Self-replication in a Diels–Alder reaction

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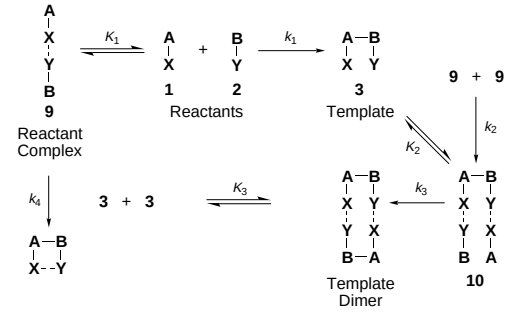
The Diels–Alder reaction between ene 1 and diene 2 at 23 and 40 °C shows sigmoidal characteristics for the formation of product 3 and a response to added 3 that indicates that it is an efficient catalyst for the reaction.

Replication is an essential feature of biological systems and simple chemical analogues have been studied, usually as possible models for prebiotic replication.[1,2] The simplest example of a self-replicating system is the autocatalytic synthesis of a self-complementary molecular template (Scheme 1) and examples of such systems involving self-complementary oligonucleotides have been described[1,3] by von Kiedrowski and Orgel. Other examples which have been developed have been based upon amide formation, studied[4] by Rebek and co-workers and recently the subject[5] of a careful kinetic analysis, and anil formation studied[6] by von Kiedrowski's group. Recently Rebek has described[7] a more complex system based upon four different reactants giving two complementary templates.

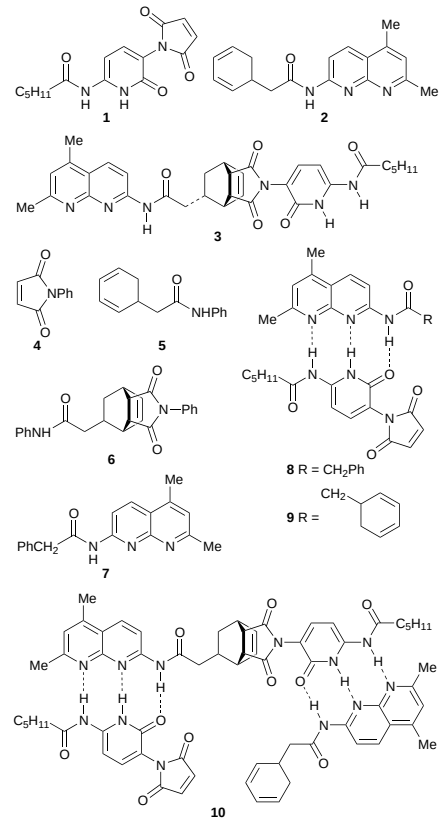
Here we describe a novel self-replicating system of the type shown in Scheme 1 which is very different from the original examples inspired by consideration of prebiotic evolution. The reaction centres (**A** and **B** in Scheme 1) were selected as the ene and diene components of the classical Diels–Alder reaction because it is known[8] that the Diels–Alder reaction can be catalysed effectively by complexation of the reactants in a suitably designed ditopic host. The binding sites (**X** and **Y** in Scheme 1) were selected on the basis of work[9] by Kelly and co-workers. After careful consideration of molecular models,[10] the existing kinetic data for Diels–Alder reactions, solubility requirements and synthetic accessibility, the 6-acylamino-2-pyridone derivative **1** and the 2-acylaminonaphthyridine **2** were selected as target ene and diene systems and were synthesised by conventional procedures.

The model compounds **4** and **5** lacking the binding sites reacted very slowly in CD_2Cl_2 at 23 and 40 °C and the course of the reaction could be followed by ^{1}H NMR spectroscopy; the product **6** is assumed to have *endo*-stereochemistry but may consist of one or both of the two possible *endo*-diastereoisomers. Reactant pairs **4** and **2** and **5** and **1** reacted together at similar rates but the pair of reactants **1** and **2** with complementary binding sites reacted relatively rapidly at both 23 and 40 °C to give product **3**, probably a mixture of *endo*-diastereoisomers, in good yield. Fig. 1, based upon integration of alkenic ^{1}H NMR signals in diene **2** and product **3**, shows the rate of product formation at 40 °C; the signals of the diastereoisomers of **3** overlap and no attempt has been made to separate the diastereoisomeric reaction pathways. The sigmoidal character of the reaction curves at both temperatures indicates that an autocatalytic process of the type shown in Scheme 1 could be operating, whereas the reaction of **4** and **5** shows simple second order characteristics. The catalysis of the reaction of **1** and **2** by product **3** was confirmed by carrying out the reaction in the presence of 0.05 and 0.1 equiv. of product **3** (see Fig. 1 which shows the results); the reaction under these conditions shows initial catalysis and a loss of the induction period associated with sigmoidal character.



