A deep cavitand catalyzes the Diels–Alder reaction of bound maleimides†

Richard J. Hooley and Julius Rebek Jr.*

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A deep cavitand catalyzes Diels–Alder reactions of bound maleimides *via* activation of the dienophile by interaction with the organized hydrogen bonding network at the cavitand rim. Rapid in–out exchange of reactant and product allows efficient turnover. The increase in steric bulk of the reaction product lessens its binding affinity, reducing (and in some cases completely eliminating) product inhibition.

Introduction

Selective binding of a substrate, followed by activation of that species for reaction and subsequent product release from the active site are the core features of catalysis, enzymatic or otherwise.[1] Enzymes have exquisite selectivities for transition states, but this property is difficult to attain in most synthetic mimics[2] and product inhibition,[3] particularly for condensation reactions, thwarts catalysis. Building steric hindrance into products can facilitate displacement by reactants and stimulate turnover. This tactic has led to acceleration[4] of cycloadditions in nonhydroxylic media using capsules. Even catalysis was recently observed using a bowl-shaped, metal–ligand receptor in water by Fujita *et al*.[5] Here we report the application of this method of reducing product inhibition to cavitands in organic solvents.

Cavitands such as **1** are vase-like structures capable of binding neutral and cationic guests that fill the appropriate amount of its space.[6] The base of the cavitand presents an electron-rich π surface to guests. At the rim, eight secondary amides stabilize the vase-like conformation shown and also provide a polar environment and organized H-bonding sites for guests. The amides can rotate to present hydrogen bond donors and acceptors to guests held within. For example, this region of organized solvation can stabilize the buildup of positive charge during quaternization of bound amine nucleophiles,[7] or stabilize the negative charge in the formation of Meisenheimer complexes.[8] Earlier results with stoichiometric reactions led us to the possibility of catalyzing Diels–Alder reactions. Many cycloadditions of electron deficient olefins and anthracenes occur under mild conditions and are performed in the absence of catalyst at room temperature or below. Simple hydrophobic association can increase effective concentrations in water and has produced accelerations and catalysis.[5,9] Lewis acid catalysis is well-known to accelerate the Diels–Alder reaction, but Brønsted acids have also been used as catalysts especially in recent times.[10] Suitably reactive dienophiles include *N*-alkylmaleimides: a number of these show strong binding affinity (10^2–10^4 M^{-1}, see Table 1) for cavitand **1** in mesitylene-d_{12}. This solvent fits awkwardly into the cavitand and does not compete well with intended guests.[11] As shown in Fig. 1, molecular modeling indicates that medium-sized cyclic alkyl groups such as adamantanes position the reactive maleimide for its carbonyl groups to make good contacts with the organized H-bonding network at the cavitand rim. The maleimides' double bonds remain exposed above the receptor for reaction. The in–out exchange rate for species of this type is on the order of 2 s^{-1}, far faster than the cycloaddition rate.[6b] The rapid exchange of product and reactant positions the receptor to act as a catalyst, not just a promoter of the reaction. In addition, cycloaddition to this olefin would increase the steric bulk of the product with respect to reactant, lowering its binding affinity and reducing product inhibition. The proposed reaction mechanism is shown in Fig. 2.

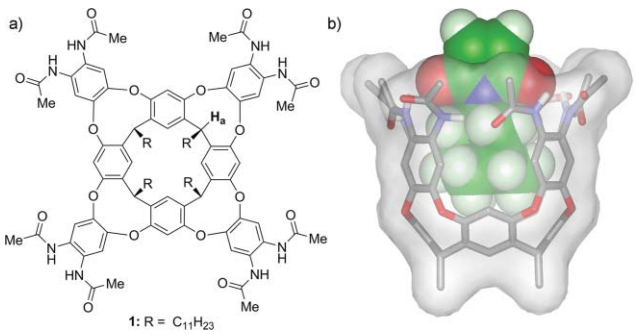


Fig. 1 The deep cavitand used as catalyst; minimized representation of the complex of **1** and adamantyl maleimide **4**, illustrating the proximity of the maleimide to the organized solvation of the amide rim.

