}]}{T\,[\mathrm{K}]} \tag{3}$$

Since the force constants can be obtained from the harmonic frequency calculations, the theoretical kinetic isotope effect can be calculated and compared with the experimental value. It has been found that, due to the vibrational anharmonicity of the experimental potential, the calculated frequencies are systematically too high by about 10%.[53] It is therefore common practice to scale the force constants from ab initio calculations by an empirical factor that is dependent on the method.[54] Scaling factors of 0.91, 0.95, 1.0, and 0.963 have been recommended for RHF/6-31G*, MP2/6-31G*, BLYP/6-31G*, and Becke3LYP/6-31G* calculations.[55] The results can also be corrected for tunneling effects.[56,57]

The Electrocyclic Ring Opening of Cyclobutene

The electrocyclic ring opening of cyclobutene to butadiene, shown in Figure 3, was one of the first reactions to be studied within the framework of orbital symmetry conservation.[58] The selection rules derived from this analysis, the Woodward−Hoffmann rules, had a tremendous impact on the development of physical organic chemistry. The concepts developed for this simple reaction have been instrumental for the understanding of pericyclic reactions in general. Due to the small size of the system and its importance for a quantitative understanding of organic reaction mechanisms, this reaction has been studied using ab initio quantum mechanical methods since the early 1970s.[59]

The Woodward−Hoffmann rules predict a concerted and conrotatory reaction pathway involving a C_2 symmetric transition state for the reaction of the parent cyclobutene. This mechanism has been confirmed by all available quantum mechanical calculations and is now generally accepted.[60] Table 1 summarizes the results obtained by different computational methods. Schaefer used MCSCF calculations with two configurations in order to assess the difference in energy between the allowed conrotatory and forbidden disrotatory modes of reaction. Although no transition state was found for the forbidden process, Schaefer estimated that it was at least 15 kcal/mol above the allowed process. This result compares well with the experimental activation barrier difference of 11−15 kcal/mol.[61]

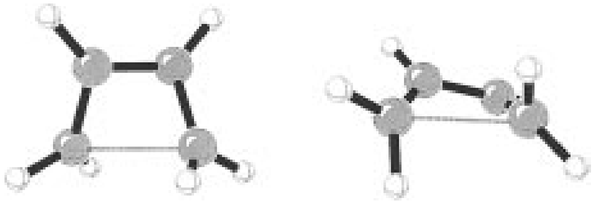

Figure 3. Electrocyclic ring opening of cyclobutene.

The transition structures obtained by each of the various methods are quite similar. The bond lengths calculated for the breaking bond range from 2.13 to 2.16 Å in most cases. The semiempirical and minimal basis set Hartree−Fock methods underestimate this value whereas the two configuration SCF and the LDA/TZVP methods predict that this bond length is larger than 2.2 Å. The predictions for the degree of bond reorganization within the carbon framework are even more similar with only insignificant variations. All the transition structures calculated show a significant twist out of planarity in the carbon skeleton of the rearranging ring. This facilitates overlap of the breaking CC σ bond with the π bond of the ring.

Although relatively low-level calculations are capable of predicting the geometry of the transition structure to a reasonable accuracy, at least in this case, precise calculation of reaction energetics and activation energies requires much higher levels of theory. Predictably, the activation energies obtained by the Hartree−Fock calculations are much too high, and in some cases they differ by a factor of 2! (See Table 1.) However, the reaction energies calculated by these methods using an appropriate basis set are in much better agreement with the experimental values, because the correlation energies of two minima on the hypersurface are about the same. The error in activation energies is largely corrected by the inclusion of electron correlation using the MP method. The activation energy and the reaction energy calculated at the MP2/6-31G* level still differ from experiment by 4.7 and 3.2 kcal/mol, respectively. The density functional approach with the local density approximation is very poor but gives excellent results with nonlocal and hybrid methods. The nonlocal as well as the hybrid DFT methods tend to overestimate the heat of reaction by up to 7 kcal/mol, using the ACM/6-31G* method.

There are two stereochemically distinct ring opening modes for the contatory ring opening. As shown in Figure 4a, a substituent can rotate either inward (IN) to give the cis-substituted butadiene or outward (OUT) to form the corresponding trans isomer. The analysis of the orbital interactions in the transition structure led to an understanding of the factors determining the selectivity between the two possible modes or rotation, the so-called torquoselectivity.[60] Based on this study, a set of rules has been developed to predict the stereochemical outcome for different types of substituents.

