

Supporting information for:

**Supramolecular Control over Diels-Alder Reactivity by
Encapsulation and Competitive Displacement**

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1. Experimental

1.1. General

All reagents and solvents were purchased from commercial sources and used as supplied. NMR spectra were recorded on a Bruker Avance DPX400 spectrometer; δ_{H} values are reported relative to the internal standard *t*BuOH ($\delta_{\text{H}} = 1.24$ ppm). Mass spectra were provided by the EPSRC National MS Service Centre at Swansea and were acquired on a Thermofisher LTQ Orbitrap XL.

1.2. Synthesis

Cage **1** was prepared as the tetramethylammonium salt according to the method reported earlier by our group.^{S1}

1.3. Kinetic experiments

A J-Young NMR tube was loaded with 0.45 mL of a 4.4×10^{-3} M solution of **1** dissolved in D₂O. To this NMR tube was added 50 μL of a 3.6×10^{-2} M of furan in D₂O. After addition, the concentration of **1** was 4.0×10^{-3} M, while the concentration of furan was 3.6×10^{-3} M (*i.e.* 0.9 equiv. furan per **1**). This solution was left to equilibrate overnight at 50 °C. For the room temperature experiments 3.20 mg (3.3 mmol) maleimide was added to the solution, while for the experiments at 5 °C 9.71 mg (10 mmol) maleimide was added. To initiate the reaction 10 μL of benzene-*d*₆ added and the solution was kept at the appropriate temperature. For the control reaction, the reaction was started directly after the addition of maleimide (*i.e.* no benzene-*d*₆ was added).

1.3.1 Monitoring exit kinetics

As hosts with a different guest are in slow exchange on the NMR timescale, simple integration of the imine peaks corresponding to the empty host **1** and its host-guest complexes allowed for the determination of these species' relative proportions as a function of time. Table S1 gives the imine peak's chemical shift for each different host species.

Table S1 Chemical shifts for the imine peaks of cage **1** in different host-guest states.

Guest	Chemical shift / ppm
Furan	9.65
Benzene	10.26
Empty	9.35

1.3.2 Monitoring Diels-Alder kinetics

At room temperature or below, the reaction between furan and maleimide leads primarily to the formation of the kinetic *endo* product.^{S2} Hence, the progress of the Diels-Alder reaction was monitored by following the formation of this product. To quantify the yield of the reaction, the integrated intensity of the *endo* product peaks was compared to the internal standard's peak. The internal standard used was *t*BuOH at a concentration of 5.3×10^{-3} M.

