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Recognition-induced control and acceleration of a pyrrole Diels–Alder reaction

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Abstract—The formation of two hydrogen bonds between an amidopyridine and a carboxylic acid controls the stereochemical outcome and significantly accelerates the rate of the Diels–Alder cycloaddition between a benzoylpyrrole and a maleimide. © 2001 Published by Elsevier Science Ltd.

The study of the chemistry of derivatives of 7-azabicyclo [2.2.1]heptane **1** has been given fresh impetus by the discovery[1] of the natural product (−)-epibatidine **2** which displays powerful analgesic properties. In principle, the bicyclic skeleton **1** should be accessible synthetically[2] through a [4+2] Diels–Alder cycloaddition between a pyrrole derivative and a suitable 2π component in an analogous manner to that employed in the synthesis of 7-oxabicyclo[2.2.1]heptane derivatives. In practice, however, the resonance energy of pyrrole (ca. 29 kcal mol^{-1}, cf. furan 16 kcal mol^{-1}) mitigates against its use as a 4π component in a cycloaddition reaction, preferring instead to react as a vinylogous enamine.

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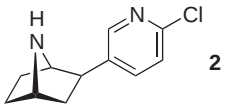

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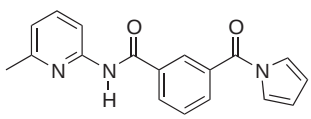
Various physical and chemical approaches including the use of Lewis acid catalysts[3] and high pressure,[4] have been developed to overcome the low reactivity of pyrrole as a diene. We have become interested in exploiting recognition processes to accelerate and direct the outcome of chemical reactions. Our previous work[5] has focussed on the use of recognition sites located on the two reactive partners, which allows the formation of a complex in which the reaction becomes pseudo-intramolecular. We have demonstrated the use of hydrogen bonding interactions between an amidopyridine and a carboxylic acid to accelerate and facilitate several Diels–Alder reactions, including some which are thermodynamically disfavoured at ambient temperature and pressure. The recalcitrant nature of pyrrole as a diene made it an obvious target for the extension of our recognition-based methodology.

Accordingly, we designed the diene **3** and the maleimide **4** as partners in a Diels–Alder cycloaddition. We envisaged that the recognition between the amidopyridine and the carboxylic acid would both accelerate and control the outcome of the cycloaddition between **3** and **4**. Additionally, we designed diene **5** and dienophile **6** as control compounds as they possess the same reactive functionality as **3** and **4**, but lack the requisite recognition sites.



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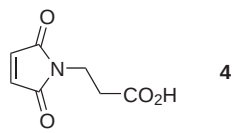

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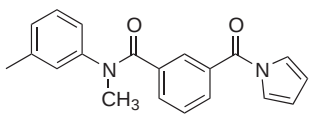

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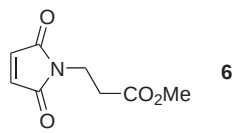

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We have demonstrated the utility of molecular mechanics calculations in predicting stereoselectivity in Diels–Alder cycloadditions through the identification of intramolecular hydrogen bonds in the products. We have found[5] that the product with the greatest number of intramolecular hydrogen bonds is favoured strongly.

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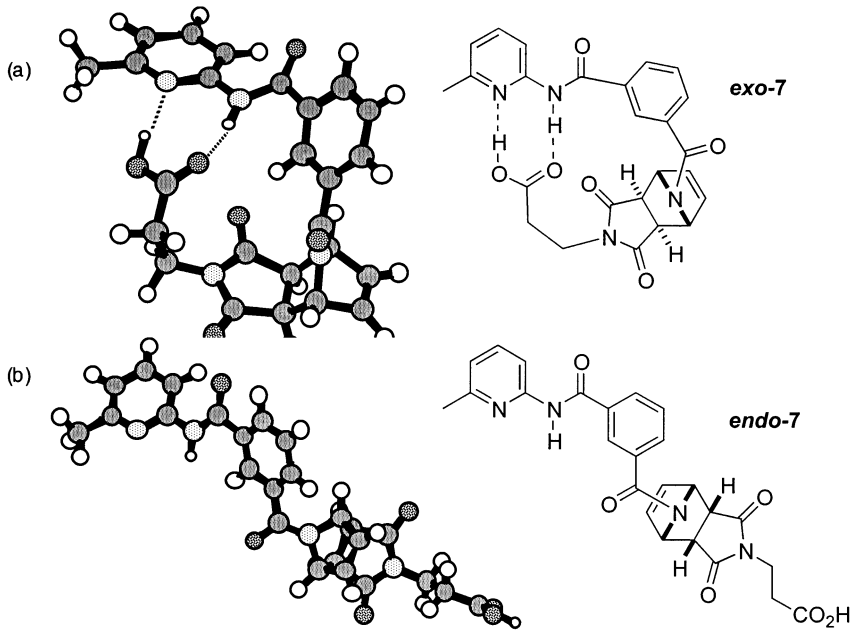


