Supporting Information

Predicting Michael-Acceptor Reactivity and Toxicity through Quantum Chemical Transition-State Calculations

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In Tables S1-S4, all 47 α,β-unsaturated carbonyls covering 16 aldehydes, 12 ketones and 19 esters are listed with calculated ground-state energies E, reaction barriers $\Delta E^{\ddagger}$, reaction energies $\Delta_r E$, and with further calculated properties. Table S5 provides the respective single-point PCM energies, and Table S6 shows the regression statistics for predicting log k_{GSH} from calculated gas-phase Gibbs free energy barriers $\Delta G^{\ddagger}$.

For methyl thiol (CH_3SH), the ground state energy was calculated to be –1151821.5 kJ·mol^{-1}, and the Gibbs free energy was calculated to be –1151763.8 kJ·mol^{-1} at 298 K.

Table S1. Energies of Neutral and Protonated Conformers of 47 α,β-Unsaturated Carbonyls Covering 16 Aldehydes, 12 Ketones and 19 Esters.

Compound	$\Delta E(A_c)$ [kJ/mol]	$\Delta E(A_t)$ [kJ/mol]	$\Delta E(HA^+_{cs})$ [kJ/mol]	$\Delta E(HA^+_{ca})$ [kJ/mol]	$\Delta E(HA^+_{ts})$ [kJ/mol]	$\Delta E(HA^+_{ta})$ [kJ/mol]
16 α,β-unsaturated aldehydes						
acrolein	–503873.8	–503880.7	–504715.0	–504730.4	–504736.3	–504739.7
methylacrolein	–607114.1	–607126.3	–607965.3	–607979.1	–607991.3	–607995.3
2-ethylacrolein	–710337.7	–710350.0	–711195.9	–711208.7	–711221.1	–711224.1
2-butylacrolein	–916788.4	–916800.7	–917651.5	–917663.9	–917677.6	–917679.3
crotonaldehyde	–607122.6	–607128.1	–608000.1	–608016.6	–608022.1	–608024.6
trans-2-pentenal	–710347.2	–710352.7	–711231.5	–711247.1	–711252.9	–711255.0
4-methyl-2-pentenal	–813574.5	–813580.0	–814464.8	–814479.8	–814485.7	–814487.7
2-heptenal	–916799.0	–916804.5	–917691.2	–917706.3	–917712.0	–917713.9
trans-octenal	–1020024.5	–1020030.0	–1020918.2	–1020933.1	–1020938.9	–1020940.7
2-nonenal	–1123250.0	–1123255.6	–1124144.7	–1124159.5	–1124165.3	–1124167.1
trans-2-decen-1-al	–1226475.5	–1226481.1	–1227370.8	–1227385.5	–1227391.3	–1227393.1
trans-2,*cis*-6-nonadienal	–1120003.9	–1120009.4	–1120901.7	–1120916.3	–1120921.3	–1120923.2
2-methyl-2-pentenale	–813579.8	–813591.5	–814471.6	–814487.4	–814497.6	–814501.1
trans-2-methyl-2-butenal	–710355.7	–710367.4	–711239.0	–711255.0	–711268.1	–711271.7
2,4-dimethyl-2,6-heptadienal	–1120003.2	–1120014.9	–1120905.8	–1120920.6	–1120930.2	–1120933.6
3-methyl-2-butenal	–710361.1	–710360.7	–711259.6	–711277.4	–711280.4	–711281.5
12 α,β-unsaturated ketones						
3-buten-2-one	–607131.5	–607130.5	–608011.2	–608022.4	–608019.4	–608020.7
1-penten-3-one	–710360.2	–710357.9	–711245.9	–711261.4	–711251.4	–711257.3
1-hexene-3-one	–813585.4	–813583.2	–814474.6	–814491.2	–814480.1	–814487.3
1-octene-3-one	–1020036.4	–1020034.3	–1020928.8	–1020946.9	–1020934.3	–1020943.1
3-pentene-2-one	–710379.1	–710376.0	–711287.7	–711300.1	–711296.9	–711296.4
3-hepten-2-one	–916829.7	–916826.7	–917747.8	–917759.6	–917757.2	–917757.3
3-octen-2-one	–1020055.3	–1020052.3	–1020975.6	–1020987.4	–1020985.0	–1020985.0
3-nonen-2-one	–1123280.8	–1123277.8	–1124202.3	–1124213.9	–1124211.6	–1124211.6
4-hexen-3-one	–813607.5	–813603.3	–814520.3	–814536.9	–814526.9	–814531.7

