



## Supplementary Materials

# Thermodynamic Overview of Bioconjugation Reactions Pertinent to Lysine and Cysteine Peptide and Protein Residues

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### Tables

Table S1: T1 and G3(MP2) energies for reaction of water and methylamine with example phenyl esters

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Table S6: T1 and G3(MP2) energies for reaction of methylamine with imidates, sulfonyl chlorides, epoxides, maleimides, and 2, 4-dinitrofluorobenzene

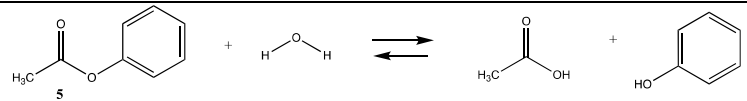
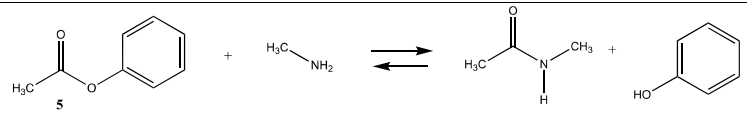
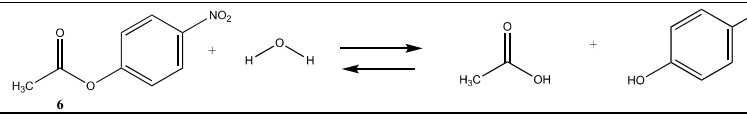
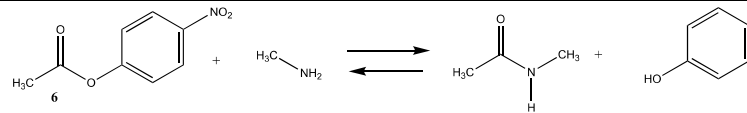
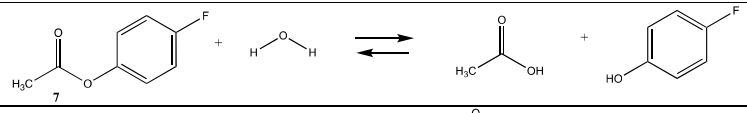
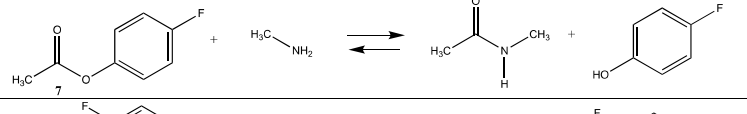
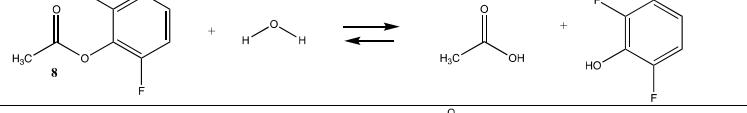
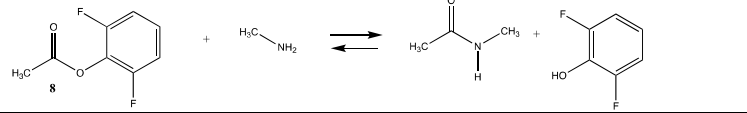
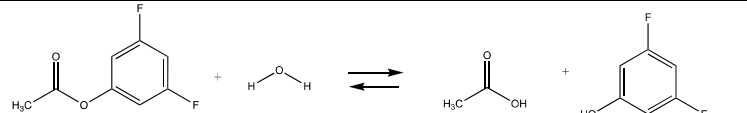
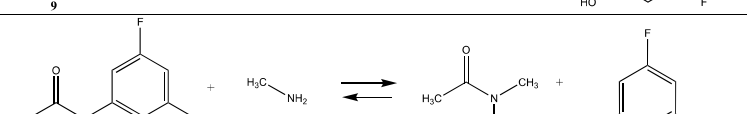
Table S7: T1 and G3(MP2) energies for reaction of methylamine with example squarate esters and aldehydes

Table S8: T1 and G3(MP2) energies for reaction of methanethiol with sulfonyl chlorides, epoxides, maleimides, and 2, 4-dinitrofluorobenzene

