1,3-Dipolar Addition of Phenylazide to the Carbon−Carbon Double Bond: An ab Initio Study

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With use of density functional methods and large basis sets, as implemented in the Jaguar v. 3.0 ab initio electronic structure package, we calculated the activation energy of the 1,3-dipolar addition of phenylazide to 19 different reactants containing a carbon−carbon double bond. The results provide an excellent prediction of the relative reaction rates observed experimentally as the substituents of the reactant are varied. Regioselectivity of the products of the reaction also are predicted reliably by the calculations. The use of a large experimental data set and full representation of the reactant species (as opposed to smaller model systems) provided a high degree of confidence in the ability of the electronic structure methods to reproduce experimental data reliably. The effects of method of geometry optimization and inclusion of solvation effects were investigated and found to be relatively small.

Introduction

The use of ab initio quantum chemical methods to study organic reaction mechanisms has been ongoing for the past two decades. A great deal of progress has been made both in calculating barrier heights and reaction rates in reasonable agreement with experimental data, and in providing physical insight into the nature of the transition state and the factors controlling the reaction rate. Representative works are those of Houk and colleagues[1−5] and Fleischer et al.[6] However, this process is presently an art, rather than an automated, reliable procedure that can be applied to an arbitrary reaction of interest. Significant issues include the ability to treat large systems, the quality of the results for a given electron correlation method, and the accuracy of the solvation model used, if this is an important influence on the reaction rate.

The explosive growth of computational power, the development of new correlation methods, and the advances in quantum chemical software performance suggest that it may now be possible to realistically treat organic reactions of large molecules and make predictions in good agreement with experimental data. In particular, our ab initio electronic structure code, Jaguar v. 3.0[7] (formerly known as PS-GVB), has demonstrated capabilities for carrying out large-scale calculations using various electron correlation methods in relatively modest CPU times. The quantitative accuracy of these correlation methods for absolute barrier heights is presently unclear; this is a very active area of basic research in electronic structure methodology. However, the calculation of relative reaction rates for a series of related reactions, often the key chemically interesting question in the design of synthetic pathways, should be a significantly less demanding task, one in which reliable prediction of experimental results may be possible with current technology.

In the present article, we begin to explore this possibility by investigation of the 1,3-dipolar addition of phenylazide to the carbon−carbon double bond. This particular reaction was chosen because it is often encountered in organic synthesis, and there is a large body of experimental data available to verify experimental findings. We use Hartree−Fock (HF) methods to optimize the geometries of the transition states of 19 complexes; geometry optimization is followed by single-point energy calculations using the BLYP and B3-LYP variants of density functional theory (DFT) and several different basis sets, the largest of which is the cc-pVTZ(-f) basis of Dunning and coworkers.[8−10] This allows the effect of both basis set and electron correlation to be examined in a systematic fashion. Tests of the effects of correlation in geometry optimization and of solvation are also performed.

In the course of this cycloaddition, the C═C acts as 1,3-dipolarophile and adds to the azide group of phenylazide to form a five-member dihydrotriazole ring. In this concerted step two π bonds are broken and two σ bonds are formed. A brief glance at the product stereochemistry easily reveals that in an unsymmetrically substituted C═C more than one isomer of the product can be formed, as seen in Figure 1.

However, experiments[11] show that the reaction follows a different path depending on the nature of the substituent on the dipolarophile. Electron-withdrawing groups show strong preference toward 4-substituted products, whereas electron-donating groups yield exclusively 5-substituted triazoles. Groups that do not have a strong electronic effect lead to a mixture of 4- and 5-substituted products. On the other hand, substituents also influence the reaction kinetics. For example, the addition of phenylazide to norbornene is 7700 times faster than the addition to cyclohexene,[12] although norbornene and cyclohexene differ only in a methylene group.

Our specific goals here are to gain a deeper understanding of the reaction mechanism using ab initio methods and to explain the influence of substituents on reaction regioselectivity and kinetics. More generally, a successful effort along these lines provides evidence that the ab initio methodology can be used effectively to approach problems encountered in the experimental laboratory.

