Pergamon

Tetrahedron Letters 39 (1998) 6987–6990

TETRAHEDRON LETTERS

Efficient recognition-induced acceleration of a [3+2] dipolar cycloaddition reaction

Ceri A. Booth and Douglas Philp*

School of Chemistry, University of Birmingham, Edgbaston, Birmingham B15 2TT, United Kingdom

Received 3 July 1998; accepted 13 July 1998

Abstract: The rational design of a system which is capable of utilising molecular recognition between an amidopyridine and a carboxylic acid to accelerate the [3+2] dipolar cycloaddition reaction between an azide and a maleimide is presented.

Keywords: Azides, Cycloadditions, Kinetics, Molecular recognition

The use of recognition processes to accelerate and control chemical reactions by rational design is an important goal for the synthetic chemist.[1] We are investigating the application of molecular recognition to the acceleration and control of solution phase [3+2] dipolar cycloaddition reactions. The location of complementary recognition sites on the reactive partners in the cycloaddition permits the 1,3-dipole and the dipolarophile to associate with each other through these mutually compatible recognition sites, rendering the reaction between them effectively intramolecular as opposed to intermolecular. In addition, the use of specific recognition to preassociate the reactive partners opens the way to control of the stereo- and/or regiochemical outcome of the reaction through the orientation of the reagents. Recently, we reported[2] the application of this methodology to the acceleration and control of a Diels-Alder reaction between a maleimide and a furan. Although good stereocontrol was achieved in this reaction, the efficiency of the reactive complex in this reaction was modest – the effective molarity (EM) achieved for the recognition-mediated reaction was only 65 mM. The poor performance of this system prompted us to investigate whether the relatively low binding constant (170 M^{-1}) for the association of the reactive partners was responsible for this poor performance and whether this methodology could be extended to other cycloaddition reactions.

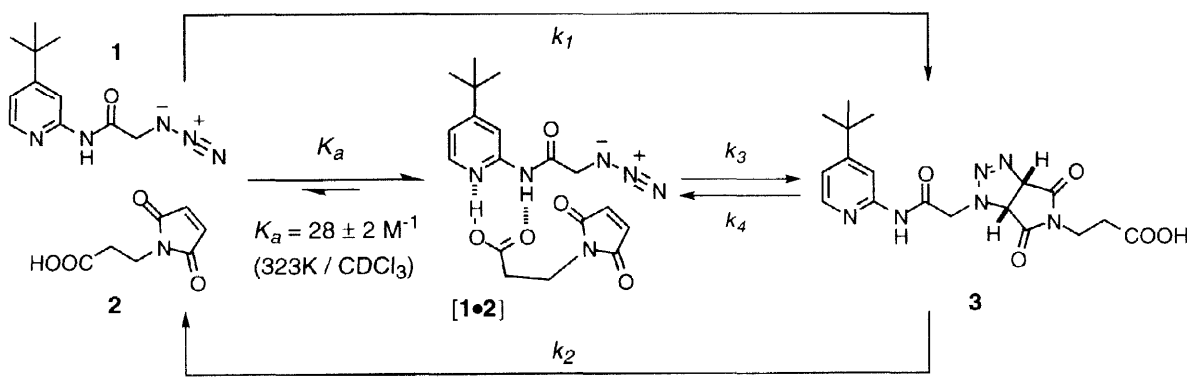

Figure 1 Kinetic scheme for recognition-mediated acceleration of a [3+2] dipolar cycloadditon reaction between **1** and **2**

PII: S0040-4039(98)01483-X

Accordingly, we designed the system shown in Figure 1 which possesses the same recognition sites as our previous system[2] (an amidopyridine and a carboxylic acid), but with an azide replacing the diene. Here, we report the efficient acceleration of the cycloaddition reaction between **1** and **2** through the **[1•2]** complex.

Azide **1** was synthesised[3] by standard methods in three steps from 4-*tert*-butylpyridine in an overall yield of 71%. Maleimide **2** was synthesised in 48% yield by reaction of commercially-available 1-aminopropionic acid with maleic anhydride in glacial acetic acid.