2. Supporting graphs and Figures

2.1. NOESY Spectrum

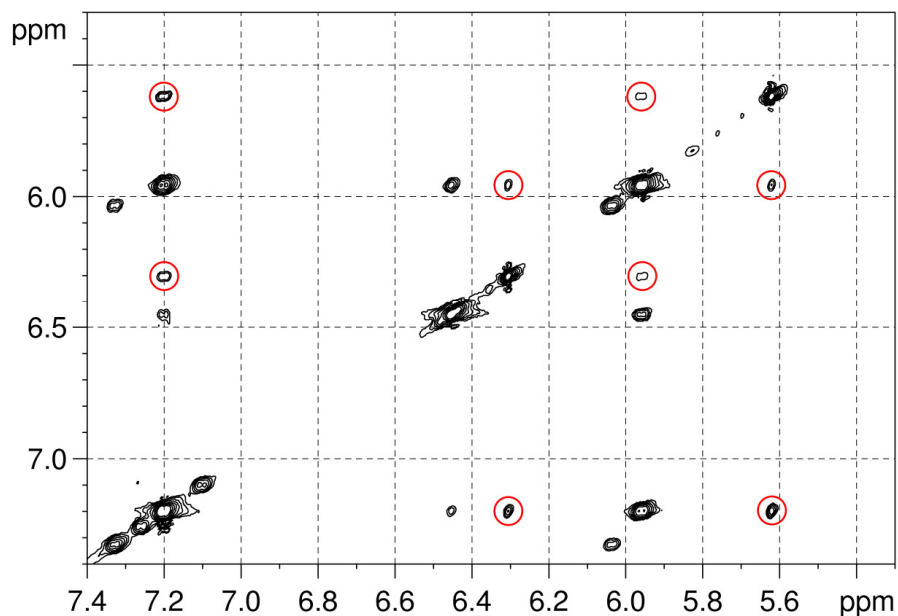


Fig. S1 NOESY spectrum of furan-**1** (4.0×10^{-3} M) in D_2O . The highlighted cross peaks indicate the NOE interactions between the two furan proton resonances (6.30 and 5.62 ppm) and the inwardly-oriented protons on the cage's ligand (*f* (7.20 ppm) and *h* (5.96 ppm); see Scheme 1 in the main text for assignment).

2.2. K_a determination for furan

To 5 mL of a 1.0×10^{-3} M solution of **1** in D_2O was added 4.0 μ L of furan, resulting in a total furan concentration of 1.1×10^{-2} M. The solution was allowed to equilibrate overnight at 50 $^{\circ}C$. Aliquots of this solution were added to 0.50 mL of a 1.0×10^{-3} M solution of **1** in D_2O . After each addition the mixture was equilibrated for 6 hours, after which the 1H NMR spectrum was recorded (Fig S2). The degree of encapsulation, $[HG]/[H]_0$, was determined by comparison of the integrals of the imine peaks of empty **1** (at 9.35 ppm) and furan-**1** (at 9.65 ppm). Plotting the degree of encapsulation as a function of the total concentration of furan yielded a binding isotherm (Fig S3), which was fitted using a 1:1 binding model we

previously derived.^{S3} In this model the degree of encapsulation, $[HG]/[H]_0$, is given by Eq S1:

$$\frac{[HG]}{[H]_0} = \frac{[1 + K([H]_0 + [G]_0)] - \sqrt{[1 + K([H]_0 + [G]_0)]^2 - 4K^2[H]_0[G]_0}}{2K[H]_0} \quad (\text{S1})$$

in which:

K = Binding constant, in M^{-1} ;

$[H]_0$ = Total host concentration, in M;

$[G]_0$ = Total guest concentration, in M.