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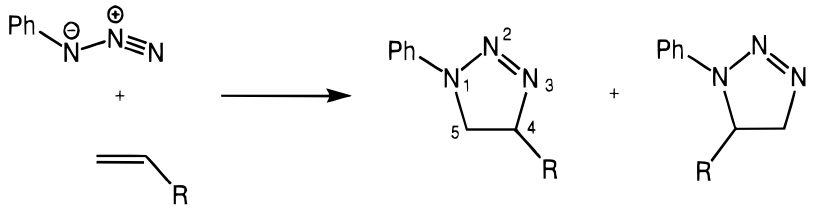

Figure 1. Possible product composition in the reaction with an asymmetrically substituted dipolarophile.

Method

The rate of a chemical reaction is given by Arrhenius Law:

$$k = A\mathrm{e}^{-E_a/RT} \tag{1}$$

where k is a rate constant, A is a preexponential factor characteristic of the reaction, and E_a the activation energy. For reactions that follow similar mechanisms, the preexponential factor can be assumed to have the same value in all cases. In the context of 1,3-dipolar addition of phenylazide only the substituent on the carbon−carbon double bond is varied from one case to the next. This substituent is not directly involved in the reacting core where bonds are being formed or broken, but rather acts as a perturbation. Hence, we can assume that the reaction mechanism will be the same throughout the series, which means that A will be relatively constant and that the reaction rate will depend primarily on the activation energy.

For reactions in which two products are formed, each of the products will have a specific transition state characterized by its geometry and energy. The transition state with lower energy will lead to the more favored product and, when the energy difference between the two transition states becomes sufficiently large, only one product will result. Therefore knowing the relative energies of different transition states can help explain why reactions with dipolarophiles carrying certain substituents give only one product isomer, whereas others give a mixture of both.

Geometry Optimization. To calculate the relevant activation energies, minimized geometries of reactants and transition state are required. Structures corresponding to all reactants were optimized by minimizing the HF energy[13] and using the 6-31G** basis set.[14,15] We used the Jaguar suite of programs[7] to carry out quantum chemical calculations.

The optimization of transition state geometries is difficult to accomplish.[16] First, a good initial guess for these geometries cannot be obtained by classical force-field optimization as it can be for the reactants. Instead, a ridge method developed by Ionova and Carter[17] was used to interpolate between geometries of reactants and product. Because the ridge search is computationally expensive compared with the minimum search, it was performed only for the smallest case discussed, the addition of hydrazoic acid to ethene. Once this transition state was fully optimized, it was used as a template to build the starting geometries for other systems in the series. This was done in two phases. In the first phase, substituents were added to the template, the dihydrotriazine-like transition state core was constrained and the structure was minimized to get the optimal conformations of substituents. In the second phase, the constraints on the reactive core were removed, and the geometry of the transition state was fully optimized. The second phase was performed using the partitioned rational function optimization (P-RFO) (vide infra) algorithm.

P-RFO Method for Transition State Geometry Optimization. As we mentioned, the optimization of transition state geometries is more complex than the search for energy minima. In the latter case, the optimization is on the right track as long as the energy decreases. This is not true in the search of transition states, for the transition state is an energy minimum along all the coordinates but one, which we refer to as the transition vector, along which it is a maximum. However, in most cases the transition vector is not known in advance. Hence choosing the coordinate along which to search for the transition state can be difficult and the optimization might not lead to the right transition state, or in some cases, to none at all. Also, the convergence range is narrow, which requires a starting geometry to be very close to the final optimized structure.

These problems can be alleviated through the use of the P-RFO technique, described elsewhere.[18] The P-RFO method approximates the potential energy not as a polynomial, but as a rational function. This makes it possible to choose a coordinate along which the energy will be optimized and ensures that the final stationary point is of the right order (typically a first-order transition state). These properties make the convergence range of P-RFO method wider, and hence more flexible.