Scheme 1 A simple self-replication cycle. **A** and **B** represent reacting groups attached to complementary binding sites **X** and **Y**. The full lines represent covalent attachment and the broken lines represent hydrogen bonding interactions.

The results at 40 °C were analysed in terms of the reactions and equilibria shown in Scheme 1 using a computer model† including all of the reactions and equilibria and the insertion of trial values for the rate constants and the equilibrium constants. The value of K_1 was found by a study of the association between pyridone **1** and the acylaminonaphthyridine **7** using an ^{1}H NMR titration procedure, in which increments of **7** were added to a 0.02 M solution of **1** in CD_2Cl_2, and the chemical shifts of the NH protons were used in association with a simple computational procedure for finding a 'best fit' value for the association constant. The values of K_1 (228 mol l^{-1} at 23 °C and 163 mol l^{-1} at 40 °C) are consistent with some inhibition of binding (*cf.* ref. 9) between the two components of the complex **8** as a result of non-bonding interactions between the 7-methyl substituent on the naphthyridine and the alkyl group of the pyridone side-chain at position 6. These interactions, which are



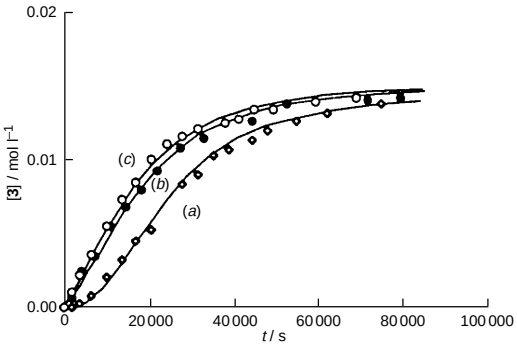


Fig. 1 Observed and calculated reaction curves for the Diels–Alder reaction between **1** and **2** at 40 °C based upon Scheme 1: (*a*) 0%, (*b*) 5% and (*c*) 10% added template. The best fit for observed and calculated data is obtained with $k_1 = k_2 = 3.5 \times 10^{-5}$ l mol^{-1} s^{-1}, $K_1 = 163$ l mol^{-1}, $K_2 = 2.66 \times 10^4$ l^2 mol^{-2}, $k_3 = 2.0 \times 10^{-3}$ s^{-1}, $K_3 = 2.66 \times 10^4$ l mol^{-1}, $k_4 = 0$ s^{-1}. Experimental errors in the concentrations of product **3** derived from NMR spectra are probably of the order ±0.0005 mol l^{-1}.

evident in molecular mechanics calculations,[10] are also expected to inhibit the dimerisation of product **3** and the formation of the templated reaction complex **10**. Accordingly a value of K_1^2 was assigned to the equilibrium constant K_2 and values of K_3 were chosen in the range $K_2/10$ to $10K_2$. Assignment of values to k_4 greater than 10^{-7} s^{-1} did not reproduce the observed induction period for the reaction and, as expected, this reaction does not appear to make a significant contribution to the formation of product **3**. The value for k_1 was based initially upon the second order rate constant for the reaction of the model ene **4** and diene **5** and the reaction between complexed pairs of reactants was assumed to have a rate constant k_2 with the same value as k_1. Trial values for the first order rate constant k_3 for the catalysed reaction were selected in association with trial values of K_3. Eventually it was found that a good fit between observed and calculated reaction curves could not be obtained unless a considerably lower value than that obtained from the reaction of **4** and **5** was selected for k_1 and k_2, and the final values for rate constants and equilibrium constants are summarised below Fig. 1 which shows the comparison of observed and calculated results. It is not clear why the reaction of **4** and **5** is not a good model for the uncatalysed reaction of **1** and **2**. We note that the experimental data points have the lack of precision associated with integration of NMR signals but in spite of this the agreement between observed and calculated data is satisfactory for the reaction at 40 °C. The results at 23 °C were more difficult to analyse in the same way and satisfactory agreement between observed and calculated data has not yet been obtained, although the data does fit the simpler reaction scheme discussed below.

