Supporting Information

Supramolecular Catalysis of a Catalysis-Resistant Diels-Alder Reaction: Almost Theoretical Acceleration of Cyclopentadiene Dimerization inside Cucurbit[7]uril

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1. Materials and Methods

All chemicals were purchased and used without further purification, with the following exceptions: cyclopentadiene (CPD) was prepared by the thermal decomposition of dicyclopentadiene (DCPD), purchased from Sigma-Aldrich. A second distillation of CPD was performed to obtain a purity higher than 99% (checked by GC). For all distillations, the receiving flask was cooled with a dry ice/acetone bath to inhibit the self-dimerization of the monomer. CPD was freshly used (within 3 h after the distillation). CB7 was synthesized according to Ref. 1.

2. Instrumentation

Gas Chromatography (GC): Chiraldex B-DP column (30 m × 0.25 mm); T_{inj} = 100 °C and T_{det} = 300 °C, both constant; oven temperature 50 °C (hold for 2 min), ramp up to 120 °C (10 °C/min, then hold for 2 min at 120 °C), ramp up to 200 °C (20 °C/min, then hold for 5 min at 200 °C) (20 min method): CPD retention time = 2.37 min, DCPD retention time = 9.40 min.

NMR measurements: NMR spectra were recorded with a JEOL ECX 400 MHz NMR spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS = 0) or relative to $CHCl_3$ (7.26 ppm) or D_2O (4.79 ppm).

pH measurements: pH measurements were performed with a pH meter (Company: WTW, Model: pH 3110).

Optical Spectroscopy: Absorption measurements were performed with a Varian Cary 4000 spectrophotometer and Fluorescence measurements were done with Varian Eclipse fluorimeter.

ITC measurements: Isothermal titration calorimetry (ITC) experiments were carried out on a VP-ITC from Microcal, Inc., at 25 °C. Typically, 27 consecutive injections of 10 μL were used. Heats of dilution were determined by titration of the CB7 solution into water. The first data point was removed from the data set prior to curve fitting with Origin 7.0 software. The knowledge of the complex stability constant (K_a) and molar reaction enthalpy ($\Delta H°$) enabled the calculation of the standard free energy ($\Delta G°$) and entropy changes ($\Delta S°$) according to $\Delta G° = -RT \ln K_a = \Delta H° - T\Delta S°$.

3. CPD Dimerization

To a solution (1 mL) of CB7 in distilled water at pH = 3.0-3.5 in an NMR tube, CPD was added. The ratio of CPD to CB7 was determined by using CB7 as an internal standard and comparing the four vinyl protons of CPD in the chemical shift range 5.7 - 6.3 ppm with the fourteen protons of CB7 in the chemical shift range 4.0 to 4.4 ppm. The reactions were monitored by ^{1}H NMR and the dimerization reactions were performed at least two times. For the catalytic turnover experiments, an excess of CPD (40 equiv., 120 mM of CPD: 1 equiv., 3 mM of CB7) in 0.1 mL CD_3OD was mixed with 0.9 mL of CB7 solution (3 mM) in D_2O. After 24 h around 50% of the CPD was converted to DCPD (following product formation) and around 10 catalytic cycles were observed. ^{1}H NMR spectra of free CPD and DCPD in $CDCl_3$ are shown in Figure S1.

