Recognition-induced control of a Diels–Alder reaction

Douglas Philp*† and Andrew Robertson

School of Chemistry, University of Birmingham, Edgbaston, Birmingham, UK B15 2TT

The rational design of a system which is capable of controlling the stereochemical outcome of a Diels–Alder reaction between a maleimide and a furan is presented.

The acceleration of chemical reactions and the control of their regio- and/or stereo-chemical outcome by the intervention of recognition processes in solution—achieved so elegantly by enzymes—has prompted synthetic chemists to design a variety[1] of unnatural systems which are capable of performing similar tasks. We are interested in achieving acceleration and control in solution phase reaction processes *via* the use of molecular recognition. In particular, we wished to investigate the acceleration and control of the Diels–Alder reaction[2] between a maleimide and a furan. In principle, this reaction can give rise to two products—the *endo* and the *exo* adducts—depending on the orientation of the approach of the diene to the dienophile. Normally, the *endo* adduct is the kinetic product and the *exo* adduct is the thermodynamic product of this reaction. In principle, rate acceleration[3]‡ can be achieved by transforming the bimolecular reaction between the diene and dienophile in solution into a unimolecular reaction within a non-covalently bound complex.

The objective can be accomplished most readily by locating complementary recognition sites on the diene and dienophile. Accordingly, we designed (Fig. 1) the maleimide **1**, which bears an amidopicoline moiety, and the furan **2**, which bears a carboxylic acid. These two species would be expected to bind to each other through the mutual recognition between the amidopicoline and the carboxylic acid. Molecular mechanics calculations§ suggested that we could expect the furan and maleimide rings to be positioned (Fig. 1) in an orientation which should accelerate the rate of the Diels–Alder cycloaddition and/or control its stereochemical outcome. The benzene ring used as a rigid spacer between the recognition site and the maleimide ring in **1** might be expected to function in a manner which would permit discrimination between the *endo* and *exo* transition states, hence generating stereoselectivity. Here, we report the observation of the control of the Diels–Alder reaction between **1** and **2** and the rationalisation and analysis of this control by kinetic simulation.

Maleimide **1** was synthesised¶ by standard methods in five steps from 4-(aminomethyl)benzoic acid in an overall yield of 32%. Furan **2** was synthesised in 88% yield by catalytic hydrogenation of commercially-available 3-furylacrylic acid.

In order to assess the efficiency of the rate acceleration and control induced by the formation of a complex betwen **1** and **2**, we followed the course of the reaction between these components in $CDCl_3$ at 30 °C. The initial concentrations of the reactants were 5 mM and the emergence of the resonances arising from **3** and **4** were monitored by 400 MHz ^{1}H NMR spectroscopy over a period of 60 h. The reaction between **2** and benzyl maleimide was chosen as the control reaction and was performed and monitored under identical conditions. The data obtained (Fig. 2) indicates that the recognition-mediated (RM) reaction proceeds significantly faster than the control reaction at this concentration and with high stereoselectivity.

Kinetic simulation and optimisation[4] of the model parameters (Fig. 1) afforded best fit values for the rate constants (Table 1) for the control reaction which, in turn, were used in the kinetic model for the RM reaction. The ratio k_7/k_3 for the *endo* product gives an estimate of 64 mM for the effective molarity (EM) achieved within the [**1**·**2**] complex. The corresponding value for the *exo* isomer (k_5/k_1) is only 6 mM. The *endo* reverse reaction is significantly slower (k_4/k_8 = 170) in the RM system. This observation is consistent with stabilisation of the *endo* product by a strong intramolecular hydrogen bond. The value of k_5/k_6 suggests that there is little or no net product of the *exo* product *via* the recognition mediated pathway.

The kinetic data shown in Table 1 can be converted into an energy profile for the recognition mediated reaction (Fig. 3) by application of standard thermodynamic relationships. In the absence of any stabilising or destabilising effect on the transition states induced by complexation, the activation barrier for the reaction within the complex [**1**·**2**] should simply be the sum of the bimolecular activation barrier and the free energy of binding. For the *exo* isomer, this relationship holds suggesting that the formation of the [**1**·**2**] complex has no net effect on the reaction leading to the *exo* isomer. By contrast, the transition state leading to the *endo* isomer is stabilised by 6.1 kJ mol^{-1}. This stabilisation is not enough to offset the increase (13.1