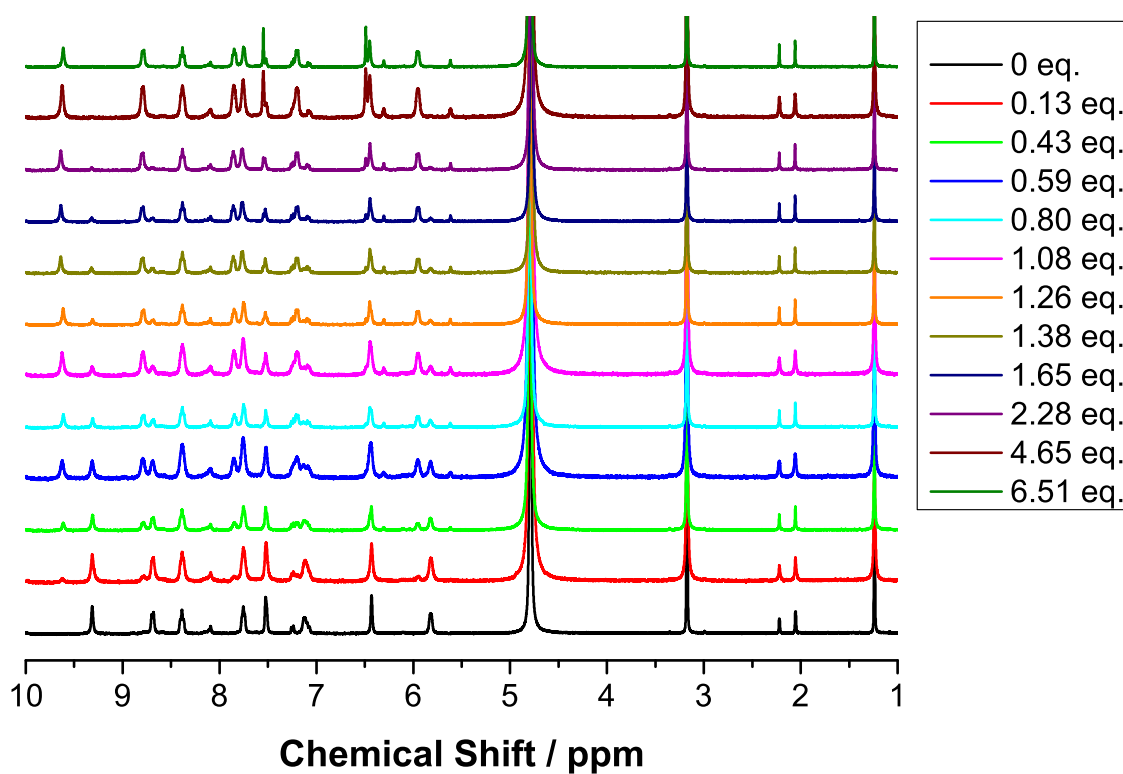


Fig. S2 ^1H NMR spectra for **1** in D_2O in the presence of increasing equivalents of furan.

Total concentration of **1**: 1.0×10^{-3} M.

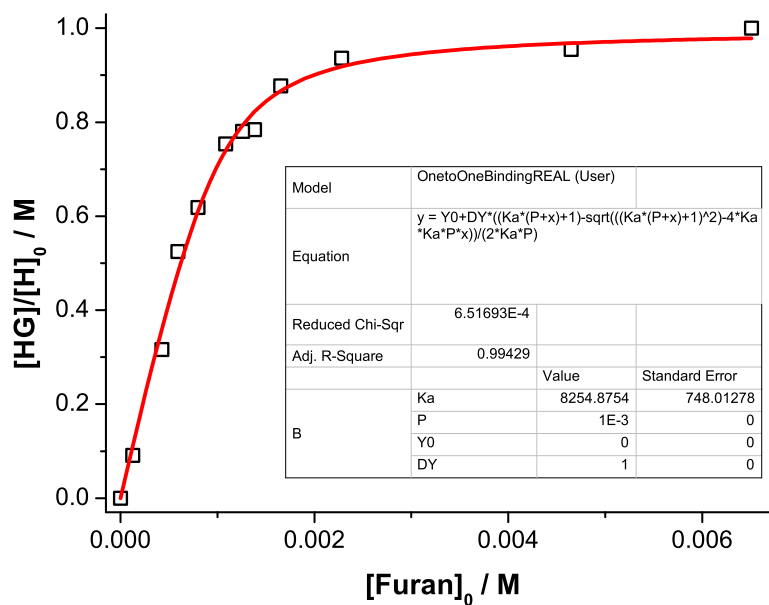


Fig. S3 Degree of encapsulation, $[HG]/[H]_0$, as a function of the total concentration of furan and corresponding fit of the data to the 1:1 binding model, revealing a binding constant of $8.3 \pm 0.7 \times 10^3 \text{ M}^{-1}$.

2.3. Furan + Maleimide in D₂O: control reaction

To 900 μL of a solution of maleimide in D₂O (4.2×10^{-2} M) was added 100 μL of a solution of furan in D₂O (2.3×10^{-2} M). After addition, the concentration of maleimide had become 3.7×10^{-2} M, while the concentration of furan had become 2.3×10^{-3} M. The progress of the Diels-Alder reaction was monitored by ¹H NMR spectroscopy by following the disappearance of the resonances of the furan (at 7.55 and 6.49 ppm).