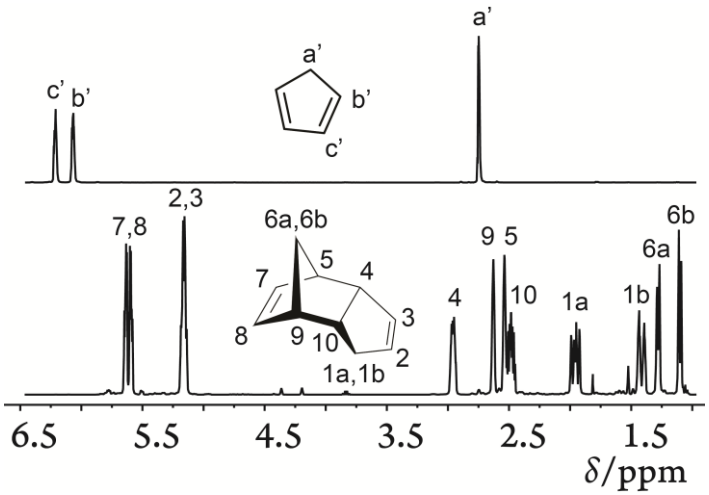

Figure S1. ^{1}H NMR spectra of CPD and DCPD in $CDCl_3$.

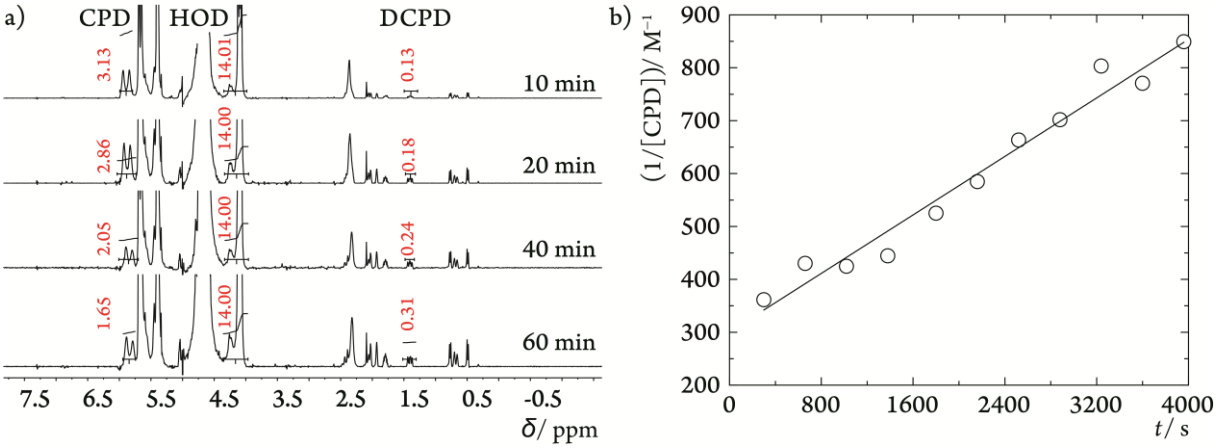

Figure S2. a) Dimerization of CPD (3.0 mM) in the presence of CB7 (3.0 mM) followed by ^{1}H NMR as a function of time. b) Plot of (1/[CPD]) *versus* reaction time monitored by ^{1}H NMR; data fitted according to the linearized second-order equation ($1/[CPD] = 1/[CPD_0] + k_{app}t$).

4. Inhibition of CPD Dimerization by Blocking the CB7 Cavity with Adamantylamine

To a D_2O solution (2 mL) of CB7 (3 mM), adamantylamine (4 mM) was added, and the mixture was sonicated for 15 min. To this mixture CPD was added and the reaction was rigorously stirred for 18 h at room temperature and then split into two equal parts, one was analyzed directly by ^{1}H NMR, the other half was extracted with $CDCl_3$ (1× ~1.5 mL) and analyzed by ^{1}H NMR, see Figure S3.

