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A completely selective and strongly accelerated Diels–Alder reaction mediated by hydrogen bonding ☆

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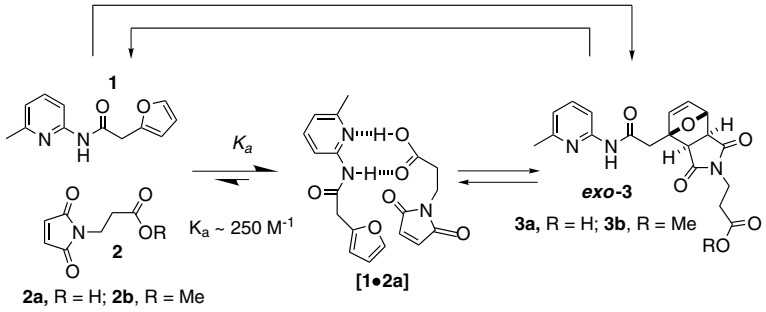
Abstract—A Diels–Alder cycloaddition between a furan and a maleimide is presented in which the presence of complementary hydrogen bonding sites dramatically accelerate the reaction and, additionally, ensure that only one of two possible diastereoisomers is formed.

Previous work within our group[1] has illustrated the potential for acceleration of cycloaddition reactions through the location of complementary recognition sites, such as an amidopicoline and carboxylic acid, on the partners in the reaction. In all of the examples we have described to date, the major role of the molecular recognition was to effect a stabilisation of the product ground state through the persistence of the noncovalent interactions in the product. In this way, high thermodynamic effective molarities (EM) (up to 11 M) could be generated from only two hydrogen bonds. These systems, however, all possessed low kinetic EMs (in the range of 10–200 mM) suggesting the molecular recognition does not stabilise the transition state leading to the observed product, indicating that the system is operating through predisposition.[2] In this work, we describe a fast and selective Diels–Alder reaction (Scheme 1), mediated by hydrogen bonding, in which the acceleration and selectivity are generated by transition state stabilisation.

Building blocks **1** and **2** were synthesised using standard protocols[3] (Scheme 1). All kinetic data were collected using 500 MHz ^{1}H NMR spectroscopy at 35 °C and the starting concentrations of **1** and **2a** or **2b** were 25 mM. The appearance of signals in the chemical shift range δ 5.18–5.39, corresponding to the resonances of the cycloadduct protons, were used to derive the



Scheme 1. Reaction scheme for the recognition-mediated formation of **3** from **1** and **2**.

Keywords: Diels–Alder; Cycloaddition; Hydrogen-bonding; Molecular recognition.
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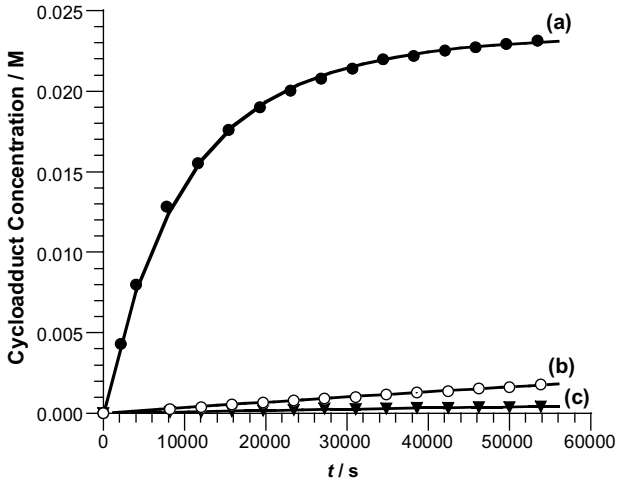


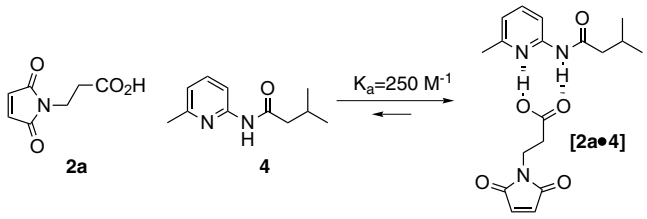
Figure 1. Rate profiles, recorded in $CDCl_3$ at 35 °C, for formation of (a) *exo*-**3a** from building blocks **1** and **2a**, (b) *exo*-**3b** and (c) *endo*-**3b** from building blocks **1** and **2b**. In all cases, the concentration of the starting materials was 25 mM. Solid lines represent the best fit of the rate profile to the appropriate kinetic model.

concentrations of the cycloadduct in the reaction mixture. In order to ascertain rate constants k_1 and k_2, representative of the bimolecular reaction, the maleimide acid **2a** was replaced with the corresponding methyl ester **2b** so as to disrupt any recognition-mediated processes.

