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Recognition-Mediated Facilitation of a Disfavored Diels–Alder Reaction

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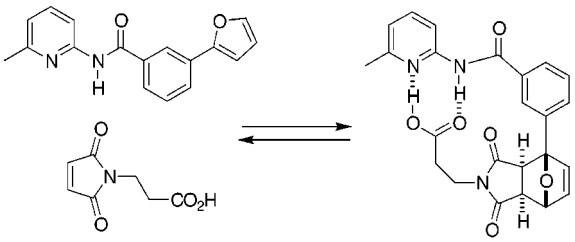
ABSTRACT



The rational design of a system which is capable of accelerating and facilitating a thermodynamically disfavored Diels–Alder cycloaddition between a furan and a maleimide is presented. The origins of the acceleration and facilitation of the cycloaddition reaction are traced by kinetic studies—allied to results from ^{1}H NMR spectroscopy and X-ray crystallography—to the formation of strong intramolecular hydrogen bonds in the cycloadduct.

Although enzymes are capable of effective and selective catalysis of many simple chemical reactions, there have, to date, been few reports of naturally occurring enzymes[1] which are capable of accelerating the Diels−Alder reaction[2] in a specific and selective manner. The design and synthesis of enzyme mimics has been a major focus[3] of supramolecular chemistry and a few recognition-based systems have been described[4] which can accelerate the rate and/or control the stereochemical outcome of Diels−Alder reactions. These approaches rely on the selective stabilization of the transition state leading to the desired product. Recently, we have adopted a different approach[5] to this problem. In principle, the location of complementary recognition sites on two reagents, A and B, in a chemical reaction permits the association of A and B through their mutually compatible recognition sites to form a complex, [A·B]. Within the [A·B] complex, the chemical reaction between A and B is effectively intramolecular as opposed to intermolecular and, therefore, we would expect the formation of the [A·B] complex to accelerate[6] the transformation involving A and B significantly. Additionally, the molecular recognition,

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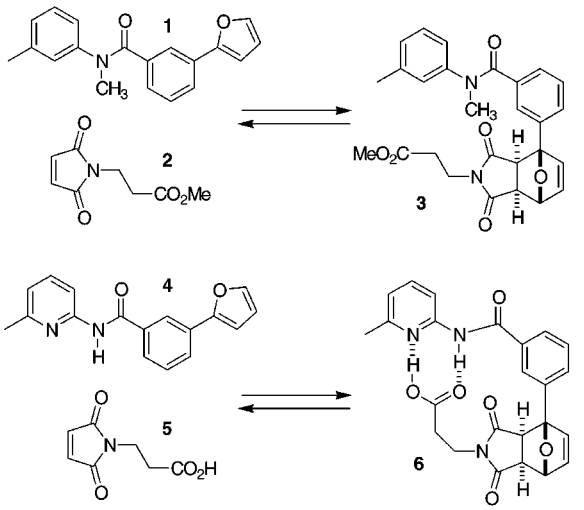
which is present in the [A·B] complex, may also persist in the final product and might therefore have a profound influence on the stability of the products of the reaction. This stabilizing effect on the product ground state will manifest itself when the reaction in question is under thermodynamic control and the selective stabilization of one product with respect to another will serve to facilitate[7] the formation of the more stable product. Therefore, unlike enzymes or enzyme mimics, our methodology is ideally suited for reactions which have unfavorable equilibrium constants under normal conditions, i.e. reactions which suffer from a thermodynamic disadvantage as opposed to a kinetic disadvantage. Here, we report the recognition-mediated facilitation of the reaction between a 2-phenylfuran derivative and a maleimide and the characterization and analysis of the origins of this facilitation by kinetic simulation, ^{1}H NMR spectroscopy, and X-ray crystallography.

