An Automated Computational Approach to Kinetic Model Discrimination and Parameter Estimation

Supporting Information

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Contents

1. Computational approach download

The MATLAB implementation of this approach is available open-source as pre-packaged code.[1]

2. Computational specifications for case studies

All computation was run in MATLAB 2020a using a GK5NR0O laptop with an 8-core AMD Ryzen 7 4800H processor. The computation time for each of the case studies are reported:

- S_NAr case study: ~9 hours
- PfBr protection case study: ~2 minutes
- Maleic acid case study: ~17 hours

3. S_NAr case study

3.1 Experimental equipment

All experiments were run in an NMR tube using a dedicated 500 MHz NMR spectrometer at The University of Cambridge, as shown in Figure S1.

Figure S1: The dedicated NMR spectrometer used for kinetic experiments in the S_NAr kinetics case study.

3.2 Kinetic experiments

In each experiment, 2,4,6-trichloropyrimidine (700 µL, 200 mM in CD_3OD) was warmed/cooled to the required temperature in the 500 MHz NMR spectrometer. The NMR machine was then locked onto the solvent, then the probe was tuned and matched to the ^1H nuclei, then shimming ensued. The spectrum of the 200 mM solution of 2,4,6-trichloropyrimidine was acquired.

To this NMR tube, a pre-cooled/warmed solution of CD_3OD containing 200 mM ethyl 4-aminobutyrate hydrochloride and 600 mM triethylamine (700 µL) was added and mixed thoroughly by shaking the NMR tube. This gave the desired reaction concentration of 100 mM pyrimidine, 100 mM amine and 300 mM triethylamine. Spectra were acquired every ~80 seconds. MestReNova was used in each case to obtain absolute integrals for each peak, which were then converted to concentrations based on the 2,4,6-trichloropyrimidine solution of known concentration.

2,4,6-Trichloropyrimide was acquired from Sigma Aldrich at 97 %. Ethyl 4-aminobutyrate hydrochloride was acquired from Alfa Asar at 98 %. Triethylamine was acquired from Alfa Asar at 99 %.

3.3 Example ^{1}H NMR spectra

NMR spectra are shown in Figure S2, showing the appearance/disappearance of peaks over time in the 25 °C experiment. Where the peak at 7.80 ppm corresponds to 2,4,6-trichloropyrimidine, 6.66 ppm corresponds to the 2-substituted product and 6.47 corresponds to the 4-substited product.