2-octen-4-one	–1020058.2	–1020054.1	–1020975.7	–1020994.5	–1020987.5	–1020989.6
3-methyl-3-penten-2-one	–813605.2	–813609.9	–814521.0	–814533.5	–814535.7	–814534.9
4-methyl-3-penten-2-one	–813614.7	–813598.3	–814540.6	–814554.8	–814542.7	–814540.8
19 α,β-unsaturated esters						
methyl acrylate	–804653.9	–804650.8	–805530.9	–805524.3	–805537.3	–805523.1
propargyl acrylate	–1004545.3	–1004542.7	–1005418.2	–1005409.3	–1005425.4	–1005409.0
2-hydroxyethyl acrylate	–1105343.2	–1105340.1	–1106226.8	–1106224.6	–1106232.4	–1106222.6
ethyl acrylate	–907893.3	–907890.4	–908781.9	–908777.0	–908788.1	–908775.7
propyl acrylate	–1011118.6	–1011115.6	–1012010.4	–1012006.6	–1012016.6	–1012005.4
butyl acrylate	–1114343.8	–1114340.8	–1115237.5	–1115234.1	–1115243.7	–1115232.9
allyl acrylate	–1007858.8	–1007856.0	–1008748.6	–1008743.1	–1008755.2	–1008742.3
tert-butyl acrylate	–1114356.1	–1114353.1	–1115262.4	–1115259.0	–1115268.4	–1115257.6
propargyl methacrylate	–1107784.0	–1107784.3	–1108666.5	–1108655.6	–1108673.2	–1108655.0
methyl methacrylate	–907892.3	–907892.6	–908778.7	–908770.7	–908785.4	–908769.7
2-hydroxyethyl methacrylate	–1208581.5	–1208581.9	–1209474.1	–1209470.3	–1209480.3	–1209469.0
ethyl methacrylate	–1011131.7	–1011132.1	–1012029.1	–1012022.8	–1012035.7	–1012021.7
vinyl crotonate	–1007889.5	–1007885.8	–1008779.9	–1008781.2	–1008786.5	–1008780.1
methyl crotonate	–907900.9	–907897.1	–908800.8	–908795.3	–908809.0	–908794.2
methyl-*trans*-2-octenoate	–1320802.7	–1320798.9	–1321712.7	–1321706.0	–1321720.1	–1321704.8
trans-ethyl crotonate	–1011140.2	–1011136.5	–1012050.5	–1012046.6	–1012058.3	–1012045.2
n-butyl crotonate	–1217590.6	–1217586.9	–1218505.4	–1218503.1	–1218513.3	–1218501.8
methyl tiglate	–1011131.9	–1011130.7	–1012038.2	–1012032.2	–1012047.4	–1012031.2
methyl-3,3-dimethylacrylate	–1011137.3	–1011127.5	–1012049.2	–1012042.0	–1012057.0	–1012040.8

Table S2. 47 α,β-Unsaturated Carbonyls Covering 16 Aldehydes, 12 Ketones and 19 Esters with Information on Ground State Gibbs Free Energies of their Neutral and Protonated Conformers and the Corresponding Mole Fractions as Calculated from Equation 1. The Mole Fraction $x(A_t)$ is not given but can be calculated as $x(A_t) = 1 - x(A_c)$.

