Organocatalysis

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Kinetics of Iminium Ion Catalysis**

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Since MacMillan's original report in 2000,[1a] iminium ion catalysis using cyclic secondary amines has been established as an effective platform for asymmetric Diels–Alder,[1] conjugate addition,[2–6] [3+2] cycloaddition,[7] [4+3] cycloaddition,[8] and conjugate reduction[9] reactions, thereby providing powerful new methods for fundamental bond-construction processes. Such reactions frequently proceed in high yield and with exceptional levels of asymmetric induction, thus forming a new mode of reactivity that has met with overwhelming acceptance from the chemical community owing to the highly practical nature of the transformations.[10]

Despite impressive recent advances, detailed mechanistic understanding of these reactions remains elusive. Knowledge of kinetics would allow the design of more-active catalysts, and hence make a fundamental contribution to this vibrant field of research. Having developed theoretical models for the formation of iminium ions and Diels–Alder cycloaddition,[11] we present kinetic and structural investigations into the individual steps of a model reaction, shedding light on the relationship between structure and activity and hence a rationale for further catalyst development.

Central to these reactions is the activation of an α,β-unsaturated carbonyl compound by a secondary amine to form an iminium ion, which is activated to cycloaddition or nucleophilic attack. The proposed catalytic cycle for the Diels–Alder reaction (Figure 1) comprises three main steps, denoted I, II, and III, which involve three discrete species containing the catalytic amine group (**A**–**C**) and four species incorporating the starting α,β-unsaturated carbonyl compound (**D**–**G**). Transformation I involves formation of the reactive iminium ion by condensation of a secondary amine with the α,β-unsaturated carbonyl compound. Transformation II is the key bond-formation process, while transformation III is the hydrolysis of an iminium ion to release the reaction product and regenerate the catalyst.

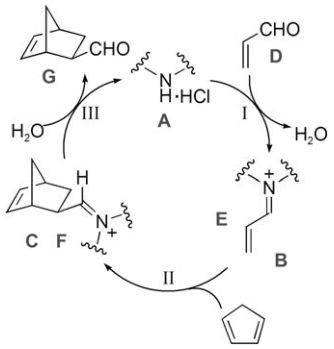
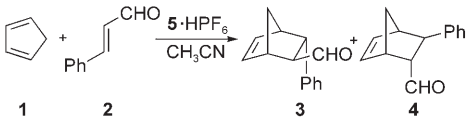


Figure 1. Proposed catalytic cycle for the iminium ion catalyzed Diels–Alder reaction. Labels **A**–**C** follow the species containing the catalytic amine group; labels **D**–**G** follow the species incorporating the starting α,β-unsaturated carbonyl compound.

We sought a suitable model system from which to obtain kinetic data for each step I–III. After examining a range of secondary amines, co-acids, and solvents, as well as dienes and dienophiles, we adopted the experimental conditions outlined in Scheme 1. 2-(Trifluoromethyl)pyrrolidine (**5**) is an active catalyst for this prototypical Diels–Alder transformation, with which the reaction proceeds to 93% conversion after 6 h (10 mol% **5**·HCl, 25 °C, 0.95 M). The reaction is easily followed by ^{1}H and ^{19}F NMR spectroscopy, permitting structural elucidation of all intermediates. Importantly, HPF_6 provides stable, crystalline iminium ion intermediates that can be stored at room temperature, easily manipulated, and analyzed by single-crystal X-ray diffraction. This combination also provides a favorable equilibrium position for step I (98% iminium ion), which exists as a single isomer, as confirmed by NOESY experiments, X-ray diffraction, and theoretical data.



Scheme 1. Model reaction used in this study.

Cinnamaldehyde (1 equiv) was added to a solution of **5**·HPF_6 in CD_3CN (0.25 M, 293 K), and the reaction resulted in disappearance of starting material and formation of the iminium ion in the ^{1}H NMR spectrum. No significant differ-

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ence in reactivity between **5**·HCl and **5**·HPF_6 was observed. In this way, the second-order rate constant for step I was determined to be $k_{293} = (2.65 \pm 0.35) \times 10^{-3}\ dm^3\,mol^{-1}\,s^{-1}$ (Supporting Information). Carrying out the same procedure at temperatures of 298 and 303 K established the activation parameters $E_a = (100.0 \pm 7.9)\ kJ\,mol^{-1}$ and $A = 5.89 \times 10^{14}\ s^{-1}$ (Figure 2; $\Delta H^{\neq} = (97.5 \pm 7.8)\ kJ\,mol^{-1}$, $\Delta S^{\neq} = (27.3 \pm 26.3)\ J\,K^{-1}\,mol^{-1}$, see the Supporting Information). By DFT calculations[11] the barrier to formation of iminium ion was estimated to be $E_a = 96.9\ kJ\,mol^{-1}$. Given the approximations involved (in basis set, functional, and solvation), this agreement is fortuitous but nonetheless provides reassurance that values from experiment and theory are reliable.

