

# Carcinogenesis of Beta-Propiolactone: A Computational Study

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Method/Basis set	$\Delta G_{gas}^{\ddagger}$ [kcal/mol] <sup>a</sup>	$\Delta\Delta G_{hydr}^{SCRF}$ [kcal/mol] <sup>b</sup>	$\Delta G_{SCRF}^{\ddagger}$ [kcal/mol] <sup>c</sup>	$\Delta G_{LD}^{\ddagger}$ [kcal/mol] <sup>d</sup>	$\Delta G_{AMSOL}^{\ddagger}$ [kcal/mol] <sup>e</sup>	$\omega^{IS}$ [i cm <sup>-1</sup> ] <sup>f</sup>	$\omega^R$ [cm <sup>-1</sup> ] <sup>g</sup>	$d^{IS}$ [Å] <sup>h</sup>	$d^R$ [Å] <sup>i</sup>
AM1	46,16	-	-	-	26,48	772	18	1,88	2,90
PM3	36,24	-	-	-	22,89	357	10	1,57	3,85
HF/6-31 G(d)	59,20	-11,00	48,20	41,57	-	263	19	1,56	3,06
HF/6-31+ G(d,p)	58,24	-11,87	46,37	38,94	-	298	17	1,56	3,11
HF/6-311++ G(d,p)	58,65	-11,54	47,11	39,96	-	309	16	1,57	3,13
B3LYP/6-31 G(d)	46,70	-8,18	38,52	34,57	-	281	20	1,57	3,01
B3LYP/6-31+ G(d,p)	45,27	-9,50	35,77	29,06	-	217	7	1,57	3,11
B3LYP/6-311++ G(d,p)	45,07	-9,52	35,55	28,83	-	188	10	1,59	3,10
MP2/6-31 G(d)	57,67	-19,47	38,20	40,37	-	389	10	1,56	2,86
MP2/6-31+ G(d,p)	55,40	-22,10	33,30	35,04	-	272	13	1,56	3,23
MP2/6-311++G(d,p)	54,62	-15,79	38,83	34,00	-	298	18	1,56	3,24
M06-2X/6-31 G(d)	48,29	-9,43	38,86	34,86	-	327	26	1,55	2,80
M06-2X/6-31+ G(d,p)	46,86	-10,69	36,17	29,84	-	320	19	1,56	2,81
M06-2X/6-311++ G(d,p)	47,32	-10,88	36,44	29,95	-	285	20	1,57	2,82
mPWPW91/6-31 G(d)	48,08	-9,19	38,89	34,28	-	259	20	1,53	2,93
mPWPW91/6-31+G(d,p)	46,67	-10,17	36,50	30,02	-	252	16	1,53	2,98
mPWPW91/6-311++ G(d,p)	46,67	-10,31	36,36	29,81	-	225	15	1,54	2,98

<sup>a</sup> Gas-phase activation energy. <sup>b</sup> Hydration free energy of the transition state minus hydration free energy of the reactant state obtained by the SCRF method. <sup>c</sup> Activation free energy obtained by the SCRF method. <sup>d</sup> Activation free energy obtained by the LD method. <sup>e</sup> Activation free energy obtained by the AM1-SM1 and PM3 SM3 methods. <sup>f</sup> The imaginary frequency corresponding to the transition state. <sup>g</sup> The lowest vibrational frequency corresponding to the reactant state. <sup>h</sup> The distance between the reacting N7 atom of methylguanine and the BPL carbonyl carbon atom in the transition state structure. <sup>i</sup> The distance between the reacting N7 atom of methylguanine and the BPL carbonyl carbon atom in the reactant state structure.

**Table S2.** The calculated activation parameters for the alkylation of methyladenine with BPL in the gas phase and solvated with the SCRF, LD and AMSOL models, lowest vibrational frequencies of reactant states, imaginary vibrational frequencies of transition states, and corresponding distances between the reactive centers.

Method/Basis set	$\Delta G_{gas}^{\ddagger}$ [kcal/mol] <sup>a</sup>	$\Delta\Delta G_{hydr}^{SCRF}$ [kcal/mol] <sup>b</sup>	$\Delta G_{SCRF}^{\ddagger}$ [kcal/mol] <sup>c</sup>	$\Delta G_{LD}^{\ddagger}$ [kcal/mol] <sup>d</sup>	$\Delta G_{AMSOL}^{\ddagger}$ [kcal/mol] <sup>e</sup>	$\omega^{TS}$ [i cm <sup>-1</sup> ] <sup>f</sup>	$\omega^R$ [cm <sup>-1</sup> ] <sup>g</sup>	$d^{TS}$ [Å] <sup>h</sup>	$d^R$ [Å] <sup>i</sup>
AM1	51,68	-	-	-	34,92	804	7	1,90	3,55
PM3	54,29	-	-	-	29,95	800	11	1,85	3,91
HF/6-31 G(d)	47,14	-17,52	29,62	22,71	-	619	17	1,99	3,44
HF/6-31+ G(d,p)	44,72	-18,30	26,42	19,16	-	609	18	2,02	3,49
HF/6-311++ G(d,p)	45,12	-20,72	26,98	19,54	-	609	17	2,02	3,50
B3LYP/6-31 G(d)	38,00	-15,56	22,44	13,88	-	487	18	1,92	3,33
B3LYP/6-31+ G(d,p)	34,50	-16,32	18,18	8,35	-	491	12	1,96	3,46
B3LYP/6-311++ G(d,p)	34,13	-16,16	17,97	8,42	-	486	12	1,97	3,44
MP2/6-31 G(d)	46,75	-21,07	25,68	21,97	-	651	13	2,02	3,22
MP2/6-31+ G(d,p)	44,10	-22,57	21,53	17,58	-	647	11	2,02	3,25
MP2/6-311++G(d,p)	44,23	-21,07	23,16	18,29	-	670	9	2,02	3,23
M06-2X/6-31 G(d)	42,26	-15,28	26,98	19,26	-	627	27	1,87	3,13
M06-2X/6-31+ G(d,p)	39,28	-15,74	23,54	15,24	-	626	23	1,90	3,15
M06-2X/6-311++ G(d,p)	39,08	-15,75	23,33	15,01	-	633	8	1,91	3,16
mPWPW91/6-31 G(d)	41,10	-15,50	25,60	18,07	-	609	19	1,89	3,27
mPWPW91/6-31+G(d,p)	38,43	-15,90	22,53	13,71	-	615	9	1,92	3,36
mPWPW91/6-311++ G(d,p)	38,27	-15,74	22,53	14,00	-	615	10	1,92	3,36

<sup>a</sup> Gas-phase activation energy. <sup>b</sup> Hydration free energy of the transition state minus hydration free energy of the reactant state obtained by the SCRF method. <sup>c</sup> Activation free energy obtained by the SCRF method. <sup>d</sup> Activation free energy obtained by the LD method. <sup>e</sup> Activation free energy obtained by the AM1-SM1 and PM3-SM3 methods. <sup>f</sup> The imaginary frequency corresponding to the transition state. <sup>g</sup> The lowest vibrational frequency corresponding to the reactant state. <sup>h</sup> The distance between the reacting N1 atom of methyladenine and the BPL  $\beta$  carbon atom in the transition state structure. <sup>i</sup> The distance between the reacting N1 atom of methyladenine and the BPL  $\beta$  carbon atom in the reactant state structure.

**Table S3.** The calculated activation parameters for the acylation of methyladenine with BPL in the gas phase and solvated with the SCRf, LD and AMSOL models, lowest vibrational frequencies of reactant states, imaginary vibrational frequencies of transition states, and corresponding distances between the reactive centers.