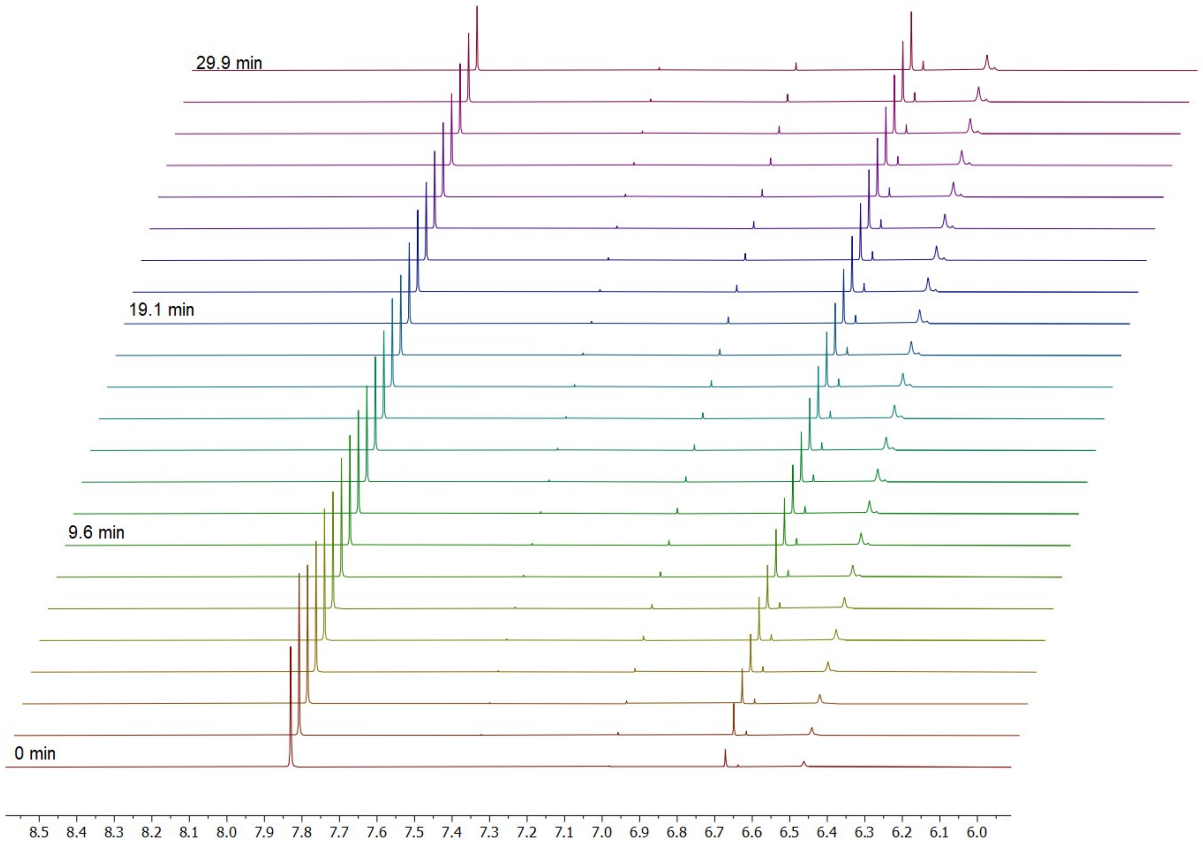


Figure S2: A 'stacked' NMR spectrum showing several NMR spectra over time in the 25 °C experiment.

3.4 Top ranked models

The top 5 ranked models from the 3320 evaluated are shown in Table S1, with their respective sum of squared error (SSE) values and AIC_C evaluations. All reactive species are first order in the elementary reaction rate law, unless denoted with a superscripted number for species 'X' such as X^0 or $X^{0.5}$, meaning the species is zero order or 0.5 order respectively.

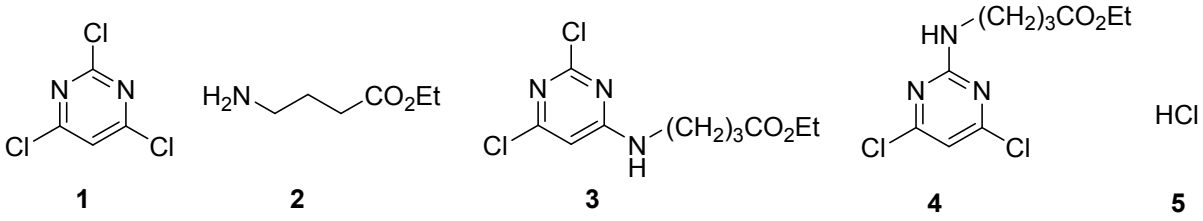


Table S1: Evaluation of the feasibility of each reaction model for the S_NAr case study, where α is variable for each model depending on the overall model order.

Rank	Reaction Model	Kinetic parameters		SSE	AIC_C
		$k_{25\,°C}$ /M^{α} min^{-1}	E_a /kJ mol^{-1}	/10^3 M	
1	1 + 2 → 3 + 5 1 + 2 → 4 + 5	0.499 0.384	44.19 36.57	1.614	-51.91
2	1 + 2 → 3 + 5 1 + $2^{0.5}$ → 4 + 5	0.407 0.073	40.61 31.01	3.723	-48.57
3	1 + 2 → 3 + 5 1^0 + 2 → 4 + 5	0.466 0.017	42.25 27.56	3.777	-48.51
4	1 + 2 → 3 + 5 1 + 2^0 → 4 + 5	0.466 0.017	42.25 27.56	3.777	-47.29
5	1 + $2^{0.5}$ → 3 + 5 1 + 2 → 4 + 5	0.092 0.298	38.06 32.27	5.127	-46.64