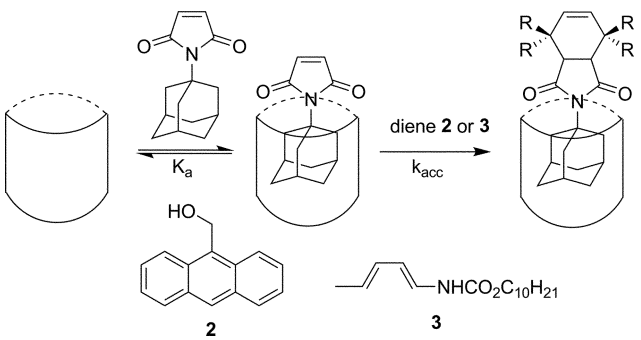
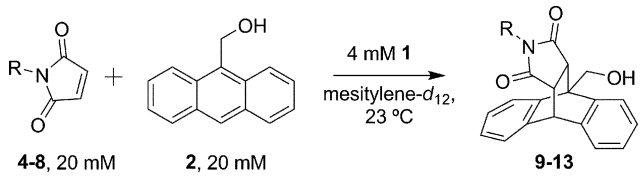


Fig. 2 Reaction mechanism.

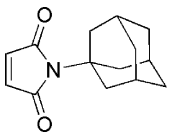
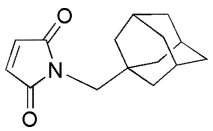
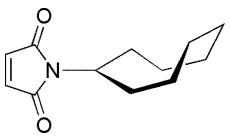
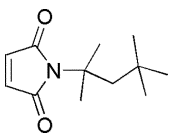
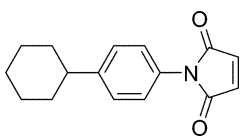
The Skaggs Institute for Chemical Biology and the Department of Chemistry, The Scripps Research Institute, La Jolla, CA, 92037, USA. E-mail: jrebek@scripps.edu; Fax: +1 858.784.2876; Tel: +1 858.784.2250

† Electronic supplementary information (ESI) available: Tabulated kinetic data. See DOI: 10.1039/b713104f

Table 1 Kinetic analysis of the Diels–Alder cycloaddition catalyzed by cavitand **1**



4-8, 20 mM **2**, 20 mM **9-13**

	Substrate	K/M^{-1}	k_{uncat}/10^{-3} M^{-1} min^{-1}	k_{cat}/10^{-3} M^{-1} min^{-1}	k_{acc}/k_{uncat}
	**4**	80	7.6	260	34
	**5**	120	27	775	29
	**6**	$>10^4$	17	980	57
	**7**	$>10^4$	3.3	140	43
	**8**	$>10^4$	22	100	4

Results and discussion

A suitable diene for this system is 9-anthracenemethanol **2**; it shows reactivity at room temperature with the chosen maleimides in hydrocarbon solvents. More appropriately, **2** shows no affinity for the cavitand. We examined the reaction of **2** with maleimides **4–8** in the presence and absence of catalytic amounts of cavitand **1** (Table 1). The reactions were monitored by ^{1}H NMR to determine the kinetic data; products **9–13** were also independently synthesized and compared to the species formed during the reaction. Experimental data were fitted to kinetics simulations of the activated reaction using KinTekSim.[12] In order to determine the rate enhancement gained upon binding, regression analysis was used to determine k_{acc}, the rate constant for the cycloaddition of the maleimide with diene while bound inside the cavitand, independent of K_a (see Supplementary Information for tabulated kinetics data†). The ratio of k_{acc} with k_{uncat} (rate constant for the cycloaddition in the absence of cavitand) provides a measure of the activation provided by the fixation of the dienophile in an environment of organized H-bond donors.

Table 1 reveals the effects of imide positioning. Maleimides **4–7** have binding "handles" of the correct size to position the maleimide at the cavitand rim. Kinetic analysis shows rate accelerations in the range of >20-fold. The *N*-cyclooctylmaleimide **6** proved to be both the best guest for the cavitand, with a binding constant $>10^4$ M^{-1} (the detection limit of the NMR spectrometer) and the best reactant, showing a 57-fold acceleration upon binding. In addition, *no product inhibition was observed*: product **11** showed no affinity for the cavitand. The *tert*-octylmaleimide **7** showed similar characteristics to **6**, with no product inhibition. The adamantyl derivatives **4** and **5** were poorer guests, with binding constants of 80 and 120 M^{-1} respectively, most likely due to steric clashes with the maleimide and the octamide rim. In the case of **5**, the cycloadduct also showed millimolar binding efficiency, and so product inhibition was observed.