Method/Basis set	$\Delta G_{gas}^\ddagger$ [kcal/mol] <sup>a</sup>	$\Delta\Delta G_{hydr}^{SCRf}$ [kcal/mol] <sup>b</sup>	$\Delta G_{SCRf}^\ddagger$ [kcal/mol] <sup>c</sup>	$\Delta G_{LD}^\ddagger$ [kcal/mol] <sup>d</sup>	$\Delta G_{AMSOL}^\ddagger$ [kcal/mol] <sup>e</sup>	$\omega^{IS}$ [i cm <sup>-1</sup> ] <sup>f</sup>	$\omega^R$ [cm <sup>-1</sup> ] <sup>g</sup>	$d^{IS}$ [Å] <sup>h</sup>	$d^R$ [Å] <sup>i</sup>
AM1	41,41	-	-	44,96	31,28	347	7	1,51	3,86
PM3	35,91	-	-	45,84	30,95	342	11	1,58	3,98
HF/6-31 G(d)	53,77	-4,39	49,38	45,93	-	360	17	1,58	3,56
HF/6-31+ G(d,p)	52,99	-4,54	48,45	30,05	-	387	18	1,58	3,74
HF/6-311++ G(d,p)	53,23	-4,57	48,66	29,20	-	372	17	1,58	3,73
B3LYP/6-31 G(d)	33,22	-3,07	30,15	29,72	-	498	18	1,63	3,69
B3LYP/6-31+ G(d,p)	33,06	-3,01	30,05	50,31	-	457	12	1,63	4,36
B3LYP/6-311++ G(d,p)	33,57	-2,98	30,59	48,35	-	453	12	1,65	4,35
MP2/6-31 G(d)	52,54	-23,66	28,88	49,62	-	793	13	1,63	3,02
MP2/6-31+ G(d,p)	50,96	-24,05	26,91	30,43	-	663	11	1,61	3,07
MP2/6-311++G(d,p)	51,84	-24,37	27,47	28,40	-	681	9	1,61	3,02
M06-2X/6-31 G(d)	32,79	-3,22	29,57	29,23	-	711	27	1,63	3,05
M06-2X/6-31+ G(d,p)	31,60	-3,55	28,05	29,95	-	699	23	1,63	3,05
M06-2X/6-311++ G(d,p)	32,30	-3,61	28,69	28,33	-	692	8	1,64	3,03
mPWPW91/6-31 G(d)	33,93	-3,54	30,39	29,24	-	701	19	1,56	3,56
mPWPW91/6-31+G(d,p)	32,75	-3,50	29,25	44,96	-	720	9	1,56	4,04
mPWPW91/6-311++ G(d,p)	33,39	-3,51	29,88	45,84	-	681	10	1,57	3,99

<sup>a</sup> Gas-phase activation energy. <sup>b</sup> Hydration free energy of the transition state minus hydration free energy of the reactant state obtained by the SCRf method. <sup>c</sup> Activation free energy obtained by the SCRf method. <sup>d</sup> Activation free energy obtained by the LD method. <sup>e</sup> Activation free energy obtained by the AM1-SM1 and PM3-SM3 methods. <sup>f</sup> The imaginary frequency corresponding to the transition state. <sup>g</sup> The lowest vibrational frequency corresponding to the reactant state. <sup>h</sup> The distance between the reacting N1 atom of methyladenine and the BPL carbonyl carbon atom in the transition state structure. <sup>i</sup> The distance between the reacting N1 atom of methyladenine and the BPL carbonyl carbon atom in the reactant state structure.

**Table S4.** The calculated activation parameters for the alkylation of methycytosine with BPL in the gas phase and solvated with the SCRf, LD and AMSOL models, lowest vibrational frequencies of reactant states, imaginary vibrational frequencies of transition states, and corresponding distances between the reactive centers.

Method/Basis set	$\Delta G_{gas}^\ddagger$ [kcal/mol] <sup>a</sup>	$\Delta\Delta G_{hydr}^{SCRf}$ [kcal/mol] <sup>b</sup>	$\Delta G_{SCRf}^\ddagger$ [kcal/mol] <sup>c</sup>	$\Delta G_{LD}^\ddagger$ [kcal/mol] <sup>d</sup>	$\Delta G_{AMSOL}^\ddagger$ [kcal/mol] <sup>e</sup>	$\omega^{IS}$ [i cm <sup>-1</sup> ] <sup>f</sup>	$\omega^R$ [cm <sup>-1</sup> ] <sup>g</sup>	$d^{IS}$ [Å] <sup>h</sup>	$d^R$ [Å] <sup>i</sup>
AM1	52,98	-	-	-	36,67	778	19	1,92	6,77
PM3	56,03	-	-	-	19,13	784	13	1,85	4,62
HF/6-31 G(d)	49,18	-21,44	27,74	19,29	-	576	18	1,99	3,62
HF/6-31+ G(d,p)	46,84	-22,31	24,53	13,14	-	561	28	2,02	3,66
HF/6-311++ G(d,p)	47,11	-21,96	25,15	13,87	-	562	29	2,03	3,69
B3LYP/6-31 G(d)	41,06	-19,56	21,50	10,84	-	486	29	1,91	3,55
B3LYP/6-31+ G(d,p)	37,37	-20,40	16,97	4,22	-	487	26	1,95	3,61
B3LYP/6-311++ G(d,p)	36,79	-20,13	16,66	3,86	-	481	29	1,96	3,62
MP2/6-31 G(d)	49,74	-25,27	24,47	17,09	-	653	11	1,88	3,43
MP2/6-31+ G(d,p)	47,29	-27,21	20,08	12,36	-	650	21	1,90	3,41
MP2/6-311++G(d,p)	47,88	-26,12	21,76	13,73	-	673	21	1,90	3,40
M06-2X/6-31 G(d)	45,74	-18,98	26,76	17,46	-	624	27	1,88	3,20
M06-2X/6-31+ G(d,p)	42,94	-19,76	23,18	12,37	-	629	32	1,91	3,23
M06-2X/6-311++ G(d,p)	42,58	-19,50	23,08	12,53	-	638	28	1,91	3,25
mPWPW91/6-31 G(d)	44,15	-19,46	24,69	15,25	-	601	13	1,90	3,47
mPWPW91/6-31+G(d,p)	41,65	-20,21	21,44	10,49	-	605	22	1,92	3,50
mPWPW91/6-311++ G(d,p)	41,37	-19,94	21,43	10,31	-	606	21	1,93	3,52

<sup>a</sup> Gas-phase activation energy. <sup>b</sup> Hydration free energy of the transition state minus hydration free energy of the reactant state obtained by the SCRf method. <sup>c</sup> Activation free energy obtained by the SCRf method. <sup>d</sup> Activation free energy obtained by the LD method. <sup>e</sup> Activation free energy obtained by the AM1-SM1 and PM3-SM3 methods. <sup>f</sup> The imaginary frequency corresponding to the transition state. <sup>g</sup> The lowest vibrational frequency corresponding to the reactant state. <sup>h</sup> The distance between the reacting N3 atom of methycytosine and the BPL  $\beta$  carbon atom in the transition state structure. <sup>i</sup> The distance between the reacting N3 atom of methycytosine and the BPL  $\beta$  carbon atom in the reactant state structure.

**Table S5.** The calculated activation parameters for the acylation of methycytosine with BPL in the gas phase and solvated with the SCRf, LD and AMSOL models, lowest vibrational frequencies of reactant states, imaginary vibrational frequencies of transition states, and corresponding distances between the reactive centers.

Method/Basis set	$\Delta G_{gas}^\ddagger$ [kcal/mol] <sup>a</sup>	$\Delta\Delta G_{hydr}^{SCRf}$ [kcal/mol] <sup>b</sup>	$\Delta G_{SCRf}^\ddagger$ [kcal/mol] <sup>c</sup>	$\Delta G_{LD}^\ddagger$ [kcal/mol] <sup>d</sup>	$\Delta G_{AMSOL}^\ddagger$ [kcal/mol] <sup>e</sup>	$\omega^{IS}$ [i cm <sup>-1</sup> ] <sup>f</sup>	$\omega^R$ [cm <sup>-1</sup> ] <sup>g</sup>	$d^{IS}$ [Å] <sup>h</sup>	$d^R$ [Å] <sup>i</sup>
AM1	39,92	-	-	-	15,99	259	24	1,51	2,87
PM3	35,68	-	-	-	18,60	361	13	1,62	3,72
HF/6-31 G(d)	55,28	-6,53	48,75	44,59	-	458	18	1,69	3,16
HF/6-31+ G(d,p)	54,85	-6,82	48,03	43,14	-	479	28	1,67	3,18
HF/6-311++ G(d,p)	54,88	-6,28	48,60	44,49	-	480	29	1,71	3,19
B3LYP/6-31 G(d)	35,31	-4,48	30,83	30,59	-	763	29	1,78	3,12
B3LYP/6-31+ G(d,p)	34,87	-4,51	30,36	29,11	-	647	26	1,78	3,15
B3LYP/6-311++ G(d,p)	34,52	-4,22	30,30	29,77	-	685	29	1,82	3,15
MP2/6-31 G(d)	57,25	-28,95	28,30	51,87	-	973	11	1,79	2,99
MP2/6-31+ G(d,p)	55,73	-30,10	25,63	54,72	-	814	21	1,78	2,97
MP2/6-311++G(d,p)	56,35	-30,47	25,88	51,76	-	868	21	1,83	2,97
M06-2X/6-31 G(d)	34,56	-4,59	29,97	29,23	-	737	27	1,76	2,86
M06-2X/6-31+ G(d,p)	33,75	-5,10	28,65	27,42	-	724	32	1,75	2,90
M06-2X/6-311++ G(d,p)	33,91	-4,45	29,46	29,10	-	758	28	1,79	2,90
mPWPW91/6-31 G(d)	37,47	-5,91	31,56	29,68	-	762	13	1,68	3,04
mPWPW91/6-31+G(d,p)	36,42	-6,22	30,20	27,48	-	704	22	1,66	3,05
mPWPW91/6-311++ G(d,p)	36,45	-5,94	30,51	27,91	-	694	21	1,68	3,06