2-Phenylfuran derivatives are notoriously poor dienes in Diels−Alder cycloaddition reactions as a direct result of their high level of π conjugation, which is destroyed by the formation of a Diels−Alder cycloadduct. Thus, when a 100 mM solution of diene **1** and maleimide **2** in $CDCl_3$ was heated at 50 °C (Scheme 1), only very small amounts of the

Scheme 1



exo cycloadduct could be detected[8] by 500 MHz ^{1}H NMR spectroscopy after 15 h. Kinetic simulation and fitting[9] of the reaction profile (Figure 1a) allowed the extraction of a

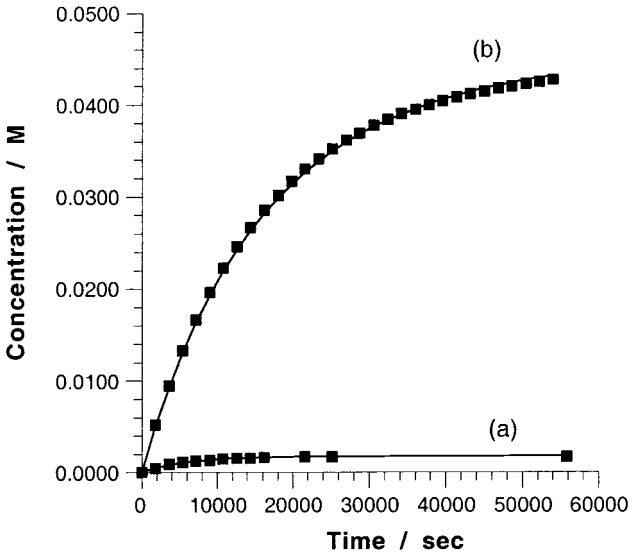


Figure 1. Rate profiles for (a) the reaction between **1** and **2** in $CDCl_3$ at 50 °C and (b) the reaction between **4** and **5** in $CDCl_3$ at 50 °C. In both cases, the starting concentrations of the reactants were 100 mM. In both plots, the filled squares represent the concentration of the appropriate *exo* cycloadduct. 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; however, errors in concentration are estimated to be ±4%.

value of the equilibrium constant (K_{eq}) for this reaction of 0.18 M^{-1}. To investigate the recognition-mediated facilitation of this cycloaddition reaction, diene **4**, bearing an amidopyridine recognition site, and maleimide **5**, bearing a complementary carboxylic acid recognition site, were prepared[10] from readily available starting materials. When a 100 mM solution of diene **4** and maleimide **5** in $CDCl_3$ was heated at 50 °C (Scheme 1), a significant quantity of the *exo* cycloadduct **6** could be detected by 500 MHz ^{1}H NMR spectroscopy after 15 h. Kinetic simulation and fitting of the reaction profile (Figure 1b) allowed the extraction of a value of the equilibrium constant (K_{eq}) for this reaction of 15.3 M^{-1}.

From these results, it is clear that the introduction of the recognition elements within the diene and dienophile has increased the extent of reaction dramatically. To assess the

(6) Page, M. I.; Jencks, W. P. *Proc. Natl. Acad. Sci. USA* **1971**, *68*, 1678. Page, M. I. *Chem. Soc. Rev.* **1973**, 2, 295. Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183. Page, M. I. In *The Chemistry of Enzyme Action*; Page, M. I., Ed.; Elsevier: Amsterdam, 1984; p 1. Menger, F. M. *Acc. Chem. Res.* **1985**, *18*, 128. Page, M. I. *Philos. Trans. R. Soc. London B* **1991**, *332*, 149. Kirby, A. J. *Philos. Trans. R. Soc. London A* **1993**, *345*, 67. Menger, F. M. *Acc. Chem. Res.* **1993**, *26*, 206. Bruice, T. C.; Lightstone, F. C. *Acc. Chem. Res.* **1999**, *32*, 127.

(7) To distinguish between transition state effects and ground-state effects, we will use the description *accelerated* when the rate of a reaction is enhanced by the lowering of the energy of the transition state by a recognition event and the description *facilitated* when the extent of reaction is enhanced by the lowering of the energy of the product by a recognition event.

(8) In all cases, only the *exo* cycloadduct was detected in solution. This is consistent with the fact that the *exo* adduct is normally the thermodynamic product of furan cyclodaddition reactions.

(9) Kinetic simulation and fitting was carried out using Gepasi (version 3.21): Mendes, P. *Comput. Appl. Biosci.* **1993**, *9*, 563. Mendes, P. *Trends Biochem. Sci.* **1997**, *22*, 361. Mendes P.; Kell, D. B. *Bioinformatics* **1998**, *14*, 869).