Figs. 3 and 4 show the most instructive regions of the ^{1}H NMR spectra. Fig. 3 shows the buildup of cycloadduct **9** from reaction of adamantylmaleimide **4** (H_g/H_g' δ 4.7, 4.9) with no replacement of the bound maleimide (δ −1.0–−2.0). Two triplets for cavitand methine H_a are seen as maleimide **4** does not completely occupy the cavitand at 20 mM—the second triplet corresponds to free cavitand (presumably solvated by mesitylene-d_{12}). Fig. 4 shows the analogous spectra for the reaction of **5** over time. Here, a new set of bound product peaks slowly grow in (denoted by * in Fig. 4), indicating that the effect of moving the reactive site further away from the cavitand is to lessen the steric hindrance between

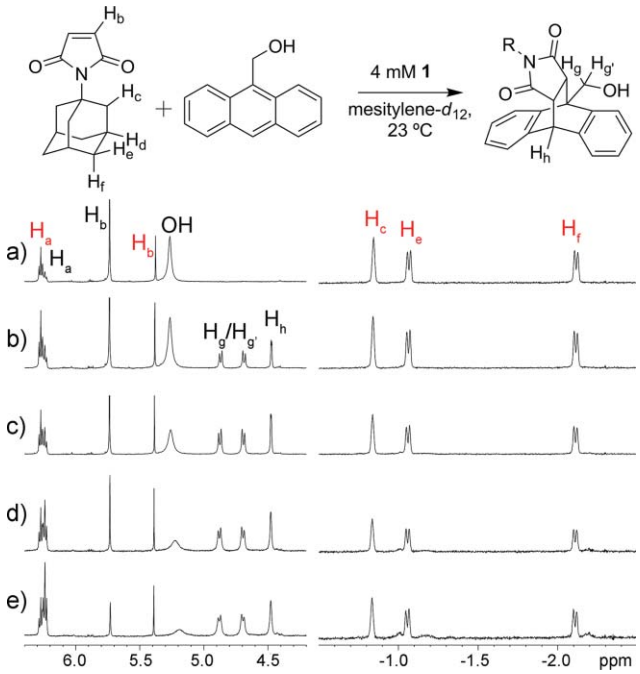


Fig. 3 ^{1}H NMR spectra of cycloaddition of maleimide **4** and diene **2** (mesitylene-d_{12}, 20 mM, 4 mM cavitand **1**) at time intervals a) 20 min, b) 1400 min, c) 2800 min, d) 8500 min, e) 13400 min showing the buildup of product, and illustrating the lack of product inhibition. Red label = bound species; black label = unbound species.

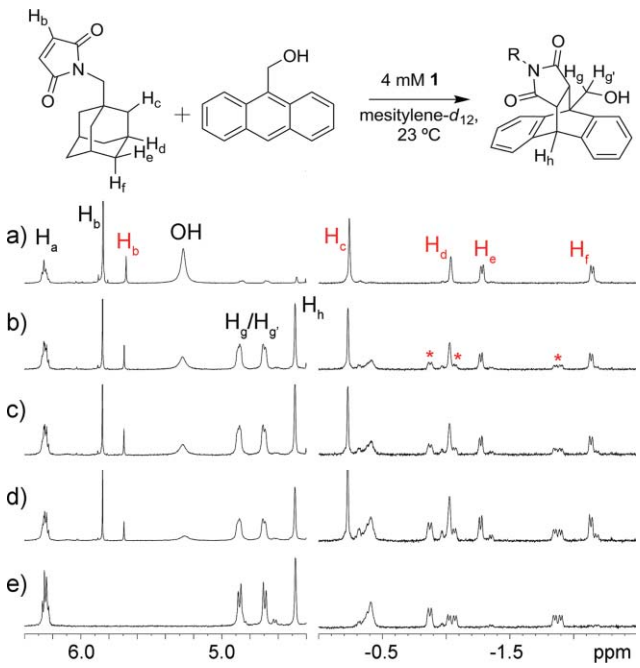


Fig. 4 ^{1}H NMR spectra of cycloaddition of maleimide **5** and diene **2** (mesitylene-d_{12}, 20 mM, 4 mM cavitand **1**) at time intervals a) 70 min, b) 1400 min, c) 1800 min, d) 3000 min and e) 4 mM cavitand **1** + 10 mM cycloadduct **10**. The binding of product in this case is labelled with *. Red label = bound species; black label = unbound species.