The results of our kinetic studies are presented in Figure 1. The bimolecular reaction between **1** and **2b** (rate profiles (**b**) and (**c**)) was very slow and unselective. Both diastereoisomers, *exo*-**3b** and *endo*-**3b** are formed in an approximately 2:1 ratio with a combined conversion of 4% in 5 h. By contrast, the recognition-mediated reaction between **1** and **2a** (rate profile (**a**)) was both fast and selective. Only the *exo*-adduct **3a** is formed and the conversion reached over 80% in around 5 h.

Such a fast reaction without an initial lag period is diagnostic of a reaction, which proceeds through a binary complex such as [**1•2a**]. However, in order to completely rule out the possibility that adduct **3a** was acting as a template for its own formation and thus as an autocatalytic self-replicator,[4] an experiment was performed in which 33 mol % of *exo*-**3a** was added to the initial reagent mixture. This experiment displayed a rate profile identical to (**a**) confirming that *exo*-**3a** could not influence its own formation.

In order to gain a deeper understanding of the kinetics of this system, we undertook simulating and fitting the raw data (Fig. 1) to the model shown in Scheme 1 using the SIMFIT[5] program. The association constant, between maleimide **2a** and 3-methyl-*N*-(6-methyl-pyridin-2-yl)-butyramide **4** (Scheme 2), was determined by the titration method using 500 MHz ^{1}H NMR spectroscopy, at 35 °C in $CDCl_3$. It provided a measure of the concentration of starting materials **1** and **2a** existing as species [**1•2a**] or, in other words, an indirect means of estimating the forward and reverse rate constants



Scheme 2. The association between **2a** and **4**.

Bimolecular reactions

$\mathbf{1} + \mathbf{2b} \underset{k_2}{\overset{k_1}{\rightleftharpoons}}$ *endo*-**3b** $\quad k_1 = 1.45 \pm 0.10 \times 10^{-5}\ M^{-1}s^{-1}$, $k_2 = 2.01 \pm 0.36 \times 10^{-6}\ M^{-1}s^{-1}$

$\mathbf{1} + \mathbf{2b} \underset{k_4}{\overset{k_3}{\rightleftharpoons}}$ *exo*-**3b** $\quad k_3 = 5.75 \pm 0.12 \times 10^{-5}\ M^{-1}s^{-1}$, $k_4 = 5.41 \pm 0.36 \times 10^{-8}\ M^{-1}s^{-1}$

Reagent Association

$\mathbf{1} + \mathbf{2a} \underset{k_6}{\overset{k_5}{\rightleftharpoons}}$ [**1•2a**] $\quad K_a = k_5 / k_6 = 250\ M^{-1}$

***Pseudo*-unimolecular reaction**

[**1•2a**] $\underset{k_8}{\overset{k_7}{\rightleftharpoons}}$ **3a** $\quad k_7 = 14.9 \pm 0.01 \times 10^{-5}\ s^{-1}$, $k_8 = 2.05 \pm 0.13 \times 10^{-6}\ s^{-1}$

Kinetic EM = k_7/k_3 = 2.59 M = 2590 mM

Thermodynamic EM = k_7k_4/k_3k_8 = 68 mM

Scheme 3. Explicit kinetic model for the reaction between **1** and **2** to which the experimental data was fitted. Rate constants k_7 and k_8 were calculated by simulation and fitting of the experimental data to this model.

($K_a = k_5/k_6$, Scheme 3) for this particular interaction (**1**+ **2a** ⇄ [**1•2a**]). Whilst the recognition motif was identical to that seen between compounds **1** and **2a**, only one reactive centre was present, eliminating the prospect of a chemical reaction and ensuring that any chemical shift changes were purely the result of association between complementary recognition sites on **2a** and **4**. The concentration of guest **2a** was varied between 0 and 71.3 mM whilst that of the host **4** was maintained at 10 mM. The observed change in chemical shift of the resonances arising from the proton in the 4 position of the pyridine ring in compound **4** was monitored as the concentration of guest was varied. From the data the association constant K_a was calculated as 250 M^{-1}.

Using the kinetic data from the control experiments involving the methyl ester **2b**, we were able to obtain good estimates for the rate constants k_1, k_2, k_3 and k_4 in our kinetic model (Scheme 3). The estimate of the stability constant for the [**1•2a**] complex obtained from the NMR titration experiment could also be expressed as a ratio of two rate constants (k_5 and k_6, Scheme 3) assuming exchange was at the diffusion limit (a reasonable assumption based on the NMR spectroscopic data). With these values in hand it was then possible to fit the experimental data to the kinetic model by variation of only rate constants k_7 and k_8. Fitting of the data gave excellent agreement between experiment and theory.

