ORGANIC LETTERS

2006
Vol. 8, No. 23
5179−5182

Probing the Limits of Rate Acceleration Mediated by Hydrogen Bonds

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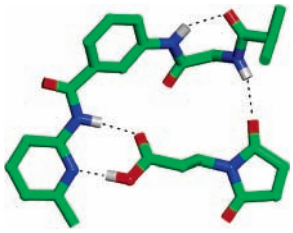
Received May 26, 2006

ABSTRACT



A simple receptor and substrate are used to probe the relationship between transition-state charge and the level of rate acceleration that can be created by stabilizing the transition state through hydrogen bonding. Pericyclic reactions are accelerated less than 2-fold by the receptor, whereas a conjugate addition reaction is accelerated more than 30-fold. Therefore, substrate polarization by hydrogen bonding would only appear to be effective for reactions that generate significant charge at the transition state.

Pericyclic reactions,[1] which have nonpolar transition states, such as the Diels−Alder reaction, are utilized extensively in modern synthetic chemistry to synthesize complex cyclic structures successfully, often with excellent control of stereochemistry. Indeed, they often form the key step in synthetic strategies[2] for the construction of natural products. Given the preponderance of fused carbocyclic and heterocyclic rings in natural products, it is therefore somewhat surprising that, to date, there have been relatively few reports[3] of enzymatic systems that are capable of performing pericyclic transformations with high levels of efficiency and selectivity. Indeed, the involvement of pericyclic processes in some of these transformations is still an open[4] question. In general catalytic antibodies, which are capable[5] of catalyzing pericyclic processes, achieve rate accelerations[6] that are, on average, 2−3 orders of magnitude lower than those observed for reactions with polar transition states or intermediates, such as amide hydrolysis. One possible explanation for the discrepancies observed in rate accelerations for these different reaction types is that it is inherently more difficult to accelerate nonpolar reactions[7] because acceleration cannot be achieved simply by stabilizing charges. Therefore we believed it was worthwhile exploring the relationship between the change in charge developed during the rate-determining step of a reaction and the rate acceleration achieved by stabilizing (or destabilizing) that charge.

If there is a simple function relating the change in charge at the key step along the reaction coordinate with rate acceleration, then this function might take one of three

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10.1021/ol061290c CCC: $33.50
Published on Web 10/20/2006

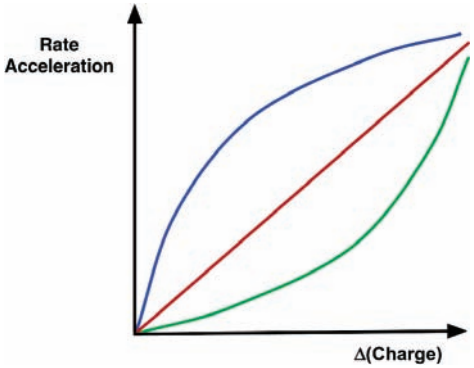
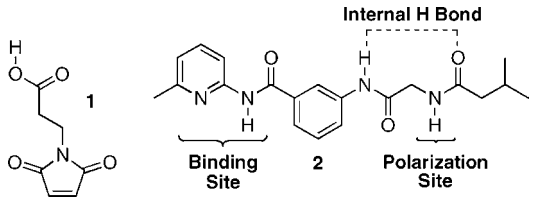


Figure 1. Possible relationships between the change in charge at the key step on the reaction coordinate (Δ(charge)) and rate acceleration.

possible forms (Figure 1). The observed rate accleration may be directly proportional to this change in charge (red line, Figure 1). Alternatively, a reaction which develops a small change in charge in the key step may lead to a disproportionately large rate acceleration (blue curve, Figure 1). In this scenario, almost all reactions should be susceptible to acceleration by charge stabilization or destablization. Alternatively, it may be necessary for a reaction to develop a significant change in charge in the key step before any rate acceleration is observed (green curve, Figure 1). In this situation, only reactions that generate polar entities in the key step should be accelerated by charge stabilization or destablization.

We recognized that one approach to determine the nature of the relationship between transition-state charge and rate acceleration is through a systematic study that uses a single model catalyst and a single common substrate capable of participating in a range of reaction types. An appropriate choice of substrate is key to the success of this approach. The chosen compound must be synthesized easily and be capable of participating in a wide range of reaction types. Based on these criteria, we selected maleimide **1** as our substrate. The maleimide ring can act as a dienophile, a dipolarophile, or an acceptor in a conjugate addition reaction. The nitrogen atom affords a convenient attachment point for the recognition site which will be used to bind the substrate to the catalyst. In this respect, we chose the carboxylic acid because a suitable recognition site as we have exploited[8] the association between this functional group and amidopyridines in recognition-mediated reactions previously.