cavitand and product. Fig. 4e shows the spectrum of cavitand **1** with cycloadduct **10** alone, for comparison.

Reaction of **8** was performed as a control—the 4-cyclohexylphenyl binding handle is so large that it positions the maleimide away from the amide network, minimizing H-bond contacts. As expected, the cavitand had only a small effect on the reaction, and the product displayed similar binding efficiency towards **1** to that of reactant, resulting in significant product inhibition and poor turnover. Product **13** is, from the point of view of the cavitand, sterically identical to reactant **8**, as they have the same binding handle and the bulky cycloadduct is distant. The binding affinity of **13** for the cavitand was essentially the same as that of **8**.

To determine that the acceleration is provided by the supramolecular association of maleimide and **1** rather than random intermolecular H-bond contacts, the cycloaddition of **2** and **3** was performed in the presence of 8 equivalents of acetanilide as an intermolecular cavitand mimic. In this case the rate of reaction was slower (2.7×10^{-3} M^{-1} min^{-1}) than the control reaction in the absence of cavitand, showing that the catalysis is indeed a supramolecular effect. In addition, the reaction of **4** with **2** was performed in benzene solvent in the presence of catalytic amounts of cavitand. Benzene is a competitive guest for the cavitand and **4** shows no binding affinity for cavitand **1** in benzene solvent. In this case, the second order rate constant of cycloaddition $k = 8.0 \times 10^{-3}$ M^{-1} min^{-1}, essentially identical to that of the control reaction in the absence of cavitand. The intermolecular H-bonding provided to the system by cavitand in the absence of binding has no effect on reaction, as one might expect at the low concentrations used. Other dienes were also tested for reaction. Anthracenes lacking a hydroxyl group did not show reactivity for **4** with or without **1**, whereas cyclopentadiene and 1,3-cyclohexadiene were competitive guests for **1**. For reaction of diene **3** with maleimide **4**, $k_{acc}/k_{uncat} = 7$. Unfortunately, the smaller diene was not able to confer significant extra steric bulk to the product and inhibition was extensive.

An explanation for the lack of reactivity in the presence of acetanilide can be postulated, based on these results and the inactivity of non-hydroxylic anthracenes (Fig. 5). It has been previously shown for the Diels–Alder reaction of *N*-methylmaleimide and anthracenemethanol in water and other polar solvents that an H-bonding interaction occurs between the two reactants.[13] This interaction gathers the two reactants, accelerating the cycloaddition. In a non-polar solvent such as mesitylene, the affinity of the two polar groups for each other is high, resulting in a measurable effect. When a protic molecule such as acetanilide is added in excess, solvation of the H-bonding groups occurs, causing a disruption of the desired interaction and a slowing of the cycloaddition rate. The hydrogen bonding to the cavitand is sufficiently strong to overcome this disruption and activate the dienophile for reaction.

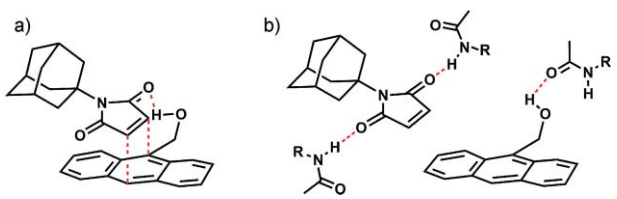


Fig. 5 Effect of non-supramolecular intermolecular hydrogen bonding on the cycloaddition process.