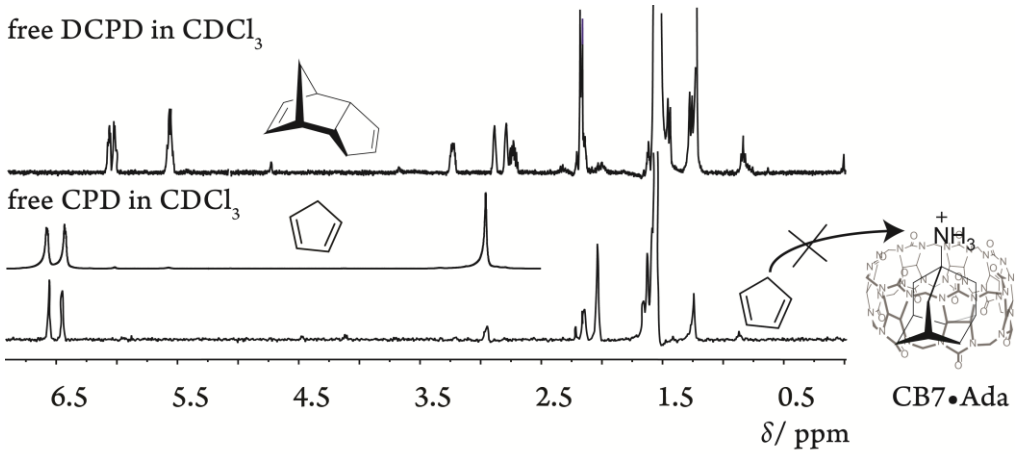

Figure S3. ^{1}H NMR control experiment indicating no CPD dimerization when the CB7 cavity is prefilled with a strong binder such as 1-adamantylamine (Ada). The experiment was done by mixing CB7 (3 mM) with adamantylamine (4 mM) in D_2O and then adding CPD (3 mM). The mixture was stirred for 24 h and then extracted with $CDCl_3$. The extract was measured by ^{1}H NMR and showed only CPD with no DCPD formation.

5. Quantum-Chemical Calculations

All calculations were performed within Gaussian 09[2] by using wB97XD/6-31G* as dispersion-corrected DFT method.[3] Computed molecular volumes of the investigated molecules and transition states were obtained by the Quantitative Structure-Activity Relationship (QSAR) module within the Hyperchem package.[4]

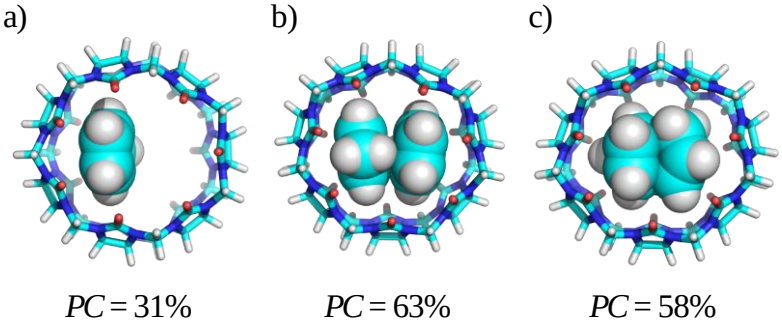

Figure S4. DFT-optimized structure for CB7 complexes with a) one CPD unit, b) two CPD units, and c) DCPD; *PC* values are given below the structures.

6. Reaction Kinetics Monitored by UV Spectrophotometry

The cyclopentadiene concentration was determined by using the known extinction coefficient (5300 $M^{-1}cm^{-1}$, taken from Wolfenden, R.; Liang, Y. L.; Matthews, M.; Williams, R. *J. Am. Chem. Soc*. **1987**, *109*, 463) at 238 nm (Figure S5). All experiments were conducted at pH 3.3, unless stated differently, in 1.0-mm cuvettes. Cuvettes were sealed by stoppers with parafilm to prevent evaporation.