3.5 Raw data

Experiment 1, -25 °C

Time /min	1 /M	3 /M	4 /M
14.55	0.088818	0.004156	0.004562
15.91667	0.088538	0.004229	0.004611
17.26667	0.088465	0.004295	0.004727
18.63333	0.088063	0.004362	0.004842
19.98333	0.08805	0.004577	0.004908
21.33333	0.087811	0.004609	0.004962
22.7	0.087412	0.004713	0.005096
24.05	0.087133	0.004827	0.005202
25.41667	0.086922	0.004901	0.005268
26.76667	0.08667	0.004993	0.005345
28.13333	0.086501	0.005049	0.005407
29.48333	0.086142	0.005142	0.005518

30.83333	0.085983	0.005268	0.005704
32.2	0.085639	0.005412	0.005803
33.55	0.085286	0.005468	0.005826
34.91667	0.085108	0.005589	0.00596
36.26667	0.084887	0.005646	0.005947
37.63333	0.084482	0.005781	0.006102
38.98333	0.084308	0.005902	0.006179
40.35	0.083927	0.005914	0.00626
41.7	0.083758	0.006021	0.00639
43.06667	0.083386	0.006157	0.006496
44.41667	0.083205	0.006154	0.006574
45.76667	0.083093	0.006298	0.006627
47.13333	0.08282	0.006377	0.006689
48.48333	0.082663	0.006475	0.006751
49.85	0.082501	0.006492	0.006786
51.2	0.082273	0.00655	0.006939
52.56667	0.08206	0.006658	0.006902
53.91667	0.08186	0.006786	0.007038
55.26667	0.081225	0.006729	0.007105

Experiment 2, 0 °C

Time /min	**1 /M**	**3 /M**	**4 /M**
7.333333	0.072103	0.007607	0.008513
8.8	0.070344	0.008018	0.008965
10.16667	0.068594	0.008452	0.009462
11.51667	0.068423	0.008887	0.009854
12.88333	0.066803	0.009266	0.01028
14.23333	0.065829	0.009635	0.010682
15.6	0.064594	0.010002	0.011061
16.95	0.063823	0.010341	0.011471
18.31667	0.062319	0.010702	0.011804
19.66667	0.061394	0.010984	0.012177
21.01667	0.060906	0.011342	0.012486
22.38333	0.059741	0.011585	0.012806
23.73333	0.058765	0.01182	0.013095
25.1	0.058315	0.012151	0.013445

26.45	0.057463	0.01241	0.013671
27.8	0.056496	0.012685	0.013978
29.16667	0.056066	0.0129	0.014287
30.51667	0.055037	0.013136	0.01449
31.88333	0.054482	0.013382	0.014789
33.23333	0.053852	0.013629	0.015023
34.58333	0.053151	0.013804	0.015225
35.95	0.052684	0.014054	0.01548
37.3	0.052192	0.014261	0.015707
38.66667	0.05156	0.014409	0.01589
40.01667	0.051008	0.014613	0.016133
41.36667	0.050399	0.014842	0.016311
42.73333	0.049812	0.015017	0.016498
44.08333	0.049557	0.015136	0.016666
45.45	0.048743	0.015301	0.016861
46.8	0.048366	0.015482	0.017042
48.16667	0.047763	0.015635	0.01723
49.51667	0.047326	0.015831	0.017433
50.86667	0.046947	0.015973	0.017573
52.23333	0.046384	0.016088	0.017747
53.58333	0.045991	0.016243	0.017903
54.95	0.045672	0.016393	0.018043
56.3	0.045107	0.016496	0.018225
57.66667	0.044674	0.016691	0.018395
59.01667	0.044423	0.016839	0.018509
60.36667	0.044113	0.016972	0.018683
61.73333	0.043619	0.017086	0.01884

Experiment 3, 25 °C

Time /min	**1 /M**	**3 /M**	**4 /M**
3.366667	0.064314	0.009652	0.009883
4.8	0.057052	0.012118	0.012863
6.15	0.051792	0.013813	0.014922
7.5	0.047939	0.015186	0.016476
8.866667	0.044748	0.016215	0.017819
10.21667	0.041922	0.017079	0.018798