Compound	$G(A_c)$ [kJ/mol]	$G(A_t)$ [kJ/mol]	$x(A_c)$	$G(HA^+_{cs})$ [kJ/mol]	$G(HA^+_{ca})$ [kJ/mol]	$G(HA^+_{ts})$ [kJ/mol]	$G(HA^+_{ta})$ [kJ/mol]	$x(HA^+_{cs})$	$x(HA^+_{ca})$	$x(HA^+_{ts})$	$x(HA^+_{ta})$
16 α,β-unsaturated aldehydes											
acrolein	–503781.5	–503788.2	0.06	–504589.3	–504602.7	–504608.3	–504611.6	0.00	0.02	0.20	0.78
methylacrolein	–606954.8	–606966.0	0.01	–607771.4	–607786.2	–607796.0	–607800.1	0.00	0.00	0.16	0.83
2-ethylacrolein	–710107.6	–710119.1	0.01	–710937.3	–710944.2	–710955	–710958.1	0.00	0.00	0.22	0.78
2-butylacrolein	–916420.6	–916432.1	0.01	–917252.4	–917261.8	–917273.8	–917275.4	0.00	0.00	0.34	0.66
crotonaldehyde	–606962.3	–606967.8	0.10	–607806.9	–607822.3	–607827.3	–607830	0.00	0.03	0.24	0.72
trans-2-pentenal	–710117.6	–710123.2	0.10	–710969.1	–710983.7	–710989.0	–710991.4	0.00	0.03	0.26	0.70
4-methyl-2-pentenal	–813275.9	–813281.5	0.10	–814133.3	–814147.4	–814152.9	–814155.0	0.00	0.03	0.29	0.68
2-heptenal	–916431.6	–916437.1	0.10	–917290.7	–917304.7	–917310.1	–917312.1	0.00	0.03	0.29	0.67
trans-octenal	–1019588.2	–1019593.8	0.09	–1020448.7	–1020462.6	–1020467.9	–1020470	0.00	0.03	0.29	0.67
2-nonenal	–1122744.9	–1122750.2	0.10	–1123606.1	–1123620	–1123625.4	–1123627.4	0.00	0.03	0.30	0.67
trans-2-decen-1-al	–1225901.4	–1225906.8	0.10	–1226763.2	–1226777.1	–1226782.5	–1226784.5	0.00	0.03	0.30	0.66
trans-2,*cis*-6-nonadienal	–1119560.3	–1119565.7	0.10	–1120424.2	–1120437.9	–1120442.7	–1120444.8	0.00	0.04	0.29	0.67
2-methyl-2-pentenale	–813284.5	–813295.4	0.01	–814143.7	–814157.6	–814167.3	–814172.2	0.00	0.00	0.12	0.87
trans-2-methyl-2-butenal	–710129.7	–710140.5	0.01	–710978.6	–710992.4	–711006.8	–711012.6	0.00	0.00	0.09	0.91
2,4-dimethyl-2,6-heptadienal	–1119561.4	–1119572	0.01	–1120429.3	–1120442.7	–1120452.6	–1120456.6	0.00	0.00	0.17	0.83
3-methyl-2-butenal	–710133.1	–710132.2	0.59	–710997.4	–711015.3	–711019.6	–711018.4	0.00	0.10	0.56	0.34
12 α,β-unsaturated ketones											
3-buten-2-one	–606972.3	–606970.7	0.66	–607824.7	–607831.1	–607824.2	–607830.8	0.04	0.49	0.03	0.44
1-penten-3-one	–710131.4	–710128.5	0.76	–710988.4	–710998.3	–710985.2	–710994.2	0.02	0.82	0.00	0.16
1-hexene-3-one	–813287.7	–813284.9	0.75	–814151.8	–814159.4	–814144.9	–814156.0	0.03	0.77	0.00	0.20
1-octene-3-one	–1019601.0	–1019598.3	0.75	–1020465.7	–1020477.4	–1020460.9	–1020474.3	0.01	0.77	0.00	0.22