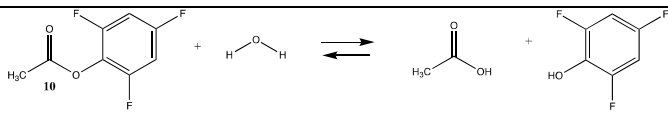
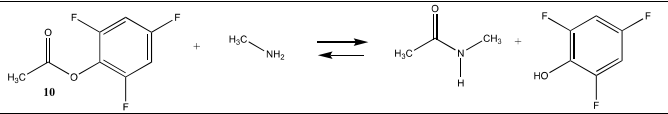
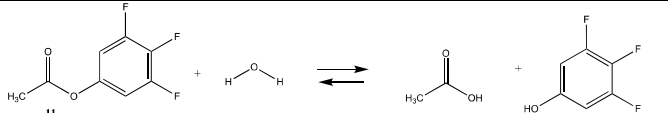
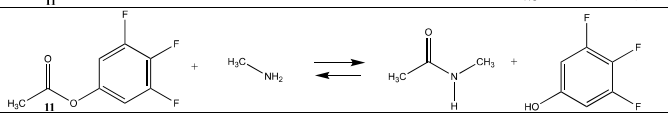
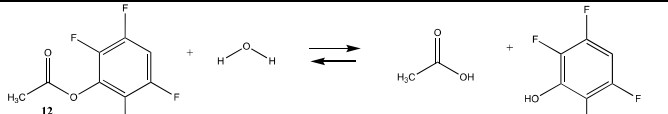
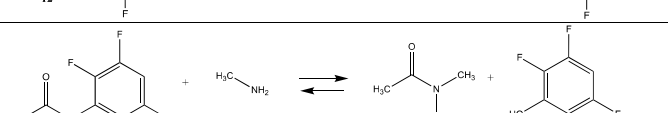

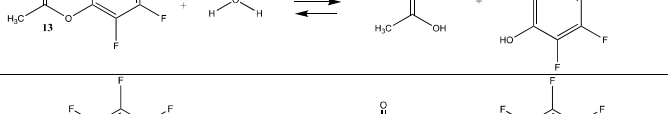
Table S9: T1 and G3(MP2) energies for reaction of methanethiol with examples of disulfides,  $\alpha$ -bromoacids and  $\alpha$ -bromoamides, dibromomaleimides, and reaction of acetaldehyde with N-acetylhydrazide

Table S10: T1 energies for examples of common click reactions

**Table S1.** T1 and G3(MP2) energies for reaction of water and methylamine with example phenyl esters

Reaction	T1 $\Delta E$ (kJ/mol)	G3(MP2) $\Delta E$ (kJ/mol)
 <chem>CC(=O)Oc1ccccc1.O&gt;&gt;CC(=O)O.Oc1ccccc1</chem>	-3.89	-2.35
 <chem>CC(=O)Oc1ccccc1.CN&gt;&gt;CC(=O)NC.Oc1ccccc1</chem>	-25.58	-27.87
 <chem>CC(=O)Oc1ccc([N+](=O)[O-])cc1.O&gt;&gt;CC(=O)O.Oc1ccc([N+](=O)[O-])cc1</chem>	-7.89	-6.05
 <chem>CC(=O)Oc1ccc([N+](=O)[O-])cc1.CN&gt;&gt;CC(=O)NC.Oc1ccc([N+](=O)[O-])cc1</chem>	-29.68	-31.57
 <chem>CC(=O)Oc1ccc(F)cc1.O&gt;&gt;CC(=O)O.Oc1ccc(F)cc1</chem>	-2.45	-0.18
 <chem>CC(=O)Oc1ccc(F)cc1.CN&gt;&gt;CC(=O)NC.Oc1ccc(F)cc1</chem>	-24.14	-25.7
 <chem>CC(=O)Oc1cc(F)c(F)cc1.O&gt;&gt;CC(=O)O.Oc1cc(F)c(F)cc1</chem>	-7.15	-4.67
 <chem>CC(=O)Oc1cc(F)c(F)cc1.CN&gt;&gt;CC(=O)NC.Oc1cc(F)c(F)cc1</chem>	-28.84	-30.19
 <chem>CC(=O)Oc1cc(F)c(F)cc1.O&gt;&gt;CC(=O)O.Oc1cc(F)c(F)cc1</chem>	-6.83	-5.35
 <chem>CC(=O)Oc1cc(F)c(F)cc1.CN&gt;&gt;CC(=O)NC.Oc1cc(F)c(F)cc1</chem>	-28.52	-30.87

