Mechanistic insights into the amination via nucleophilic aromatic substitution

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SUPPORTING INFORMATION

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S1. Kinetic study for the reaction without DBU

The differential equations for the reactions in Scheme 3(b) are shown in Eqs. (1) to (3). The parameter values and their confidence intervals are shown in Table S1. As illustrated in the materials and methods section, the generated HF was trapped by MP, resulting in two moles of MP consumption.

$$\frac{dC_{SM}}{dt} = -k_1 C_{SM} C_{MP} \quad (1)$$

$$\frac{dC_{MP}}{dt} = -2k_1 C_{SM} C_{MP} \quad (2)$$

$$\frac{dC_{DP}}{dt} = k_1 C_{SM} C_{MP} \quad (3)$$

Table S1. Parameter values and their confidence intervals for Scheme S1.

Parameter	Unit	Value	One-standard-deviation range	
A_1	$m^3\ mol^{-1}\ h^{-1}$	6.31×10^2	$(6.59 \pm 0.106) \times 10^2$	1.60%
E_1	$J\ mol^{-1}$	4.79×10^4	$(4.78 \pm 0.00460) \times 10^4$	0.10%

S2. Kinetic study for the reaction with DBU based on concerted pathways

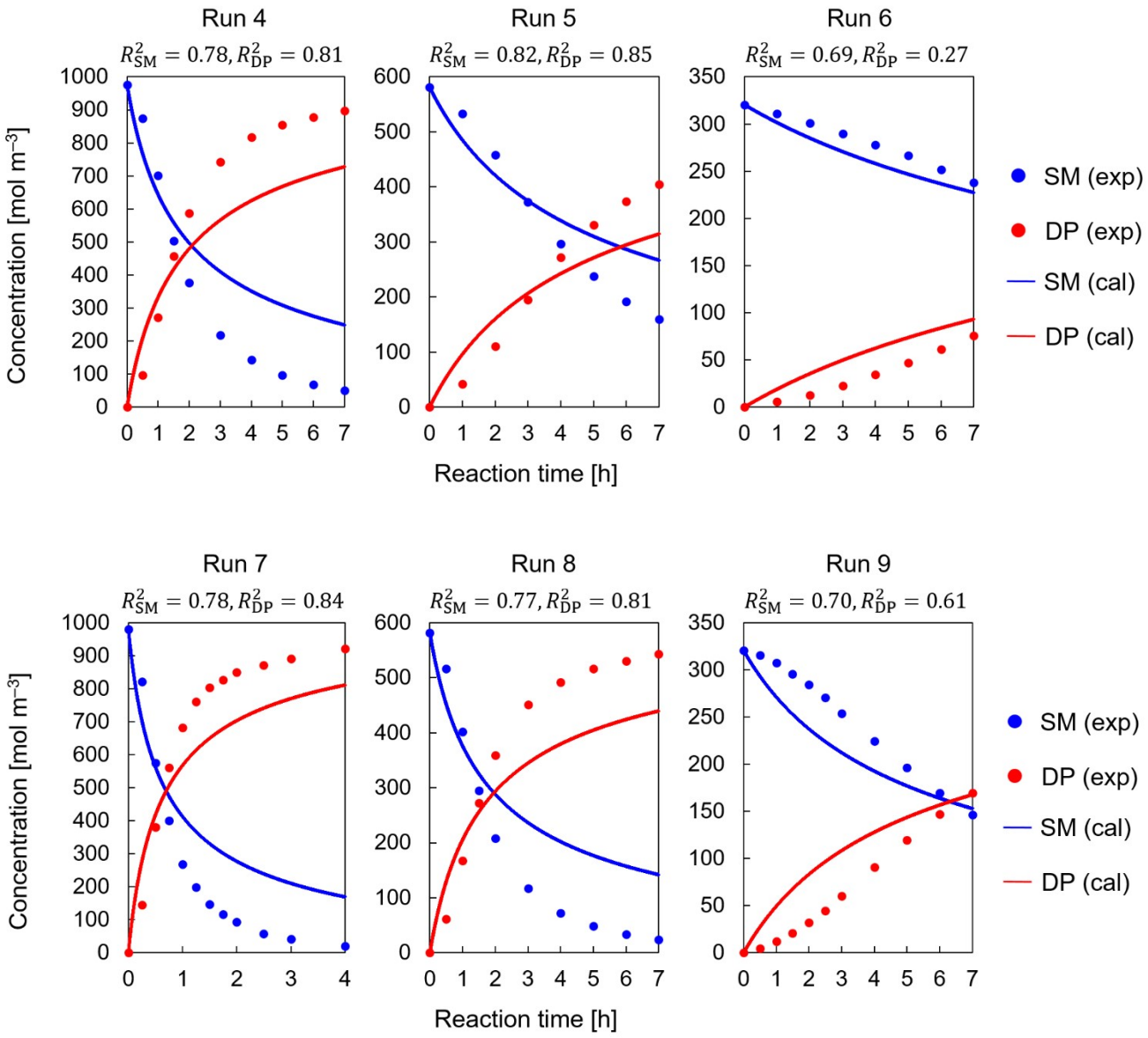
The differential equations for the reactions in Scheme 4(b) are shown in Eqs. (4) to (7). The kinetic study results for the reactions are shown in Fig. S1.

$$\frac{dC_{SM}}{dt} = -k_1 C_{SM} C_{MP} - k_2 C_{SM} C_{MP} C_{DBU} \quad (4)$$

$$\frac{dC_{MP}}{dt} = -k_1 C_{SM} C_{MP} - k_2 C_{SM} C_{MP} C_{DBU} \quad (5)$$

$$\frac{dC_{DBU}}{dt} = -k_1 C_{SM} C_{MP} - k_2 C_{SM} C_{MP} C_{DBU} \quad (6)$$

$$\frac{dC_{DP}}{dt} = k_1 C_{SM} C_{MP} + k_2 C_{SM} C_{MP} C_{DBU} \quad (7)$$


Run 4
$R^2_{SM} = 0.78, R^2_{DP} = 0.81$
Run 5
$R^2_{SM} = 0.82, R^2_{DP} = 0.85$
Run 6
$R^2_{SM} = 0.69, R^2_{DP} = 0.27$
Concentration [mol m^{-3}]
Reaction time [h]
SM (exp)
DP (exp)
SM (cal)
DP (cal)
Run 7
$R^2_{SM} = 0.78, R^2_{DP} = 0.84$
Run 8
$R^2_{SM} = 0.77, R^2_{DP} = 0.81$
Run 9
$R^2_{SM} = 0.70, R^2_{DP} = 0.61$
Concentration [mol m^{-3}]
Reaction time [h]
SM (exp)
DP (exp)
SM (cal)
DP (cal)