Figure 1. Calculated lowest energy conformations for (a) *exo*-**7** and (b) *endo*-**7**. Dotted lines represent hydrogen bonds.

Hence, we carried out molecular mechanics calculations[6] on the products of the reaction between **3** and **4** in order to determine which of the two diastereoisomeric cycloadducts—*exo*-**7** or *endo*-**7**—would be formed preferentially.

The calculated lowest energy conformations of these two cycloadducts are shown in Fig. 1. It is clear that, in these two conformations at least, *exo*-**7** can form two intramolecular hydrogen bonds, whereas *endo*-**7** does not contain any stabilising intramolecular hydrogen bonds.

In order to elucidate whether the lowest energy conformations of *exo*-**7** and *endo*-**7** were representative of the family of low energy conformations available to these two molecules, we generated a representative set of low energy conformations by Monte Carlo methods. The resultant sets of conformations were filtered to remove those which had calculated energies >50 kJ higher than the conformations shown in Fig. 1. The distances between the pyridine nitrogen atom and the carboxylic acid proton (Distance A, Fig. 2) and that between the amide proton and the carbonyl oxygen atom of the carboxylic acid (Distance B, Fig. 2) were determined

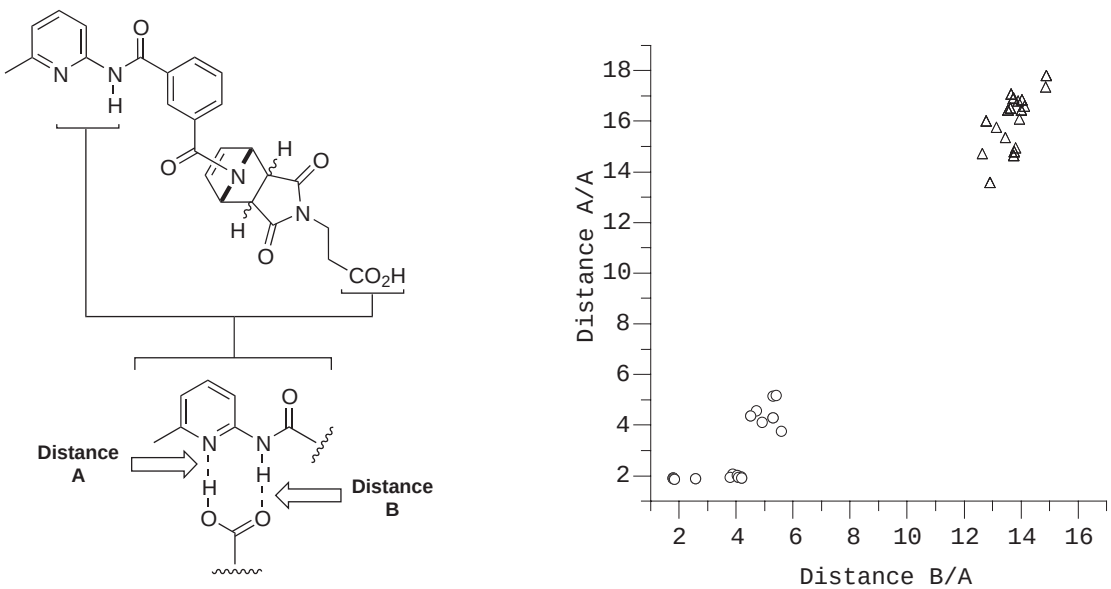


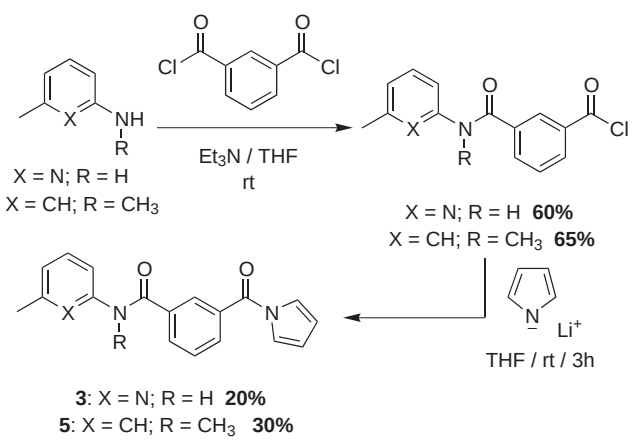
Figure 2. Structures of the 30 lowest energy conformations of *exo*-**7** and *endo*-**7** expressed as a function of key hydrogen bond distances. Open circles represent the location of conformations of *exo*-**7** and open triangles represent the location of conformations of *endo*-**7**.

for the 30 lowest energy conformations. This data was used to generate a scatterplot (Fig. 2) in which the low energy conformations of *exo*-**7** and *endo*-**7** are located as a function of these two distances.

It is clear from the results presented in Fig. 2 that the low energy conformations of *exo*-**7** and *endo*-**7** occupy quite different regions of conformational space. More than 70% of the low energy conformations of *exo*-**7** sampled contain at least one stabilising intramolecular hydrogen bond. By contrast, *endo*-**7** prefers to adopt extended conformations that contain no stabilising intramolecular hydrogen bonds. These results indicate that the recognition-mediated reaction should show a strong preference for the formation of the *exo* cycloadduct.