(10) Selected spectroscopic data for **4**: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.71 (1H, s), 8.21 (1H, d, $^3J_{HH}$ = 7.3 Hz), 8.19 (1H, s), 7.85−7.78 (2H, m), 7.65 (1H, t, $^3J_{HH}$ = 7.3 Hz), 7.49 (1H, d, $^4J_{HH}$ = 0.7 Hz), 7.48 (1H, t, $^3J_{HH}$ = 7.7 Hz), 6.92 (1H, d, $^3J_{HH}$ = 7.3 Hz), 6.74 (1H, d, $^3J_{HH}$ = 3.3 Hz, $^4J_{HH}$ = 0.7 Hz), 6.49 (1H, dd, $^3J_{HH}$ = 1.5, 3.3 Hz), 2.45 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 165.7, 156.8, 152.7, 151.0, 142.6, 138.7, 135.0, 131.4, 129.1, 127.0, 126.0, 122.6, 119.5, 111.8, 111.3, 106.1, 23.8; *m/z* (EIMS) $[M]^+$ 278 (55), 249 (88), 171 (100). Selected spectroscopic data for **5**: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.7 (2H, s), 3.82 (2H, t, $^3J_{HH}$ = 6.9 Hz), 2.69 (2H, t, $^3J_{HH}$ = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 176.6, 170.4, 134.3, 33.3, 32.6; *m/z* (EIMS) $[M]^+$ 169 (9), 123 (51), 44 (100).

origin of this facilitation of the cycloaddition reaction, several lines of investigation were employed.

Evidence for the presence of strong intramolecular hydrogen bonding in the product **6** was obtained from X-ray crystallography and ^{1}H NMR spectroscopy. Single crystals of **6** suitable for X-ray diffraction were grown by slow diffusion of hexane into a saturated solution of **6** in chloroform. Compound **6** crystallizes in the $P2_1/n$ space group with four molecules of **6** occupying the unit cell. In the solid state, individual molecules of **6** adopt a conformation (Figure 2) in which two intramolecular hydrogen bonds are present.

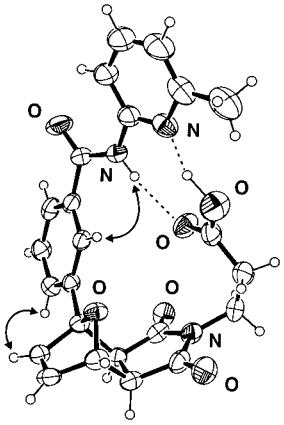


Figure 2. X-ray crystal structure of cycloadduct **6**. Hydrogen bonds are marked by dashed lines. Double-headed arrows show nOes which are observed in the 500 MHz ^{1}H NMR spectrum recorded in $CDCl_3$ solution at 30 °C.

Evidence for the persistence of these intramolecular hydrogen bonds in solution comes from 500 MHz ^{1}H NMR spectroscopy. In the ^{1}H NMR spectrum of **6**, recorded in $CDCl_3$ at 30 °C, the resonance arising from the amide NH proton of the amidopyridine recognition unit is shifted downfield by around 2.7 ppm[11] and appears as a sharp singlet at δ 11.45. This dramatic change in chemical shift is indicative of the amide proton being involved in a strong hydrogen bond. The intramolecular nature of this hydrogen bond is confirmed by the absence of a concentration dependence of the chemical shift of the amide NH resonance. Further evidence for the persistence of the conformation supporting two intramolecular hydrogen bonds in solution comes from gradient nOe experiments performed in $CDCl_3$ at 30 °C. Significant and diagnostic nOes are observed (Figure 2) between a proton on the disubstituted benzene ring and an alkene proton of the cycloadduct or a proton on the disubstituted benzene ring and the amide NH proton. Additionally, the intramolecular hydrogen bonding forces the CH_2CH_2 chain, connecting the carboxylic acid to the cycloadduct, to adopt a conformation in which all four protons are anisochronous in the 500 MHz ^{1}H NMR spectrum. Molecular mechanics calculations suggest that the origin of the strong preference for the formation of **6** as its *exo* stereoisomer arise from the ability of the cycloadduct to form intramolecular hydrogen bonds. The 10 lowest energy conformations calculated[12] for *exo*-**6** all contain two intramolecular hydrogen bonds, whereas 7 of the 10 lowest energy conformations calculated for *endo*-**6** contain no intramolecular hydrogen bonds and the remaining three conformations contain only one intramolecular hydrogen bond.