TABLE 1: Activation Energies (in kcal/mol) Calculated for the Lowest Energy Transition States: (a) HF/6-31G, (b) BLYP/6-31G**, (c) BLYP/cc-pVTZ(-f), (d) B3-LYP/6-31G**, and (e) B3-LYP/cc-pVTZ(-f)[a]**

	dipolarophile	activation energy (a)	(b)	(c)	(d)	(e)
I	1-hexene	42.071	14.800	19.800	17.713	22.477
	isoprene	42.039	14.666	19.927	17.621	22.622
	cyclopentene	40.099	13.170	18.554	16.087	21.106
	1-methylcyclopentene	42.068	15.110	20.672	18.069	23.129
	cyclohexene	44.490	16.347	21.718	19.649	24.501
	norbornene	37.514	10.708	16.002	13.650	18.574
	norbornadiene	37.467	10.506	15.916	13.582	18.705
	[2,2,2]-bicyclooctene	42.054	13.977	19.532	17.072	22.214
II	methyl acrylate	37.876	14.413	19.068	16.434	20.965
	acrylonitrile	38.418	14.533	19.079	16.729	21.057
	maleic anhydride	39.663	14.680	19.568	16.943	21.500
	N-phenylmaleimide	36.470	12.880	17.446	15.079	19.330
	dimethyl maleate	40.789	16.043	21.424	18.074	23.008
	methyl *trans*-cinnamate	42.723	17.437	22.475	19.888	24.490
III	ethyl vinyl ether	39.229	12.643	18.163	16.018	21.268
IV	styrene	41.293	13.945	19.096	16.922	21.715
	4-methylstyrene	41.263	13.744	18.837	16.778	21.576
	4-chlorostyrene	42.280	14.189	19.276	17.122	21.887
	4-methoxystyrene	41.144	13.386	18.551	16.568	21.421

[a] Dipolarophiles are grouped as: I, aliphatic; II, electron-withdrawing; III, electron-donating; IV, aromatic.

Energy Calculations. Activation energies for 1,3-dipolar addition are calculated as differences between ab initio energies of transition states and reactants and are given in Table 1. Calculations are done at the HF and DFT[19,20] level using 6-31G** and Dunning's triple-ζ cc-pVTZ(-f)[8−10] basis sets. The cc-pVTZ(-f) basis set has been modified by removing *f* functions on the first row atoms, and *d* functions on hydrogens. Two different functionals are used for the DFT method, namely BLYP and B3-LYP. BLYP uses the Becke 88 nonlocal gradient correction to exchange[21] and the Lee−Yang−Parr (LYP) nonlocal correlation functional.[22] B3-LYP uses Becke's three-parameter exchange functional[23] in combination with the LYP.

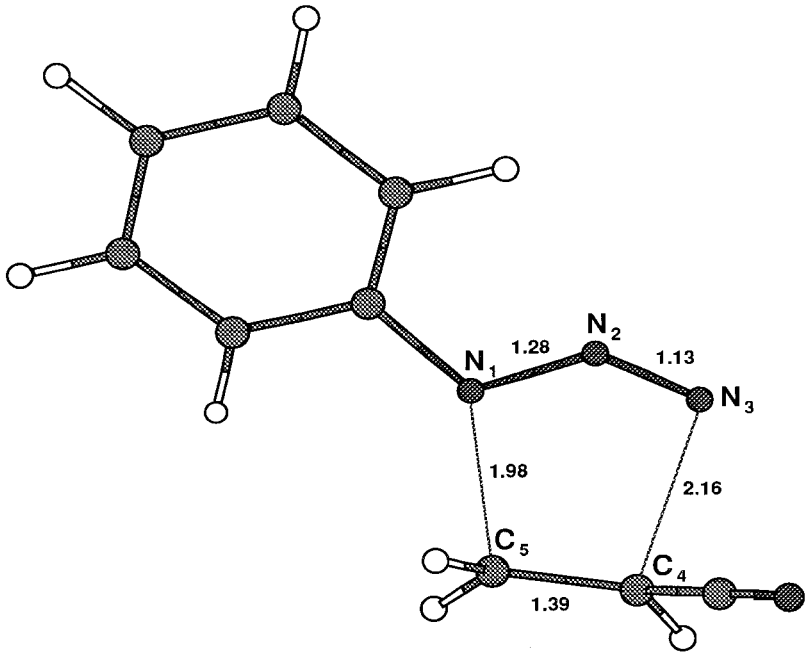

Figure 2. Transition state geometry for phenylazide addition to acrylonitrile. Bond lengths in angstroms are shown for the reaction core.

