Cyclopropanecarboxylic acid esters as potential prodrugs with enhanced hydrolytic stability

David M. Bender, Jeffrey A. Peterson, James R. McCarthy*

Eli Lilly and Co., Lilly Corporate Center, Indianapolis, IN 46285

Hakan Gunaydin, Yu Takano and K. N. Houk*

Department of Chemistry and Biochemistry, University of California, Los Angeles, CA 90095

Supporting Information

I. Synthesis and Characterization of Compounds

General Methods

Reactions were carried out in oven-dried glassware sealed with rubber septa under a positive pressure of nitrogen, unless otherwise indicated. Liquids and solutions were transferred via syringe. Analytical TLC was performed with 0.25 mm silica gel 60F plates with a 254 nm fluorescent indicator from Merck. TLC plates were visualized by ultraviolet light. Chromatographic purification of products was accomplished by flash chromatography using an ISCO CombiFlash 100c separations system with RediSep disposable silica gel cartridges. Ion exchange chromatography was performed on Varian Mega BondElut SCX cartridges as indicated (Varian part numbers: 1225-6027 (5g) and 1225-6035 (10g)).

NMR spectra were measured on Varian INOVA 400 (^{1}H at 400 MHz, ^{13}C at 100 MHz). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant *(*J,Hz), and integration. Data for ^{13}C are reported in terms of chemical shift, multiplicity, coupling constant, and quantity of carbons, as necessary. High-resolution mass spectra (HRMS) were recorded at Eli Lilly and Co. in Indianapolis, IN. Reported mass values are within error limits of ±1 millimass unit.

Unless otherwise indicated reagents were purchased and used without further purification. AcroSeal™ anhydrous solvents were obtained from Acros Organics. 9-[(2-Hyrdoxyethoxy)methyl]-guanine (Acyclovir) was purchased from Sigma (Cat. # A4669). N-*tert*-Butoxycarbonyl-1-aminocyclopropane-1-carboxlic acid was purchased from Chem-Impex (Cat. # 04052). The following compounds were purchased from Aldrich Chemical: benzyl acetate **(2a):** CAS 140-11-4, Catalog #W21,351-9, benzyl isobutyrate **(3a):** CAS 103-28-6, Catalog #W21,410-8, benzyl benzoate **(9a):** CAS 120-51-4, Catalog #W21,381-0, benzyl phenylacetate **(7a):** CAS 102-16-9, Catalog #W21,490-6. Cyclopropanecarboxylic acid benzyl ester **(1a)**[1]**,** cyclobutanecarboxylic acid benzyl ester **(4a)**[2]**,** cyclopentanecarboxylic acid benzyl ester **(5a)**[3]**,** cyclohexanecarboxylic acid benzyl ester **(6a)**[4]**,** 2-amino-2-methyl-propionic acid benzyl ester hydrochloride **(8a)**[7], 1-amino-cyclopropanecarboxylic acid benzyl ester hydrochloride **(11a)**[6] and 2,2-dimethyl-propionic acid benzyl ester **(12a)**[5]**,** and have all been previously described. (S)-2-Amino-3-methyl-butyric acid 2-(2-amino-6-oxo-1,6-dihydro-purin-9-ylmethoxy)-ethyl ester (valacyclovir) (**13**) was purchased from Moravek Biochemicals, Inc.

(1) Folmer, J. J.; Weinreb, S.M. *Tetrahedron Lett.* **1993**, 34(17), 2737-40.

(2) Hale, J.J.; Lynch, C. L.; Caldwell, C.G.; Willoughby, C.A.; Kim, D.; Shen, D-M.; Mills, S.G.; Chapman, K.T.; Chen, L.; Gentry, A.; Maccoss, M.; Konteatis, Z.D. US 2002094989 A1 103 pp.

(3) Olson, R.E. PCT Int. Appl. (2001), WO 2001092235 A1 254 pp.

(4) Reynolds, N.T.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2004,** 126(31), 9518-9519.

(5) Leibfritz, D.; Haupt, E.; Dubischar, N.; Lachmann, H.; Oekonomopulos, R.; Jung, G. *Tetrahedron* **1982**, 38(14), 2165-81.

(6) Farouz-Grant, F.; Miller, M.J. *Bioorg. Med. Chem. Lett*. **1993,** 3(11), 2423-8.