The role of the organic catalyst is to polarize the substrate π-system through the formation of one or more hydrogen bonds to the carbonyl groups of the maleimide. Molecular mechanics calculations were used to design receptor **2**, which is complementary to maleimide **1**. This receptor should be capable of binding **1** through the formation of two hydrogen bonds between the amidopyridine present in the binding site of **2** and the carboxylic acid present in **1**. The bisamide arm, appended to the meta-substituted benzamide, is then able to form a third hydrogen bond (the polarization site) to one of the carbonyl groups on the maleimide ring. It is this hydrogen bond that should polarize the substrate π-system. It is interesting to note that the calculations[9] predict that the minimum energy conformation of **2** (Figure 2a) contains a

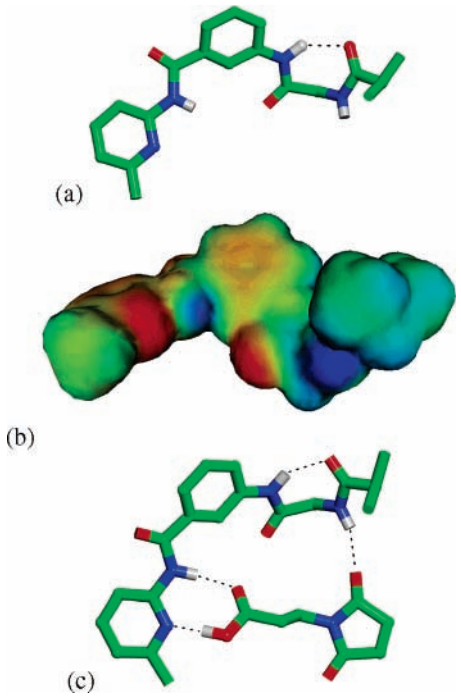


Figure 2. (a) Stick representation of the minimum energy conformation of receptor **2**. (b) Electrostatic potential surface for the minimum energy conformation of receptor **2**. Regions of positive charge are encoded blue and regions of negative charge are encoded red. (c) Stick representation of the minimum energy conformation of the complex [**1**·**2**]. In all molecular structures, carbon atoms are green, nitrogen atoms are blue, oxygen atoms are red, and hydrogen atoms are white. Most hydrogen atoms are omitted for clarity. Hydrogen bonds are shown by dotted lines.

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(7) We define a nonpolar reaction as one in which no entities with significant charge separation exist at any point on the reaction coordinate.

fourth internal hydrogen bond between the aromatic amide NH of the *m*-phenyl spacer and the carbonyl group of the isovaleryl amide.

This fourth hydrogen bond serves to increase the hydrogen-bond-donating ability, as judged by the electrostatic potential surface[10] of **2** (Figure 2b), of the NH that binds to the substrate. The calculations demonstrate (Figure 2c) that **1** and **2** are, indeed, complementary. It should be noted at the outset that this receptor was designed to probe the hypothesis set out above and was *not* designed to achieve large catalytic effects on the reactions studied.

The presence of all of these hydrogen bonds was confirmed directly and indirectly by two methods. First, we performed a $^1H-^{15}N$ HSQC experiment on a sample of **2** ([**2**] = 15 mM) in $CDCl_3$ at room temperature and on a mixture of **1** and **2** ([**1**] = [**2**] = 15 mM) under the same conditions. There are significant chemical shift changes in both the ^1H and ^{15}N dimensions for all three NH resonances on moving from receptor **2** to the complex [**1**·**2**]. Second, we determined the association constant (K_a) for the [**1**·**2**] complex in $CDCl_3$ at 35 °C by using the ^1H NMR titration method. Nonlinear curve fitting of the chemical shift change data for four protons to a 1:1 binding model afforded a value for the K_a of 750 ± 30 M^{-1}. This value corresponds to a free energy of binding of −17.0 kJ mol^{-1} at 35 °C. The observed K_a is significantly higher than that measured for an isolated amidopyridine-carboxylic acid complex under the same conditions (95 M^{-1}, −11.7 kJ mol^{-1}). These results are entirely consistent with the calculated structure for [**1**·**2**].