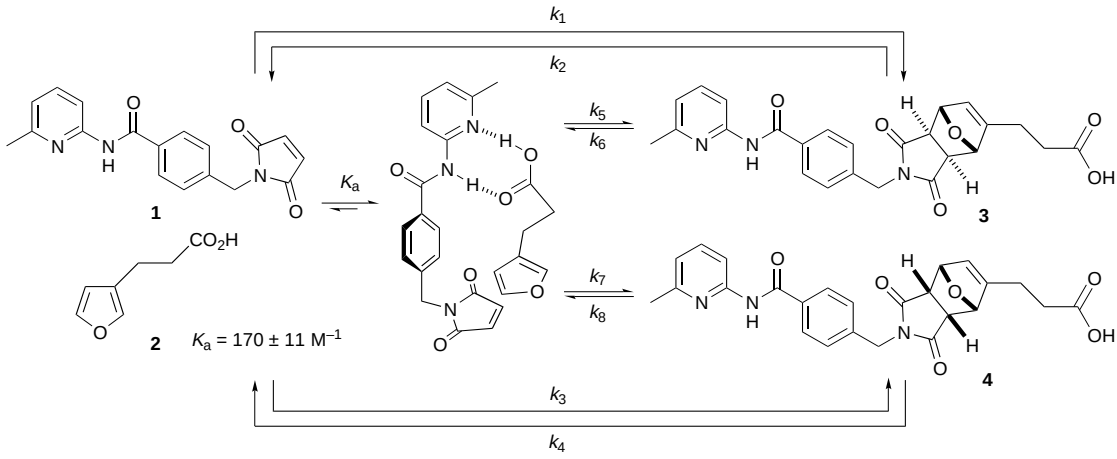

Fig. 1 The design and kinetic scheme for the recognition-mediated Diels–Alder cycloaddition between **1** and **2**. Rate constants are given in Table 1.

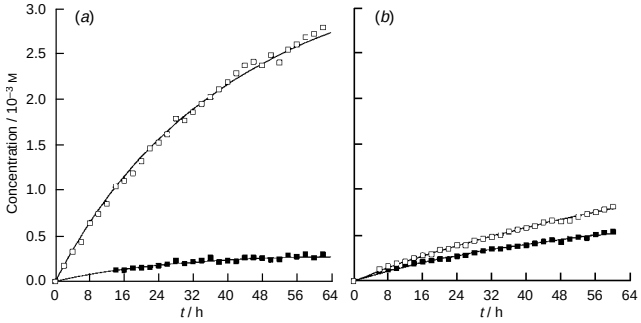

Fig. 2 Concentration–time profiles for (*a*) the reaction between **1** and **2** in $CDCl_3$ at 30 °C and (*b*) the reaction between benzyl maleimide and **2** in $CDCl_3$ at 30 °C. In both cases, the starting concentrations of the reactants were 5 mM. In both plots, the open squares represent the concentration of the *endo* product and the filled squares represent the concentration of the *exo* product. The solid lines represent the best fit of the appropriate kinetic model to the experimental data. For clarity, error bars are omitted from the graphs (errors in concentration are ±3%).

Table 1 Kinetic parameters for the recognition-mediated reaction obtained from the simulation and fitting of the experimental data to the kinetic scheme shown in Fig. 1

$k_1/10^{-5}$ M^{-1} s^{-1}	160 ± 3
$k_2/10^{-5}$ s^{-1}	1.68 ± 0.13
$k_3/10^{-5}$ M^{-1} s^{-1}	209 ± 4
$k_4/10^{-5}$ s^{-1}	0.34 ± 0.03
$k_5/10^{-5}$ s^{-1}	0.99 ± 0.06
$k_6/10^{-5}$ s^{-1}	0.89 ± 0.04
$k_7/10^{-5}$ s^{-1}	13.3 ± 0.11
$k_8/10^{-5}$ s^{-1}	0.002

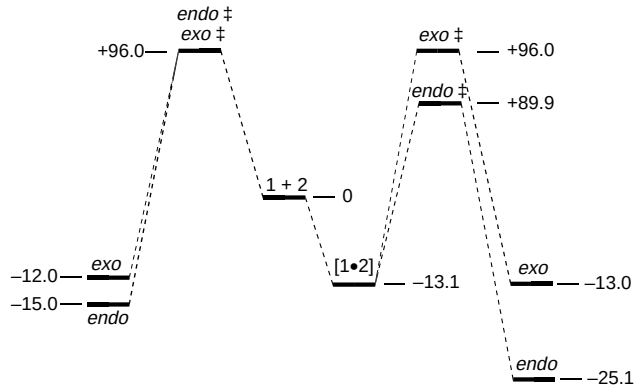

Fig. 3 Thermodynamic profile for the recognition-mediated reaction obtained by the simulation and fitting of the experimental data. The zero point for energy comparisons is set at the energy of the uncomplexed reactants **1** and **2**. All energy values are in kJ mol^{-1}. Data shown to the left of the zero energy point refer to the bimolecular reaction (k_1 to k_4). Data shown to the right of the zero energy point refer to the recognition-mediated reaction (k_5 to k_8).

kJ mol^{-1}) in activation barrier brought about by complexation (thus reflecting the fact that EM < 1 M), however, it does ensure that the *endo* product is produced at a faster rate than the *exo* product within the [**1**·**2**] complex. A more profound effect is observed on the stabilities of the products themselves. Molecular mechanics calculations indicate that the most stable conformation of the *endo* isomer contains an intramolecular hydrogen bond. The *exo* product is incapable of forming an intramolecular hydrogen bond—mechanics calculations indicate that the closest approach of the acid to the amidopyridine is 6.9 Å. This intramolecular interaction is the source of the large discrimination (12.1 kJ mol^{-1}) between the product ground states and, hence, in conjunction with the difference in activation barriers, the selectivity expressed by the reaction for the *endo* isomer.