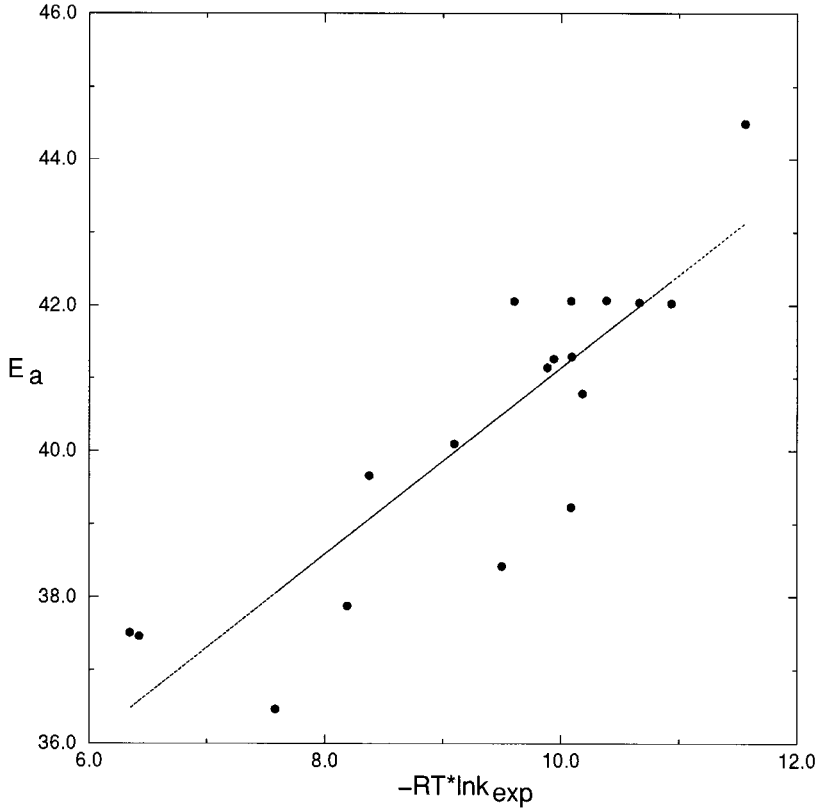

Figure 3. Activation energies in kilocalories per mole calculated by HF/6-31G** method versus experimental reaction rate constants.

Computed activation energies are compared with the experimental rate constants, or more precisely, with $RT \ln k_{exp}$.

Results and Discussion

Geometries of Transition States. Transition state geometries for the 1,3-dipolar addition are generated by unconstrained ab initio optimizations for a series of different dipolarophiles. As expected, all transition states have a common dihydrotriazole-like reaction core of which the structure varies only slightly. The substituents on the ring represent the variable part of the geometries, and their conformation varies from case to case. A typical transition state geometry is shown in Figure 2.

The least variable bonds in the five-member reaction core are N_1—N_2 and C_4—C_5, their average lengths being 1.27 and 1.38 Å, respectively. The lengths of the other bonds in the ring depend more on the nature of a dipolarophile substituent. For aliphatic, aromatic, and electron-donating groups the N_3—C_4 bond is ~20% shorter than the N_1—C_5 bond, and the discrepancy in the bond length increases with the electron-donating ability of the substituent. The presence of an electron-donating group