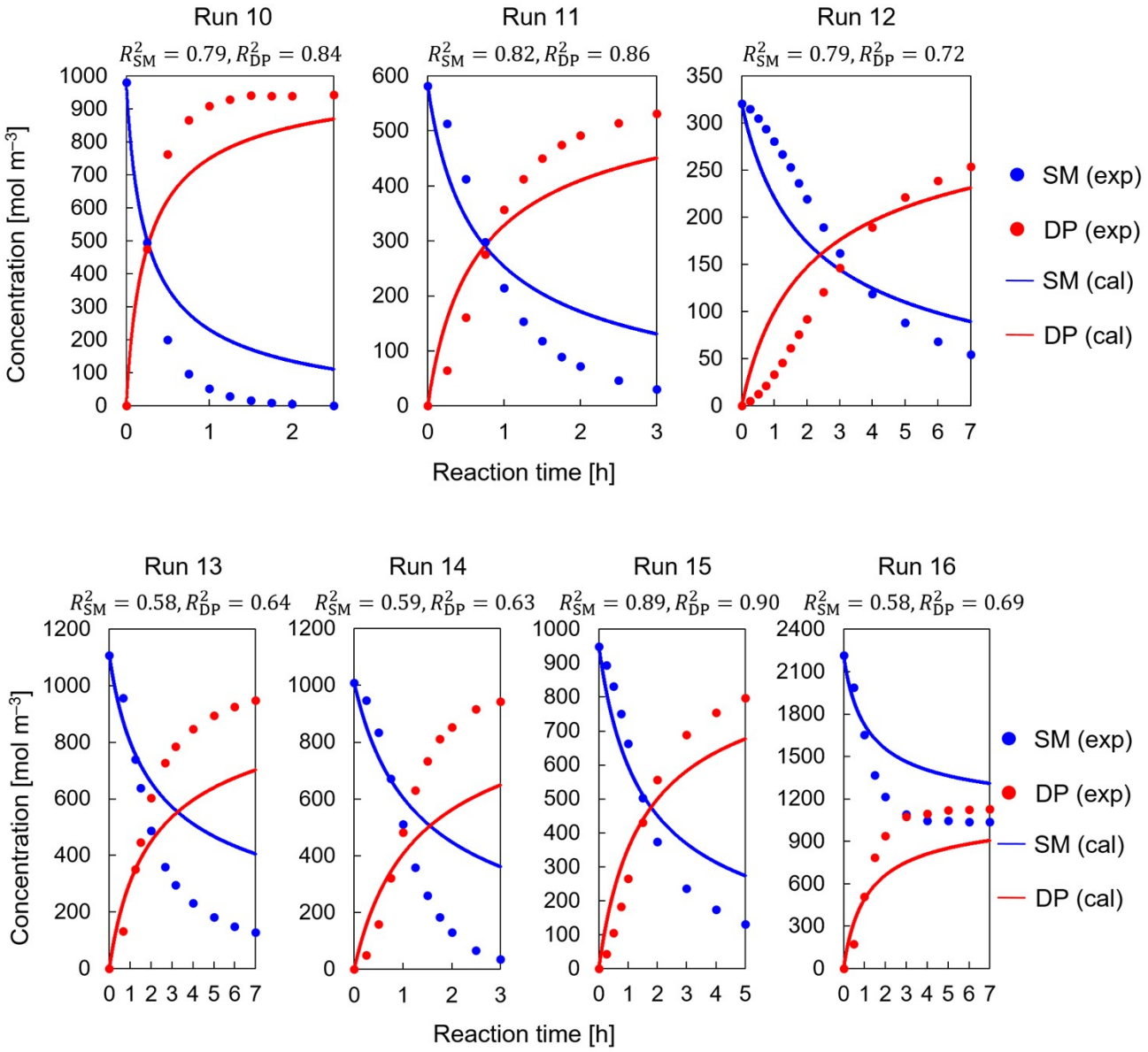


Fig. S1. Kinetic study results showing concentrations of the starting material and desired product based on the concerted pathway based on Scheme 4(b).

S3. Kinetic study for the reaction with DBU based on stepwise pathways

The differential equations for the reactions in Scheme 4(c) are shown in Eqs. (8) to (12). The kinetic study results for the reactions are shown in Fig. S2.

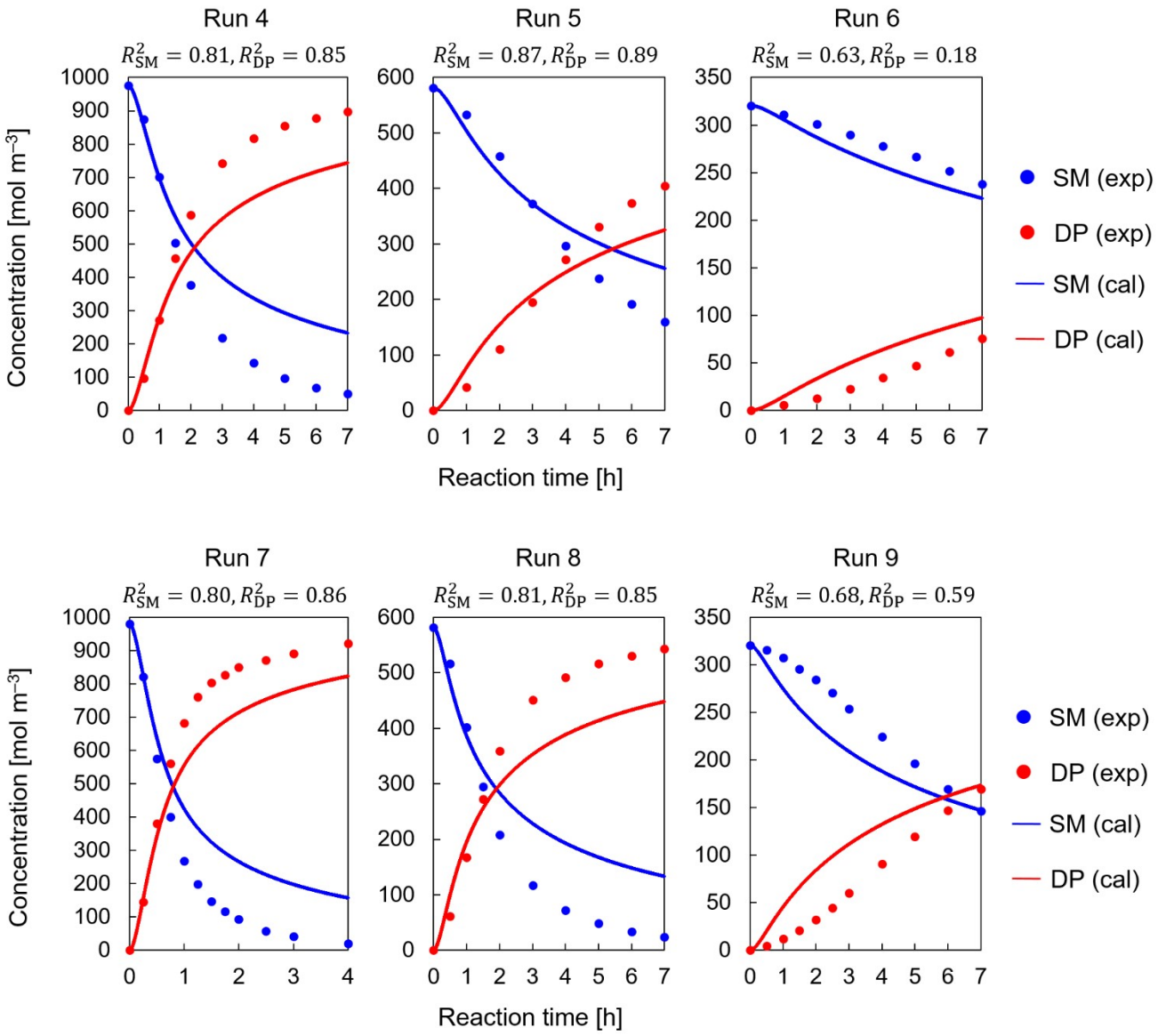
$$\frac{dC_{SM}}{dt} = -k_1 C_{SM} C_{MP} - k_5 C_{SM} C_{MP} C_{DBU} \quad (8)$$