With our receptor and substrate in place, we selected a series of reactions whose rate-determining steps featured transition states of varying charge separation (Figure 3).

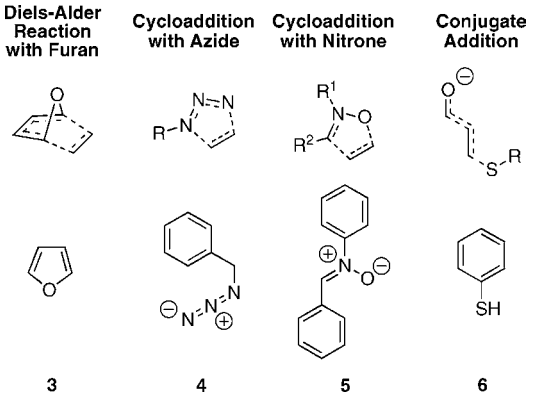

Figure 3. Reaction types and corresponding reagents selected for comparison using catalyst **2**.

The Diels−Alder reaction was performed by using furan **3** as the diene, the azide cycloaddition was performed by using benzyl azide **4** as the dipole, the 1,3-dipolar cycloaddition was performed by using diphenylnitrone **5** as the dipole, and the conjugate addition was performed by using thiophenol **6** as the nucleophile. We performed each of the four reaction types under the same conditions in the presence and in the absence of 20 mol % of **2**. In each case, the starting concentrations of **1** and the appropriate reaction partner were 50 mM and the progress of the reactions were monitored by 500 MHz ^1H NMR spectroscopy for 16 h at 35 °C. Deconvolution of the appropriate resonances arising from the starting material and the product, from spectra recorded at 30 min intervals, allowed concentration−time profiles for each reaction to be extracted. Each reaction was performed at least three times. These concentration−time profiles were used as the basis for simulation and fitting of the data, which allow kinetic parameters to be extracted. For each reaction, we determined the rate constant for the reaction in the absence of receptor **2** (k_{uncat}) and the rate constant for the reaction in the presence of catalyst **2** (k_{cat}). These rate constants[11] were, in turn, used to assess the level of rate acceleration observed in each reaction through the k_{cat}/k_{uncat} ratio.

The measured k_{cat}/k_{uncat} ratios[12] for the four reactions were: Diels−Alder reaction, $k_{cat}/k_{uncat} = 1.0$; azide cycloaddition, $k_{cat}/k_{uncat} = 1.5$ nitrone cycloaddition, $k_{cat}/k_{uncat} = 1.8$; conjugate addition, $k_{cat}/k_{uncat} = 37$. Qualitatively, it is obvious from these data that there is a significant difference in the performance of catalyst **2** between the cycloadditions which all have rather nonpolar transition states and the conjugate addition, which develops significant negative charge in the rate determining step. These data alone, however, are not enough to establish the nature of the relationship between transition-state charge and the rate acceleration that can be developed by stabilizing that charge. In an attempt to establish a more quantitative relationship, we need to derive a metric that describes the change in charge distribution as we move toward the transition state in the rate-determining step of each of the four reactions. In other words, having established a quantitative *y*-axis for the graph shown in Figure 1 by determining the k_{cat}/k_{uncat} ratio, we now needed to establish a quantitative *x*-axis.

In order to accomplish this task, we turned to electronic structure calculations. Transition states were successfully located at the B3LYP/6-31G(d) level of theory for all four

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(9) Molecular mechanics calculations were performed by using the AMBER* force field and GB/SA solvation model for $CHCl_3$ as implemented in Macromodel (Version 7.1, Schrodinger Inc., 2000).

(10) The lowest energy conformation of **2**, located by the molecular mechanics conformational search, was used as the basis for an electronic structure calculation at the HF/6-31G(d) level of theory and the electrostatic potential surface of **2** was computed and visualized by using data from this calculation.

(11) In the Diels−Alder reaction between **1** and **3**, both possible diastereoisomers, *endo* and *exo*, are formed in an approximately 1:1 ratio. In analyzing the kinetic data for this reaction, we summed the concentrations of these two products and fitted the formation of total cycloadduct to the kinetic model. Similarly, we considered only total cycloadduct concentration in the reaction between **1** and **5** which also affords two diastereoisomeric products. The presence of catalyst **2** had an insignificant effect on the diastereoselectivity of the dipolar cycloaddition between **1** and **5**.