The kinetic EM (k_7/k_3) and the thermodynamic EM (k_7k_4/k_8k_3) for this system were subsequently found to be 2.59 M and 68 mM, respectively. These data suggest that the complex [**1•2a**] serves to preorganise the system towards the *exo* transition state, but that any hydrogen bonding present in the product *exo*-**3a** has little effect on its stability. It would therefore appear that, in contrast to all of the systems we have reported previously, this system accelerates the Diels–Alder reaction through a transition state effect rather than a ground state effect.

Confusingly, ^{1}H NMR spectroscopic evidence pointed to the presence of intramolecular hydrogen bonding in *exo*-**3a**—the large downfield shift change of the NH proton from the amidopicoline unit (+2.6 ppm) was diagnostic of the presence of a hydrogen bond to that proton. Therefore, in order to understand the origins of this transition state effect more fully, we have undertaken an extensive molecular mechanics study[6] of this system. Conformational searches revealed that the lowest energy conformations of *exo*-**3a** fell into two major families—representatives of which are shown in Figures 2 and 3. One of the clusters located (Fig. 2) exhibited the expected closed structure with two intramolecular hydrogen bonds, which are associated in other systems with stabilisation of the product ground state. Importantly, these closed conformations did not represent the lowest energy family.

A second family of fully closed templates (Fig. 3) was located in which an unexpected hydrogen bonding pattern was observed. Instead of the amide NH associating with the acid C=O as expected, the NH is associated with the maleimide C=O. The significance of this observation lies in the events leading up to the reaction between the diene and the dienophile. Assuming that this hydrogen bond is also present in the transition state, we would expect a lowering of the dienophile LUMO energy to occur through hydrogen bond mediated polarisation[7] of the maleimide π-system. This effect would serve to stabilise the transition state leading to *exo*-**3a** and, hence, increase the rate of reaction. The presence of this hydrogen bond is entirely consistent with the NMR spectroscopic data recorded for *exo*-**3a**.

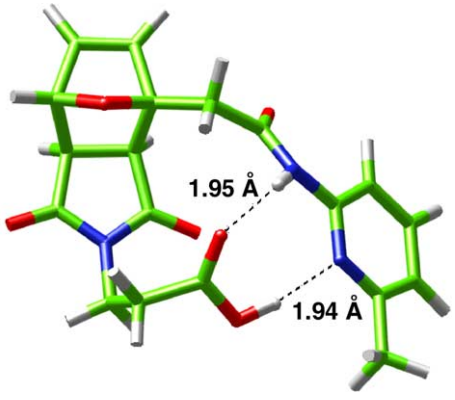


Figure 2. A closed structure for *exo*-**3a**, derived from molecular mechanics calculations, containing both of the predicted hydrogen bonding interactions (atom colours—carbon: green, nitrogen: blue, oxygen: red, hydrogen: grey. Hydrogen bonds are shown as dashed lines together with the appropriate H to acceptor atom distance).

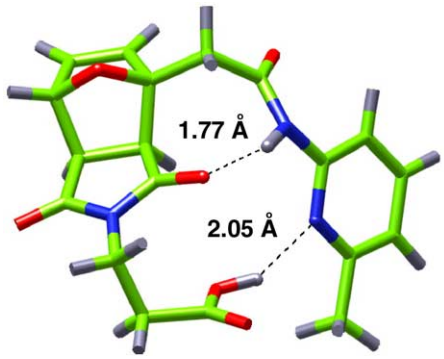


Figure 3. An alternative closed structure for *exo*-**3a**, derived from molecular mechanics calculations, containing one of the two predicted hydrogen bonding interactions and an anomalous hydrogen bond (atom colours as for Fig. 2. Hydrogen bonds are shown as dashed lines together with the appropriate H to acceptor atom distance).

In summary, we have described a simple binary complex, which accelerates the Diels–Alder cycloaddition between a maleimide and a furan such that only one of the two possible diastereoisomeric products is formed. Kinetic simulation and fitting suggests that the origin of the rate acceleration and selectivity is through stabilisation of the transition state leading to the *exo* product. Molecular mechanics calculations suggest that the origin of this effect is an anomalous hydrogen bond, which is present in *exo*-**3a** and, by implication, in the transition state leading to *exo*-**3a**. The presence of the polarising hydrogen bond in this system is key to its success. Our current studies are targeted at understanding the design elements required to ensure the presence of such a polarising hydrogen bond within a reactive complex such as [**1•2a**].

Acknowledgements

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