(7) Gros, P.; Le Perchec, P.; Cauthier, P.; Senet, J. P. *Synth. Commun*. **1993**, 23(13), 1835-42.

General Procedure for the Preparation of Benzyl Esters

Benzyl alcohol (1.0 g, 9.3 mmol) is dissolved in methylene chloride (30 mL) and cooled to 0°C while stirring under nitrogen. Triethylamine (3.2 mL, 23.1 mmol) is added followed by careful dropwise addition of 1.5 equivalents of the desired acid chloride. The reaction mixture is allowed to warm to ambient temperature and stirred for 4 hours. The reaction is diluted with ethyl acetate and washed with 1.0 M HCl solution, saturated sodium bicarbonate solution and saturated sodium chloride solution. The organic layer is dried ($MgSO_4$) and concentrated in vacuo. Pure products are isolated following flash chromatography eluting with 100% hexanes.

Cyclopropanecarboxylic acid benzyl ester (1a): Prepared by General Procedure, obtained 0.9 g (54%) of a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84-0.88 (m, 2H), 1.00-1.04 (m, 2H), 1.62-1.68 (m, 1H), 5.11 (s, 1H), 7.30-7.37 (m, 5H).

Benzyl acetate (2a): CAS 140-11-4, Commercially available from Aldrich Chemical, Catalog #W21,351-9

Benzyl isobutyrate (3a): CAS 103-28-6, Commercially available from Aldrich Chemical, Catalog #W21,410-8

Cyclobutanecarboxylic acid benzyl ester (4a): Prepared by General Procedure, obtained 0.8 g (47%) of a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84-2.01 (m, 2H), 2.14-2.35 (m, 4H), 3.17 (quint. d, J = 8.4, 0.8 Hz, 1H), 5.10 (s, 1H), 7.28-7.37 (m, 5H).

Cyclopentanecarboxylic acid benzyl ester (5a): Prepared by General Method A, obtained 1.3 g (69%) of a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53-1.94 (m, 8H), 2.77 (quint. 1H), 5.10 (s, 1H), 7.28-7.37 (m, 5H).

Cyclohexanecarboxylic acid benzyl ester (6a): Prepared by General Procedure, obtained 1.6 g (79%) of a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18-1.32 (m, 3H), 1.41-1.50 (m, 2H), 1.59-1.64 (m, 1H), 1.71-1.76 (m, 2H), 1.89-1.95 (m, 2H), 2.30-2.38 (m, 1H), 5.10 (s, 1H), 7.24-7.37 (m, 5H).

Benzyl Phenylacetate (7a): CAS 102-16-9, Commercially available from Aldrich Chemical, Catalog #W21,490-6

2-amino-2-methyl-propionic acid benzyl ester hydrochloride (8a)
2-*tert*-Butoxycarbonylamino-2-methyl-propionic acid (2.07 g, 10.17 mmol) was combined with with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

(EDC) (1.95 g, 10.17 mmol) and 1-hydroxybenzotriazole (HOBt) (1.37 g, 10.17 mmol) in methylene chloride (46 mL) and stirred for 30 minutes at room temperature under nitrogen. Benzyl alcohol (1.00 g, 9.25 mmol) was added followed by diisopropylethyl amine (2.99 g, 23.12 mmol) and the reaction was stirred overnight. The reaction mixture was diluted with ethyl acetate and washed with 1 M HCl, saturated sodium bicarbonate solution, water and saturated sodium chloride solution, dried (MgSO4) and concentrated in vacuo. The crude material was purified by silica gel chromatography (ISCO, 12g) eluting with 0% to 10% ethyl acetate in hexanes to obtain 3.0 g (77%) of 2-*tert*-Butoxycarbonylamino-2-methyl-propionic acid benzyl ester. The Boc-derivative (0.20 g, 0.68 mmol) was dissolved in methylene chloride (2 mL) and treated with trifluoroacetic acid (2.0 mL, 3.43.mmol) and stirred at room temperature under nitrogen until starting material had been consumed. The reaction mixture was concentrated in vacuo and the resulting crude material was purified by SCX resin, eluting with a 2.0 M solution of ammonia in methanol. Product containing fractions were combined and concentrated and the resulting solid was dissolved in diethyl ether and treated with a 1.0 M solution of hydrochloric acid in diethyl ether. The precipitated salt was collected by filtration to give 0.11 g (84%) of the title compound **8a** as an off-white solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.46 (s, 6H), 5.20 (s, 2H), 7.27-7.39 (m, 5H).
MS (ES+): 194.3 (M+1).