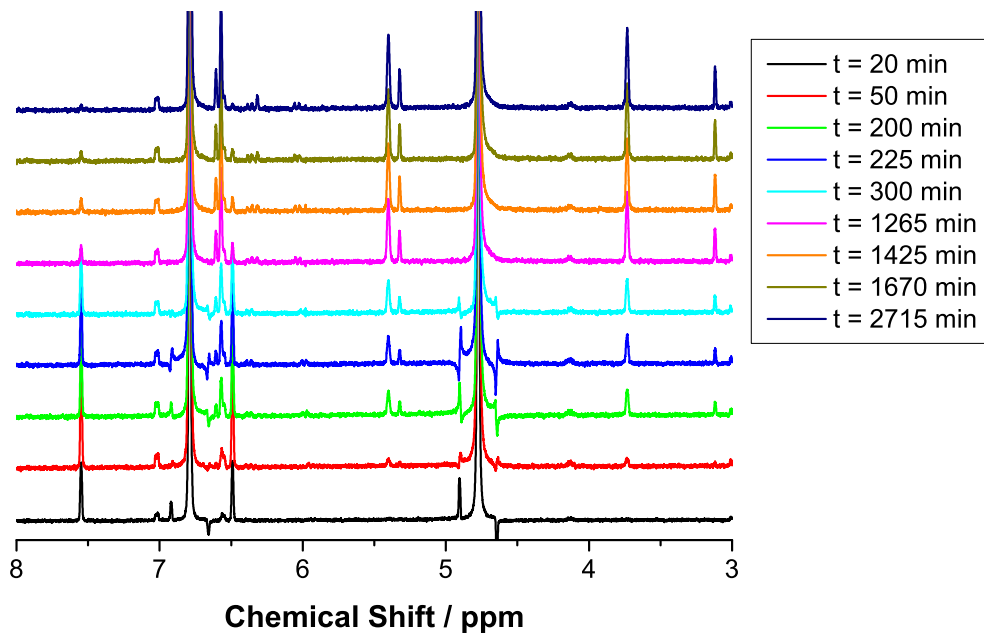


Fig. S4 ¹H NMR spectra showing the progress of the Diels-Alder reaction between furan (resonances at 7.55 and 6.49 ppm) and maleimide (6.79 ppm) in D₂O. The resonances of the *endo* product appear at 6.57, 5.40 and 3.73 ppm, while those of the *exo* product appear at 6.61, 5.32 and 3.12 ppm.

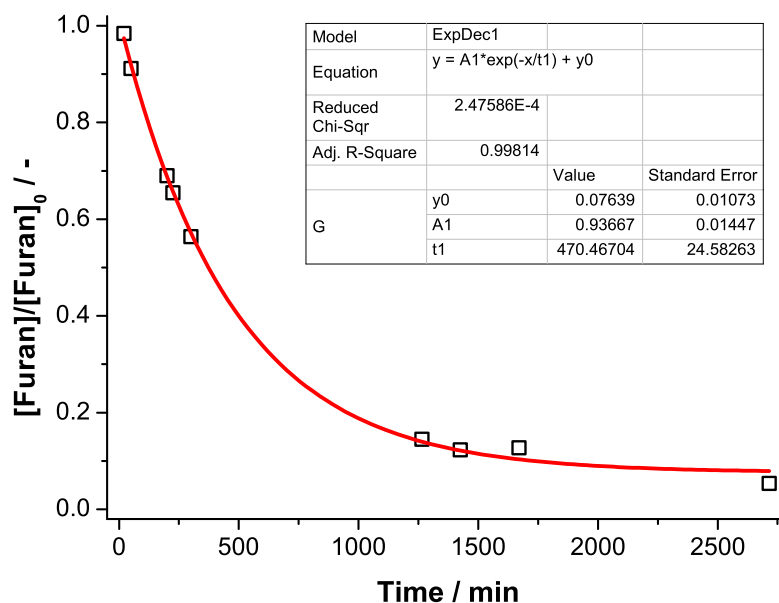


Fig. S5 Progress of the Diels-Alder reaction between furan and maleimide. The consumption of furan could be fitted with a mono-exponential decay function, confirming the validity of *pseudo*-first order conditions.