(12) Hamilton and co-workers (Fan, E. K.; Vicent, C.; Hamilton, A. D.; *New J. Chem.* **1997**, *21*, 81−85) have reported a receptor, similar in structure to **2**, which is also capable of accelerating the reaction between a maleimide and a thiolate anion.

reactions studied. As the mode of action for catalyst for **2** to accelerate these reactions involves stabilizing the charge at the carbonyl oxygen atom, we next computed the percentage change in the electrostatic potential[13] at these oxygen atoms going from the ground state of maleimide **1** to each of the four transition states. In cases where the transition state does not possess a symmetry operation relating the two C═O groups on the maleimide ring (hence, the electrostatic potentials on the two oxygen atoms are different), we used the average of the two values for the two carbonyl oxygen atoms. This procedure allowed us to construct a Δ(ESP C═O) scale (Figure 4) on which to place our measured rate

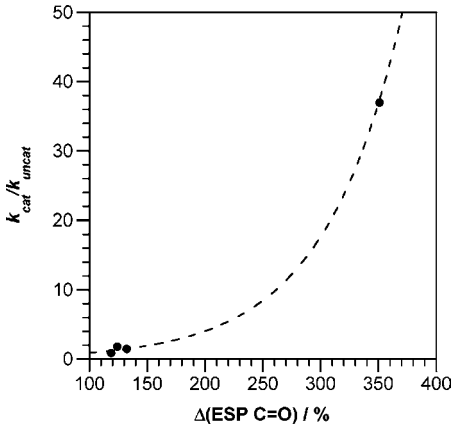

Figure 4. Plot of $\log(k_{cat}/k_{uncat})$ vs Δ(ESP C═O). Points represent the experimental results. The dashed line represents the fit of an exponential function ($k_{cat}/k_{uncat} = e^{(\Delta(ESP(C=O)))}$) relating transition state charge and k_{cat}/k_{uncat} to the experimental data and is provided only to guide the eye.

accelerations for the four reactions. Despite the significant limitations[14] of this approach, it is clear from Figure 4 that a strongly nonlinear relationship exists between the change in charge at the carbonyl oxygen atoms and the rate acceleration achieved receptor **2**.

We have described a simple model system in which the same catalyst, binding the same substrate, is capable of accelerating two pericyclic reactions and one conjugate addition reaction by means of a single hydrogen bond to the maleimide substrate. The rate accelerations observed vary from zero, in the case of the Diels−Alder reaction, to over 30-fold in the case of the conjugate addition, which involves the thiophenolate anion. The results suggest that significant transition state charge must be present before any rate acceleration can be induced by the formation of polarizing hydrogen bonds to the substrate. These results may be of some utility in the rational design of catalysts for organic chemical reactions.

Acknowledgment. We thank the University of St Andrews, the Engineering and Physical Sciences Research Council (Research Studentship to R.M.C.), and the Biotechnology and Biological Sciences Research Council (Grant No. B20402) for financial support. Technical assistance at the University of St Andrews was provided by Melanja Smith (NMR) and Caroline Horsburgh (MS). One of us (D.P.) gratefully acknowledges the use of facilities at the Department of Chemistry and Biochemistry, University of California, Los Angeles, during the preparation of this manuscript.

Supporting Information Available: Description of the synthesis of **2**. Spectroscopic data for receptor **2**. Spectroscopic data for the products of the reactions between **1** and **3**−**6**. Details of kinetic simulation and fitting. Cartesian coordinates for receptor **2** and complex [**1**·**2**]. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) The molecular electostiatic potential was calculated using GAMESS (Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S.; Windus, T. L.; Dupuis, M.; Montgomery, J. A., Jr. *J. Comput. Chem.* **1993**, *14*, 1347−1363) at the B3LYP/6-31G(d), and the potential was mapped on to a Connolly surface describing the transition state.

(14) In fact it is hard to envisage other reactions that can occur at a maleimide ring, proceed within the constraints of the kinetic assay, and are likely to have values of Δ(ESP C═O) that are intermediate in value between the cycloaddition reactions and the conjugate addition reactions used here. This problem is a significant limitation of the approach used here. Despite this fact, it is worth noting that a linear extrapolation from the pericyclic reactions would predict an approximately 10-fold rate enhancement for the thiophenol conjugate addition. The observed rate acceleration is clearly much higher than this prediction.