In order to assess the efficiency of the rate acceleration induced by the formation of a complex between **1** and **2**, we followed the course of the reaction between these components in $CDCl_3$ at 50°C. The initial concentrations of **1** and **2** were 50 mM and the emergence of the resonances arising from **3** were monitored by 270 MHz ^{1}H NMR spectroscopy over a period of 20 hours. The reaction between **1** and *N*-ethylmaleimide was chosen[4] as the control reaction in order to estimate the rate constants k_1 and k_2 for the bimolecular reaction between **1** and **2** (Figure 1). The reaction between **1** and *N*-ethylmaleimide proceeds slowly from a starting concentration of reagents of 50 mM in $CDCl_3$ at 50°C. Therefore, although we performed the reaction between **1** and *N*-ethylmaleimide from a starting concentration of 50 mM in order that a direct comparison could be made with the reaction between **1** and **2**, the kinetic data used to obtain rate constants were obtained from a reaction performed and monitored from a starting concentration of 100 mM in $CDCl_3$ at 50°C. The data obtained are shown in Figure 2.

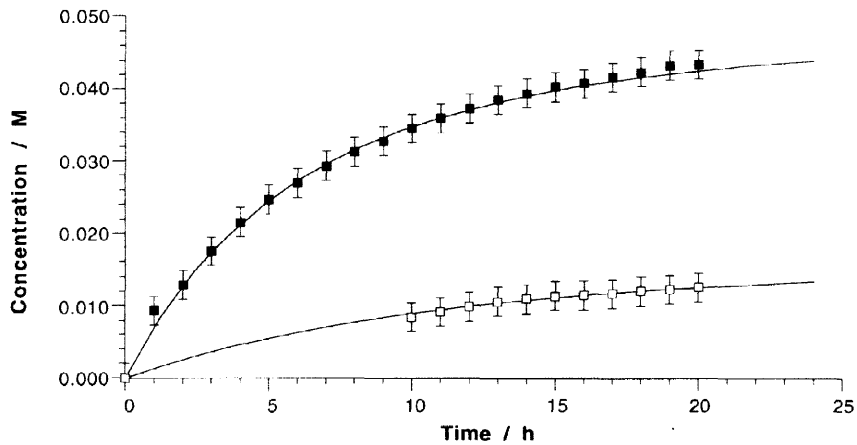

Figure 2 Concentration-time profiles for the recognition-mediated reaction between **1** and **2** (solid squares) and the control reaction between **1** and *N*-ethylmaleimide (open squares) performed in $CDCl_3$ at 50°C from a starting concentration of reagents of 50 mM. The solid lines represent the best fit of the appropriate kinetic model to the experimental data. Note: The best fit line in the case of the control reaction was generated from rate constants dervied from kinetic data obtained at 100 mM.

Kinetic simulation and optimisation[5] of the model parameters (Figure 1) afforded best fit values for the rate constants (Table 1) for the control reaction which, in turn, were used, together with the association constant[6] for the **[1•2]** complex, measured in $CDCl_3$ at 50°C, in the kinetic model for the recognition-mediated reaction. The ratio k_3/k_1 gives an estimate of 2.16 M for the kinetic effective molarity[7] (EM) achieved within the **[1•2]** complex.

Table 1 Best fit values of the rate constants shown in the kinetic scheme (Figure 1) for the reaction between **1** and **2**

Rate Constant	Best Fit Value
k_1	$5.42 \pm 0.05 \times 10^{-5}$ $M^{-1}s^{-1}$
k_2	$8.07 \pm 0.24 \times 10^{-9}$ s^{-1}
k_3	$1.17 \pm 0.02 \times 10^{-4}$ s^{-1}
k_4	$1.63 \pm 0.11 \times 10^{-8}$ s^{-1}

The kinetic data shown in Table 1 can be converted into an energy profile for the recognition-mediated reaction (Figure 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**] can be determined by calculating the sum of the bimolecular activation barrier and the free energy of binding. It is clear from Figure 3 that the transition state leading to **3** is stabilised by 11.0 kJmol^{-1} with respect to the bimolecular reaction as a result of complex formation. This stabilisation is sufficient to offset the increase (8.9 kJmol^{-1}) in activation barrier brought about by formation of the [**1**•**2**] complex, thus the activation barrier for the reaction between **1** and **2** is lower in the [**1**•**2**] complex by 2.1 kJmol^{-1} with respect to the model bimolecular reaction (in accordance with the fact that EM > 1M).