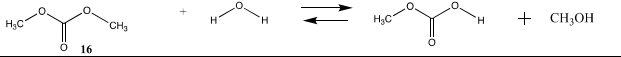
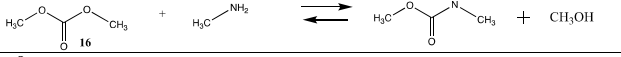
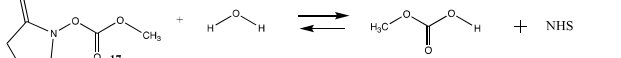
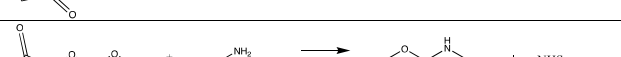
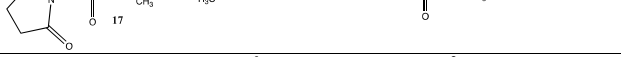
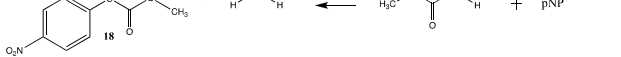
**Table S2.** T1 and G3(MP2) energies for reaction of water and methylamine with example phenyl esters

Reaction	T1 $\Delta E$ (kJ/mol)	G3(MP2) $\Delta E$ (kJ/mol)
	-5.03	-1.84
	-26.72	-27.36
	-4.87	-3.13
	-26.56	-28.65
	-8.01	-5.64
	-29.7	-31.16
	-5.81	-3.25
	-27.50	-28.77

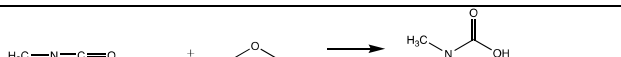
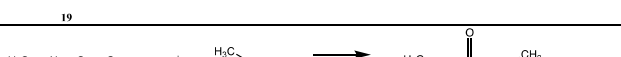
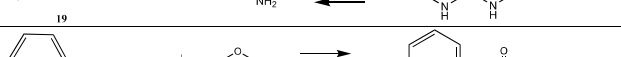

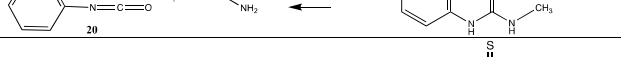
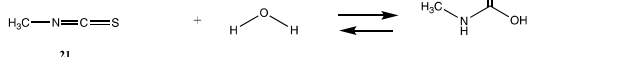
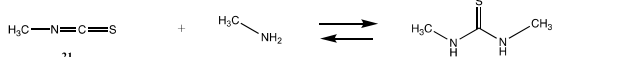
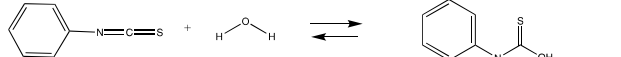
**Table S3.** T1 and G3(MP2) energies for reaction of water and methylamine with example N-hydroxysuccinimide esters

Reaction	T1 $\Delta E$ (kJ/mol)	G3(MP2) $\Delta E$ (kJ/mol)
	5.38	9.67
	-16.35	-15.85
	8.47	15.91
	-13.22	-9.61

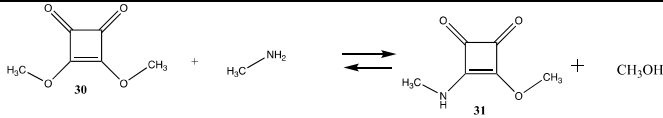
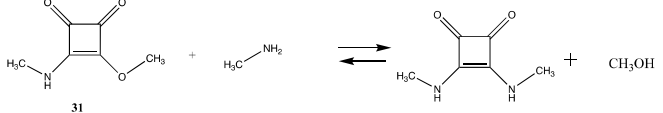
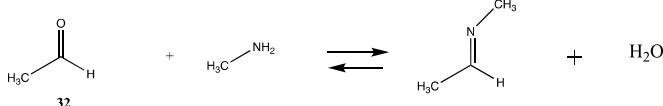
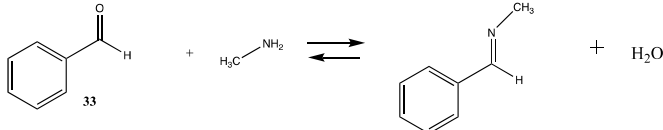
**Table S4.** T1 and G3(MP2) energies for reaction of water and methylamine with example carbonates