$$\frac{dC_{MP}}{dt} = -k_1 C_{SM} C_{MP} - k_5 C_{SM} C_{MP} C_{DBU} \quad (9)$$

$$\frac{dC_{DBU}}{dt} = -k_1 C_{SM} C_{MP} - k_6 C_{MC} \quad (10)$$

$$\frac{dC_{MC}}{dt} = k_5 C_{SM} C_{MP} C_{DBU} - k_6 C_{MC} \quad (11)$$

$$\frac{dC_{DP}}{dt} = k_1 C_{SM} C_{MP} + k_6 C_{MC} \quad (12)$$


Run 4
$R^2_{SM} = 0.81, R^2_{DP} = 0.85$
Run 5
$R^2_{SM} = 0.87, R^2_{DP} = 0.89$
Run 6
$R^2_{SM} = 0.63, R^2_{DP} = 0.18$
Concentration [mol m^{-3}]
Reaction time [h]
SM (exp)
DP (exp)
SM (cal)
DP (cal)
Run 7
$R^2_{SM} = 0.80, R^2_{DP} = 0.86$
Run 8
$R^2_{SM} = 0.81, R^2_{DP} = 0.85$
Run 9
$R^2_{SM} = 0.68, R^2_{DP} = 0.59$
Concentration [mol m^{-3}]
Reaction time [h]
SM (exp)
DP (exp)
SM (cal)
DP (cal)

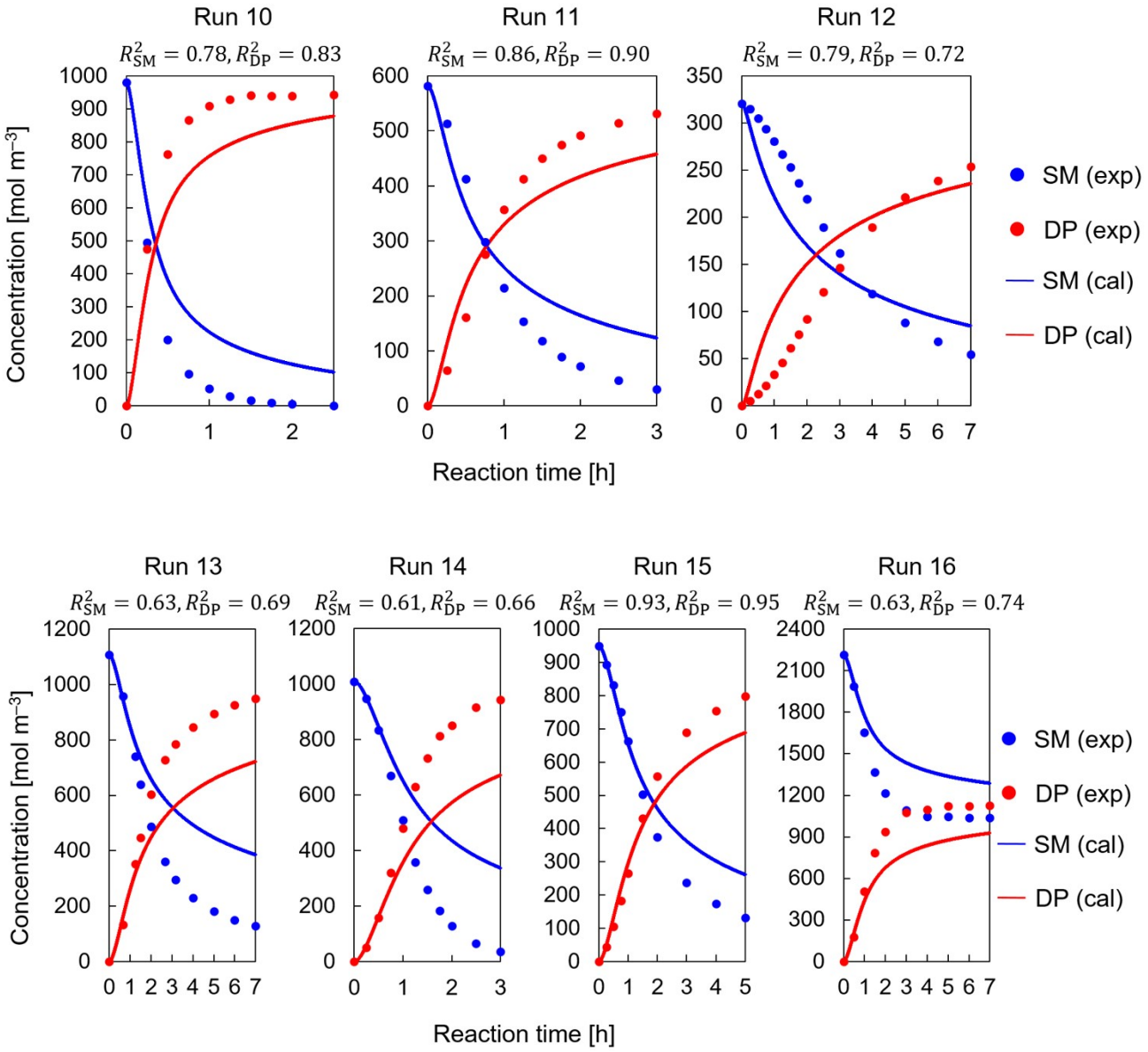
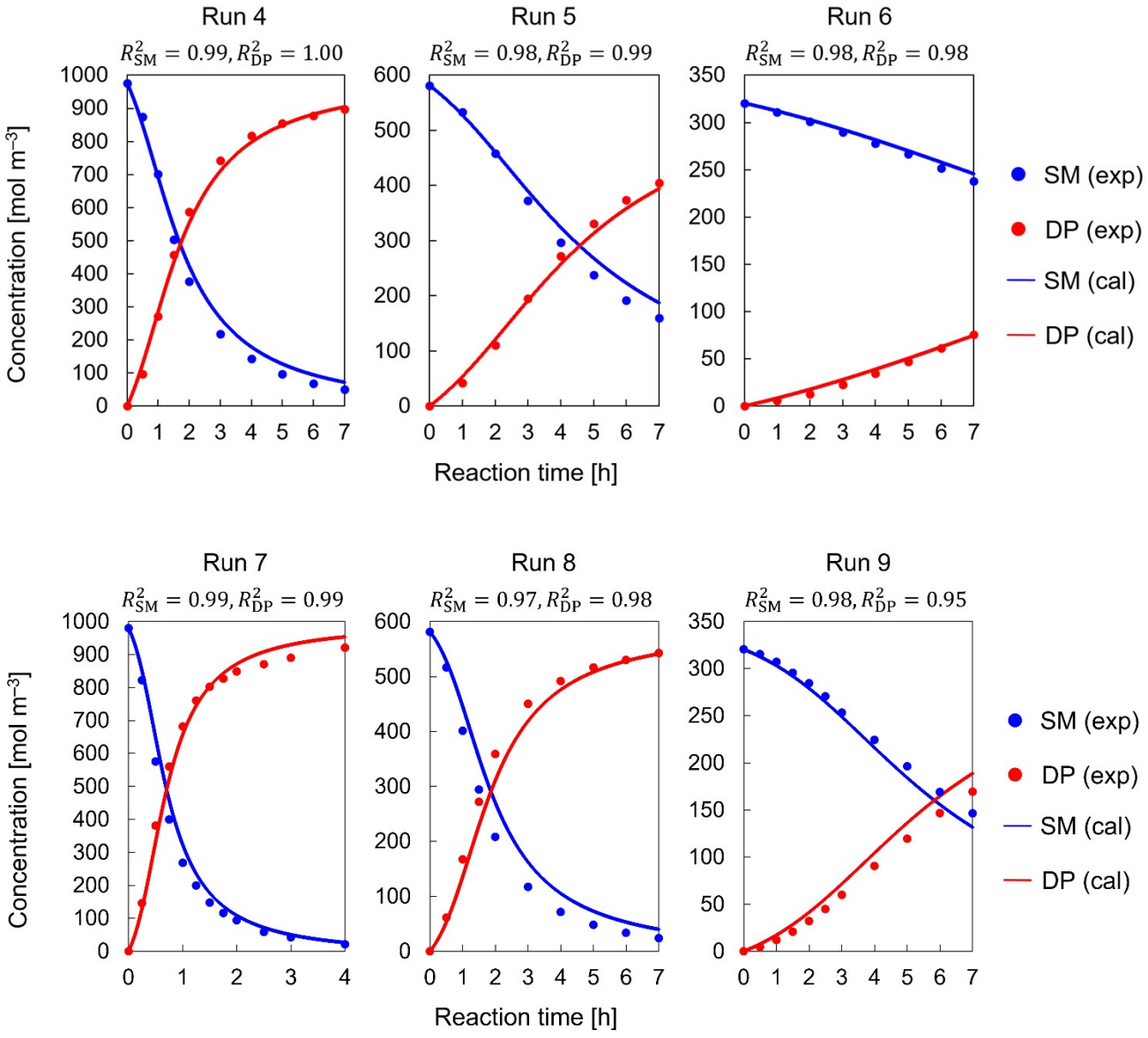