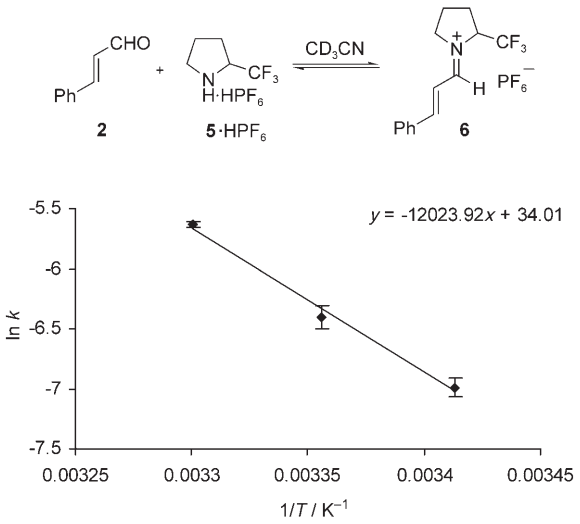

Figure 2. Arrhenius plot for iminium ion formation, with standard error of mean shown as error bars.

Use of HPF_6 allows isolation of iminium ion intermediates, and the single-crystal X-ray structure of **6** is shown in Figure 3. This result is not unique to **5**; PF_6 salts of many iminium ions can be isolated (the structure of pyrrolidine·HPF_6 is reported in the Supporting Information). The structure of **6** confirms the expected geometry, with *E* orientation of the iminium ion and essentially coplanar arrangement of the iminium ion and phenyl ring. X-ray and DFT-optimized geometries show much similarity (Figure 3). The DFT data also confirm that the *E* isomer of the iminium ion is 10.6 $kJ\,mol^{-1}$ more stable than the *Z* isomer.

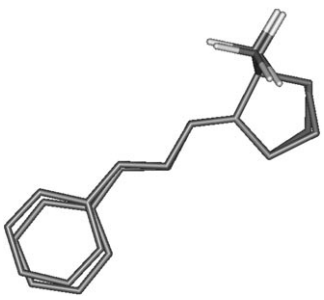

Figure 3. Overlay of X-ray and DFT structures of iminium ion **6**; hydrogen atoms are omitted for clarity. Full crystal and geometrical details are reported in the Supporting Information.

In addition to structural characterization, isolation of this reactive species is made possible by the stability of the PF_6 salt, and hence, independent study of step II is possible. Cyclopentadiene (3 equiv) was added to a solution of **6** in CD_3CN (0.25 M, 293 K), the reaction was followed by ^1H NMR spectroscopy, and the second-order rate constant was determined to be $k_{293} = (3.74 \pm 0.02) \times 10^{-4}\ dm^3\,mol^{-1}\,s^{-1}$, which is considerably slower than formation of the iminium ion at 293 K. Rate constants at 298 and 303 K give $E_a = (45.1 \pm 1.7)\ kJ\,mol^{-1}$ and $A = 4.14 \times 10^4\ s^{-1}$ (Figure 4; $\Delta H^{\neq} = (42.7 \pm 1.7)\ kJ\,mol^{-1}$, $\Delta S^{\neq} = (-164.9 \pm 5.9)\ J\,K^{-1}\,mol^{-1}$). DFT calculations support this data, giving $E_a = 62.3\ kJ\,mol^{-1}$, which is in reasonable agreement with experiment.

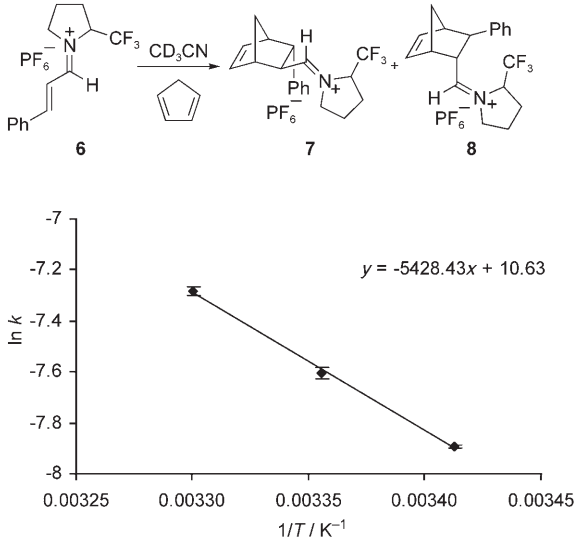

Figure 4. Arrhenius plot for the Diels–Alder cycloaddition, with standard error of mean shown as error bars.