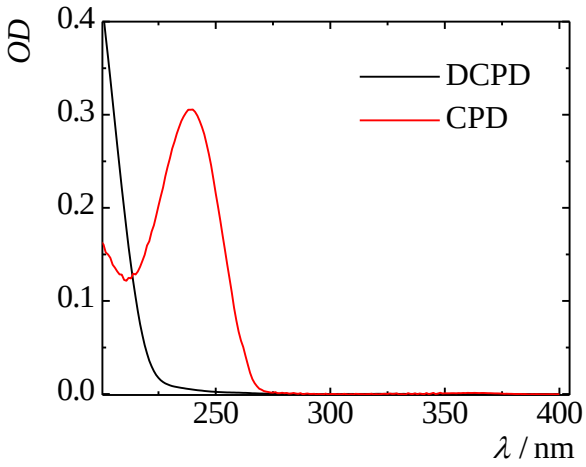

Figure S5. UV spectra of CPD (60 μM) and DCPD (30 μM) in water.

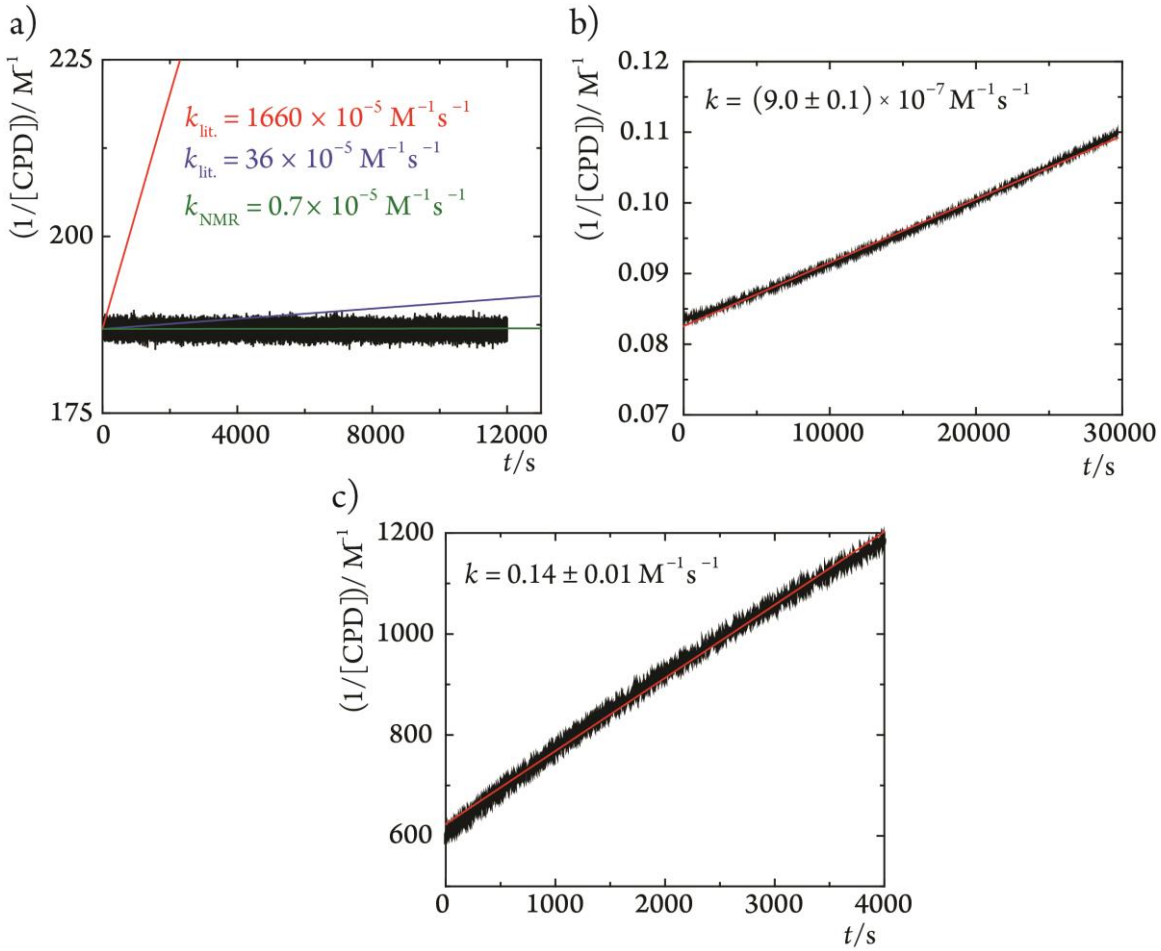

Figure S6. Dimerization of CDP followed with UV spectrophotometry at λ = 238 nm for a) CPD (5 mM) in water; lines represent simulated dimerization profiles with different rate constants (red line according to Sangwan, N. K.; Schneider, H. J., *J. Chem. Soc., Perkin Trans. 2* **1989**, 1223, blue line according to Breslow, R.; Zhu, Z. N. *J. Am. Chem. Soc.* **1995**, 117, 9923, green line according to our ^{1}H NMR-based measurements (Table 2). b) Neat CPD dimerization. c) CPD (3 mM) dimerization in water in the presence of CB7 (3 mM). Rate constants were determined by using the equation ($1/[A] = 1/[A_0] + kt$) for second order reactions.