3-pentene-2-one	–710151.9	–710148.2	0.82	–711032.9	–711038.3	–711034.3	–711033.7	0.08	0.68	0.14	0.11
3-hepten-2-one	–916464.3	–916460.8	0.81	–917354.2	–917363.6	–917360.8	–917358.9	0.01	0.67	0.21	0.10
3-octen-2-one	–1019621.0	–1019617.5	0.81	–1020512.9	–1020522.1	–1020519.4	–1020517.7	0.02	0.65	0.23	0.11
3-nonen-2-one	–1122777.7	–1122774.1	0.81	–1123670.3	–1123679.6	–1123677.2	–1123675.3	0.01	0.64	0.24	0.11
4-hexen-3-one	–813310.7	–813305.9	0.88	–814193.2	–814206.8	–814192.9	–814201.8	0.00	0.88	0.00	0.12
2-octen-4-one	–1019623.7	–1019618.8	0.88	–1020511.9	–1020526.9	–1020518.5	–1020523.4	0.00	0.78	0.03	0.19
3-methyl-3-penten-2-one	–813309.6	–813314.1	0.14	–814194.5	–814206.7	–814208.7	–814204.5	0.00	0.28	0.61	0.11
4-methyl-3-penten-2-one	–813320.0	–813302.2	1.00	–814214.7	–814227.1	–814215.8	–814213.3	0.01	0.98	0.01	0.00
19 α,β-unsaturated esters											
methyl acrylate	–804483.2	–804480.3	0.76	–805329.5	–805321.1	–805333.9	–805319.7	0.14	0.00	0.85	0.00
propargyl acrylate	–1004360.5	–1004358.1	0.73	–1005204.6	–1005192.7	–1005209	–1005192.2	0.15	0.00	0.85	0.00
2-hydroxyethyl acrylate	–1105097.3	–1105094.5	0.76	–1105951.5	–1105946.6	–1105954.8	–1105944.5	0.20	0.03	0.76	0.01
ethyl acrylate	–907654.1	–907651.3	0.75	–908513.7	–908505.5	–908516.6	–908503.9	0.23	0.01	0.75	0.00
Propyl acrylate	–1010810.5	–1010807.8	0.75	–1011672.7	–1011666.1	–1011676.1	–1011664.6	0.20	0.01	0.78	0.01
butyl acrylate	–1113966.8	–1113964.1	0.75	–1114831.0	–1114824.7	–1114834.3	–1114823.3	0.21	0.02	0.77	0.01
allyl acrylate	–1007612.0	–1007609.5	0.74	–1008473.0	–1008464.0	–1008476.1	–1008463.0	0.21	0.01	0.78	0.00
tert-butyl acrylate	–1113977.1	–1113974.4	0.74	–1114859.7	–1114855.1	–1114859.2	–1114853.3	0.49	0.07	0.40	0.04
propargyl methacrylate	–1107530.7	–1107531.9	0.39	–1108382.9	–1108371.1	–1108388.3	–1108370.3	0.10	0.00	0.90	0.00
methyl methacrylate	–907653.0	–907654.1	0.38	–908504.9	–908499.4	–908513.6	–908498.2	0.03	0.00	0.97	0.00
2-hydroxyethyl methacrylate	–1208267.0	–1208268.3	0.37	–1209129.4	–1209124.2	–1209134.1	–1209122.8	0.13	0.02	0.85	0.01
ethyl methacrylate	–1010824.0	–1010825.2	0.38	–1011687.2	–1011683.2	–1011695.7	–1011681.9	0.03	0.01	0.96	0.00
vinyl crotonate	–1007642.3	–1007638.9	0.80	–1008503.1	–1008502.7	–1008508.3	–1008501.6	0.10	0.08	0.77	0.05
methyl crotonate	–907662.2	–907658.7	0.81	–908531.7	–908524.9	–908537.8	–908523.4	0.08	0.01	0.92	0.00
methyl-*trans*-2-octenoate	–1320288.0	–1320284.5	0.80	–1321167.4	–1321159.6	–1321172.9	–1321158.1	0.10	0.00	0.90	0.00
trans-ethyl crotonate	–1010833.0	–1010829.5	0.81	–1011713.5	–1011707.8	–1011719.1	–1011706.2	0.09	0.01	0.90	0.00
n-butyl crotonate	–1217145.6	–1217142.1	0.81	–1218030.7	–1218026.3	–1218036.1	–1218024.7	0.10	0.02	0.88	0.01
methyl tiglate	–1010824.8	–1010825.2	0.46	–1011697.6	–1011694.6	–1011708.2	–1011693.2	0.01	0.00	0.98	0.00

methyl-3,3-dimethylacrylate	–1010830.7	–1010822.9	0.96	–1011710.7	–1011704.3	–1011718.1	–1011702.7	0.05	0.00	0.95	0.00

Table S3. 47 α,β-Unsaturated Carbonyls Covering 16 Aldehydes, 12 Ketones and 19 Esters with Information on their Minimum Reaction Barriers, $\Delta E^{\ddagger}$, of Neutral and Protonated Conformers.