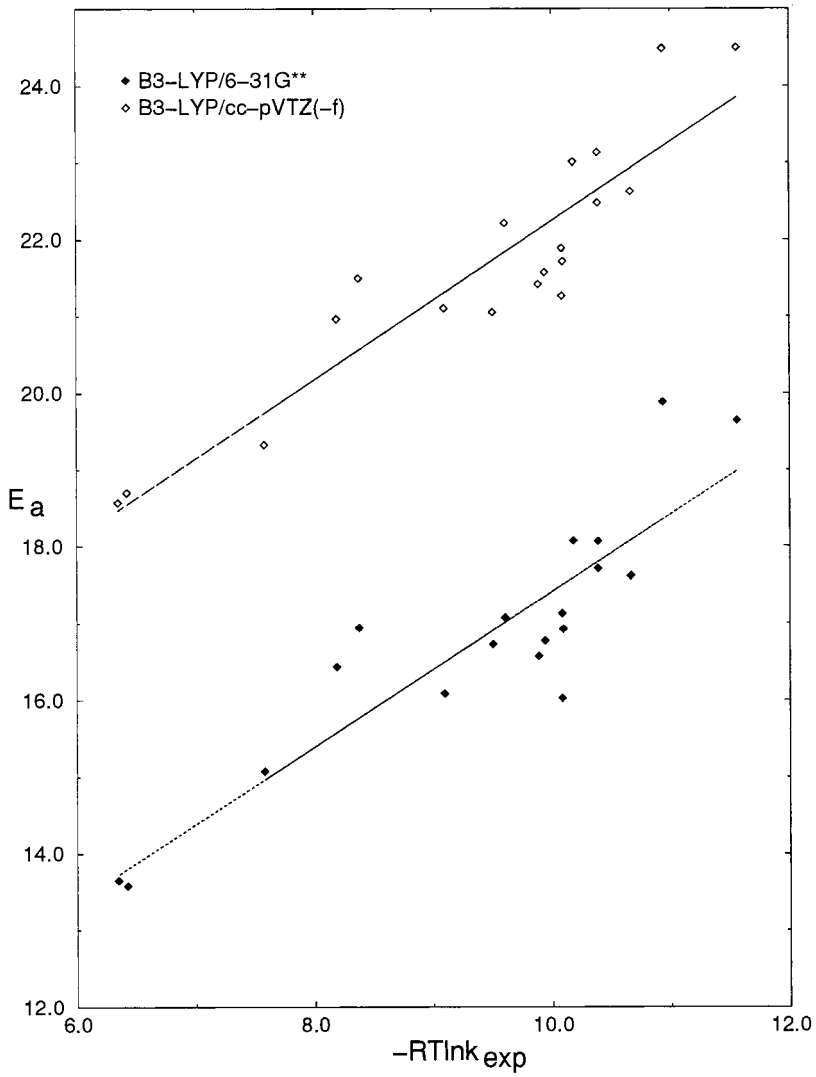

Figure 4. Activation energies in kilocalories per mole calculated by DFT(B3-LYP) method with 6-31G** and cc-pVTZ(-f) basis sets correlated with experimental rate constants.

also causes the N_2—N_3 bond to be somewhat longer (1.164 Å), hence indicating a relatively late transition state. On the other hand, the electron-withdrawing groups affect the N—C bond lengths in opposite way, causing the N_1—C_5 bond to be ~5% shorter. Also, the short N_2—N_3 bond indicates the early transition state. The asymmetric character of the transition states and the influence of substituents with different electronic effects can be explained through the interaction of frontier orbitals. More will be said about this later in the text.

Kinetics. The computed gas-phase activation energies (see Table 1) are surprisingly well correlated with experimental rate constants measured in solutions, as can be seen in Figures 3, 4, and 5. This shows that thermodynamic quantities calculated in the gas phase can be compared successfully with the corresponding quantities measured in solution as long as the solvation effects are negligible (see below for an explicit test of this hypothesis).

DFT(B3-LYP) performs better than either HF or DFT(BLYP), as can be seen from the statistical analysis of the data (Table 2). This is in agreement with the fact that the hybrid exchange functional used in B3-LYP gives more accurate energies, for example in calculation of atomization energies for the G2 database of Pople and coworkers.[24] Also, B3-LYP, like other DFT methods, has an advantage over HF for taking into account electron correlation. As expected, calculations done using the larger basis set, cc-pVTZ(-f), are in better agreement with experimental data than those done using 6-31G**, although the effects here are quantitative, not qualitative, in nature.