Figure 4b shows the orbital interactions that lead to these rules. A donor substituent with high-lying filled orbitals will rotate outward in order to minimize the destabilizing interaction with the electron pair of the breaking σ bond. At the same time, the bonding interaction between the filled orbital of the substituent and the vacant σ* orbital of the breaking bond is maximized by outward rotation. Therefore, this mode of rotation is preferred by donor substituents. Acceptor substituents will tend to rotate inward to maximize the stabilizing interaction of a low-lying vacant orbital of the substituent with the filled σ orbital of the breaking bond. This theory provided a rational-

TABLE 1: Selected Results for the Electrocyclic Ring Opening of Cyclobutene

method	R_{C3-C4} (Å)	R_{C2-C3} (Å)	R_{C1-C2} (Å)	$\varphi_{C4-C1-C2-C3}$ (deg)	E_A (kcal/mol)	ΔE (kcal/mol)	ref
MINDO/3	2.058	1.418	1.388	21.0			61a
AM1	2.1196	1.4278	1.3889	18.7	35.3[a]	−15.9[a]	62b
RHF/STO-3G	2.1022	1.4555	1.3880	22.7	79.7	−12.5	62b
RHF/3-21G	2.1384	1.4212	1.3692	21.9	41.6	−18.0	62b
RHF/4-31G	2.1300	1.4187	1.3654	21.2	41.9	−20.1	62b
RHF/6-31G*	2.1298	1.4125	1.3680	21.3	46.9	−10.6	62b
MP2/3-21G	2.1680	1.4477	1.3878	21.3	32.7	−22.0	62b
MP2/6-31G*	2.1332	1.4233	1.3794	22.2	37.6	−7.8	62b
MP4(DQ)/6-31G*[b]					40.5		62b
MP4(SDQ)/6-31G*[b]					39.8		62b
MP4(SDTQ)/6-31G*[b]					36.6		62b
CISD/DZVP//TCSCF/DVZP	2.238	1.462	1.351	16.4	35.8		61a
LDA//DZVP	2.142	1.421	1.382		33.0	−6.3	62d
LDA//TZVP	2.203	1.417	1.371	20.5	32.0	−8.3	62c
NLDF//DZVP	2.155	1.437	1.388		31.9	−10.7	62d
BP/TZVP	2.148	1.433	1.374	20.2	29.7	−14.5	62c
BLYP/6-31G*	2.161	1.440	1.385	20.0	29.8	−12.5	55b
ACM/6-31G*	2.142	1.420	1.379	21.3	36.1	−18.5	62e
B3LYP/6-31G*	2.144		1.376	20.7	33.9	−12.7	62f
experimental					32.9 0.5	−10.9	79

[a] Enthalpy of activation/reaction enthalpy. [b] On MP2/6-31G* optimized geometries.

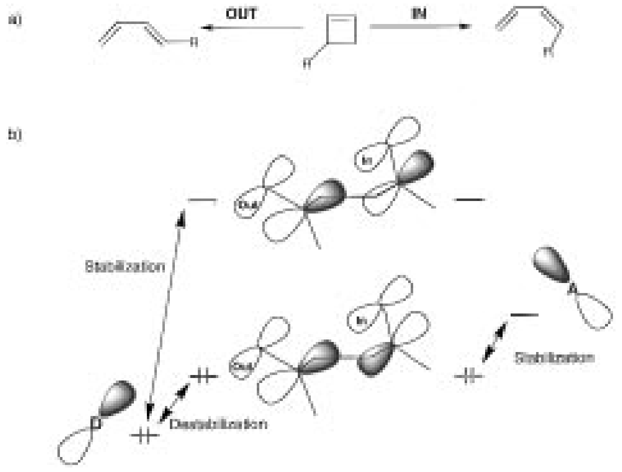

Figure 4. Torquoselectivity in the electrocyclic ring opening of substituted cyclobutenes.