Conclusions

Cavitand **1** is capable of binding species bearing aliphatic binding handles and reactive maleimide groups, then activating them towards Diels–Alder reaction with suitable dienes through hydrogen bonding. The region of secondary amides is permanently located at the cavitand rim, and only simple rotations are needed to bring these hydrogen bonds to bear on the reactants held temporarily inside. These amides are not the conventional complements to imides but they are there in number and cannot diffuse away.[14] On cycloaddition the increase in steric bulk lowers the binding affinity of product with respect to reactant and reduces product inhibition, in some cases completely. Further studies on supramolecular effects on reaction promotion and catalysis are currently underway.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on an Avance Bruker DRX-600 spectrometer with a 5 mm QNP probe. Proton (^{1}H) chemical shifts are reported in parts per million (δ) with respect to tetramethylsilane (TMS, $\delta = 0$), and referenced internally with respect to the monoprotio solvent impurity. Deuterated NMR solvents were obtained from Cambridge Isotope Laboratories, Inc., Andover, MA, and used without further purification. ESI-HRMS data were recorded on an Agilent Electrospray TOF Mass Spectrometer. Melting points were recorded on a Thomas-Hoover capillary melting point apparatus. Maleimides **4–7**,[2f] cavitand **1**[6b] and *trans*-2,4-hexadienoic acid[15] were synthesized according to published procedures. 9-Anthracenemethanol **2**, acetanilide and synthesis precursors were obtained from Sigma-Aldrich Chemical Company, St. Louis, MO and used as received. 4-Cyclohexylaniline was obtained from Alfa Aesar, Ward Hill, MA. Molecular modeling (molecular mechanics calculations) was carried out using the AMBER force field[16] with the solvation (dielectric) setting for water as implemented by Macromodel (Schrödinger, Inc.) on a Silicon Graphics Octane workstation.

N-(4-Cyclohexylphenyl)-maleimide 8

Maleic anhydride (150 mg, 1.25 mmol) was added to a 50 mL round-bottomed flask equipped with a magnetic stirbar followed by anhydrous ether (10 mL). 4-Cyclohexylaniline (200 mg, 1.14 mmol) was added dropwise *via* syringe and the mixture stirred for 3 h, yielding a yellow precipitate of *N*-(4-cyclohexyl)-maleamic acid, which was isolated by suction filtration and used in the next step without further purification. *N*-(4-Cyclohexyl)-maleamic acid (250 mg, 0.91 mmol) was added to a 10 mL round-bottomed flask equipped with a magnetic stirbar and condenser. Acetic anhydride (2.5 mL) and sodium acetate (2.22 mmol, 224 mg, 449 μL) were added and the mixture was heated at 100 °C for 6 h, then cooled to room temperature. Ether (50 mL) and saturated aqueous ammonium chloride (20 mL) were added, and the mixture transferred to a separatory funnel. The layers were separated, and the aqueous layer extracted with ether (3 × 10 mL). The organic fractions were combined and washed with saturated brine (20 mL) and water (20 mL), dried ($MgSO_4$), filtered and the solvent removed by rotary evaporation. Column chromatography (SiO_2; hexanes–ether 9 : 1) gave *N*-(4-cyclohexylphenyl)-maleamide **8** (232 mg, 91%) as a yellow powder. ^{1}H NMR (600 MHz, C_6D_6) δ 1.05–1.15 (m, 1H); 1.17–1.30 (m, 5H); 1.55–1.76 (m, 4H); 2.31 (tt, $J = 11.4$, 3.0 Hz, 1H); 5.73 (s, 2H); 7.08 (d, $J = 8.4$ Hz, 2H); 7.34 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (150 MHz, C_6D_6) δ 26.3; 27.1; 34.6; 44.4; 126.0; 128.3; 130.0; 133.1; 147.4; 169.2; ESI-HRMS *m*/*z*: calcd for $C_{16}H_{17}NO_2$ (M + H$^+$) 256.1332; found 256.1337.