Compound	$\Delta E^{\ddagger}(A_c)$ [kJ/mol]	$\Delta E^{\ddagger}(A_t)$ [kJ/mol]	$\Delta E^{\ddagger}(HA^{+}_{cs})$ [kJ/mol]	$\Delta E^{\ddagger}(HA^{+}_{ca})$ [kJ/mol]	$\Delta E^{\ddagger}(HA^{+}_{ts})$ [kJ/mol]	$\Delta E^{\ddagger}(HA^{+}_{ta})$ [kJ/mol]
16 α,β-unsaturated aldehydes						
acrolein	187.59	191.89	7.41	5.07	24.18	24.31
methylacrolein	198.42	203.37	22.54	16.39	42.19	42.59
2-ethylacrolein	201.38	206.02	27.45	20.66	48.20	48.37
2-butylacrolein	193.74	200.56	27.74	20.85	49.17	48.85
crotonaldehyde	187.55	190.05	53.08	52.52	70.16	69.59
trans-2-pentenal	182.88	185.58	54.19	53.46	69.82	70.14
4-methyl-2-pentenal	184.99	187.41	58.79	58.02	74.51	74.68
2-heptenal	183.29	185.96	59.11	58.39	74.68	74.68
trans-octenal	183.26	185.93	59.74	59.01	75.28	75.21
2-nonenal	183.27	185.99	60.22	59.48	75.75	75.61
trans-2-decen-1-al	183.25	185.95	60.50	59.74	75.99	75.83
trans-2,*cis*-6-nonadienal	180.55	189.38	64.41	63.73	80.10	79.22
2-methyl-2-pentenale	189.17	193.55	63.75	59.89	80.98	81.11
trans-2-methyl-2-butenal	194.01	198.17	61.82	57.29	81.74	81.82
2,4-dimethyl-2,6-heptadienal	193.01	197.20	72.97	69.97	89.67	89.66
3-methyl-2-butenal	184.47	186.20	81.94	88.03	94.90	92.93
12 α,β-unsaturated ketones						
3-buten-2-one	186.91	186.53	33.18	26.59	40.39	40.72
1-penten-3-one	187.02	186.21	39.53	36.92	45.01	48.50
1-hexene-3-one	186.92	186.12	40.10	37.41	45.06	50.10

1-octene-3-one	186.88	186.10	40.54	39.28	45.89	51.79
3-pentene-2-one	185.34	182.05	71.33	66.68	80.05	78.27
3-hepten-2-one	180.78	177.71	73.58	69.40	83.01	82.07
3-octen-2-one	180.90	177.81	74.56	70.55	84.05	83.07
3-nonen-2-one	180.86	177.78	74.89	70.98	84.40	83.40
4-hexen-3-one	185.27	181.60	75.77	75.15	82.80	85.30
2-octen-4-one	185.13	181.50	75.79	76.19	87.56	87.32
3-methyl-3-penten-2-one	192.20	188.84	85.26	76.93	94.61	91.62
4-methyl-3-penten-2-one	180.37	173.74	96.66	99.36	107.57	104.18
19 α,β-unsaturated esters						
methyl acrylate	190.60	189.82	75.08	64.45	63.87	63.80
propargyl acrylate	190.98	190.72	76.57	65.95	64.73	65.05
2-hydroxyethyl acrylate	190.67	189.42	78.50	67.95	67.38	67.88
ethyl acrylate	190.37	189.40	80.77	69.80	69.04	69.29
propyl acrylate	190.35	189.38	82.31	71.36	70.32	70.68
butyl acrylate	190.33	189.37	83.24	72.27	71.10	71.62
allyl acrylate	189.99	189.26	83.31	73.87	71.32	73.34
tert-butyl acrylate	189.63	188.25	92.57	79.44	79.28	80.03
propargyl methacrylate	202.58	201.94	96.91	81.06	81.71	80.24
methyl methacrylate	202.14	200.99	95.36	80.21	82.66	79.56
2-hydroxyethyl methacrylate	202.15	200.56	98.52	83.25	86.23	83.78
ethyl methacrylate	201.84	200.54	100.81	85.21	87.67	84.87
vinyl crotonate	190.75	189.70	107.48	96.62	98.40	96.52
methyl crotonate	188.54	186.83	107.34	98.57	98.85	97.90
methyl-*trans*-2-octenoate	184.10	182.45	108.45	99.88	99.70	99.15
trans-ethyl crotonate	188.17	186.19	111.97	102.76	102.84	102.10
n-butyl crotonate	188.10	186.14	113.93	104.73	104.50	104.05
methyl tiglate	196.71	194.04	122.54	108.40	111.50	109.08
Methyl-3,3-dimethylacrylate	184.56	180.88	126.93	122.48	124.67	122.19