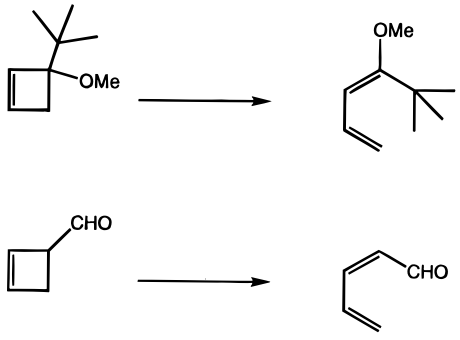

Figure 5. Selected experimental results predicted by theoretical calculations.

ization of some data but also gave several remarkable quantitative predictions. For example, even RHF calculations with modest basis sets predicted that outward rotation of a fluorine or methoxy substituent would be around 15 kcal/mol easier than inward rotation.[63] This is due to the strong repulsive interaction between the lone pair of a fluorine or oxygen with the breaking bond upon inward rotation. Indeed, later experimental studies, summarized in Figure 5, showed that the tendency of the methoxy substituent for outward rotation even forces a bulky *tert*-butyl to rotate inward.[64] Theory made a number of other remarkable, somewhat counterintuitive, predictions, such as the preference for inward rotation of the formyl group in formylcyclobutene.[65] Here, the low-lying vacant orbital of the formyl group provides a stabilizing interaction with the filled orbital of the breaking bond upon inward rotation. Calculations at numerous levels of theory have now been performed for about 20 substituted systems, and experiments have shown that they provide excellent predictions of both reactivity and stereoselectivity.[66]

Diels−Alder Reaction of Butadiene and Ethylene

One of the most commonly used reactions in organic chemistry is the Diels−Alder reaction, due to the high stereoselectivity and regioselectivity usually observed in these reactions.[67] Using the Woodward−Hoffmann rules and the concept of secondary orbital interactions, the preferred product can be easily predicted. The parent reaction is the addition of butadiene to ethylene to form cyclohexene, shown in Figure 6. Although this reaction has a relatively high activation energy of 27.5 kcal/mol,[62a] the reaction of appropriately substituted molecules proceeds rapidly and with high chemical yields.

The mechanism of this reaction has been the subject of a long and passionate debate, which has been documented in a recent review.[7b] As shown in Figure 6, both a concerted mechanism, involving a single, aromatic transition state, and a stepwise reaction pathway, involving a biradicaloid intermediate, have been proposed. Although most available data support the concerted mechanism, the stepwise pathway may be preferred in some substituted cases. Thus, the “energy of concert”, which is the energy difference between the stepwise and the concerted pathway, and the geometric and electronic structures of the species involved have been of considerable interest. Before we compare the computational results for the two pathways, we will discuss the geometries and energies obtained for the different species.

The concerted pathway has been studied by a number of different methods. Figure 7 shows the concerted, C_s symmetric transition structure TS_c. Selected parameters obtained from the various methods are summarized in Table 2.

There are some noticeable differences in the values computed for the lengths of the forming bond in the transition structure TS_c, depending on the method used. The RHF methods give very similar results for the geometry of the transition structure, independent of the basis set used. These methods predict a bond

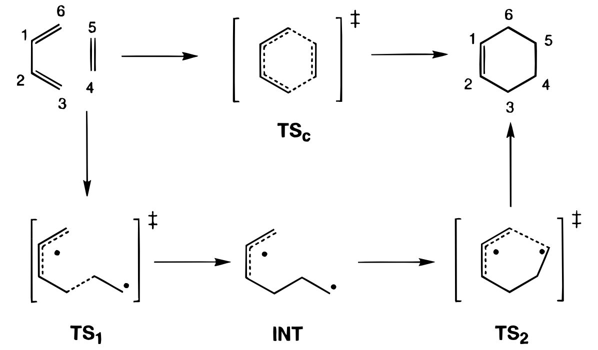

Figure 6. Concerted (top) and stepwise (bottom) reaction mechanisms for the Diels−Alder reaction.

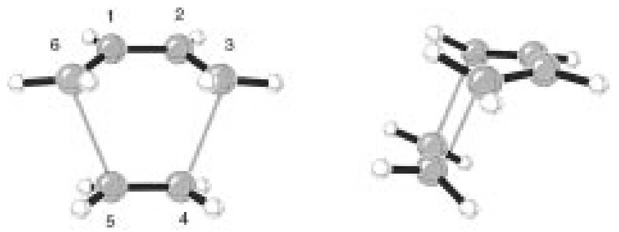

Figure 7. C_s transition structure for the concerted mechanism of the Diels−Alder reaction.