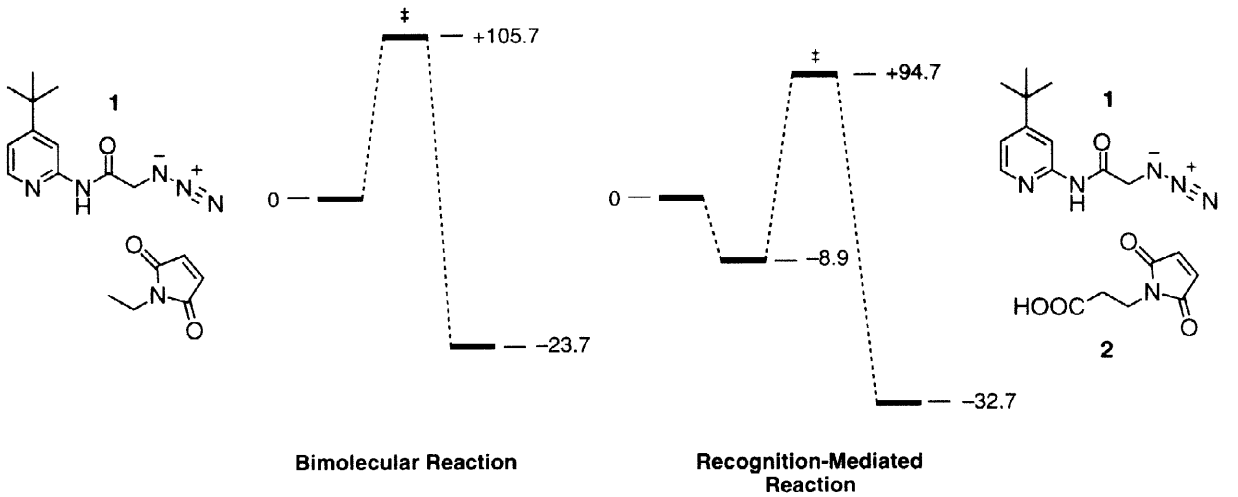

Figure 3 Thermodynamic profile for the recognition-mediated reaction obtained from the experimental data for the reaction between **1** and **2** and **1** and *N*-ethylmaleimide. All energy values are in kJmol^{-1}. The zero point for energy comparison is set at the energy of the uncomplexed reactants **1** and **2**.

In order to assess the effect of the alkyl spacer placed between the carboxylic acid and the maleimide, we prepared compounds **4** and **5**. Compound **4** reacts with azide **1** at 50 mM in $CDCl_3$ at 50°C at a rate similar to that of the control compound indicating that the simple methylene spacer is too short to permit the azide and the maleimide to react within the [**1**•**4**] complex in this case. Conversely, maleimide **5** reacts significantly faster with **1** than the control compound under the same conditions. However, analysis of the kinetic data for the reaction between **1** and **5** reveals that the EM achieved within the [**1**•**5**] complex is only 341 mM.

4 **5**

These results indicate that maleimide **2** contains the optimum spacer for the acceleration of the reaction within the supramolecular assembly. If we assume that the difference in EM is entirely the result of the addition of the extra methylene rotor, we can estimate that the addition of a single CH_2 rotor costs this system 15.3 Jmol^{-1}K^{-1} entropically. Therefore, the drop in the EM value between [**1**•**2**] and [**1**•**5**] is approximately that expected[8] for the addition of the extra methylene rotor into the system.