11.58333	0.039664	0.017878	0.019678
12.93333	0.037598	0.018491	0.020463
14.28333	0.035777	0.019052	0.021122
15.65	0.034195	0.019558	0.021718
17	0.032928	0.019875	0.022181
18.36667	0.031709	0.020362	0.022676
19.71667	0.030632	0.020622	0.023126
21.06667	0.029623	0.020886	0.023404
22.43333	0.028668	0.02128	0.023818
23.78333	0.027704	0.021452	0.02409
25.15	0.026937	0.021641	0.024389
26.5	0.026303	0.021884	0.024635
27.86667	0.025572	0.022112	0.024925
29.21667	0.024988	0.022265	0.025126
30.56667	0.024358	0.022417	0.025261
31.93333	0.023747	0.022601	0.025533
33.28333	0.023156	0.022788	0.025713
34.63333	0.022678	0.022896	0.025943
36	0.022158	0.022984	0.026042
37.35	0.021731	0.023193	0.026254
38.71667	0.021252	0.023299	0.026356
40.06667	0.020811	0.023542	0.026561
41.43333	0.020451	0.023635	0.026706
42.78333	0.019954	0.023675	0.026824
44.13333	0.01972	0.023743	0.026953
45.5	0.019374	0.023807	0.027033
46.85	0.019129	0.023925	0.027167
48.21667	0.018686	0.024057	0.027249
49.56667	0.018359	0.024079	0.027301
50.93333	0.018011	0.024171	0.027439
52.28333	0.017894	0.024265	0.027549
53.63333	0.017535	0.024319	0.027649
55	0.017377	0.024477	0.027784
56.35	0.01712	0.024351	0.027716
57.71667	0.016878	0.024502	0.027857

Experiment 4, 50 °C

Time /min	1 /M	3 /M	4 /M
3.35	0.044859	0.017049	0.028158
5.066667	0.033058	0.020402	0.034142
6.416667	0.028533	0.021812	0.036713
7.766667	0.025543	0.022842	0.038521
9.133333	0.022916	0.0235	0.039813
10.5	0.021041	0.024107	0.04121
11.85	0.019498	0.024602	0.041829
13.2	0.018156	0.025096	0.042681
14.56667	0.016918	0.025264	0.043145
15.91667	0.015895	0.025503	0.043496
17.28333	0.015031	0.025778	0.043978
18.63333	0.014386	0.025935	0.044504
20	0.013754	0.026166	0.044669
21.35	0.013006	0.026135	0.045027
22.7	0.012731	0.02645	0.04525
24.06667	0.012071	0.026529	0.045439
25.41667	0.011723	0.026593	0.045892
26.78333	0.011273	0.026724	0.046128
28.13333	0.01075	0.026737	0.04605
29.5	0.010443	0.026863	0.046276
30.85	0.010126	0.026964	0.046178
32.21667	0.009967	0.027158	0.046613
33.56667	0.009483	0.0272	0.046695
34.93333	0.009351	0.027183	0.047223
36.28333	0.009066	0.027134	0.047014
37.63333	0.008787	0.027312	0.047229
39	0.008496	0.027291	0.047245
40.35	0.00833	0.027346	0.047363
41.71667	0.00802	0.027313	0.047267
43.06667	0.007943	0.027459	0.047585
44.43333	0.007797	0.027504	0.047612
45.78333	0.007612	0.027442	0.047469
47.13333	0.007363	0.027731	0.047777
48.5	0.007162	0.027549	0.047689

49.85	0.007122	0.027588	0.047921
51.2	0.006956	0.027672	0.048034
52.56667	0.006869	0.027621	0.047948
53.91667	0.006654	0.02781	0.048184
55.28333	0.006511	0.027703	0.048181
56.63333	0.006367	0.027739	0.048193
57.98333	0.006367	0.027751	0.048241