Step III, hydrolysis of the product iminium ion, is irrelevant to the overall kinetics of the catalytic cycle, as based upon the following observations. Isolation of a Diels–Alder cycloadduct iminium ion proved impossible, as these compounds immediately hydrolyzed to the corresponding aldehydes. Diels–Alder cycloaddition in the presence of a trace amount of water initially showed formation of the aldehyde products **3** ($\delta = 9.85$ ppm) and **4** ($\delta = 9.54$ ppm), but after complete consumption of water, the corresponding iminium ions **7** and **8** were observed by ^1H NMR spectroscopy ($\delta = 8.63$–8.78 ppm). The equilibrium between the Diels–Alder adducts **3** and **4** with the catalyst **5**·HPF_6 shows no indication of the corresponding iminium ions under the reaction conditions. Finally, DFT calculations give a barrier of 73 $kJ\,mol^{-1}$, that is, considerably less than for step I.

These data allow us to draw several chemically relevant conclusions. Firstly, the Diels–Alder cycloaddition (step II) is the rate-determining step of the catalytic cycle; under the conditions used, this step is six times slower than iminium ion formation, despite the activation energy for step II being

much smaller than for step I. The Arrhenius parameter A gives rise to this kinetic profile, with A approximately 10 orders of magnitude smaller for the cycloaddition step, as a result of stricter steric requirements for step II. The Arrhenius parameter A derived for step II is of similar magnitude to previously reported values for noncatalyzed Diels–Alder reactions.[12]

To examine the effect of the CF_3 group in **5**, we compared the reactivity of **5**·HCl with pyrrolidine·HCl (**9**·HCl) and proline methyl ester hydrochloride (**10**·HCl) as catalysts for the Diels–Alder cycloaddition of cinnamaldehyde and cyclopentadiene. Under identical reaction conditions (MeOH, 298 K, 0.95 M, 10 mol% cat., 6 h), the yields of isolated product for the transformations for **9**·HCl, **10**·HCl, and **5**·HCl were 5, 62, and 93%, respectively.

The agreement between experiment and theory for steps I and II is pleasing to note, and lends experimental support to our theoretical studies.[11] However, experimental data show that steric and collision parameters, accounted for in the parameter A, are as important as activation energy. These parameters are not accessible from single-molecule DFT studies, such that we do not have a fully predictive theoretical model. In the absence of these data, we sought indicators of potential reactivity. Since cycloaddition is the rate-determining step, the LUMO energy of the dienophile should play a major role.[13] Indeed, the E_{LUMO} value of the iminium ion derived from **5** and cinnamaldehyde is found to be considerably lower (−2.78 eV) than that from either **9** or **10** (−2.50 and −2.61 eV, respectively). A plot of this LUMO (Figure 5) shows its location on the iminium C=C bond and π system. Thus, the CF_3 substituent lowers the E_{LUMO} value of the iminium ion compared to the parent pyrrolidine, and thus accelerates the C–C bond-forming step.

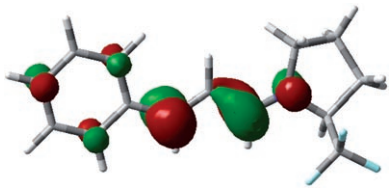

Figure 5. LUMO of iminium ion derived from **5**, with isosurface plotted at 0.05 au.

In summary, we report kinetic and theoretical investigations into an iminium ion catalyzed Diels–Alder reaction using 2-(trifluoromethyl)pyrrolidine as the catalyst. We show that iminium ion formation and hydrolysis of the Diels–Alder adducts are rapid, and that C–C bond formation is the rate-determining step. This kinetic profile is due to the steric requirements of the cycloaddition reaction, since the activation energy of this step is much less than that of iminium ion formation. Activation barriers calculated using DFT are in general agreement with experiment for both steps. This kinetic and mechanistic information will enable the derivation of structure–reactivity relationships for the development of novel catalyst architectures. In particular, the LUMO energy of the iminium ion was identified as a key parameter, and the future design of more-active catalysts will target this aspect.

Experimental Section

Crystal data for **6**: $C_{14}H_{15}F_9NP$, $M_r = 399.24$, crystallized from methanol, colorless block needles, monoclinic, space group $P2_1/c$, $a = 18.5797(5)$, $b = 10.6257(3)$, $c = 8.38670(10)$ Å, $\beta = 98.718(2)°$, $V = 1636.59(7)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.620$ Mg m^{-3}, $T = 120(2)$ K; 19829 reflections collected, 3737 independent ($R_{int} = 0.0411$) which were used in calculations $R1 = 0.0395$, $wR2 = 0.0978$ for observed unique reflections [$F^2 > 2\sigma(F^2)$] and $R1 = 0.0530$, $wR2 = 0.1047$ for all 3737 unique reflections. The maximum and minimum residual electron densities on the final difference Fourier map were 0.328 and −0.442 e Å^{-3}, respectively. CCDC-657257 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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