2.4. Furan release kinetics at 25 °C

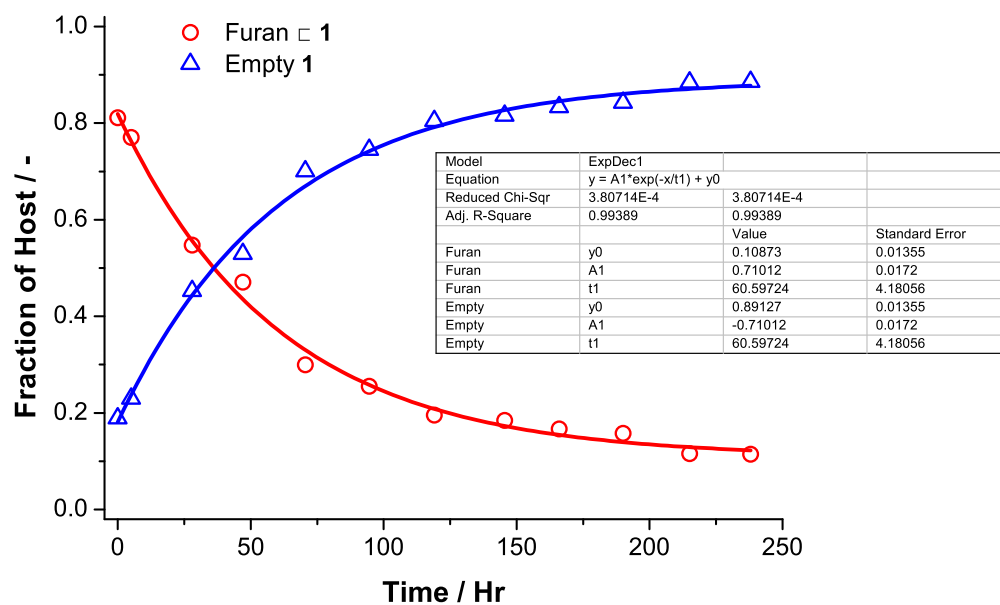


Fig. S6 Release kinetics of furan from cage **1** at 25 °C in the absence of benzene (*i.e.* the control reaction). The release of furan was fitted to a mono-exponential decay function, resulting in a first-order rate constant (inverse of the life time t_1) of $1.65 \pm 0.11 \times 10^{-2} \text{ h}^{-1}$.

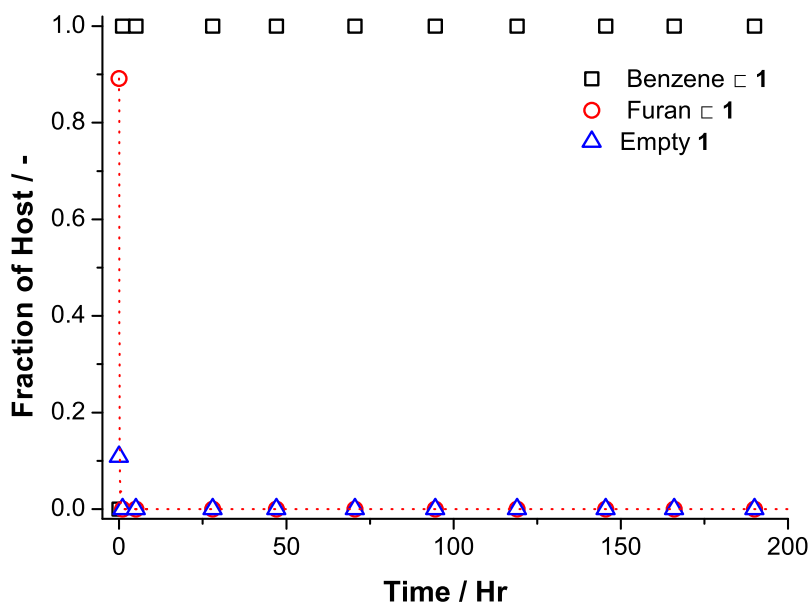


Fig. S7 Release kinetics of furan from cage **1** at 25 °C. At $t = 0$ benzene was added to the sample, leading to an almost instant release of furan from the cage and encapsulation of benzene. As the release of furan was too fast to be monitored, it could not be fitted to a mono-exponential decay function. The dotted line is a simulated trace assuming a first-order rate constant of 10 h^{-1} , showing that the release of furan upon addition of benzene is at least three orders of magnitude faster than in the control reaction.