4. PfBr protection case study

4.1 Synthesis of PfBr material

To synthesise the PfBr material, the synthesis reported by Tian and Menard was approximately followed.[2] To a suspension of magnesium turnings (9.2 g, 382 mmol) in anhydrous THF (5 mL) in a nitrogen atmosphere, was added 0.5 mL of bromobenzene (99 %, Sigma Aldrich) at room temperature to initiate the reaction. The reaction vessel was cooled to 0 °C using an ice bath and a solution of bromobenzene in THF (1.2 M, 270 mL) was added dropwise at 0 °C. The reaction medium was allowed to reach room temperature and stirred vigorously for 2 hours. To this solution was added 9-fluorenone (99+ %, Fisher Scientific) (30.1 g, 186 mmol) in small portions left to stir at room temperature for 1 hour. The reaction was quenched with dropwise addition of hydrochloric acid (1 M, 100 mL) at 0 °C. The solution was extracted with Et_2O (3 x 150 mL), and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield PfOH (42.6 g, 89 %). NMR, IR and mass spectroscopy analysis confirmed the identity of the material.

To prepare PfBr, PfOH (36.1 g, 140 mmol) was dissolved in toluene (150 mL) and aqueous HBr (48 % w/w, Fisher Scientific, 50 mL) was added at room temperature. This suspension was stirred vigorously at room temperature for 48 hours, with the vessel wrapped in foil to reduce light. The mixture was extracted with toluene (3 x 100 mL) then the combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product. The product was then recrystallised with hexane to afford PfBr (39 g, 87 %). NMR, IR and HPLC analysis confirmed the identity and purity of the material.

4.2 Kinetic experiments

Three kinetic experiments were conducted in a three-neck round bottomed flask, at 30 °C, 35 °C and 40 °C. Samples (0.5 mL) were extracted manually from the bulk reaction medium with a syringe, followed by syringing approximately 0.3 mL of water and shaking the syringe - this dissolves the suspended potassium phosphate and allows injection into the sample loop for analysis via HPLC. The batch setup for experimentation is shown in Figure S3.

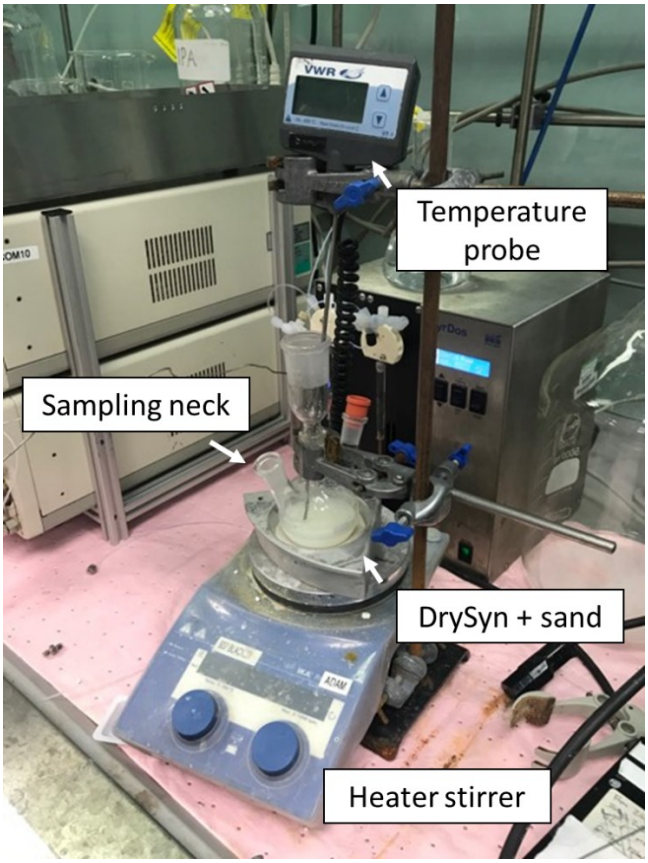


Figure S3: The batch setup for experimentation in the PfBr protection case study, where the temperature probe is submerged in the reaction medium that is heated via a heater stirrer.

For the first experiment at 30 °C, alanine methyl ester hydrochloride (0.940 g, 0.007 mol), biphenyl (0.195 g, 0.001 mol) and potassium phosphate (3.5 g, 0.017 mol) were added to 50:50 acetonitrile/dichloromethane (37.5 mL) in a vessel. A solution was then prepared of PfBr (0.958 g, 0.003 mol) in 50:50 acetonitrile/dichloromethane (37.5 mL) and added to the reaction vessel. A sample was then immediately taken via HPLC, then the stopwatch was started to track the time of each injection. This first HPLC serves as the artificial zero time point, then each subsequent HPLC injection followed every ~10 minutes thereafter.