Benzyl Benzoate (9a): CAS 120-51-4, Commercially available from Aldrich Chemical, Catalog #W21,381-0

1-Methyl-cyclopropanecarboxylic acid benzyl ester (10a): 1-methylcyclopropane carboxcylic acid (1.02 g, 10.17 mmol) was combined with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (1.95 g, 10.17 mmol) and 1-hydroxybenzotriazole (HOBt) (1.37 g, 10.17 mmol) in methylene chloride (46 mL) and stirred for 30 minutes at room temperature under nitrogen. Benzyl alcohol (1.00 g, 9.25 mmol) was added followed by diisopropylethyl amine (2.99 g, 23.12 mmol) and the reaction was stirred overnight. The reaction mixture was diluted with ethyl acetate and washed with 1 M HCl, saturated sodium bicarbonate solution, water and saturated sodium chloride solution, dried (MgSO4) and concentrated in vacuo. The crude material was purified by silica gel chromatography (ISCO, 12g) eluting with 0% to 10% ethyl acetate in hexanes to obtain 1.1g (57%) of **10a** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.68 (q, J = 3.8, 2.8 Hz, 2H), 1.25 (q, J = 4.0, 2.8 Hz, 2H), 1.31 (s, 3H), 5.09 (s, 1H), 7.29-7.36 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 136.3, 128.5, 128.0, 127.8, 66.2, 19.4, 18.6, 16.9.

1-amino-cyclopropanecarboxylic acid benzyl ester hydrochloride (11a)
1-*tert*-butoxycarbonylamino-cyclopropane carboxcylic acid (2.05 g, 10.17 mmol) was combined with with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (1.95 g, 10.17 mmol) and 1-hydroxybenzotriazole (HOBt) (1.37 g, 10.17 mmol) in methylene chloride (46 mL) and stirred for 30 minutes at room temperature under nitrogen. Benzyl alcohol (1.00 g, 9.25 mmol) was added followed by diisopropylethyl amine (2.99 g, 23.12 mmol) and the reaction was stirred overnight. The reaction mixture was diluted with ethyl acetate and washed with 1 M HCl, saturated sodium bicarbonate

solution, water and saturated sodium chloride solution, dried (MgSO4) and concentrated in vacuo. The crude material was purified by silica gel chromatography (ISCO, 12g) eluting with 0% to 10% ethyl acetate in hexanes to obtain 2.2 g (74%) of 1-*tert*-butoxycarbonylamino-cyclopropanecarboxylic acid benzyl ester. The Boc-derivative (0.20 g, 0.69 mmol) was dissolved in methylene chloride (2 mL) and treated with trifluoroacetic acid (2.0 mL, 3.43.mmol) and stirred at room temperature under nitrogen until starting material had been consumed. The reaction mixture was concentrated in vacuo and the resulting crude material was purified by SCX resin, eluting with a 2.0 M solution of ammonia in methanol. Product containing fractions were combined and concentrated and the resulting solid was dissolved in diethyl ether and treated with a 1.0 M solution of hydrochloric acid in diethyl ether. The precipitated salt was collected by filtration to give 0.09 g (69%) of the title compound **11a** as an off-white solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.36 (m, 4H), 5.15 (s, 2H), 7.30-7.38 (m, 5H).
MS (ES+): 192.3 (M+1).

2,2-Dimethyl-propionic acid benzyl ester (12a): Prepared by General Procedure, obtained 0.9 g (51%) product isolated as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 9H), 5.10 (s, 2H), 7.29-7.35 (m, 5H).

(S)-2-Amino-3-methyl-butyric acid 2-(2-amino-6-oxo-1,6-dihydro-purin-9-ylmethoxy)-ethyl ester (valacyclovir hydrochloride) (13): CAS 124832-26-4, purchased from Moravek Biochmemicals, Inc., Brea, CA.