Decyl (1*E*,3*E*)-penta-1,3-dienylcarbamate 3

A 250 mL three-necked flask equipped with a thermometer, magnetic stirrer and dropping funnel was placed under an argon atmosphere and charged with *trans*-2,4-hexadienoic acid (5.00 g, 44.6 mmol), *N*,*N*′-diisopropylethylamine (7.15 g, 9.63 mL, 55.3 mmol), and acetone (50 mL), then cooled to 0 °C. A solution of methyl chloroformate (4.21 g, 3.43 mL, 44.6 mmol) in acetone (30 mL) was added over 30 min, keeping the temperature at 0 °C. The solution was stirred for 30 min at 0 °C, followed by addition of sodium azide (89.2 mmol, 5.80 g) in water (30 mL). After 15 min additional stirring, the mixture was poured into ice water (200 mL). The product was extracted with toluene (5 × 50 mL), dried ($MgSO_4$) and the solvent removed by rotary evaporation until ~30 mL solvent remains. This solution of acyl azide was added over 30 min to a stirred solution of 1-decanol (35.7 mmol, 5.65 g, 6.80 mL) and *tert*-butyl catechol (25 mg) in dry toluene (100 mL) at reflux. After 30 min reflux, the solution was cooled to 23 °C and the solvent removed by rotary evaporation. The product was rapidly recrystallized from ethyl acetate to give carbamate **3** as a white solid (7.2 g, 60%), which was immediately placed under an argon atmosphere and stored in the dark at −5 °C. ^{1}H NMR (600 MHz, $C_6D_5CD_3$) δ 0.91 (t, $J = 7.2$ Hz, 3H); 1.14–1.30 (m, 15H); 1.41–1.48 (m, 2H); 1.61 (d, $J = 6.6$ Hz, 3H); 3.96 (t, $J = 6.6$ Hz, 2H); 5.01 (dd, $J = 7.2$, 5.4 Hz, 1H); 5.29 (dq, $J = 7.2$, 6.6 Hz, 1H); 5.45 (d, $J = 7.2$ Hz, 1H); 5.66 (dd, $J = 7.2$ Hz, 5.4 Hz, 1H); ^{13}C NMR (150 MHz, CD_2Cl_2) δ 14.5; 18.4; 23.3; 26.4; 29.5 (two overlapping peaks); 29.8; 29.9; 30.1; 32.5; 66.2; 111.9; 125.2; 125.8; 129.2; 154.2; ESI-HRMS *m*/*z*: calcd for $C_{16}H_{29}NO_2$ (M + H$^+$) 268.2271; found 268.2275.

Representative procedure for independent synthesis of products 9–13

Maleimide (0.2 mmol), 9-anthracenemethanol (0.2 mmol) and anhydrous toluene (5 mL) were added to a 25 mL round-bottomed flask equipped with magnetic stirrer and reflux condenser. The mixture was heated at 100 °C for 6 h, then cooled to room temperature and the solvent removed by rotary evaporation. The crude product was purified by column chromatography (SiO_2; CH_2Cl_2–MeOH).

Adduct 9

Synthesized using the above procedure from adamantyl-maleimide **4** in 89% yield, mp 283–284 °C. ^{1}H NMR (600 MHz, C_6D_6) δ 1.38 (d, $J = 12.0$ Hz, 3H); 1.49 (d, $J = 12.0$ Hz, 3H); 1.83 (s, 3H); 2.09 (s, 6H); 2.61 (m, 1H); 2.63 (dd, $J = 8.4$, 3.6 Hz, 1H); 2.74 (d, $J = 8.4$ Hz, 1H); 4.59 (d, $J = 3.6$ Hz, 1H); 4.75 (dd, $J = 12.0$, 6.0 Hz, 1H); 5.01 (dd, $J = 12.0$, 6.0 Hz, 1H); 6.89–6.94 (m, 3H); 6.97–7.03 (m, 2H); 7.07–7.16 (m, 2H); 7.57 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR (150 MHz, CD_2Cl_2) δ 30.1; 36.4; 39.2;

46.0; 47.6; 50.0; 60.8; 61.2; 122.9; 123.4; 124.4; 125.7; 126.7 (two overlapping peaks); 127.0 (two overlapping peaks); 139.7; 140.2; 142.9; 143.0; 178.6; 179.8 ESI-HRMS *m/z*: calcd for $C_{29}H_{30}NO_3$ ($M + H^+$) 440.2220; found 440.2222.