The calculated effective molarity of the catalysed reaction (7 mol l^{-1} at 40 °C) is based upon the value of k_3 and the value of the bimolecular rate constant k for the model reaction of **4** and **5** (6.98×10^{-5} mol^{-1} s^{-1} at 23 °C and 2.81×10^{-4} mol^{-1} l s^{-1} at 40 °C) rather than the rate constant k_1 which cannot be measured directly, although the value of the latter suggests that this effective molarity may be an underestimate. It indicates that transition state binding by the template is reasonably efficient since it is of the same order as the effective molarity (4 mol l^{-1}) observed for the acceleration of a Diels–Alder reaction within a well designed cavity as reported by Sanders and co-workers.[8] It is evident from the calculations that a good sigmoidal reaction curve for the reaction in the absence of added template (see Fig. 1) requires both a moderately high effective molarity in the template catalysed reaction and a reasonably low value for the dimerisation constant K_3. That the Diels–Alder reaction allows this is a consequence of a transition state that resembles product but has partial bonds that are more flexible than those of the rigid bicyclic system in the product. Furthermore the template **3** holds the reactive groups of the ene **1** and diene **2** in close proximity and the intramolecular reaction in the reactant complex **9** is prevented by preference for an *endo*-transition state which requires the extended arrangement for reactants shown in **10**.

Other self-replicating systems have often been analysed[1b,3c,4] in terms of Scheme 2 involving only two reactions with a value for α of 0.5. This simple scheme with $\alpha = 0.5$ did not produce calculated reaction curves in accord with our results but more extended calculations using values for α between 0.5 and 1.0 gave a good fit for a rate law of the type shown in Scheme 2 and a value for α of 0.8 (details of calculated rate constants are given below the scheme). This value for α is based upon a value for k_1 equal to that computed for rate constants k_1 and k_2 in Scheme 1 and we note that the 'best fit' value for α varies as k_1 varies. An ideal system would have a value for α close to 1.0 which would require a value for K_3 much lower than that for K_1^2.

$$\mathbf{A} + \mathbf{B} \xrightarrow{k_1} \mathbf{C}$$

$$\mathbf{A} + \mathbf{B} + \alpha\mathbf{C} \xrightarrow{k_2} (1+\alpha)\mathbf{C}$$

Overall rate: $dC/dt = k_1[A][B] + k_2[A][B][C]^{\alpha}$

Scheme 2 A simplified reaction scheme for a self replication cycle. **A** and **B** are the two reactants giving **C** which is a catalytic template for the reaction, and α lies between 0 and 1. A satisfactory agreement between observed and experimental data is obtained with the following values of rate constants and a value for α of 0.8: at 23 °C, $k_1 = 6.98 \times 10^{-6}$ l mol^{-1} s^{-1} and $k_2 = 0.133$ l$^{1.8}$ mol$^{-1.8}$ s^{-1}; at 40 °C, $k_1 = 3.5 \times 10^{-5}$ and $k_2 = 0.350$ l$^{1.8}$ mol$^{-1.8}$ s^{-1}.

The Diels–Alder reaction of **1** and **2** differs from reactions reported in other work in that reactant **2** and product **3** are chiral and that **3** can, in principle, be formed as four possible diastereoisomers. These stereochemical features, which will be discussed in the full paper, lead to diastereoisomeric reaction pathways which have not been separated in the kinetic analysis above.

We conclude that the Diels–Alder reaction with a well-defined bicyclic transition state offers a basis for efficient self-replicating systems that could be investigated for transfer of chemical information coded in terms of the regio- and stereo-selectivity[1b] of template catalysed bond formation. Other reactions with well-defined transition states which generate stereo- and regio-isomers may offer similar possibilities.

Footnotes and References

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