In order to test this hypothesis, we embarked on the synthesis of the target pyrroles **3** and **5** (Scheme 1). Reaction of the appropriate aromatic amine with one equivalent of isophthaloyl chloride in THF at room temperature afforded the corresponding monoamides in either 60 or 65% yield. Reaction of these amides with the lithium salt of pyrrole, generated by treatment of pyrrole with *n*-butyllithium at room temperature, afforded the target dienes **3**, in 20% yield, and **5**, in 30% yield. The synthesis of **4** was accomplished by treatment of β-alanine with maleic anhydride in glacial acetic acid. Ester **6** was prepared by treatment of **4** with methyl iodide and caesium carbonate in dimethylformamide.

In order to determine the influence of recognition process on the cycloaddition reaction, a series of reactions were carried out between **3** and **4**. All attempts to achieve a successful conversion of **3** and **4** to **7** at ambient pressure failed. This outcome is unsurprising since even the facilitation afforded by the presence of two intramolecular hydrogen bonds in *exo*-**7** (ca. 4 kcal mol^{-1}) is far less than the loss of resonance energy experienced by the system upon transformation of the pyrrole ring to the corresponding cycloadduct. We therefore turned to the use of high pressure in order to facilitate the reaction between **3** and **4**. Accordingly, we prepared 200 mM solutions of **3** and **4** in CD_2Cl_2. Equal volumes of these two solutions were mixed and the resulting solution compressed to 10 kbar for varying periods of time. The reaction mixture was then analysed by 250 MHz ^{1}H NMR spectroscopy and the percentage conversion of **3** and **4** to cycloadduct **7** was determined. For comparison purposes, the same set of reactions was performed under identical conditions between **5** and **6**, which lack recognition sites. The results are presented in Fig. 3.



Scheme 1.

From these data it is clear that the recognition-mediated reaction proceeds at a significantly faster rate than the control reaction under the conditions employed. It was also clear from the ^{1}H NMR spectra of the reaction mixtures that the stereochemical outcome of the reaction was significantly different between the two sets of reactions. However, in order to assign the stereochemistry of the cycloadducts unambiguously, it was necessary to record NMR spectra at low temperature to remove line broadening which arises as a result of rotation about the R_2N–C=O bond in the cycloadduct which is relatively slow on the NMR timescale.