Adduct 10

Synthesized using the above procedure from adamantylmethyl-maleimide **5** in 95% yield, mp 239–240 °C. ^{1}H NMR (600 MHz, C_6D_6) δ 1.04 (s, 6H); 1.44 (d, $J = 6.0$ Hz, 3H); 1.53 (d, $J = 6.0$ Hz, 3H); 1.76 (s, 3H); 2.71 (dd, $J = 9.0$, 3.0 Hz, 1H); 2.82 (m, 1H); 2.85 (s, 2H); 2.86 (d, $J = 9.0$ Hz, 1H); 4.58 (d, $J = 3.6$ Hz, 1H); 4.72 (dd, $J = 11.4$, 5.4 Hz, 1H); 4.97 (dd, $J = 11.4$, 4.8 Hz, 1H); 6.84–6.90 (m, 3H); 6.94–7.00 (m, 2H); 7.09–7.18 (m, 2H); 7.49 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR (150 MHz, CD_2Cl_2) δ 28.8; 35.0; 36.9; 40.6; 46.1; 47.3; 48.5; 49.7; 61.5; 123.4; 123.5; 124.5; 125.8; 126.9 (two overlapping peaks); 127.5; 127.6; 140.3; 140.7; 143.3; 143.4; 177.8; 178.4; ESI-HRMS *m/z*: calcd for $C_{30}H_{32}NO_3$ ($M + H^+$) 454.2377; found 454.2387.

Adduct 11

Synthesized using the above procedure from cyclooctyl-maleimide **6** in 93% yield, mp 172–174 °C. ^{1}H NMR (600 MHz, CD_2Cl_2) δ 0.75–0.85 (m, 2H); 1.22–1.28 (m, 2H); 1.32–1.60 (m, 8H); 1.65–1.73 (m, 2H); 2.85 (br s, 1H); 3.17 (dd, $J = 8.4$, 3.6 Hz, 1H); 3.23 (d, $J = 8.4$ Hz, 1H); 3.73 (tt, $J = 10.8$, 3.6 Hz, 1H); 4.70 (d, $J = 3.6$ Hz, 1H); 4.93 (dd, $J = 11.4$, 5.4 Hz, 1H); 5.09 (dd, $J = 12.0$, 5.4 Hz, 1H); 7.11–7.27 (m, 6H); 7.37 (d, $J = 7.8$ Hz, 1H); 7.57 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (150 MHz, CD_2Cl_2) δ 15.7; 25.6 (two overlapping peaks); 26.7 (two overlapping peaks); 30.8 (two overlapping peaks); 46.3; 48.0; 50.0; 52.5; 61.0; 64.3; 123.0; 123.8; 124.5; 125.8; 126.9 (two overlapping peaks); 127.2 (two overlapping peaks); 139.8; 140.1; 142.9; 143.0; 176.9; 177.2; ESI-HRMS *m/z*: calcd for $C_{27}H_{30}NO_3$ ($M + H^+$) 416.2220; found 416.2225.

Adduct 12

Synthesized using the above procedure from *tert*-octyl-maleimide **7** in 94% yield, mp 206–208 °C.^{1}H NMR (600 MHz, CD_2Cl_2) δ 0.82 (s, 9H); 1.11 (s, 3H); 1.12 (s, 3H); 1.57 (d, 2H); 2.78 (t, $J = 6.6$ Hz, 1H); 3.09 (dd, $J = 8.4$, 3.0 Hz, 1H); 3.13 (d, $J = 8.4$ Hz, 1H); 4.70 (d, $J = 3.0$ Hz, 1H); 4.92 (dd, $J = 11.4$, 6.6 Hz, 1H); 5.07 (dd, $J = 12.0$, 6.6 Hz, 1H); 7.14–7.21 (m, 4H); 7.26 (dd, $J = 7.2$, 1.8 Hz, 1H); 7.30 (dd, $J = 7.2$, 2.4 Hz, 1H); 7.38 (dd, $J = 7.2$, 1.2 Hz, 1H); 7.56 (d, $J = 7.2$ Hz, 1H); ^{13}C NMR (150 MHz, CD_2Cl_2) δ 29.0; 31.3; 31.9; 46.1; 46.6; 47.8; 50.1; 50.4; 61.0; 62.6; 123.0; 123.6; 124.5; 125.8; 126.9 (two overlapping peaks); 127.3 (two overlapping peaks); 139.9; 140.4; 143.0; 143.1; 178.6; 179.0; ESI-HRMS *m/z*: calcd for $C_{27}H_{32}NO_3$ ($M + H^+$) 418.2377; found 418.2384.