length of ~2.20 Å for the forming bond, with the values from smaller basis sets being slightly longer. The values from the semiempirical methods are close to the ones from minimum basis set ab initio calculations. It is interesting to note that the UHF method predicts a more advanced rehybridization process, leading to a lengthening of the C1−C2 and C5−C6 bonds in the transition structure. Otherwise, there are only very small changes in the geometrical values. In particular, the angle of attack, $\Phi_{C3-C4-C5}$, is very similar in all calculations and resembles the bond angle of the sp^3 center to be formed. Inclusion of electron correlation by the MP2 method leads to a substantially longer forming bond. If electron correlation is included using multiconfiguration techniques, the calculated bond length is quite similar to the RHF values. The use of local or nonlocal DFT methods gives even higher values for the forming bond distance, with a maximum of 2.411 Å for the local spin density approximation with a double-ζ basis set. Not surprisingly, the results from the hybrid DFT methods are between the ones from the nonlocal DFT and the Hartree−Fock calculations. The main lesson to be learned from these calculations is that a variety of methods quite faithfully represent the geometries of the transition structure, and this information is therefore readily available from computations.

As in the case of the cyclobutene ring opening, the energetics of the reaction differ widely by various methods. For example, the RHF/6-31G* calculations yield an activation energy of 47.4 kcal/mol, a value nearly twice the experimental result. The local spin density and the semiempirical methods perform even more poorly and are clearly incapable of treating the reaction energetics even qualitatively. The results from the MP2 calculations show again that these methods tend to overestimate electron correlation and therefore underestimate the activation energy by 7.5 kcal/mol. A more balanced, albeit computationally much more demanding, description of the correlation energy using the RQCISD(T)/6-31G* method with the MP2 optimized geometries yields results within the experimental error of the observed value. The multiconfiguration methods overestimate the activation energy, indicating that a balanced description of the dynamical electron correlation is crucial for a proper description of the reaction energetics of the Diels−Alder reaction. The use of the gradient corrected, nonlocal DFT methods offers significant improvements over the earlier methods, and a recently reported study using the hybrid Becke3LYP/6-31G* method gives an activation energy of 24.8 kcal/mol and a reaction energy of −36.6 kcal/mol, matching the experimental results closely.[72] The reaction energy is well reproduced by the Hartree−Fock methods, independent of the basis set, while the semiempirical and local DFT methods perform poorly.

The study of the transition structures for the stepwise, diradical pathway has yielded two possible transition structures for the initial attack of the diene, TS$_1$, with two corresponding conformations of the diradical intermediate, INT. So far, the third possible conformation of the intermediate and the transition structure for the ring closure of the biradical, TS$_2$, have not been reported. Although fewer methods have been applied to these structures, there are sufficient data available to analyze the trends followed by the different methods and to examine as well the relative importance of the stepwise and concerted mechanisms.[72] Figure 8 shows the anti transition structure and the anti conformation of the intermediate for the biradicaloid reaction. Selected results are summarized in Table 3.

As before, variation of the basis set in the Hartree−Fock methods does not cause large changes in the geometries of either TS$_1$ or INT. Inclusion of electron correlation by CASSCF or

TABLE 2: Selected Results for the Concerted Diels−Alder Reaction of Butadiene and Ethylene

method	R_{C3-C4} (Å)	R_{C2-C3} (Å)	R_{C1-C2} (Å)	R_{C4-C5} (Å)	$\varphi_{C2-C3-C4}$ (deg)	E_A (kcal/mol)	ΔE (kcal/mol)	ref
AM1						35.3[a]	−15.9[a]	62a
MINDO/3	2.19	1.38	1.425	1.37		95.9[a]	−58.2[a]	
RHF/STO-3G	2.217	1.359	1.421	1.366	103.9	36.0	−38.6	68
RHF/3-21G	2.210	1.370	1.402	1.376	103.5	35.9	−38.3	68, 69
RHF/6-31G*	2.201	1.378	1.393	1.383	102.6	47.4	−36.0	69, 72
UHF/3-21G	2.195	1.406	1.399	1.412			−26.9	68
MP2/6-31G*	2.286	1.378	1.410	1.380	101.6	20	−45.9	69, 72
UQCISD(T)/6-31G*[b]						29.4		71
RQCISD(T)/6-31G*[b]						25.5		71
CASSCF/3-21G (6e/6o)	2.217	1.392	1.397	1.400	101.9	37.3		69, 71
CASSCF/6-31G* (6e/6o)	2.223	1.398	1.397	1.404	103.1	43.8		69, 71
SVWN/6-31G**	2.400	1.363	1.415	1.361	100.8	3.6		73b
LDF/DZVP	2.411	1.368	1.420	1.367		6	−61.5	62d
NLDF/DZVP	2.322	1.389	1.420	1.391		20.4	−37.6	62d
BP88/6-31G**	2.318	1.378	1.410	1.381		18.7		25d
BLYP/6-31G*	2.292	1.395	1.415	1.398	102.6	22.8	29.8	62e, 55b
ACM/6-31G*	2.301	1.377	1.410	1.378	101.7	20.3		62e
B3LYP/6-31G*	2.272	1.383	1.407	1.386	102.4	24.9	−36.6[c]	72, 73a
experimental						27.5 ±2	−36.3	62a