<sup>a</sup> Gas-phase activation energy. <sup>b</sup> Hydration free energy of the transition state minus hydration free energy of the reactant state obtained by the SCRf method. <sup>c</sup> Activation free energy obtained by the SCRf method. <sup>d</sup> Activation free energy obtained by the LD method. <sup>e</sup> Activation free energy obtained by the AM1-SM1 and PM3-SM3 methods. <sup>f</sup> The imaginary frequency corresponding to the transition state. <sup>g</sup> The lowest vibrational frequency corresponding to the reactant state. <sup>h</sup> The distance between the reacting N3 atom of methycytosine and the BPL carbonyl carbon atom in the transition state structure. <sup>i</sup> The distance between the reacting N3 atom of methycytosine and the BPL carbonyl carbon atom in the reactant state structure.



**Table S6.** The calculated activation parameters for the alkylation of methythymine with BPL in the gas phase and solvated with the SCRf, LD and AMSOL models, lowest vibrational frequencies of reactant states, imaginary vibrational frequencies of transition states, and corresponding distances between the reactive centers.

Method/Basis set	$\Delta G_{gas}^\ddagger$ [kcal/mol] <sup>a</sup>	$\Delta\Delta G_{hydr}^{SCRf}$ [kcal/mol] <sup>b</sup>	$\Delta G_{SCRf}^\ddagger$ [kcal/mol] <sup>c</sup>	$\Delta G_{LD}^\ddagger$ [kcal/mol] <sup>d</sup>	$\Delta G_{AMSOL}^\ddagger$ [kcal/mol] <sup>e</sup>	$\omega^{IS}$ [i cm <sup>-1</sup> ] <sup>f</sup>	$\omega^R$ [cm <sup>-1</sup> ] <sup>g</sup>	$d^{IS}$ [Å] <sup>h</sup>	$d^R$ [Å] <sup>i</sup>
AM1	66,96	-	-	-	29,76	788	13	1,89	4,43
PM3	94,60	-	-	-	58,17	773	18	1,85	4,75
HF/6-31 G(d)	71,71	-24,19	47,52	41,51	-	560	28	1,97	3,63
HF/6-31+ G(d,p)	66,91	-25,09	41,82	34,01	-	543	28	2,00	3,67
HF/6-311++ G(d,p)	67,16	-24,55	42,61	34,25	-	542	29	2,01	3,70
B3LYP/6-31 G(d)	60,38	-20,67	39,71	31,57	-	479	18	1,89	3,54
B3LYP/6-31+ G(d,p)	55,01	-21,84	33,17	22,46	-	478	24	1,89	3,63
B3LYP/6-311++ G(d,p)	54,71	-21,52	33,19	22,98	-	473	24	1,94	3,64
MP2/6-31 G(d)	72,23	-29,91	42,32	40,25	-	648	26	1,97	3,40
MP2/6-31+ G(d,p)	66,98	-32,07	34,91	33,09	-	647	29	1,85	3,39
MP2/6-311++G(d,p)	67,61	-31,77	35,84	34,69	-	670	29	1,88	3,39
M06-2X/6-31 G(d)	64,34	-20,83	43,51	37,05	-	634	30	1,86	3,28
M06-2X/6-31+ G(d,p)	59,54	-21,58	37,96	29,66	-	641	25	1,89	3,33
M06-2X/6-311++ G(d,p)	59,58	-21,23	38,35	28,62	-	648	24	1,90	3,37
mPWPW91/6-31 G(d)	64,52	-19,75	44,77	36,33	-	596	26	1,87	3,46
mPWPW91/6-31+G(d,p)	59,89	-20,56	39,33	29,05	-	600	23	1,90	3,50
mPWPW91/6-311++ G(d,p)	59,76	-20,15	39,61	27,97	-	601	23	1,91	3,53

<sup>a</sup> Gas-phase activation energy. <sup>b</sup> Hydration free energy of the transition state minus hydration free energy of the reactant state obtained by the SCRf method. <sup>c</sup> Activation free energy obtained by the SCRf method. <sup>d</sup> Activation free energy obtained by the LD method. <sup>e</sup> Activation free energy obtained by the AM1-SM1 and PM3-SM3 methods. <sup>f</sup> The imaginary frequency corresponding to the transition state. <sup>g</sup> The lowest vibrational frequency corresponding to the reactant state. <sup>h</sup> The distance between the reacting N3 atom of methythymine and the BPL β carbon atom in the transition state structure. <sup>i</sup> The distance between the reacting N3 atom of methythymine and the BPL β carbon atom in the reactant state structure.

**Table S7.** The calculated activation parameters for the acylation of methythymine with BPL in the gas phase and solvated with the SCRf and LD and AMSOL models, lowest vibrational frequencies of reactant states, imaginary vibrational frequencies of transition states, and corresponding distances between the reactive centers.

Method/Basis set	$\Delta G_{gas}^\ddagger$ [kcal/mol] <sup>a</sup>	$\Delta\Delta G_{hydr}^{SCRf}$ [kcal/mol] <sup>b</sup>	$\Delta G_{SCRf}^\ddagger$ [kcal/mol] <sup>c</sup>	$\Delta G_{LD}^\ddagger$ [kcal/mol] <sup>d</sup>	$\Delta G_{AMSOL}^\ddagger$ [kcal/mol] <sup>e</sup>	$\omega^{IS}$ [i cm <sup>-1</sup> ] <sup>f</sup>	$\omega^R$ [cm <sup>-1</sup> ] <sup>g</sup>	$d^{IS}$ [Å] <sup>h</sup>	$d^R$ [Å] <sup>i</sup>
AM1	75,32	-	-	-	41,81	314	13	1,53	3,20
PM3	96,20	-	-	-	78,08	471	18	1,59	3,47
HF/6-31 G(d)	104,01	-16,41	87,60	83,93	-	560	28	1,57	3,02
HF/6-31+ G(d,p)	100,53	-18,06	82,47	76,63	-	289	28	1,56	3,05
HF/6-311++ G(d,p)	100,17	-17,71	82,46	76,27	-	298	29	1,57	3,06
B3LYP/6-31 G(d)	82,38	-9,34	73,04	70,31	-	304	18	1,60	2,96
B3LYP/6-31+ G(d,p)	80,18	-10,64	69,54	64,78	-	272	24	1,59	3,00
B3LYP/6-311++ G(d,p)	79,80	-10,76	69,04	64,26	-	253	24	1,60	3,02
MP2/6-31 G(d)	108,61	-39,47	69,14	92,31	-	385	26	1,61	2,85
MP2/6-31+ G(d,p)	104,82	-42,60	62,22	86,21	-	363	29	1,61	2,86
MP2/6-311++G(d,p)	104,66	-42,88	61,78	86,46	-	379	29	1,59	2,86
M06-2X/6-31 G(d)	80,98	-10,34	70,64	68,70	-	371	30	1,59	2,79
M06-2X/6-31+ G(d,p)	78,45	-11,21	67,24	63,67	-	359	25	1,58	2,83
M06-2X/6-311++ G(d,p)	78,64	-11,45	67,19	62,45	-	346	24	1,59	2,83
mPWPW91/6-31 G(d)	85,50	-9,28	76,22	72,65	-	354	26	1,55	2,87
mPWPW91/6-31+G(d,p)	82,85	-10,12	72,73	67,09	-	342	23	1,54	2,90
mPWPW91/6-311++ G(d,p)	82,62	-10,32	72,30	65,07	-	308	23	1,55	2,91

<sup>a</sup> Gas-phase activation energy. <sup>b</sup> Hydration free energy of the transition state minus hydration free energy of the reactant state obtained by the SCRf method. <sup>c</sup> Activation free energy obtained by the SCRf method. <sup>d</sup> Activation free energy obtained by the LD method. <sup>e</sup> Activation free energy obtained by the AM1-SM1 and PM3-SM3 methods. <sup>f</sup> The imaginary frequency corresponding to the transition state. <sup>g</sup> The lowest vibrational frequency corresponding to the reactant state. <sup>h</sup> The distance between the reacting N3 atom of methythymine and the BPL carbonyl carbon atom in the transition state structure. <sup>i</sup> The distance between the reacting N3 atom of methythymine and the BPL carbonyl carbon atom in the reactant state structure.