In conclusion, we have demonstrated that it is possible to design rationally a simple system which is capable of accelerating a chemical reaction efficiently. Through the attachment of appropriate recognition sites to

an azide and a maleimide, it is possible to accelerate the [3+2] dipolar cycloaddition reaction efficiently. This acceleration arises through the stabilisation of the transition state leading to **3** in the [**1•2**] complex. The results presented here indictate that, although the association constant for the [**1•2**] complex is low (28 ± 2 M^{-1}), this does not affect the ability of this recognition-mediated system to accelerate the reaction between the azide and the maleimide. We are currently attempting to combine the acceleration observed in this system with regiospecific addition of the dipole to an unsymmetrical dipolarophile.

Acknowledgements This research was supported by the University of Birmingham and the Biotechnology and Biological Sciences Research Council (Studentship Award to CAB). We thank Prof G. von Kiedrowski for providing us with a copy of his SimFit program. We thank Mr P.R. Ashton for performing mass spectrometric analyses and Dr N. Spencer and Mr M.S. Tolley for their assistance with NMR spectroscopic studies.

REFERENCES AND NOTES

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*, Third Edition, Springer-Verlag, New York, **1996**. For some efficient examples, see M.W. Hosseini, J.M. Lehn, K.C. Jones, K.E. Plute, K.B. Mertes, M.P. Mertes *J. Am. Chem. Soc.* **1989**, *111*, 6330. I. Huc, J. Pieters, J. Rebek Jr *J. Am. Chem. Soc.* **1994**, *116*, 10296. P. Tecilla, V. Jubian, A.D. Hamilton *Tetrahedron* **1995**, *51*, 435.
2. D. Philp, A. Robertson *Chem. Commun.* **1998**, 879.
3. Selected spectroscopic data for **1**: δ_H (300 MHz, $CDCl_3$); 8.63 (1H, br s), 8.28 (1H, s), 8.18 (1H, d, $^3J_{HH}$ = 7 Hz), 7.08 (1H, d, $^3J_{HH}$ = 7 Hz), 4.11 (2H, s), 1.32 (9H, s). δ_C (75 MHz, $CDCl_3$) 161.2, 149.2, 148.2, 147.5, 117.7, 111.0, 56.3, 52.9, 30.4. EIMS: *m/z* 233 $[M]^+$.
4. Severe difficulties were encountered in obtaining good control reaction data. Attempts to utilise the reactions of azides lacking the amidopyridine recognition site with **2** gave reaction rates which were well below those obtained from the reaction of **1** with *N*-ethyl maleimide. Therefore, the use of the reaction between **1** and *N*-ethyl maleimide to estimate the bimolecular rate constants can be regarded as providing an upper limit for k_1 and k_2 and may, in fact, underestimate the performance of the [**1•2**] complex.
5. *SimFit*, A Program for the Analysis of Kinetic Data, Version 1.0, G. von Kiedrowski, **1994**.
6. Since the reaction between **1** and **2** is rapid at 50°C in $CDCl_3$, the association constant for the [**1•2**] complex cannot be measured directly. Therefore, the association constant for the [**1•2**] complex was estimated by determining the association constant for the [**1**•CH_3CO_2H] complex by 270 MHz ^1H NMR titration and dilution experiments in $CDCl_3$ at 50°C. Analysis of the data by non-linear curve fitting, performed using Deltagraph (Version 4.0.4, SPSS Inc., **1998**) running on an Apple PowerMacintosh, afforded a value of the association constant of 28 ± 2 M^{-1} for the [**1**•CH_3CO_2H] complex.
7. The value of the thermodynamic effective molarity for this system (k_3k_2/k_1k_4) is 1.07 M, indicating that stabilisation of the transition state leading to **3** in the [**1•2**] complex, rather than product stabilisation, is the dominant effect in this system.
8. *The Chemistry of Enzyme Action*, Ed. M.I. Page, Elsevier, Amsterdam, **1984**, p. 19.