In conclusion, we have demonstrated that by attaching appropriate recognition sites to a diene and a dienophile, it is possible to exert a high degree of stereocontrol on a Diels–Alder cycloaddition reaction between maleimide and a furan. This control is achieved through the intermediacy of the mutual recognition between reactive partners and by ensuring that only one product—in this case, the *endo* product—is capable of forming stabilising intramolecular hydrogen bonds. The reaction reported here is accelerated only modestly (EM = 64 mM for the *endo* isomer). We are currently addressing this matter and exploring the use of the methodology reported here in the regio- and stereo-control of other [4 + 2] and [3 + 2] cycloaddition reactions.

This research was supported by the University of Birmingham and the EPSRC (Quota Award to A. R.). We thank Professor G. von Kiedrowski for providing us with a copy of his SimFit program. We thank Mr P. Ashton for performing mass spectrometric analyses and Dr Neil Spencer and Mr Malcolm Tolley for the acquisition of the NMR data.

Notes and References

† E-mail: d.philp@birmingham.ac.uk

‡ In the present context, we are not concerned with catalysis in the sense of turnover, but rather ensuring that, by encoding the appropriate recognition features within the reagents, the Diels–Alder reaction is accelerated and its stereochemical outcome controlled.

§ Molecular mechanics calculations on the [**1**·**2**] complex were carried out using the AMBER* forcefield as implemented in Macromodel (Version 5.0, F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson and W. C. Still, *J. Comput. Chem*., 1990, **11**, 440) together with the GB/SA solvation model (W. C. Still, A. Tempczyk, R. C. Hawley and T. Hendrickson; *J. Am. Chem. Soc*., 1990, **112**, 6127) for $CHCl_3$. Conformational searching was carried out using 10 000 step Monte Carlo simulations and all conformations generated within 10 kcal mol^{-1} of the global minimum were minimised. The sets of low energy conformations generated were then filtered to locate those conformations where the maleimide and furan were in close proximity (centroid–centroid distance < 5 Å). This produced a significant number (> 10% of total set size) of conformations corresponding to the pro-*endo* complex.

¶ *Selected data* for **1**: δ_H(300 MHz, $CDCl_3$) 8.75 (1 H, br s), 8.18–8.12 (1 H, m), 7.89–7.81 (2 H, m), 7.65–7.56 (1 H, m), 7.43–7.37 (2 H, m), 6.90–6.85 (1 H, m), 6.72 (2 H, s), 4.70 (2 H, s), 2.39 (3 H, s); δ_C(75 MHz, $CDCl_3$) 170.2, 165.2, 156.9, 150.8, 140.3, 138.8, 134.3, 133.9, 128.6, 127.7, 119.5, 111.1, 41.0, 23.9 [EIMS: *m/z* 321 (70%), 214 (100%)].

1 For excellent general reviews, see A. J. Kirby, *Angew. Chem., Int. Ed. Engl*., 1996, **35**, 707; H. Dugas, *Bioorganic Chemistry—A Chemical Approach to Enzyme Action*, Springer-Verlag, New York, 3rd edn., 1996. For some efficient examples, see M. W. Hosseini, J. M. Lehn, K. C. Jones, K. E. Plute, K. B. Mertes and M. P. Mertes, *J. Am. Chem. Soc*., 1989, **111**, 6330; I. Huc, J. Pieters and J. Rebek, Jr., *J. Am. Chem. Soc*., 1994, **116**, 10 296; P. Tecilla, V. Jubian and A. D. Hamilton, *Tetrahedron*, 1995, **51**, 435.

2 M. C. Carreno, J. L. G. Ruano and A. Urbano, *J. Org. Chem*., 1996, **61**, 6136; D. S. Millan, T. T. Pham, J. A. Lavers and A. G. Fallis, *Tetrahedron Lett*., 1997, **38**, 795; M. J. Lilly and M. S. Sherburn, *Chem. Commun*., 1997, 967; T. Wong, P. D. Wilson, S. Woo and A. G. Fallis *Tetrahedron Lett*., 1997, **38**, 7045; E. J. Bush and D. W. Jones, *J. Chem. Soc., Perkin Trans. 1*, 1997, 3531.

3 T. R. Kelly, V. S. Ekkundi and P. Meghani, *Tetrahedron Lett*., 1990, **31**, 3381; S. C. Hirst and A. D. Hamilton, *J. Am. Chem. Soc*., 1991, **113**, 382; C. J. Walter and J. K. M. Sanders, *Angew. Chem., Int. Ed. Engl*., 1995, **34**, 217; H. L. Anderson and J. K. M. Sanders, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2223; J. Rebek, Jr. and J. Kang, *Nature*, 1997, **385**, 50; B. Wang and I. O. Sutherland *Chem. Commun*., 1997, 1495.

4 SimFit, A Program for the Analysis of Kinetic Data, Version 1.0, G. von Kiedrowski, 1994.

Received in Liverpool, UK, 20th January 1998; 8/00559A