1-*tert*-Butoxycarbonylamino-cyclopropanecarboxylic acid 2-(2-amino-6-oxo-1,6-dihydro-purin-9-ylmethoxy)-ethyl ester
9-[(2-Hyrdoxyethoxy)methyl]-guanine (Acyclovir) (0.50 g, 2.22 mmol) was combined with Boc-aminocyclopropyl carboxcylic acid (0.58 g, 2.89 mmol) , 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (0.64 g, 3.33 mmol) and 4-dimethylaminopyridine (0.05 g, 0.36 mmol) in dry N,N-dimethylformamide (3 mL) . Triethylamine (0.31 g, 3.11 mmol) was added and the resulting suspension was stirred at room temperature under nitrogen overnight. The reaction mixture was cooled to 0ºC and 10 mL of a 0.3 M solution of hydrochloric acid was added to precipitate a white solid. The solid was collected by vacuum filtration and washed with diethyl ether. The resulting crude solid was recrystallized from isopropanol to give 0.85 g (94%) of the title compound as a white solid. ^{1}H NMR (400 MHz, d_6-DMSO): δ 0.93-0.96 (m, 2H); 1.20-1.23 (m, 2H); 1.31 (s, 9H); 3.58 (m, 2H); 4.05 (m, 2H); 5.30 (s, 2H); 6.48 (s, 2H); 7.48 (s, 1H); 7.76 (s, 1H); 10.60 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.36, 28.53, 33.94, 63.95, 66.84, 72.26, 78.49, 116.87, 130.02, 151.79, 154.34, 156.09, 157.14, 173.02. HRMS calc'd for $C_{17}H_{24}N_6O_6$, 408.1757 *m/z* (M+); observed 408.1779 *m/z* (M+); purity (LC-MS) 100%.

1-amino-cyclopropanecarboxylic acid 2-(2-amino-6-oxo-1,6-dihydro-purin-9-ylmethoxy)-ethyl ester trifluoroacetic acid salt (14)
1-tert-Butoxycarbonylamino-cyclopropanecarboxylic acid 2-(2-amino-6-oxo-1,6-dihydro-purin-9-ylmethoxy)-ethyl ester (0.20 g, 0.49 mmol) was suspended in methylene chloride (2 mL) and stirred at room temperature. Trifluoroacetic acid (2.0 mL, 2.45 mmol) was added dropwise and the reaction was stirred at room temperature under

nitrogen. The reaction mixture was concentrated in vacuo and triturated several times with ethyl acetate to isolate 0.14 g (68%) of the title compound as a white solid. ^{1}HNMR (400 MHz, d_6–DMSO): δ 1.26-1.30 (m, 4H); 3.65 (t, 2H); 4.21 (t, 2H); 5.33 (s, 2H); 6.49 (s, 2H); 7.82 (s, 1H); 8.64 (s, 2H); 10.66 (s, 1H).

1-amino-cyclopropanecarboxylic acid 2-(2-amino-6-oxo-1,6-dihydro-purin-9-ylmethoxy)-ethyl ester (14a)

The trifluoroacetic acid salt was converted to the corresponding free base by ion exchange chromatography (Varian Mega BondElut SCX – 5g cartridge) eluting with a 2 M solution of ammonia in methanol. The free base was isolated as a white solid.

^{1}HNMR (400 MHz, d_6–DMSO): δ 0.77 (q, 2H); 0.99 (q, 2H); 4.61 (m, 2H); 4.04 (m, 2H); 5.31 (s, 2H); 6.47 (s, 2H); 7.78 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ18.1, 35.8, 63.6, 66.8, 72.2, 116.9, 138.1, 151.8, 154.3, 157.2, 176.1. HRMS calc'd for $C_{12}H_{16}N_6O_4$, 308.1233 *m/z* (M+); observed 308.1237 *m/z* (M+).

II. Stability Analysis

Summary:
Solution stability testing was performed using a semi-automated high performance liquid chromatography (HPLC) technique. The procedure monitors the compound peak area over a 24-hour period with automated sampling at 2-hour intervals. Hydrolytic degradation products are separated from the intact esters. A plot of ester peak area versus time is generated to obtain a first order degradation rate constant and half-life ($t_{1/2}$).

Semi-Automated Parameters:

- 2-hour timepoints for 24 hours (total of 13 data points)
- Incubation temperature = 40ºC

HPLC Method and Equipment:

The HPLC system consisted of an Agilent 1100 autoinjector, pump, degasser and UV detector. A Waters Atlantis dC-18 column (3micron, 150 x 4.6 mm I.D.) was used to separate the degradation (hydrolysis) products from the ester compounds. An isocratic reversed-phase system using ultraviolet detection was used to monitor the peak areas of the compound over a 24-hour period. The mobile phase composition was 15% acetonitrile and 85% water with 0.1% trifluoroacetic acid added to the mixture. The flow rate was set at 1.5 mL/min. The column temperature was set at 50 degrees Celsius and the injection volume was 10 µL. The UV detector was set at 210nm and the run time was 9 minutes. Timepoints were analyzed every 2-hours for each buffer while being incubated at 40 degrees Celsius by the thermostat controlled autosampler.