For the second experiment at 35 °C, alanine methyl ester hydrochloride (0.977 g, 0.007 mol), biphenyl (0.199 g, 0.001 mol) and potassium phosphate (3.5 g, 0.017 mol) were added to 50:50 acetonitrile/dichloromethane (37.5 mL) in a vessel. A solution was then prepared of PfBr (1.017 g, 0.003 mol) in 50:50 acetonitrile/dichloromethane (37.5 mL) and added to the reaction vessel. A sample was then immediately taken via HPLC, then the stopwatch was started to track the time of each injection. This first HPLC serves as the artificial zero time point, then each subsequent HPLC injection followed every ~10 minutes thereafter.

For the third experiment at 40 °C, alanine methyl ester hydrochloride (0.841 g, 0.006 mol), biphenyl (0.219 g, 0.001 mol) and potassium phosphate (3.5 g, 0.017 mol) were added to 50:50 acetonitrile/dichloromethane (37.5 mL) in a vessel. A solution was then prepared of PfBr (1.064 g, 0.003 mol) in 50:50 acetonitrile/dichloromethane (37.5 mL) and added to the reaction vessel. A sample was then immediately taken via HPLC, then the stopwatch was started to track the time of each injection. This first HPLC serves as the artificial zero time point, then each subsequent HPLC injection followed every ~10 minutes thereafter.

Alanine methyl ester hydrochloride was acquired from Merck Life Science at 99 %. Biphenyl was acquired from Sigma Aldrich at 99.5 %. Potassium phosphate was acquired from Sigma Aldrich at ≥98 %.

4.3 Example HPLC chromatogram

All HPLC analysis was conducted using an Agilent 1100 series HPLC instrument fitted with a Sigma Ascentis Express C18 reverse phase column (5cm x 4.6mm, 2.7 µm). Biphenyl was used as an internal standard. The column temperature was 40 °C and the HPLC method is shown:

Time /min	%A (water, 0.1 % TFA)	%B (acetonitrile, 0.1 % TFA)	Flow rate /mL min^{-1}
0.00	80	20	1
7.00	15	85	1
8.00	15	85	1
8.10	80	20	1

An example HPLC chromatogram during a kinetic experiment is shown in Figure S4:

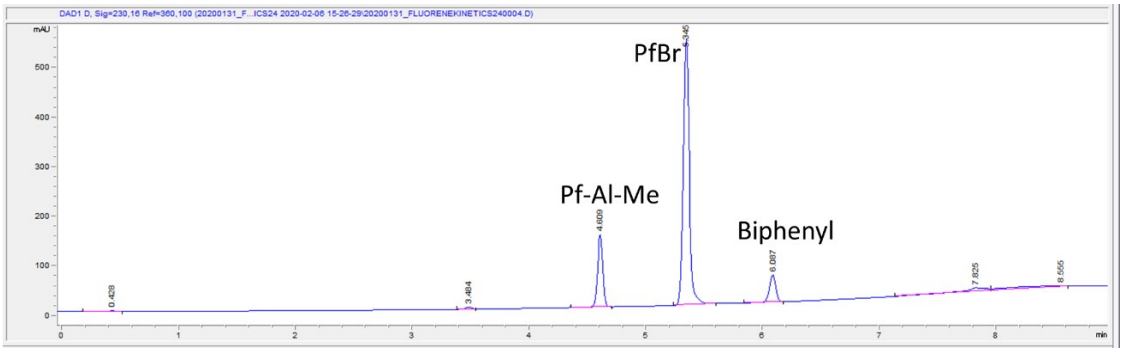
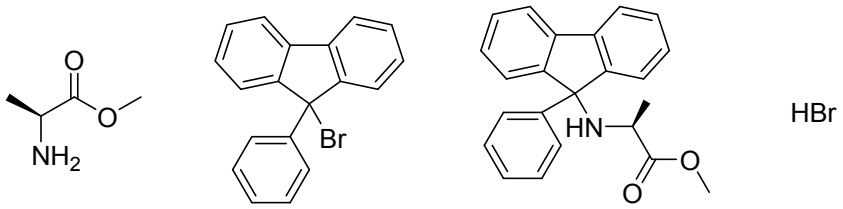


Figure S4: A sample HPLC chromatogram for the PfBr protection case study.

