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Acceleration of a dipolar cycloaddition by a simple bisamide receptor

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Abstract

A bisamide receptor has been synthesized which is capable of binding and, hence, polarizing maleimide. The hydrogen bonds formed between the receptor and maleimide alter its inherent reactivity. Full kinetic investigations, performed using ^{1}H NMR spectroscopy and computer-based simulation, reveal that the formation of the 1:1 complex increases the rate of the cycloaddition between maleimide and diphenylnitrone fivefold. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: hydrogen bonding; catalysis; cycloadditions; isoxazolidines.

Many examples of efficient Lewis acid catalysts capable of accelerating cycloaddition reactions, often stereoselectively, have appeared[1] in the literature in recent years. We have become interested in achieving the same catalytic effect through the use of recognition processes based on hydrogen bonding. The formation of hydrogen bonds to a substrate **G** (Fig. 1) results in a partial proton transfer from the donor moiety of the host **H** to the acceptor atom of the substrate **G**. This partial protonation alters the electronic properties of the substrate **G** thereby influencing its reactivity.

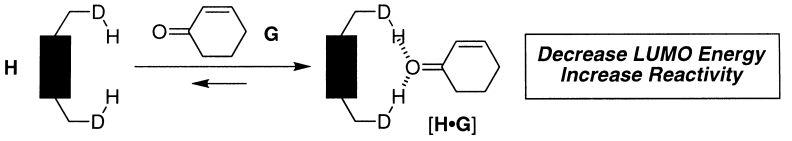

Figure 1. Hydrogen bonding between **H** and **G** polarizes **G** and increases its reactivity

This approach should be particularly suitable for catalyzing cycloaddition reactions since the reactivity of 2π components in cycloadditions should be enhanced by hydrogen bond induced polarization through the lowering of the LUMO energy of the 2π component. Surprisingly, reports[2]

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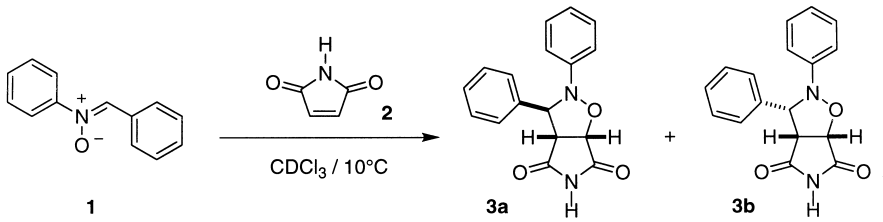
of synthetic hosts capable of effecting such polarization-induced changes in either dienophiles, in Diels–Alder reactions, or dipolarophiles, in dipolar cycloadditions, are somewhat sparse. Previously, we have reported the use[3] of hydrogen bond-facilitated polarization to enhance the acceptor ability of a water molecule towards a weak hydrogen bond donor and the hydrogen bond-facilitated enhancement[4] of amine nucleophilicity by a simple bis(phosphine oxide) host. In this communication, we report the acceleration of a [3+2] dipolar cycloaddition reaction between diphenyl nitrone and maleimide using a simple, symmetric bisamide host. The origin of this acceleration is traced, through binding studies, control reactions and kinetic simulation, to the formation of a hydrogen-bonded complex between the host and the dipolarophile, maleimide.

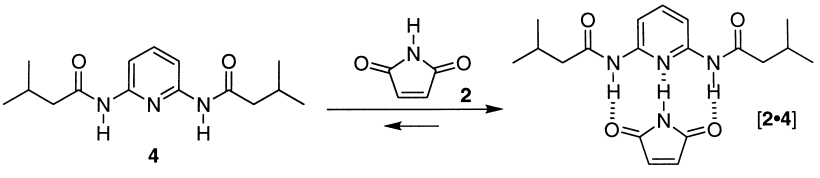
We identified the reaction (Scheme 1) between diphenylnitrone **1** and maleimide **2** as a suitable target reaction for catalysis for two reasons. Firstly, the reaction between **1** and **2** to afford the two diastereoisomeric products **3a** and **3b** is relatively slow in $CDCl_3$ at 10°C. Secondly, the dipolarophile, maleimide **2**, possesses an array of hydrogen bond donors and acceptors which are suitable targets for an appropriately designed host.



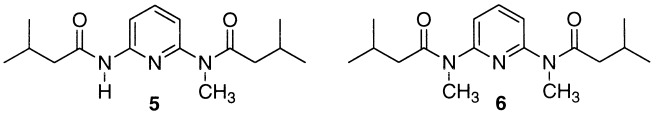
Scheme 1.

Accordingly, we designed host **4**, which, we reasoned, would bind to maleimide, forming the 1:1 complex [**2**·**4**], by virtue of its complementary array of hydrogen bond donors and acceptors and which could be synthesized readily, in one step from commercially available starting materials.

The addition of receptor **4** to solutions of maleimide **2** in $CDCl_3$ at 21°C resulted in strong downfield shifts of the resonance arising from the maleimide NH proton (saturation $\Delta\delta = +5.02$). Additionally, smaller downfield chemical shift changes were observed in the resonances arising from the amide NH protons of **4**. These chemical shift changes are strongly indicative of the formation of a complex between **2** and **4** which possesses the structure [**2**·**4**] shown in Scheme 2. A ^{1}H NMR spectroscopic titration[5] was used to establish the association constant for the complex [**2**·**4**] in $CDCl_3$ at 21°C. Non-linear curve fitting[6] of the experimental ^{1}H NMR spectroscopic data afforded a value of 25 M^{-1} for the association constant in $CDCl_3$ at 21°C. This value of association constant, although low, is in the range expected[7] for triply hydrogen bonded complexes of bis(amido)pyridines.