Fig. S2. Kinetic study results showing concentrations of the starting material and desired product based on the concerted pathway based on Scheme 4(c).

S4. Kinetic study for the reaction with DBU based on the proposed reaction pathways (concerted (a) and stepwise (b) with a reverse reaction in Scheme 5)

The kinetic analysis results for the reactions in Scheme 6 are shown in Fig. S3. The parameter values and their confidence intervals are shown in Table S2.



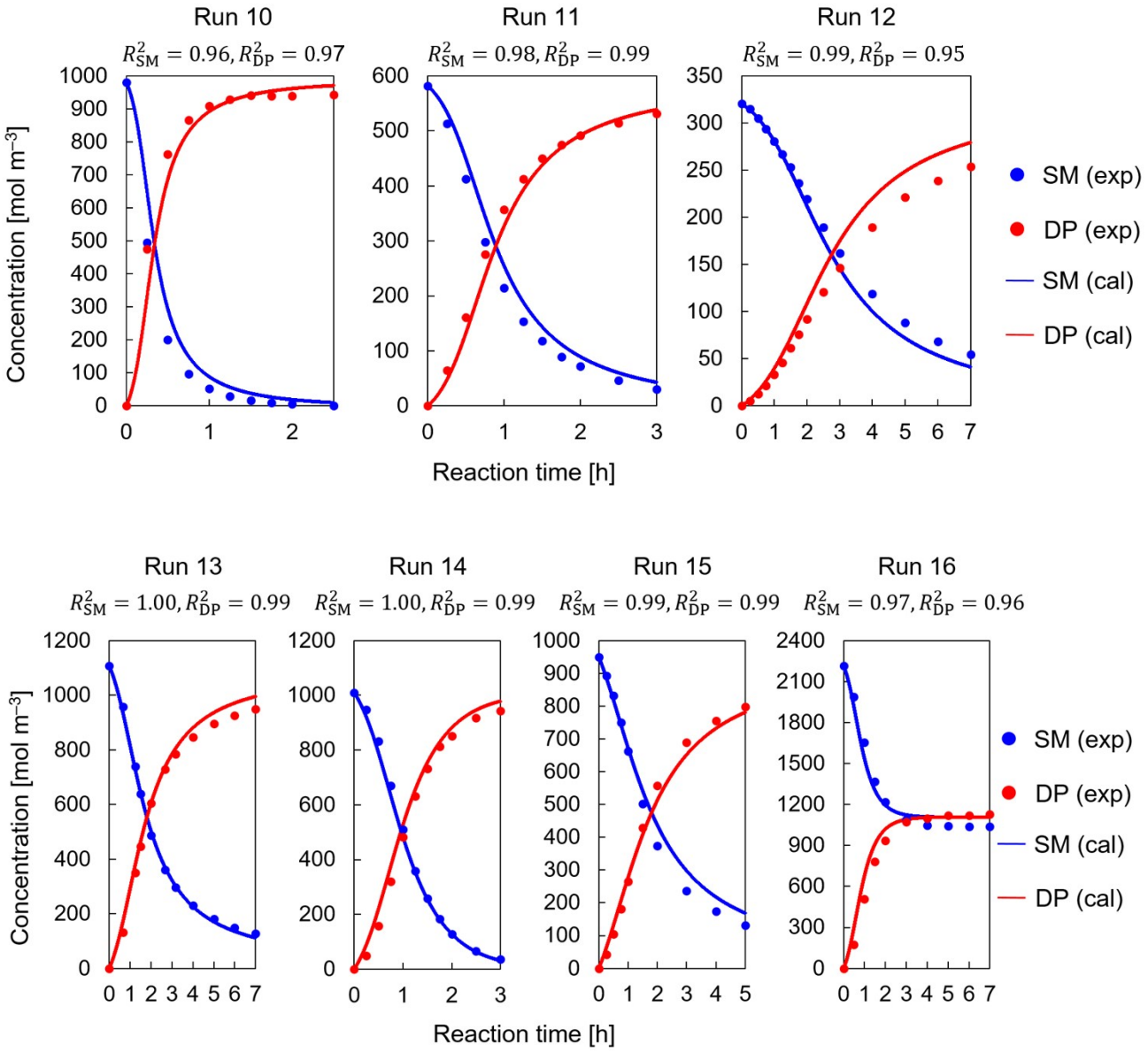


Fig. S3. Kinetic study results for the reactions with DBU based on concerted (a) and stepwise (b) with a reverse reaction in Scheme 5.