4.4 Top ranked models

The top 5 ranked models from the 30 evaluated are shown in Table S2, with their respective sum of squared error (SSE) values and AIC_C evaluations. All reactive species are first order in the

elementary reaction rate law, unless denoted with a superscripted number for species 'X' such as X^0 or $X^{0.5}$, meaning the species is zero order or 0.5 order respectively.



6 **7** **8** **9**

Table S2: Evaluation of the feasibility of each reaction model for the PfBr protection case study, where α is variable for each model depending on the overall model order.

Rank	Reaction Model	Kinetic parameters		SSE	AIC_C
		$k_{35\,°C}$ /M^{α} min^{-1}	E_a /kJ mol^{-1}	/10^{-5} M	
1	$6^0 + 7 \rightarrow 8 + 9$	0.0106	62.91	3.51	-238.15
2	$6^0 + 7 \rightarrow 8 + 9$ $8 + 9^{0.5} \rightarrow 6 + 7$	0.0115 0.0144	67.09 70.00	2.76	-238.05
3	$6^0 + 7 \rightarrow 8 + 9$ $8 + 9^0 \rightarrow 6 + 7$	0.0129 0.0034	65.27 70.00	2.76	-238.04
4	$6^0 + 7 \rightarrow 8 + 9$ $8^0 + 9 \rightarrow 6 + 7$	0.0128 0.0057	65.71 70.00	2.81	-237.64
5	$6^0 + 7 \rightarrow 8 + 9$ $8^{0.5} + 9 \rightarrow 6 + 7$	0.0112 0.0167	66.06 70.00	2.95	-236.54

4.5 Raw data

Experiment 1, 30 °C

Time /min	7 /M	8 /M
0	0.029401	0.009756
9.5	0.028029	0.011516
19.5	0.026429	0.013131
29	0.024664	0.014922
40	0.022779	0.016856
50	0.021252	0.019153
60.5	0.019363	0.020372

71	0.017813	0.022065
83	0.01612	0.023823

Experiment 2, 35 °C

Time /min	**7 /M**	**8 /M**
0	0.036314	0.006684
9.5	0.030494	0.011469
20	0.028083	0.01372
31.5	0.025271	0.016536
41	0.023355	0.018562
51	0.021259	0.020741
62.5	0.017572	0.023705

Experiment 3, 40 °C

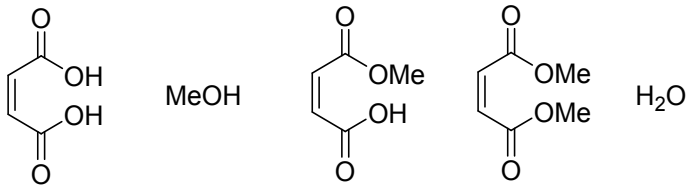
Time /min	**7 /M**	**8 /M**
0	0.037032	0.005772
10.5	0.029931	0.013994
20.5	0.026302	0.017446
30.5	0.022947	0.02101
40	0.020038	0.023665
50.5	0.017687	0.025741
60.5	0.016003	0.027979

5. Maleic acid case study

All experimental details can be found in the original publication, including analysis and preparations for kinetic experiments.[3]

5.2 Top ranked models

The top 5 ranked models from the 5086 evaluated are shown in Table S3, with their respective sum of squared error (SSE) values and AIC_C evaluations. All reactive species are first order in the elementary reaction rate law, unless denoted with a superscripted number for species 'X' such as X^0 or $X^{0.5}$, meaning the species is zero order or 0.5 order respectively.



10 **11** **12** **13** **14**

Table S3: Evaluation of the feasibility of each reaction model for the maleic acid case study, where α is variable for each model depending on the overall model order.