**Table S8.** The calculated activation parameters for the glutathione alkylation with BPL in the gas phase and solvated with the SCRF and LD models, lowest vibrational frequencies of reactant states, imaginary vibrational frequencies of transition states, and corresponding distances between the reactive centers.

Method/Basis set	$\Delta G_{gas}^\ddagger$ [kcal/mol] <sup>a</sup>	$\Delta\Delta G_{hydr}^{SCRF}$ [kcal/mol] <sup>b</sup>	$\Delta G_{SCRF}^\ddagger$ [kcal/mol] <sup>c</sup>	$\Delta G_{LD}^\ddagger$ [kcal/mol] <sup>d</sup>	$\omega^{IS}$ [i cm <sup>-1</sup> ] <sup>e</sup>	$\omega^R$ [cm <sup>-1</sup> ] <sup>f</sup>	$d^{IS}$ [Å] <sup>g</sup>	$d^R$ [Å] <sup>h</sup>
HF/6-31 G(d)	22,55	-0,35	22,20	22,78	619	12	2,55	3,93
HF/6-31+ G(d,p)	20,37	-1,44	18,93	19,51	617	10	2,58	4,10
HF/6-311++ G(d,p)	20,85	-1,61	19,24	18,78	629	10	2,58	4,08
B3LYP/6-31 G(d)	15,95	1,31	17,26	18,78	435	13	2,61	3,73
B3LYP/6-31+ G(d,p)	1,98	3,18	5,16	5,20	443	12	2,63	3,83
B3LYP/6-311++ G(d,p)	1,78	3,21	4,99	5,28	443	12	2,64	3,81
MP2/6-31 G(d)	23,16	0,18	23,33	25,80	583	13	2,55	3,64
MP2/6-31+ G(d,p)	22,55	-3,64	18,91	19,75	585	10	2,47	3,93
MP2/6-311++G(d,p)*	22,00	2,01	24,01	22,84	585	10	2,47	3,93
M06-2X/6-31 G(d)	23,57	2,15	25,72	27,63	549	16	2,46	3,81
M06-2X/6-31+ G(d,p)	20,62	1,00	21,62	30,00	564	14	2,48	3,70
M06-2X/6-311++ G(d,p)	20,37	1,37	21,74	22,79	571	16	2,48	3,68
mPWPW91/6-31 G(d)	20,44	0,81	21,25	22,54	552	13	2,49	3,68
mPWPW91/6-31+G(d,p)	18,16	-0,32	17,84	18,51	561	13	2,51	3,74
mPWPW91/6-311++ G(d,p)	18,38	0,44	17,94	19,80	566	12	2,51	3,72

<sup>a</sup> Gas-phase activation energy. <sup>b</sup> Hydration free energy of the transition state minus hydration free energy of the reactant state obtained by the SCRF method. <sup>c</sup> Activation free energy obtained by the SCRF method. <sup>d</sup> Activation free energy obtained by the LD method. <sup>e</sup> The imaginary frequency corresponding to the transition state. <sup>f</sup> The lowest vibrational frequency corresponding to the reactant state. <sup>g</sup> The distance between the reacting sulfur atom of deprotonated glutathione and BPL  $\beta$  carbon atom in the transition state structure. <sup>h</sup> The distance between the reacting sulfur atom of deprotonated glutathione and the BPL  $\beta$  carbon atom in the reactant state structure. \* Activation free energy of alkylation obtained by the SCRF method with single point calculation from MP2 6-31+G(d,p) structure.

**Table S9.** The calculated activation parameters for the glutathione acylation with BPL in the gas phase and solvated with the SCRF and LD models, lowest vibrational frequencies of reactant states, imaginary vibrational frequencies of transition states, and corresponding distances between the reactive centers.

Method/Basis set	$\Delta G_{gas}^\ddagger$ [kcal/mol] <sup>a</sup>	$\Delta\Delta G_{hydr}^{SCRF}$ [kcal/mol] <sup>b</sup>	$\Delta G_{SCRF}^\ddagger$ [kcal/mol] <sup>c</sup>	$\Delta G_{LD}^\ddagger$ [kcal/mol] <sup>d</sup>	$\omega^{IS}$ [i cm <sup>-1</sup> ] <sup>e</sup>	$\omega^R$ [cm <sup>-1</sup> ] <sup>f</sup>	$d^{IS}$ [Å] <sup>g</sup>	$d^R$ [Å] <sup>h</sup>
HF/6-31 G(d)	37,44	-4,56	32,88	29,86	387	12	1,89	5,02
HF/6-31+ G(d,p)	35,21	-5,35	29,86	27,07	410	10	1,88	5,11
HF/6-311++ G(d,p)	35,14	-5,23	29,91	25,90	414	10	1,89	5,10
B3LYP/6-31 G(d)	23,07	-4,27	18,80	16,11	166	13	1,54	4,84
B3LYP/6-31+ G(d,p)	8,54	-0,98	7,56	7,00	173	12	1,95	4,88
B3LYP/6-311++ G(d,p)	8,53	-0,98	7,55	7,20	148	12	1,98	4,87
MP2/6-31 G(d)	36,30	-22,33	13,97	31,66	240	13	1,89	4,71
MP2/6-31+ G(d,p)	35,37	-27,71	7,66	24,96	224	10	1,90	4,91
MP2/6-311++G(d,p)	35,16	-25,34	9,82	24,91	224	10	1,90	4,91
M06-2X/6-31 G(d)	25,97	-4,99	20,98	19,81	246	16	1,89	4,74
M06-2X/6-31+ G(d,p)	22,99	-6,66	16,33	22,99	237	14	1,89	4,68
M06-2X/6-311++ G(d,p)	22,92	-6,56	16,36	15,26	239	16	1,90	4,66
mPWPW91/6-31 G(d)	25,13	-4,93	20,20	17,35	233	13	1,87	4,77
mPWPW91/6-31+G(d,p)	9,72	-1,14	8,58	7,86	263	13	1,87	4,78
mPWPW91/6-311++ G(d,p)	9,91	-1,05	8,86	8,05	261	12	1,88	4,76

<sup>a</sup> Gas-phase activation energy. <sup>b</sup> Hydration free energy of the transition state minus hydration free energy of the reactant state obtained by the SCRF method. <sup>c</sup> Activation free energy obtained by the SCRF method. <sup>d</sup> Activation free energy obtained by the LD method. <sup>e</sup> The imaginary frequency corresponding to the transition state. <sup>f</sup> The lowest vibrational frequency corresponding to the reactant state. <sup>g</sup> The distance between the reacting sulfur atom of deprotonated glutathione and BPL carbonyl carbon atom, in the transition state structure. <sup>h</sup> The distance between the reacting sulfur atom of deprotonated glutathione and the BPL carbonyl carbon atom in the reactant state structure. \* Activation free energy of alkylation obtained by the SCRF method with single point calculation from MP2 6-31+G(d,p) structure.

**Table S10.** The comparison of the activation free energies for BPL alkylation of the two thymine tautomeric forms used in our calculations.