Effects of Inclusion of Electron Correlation in Geometry Optimization and Solvation on Activation Energies. The excellent correlation between theory and experiment shown above for relative rate constants and activation energies suggests that effects not included in the theoretical protocol are relatively small. To test this assumption explicitly, we consider two systems, reactions of phenylazide with ethyl vinyl ether and methyl *trans*-cinnamate, respectively, which display significant deviations from the best-fit line in Figure 4, in opposite directions. There are many possible explanations for these deviations; experimental error, variations in the preexponential factor, solvation effects, and an inadequate level of electron correlation. If a specific explanation is correct, one would expect there to be substantial changes, in opposite directions, as the missing ingredient is included in the calculations.

We test two possible effects here: the use of DFT, rather than HF, methods to carry out geometry optimization and the inclusion of solvation free energy in the calculations. Geometry optimizations are carried out with the B3-LYP/6-31G** approach. Solvation free energies in CCl_4 are computed via our self-consistent reaction field (SCRF) formalism, which was described in detail in refs 25 and 26. The results of the

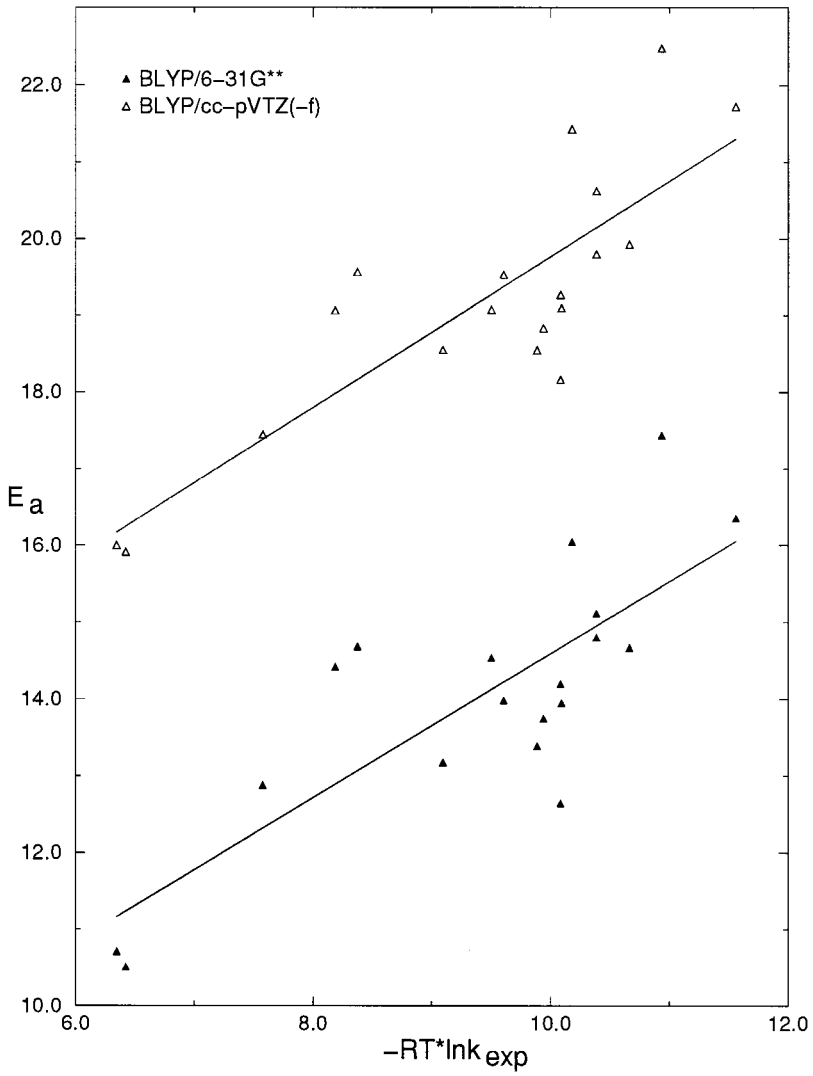

Figure 5. Activation energies in kilocalories per mole calculated by DFT(BLYP) method with 6-31G** and cc-pVTZ(-f) basis sets correlated with experimental rate constants.