2.5. Diels-Alder kinetics at 25 °C

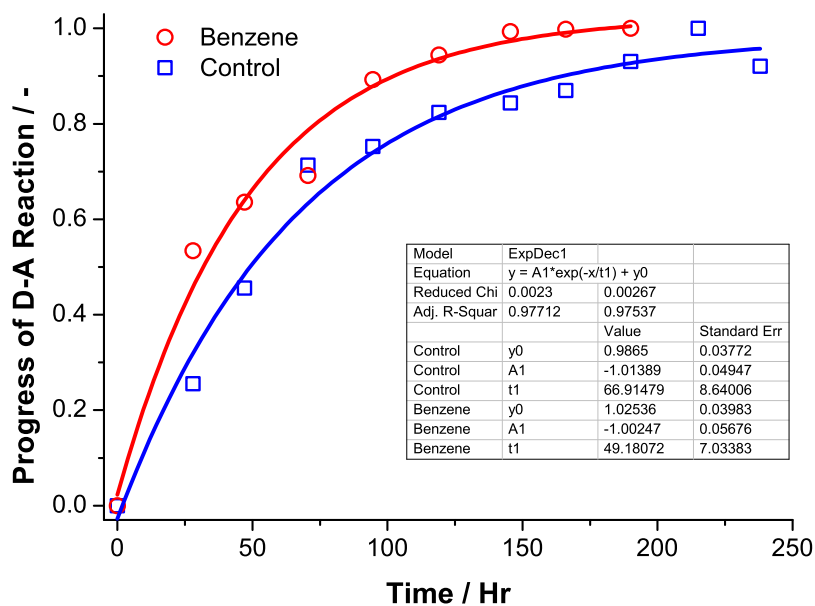


Fig. S8 Progress of the Diels-Alder reaction between furan and maleimide at 25 °C. The formation of the Diels-Alder product was fitted to a mono-exponential growth function, resulting in a rate constant (inverse of the life time t_1) of $1.49 \pm 0.19 \times 10^{-2} \text{ h}^{-1}$ for the control reaction and $2.03 \pm 0.29 \times 10^{-2} \text{ h}^{-1}$ for the benzene-initiated reaction. This means that at 25 °C the benzene-initiated Diels-Alder reaction is 36% faster compared to the control reaction.

2.6. Furan release kinetics at 5 °C

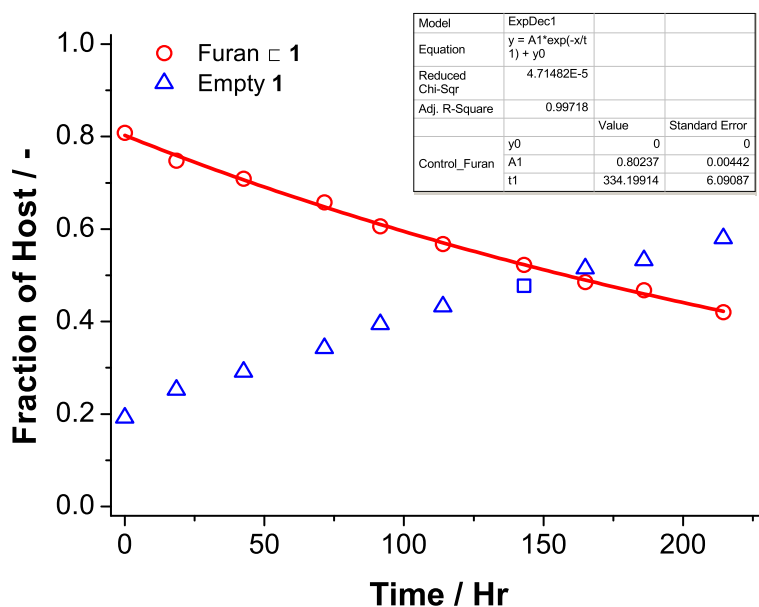


Fig. S9 Release kinetics of furan from cage **1** at 5 °C in the absence of benzene (*i.e.* the control reaction). The release of furan was fitted to a mono-exponential decay function, resulting in a first-order rate constant (inverse of the life time t_1) of $2.99 \pm 0.05 \times 10^{-3} \text{ h}^{-1}$.