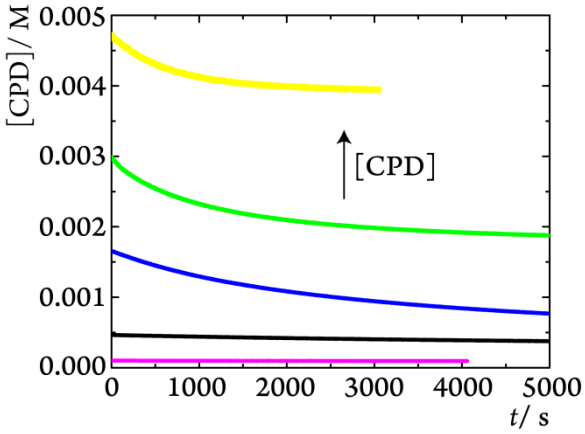

Figure S7. Following the dimerization of CPD (from 0.1 – 5 mM) with 1 mM CB7 by UV spectrophotometry.

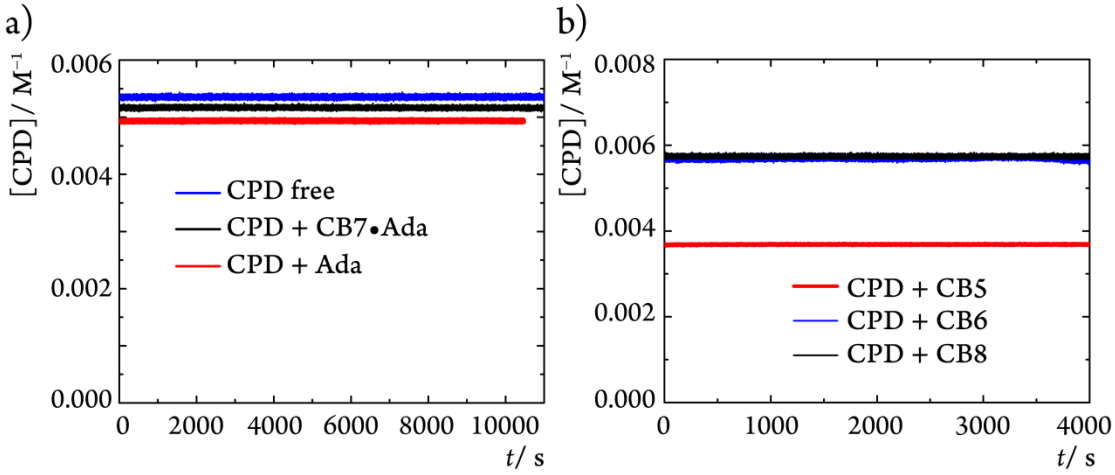

Figure S8. a) Control experiments revealed no dimerization of CDP in the presence of smaller or larger CB*n* homologues (namely, CB5, CB6, and CB8), monitored by UV spectrophotometry. b) Control experiment for the dimerization of CPD in the presence of CB7 (1 mM) pre-complexed with 1-adamantylamine (2 mM) as a competitive cavity binder. This experiment confirmed that the CPD dimerization occurs inside the cavity of CB7.