TABLE 2: Regression Analysis of Correlation between Computational Activation Energies and Experimental Rate Constants

method	correlation coeff	standard dev	regression coeff
HF/6-31G**	0.8699	2.11	1.28
DFT(BLYP)/6-31G**	0.7941	1.70	0.94
DFT(BLYP)/cc-pVTZ	0.8375	1.69	0.98
DFT(B3-LYP)/6-31G**	0.8970	1.62	1.01
DFT(B3-LYP)/cc-pVTZ	0.9181	1.62	1.03

TABLE 3: Effects of Inclusion of Solvation and Electron Correlation in Geometry Optimization on Activation Energies[a]

method	E^1_{act}	E^2_{act}	ΔE_{act}
B3LYP/6-31G**//HF/6-31G**	16.018	19.888	3.87
ditto in CCl_4	14.112	18.320	4.21
B3LYP/6-31G**//B3LYP/6-31G**	17.446	20.954	3.51
B3LYP/cc-pVTZ//HF/6-31G**	21.268	24.490	3.22
B3LYP/cc-pVTZ//B3LYP/6-31G**	21.507	24.658	3.14

[a] The activation energies are calculated for the reactions for which the activation energy deviates the most from the linear fit: addition of phenylazide to (1) ethyl vinyl ether and (2) methyl *trans*-cinnamate.

calculations are shown in Table 3. It can be seen that although nontrivial shifts occur in the absolute activation energies of the two compounds, the relative values are much less affected, altering by ~0.3−0.7 kcal/mol in each case. These calculations confirm that the effects we have neglected in producing the results of Figure 4 are rather small.

TABLE 4: HF/6-31G Activation Energies (in kcal/mol) of Isomeric Reactions**[a]

substituent on C=C	E_a[b] 4-subs.	E_a[b] 5-subs.	isomer ratio
cyano	**38.418**	42.428	880:1
ethoxy	45.593	**39.229**	1:47000
phenyl	41.711	41.293	1:2

[a] Representative cases include the reactions with dipolarophile bearing electron-withdrawing, electron-donating, and neutral groups. The activation energy of a dominant isomer is printed in **bold**. [b] subs. = substituted.

Regioselectivity. As was mentioned before, the activation energy was calculated for all possible product isomers. The differences between these activation energies determine the product composition, assuming kinetic equilibrium. Some representative data that help explain this principle are shown in Table 4. If the energy difference is more than 3 kcal/mol there will be less than 1% of the kinetically disadvantaged isomer in the product mixture. This is the case for all systems with electron-withdrawing or electron-donating substituents. For instance, consider the addition of phenylazide to acrylonitrile.

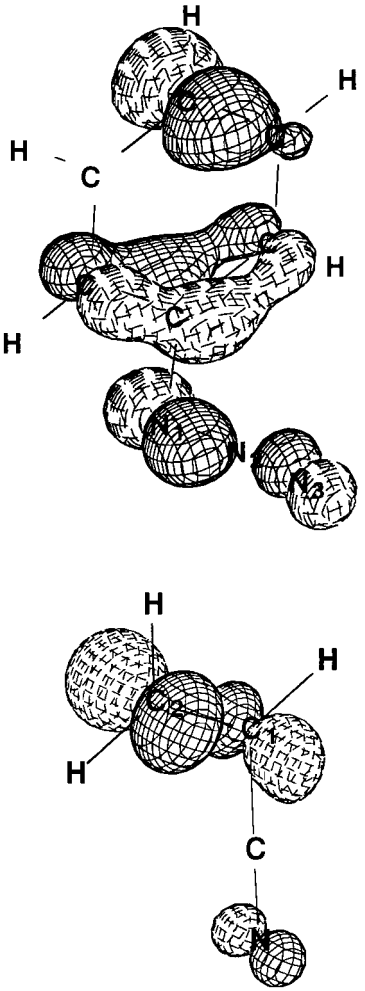

Figure 6. Phenylazide HOMO and acrylonitrile LUMO from HF/6-31G** wavefunctions. The relative orientation of phenylazide and the dipolarophil that leads to the 4-substituted product, as shown here, ensures more efficient overlap between molecular orbitals.