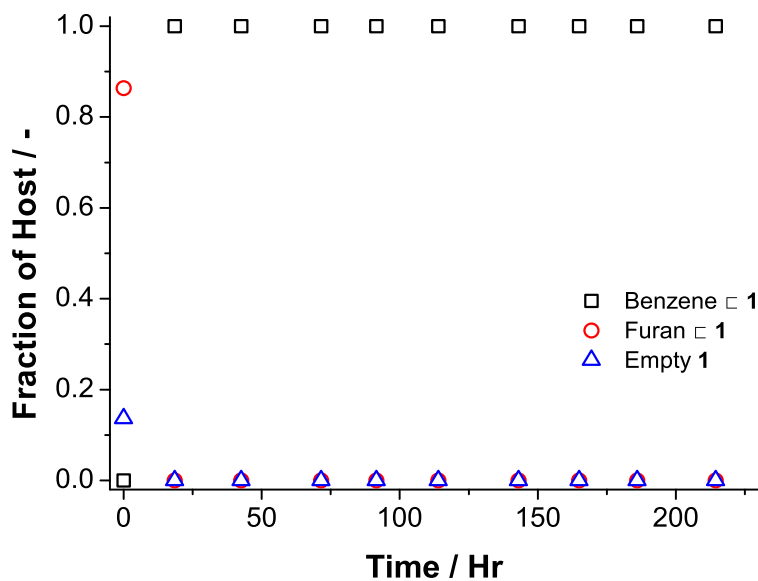


Fig. S10 Release kinetics of furan from cage **1** at 5 °C. At $t = 0$ benzene was added to the sample, leading to an almost instant release of furan from the cage and encapsulation of benzene.

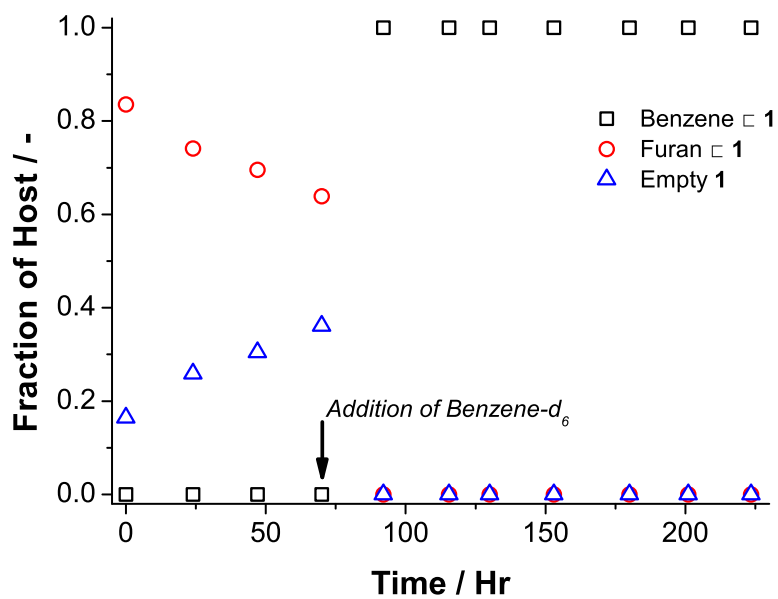


Fig. S11 Release kinetics of furan from cage 1 at 5 °C. At $t = 70$ h benzene was added to the sample, followed by an almost instant release of furan from the cage and encapsulation of benzene.