Buffers:

Six buffers representing the biological pH range of the human gastrointestinal tract were used to evaluate pH dependent hydrolysis.

- pH1 (0.1N HCl)
- pH2 (50 mM phosphate)
- pH4 (50 mM phosphate)
- pH6 (50 mM phosphate)
- pH8 (50 mM phosphate)
- pH10 (50 mM phosphate)

Sample Preparation;

Samples were prepared at 100 microgram/mL concentrations in buffers with the addition of 25% acetonitrile (ACN) to insure the compounds remained in solution during the experiment. The addition of ACN was not necessary for either valacyclovir or the cyclopropane ester of acyclovir.

Rate Constant and Half-Life Calculations:

The HPLC peak area of the ester was monitored over a 24-hour period and sampled at 2-hour intervals. The peak area of the ester was plotted versus time for each of the buffers tested. The loss of peak area over time exactly followed first order kinetics and a rate

constant (k) for each buffer was obtained. The $t_{1/2}$ was calculated by dividing 0.693 by the rate constant ($t_{1/2}$=0.693/k). Half-lives reported as ">300 hours" reflect the limitation of the procedure. Accurate $t_{1/2}$ values greater than 300 hours were not reported since only a miniscule loss of peak area was observed during the 24-hour experiment and the variability of the HPLC analysis and peak area integration could misrepresent the results. Longer experiment times or Arrhenius plots are necessary to get accurate half-lives greater than 300 hours.

Arrhenius Calculation for Cyclopropyl Acyclovir:

Samples of the cyclopropane ester prodrug of acyclovir were prepared in pH 6 phsophate buffer (100 micrograms/mL) and stored in ovens at approximately 45ºC, 55ºC and 65ºC for up to 7 days. Samples were taken at various timepoints including initial and stored at -70ºC until a pooled HPLC analysis was performed at the end of the study. A rate constant (k) was determined for each temperature condition and then plotted versus temperature (°K). Results show a linear fit from which a 5ºC half-life could be extrapolated and calculated.