Rank	Reaction Model	Kinetic parameters		SSE /10^{-2} M	AIC_C
		$k_{50\,°C}$ /10^{-3} M^{α} min^{-1}	E_a /kJ mol^{-1}		
1	$10^{1.5} + 11^0 \rightarrow 12 + 10^{0.5} + 14$ $10^{0.5} + 12 + 11^0 \rightarrow 13 + 10^{0.5} + 14$	3.85 0.47	72.61 69.74	0.28	-49.68
2	$10^{1.5} + 11^0 \rightarrow 12 + 10^{0.5} + 14$ $10 + 12^2 \rightarrow 10^2 + 13$	4.08 1.92	78.32 79.77	0.33	-49.08
3	$10^{1.5} + 11^0 \rightarrow 12 + 10^{0.5} + 14$ $10 + 12 + 11^0 \rightarrow 13 + 10 + 14$	3.91 1.03	74.19 79.95	0.33	-49.02
4	$10^{1.5} + 11^0 \rightarrow 12 + 10^{0.5} + 14$ $10^{0.5} + 12^2 \rightarrow 10^{1.5} + 13$	3.97 0.76	76.52 73.06	0.42	-48.06
5	$10^2 + 11^0 \rightarrow 12 + 10 + 14$ $10 + 12 + 11^0 \rightarrow 13 + 10 + 14$	5.60 0.78	79.98 79.36	0.53	-47.15

5.3 Raw data

Experiment 1, 40 °C

Time /min	10 /M	12 /M	13 /M
0	0.761	0	0
120	0.66207	0.097408	0.002283
240	0.554769	0.201665	0.004947
360	0.485518	0.265589	0.009893

Experiment 2, 50 °C

Time /min	10 /M	12 /M	13 /M
0	0.404344	0.003268	0
32.5	0.364451	0.037657	1.86E-05
60.5	0.346181	0.071026	0.000373
87.5	0.319523	0.095447	0.001659
122.5	0.299017	0.113343	0.003225
217.5	0.234143	0.1661	0.006264
288.5	0.204502	0.198537	0.009507
417.5	0.15883	0.230601	0.015846
687.5	0.107378	0.276833	0.028336
1342.5	0.052198	0.313931	0.053689
1782.5	0.033649	0.310389	0.063196
2837.5	0.01799	0.307033	0.083516

Experiment 3, 50 °C

Time /min	10 /M	12 /M	13 /M
0	0.787537	0.007088	0
28	0.706604	0.088537	5.65E-04
60	0.625073	0.164707	0.002563
95	0.556919	0.226165	0.006126
118	0.530477	0.271021	0.007904
148	0.480567	0.308812	0.011678
178	0.426661	0.316753	0.01425

208	0.405376	0.35592	0.020026
242	0.384453	0.382377	0.021991
298	0.344452	0.431289	0.029072
358	0.299951	0.456885	0.034314
613	0.205957	0.541791	0.061416
1306	0.092916	0.582232	0.105274
1549	0.076529	0.596801	0.119691
1768	0.063259	0.597105	0.130915

Experiment 4, 55 °C

Time /min	**10 /M**	**12 /M**	**13 /M**
0	0.687045	0.103644	0.000811
30	0.597449	0.19108	2.97E-03
60	0.531145	0.252908	0.007448
90	0.479052	0.301502	0.010947
168	0.365378	0.402913	0.023209
228	0.31788	0.443385	0.030235
283	0.28467	0.469404	0.037426
348	0.221288	0.520375	0.049837
408	0.200913	0.533579	0.057007

Experiment 5, 60 °C

Time /min	**10 /M**	**12 /M**	**13 /M**
0	0.738693	0.014307	0
60	0.442764	0.296682	1.36E-02

120	0.335085	0.389301	0.029367
180	0.265809	0.447282	0.040662
240	0.224394	0.475143	0.053463
360	0.117468	0.551196	0.084336
480	0.070029	0.575292	0.107679
1320	0.015813	0.538395	0.198792

6. References

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3. Ashworth, I.W., et al., *Where has my acid gone? Understanding the self-catalyzed esterification of maleic acid in methanol during salt formation.* Organic Process Research & Development, 2012. **16**(10): p. 1646-1651.