In this case, the cyano group exerts a strong electron-withdrawing effect. The preferred product is 4-cyano-l-phenyl-4,5-dihydrotriazine with the activation energy 4.01 kcal/mol lower than that of the 5-substituted product.

A qualitative explanation of why one of the isomers has activation energy so much lower than the other can be obtained by studying the electronic structure of the reactants. The orbitals playing the dominant role during bond formation are frontier orbitals.[27] Both highest occupied molecular (HOMO) and lowest unocuppied molecular (LUMO) orbitals of phenylazide show an uneven distribution of electronic density along the N—N—N dipole. In the HOMO case (see Figure 6), the orbital coefficient on N_1 is larger than on N_3, whereas LUMO (not shown) presents the opposite picture. Now consider the dipolarophile. If the substitution arrangement on the carbon−carbon double bond preserves the symmetry, the orbital coefficients on C_1 and C_2 will be the same and the orientation of the reactant during the addition has no effect on transition state energy. This also holds in the substituents with weak electronic effect, like alkyl or aryl. However, the presence of a strong electron-withdrawing group on the C═C polarizes the electron density distribution along the double bond. In the LUMO of acrylonitrile (see Figure 6) the orbital coefficient on C_2 is larger that on the C_1, and vice versa in the HOMO. This asymmetric distribution

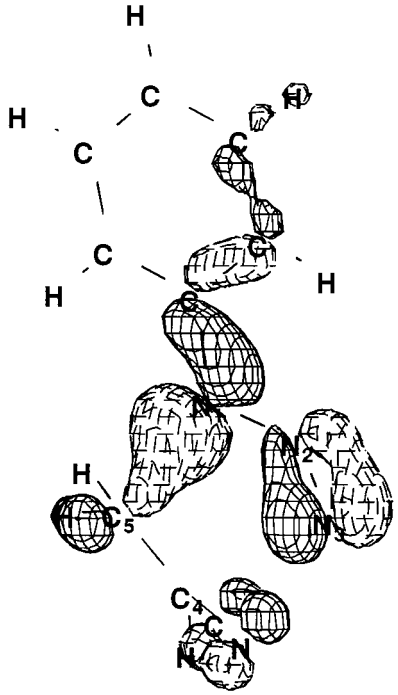

Figure 7. Transition state: phenylazide + acrylonitrile. This HF/6-31G** molecular orbital depicts the formation of the N_1—C_5 bond.

of electronic density implies that the overlap of the frontier orbitals in the course of the reaction depends on the orientation of the reactants. The orientation of the cyano group that leads to the 4-substituted product offers better orbital overlap, and therefore lower transition state energy, than the alternative. An equivalent argument can be made for electron-donating substituents, like the ethoxy group, which prefer 5-substituted products.

Figure 7 shows a molecular orbital of a typical transition state for this reaction. The C—N bonds have uneven length, the N_1—C_5 bond being somewhat shorter. This means that one of the bonds is formed earlier than the other one and, taking an overall look, the 1,3-dipolar addition is not a perfectly concerted process.

Conclusions

We have shown here that it is possible to handle a suite of relatively large organic reactions in a completely ab initio fashion. We compared experimental reaction rates as a function of different substituents on carbon−carbon double bond measured in solution to theoretical gas-phase activation energies and found an excellent correlation between the two data sets. Our method involved ab initio geometry optimization of reactants and transition states for each substituent and calculating single-point DFT energies for these geometries to get activation energies.

With use of the same principle of calculating activation energies we could predict the product composition depending on the substituent on the dipolarophile. It shows that strong electron-withdrawing and -donating group give only one product isomer (4- and 5-substituted, respectively), whereas aliphatic and aromatic substituents produce a mixture. This result is in agreement with the experimental findings.

The approach described here can be applied systematically to the study of a wide range of important organic reaction mechanisms. Reactions of interest would include aromatic substitutions and nucleophilic displacement on benzylic carbon atom. These problems will be the subject of future publications.

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Appendix

A full set of parameters, encompassing all the compounds addressed in this work, along with molecular structures are available from the authors upon request.

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