Table S4. 47 α,β-Unsaturated Carbonyls Covering 16 Aldehydes, 12 Ketones and 19 Esters with Information on their reaction energies, $\Delta_r E$, of Neutral and Protonated Conformers.

Compound	$\Delta_r E$ (A_c) [kJ/mol]	$\Delta_r E$ (A_t) [kJ/mol]	$\Delta_r E$ (HA^+_{cs}) [kJ/mol]	$\Delta_r E$ (HA^+_{ca}) [kJ/mol]	$\Delta_r E$ (HA^+_{ts}) [kJ/mol]	$\Delta_r E$ (HA^+_{ta}) [kJ/mol]
16 α,β-unsaturated aldehydes						
acrolein	–85.25	–78.38	–72.68	–57.28	–51.35	–48.03
methylacrolein	–69.26	–57.02	–59.30	–45.55	–33.30	–29.31
2-ethylacrolein	–64.93	–52.61	–53.74	–40.97	–28.59	–25.49
2-butylacrolein	–65.94	–53.66	–108.56	–96.14	–82.50	–80.83
crotonaldehyde	–62.67	–57.15	–18.51	–2.04	3.47	5.97
trans-2-pentenal	–60.37	–54.84	–83.98	–68.36	–62.59	–60.41
4-methyl-2-pentenal	–53.97	–48.43	–74.82	–59.88	–53.92	–52.00
2-heptenal	–53.73	–48.20	–72.29	–57.24	–51.48	–49.56
trans-octenal	–53.74	–48.20	–71.68	–56.77	–51.00	–49.14
2-nonenal	–53.71	–48.15	–71.19	–56.37	–50.61	–48.79
trans-2-decen-1-al	–50.10	–44.53	–71.22	–56.46	–50.71	–48.91
trans-2,*cis*-6-nonadienal	–58.01	–52.58	–77.08	–62.54	–57.55	–55.65
2-methyl-2-pentenale	–46.54	–34.81	–81.85	–66.07	–55.84	–52.33
trans-2-methyl-2-butenal	–46.86	–35.16	–67.55	–51.54	–38.46	–34.82
2,4-dimethyl-2,6-heptadienal	–41.40	–29.71	–68.19	–53.32	–43.72	–40.33
3-methyl-2-butenal	–35.77	–36.20	–54.96	–37.11	–34.15	–33.08
12 α,β-unsaturated ketones						
3-buten-2-one	–84.75	–85.79	–73.72	–62.45	–65.49	–64.24
1-penten-3-one	–84.00	–86.30	–75.57	–60.09	–70.15	–64.21
1-hexene-3-one	–84.04	–86.20	–77.22	–60.59	–71.65	–64.45
1-octene-3-one	–84.04	–86.22	–78.97	–60.86	–73.44	–64.60
3-pentene-2-one	–63.56	–66.67	–28.02	–15.62	–18.82	–19.38
3-hepten-2-one	–61.45	–64.47	–75.11	–63.26	–65.70	–65.60
3-octen-2-one	–61.34	–64.34	–73.93	–62.17	–64.54	–64.54
3-nonen-2-one	–61.32	–64.31	–73.46	–61.79	–64.10	–64.15