[a] Enthalpy of activation/reaction enthalpy. [b] On CASSCF/6-31G* optimized geometries. [c] Alternative value: 46.6 kcal/mol (ref 73a).

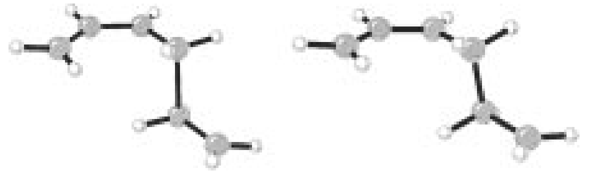

Figure 8. Transition structure TS_1 and intermediate for the stepwise pathway of the Diels−Alder reaction.

TABLE 3: Selected Results for the Stepwise Diels−Alder Reaction of Butadiene and Ethylene

	TS_1		intermediate		
methods	R_{C3-C4}	E_A	R_{C3-C4}	E_{rel}	ref
RHF/4-31G				37.5	75
UHF/3-21G	2.026				69
UHF/6-31G*	2.037				69
UQCISD(T)/6-31G* [b]		39.2		30.3	71
RQCISD(T)/6-31G* [b]		35.7		29.8	71
CASSCF/3-21G*	1.835	43.1	1.630	41.1	71
CASSCF/6-31G*	1.869	45.7	1.596	40.7	71
B3LYP/6-31G*	1.875	33.6	1.596	29.0	72

[a] Enthalpy of activation. [b] At CASSCF/6-31G* optimized geometry.

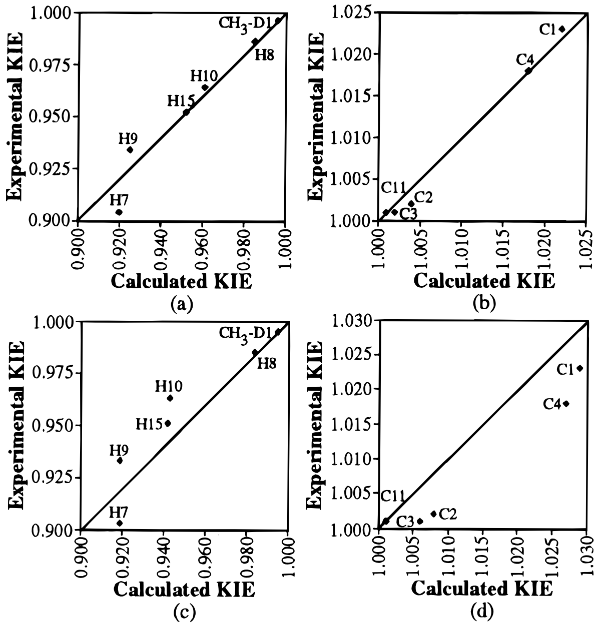

Figure 9. Comparison of experimental and computed Becke3LYP KIE for a Diels−Alder reaction.

DFT methods substantially shortens the forming bond in TS_1 to 1.835−1.874 Å. On the other hand, the C−C bond lengths in the intermediate INT are elongated by the inclusion of electron correlation. It is also interesting to note that, after a number of papers claimed a stepwise mechanism of the Diels−Alder reaction based on results from semiempirical MINDO/3 calculations,[70b] no such pathway could be calculated with the improved semiempirical AM1 method.[75] On the basis of the available data, it can be estimated that the intermediate is only a few kcal/mol lower in energy than TS_1.