In the case of the recognition mediated reaction between **3** and **4**, the 400 MHz ^{1}H NMR spectrum of the reaction mixture, recorded at −10°C in CD_2Cl_2, displayed a sharp resonance at δ 5.47 corresponding to

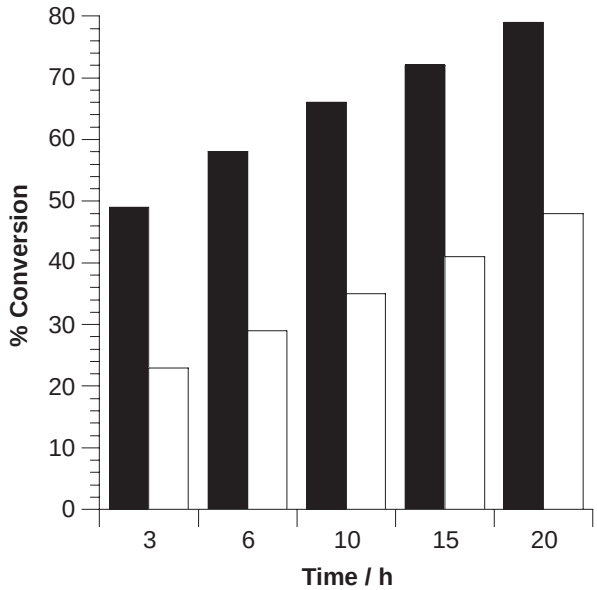
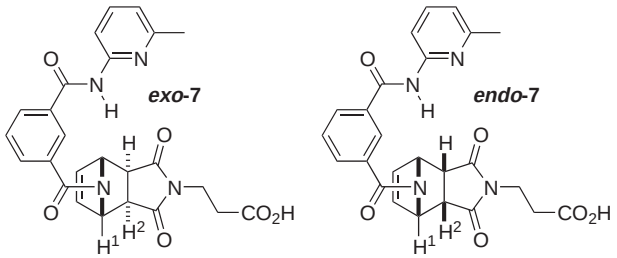


Figure 3. Percentage conversion to product for the recognition-mediated reaction between **3** and **4** (filled bars) and for the control reaction between **5** and **6**. In the case of the reaction between **3** and **4**, only the *exo* cycloadduct is observed. In the case of the reaction between **5** and **6**, only the *endo* cycloadduct is observed.

the bridgehead proton (H^1) in cycloadduct **7**. This chemical shift and the absence of any significant coupling between H^1 and H^2 is only consistent[4] with the product of the reaction between **3** and **4** having *exo* stereochemistry.



In the case of the control reaction between **5** and **6**, the 400 MHz ^{1}H NMR spectrum of the reaction mixture, recorded at −10°C in CD_2Cl_2, displayed a sharp resonance at δ 5.35 corresponding to the bridgehead proton (H^1) in cycloadduct. This chemical shift and the significant coupling ($^3J_{HH} = 5.7$ Hz) between H^1 and H^2 are only consistent[4] with the product of the reaction between **5** and **6** having *endo* stereochemistry.

In conclusion, we have demonstrated the rational design of a recognition-based system which is capable of accelerating the Diels–Alder cycloaddition between a benzoylpyrrole and a maleimide under high pressure conditions. Further, the use of molecular recognition facilitates the formation of the disfavoured[7] *exo* cycloadduct (*exo*-**7**) with complete selectivity through the intermediacy of two hydrogen bonds which persist in *exo*-**7**. Therefore, the overall effect of the introduction of molecular recognition is both to accelerate the reaction and to reverse the product stereochemistry.

Acknowledgements

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6. All molecular mechanics calculations were carried out using the AMBER* forcefield as implemented in Macromodel (Version 5.0: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440) together with the GB/SA solvation model for $CHCl_3$. All calculations were performed on a Silicon Graphics Indigo^2 computer. Conformational searching was carried out using 10 000 step Monte Carlo simulations, and all conformation located within 50 kJ of the global minimum were minimised.
7. It should be noted that under high pressure conditions, the *endo* cycloadduct will be favoured as it has a more compact transition state and, hence, a larger change in the free volume as the system moves towards the transition state.