Table S2. Parameter values and their confidence intervals for Scheme 6

Parameter	Unit	Value	One-standard-deviation range	
A_2	$m^6\ mol^{-2}\ h^{-1}$	4.57×10^{-4}	$(4.53 \pm 0.125) \times 10^{-4}$	2.76%
A_3	$m^6\ mol^{-2}\ h^{-1}$	1.61×10^{-2}	$(1.63 \pm 0.0224) \times 10^{-2}$	1.38%
A_4	h^{-1}	6.54×10^{7}	$(6.46 \pm 0.101) \times 10^{7}$	1.57%
A_{-3}	h^{-1}	1.55×10^{2}	$(1.56 \pm 0.0291) \times 10^{2}$	1.85%
E_2	$J\ mol^{-1}$	2.12×10^{4}	$(2.13 \pm 0.00732) \times 10^{4}$	0.34%
E_3	$J\ mol^{-1}$	1.93×10^{4}	$(1.92 \pm 0.00370) \times 10^{4}$	0.19%
E_4	$J\ mol^{-1}$	4.14×10^{4}	$(4.14 \pm 0.00415) \times 10^{4}$	0.10%
E_{-3}	$J\ mol^{-1}$	3.46×10^{3}	$(3.46 \pm 0.0490) \times 10^{3}$	1.42%

S5. Kinetic study for the reaction with DBU based on the proposed reaction pathways (concerted (a) and stepwise (b) without a reverse reaction in Scheme 5)

The differential equations for the reactions in Scheme 7 are shown in Eqs. (13) to (18). The kinetic study results for the reactions are shown in Fig. S4. The parameter values and their confidence intervals are shown in Table S3.

$$\frac{dC_{SM}}{dt} = -k_1 C_{SM} C_{MP} - k_2 C_{SM} C_{MP} C_{DBU} - k_3 C_{SM} C_{MP} C_{DBUH^+} \quad (13)$$

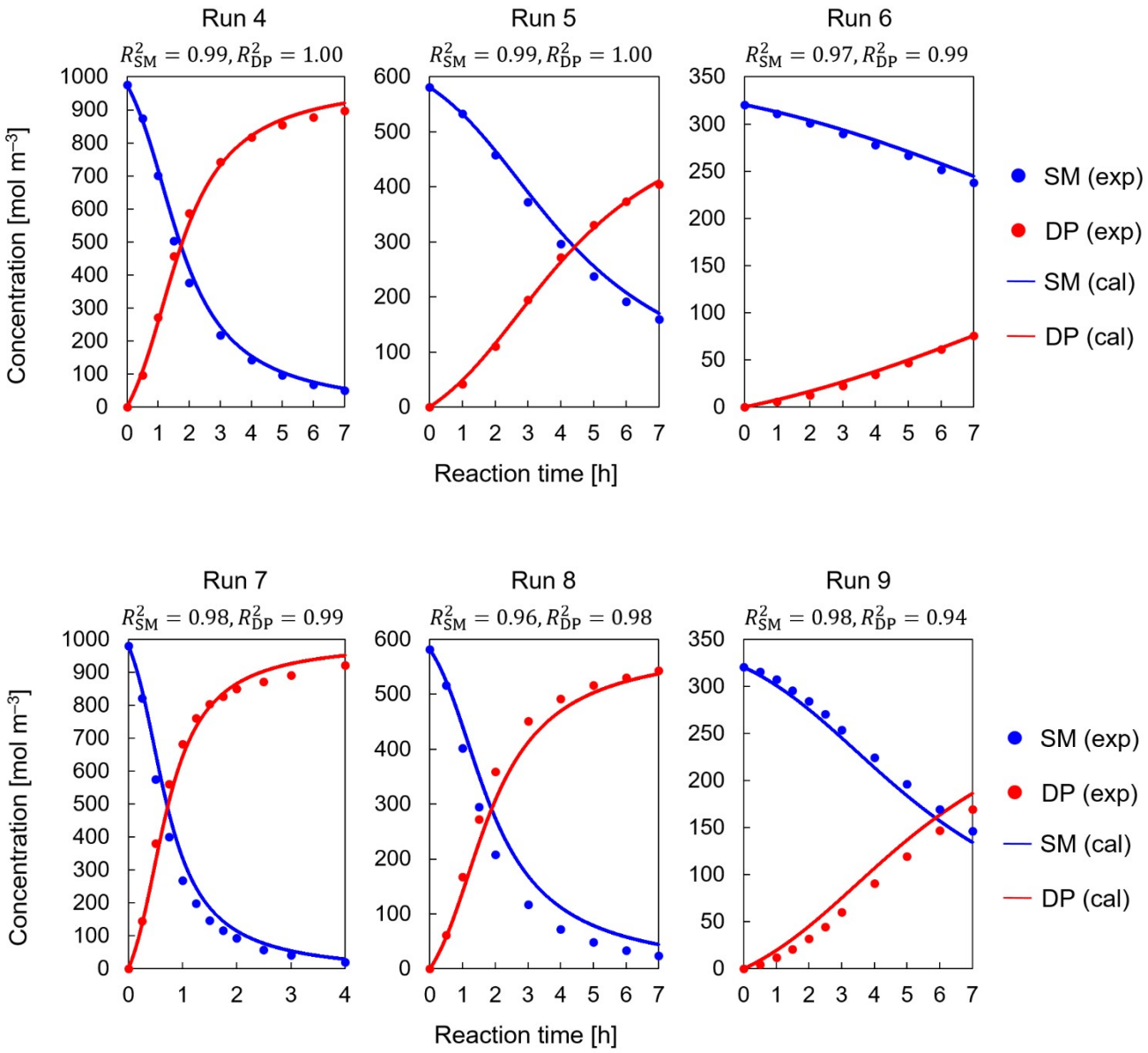
$$\frac{dC_{MP}}{dt} = -k_1 C_{SM} C_{MP} - k_2 C_{SM} C_{MP} C_{DBU} - k_3 C_{SM} C_{MP} C_{DBUH^+} \quad (14)$$

$$\frac{dC_{DBU}}{dt} = -k_1 C_{SM} C_{MP} - k_2 C_{SM} C_{MP} C_{DBU} - k_4 C_{MC} \quad (15)$$

$$\frac{dC_{MC}}{dt} = k_3 C_{SM} C_{MP} C_{DBUH^+} - k_4 C_{MC} \quad (16)$$

$$\frac{dC_{DP}}{dt} = k_1 C_{SM} C_{MP} + k_2 C_{SM} C_{MP} C_{DBU} + k_4 C_{MC} \quad (17)$$

$$\frac{dC_{DBUH^+}}{dt} = k_1 C_{SM} C_{MP} + k_2 C_{SM} C_{MP} C_{DBU} + k_4 C_{MC} \quad (18)$$


Run 4
$R^2_{SM} = 0.99, R^2_{DP} = 1.00$
Run 5
$R^2_{SM} = 0.99, R^2_{DP} = 1.00$
Run 6
$R^2_{SM} = 0.97, R^2_{DP} = 0.99$
Run 7
$R^2_{SM} = 0.98, R^2_{DP} = 0.99$
Run 8
$R^2_{SM} = 0.96, R^2_{DP} = 0.98$
Run 9
$R^2_{SM} = 0.98, R^2_{DP} = 0.94$
Concentration [mol m^{-3}]
Reaction time [h]
SM (exp)
DP (exp)
SM (cal)
DP (cal)