One important objective of this work is to understand whether the Diels−Alder reaction proceeds via a stepwise or a concerted pathway and to determine how large the energy difference between these two pathways is. On the basis of experimental results, it has been estimated that the concerted pathway is favored by an "energy of concert" of 2−7 kcal/mol.[76] The results from the CASSCF/6-31G* and the Becke3LYP/6-31G* methods confirm the experimental estimates for the "energy of concert". Recently, a more direct validation of computational results has been provided by a direct comparison of high-precision primary and secondary kinetic isotope effects with predictions from DFT.[77] For the reaction of rather highly substituted compounds, the results from theory and experiment are in excellent agreement, as shown in Figure 9. This gives us confidence in the predicted transition structure, for significant errors in the calculated geometries would be expected to give deviations from the measured isotope effects.

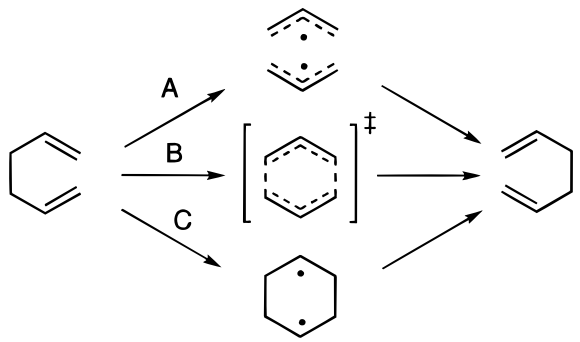

Figure 10. Possible pathways for the Cope rearrangement of 1,5-hexadiene.

Cope Rearrangement of 1,5-Hexadiene

The mechanism of the degenerate [3,3]-sigmatropic rearrangement of 1,5-hexadiene, the Cope rearrangement, has been the topic of heated discussions for nearly 50 years! The following questions have been raised: Which transition structure has the lowest energy? Does the 1,4-diyl structure correspond to an intermediate or a transition structure? Is the reaction synchronous or asynchronous? What is the electronic structure of the transition state: aromatic or diradicaloid? How does the transition state for the reaction via the boatlike transition state, which is approximately 11 kcal/mol higher in energy,[78] relate to these transition states? A variety of experimental studies attempted to answer these questions, but the results were subject to different interpretations by different investigators.[79] Almost every available method has been applied to this reaction, and only those of special interest will be discussed here. Selected results from the many theoretical studies that have been performed are summarized in Table 4.

Of the three possible pathways depicted in Figure 10, the dissociation of 1,5-hexadiene into two allyl radicals (pathway A) can be ruled out on energetic grounds. Using the group enthalpy increment method,[84] the two allyl fragments have been calculated to be 59.7 kcal/mol higher in energy than 1,5-hexadiene.[85] This is 26.2 kcal/mol more than the experimentally determined activation energy of 33.5 ± 0.5 kcal/mol.[86] However, the results from similar calculations on the two other pathways have been less clear.

Pathway B was proposed shortly after the original paper on the Cope rearrangement was published.[87] The picture of the Cope rearrangement as a concerted reaction, involving a single aromatic-type transition state, is in agreement with the Woodward−Hoffmann rules and is the most widely accepted mechanism.[88] This mechanism is also supported by Hartree−Fock, multiconfiguration methods (CI and CASSCF (only with a small basis set)) and DFT calculations. For the chair transition states, these methods predict bond lengths from 1.933 to 2.189 Å. The RHF and CASSCF methods overestimate the activation energy, but inclusion of dynamic correlation[89] by CI, MP2, or the nonlocal and hybrid DFT methods gives anything from good to excellent agreement with the experimental data. The boat transition states calculated with these methods are uniformly