2.7. Diels-Alder kinetics at 5 °C

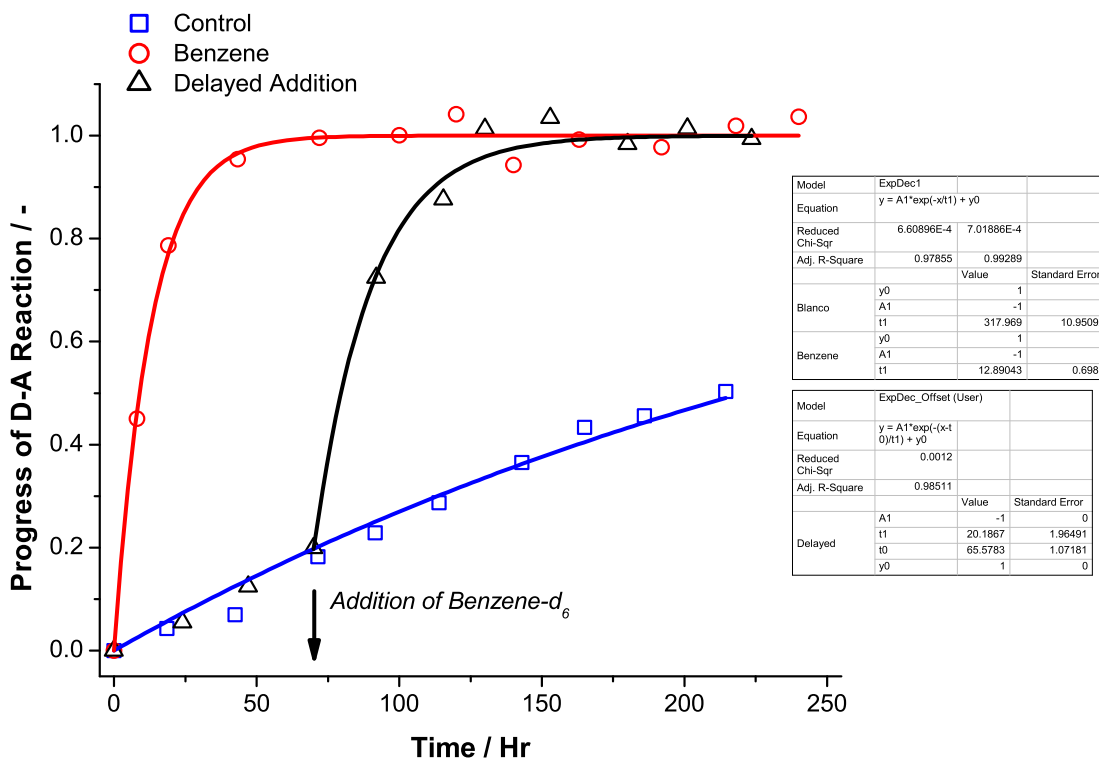


Fig. S12 Progress of the Diels-Alder reaction between furan and maleimide at 5 °C. The formation of the Diels-Alder product was fitted to a mono-exponential growth function, resulting in a rate constant (the inverse of the life time t_1) of $3.14 \pm 0.11 \times 10^{-3} \text{ h}^{-1}$ for the control reaction and $7.76 \pm 0.42 \times 10^{-2} \text{ h}^{-1}$ for the benzene-initiated reaction. This means that at 5 °C the benzene-initiated Diels-Alder reaction is 25 times faster compared to the control reaction. For the experiment where the benzene was added at $t = 70 \text{ h}$, the following data points were fitted to a mono-exponential growth function, resulting in a rate constant (the inverse of the life time t_1) of $4.95 \pm 0.48 \times 10^{-2} \text{ h}^{-1}$.

3. References

- S1. I. A. Riddell, M. M. J. Smulders, J. K. Clegg and J. R. Nitschke, *Chem. Commun.*, 2011, **47**, 457.
- S2. H. Kwart and I. Burchuk, *J. Am. Chem. Soc.*, 1952, **74**, 3094.
- S3. Y. R. Hristova, M. M. J. Smulders, J. K. Clegg, B. Breiner and J. R. Nitschke, *Chem. Sci.*, 2011, **2**, 638.