Adduct 13

Synthesized using the above procedure from 4-cyclohexylphenyl-maleimide **8** in 86% yield, mp 233–235 °C. ^{1}H NMR (600 MHz, CD_2Cl_2) δ 1.20–1.30 (m, 2H); 1.32–1.42 (m, 4H); 1.32–1.60 (m, 4H); 1.75–1.88 (m, 4H); 2.48 (m, 1H); 2.62 (t, $J = 5.4$ Hz, 1H); 3.45 (dd, $J = 8.4$, 3.6 Hz, 1H); 3.51 (d, $J = 8.4$ Hz, 1H); 4.83 (d, $J = 3.6$ Hz, 1H); 5.00 (dd, $J = 12.6$, 5.4 Hz, 1H); 5.13 (dd, $J = 12.6$, 5.4 Hz, 1H); 6.39 (d, $J = 8.4$ Hz, 2H); 7.14 (d, $J = 8.4$ Hz, 2H); 7.19–7.30 (m, 5H); 7.36 (d, $J = 7.2$ Hz, 1H); 7.44 (d, $J = 7.2$ Hz, 1H); 7.65 (d, $J = 7.2$ Hz, 1H); ^{13}C NMR (150 MHz, CD_2Cl_2) δ 26.6; 27.3; 34.9; 44.8; 46.5; 46.8; 48.6; 50.3; 60.7; 123.0; 124.0; 124.7; 125.9; 126.9; 127.1; 127.5; 128.0; 129.7; 139.8; 140.2; 142.6; 142.7; 149.6; 176.5; 176.6; ESI-HRMS *m/z*: calcd for $C_{31}H_{30}NO_3$ ($M + H^+$) 464.2220; found 464.2220.

Kinetic measurements

In a typical experiment, maleimide (20.0 mM), diene (20.0 mM) and cavitand **1** (4.0 mM) were dissolved in 600 μL mesitylene-d_{12} in an NMR tube. The sample (at room temperature, 23 °C) was periodically placed in the NMR spectrometer and a spectrum was recorded. Concentrations were monitored by reference to the methine peak of **1** (4H) at δ 6.24 ppm, which was at nearly constant chemical shift in an open window of the ^{1}H spectrum irrespective of the molecule occupying **1**. The concentrations of free maleimide, bound maleimide, and cycloadduct (free and bound) were monitored by integration of their peaks at δ 5.73, 5.39 and 4.87 ppm respectively. Concentrations were tabulated with respect to time. Control experiments were carried out under the same conditions but in the absence of **1**. KinTekSim[12] was used to simulate the Diels–Alder reactions in the presence and absence of **1**. Simulations were based on the mechanism described by the simultaneous operation of eqn (1)–(4) (Fig. 6). In the equations, M, C, D, P, M·C and C·P correspond to free maleimide, cavitand **1**, diene (either 9-anthracenemethanol or carbamate **3**), product, bound maleimide and bound product respectively. The parameters K_a and K_d were determined by independent NMR experiments. The control (*i.e.* background) reaction was studied in separate experiments, allowing for the independent determination of k_{uncat} by plotting $1/[M] - 1/[M]_0$ against time, in accordance with the integrated rate law for a second order process. It was assumed that both equilibria K_a and K_d were fast compared to the rate-limiting alkylation step; this is in agreement with NMR observations. The only remaining parameter, k_{acc}, describing the reaction of bound maleimide, was varied to fit simulated kinetics to experimental data (the concentrations of free maleimide, bound maleimide, and bound product with respect to time).

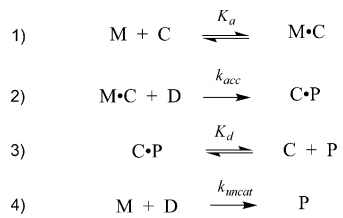


Fig. 6

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