Method/Basis set	Thymine lactam tautomeric form [kcal/mol]			Thymine lactim tautomeric form [kcal/mol]		
	$\Delta G_{gas}^{\ddagger}$ <sup>a</sup>	$\Delta G_{SCRF}^{\ddagger}$ <sup>b</sup>	$\Delta G_{LD}^{\ddagger}$ <sup>c</sup>	$\Delta G_{gas}^{\ddagger}$ <sup>a</sup>	$\Delta G_{SCRF}^{\ddagger}$ <sup>b</sup>	$\Delta G_{LD}^{\ddagger}$ <sup>c</sup>
AM1	66,96	-	-	54,39	-	-
PM3	94,60	-	-	60,79	-	-
HF/6-31 G(d)	71,71	47,52	41,51	55,70	33,14	40,03
HF/6-31+ G(d,p)	66,91	41,82	34,01	52,90	29,25	32,66
HF/6-311++ G(d,p)	67,16	42,61	34,25	52,93	29,75	32,95
B3LYP/6-31 G(d)	60,38	39,71	31,57	46,70	27,37	30,46
B3LYP/6-31+ G(d,p)	55,01	33,17	22,46	42,82	22,17	21,54
B3LYP/6-311++ G(d,p)	54,71	33,19	22,98	42,05	21,72	22,09
MP2/6-31 G(d)	72,23	42,32	40,25	56,36	30,29	39,32
MP2/6-31+ G(d,p)	66,98	34,91	33,09	53,49	25,16	31,92
MP2/6-311++ G(d,p)	67,61	35,84	34,69	53,83	26,68	33,47
M06-2X/6-31 G(d)	64,34	43,51	37,05	51,90	32,52	35,34
M06-2X/6-31+ G(d,p)	59,54	37,96	29,66	42,76	28,47	28,14
M06-2X/6-311++ G(d,p)	59,58	38,35	28,62	48,25	28,34	28,62
mPWPW91/6-31 G(d)	64,52	44,77	36,33	50,41	30,85	34,56
mPWPW91/6-31+G(d,p)	59,89	39,33	29,05	47,59	27,09	27,50
mPWPW91/6-311++ G(d,p)	59,76	39,61	27,97	47,06	26,97	27,97

<sup>a</sup> Gas-phase activation energy. <sup>b</sup> Activation free energy obtained by the SCRF-PCM method. <sup>c</sup> Activation free energy obtained by the LD method.

**Table S11.** Absolute energies and Cartesian atomic coordinates for the alkylation reaction of methylguanine at the M06-2X/6-311++G(d,p) level of theory

$E^\ddagger$ [hartree]	Cartesian atomic coordinates (Å)			
	Atom	x	y	z

Transition state	- 848,886				
		N	- 0.302393	0.357592	0.222139
		C	-0.302257	0.061376	1.558216
		C	0.978968	0.321505	2.004169
		N	1.746122	0.766541	0.954191
		C	0.956960	0.777742	-0.090018
		C	1.305858	0.089577	3.386429
		N	0.148098	0.388566	4.066099
		C	-1.088574	0.601451	3.516323
		N	-1.369818	0.384034	2.259091
		O	2.346469	0.233947	3.972955
		N	-2.045660	1.107351	4.341771
		C	-1.446541	0.234760	-0.669256
		H	0.316369	0.629133	5.035368
		H	1.244807	1.077491	-1.086028
		H	-1.977746	0.955302	5.335077
		H	-2.976716	1.120552	3.955036
		H	-1.138271	0.529690	-1.670351
		H	-1.793464	0.797703	-0.679626
		H	-2.251214	0.883366	-0.325296
		H	3.891834	0.287725	1.400157
		C	3.592563	1.255251	1.029093
		H	3.420332	2.020158	1.769757
		H	3.703531	0.798835	-1.101620
		O	5.556984	1.793135	1.017606
		C	3.835270	1.629986	-0.406667
		C	5.327427	1.994506	-0.223342
		O	6.045726	2.379394	-1.121232
		H	3.247797	2.489525	-0.734831

Reactant state	- 848,950	N	-0.047740	-0.009359	0.225886
		C	-0.202011	0.147300	1.570976
		C	0.824811	0.989188	1.965734
		N	1.601175	1.345340	0.891604
		C	1.057861	0.734237	-0.123482
		C	0.968729	1.301414	3.358047
		N	-0.076535	0.678408	4.099220
		C	-1.063779	-0.123204	3.589505
		N	-1.178713	-0.418181	2.327476
		O	1.806819	1.959245	3.932850
		N	-1.934288	-0.667640	4.501848
		C	-0.884641	-0.821552	-0.638040
		H	0.004020	0.794138	5.101453
		H	1.424327	0.772086	-1.140174
		H	-2.158968	-0.118838	5.317753
		H	-2.727539	-1.119705	4.071625
		H	-0.499724	-0.750497	-1.653814
		H	-0.860833	-1.861050	-0.311081
		H	-1.912669	-0.460405	-0.610066
		H	3.873752	1.625005	2.436135
		C	4.631222	1.818347	1.679069
		H	5.633016	1.868857	2.101245
		H	3.313006	3.417029	0.832271
		O	4.574648	0.805966	0.626955
		C	4.254651	2.902773	0.663765
		C	4.140114	1.717069	-0.278106
		O	3.806125	1.514904	-1.401934
		H	5.052244	3.592244	0.390390



**Table S12.** Absolute energies and Cartesian atomic coordinates for the acylation reaction of methylguanine at the M06-2X/6-311++G(d,p) level of theory

$E^\ddagger$ [hartree]	Cartesian atomic coordinates (Å)		
	Atom	x	y

Transition state	848,875				
		N	0.474625	-0.064308	0.267899
		C	0.074994	0.022131	1.581770
		C	1.009468	0.803259	2.223523
		N	1.950614	1.176827	1.285348
		C	1.617878	0.642074	0.125418
		C	0.827169	1.146028	3.607564
		N	-0.333447	0.478217	4.096170
		C	-1.191630	-0.300391	3.367318
		N	-1.039388	-0.546494	2.093591
		O	1.469447	1.867710	4.324108
		N	-2.230101	-0.867300	4.042923
		C	-0.223208	-0.805425	-0.773729
		H	-0.494728	0.616343	5.086207
		H	0.316733	-0.665699	-1.707483
		H	-0.251774	-1.862778	-0.513648
		H	-1.239938	-0.427178	-0.870069
		C	3.125229	3.174810	-0.342529
		H	4.311058	3.710984	1.416270
		C	3.319029	3.330209	1.172607
		C	3.323022	1.878726	1.577347
		O	4.042025	1.260611	2.281162
		H	2.562125	3.887195	1.737649
		O	3.659767	1.931147	-0.598075
		H	3.604404	3.996611	-0.896156
		H	2.036060	3.246880	-0.572690
		H	-2.921146	-1.312653	3.459091
		H	-2.573270	-0.430904	4.883273
		H	2.303982	0.848566	-0.725209

Reactant state	848,950	N	-0.047740	-0.009359	0.225886
		C	-0.202011	0.147300	1.570976
		C	0.824811	0.989188	1.965734
		N	1.601175	1.345340	0.891604
		C	1.057861	0.734237	-0.123482
		C	0.968729	1.301414	3.358047
		N	-0.076535	0.678408	4.099220
		C	-1.063779	-0.123204	3.589505
		N	-1.178713	-0.418181	2.327476
		O	1.806819	1.959245	3.932850
		N	-1.934288	-0.667640	4.501848
		C	-0.884641	-0.821552	-0.638040
		H	0.004020	0.794138	5.101453
		H	1.424327	0.772086	-1.140174
		H	-2.158968	-0.118838	5.317753
		H	-2.727539	-1.119705	4.071625
		H	-0.499724	-0.750497	-1.653814
		H	-0.860833	-1.861050	-0.311081
		H	-1.912669	-0.460405	-0.610066
		H	3.873752	1.625005	2.436135
		C	4.631222	1.818347	1.679069
		H	5.633016	1.868857	2.101245
		H	3.313006	3.417029	0.832271
		O	4.574648	0.805966	0.626955
		C	4.254651	2.902773	0.663765
		C	4.140114	1.717069	-0.278106
		O	3.806125	1.514904	-1.401934
		H	5.052244	3.592244	0.390390

**Table S13.** Absolute energies and Cartesian atomic coordinates for the alkylation reaction of methyladenine at the M06-2X/6-311++G(d,p) level of theory