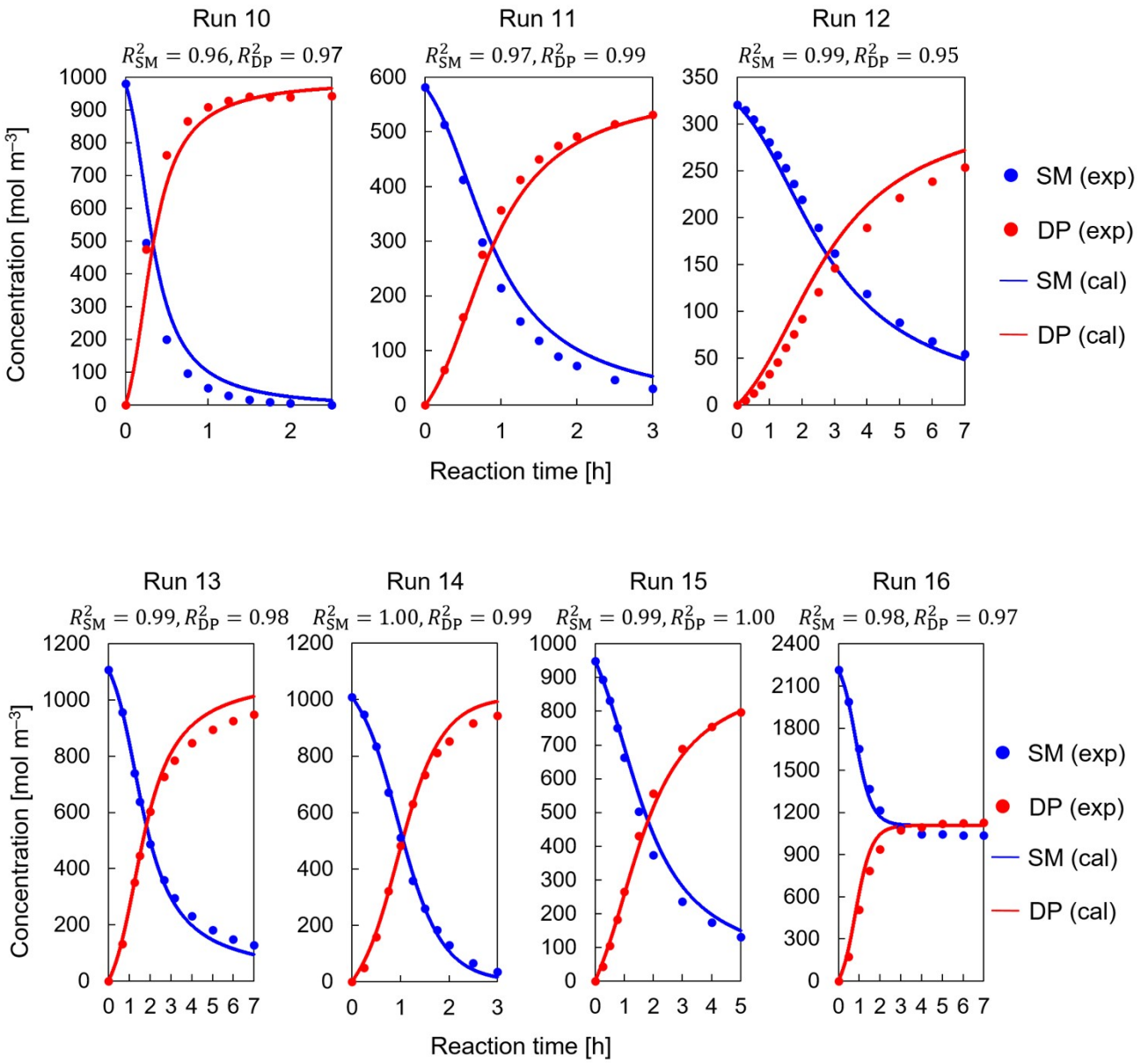


Fig. S4. Kinetic study results for the reaction with DBU based on the proposed reaction pathways where concerted (a) and stepwise (b) without a reverse reaction in Scheme 5.

Table S3. Parameter values and their confidence intervals for Scheme 7.

Parameter	Unit	Value	One-standard-deviation range	
A_2	$m^6\ mol^{-2}\ h^{-1}$	5.39×10^{-2}	$(5.77 \pm 0.135) \times 10^{-2}$	2.33%
A_3	$m^6\ mol^{-2}\ h^{-1}$	2.64	2.71 ± 0.0359	1.32%
A_4	h^{-1}	3.83×10^9	$(3.52 \pm 0.172) \times 10^9$	4.89%
E_2	$J\ mol^{-1}$	3.38×10^4	$(3.37 \pm 0.00622) \times 10^4$	0.18%
E_3	$J\ mol^{-1}$	3.68×10^4	$(3.67 \pm 0.00355) \times 10^4$	0.10%
E_4	$J\ mol^{-1}$	5.26×10^4	$(5.28 \pm 0.0127) \times 10^4$	0.24%

S6. Kinetic study for the reaction with DBU based on the proposed reaction pathways (concerted (a) and (b) in Scheme 5)

The differential equations for the reactions in Scheme 8 are shown in Eqs. (19) to (23). The kinetic study results for the reactions are shown in Fig. S5. The parameter values and their confidence intervals are shown in Table S4.

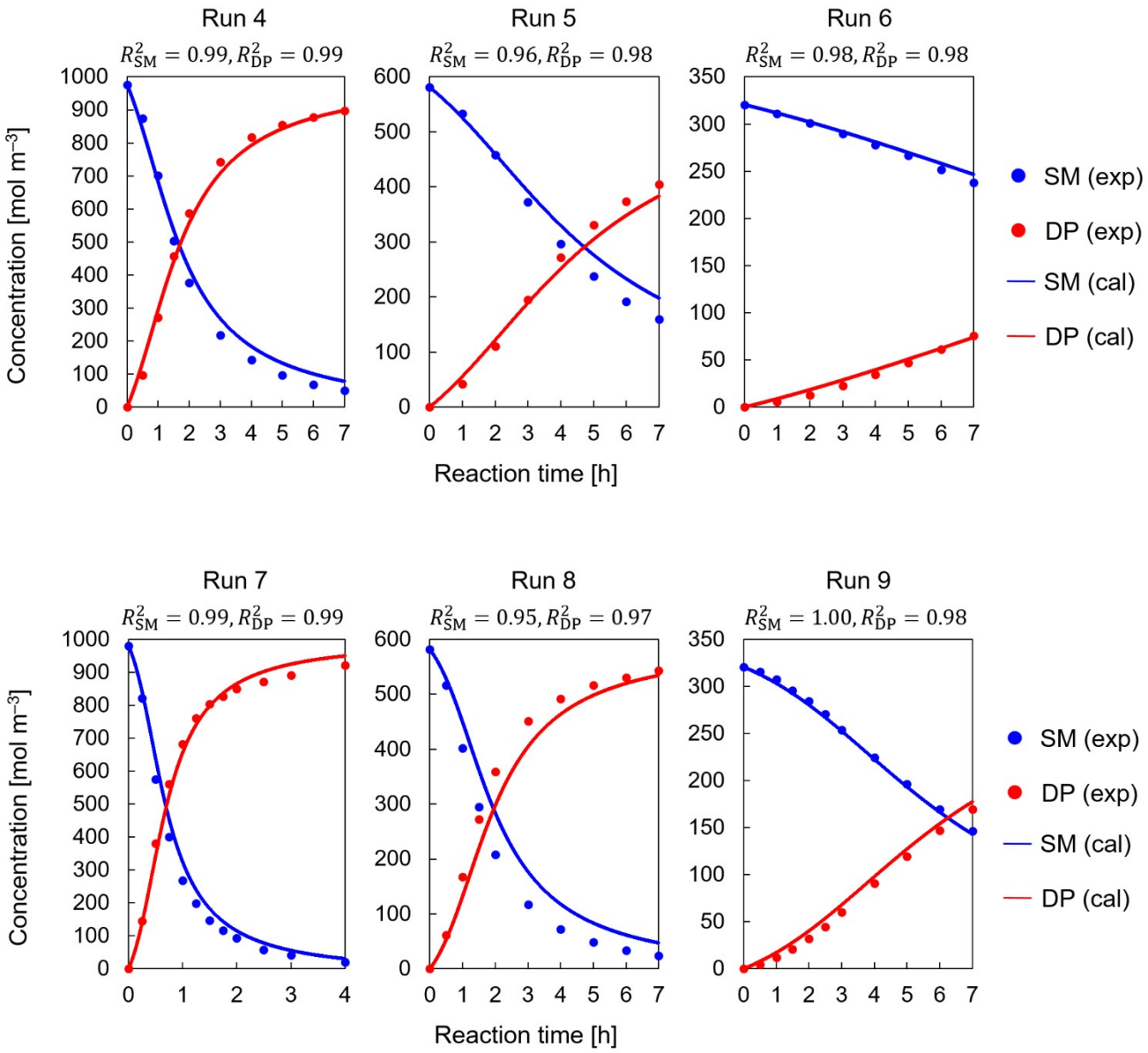
$$\frac{dC_{SM}}{dt} = -k_1 C_{SM} C_{MP} - k_2 C_{SM} C_{MP} C_{DBU} - k_7 C_{SM} C_{MP} C_{DBUH^+} \quad (19)$$