TABLE 4: Selected Results for the [3,3]-Sigmatropic Shift of 1,5-Hexadiene

	chair TS		boat TS		
method	R_{C-C}	E_a	R_{C-C}	E_a	ref
AM1	1.656	37.1[a]	1.661	47.8[a]	91c
RHF/3-21G	2.020	45.7	2.140	55.6	81a
RHF/6-31G*	2.046	56.6	2.203	64.6	81b
MP2(fc)/6-31G*	1.784	31.4	2.055		80
MP4SDTQ/6-31G*//MP2(fc)/6-31G*	1.784	32.1[c]	2.055	43.1[c]	80
MP4SDTQ/6-31G*	1.794				82
CID/6-31G*	1.933		2.121		80
CISD/6-31G*	1.936		2.127		80
QCISD(T)/6-31G* [b]	1.769	35.9			80
CASSCF/3-21G	2.086	37.7	2.316	43.6	81b
CASSCF/6-31G*	2.189	45.8	2.615	49.0	93a
CASPT2N/6-31G* [b]	1.745	30.8	2.139	44.0	82
CASPT2N/6-311G** [b]	1.775	32.3	2.139	42.8	82
CASPT2N/6-311G(2d,2p)[b]	1.885	32.2	2.204	43.3	82
SVWN/6-31G*	1.753	19.8	1.966	33.2	83
BLYP/6-31G*	2.034	29.7	2.289	36.0	83
BLYP/6-311+G**	2.145	30.0	2.376	35.0	83
Becke3LYP/6-31G*	1.971	34.2	2.208	42.0	83
Becke3LYP/6-311+G**	2.043	34.8	2.279	41.2	83
experimental		33.5 ± 0.5		44.7 ± 2.0	86

[a] Enthalpy of activation. [b] Partial optimization. [c] On MP2(fc)/6-31G* optimzed geometries. [d] Activation enthalpies at 500 K.

looser by as much as 0.43 Å at the CASSCF/6-31G* level and are higher in energy by 3.2−9.9 kcal/mol.

A pathway involving a 1,4-diyl was first proposed by Grob et al.[90] and has been supported by Doering et al. based on thermochemical calculations that gave a relative energy of 33.7 kcal/mol for the diyl relative to the 1,5-hexadiene. However, the underlying experimental reference data were later found to be inaccurate, and the value for the relative energy has since been revised to 42 kcal/mol.

Several versions of the 1,4-diyl pathway were championed by Dewar et al. based on semiempirical calculations.[91] The semiempirical AM1 methods, for example, yield a tight 1,4-diyl intermediate with a bond length of 1.656 Å. Calculations based on perturbation theory of either a single or a multideterminant wave function (MP2 and CASPT2) also yield a 1,4-diyl with bond lengths of 1.769−1.794 Å, but these tight structures correspond to an aromatic transition state at the CASPT2 level of theory. The MP2 method overestimates the stability of radical species, and an analysis by Davidson et al. shows that this is also true for the CASPT2 method.[92] Nevertheless, the calculated activation energies are close to the experimental values. Aromatic and 1,4-diyl structures have been found to coexist on the CASSCF hypersurface![93] So which one is the "right" transition state?

The experiments that clarify this situation are the kinetic isotope effects (KIE) and their comparison with theoretical predictions.[94] The plot of the theoretical KIE versus the lengths of the forming/breaking bond, shown in Figure 11, demonstrates that there is indeed a good correlation between these parameters. Table 5 summarizes the results from various quantum mechanical calculations and compares them with the experimental values. From these calculations, it is clear that the theoretical KIE from methods predicting a tight, 1,4-like transition structure (such as AM1, MP2, and SWVN) are not in good agreement with the experimental values. The other methods, predicting a looser transition state, reproduce the experimental data much better.

Further insight into the nature of the transition state can be obtained by a closer analysis of the properties of the hydrogens. It can be seen for the calculated transition structure shown in Figure 12 that there are two stereochemically distinct sets of protons, labeled IN and OUT. The two diastereotopically different protons IN and OUT have different KIE, reflecting the slightly different environment of the two protons. An analysis of these differences shows that the OUT protons are attached to a typical sp^2-hybridized carbon, whereas the KIE

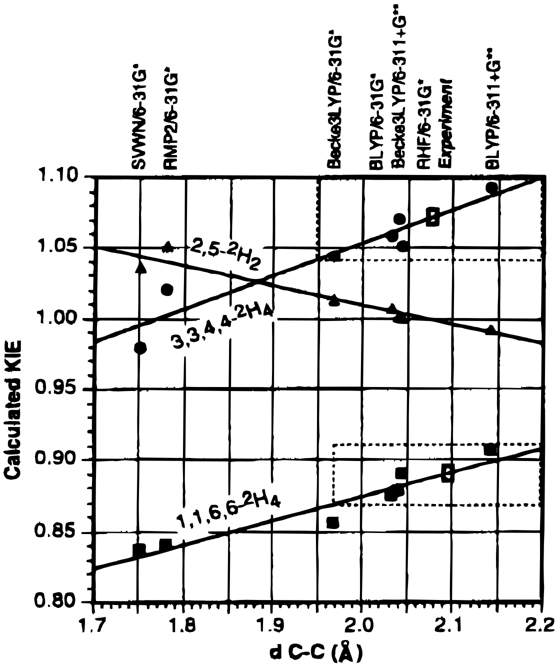

Figure 11. Plot of KIE vs interallylic distance for the cope rearrangement.