$E^\ddagger$ [hartree]		Cartesian atomic coordinates (Å)			
		Atom	x	y	z
Transition state	- 773,649	N	-0.43930	0.05153	0.28317
		C	-0.25016	0.01558	1.61007
		C	0.95827	0.15400	2.28275
		C	2.10429	0.34599	1.49175
		N	1.92095	0.39204	0.16121
		C	0.68625	0.24230	-0.36539
		N	-1.18476	-0.17305	2.58788
		C	-0.49679	-0.13684	3.77703
		N	0.78804	0.05452	3.64127
		N	3.32275	0.49001	2.03406
		H	0.64202	0.28644	-1.44931
		H	-1.01100	-0.26400	4.71922
		C	-2.61263	-0.35111	2.37723
		H	-2.77205	-1.11848	1.62099
		H	-3.06629	-0.66286	3.31640
		H	-3.06358	0.58302	2.04229
		H	4.15530	0.52010	1.46914
		H	3.41354	0.39680	3.03375
		H	3.82396	1.42489	-0.45286
		H	4.29377	-1.12512	-0.10690
		C	3.94637	-0.75703	-1.07417
		C	3.37706	0.64188	-1.04688
		C	5.09527	-0.41632	-2.04229
		O	4.91214	0.83012	-2.29734
		O	5.94100	-1.19020	-2.42861
		H	3.24729	-1.48510	-1.48775
		H	2.72103	0.97156	-1.83825

Reactant state	- 773,711	N	-1.72447	-1.16325	-0.03291
		C	-0.43485	-0.76067	-0.30204
		C	-0.33456	0.62526	-0.31559
		N	-1.59876	1.08032	-0.04923
		C	-2.37632	-0.04211	0.11036
		N	0.76898	1.34736	-0.53998
		C	1.81611	0.56553	-0.75415
		N	1.87962	-0.77467	-0.77032
		C	0.75519	-1.47334	-0.54836
		N	0.78243	-2.81781	-0.59135
		H	2.75624	1.07677	-0.94479
		C	-1.99381	2.47208	0.05377
		H	-3.43075	0.04303	0.33313
		H	1.68074	-3.28293	-0.59894
		H	-0.03268	-3.31776	-0.27490
		H	-3.06969	2.51763	0.21602
		H	-1.47761	2.94851	0.88756
		H	-1.74074	2.99752	-0.86692
		H	5.33245	-2.95080	-1.85254
		C	4.52502	-2.39249	-1.38337
		H	3.87221	-1.91260	-2.10819
		H	5.94016	-1.56619	0.14029
		O	3.74250	-3.27075	-0.51725
		C	4.89957	-1.52384	-0.17752
		C	3.99804	-2.48488	0.57664
		O	3.58144	-2.63583	1.67287
		H	4.52703	-0.50312	-0.18184

**Table S14.** Absolute energies and Cartesian atomic coordinates for the acylation reaction of methyladenine at the M06-2X/6-311++G(d,p) level of theory

$E^+$ [hartree]		Cartesian atomic coordinates (Å)			
		Atom	x	y	z
Transition state	- 773,660	C	-1.645869	-1.219486	1.108091
		N	-1.111765	-0.636966	2.205350
		C	-0.099181	0.123085	1.903724
		N	0.405495	0.376814	0.663478
		C	-0.115611	-0.221969	-0.466865
		C	-1.226101	-1.071309	-0.199345
		N	0.399088	0.006317	-1.642732
		C	1.276740	2.856346	-0.676036
		H	2.267789	3.284741	1.231912
		C	1.404115	2.747925	0.840145
		C	1.784458	1.264543	0.770310
		O	2.671191	0.687062	1.318598
		H	0.519143	2.966886	1.439452
		O	1.994151	1.667024	-0.981330
		H	1.741545	3.735870	-1.123295
		H	0.233989	2.790592	-1.014591
		H	-0.047204	-0.472291	-2.412701
		H	1.263584	0.818820	-1.577837
		H	-2.914280	-2.365843	3.094517
		C	-3.493765	-2.536167	2.188732
N	-2.697218	-2.089372	1.057771		
H	-4.426696	-1.974531	2.247633		
C	-2.853339	-2.411620	-0.269088		
H	-3.707711	-3.599277	2.086586		
N	-1.990251	-1.823577	-1.054307		
H	-3.627471	-3.093854	-0.590047		
H	0.430863	0.619976	2.709394		
Reactant state	- 773,711	N	-1.72447	-1.16325	-0.03291
		C	-0.43485	-0.76067	-0.30204

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C	-0.33456	0.62526	-0.31559
N	-1.59876	1.08032	-0.04923
C	-2.37632	-0.04211	0.11036
N	0.76898	1.34736	-0.53998
C	1.81611	0.56553	-0.75415
N	1.87962	-0.77467	-0.77032
C	0.75519	-1.47334	-0.54836
N	0.78243	-2.81781	-0.59135
H	2.75624	1.07677	-0.94479
C	-1.99381	2.47208	0.05377
H	-3.43075	0.04303	0.33313
H	1.68074	-3.28293	-0.59894
H	-0.03268	-3.31776	-0.27490
H	-3.06969	2.51763	0.21602
H	-1.47761	2.94851	0.88756
H	-1.74074	2.99752	-0.86692
H	5.33245	-2.95080	-1.85254
C	4.52502	-2.39249	-1.38337
H	3.87221	-1.91260	-2.10819
H	5.94016	-1.56619	0.14029
O	3.74250	-3.27075	-0.51725
C	4.89957	-1.52384	-0.17752
C	3.99804	-2.48488	0.57664
O	3.58144	-2.63583	1.67287
H	4.52703	-0.50312	-0.18184

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**Table S15.** Absolute energies and Cartesian atomic coordinates for the alkylation reaction of methylcytosine at the M06-2X/6-311++G(d,p) level of theory

$E^\ddagger$ [hartree]	Cartesian atomic coordinates (Å)			
	Atom	x	y	z



Transition state	- 701,272	N	-0.12342	-0.55336	0.46008
		C	-0.63189	0.55706	-0.05271
		C	0.20662	1.56142	-0.62681
		C	1.54109	1.32939	-0.60406
		N	2.06123	0.20563	-0.06652
		C	1.23549	-0.78673	0.50306
		N	-1.96425	0.73116	-0.03850
		O	1.73029	-1.77361	0.99018
		H	-0.20238	2.46491	-1.05247
		H	2.25354	2.03600	-1.01249
		H	-2.56705	0.08571	0.44653
		H	-2.36491	1.58931	-0.37633
		C	3.50045	-0.04938	-0.02135
		H	3.82531	-0.13575	1.01496
		H	3.72046	-0.98644	-0.53100
		H	4.01487	0.77541	-0.51045
		H	-0.45257	-2.69089	1.04799
		H	-0.63577	-1.36187	3.15452
		C	-1.52845	-1.39401	2.52873
		C	-1.22908	-1.95097	1.15827
		C	-2.49491	-2.52301	2.93730
		O	-2.47232	-3.32731	1.93840
		O	-3.11219	-2.56465	3.97915
		H	-1.99513	-0.40658	2.53714
		H	-1.93759	-1.87572	0.34658
Reactant state	- 701,339	N	-0.41778	-0.50081	1.12897
		C	-1.04139	0.50051	0.53765
		C	-0.37105	1.41463	-0.34629
		C	0.95053	1.20344	-0.53932
		N	1.59995	0.18161	0.06621
		C	0.90936	-0.71339	0.92191
		N	-2.35309	0.65968	0.78259

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O	1.54063	-1.62868	1.42514
H	-0.88737	2.23051	-0.82988
H	1.55138	1.83637	-1.18190
H	-2.82053	0.02956	1.42654
H	-2.86763	1.41139	0.36010
C	3.02226	-0.06353	-0.13644
H	3.54401	-0.02413	0.81945
H	3.17000	-1.05523	-0.56374
H	3.41669	0.69599	-0.80981
H	-1.20523	-4.71951	1.65950
H	-1.28064	-3.56693	3.88916
C	-1.07706	-2.93957	3.02283
C	-1.05272	-3.64214	1.66232
C	-2.30829	-2.27280	2.44667
O	-2.28964	-2.95779	1.28282
O	-3.09497	-1.43455	2.76868
H	-0.25687	-2.24751	3.19919
H	-0.23493	-3.33391	1.01672

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**Table S16.** Absolute energies and Cartesian atomic coordinates for the acylation reaction of methylcytosine at the M06-2X/6-311++G(d,p) level of theory