$$\frac{dC_{MP}}{dt} = -k_1 C_{SM} C_{MP} - k_2 C_{SM} C_{MP} C_{DBU} - k_7 C_{SM} C_{MP} C_{DBUH^+} \quad (20)$$

$$\frac{dC_{DBU}}{dt} = -k_1 C_{SM} C_{MP} - k_2 C_{SM} C_{MP} C_{DBU} - k_7 C_{SM} C_{MP} C_{DBUH^+} \quad (21)$$

$$\frac{dC_{DP}}{dt} = k_1 C_{SM} C_{MP} + k_2 C_{SM} C_{MP} C_{DBU} + k_7 C_{SM} C_{MP} C_{DBUH^+} \quad (22)$$

$$\frac{dC_{DBUH^+}}{dt} = k_1 C_{SM} C_{MP} + k_2 C_{SM} C_{MP} C_{DBU} + k_7 C_{SM} C_{MP} C_{DBUH^+} \quad (23)$$


Run 4
$R^2_{SM} = 0.99, R^2_{DP} = 0.99$
Run 5
$R^2_{SM} = 0.96, R^2_{DP} = 0.98$
Run 6
$R^2_{SM} = 0.98, R^2_{DP} = 0.98$
Concentration [mol m^{-3}]
Reaction time [h]
SM (exp)
DP (exp)
SM (cal)
DP (cal)
Run 7
$R^2_{SM} = 0.99, R^2_{DP} = 0.99$
Run 8
$R^2_{SM} = 0.95, R^2_{DP} = 0.97$
Run 9
$R^2_{SM} = 1.00, R^2_{DP} = 0.98$
Concentration [mol m^{-3}]
Reaction time [h]
SM (exp)
DP (exp)
SM (cal)
DP (cal)

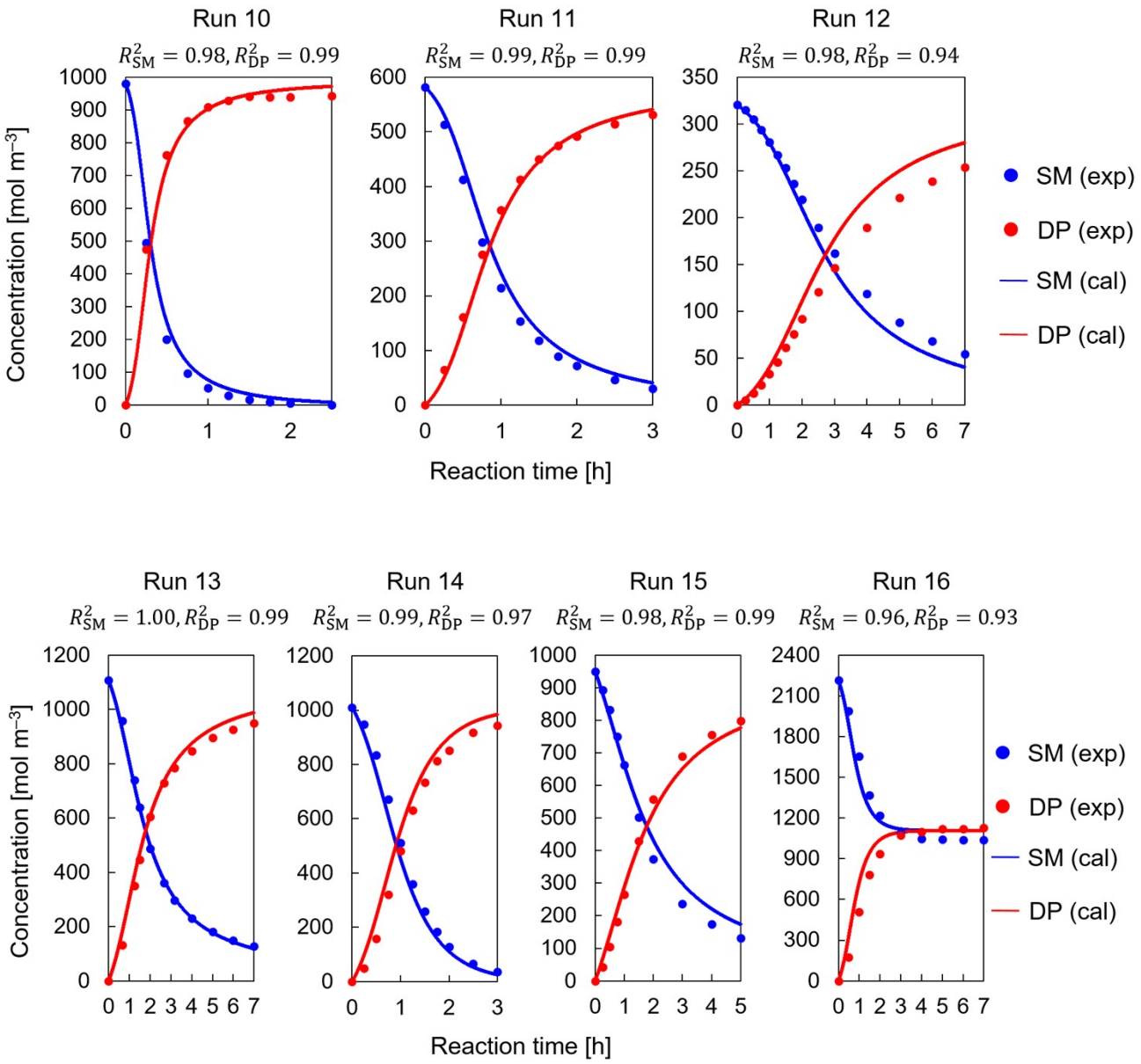


Fig. S5. Kinetic study results for the reaction with DBU based on the proposed reaction pathways where concerted (a) and (b) in Scheme 5.

Table S4. Parameter values and their confidence intervals for Scheme 8.