4-hexen-3-one	–63.17	–67.42	–31.16	–14.49	–24.54	–19.76
2-octen-4-one	–63.27	–67.39	–34.69	–15.90	–22.92	–20.82
3-methyl-3-penten-2-one	–52.64	–47.97	–18.32	–5.82	–3.55	–4.42
4-methyl-3-penten-2-one	–46.53	–62.90	2.15	16.35	4.23	2.38
19 α,β-unsaturated esters						
methyl acrylate	–83.56	–86.63	–77.10	–83.63	–70.64	–84.81
propargyl acrylate	–83.26	–85.86	–77.99	–86.88	–70.79	–87.25
2-hydroxyethyl acrylate	–83.71	–86.88	–77.69	–79.88	–72.01	–81.79
ethyl acrylate	–83.67	–86.62	–77.89	–82.78	–71.67	–84.09
propyl acrylate	–83.70	–86.65	–77.92	–81.70	–71.76	–82.95
butyl acrylate	–83.71	–86.65	–77.97	–81.35	–71.79	–82.56
allyl acrylate	–83.59	–86.40	–78.22	–83.74	–71.68	–84.55
tert-butyl acrylate	–83.87	–86.88	–78.93	–82.36	–72.99	–83.70
propargyl methacrylate	–67.32	–67.01	–60.98	–71.78	–54.21	–72.42
methyl methacrylate	–67.69	–67.44	–61.00	–68.95	–54.21	–69.96
2-hydroxyethyl methacrylate	–68.01	–67.62	–61.30	–65.16	–55.14	–66.45
ethyl methacrylate	–67.89	–67.52	–61.53	–67.90	–54.99	–68.97
vinyl crotonate	–61.22	–64.89	–37.48	–36.13	–30.92	–37.32
methyl crotonate	–63.48	–67.30	–39.05	–44.48	–30.87	–45.67
methyl-*trans*-2-octenoate	–61.70	–65.51	–43.35	–50.13	–36.00	–51.30
trans-ethyl crotonate	–63.76	–67.47	–40.68	–44.56	–32.82	–45.92
n-butyl crotonate	–63.83	–67.52	–41.28	–43.66	–33.40	–44.88
methyl tiglate	–51.99	–53.15	–46.79	–52.75	–37.55	–53.84
methyl-3,3-dimethylacrylate	–42.89	–52.65	–29.13	–36.24	–21.27	–37.51

Table S5. 47 α,β-Unsaturated Carbonyls Covering 16 Aldehydes, 12 Ketones and 19 Esters with Information on their Reaction Barriers, $\Delta E^{\ddagger}_{solv}$, of Protonated Conformers from single point polarisable continuum solvation model calculations.

Compound	$\Delta E^{\ddagger}_{solv}(HA^{+}_{cs})$ [kJ/mol]	$\Delta E^{\ddagger}_{solv}(HA^{+}_{ca})$ [kJ/mol]	$\Delta E^{\ddagger}_{solv}(HA^{+}_{ts})$ [kJ/mol]	$\Delta E^{\ddagger}_{solv}(HA^{+}_{ta})$ [kJ/mol]	$\Delta E^{\ddagger}_{solv}{}^{a}$ [kJ/mol]
16 α,β-unsaturated aldehydes					
acrolein	52.89	53.57	68.22	71.16	65.22
methylacrolein	66.54	63.39	81.60	89.21	78.42
2-ethylacrolein	72.64	68.80	89.59	94.85	83.53
2-butylacrolein	72.17	67.83	87.99	94.18	82.47
crotonaldehyde	94.62	91.66	107.67	109.72	104.33
trans-2-pentenal	94.27	89.37	107.02	108.92	102.56
4-methyl-2-pentenal	98.87	91.54	109.88	112.04	104.92
2-heptenal	95.35	89.42	107.62	109.46	103.38
trans-octenal	95.42	88.91	107.74	109.45	103.01
2-nonenal	94.91	89.34	107.91	109.66	103.64
trans-2-decen-1-al	95.02	89.22	107.78	109.53	103.51
trans-2,*cis*-6-nonadienal	95.09	89.80	107.73	109.79	103.29
2-methyl-2-pentenale	105.03	94.90	115.25	123.44	113.69
trans-2-methyl-2-butenal	102.76	94.63	116.92	123.64	117.26
2,4-dimethyl-2,6-heptadienal	108.55	98.62	119.09	128.63	116.98
3-methyl-2-butenal	115.20	118.64	126.36	127.78	125.53
12 α,β-unsaturated ketones					
3-buten-2-one	80.37	79.62	92.24	93.69	82.47
1-penten-3-one	84.72	74.57	95.80	92.75	82.43
1-hexene-3-one	84.56	77.14	94.99	92.52	83.37
1-octene-3-one	83.76	74.83	94.99	92.29	80.40
3-pentene-2-one	115.34	110.65	124.26	124.82	114.29
3-hepten-2-one	115.85	109.47	123.62	125.23	113.37
3-octen-2-one	115.60	108.53	123.41	125.03	113.19
3-nonen-2-one	115.85	108.51	123.76	125.27	113.04