7. Binding Titrations

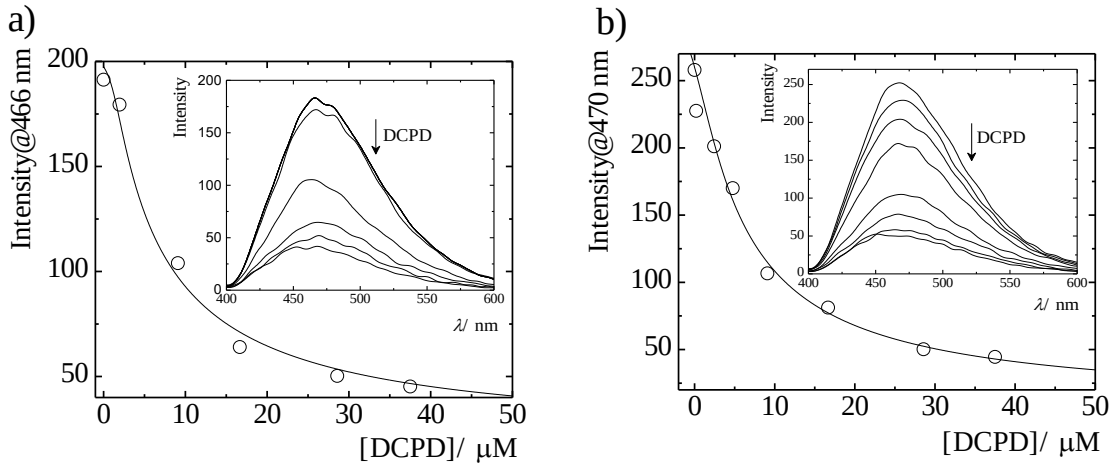

Figure S9. Fluorescence displacement titrations of 4′,6-diamidino-2-phenylindole (DAPI, 1.0 μM) from CB7 (2.4 μM) by addition of DCPD a) in water and b) in water:methanol 9:1 mixture.

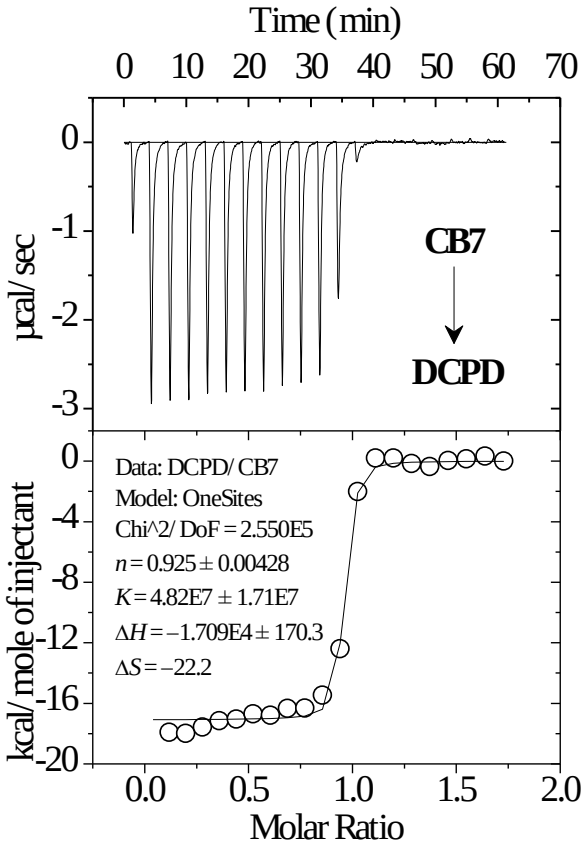

Figure S10. Raw ITC data for sequential twenty-seven injections of a 0.5 mM CB7 solution injected into a DCPD solution (0.05 mM, top) and apparent reaction heats obtained from the integration of the calorimetric traces (bottom).