Scheme 2.



In order to determine unambiguously the effect of **4** upon the reactivity of **2**, adequate control compounds were required. Accordingly, partially or fully methylated control compounds **5** and **6**, in which the hydrogen bonding sites for the guest **2** were either partially or fully blocked, were also prepared. The association between control compounds **5** and **6** and maleimide was examined via a simple binding investigation[8] by ^{1}H NMR spectroscopy. Although the magnitude of the change in the chemical shifts in the ^{1}H NMR spectrum of a complex gives little indication of the value of the association constant, when a system is involved in a complex, it is likely that some significant changes would be observed.

For the dimethylated receptor **6**, there was a small (0.16 ppm) change in chemical shift of the NH maleimide proton and the remaining resonances in the ^{1}H NMR spectrum were unaffected. The monomethylated receptor **5** showed a similar change in the NH chemical shift of maleimide (0.15 ppm) and a small change in the NH resonance of the receptor (0.04 ppm). For comparison, in the same type of experiment, the presence of **4** induces a change of 1.97 ppm in the chemical shift of the maleimide NH resonance.

Further evidence for the formation of the [**2**·**4**] complex came from infra-red spectroscopy. Since hydrogen bonds can be considered as partial proton transfer between a donor and an acceptor, in the [**2**·**4**] complex, this association should cause weakening of the NH bonds in both **2** and **4**. Hence, we recorded the infra-red spectrum of the [**2**·**4**] complex in a KBr disk. Although the NH stretching vibration of maleimide **2** was obscured, the NH stretching vibration of the receptor **4** exhibited a red shift of 88 cm^{-1}, indicative of a lengthening and reduction in force constant of the NH bond arising from hydrogen bond formation. By contrast, the two spectra arising from 1:1 mixtures of the methylated control compounds **5** and **6** with maleimide **2** showed no significant change in any of the NH stretching vibrations.

In order to assess the effect of the formation of the [**2**·**4**] complex on the reactivity of **2**, we performed the reaction between **1** and **2** in $CDCl_3$ at 10°C in the presence of one equivalent[9] of either **4**, **5** or **6**. In all experiments, the initial concentration of reagents was 20 mM and kinetic data were obtained by 400 MHz ^{1}H NMR spectroscopy, with spectra being recorded at 30 minute intervals over a period of 15 hours. Product concentrations were calculated from the ^{1}H NMR spectra using previously developed[10] deconvolution procedures and the total product concentration determined by summation of the values obtained for each of the diastereoisomers **3a** and **3b**. The results obtained are presented in Fig. 2.

It is clear from the data that, in the presence of receptor **4**, the reaction between **1** and **2** proceeds at an enhanced rate when compared with the reactions performed in the presence of either **5** or **6**. In fact, the presence of either **5** or **6** in the reaction mixture has no measurable effect on the rate of the reaction between **1** and **2**. Kinetic simulation and fitting[11] of the experimental data to the appropriate kinetic models allowed the extraction of rate constants for the reaction between **1** and **2** in the presence and absence of **4**. The rate constants extracted from this analysis indicate that the reaction between **1** and **2** is accelerated fivefold when maleimide **2** is bound to host **4**.

In conclusion, we have demonstrated that a simple bisamide receptor, prepared in one step from commercially-available starting materials, is capable of accelerating a cycloaddition reaction

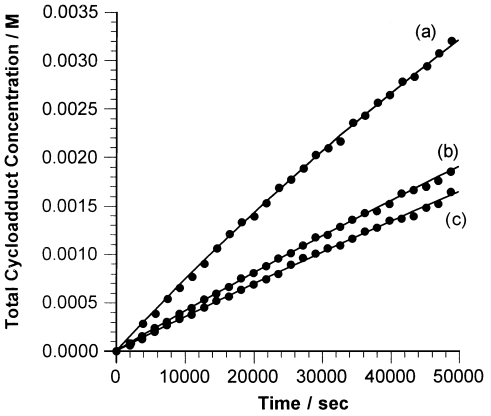


Figure 2. Rate profiles for the reaction between **1** and **2**, (a) in the presence of one equivalent of **4**, (b) in the presence of one equivalent of **5** and (c) in the presence of one equivalent of **6**. In each case, filled circles represent the total concentration of cycloadduct ([**3a**]+[**3b**]) and the solid line represents the best fit of the appropriate kinetic model to the experimental data. Note: in the absence of *any* receptor, the reaction between **1** and **2** proceeds at a rate identical to (c) above

through hydrogen-bond mediated polarization of the reaction substrate. The level of acceleration displayed by host **4** is modest, however, this is not unexpected[12] given its simple design. We are currently engaged in extending the methodology described here to other classes of reaction and in the design of more complex host systems which separate the binding and polarization sites spatially.

Acknowledgements

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recorded at 21°C in $CDCl_3$ solution at the same concentration, of the host and guest in isolation. The chemical shift changes determined for the [**2**·**4**] complex in these experiments are, of course, much smaller than the saturation chemical shift change determined from the ^1H NMR titration experiment.
9. Significant acceleration is also observed when only 0.2 equivalents of **4** are added to the reaction mixture.
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12. The performance of host **4** is hampered by several factors. In particular, the low binding constant ($25\,M^{-1}$), coupled with the low solubility of maleimide in $CDCl_3$ (Saturated solution = ca. 20 mM), limits the magnitude of the rate acceleration possible.