TABLE 5: Theoretical and Experimental KIE for the Cope Rearrangement (Chair Transition State, 521.15 K)

method	R_{C-C}	1,1,6,6-$^2D_4$	3,3,4,4-$^2D_4$	ref
AM1[a]	1.656	0.88	1.00	91c
RHF/6-31G*	2.046	0.89	1.05	81b
MP2/6-31G*	1.784	1.05	1.28	81b
CASSCF/3-21G	2.086	0.85	1.12	81b
SVWN/6-31G*	1.753	0.837	0.979	83
BLYP/6-31G*	2.034	0.875	1.058	83
BLYP/6-311+G**	2.145	0.906	1.092	83
Becke3LYP/6-31G*	1.971	0.855	1.044	83
Becke3LYP/6-311+G**	2.043	0.878	1.070	83
experimental[b]		0.89 ± 0.02	1.07 ± 0.03	94

[a] For 1,4-diyl structure. [b] Experimental KIE are for the 1-methyl and the 4-methyl derivatives.

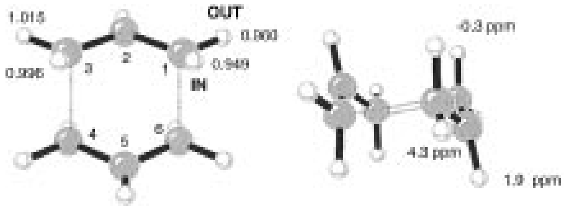

Figure 12. Chair transition structure for the Cope rearrangement with theoretical KIE (BLYP/6-31G*) and ^{1}H NMR shifts (IGLO/II//CISD/6-31G*).

of the IN proton is also affected by the nonbonding interactions of these hydrogens with nearby hydrogens in the transition state. A similar effect of diastereotopically different protons showing different KIE has been observed experimentally for electrocyclic reactions.[95] The aromaticity of the transition structure also has a profound effect on the magnetic properties of these protons. The chemical shifts calculated with the IGLO method[96] predicted that the axial or IN hydrogens will be shifted upfield as compared to the corresponding chemical shifts in the reactant. The equatorial or OUT protons are shifted downfield, reflecting the aromatic nature of the transition state.[80]

Conclusions

This article provides examples of how quantum mechanical tools can be used by chemists to explore mechanisms of pericyclic reactions. It is clear from the results presented that semiempirical methods and local spin density functional theory are not adequate for the calculation of organic transition structures. Hartree−Fock theory with appropriate basis sets provides reasonable geometries in many cases, even though the activation energies are severely overestimated due to the neglect of electron correlation. Relative energies and substituent effects can, however, be predicted with relatively high precision. Quantitatively accurate calculations require the balanced inclusion of electron correlation by configuration interaction, multiconfiguration, and perturbation theory or a combination of these. Although these methods can be highly accurate, they are computationally prohibitive for all but relatively small systems. Modern DFT techniques, in particular the Becke3LYP hybrid method, are much faster and have been remarkably successful in predicting geometries and energetics for a large number of organic reactions.

There are four areas where further theoretical developments are necessary to enable organic chemists to address new questions and problems. First, the reliability of calculations can be further improved by the development of new higher accuracy methods. Several new methods such as the CASPT2 or the CBS method have been introduced recently, and more techniques such as pseudospectral methods are under development. Second, the speed of the available methods has to be improved, to allow the study of larger systems. Here, the introduction of fast multipole methods, possibly in combination with new DFT methods, offers great promise. Third, realistic models of chemical reactions have to consider the environment in which they take place. The development of implicit and explicit solvent models is therefore a very active field of research. Last, the need to link experimental and theoretical results makes the development of new methods for the calculation of observable properties highly desirable. Future developments in these areas will give organic chemists a better understanding of the origins of chemical reactivity and will allow them to predict more confidently the mechanisms of reactions using quantum mechanical methods.

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