$E^\ddagger$ [hartree]		Cartesian atomic coordinates (Å)			
		Atom	x	y	z
Transition state	-701,285	C	-1.620635	-1.361064	1.160391
		N	-1.010031	-0.725932	2.195127
		C	0.038852	0.184483	1.976247
		N	0.406634	0.408706	0.666724
		C	-0.205046	-0.199176	-0.388626
		C	-1.267527	-1.138526	-0.122512
		O	0.563159	0.732465	2.926161
		N	0.185290	0.115231	-1.597345
		C	1.355522	2.871293	-0.538009
		H	2.778056	3.032431	1.117696
		C	1.797262	2.603906	0.896592
		C	2.009914	1.122201	0.613404
		O	2.847876	0.334140	0.890086
		H	1.103939	2.803326	1.713386
		O	1.930771	1.696618	-1.095727
		H	1.759257	3.778233	-0.996939
		H	0.260228	2.874565	-0.642660
		H	-0.261472	-0.364534	-2.366452
		H	1.070138	0.925095	-1.594264
		C	-1.383068	-0.950612	3.586382
	H	-1.765299	-1.641784	-0.940362	
	H	-2.411415	-2.052668	1.432972	
	H	-2.188266	-1.685557	3.616034	
	H	-1.714845	-0.013829	4.038084	

		H	-0.520365	-1.315561	4.146372
Reactant state	- 701,339	N	-0.41778	-0.50081	1.12897
		C	-1.04139	0.50051	0.53765
		C	-0.37105	1.41463	-0.34629
		C	0.95053	1.20344	-0.53932
		N	1.59995	0.18161	0.06621
		C	0.90936	-0.71339	0.92191
		N	-2.35309	0.65968	0.78259
		O	1.54063	-1.62868	1.42514
		H	-0.88737	2.23051	-0.82988
		H	1.55138	1.83637	-1.18190
		H	-2.82053	0.02956	1.42654
		H	-2.86763	1.41139	0.36010
		C	3.02226	-0.06353	-0.13644
		H	3.54401	-0.02413	0.81945
		H	3.17000	-1.05523	-0.56374
		H	3.41669	0.69599	-0.80981
		H	-1.20523	-4.71951	1.65950
		H	-1.28064	-3.56693	3.88916
		C	-1.07706	-2.93957	3.02283
		C	-1.05272	-3.64214	1.66232
		C	-2.30829	-2.27280	2.44667
		O	-2.28964	-2.95779	1.28282
		O	-3.09497	-1.43455	2.76868
		H	-0.25687	-2.24751	3.19919
		H	-0.23493	-3.33391	1.01672

**Table S17.** Absolute energies and Cartesian atomic coordinates for the alkylation reaction of methylthymine lactim tautomeric form at the M06-2X/6-311++G(d,p) level of theory

$E^\ddagger$ [hartree]		Cartesian atomic coordinates (Å)			
		Atom	x	y	z
Transition state	-760,444	C	2.228723	1.026875	0.409938
		C	3.293421	0.193349	-0.033965
		C	3.906770	0.624055	-1.167461
		N	3.536106	1.752706	-1.818315
		C	2.481876	2.558358	-1.364509
		N	1.862812	2.130670	-0.198182
		C	3.665884	-1.054002	0.710709
		O	2.157280	3.551277	-1.966719
		O	1.598092	0.629189	1.504405
		C	4.198945	2.199469	-3.044541
		H	4.500914	-1.553119	0.218670
		H	2.823841	-1.747066	0.754838
		H	3.954827	-0.823451	1.737690
		H	4.729490	0.073771	-1.609831
		H	0.852241	1.208318	1.712041
		H	4.617476	3.193401	-2.890591
		H	4.987511	1.492100	-3.291329
		H	3.470866	2.252690	-3.853081
		H	0.738187	4.058097	-0.153877
		C	0.436032	3.207083	0.435827
	H	-0.824069	2.336701	-1.096510	
	O	-1.151609	4.269224	1.141844	
	C	-0.753141	2.390526	-0.009569	
	H	0.777040	3.202516	1.462334	

		C	-1.823442	3.317655	0.611301
		O	-3.015059	3.105906	0.566894
		H	-0.800846	1.374802	0.391780
Reactant state	- 760,521	C	-1.407287	-1.318594	1.210110
		N	-0.768908	-0.677544	2.225979
		C	0.049447	0.439502	1.983503
		N	0.190985	0.839145	0.682769
		C	-0.431912	0.209050	-0.274455
		C	-1.286528	-0.927076	-0.080957
		O	0.591501	0.995825	2.924170
		O	-0.289135	0.612728	-1.526141
		C	1.143031	3.942519	1.597915
		H	3.265075	3.711469	0.908309
		C	2.325298	3.170417	1.003374
		C	1.469082	3.190435	-0.243615
		O	1.515641	2.749746	-1.355270
		H	2.467894	2.167683	1.400428
		O	0.473897	3.918469	0.293949
		H	1.328261	4.970158	1.903281
		H	0.565145	3.382288	2.328345
		C	-0.912255	-1.097713	3.615097
		H	0.070741	-1.298541	4.039813
		H	-1.526669	-1.995753	3.648738
		H	-1.378421	-0.302452	4.197220
		H	0.311124	1.385912	-1.563087
		C	-1.965014	-1.596610	-1.237451
		H	-1.231513	-1.964980	-1.957529
		H	-2.611693	-0.894540	-1.767548
		H	-2.569604	-2.437218	-0.894089
		H	-2.020422	-2.166066	1.495979

**Table S18.** Absolute energies and Cartesian atomic coordinates for the acylation reaction of methylthymine lactim tautomeric form at the M06-2X/6-311++G(d,p) level of theory

$E^\ddagger$ [hartree]		Cartesian atomic coordinates (Å)			
		Atom	x	y	z
Transition state	-760,413	C	-0.987236	-1.348228	1.118223
		N	-1.097841	-0.485899	2.131379
		C	-1.397665	0.889317	1.876155
		N	-0.964938	1.288679	0.567186
		C	-0.839098	0.413302	-0.412431
		C	-0.943027	-0.976553	-0.207252
		O	-2.173974	1.502262	2.538464
		O	-0.541709	0.852560	-1.632244
		C	1.513351	1.276287	1.762874
		H	2.026971	3.053165	0.587050
		C	1.443029	2.136641	0.498639
		C	-0.014731	2.558090	0.672812
		O	-0.510829	3.625538	0.533948
		H	1.656075	1.664499	-0.465773
		O	0.410293	1.772130	2.458771
		H	2.454094	1.395033	2.312393
		H	1.414990	0.200703	1.518971
		C	-1.098078	-0.870408	3.539408
		H	-0.929639	-2.396650	1.396200
		H	-0.462890	-0.157991	4.067265
	H	-0.697468	-1.878672	3.630171	
	H	-2.109770	-0.821552	3.942340	
	H	-0.619476	1.816701	-1.672192	
	C	-0.869528	-1.947562	-1.350759	

	H	0.053541	-1.822328	-1.920112
	H	-1.704425	-1.810354	-2.040880
	H	-0.905504	-2.971431	-0.976934
Reactant state	C	-1.407287	-1.318594	1.210110
- 760,521	N	-0.768908	-0.677544	2.225979
	C	0.049447	0.439502	1.983503
	N	0.190985	0.839145	0.682769
	C	-0.431912	0.209050	-0.274455
	C	-1.286528	-0.927076	-0.080957
	O	0.591501	0.995825	2.924170
	O	-0.289135	0.612728	-1.526141
	C	1.143031	3.942519	1.597915
	H	3.265075	3.711469	0.908309
	C	2.325298	3.170417	1.003374
	C	1.469082	3.190435	-0.243615
	O	1.515641	2.749746	-1.355270
	H	2.467894	2.167683	1.400428
	O	0.473897	3.918469	0.293949
	H	1.328261	4.970158	1.903281
	H	0.565145	3.382288	2.328345
	C	-0.912255	-1.097713	3.615097
	H	0.070741	-1.298541	4.039813
	H	-1.526669	-1.995753	3.648738
	H	-1.378421	-0.302452	4.197220
	H	0.311124	1.385912	-1.563087
	C	-1.965014	-1.596610	-1.237451
	H	-1.231513	-1.964980	-1.957529
	H	-2.611693	-0.894540	-1.767548
	H	-2.569604	-2.437218	-0.894089
	H	-2.020422	-2.166066	1.495979