4-hexen-3-one	118.78	105.19	126.59	123.22	113.27
2-octen-4-one	117.42	105.48	126.64	124.18	112.40
3-methyl-3-penten-2-one	129.30	120.70	131.17	137.33	122.93
4-methyl-3-penten-2-one	127.94	134.48	145.57	146.37	134.93
19 α,β-unsaturated esters					
methyl acrylate	98.83	102.82	101.10	102.03	101.08
propargyl acrylate	96.28	100.90	98.97	100.90	98.92
2-hydroxyethyl acrylate	99.92	108.01	97.77	107.24	97.81
ethyl acrylate	101.59	109.24	99.61	108.08	99.63
propyl acrylate	101.03	108.75	99.27	107.84	99.29
butyl acrylate	101.20	109.17	99.72	108.45	99.74
allyl acrylate	103.87	112.75	101.83	114.52	101.90
tert-butyl acrylate	102.46	111.20	103.02	109.60	102.99
propargyl methacrylate	114.75	114.84	107.32	113.73	109.70
methyl methacrylate	117.05	116.54	109.50	115.56	110.48
2-hydroxyethyl methacrylate	118.58	118.64	110.39	117.42	113.49
ethyl methacrylate	119.80	119.59	112.06	118.53	113.72
vinyl crotonate	132.30	125.68	125.76	125.83	125.85
methyl crotonate	131.31	132.77	131.45	132.10	131.44
methyl-*trans*-2-octenoate	138.09	131.51	130.23	131.96	130.33
trans-ethyl crotonate	134.19	135.53	133.39	134.74	133.42
n-butyl crotonate	133.28	135.22	133.15	135.32	133.16
methyl tiglate	142.15	141.07	138.75	142.11	140.09
methyl-3,3-dimethylacrylate	148.67	150.81	151.59	153.05	151.59

[a] Weighted reaction barrier calculated with equation (2)

Table S6. Regression models for predicting the logarithmic rate constant of reaction with glutathione, log k_{GSH}, of α,β-unsaturated aldehydes, esters and ketones from calculated Michael-addition Gibbs free energy barriers.[a]

Compound type	*n*	*a*	*b*	*c*	r^2	*rms*	q^2_{cv}	rms_{cv}	*F*
Log k_{GSH} [L mol^{-1} min^{-1}] = a • $\Delta G^{\ddagger}$ [kJ/mol] + b • I_α + c									
α–substituted	9	–0.0553±(0.005)	-	6.74±(0.7)	0.939	0.378	0.901	0.332	107
Not α-substituted	26	–0.0536±(0.004)	-	7.70±(0.4)	0.906	0.317	0.901	0.480	231
All	35	–0.0558±(0.005)	-	7.67±(0.7)	0.765	0.616	0.750	0.645	107
All	35	–0.0543±(0.003)	–1.17±(0.12)	7.77±(0.4)	0.936	0.327	0.930	0.424	234

[a] The parameters are: n = number of compounds; a, b, c = regression parameters; $\Delta G^{\ddagger}$ [kJ/mol] = B3LYP/6-31G**//B3LYP/6-31G** conformer-averaged protonated pathway Gibbs free energy barriers of the Michael addition of CH_3SH; I_α = indicator variable discriminating between the absence (I_α = 0) and presence (I_α = 1) of a substituent at the α-carbon of the Michael acceptor; r^2 = squared correlation coefficient, q^2_{cv} = squared predictive correlation coefficient estimated through leave-one-out cross validation,[50] *rms* = root-mean-square error, rms_{cv} = cross-validated root-mean-square error, F = F-test value referring to one ($F_{1,n-2}$) or two ($F_{2,n-3}$) regression variables.