The role of the noncovalent interactions in stabilizing the cycloadduct **6** could be demonstrated by the disruption of the intramolecular hydrogen bonds by preparing a 50 mM solution of **6** in d_6-DMSO. Under these conditions, the retro Diels−Alder reaction to afford the starting diene **4** and maleimide **5** is rapid[13] (Figure 3), as assessed by recording

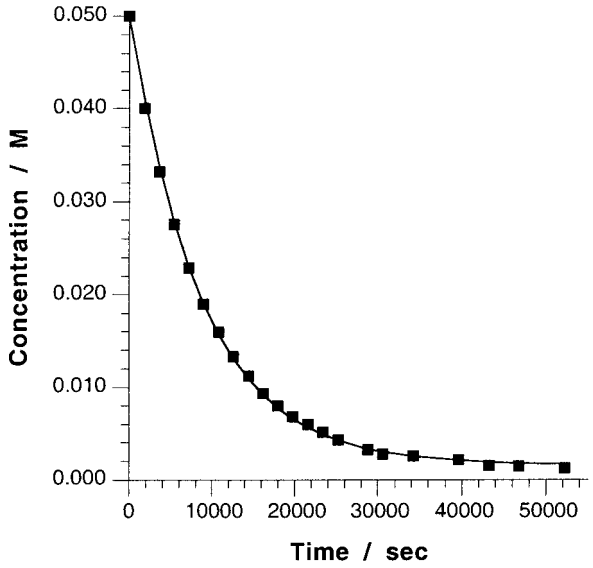


Figure 3. Rate profile for the retro Diels−Alder reaction of **6** in d_6-DMSO at 50 °C from a starting concentration of **6** of 50 mM. The filled squares represent the concentration of **6**. The solid lines represent the best fit of the appropriate kinetic model to the experimental data. For clarity, error bars are omitted from the graph; however, errors in concentration are estimated to be ±4%.

500 MHz ^{1}H NMR spectra of the solution over a period of 15 h. Kinetic simulation and fitting of the reaction profile (Figure 3) allowed the extraction of a value of the equilibrium

(11) A suitable comparison compound is **4**, in which no intramolecular hydrogen bonding is possible. In compound **4**, the amide NH resonance appears at δ 8.67.

(12) All molecular mechanics calculations were carried out using the AMBER* force field as implemented in Macromodel (version 5.0: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G. 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 Power Indigo^2 computer. Conformational searching was carried out using 10 000-step Monte Carlo simulations, and all conformations generated within 50 kJ of the global minimum were minimized.

(13) The retro Diels−Alder reaction has also been observed and characterized in $CDCl_3$ solutions containing between 1 and 5% of CD_3OD. The equilibrium constants derived from all of these retro Diels−Alder reactions are in close agreement.

constant (K_{eq}) for this reaction of 0.05 M^{-1}, which is in reasonable agreement with that determined from the Diels−Alder reaction between **1** and **2**.

Using the thermodynamic and kinetic studies described above, it is possible to derive a value[14] for the stabilization of the ground state of **6** of 11.8 kJ mol^{-1}, with respect to **3**, as a result of the presence of the two intramolecular hydrogen bonds in cycloadduct **6**. Additionally, the rate of recognition-mediated reaction is enhanced[9] 7-fold over that for the control reaction, indicating that there is significant recognition-induced enhancement in the rate of the Diels−Alder cycloaddition reaction leading to **6**. Thus, we can conclude that the introduction of recognition sites has both facilitated and accelerated the Diels−Alder cycloaddition reaction between **4** and **5**. In other words, the recognition sites change both the position of the equilibrium in this cycloaddition reaction and the rate at which that equilibrium position is reached.

(14) It is possible that the reaction between **1** and **2** is not a perfect control reaction. In particular, the electronic properties of the tertiary amide in **1** are likely to be markedly different from those of the amidopyridine in **4**. The equilibrium constants derived from the retro Diels−Alder reactions are all much smaller (0.03−0.06 M^{-1}) than that derived for the reaction between **1** and **2**. The use of these values in the comparison between the recognition-mediated reaction and that in the absence of recognition leads to much higher values for the recognition-induced stabilization of **6**—around 15.3 kJ mol^{-1}. We therefore regard the value for the recognition-induced stabilization of **6** stated in the text as a lower limit.

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Supporting Information Available: Data, in CIF format, for the X-ray crystal structure of **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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