**Table S19.** Absolute energies and Cartesian atomic coordinates for the alkylation reaction of glutathione at the M06-2X/6-311++G(d,p) level of theory

$E^\ddagger$ [hartree]		Cartesian atomic coordinates (Å)			
		Atom	x	y	z
Transition state	-1671.076	S	-1.456648	-3.121415	-2.279412
		O	0.017973	1.951763	-2.159099
		O	-3.441805	0.350286	-0.828665
		O	4.704819	1.138147	-0.164961
		O	4.833606	0.705814	2.051969
		O	0.153599	-1.111577	2.141200
		O	-0.615678	0.665686	3.256476
		N	-0.206020	-0.303056	-2.221305
		N	2.298139	0.251267	2.341261
		N	-1.579454	-0.494108	0.156564
		C	1.815369	1.016021	0.050854
		C	1.896436	0.647527	-1.444213
		C	-1.654280	-0.309842	-2.288808
		C	2.794299	0.254359	0.933753
		C	0.501547	0.840744	-2.008340
		C	-2.149020	-1.584517	-2.986818
		C	-2.319500	-0.128876	-0.908470
		C	4.271722	0.767150	0.932191
		C	-1.986948	-0.288680	1.531205
		C	-0.724665	-0.225269	2.407259
H	0.802729	0.793437	0.404370		
H	1.967940	2.092851	0.164126		
H	2.616638	1.287739	-1.950556		
H	2.224971	-0.388705	-1.560184		

	H	-1.972962	0.565302	-2.858895	
	H	0.225489	-1.208663	-2.073203	
	H	3.134277	0.094967	2.917817	
	H	1.455431	-0.451520	2.437272	
	H	-0.773316	-1.090368	0.020815	
	H	-2.628576	-1.106643	1.883178	
	H	-2.541988	0.644678	1.602292	
	H	-1.882393	-1.507149	-4.045357	
	H	-3.241747	-1.590688	-2.911112	
	H	1.914131	1.162210	2.597136	
	C	-3.358814	-4.583610	-2.924030	
	H	-2.235553	-4.815420	-4.783081	
	C	-3.191550	-4.443618	-4.417866	
	O	-4.762677	-5.654009	-3.490023	
	C	-4.373064	-5.365813	-4.694527	
	O	-4.831240	-5.742890	-5.754621	
	H	2.808480	-0.798273	0.631902	
	H	-3.950262	-3.884798	-2.354739	
	H	-2.834651	-5.353346	-2.383417	
	H	-3.337105	-3.426708	-4.781549	
Reactant state	- 1671.108	C	-1.407287	-1.318594	1.210110
		N	-0.768908	-0.677544	2.225979
		C	0.049447	0.439502	1.983503
		N	0.190985	0.839145	0.682769
		C	-0.431912	0.209050	-0.274455
		C	-1.286528	-0.927076	-0.080957
		O	0.591501	0.995825	2.924170
		O	-0.289135	0.612728	-1.526141
		C	1.143031	3.942519	1.597915
		H	3.265075	3.711469	0.908309
		C	2.325298	3.170417	1.003374
		C	1.469082	3.190435	-0.243615

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O	1.515641	2.749746	-1.355270
H	2.467894	2.167683	1.400428
O	0.473897	3.918469	0.293949
H	1.328261	4.970158	1.903281
H	0.565145	3.382288	2.328345
C	-0.912255	-1.097713	3.615097
H	0.070741	-1.298541	4.039813
H	-1.526669	-1.995753	3.648738
H	-1.378421	-0.302452	4.197220
H	0.311124	1.385912	-1.563087
C	-1.965014	-1.596610	-1.237451
H	-1.231513	-1.964980	-1.957529
H	-2.611693	-0.894540	-1.767548
H	-2.569604	-2.437218	-0.894089
H	-2.020422	-2.166066	1.495979

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**Table S20.** Absolute energies and Cartesian atomic coordinates for the acylation reaction of glutathione at the M06-2X/6-311++G(d,p) level of theory

		Cartesian atomic coordinates (Å)			
$E^\ddagger$ [hartree]		Atom	x	y	z
Transition state	-1671.072	S	-3.157312	-3.174481	-0.492322
		O	-0.316882	0.910661	-2.538027
		O	-3.848047	0.605841	-0.133314
		O	4.544845	-0.429446	-1.069588
		O	5.013671	-0.253407	1.135364
		O	0.170160	-0.252371	2.418950
		O	-0.508366	1.479544	3.674927
		N	-0.985629	-1.054111	-1.595055
		N	2.584935	0.267648	1.829350
		N	-1.855327	-0.020797	0.751528
		C	1.795611	0.307776	-0.501037
		C	1.376162	-0.571313	-1.698563
		C	-2.378948	-0.681049	-1.541522
		C	2.739407	-0.370525	0.483032
		C	-0.052036	-0.176208	-2.030572
		C	-3.303336	-1.881839	-1.762798
		C	-2.766301	0.034659	-0.230945
		C	4.264225	-0.344800	0.129702
		C	-2.011657	0.609759	2.041239
		C	-0.666506	0.634866	2.793320
H	0.891030	0.582350	0.053785		
H	2.245342	1.234669	-0.868874		
H	2.036761	-0.391501	-2.545574		
H	1.416535	-1.632090	-1.438256		

		H	-2.572612	0.054001	-2.328454
		H	-0.691525	-2.022177	-1.299903
		H	3.418696	-0.020212	2.354537
		H	1.597115	0.036328	2.264307
		H	-1.035223	-0.603423	0.639208
		H	-2.741925	0.072713	2.659839
		H	-2.376908	1.629796	1.918724
		H	-3.083918	-2.365479	-2.718167
		H	-4.334630	-1.529011	-1.760471
		H	2.651628	1.279824	1.726708
		H	2.435286	-1.413177	0.620398
		O	-2.265521	-4.599469	-2.602770
		C	-2.039842	-4.389673	-1.433679
		O	-0.305430	-3.581478	-1.125440
		H	-1.017425	-6.204960	-0.992223
		C	-1.418343	-5.364093	-0.421639
		C	-0.319848	-4.388657	0.010364
		H	0.649242	-4.871832	0.206973
		H	-2.126602	-5.721070	0.334161
		H	-0.614083	-3.842176	0.921827
Reactant state	- 1671.108	S	-1.373821	-2.455622	-2.382194
		O	0.115202	2.543497	-1.882737
		O	-3.844057	0.682901	-1.397472
		O	3.902036	-2.017124	-0.007635
		O	2.293175	-3.279142	0.950045
		O	-0.594774	0.101253	2.110944
		O	-2.223695	0.701486	3.539927
		N	-0.301830	0.326980	-2.125106
		N	0.330766	-1.713327	0.344734
		N	-2.039035	0.633005	-0.030751
		C	1.989338	0.158662	-0.118478
		C	1.906291	1.000660	-1.408363

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C	-1.712901	0.368329	-2.442283
C	1.638931	-1.331383	-0.262943
C	0.493777	1.381390	-1.837648
C	-2.081039	-0.948093	-3.160798
C	-2.634781	0.578264	-1.227781
C	2.741115	-2.300458	0.309659
C	-2.729685	0.749302	1.232116
C	-1.761810	0.494461	2.417352
H	1.371047	0.607903	0.666641
H	3.026587	0.193771	0.218413
H	2.436736	1.942602	-1.264758
H	2.402408	0.456351	-2.219567
H	-1.911306	1.217736	-3.103483
H	1.583087	-1.613424	-1.321345
H	0.070971	-0.619904	-2.138956
H	0.554490	-2.596397	0.838476
H	-0.391787	-1.898561	-0.388702
H	-1.034585	0.576682	0.034401
H	-3.542930	0.020007	1.278564
H	-3.175096	1.740343	1.354335
H	-1.717034	-0.881876	-4.189985
H	-3.168972	-1.008880	-3.183548
H	2.703345	-3.860288	-1.814522
H	1.180048	-4.991987	-0.249518
C	0.866901	-5.013451	-1.293219
C	1.809262	-4.293944	-2.260895
C	1.307181	-6.247205	-2.058400
O	2.136633	-5.580661	-2.899472
O	1.100593	-7.421922	-2.045742
H	-0.191121	-4.773334	-1.406271
H	1.316517	-3.629862	-2.968697
H	-0.041096	-1.011719	1.046803

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