Parameter	Unit	Value	One-standard-deviation range	
A_2	$m^6\ mol^{-2}\ h^{-1}$	2.84×10^{-4}	$(2.59 \pm 0.0756) \times 10^{-4}$	2.92%
A_7	$m^6\ mol^{-2}\ h^{-1}$	1.62×10^{2}	$(1.56 \pm 0.0223) \times 10^{2}$	1.43%
E_2	$J\ mol^{-1}$	1.98×10^{4}	$(2.00 \pm 0.00771) \times 10^{4}$	0.38%
E_7	$J\ mol^{-1}$	4.83×10^{4}	$(4.84 \pm 0.00382) \times 10^{4}$	0.08%

S7. Raw data

Run1			Run2		
Time [h]	SM [mol m-3]	DP [mol m-3]	Time [h]	SM [mol m-3]	DP [mol m-3]
0.00	1009.86	0.00	0.00	1009.86	0.00
0.50	997.48	4.90	0.50	986.07	16.14
1.00	991.22	9.41	1.00	969.62	30.66
1.50	980.21	14.40	1.50	952.65	47.27
2.00	976.12	19.76	2.00	935.23	64.57
3.00	967.39	30.41	3.00	900.23	98.37
4.00	954.93	41.36	4.00	866.30	132.85
5.00	944.40	53.26	5.00	828.82	166.98
6.00	942.22	65.77	6.00	794.56	203.64

Run3			Run4		
Time [h]	SM [mol m-3]	DP [mol m-3]	Time [h]	SM [mol m-3]	DP [mol m-3]
0.00	1009.86	0.00	0.00	976.38	0.00
0.25	978.66	18.52	0.50	873.83	96.45
0.50	951.03	36.09	1.00	701.87	271.80
0.75	925.76	53.72	1.50	502.54	457.15
1.00	905.52	73.40	2.00	376.72	586.44
1.50	863.93	111.18	3.00	217.99	742.59
2.00	822.61	151.30	4.00	142.55	817.86
3.00	745.71	228.35	5.00	96.87	853.70
4.00	679.34	294.55	6.00	68.90	878.43
5.00	622.87	359.37	7.00	50.39	898.18

Run5			Run6		
Time [h]	SM [mol m-3]	DP [mol m-3]	Time [h]	SM [mol m-3]	DP [mol m-3]
0.00	581.34	0.00	0.00	320.50	0.00
1.00	533.44	42.04	1.00	310.70	6.09
2.00	458.28	110.61	2.00	300.91	12.66
3.00	372.29	194.72	3.00	289.47	22.37
4.00	296.54	271.64	4.00	277.91	34.44
5.00	237.75	331.05	5.00	266.41	47.02
6.00	192.17	373.91	6.00	251.73	61.16
7.00	159.31	404.43	7.00	237.92	75.44

Run7			Run8		
Time [h]	SM [mol m-3]	DP [mol m-3]	Time [h]	SM [mol m-3]	DP [mol m-3]
0.00	980.24	0.00	0.00	581.34	0.00
0.25	821.71	146.16	0.50	516.64	61.60
0.50	575.30	380.75	1.00	401.43	167.17
0.75	399.99	560.32	1.50	294.40	271.84
1.00	268.62	681.43	2.00	208.31	358.85
1.25	199.53	760.75	3.00	117.22	450.46
1.50	147.68	802.87	4.00	71.77	491.92
1.75	116.46	826.89	5.00	48.43	516.40
2.00	94.00	848.98	6.00	33.73	530.12
2.50	58.78	870.52	7.00	23.77	542.95
3.00	42.29	890.09			
4.00	21.26	921.05			

Run9			Run10		
Time [h]	SM [mol m-3]	DP [mol m-3]	Time [h]	SM [mol m-3]	DP [mol m-3]
0.00	320.50	0.00	0.00	980.24	0.00
0.50	315.59	4.65	0.25	493.89	474.93
1.00	307.35	11.99	0.50	200.04	762.67
1.50	295.54	20.81	0.75	97.44	865.40
2.00	284.51	32.14	1.00	53.40	908.20
2.50	270.58	44.92	1.25	30.08	927.70
3.00	253.43	59.91	1.50	17.27	940.78
4.00	224.48	90.59	1.75	9.84	938.66
5.00	196.30	119.42	2.00	5.52	939.16
6.00	169.17	146.65	2.50	0.00	941.42
7.00	146.33	169.32			

Run11			Run12		
Time [h]	SM [mol m-3]	DP [mol m-3]	Time [h]	SM [mol m-3]	DP [mol m-3]
0.00	581.34	0.00	0.00	320.50	0.00
0.25	513.28	65.11	0.25	314.55	5.39
0.50	412.11	161.40	0.50	304.55	12.95
0.75	297.66	275.16	0.75	293.56	21.75
1.00	214.71	356.36	1.00	280.54	33.45
1.25	153.52	412.59	1.25	266.61	46.07
1.50	118.25	449.82	1.50	253.15	61.17
1.75	89.85	474.30	1.75	236.18	76.02
2.00	71.98	491.34	2.00	219.36	92.19
2.50	46.76	514.06	2.50	189.29	120.67
3.00	30.80	530.99	3.00	161.81	146.40
			4.00	119.00	189.32
			5.00	88.33	220.95
			6.00	68.11	238.57
			7.00	54.32	253.43

Run13			Run14		
Time [h]	SM [mol m-3]	DP [mol m-3]	Time [h]	SM [mol m-3]	DP [mol m-3]
0.00	1107.01	0.00	0.00	1009.64	0.00
0.67	957.24	131.77	0.25	947.05	49.85
1.25	739.98	350.85	0.50	833.38	157.73
1.50	639.18	446.51	0.75	670.83	320.48
2.00	487.61	604.05	1.00	510.41	481.20
2.67	359.98	727.87	1.25	358.90	630.70
3.17	295.76	785.41	1.50	258.78	732.99
4.00	230.29	846.68	1.75	184.11	812.21
5.00	180.80	895.17	2.00	128.58	851.60
6.00	148.94	926.59	2.50	65.58	917.38
7.00	127.88	949.60	3.00	35.09	943.70

Run15			Run16		
Time [h]	SM [mol m-3]	DP [mol m-3]	Time [h]	SM [mol m-3]	DP [mol m-3]
0.00	949.77	0.00	0.00	2214.02	0.00
0.25	893.33	42.46	0.50	1986.60	174.04
0.50	832.24	104.83	1.00	1652.36	506.46
0.75	750.57	181.65	1.50	1368.42	782.49
1.00	662.50	265.14	2.00	1216.08	937.38
1.50	502.41	429.83	3.00	1090.24	1073.85
2.00	373.37	556.70	4.00	1046.69	1096.49
3.00	236.34	689.34	5.00	1044.05	1120.10
4.00	174.07	755.06	6.00	1038.41	1121.65
5.00	130.81	797.70	7.00	1036.97	1126.80

S8. HPLC method for analysis

Column: Waters Xbridge C18, 4.6 × 150 mm, 5 μm

Mobile phase A: 0.1% HCOOH in purified water. Mobile phase B: MeCN.

B concentration (Gradient): 0.0-20.0 min 5-90%, 20.0-25.0 min 90%, 25.0-25.1 min 90-5%, 25.1-30.0 min 5%.

Flow rate: 1.0 mL/min

Injection volume: 10 μL

Column temperature: 40°C

Wavelength: 254 nm

Sample was diluted with MeCN/H2O (80/20 (v/v)) containing 0.1 vol% of HCOOH