Reaction	T1 $\Delta E$ (kJ/mol)	G3(MP2) $\Delta E$ (kJ/mol)
 <chem>CCOC(=O)OC + O &gt;&gt; CCOC=O + CO</chem>	19.32	22.14
 <chem>CCOC(=O)OC + CN &gt;&gt; CCOC(=O)N + CO</chem>	-17.02	-16.23
 <chem>COC(=O)N1CCCC1=O + O &gt;&gt; CCOC=O + N1CCCC1=O</chem>	-3.18	0.96
 <chem>COC(=O)N1CCCC1=O + CN &gt;&gt; CCOC(=O)N + N1CCCC1=O</chem>	-39.56	-37.41
 <chem>CCOC(=O)Oc1ccc([N+](=O)[O-])cc1 + O &gt;&gt; CCOC=O + Oc1ccc([N+](=O)[O-])cc1</chem>	-9.64	-5.86
 <chem>CCOC(=O)Oc1ccc([N+](=O)[O-])cc1 + CN &gt;&gt; CCOC(=O)N + Oc1ccc([N+](=O)[O-])cc1</chem>	-46.01	-44.23

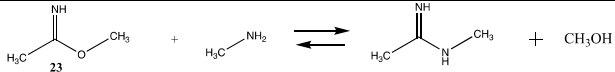
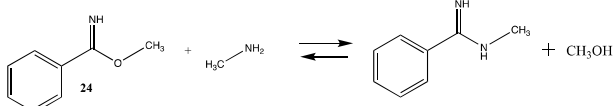
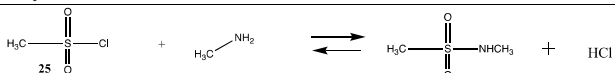
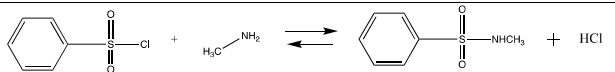
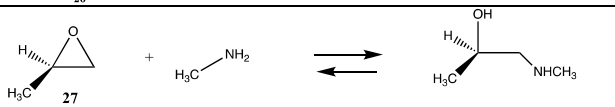
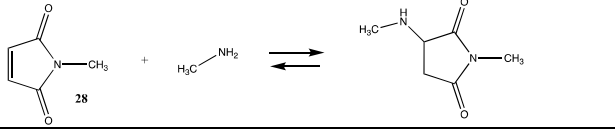
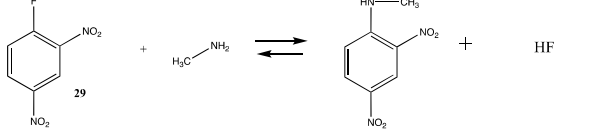
**Table S5.** T1 and G3(MP2) energies for reaction of water and methylamine with example isocyanates and isothiocyanates

Reaction	T1 $\Delta E$ (kJ/mol)	G3(MP2) $\Delta E$ (kJ/mol)
 <chem>CN=C=O + O &gt;&gt; OC=O</chem>	-64.26	-78.19
 <chem>CN=C=O + CN &gt;&gt; CN(C)C=O</chem>	-75.77	-93.84
 <chem>c1ccccc1N=C=O + O &gt;&gt; OC=O</chem>	-66.13	-79.54
 <chem>c1ccccc1N=C=O + CN &gt;&gt; CN(C)C=O</chem>	-77.45	-96.78
 <chem>CN=C=S + O &gt;&gt; OS=C</chem>	-38.12	-57.55
 <chem>CN=C=S + CN &gt;&gt; CN(C)C=S</chem>	-64.82	-81.91
 <chem>c1ccccc1N=C=S + O &gt;&gt; OS=C</chem>	-27.32	-42.55
 <chem>c1ccccc1N=C=S + CN &gt;&gt; CN(C)C=S</chem>	-63.36	-83.51