8. Fitting Function for the CPD Kinetics

The reaction of CPD (guest), inside the cavity of CB7 (host), is contingent on the formation of a 2:1 ternary complex. Whereas the formation of 2:1 complex leads to CPD dimerization and product formation, the 1:1 complex does not lead to dimerization inside the cavity. The following equations describe the kinetics based on the binding equilibria:

$$H + 2G \overset{K_{a1}}{\rightleftharpoons} HG + G \overset{K_{a2}}{\rightleftharpoons} HG_2 \overset{k_{cat}}{\rightleftharpoons} HP$$

$$K_1 = [HG]/([H][G])$$

$$K_2 = [HG_2]/([HG][G])$$

$$\upsilon_o = k_{cat}\,[HG_2]$$

$$[H_t] = [H]+[HG]+[HG_2]$$

$$[G_t] = [G]+[HG]+2[HG_2]$$

$$[HG] = (K_{a1}[G][H_t])/(1+K_{a1}[G]+K_{a1}K_{a2}[G]^2)$$

$$[HG_2] = (K_{a1}K_{a2}[G]^2[H_t])/(1+K_{a1}[G]+K_{a1}K_{a2}[G]^2)$$

$$[G_t] = [G]+((K_{a1}[G]+2K_{a1}K_{a2}[G]^2)/(1+K_{a1}[G]+K_{a1}K_{a2}[G]^2))[H_t]$$

$$0 = K_{a1}K_{a2}[G]^3+(K_{a1}+2K_{a1}K_{a2}[H_t]-K_{a1}K_{a2}[G_t])[G]^2+(1+K_{a1}[H_t]-K_{a1}[G_t])[G]-[G_t]$$

$$\boxed{\upsilon_o = k_{cat}[HG_2] = k_{cat}((K_{a1}K_{a2}[G]^2[H_t])/(1+K_{a1}[G]+K_{a1}K_{a2}[G]^2))}$$

K_{a1}: first binding constant; K_{a2}: second binding constant; $[H_t]$: total host concentration; k_{cat}: first-order reaction rate constant; [G]: guest concentration; $[G_t]$: total guest concentration; v_o: initial rate.

With these equations in hand, a script can be written to fit the experimental data, by plotting v_o against the $[G_t]$ (see, for example, a script for nonlinear curve fitting by using the Origin software below). First, a numerical solution for [G] is required, which can be achieved by applying Newton's method to iteratively determine numerical values for [G], and subsequently fitting the data by using the final rate equation.

OriginLab function:

```
static double rac(double K1, double K2, double Ht, double x)
{
	double G,a,b,c,d,dx;
	G=1;
	dx=0.1;
	a=K1*K2;
	b=K1+2*K1*K2*Ht-K1*K2*x;
	c=1+K1*Ht-K1*x;
	d=-x;

	while (fabs(dx)>1e-15)
	{
	dx=(a*G*G*G+b*G*G+c*G+d)/(3*a*G*G+2*b*G+c);
```

```
        G=G-dx;
        }
        return G;
}

double K1, double K2, double k, double Ht,
// Independent Variable(s):
double x,
// Dependent Variable(s):
double& y)
{
        // Beginning of editable part
        y=k*((K1*K2*rac(K1,K2,Ht,x)*rac(K1,K2,Ht,x)*Ht)/(1+K1*rac(K1,K2,Ht,x)+K1*K2*rac(K
1,K2,Ht,x)*rac(K1,K2,Ht,x)))
        // End of editable part
}
```

9. References

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(2) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; T. Nakajima; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J., J. A. ; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; J., F. D., Gaussian, Inc., Wallingford CT, Gaussian 09, **2010**.

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