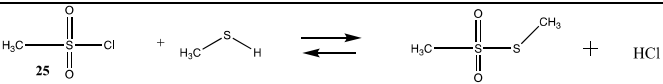
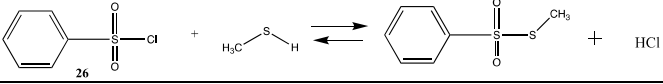
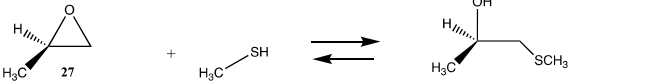
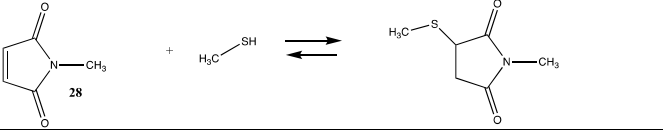
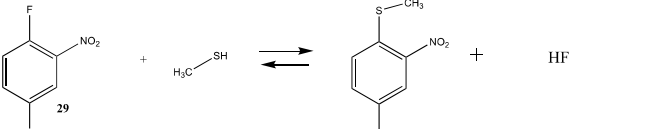
**Table S7.** T1 and G3(MP2) energies for reaction of methylamine with example squarate esters and aldehydes

Reaction	T1 $\Delta E$ (kJ/mol)	G3(MP2) $\Delta E$ (kJ/mol)
	-43.40	-42.02
	-22.09	-21.21
	-20.75	-20.79
	-14.26	-17.60

**Table S6.** T1 and G3(MP2) energies for reaction of methylamine with imidates, sulfonyl chlorides, epoxides, maleimides, and 2, 4-dinitrofluorobenzene

Reaction	T1 $\Delta E$ (kJ/mol)	G3(MP2) $\Delta E$ (kJ/mol)
	2.46	1.7
	-7.82	-7.79
	-41.27	-45.13
	-41.71	-46.47
	-130.77	-131.53
	-83.71	-86.89
	-95.89	-98.88

**Table S8.** T1 and G3(MP2) energies for reaction of methanethiol with sulfonyl chlorides, epoxides, maleimides, and 2, 4-dinitrofluorobenzene

Reaction	T1 $\Delta E$ (kJ/mol)	G3(MP2) $\Delta E$ (kJ/mol)
	-24.31	-23.90
	-27.63	-34.21
	-139.38	-146.23
	-98.05	-97.40
	-63.13	-57.03

**Table S9.** T1 and G3(MP2) energies for reaction of methanethiol with examples of disulfides,  $\alpha$ -bromoacids and  $\alpha$ -bromoamides, dibromomaleimides, and reaction of acetaldehyde with N-acetylhydrazide

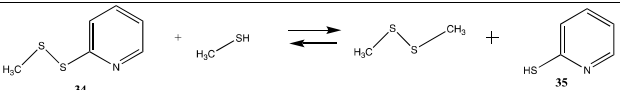
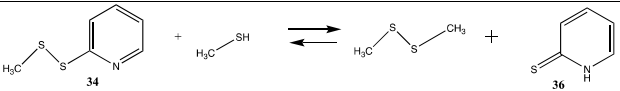
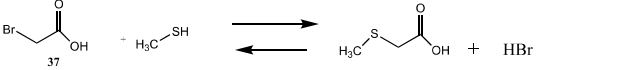
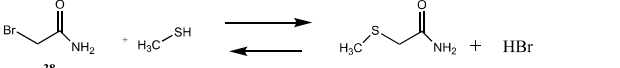
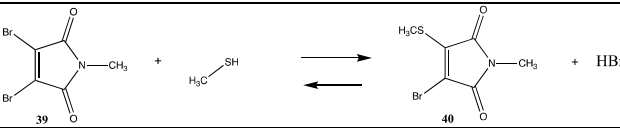

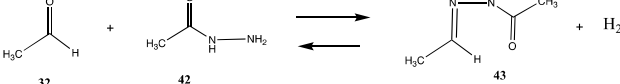
Reaction	T1 $\Delta E$ (kJ/mol)	G3(MP2) $\Delta E$ (kJ/mol)
	-0.82	-2.37
	4.33	4.83
	-26.32	-29.38
	-21.82	-24.96
	-44.54	-42.34
	-38.58	-35.37
	-29.17	-33.82

Table S10. T1 energies for examples of common click reactions

Reaction	T1 $\Delta E$ (kJ/mol)
<p>44 + 45 <math>\rightleftharpoons</math> 46</p>	-252.43
<p>44 + 47 <math>\rightleftharpoons</math> 48</p>	-290.38
<p>44 + 49 <math>\rightleftharpoons</math> 50</p>	-290.18
<p>51 + 52 <math>\rightleftharpoons</math> 53 + N<sub>2</sub></p>	-282.85