Figure S1. Arrhenius Plot for Cyclopropyl Acyclovir

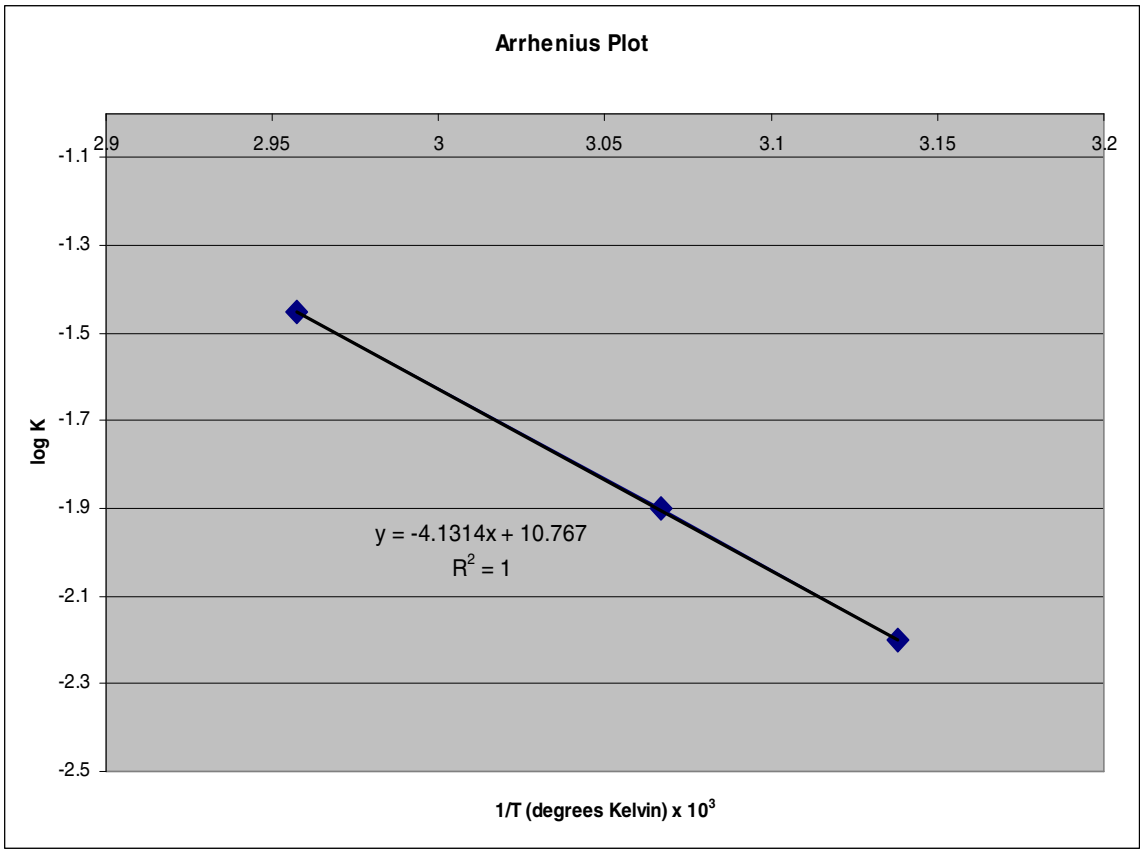


Figure S2. Overlaid chromatogram showing the degradation of valacyclovir (1) in pH 10 buffer stored at 40°C over a 24-hour period

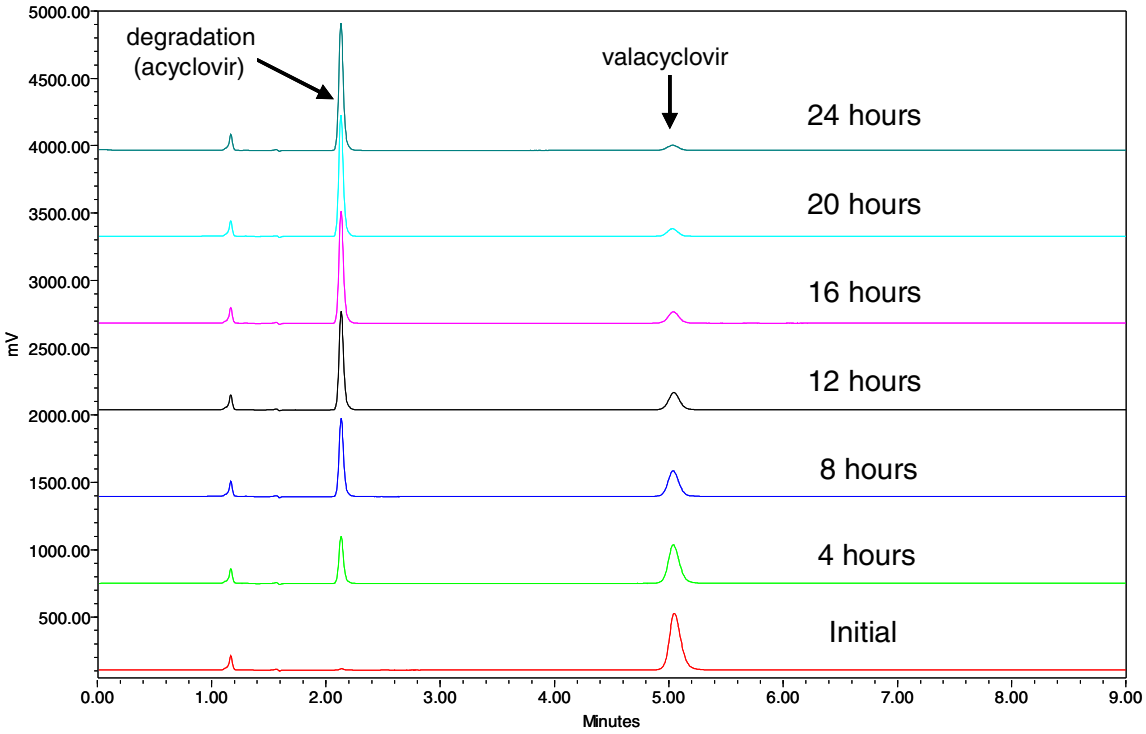


Figure S3. pH Stability Plot – Rate Constant and $t_{1/2}$ Determination:
Plot of raw data showing the degradation rate of valacyclovir (1) in pH1-10 buffers stored at 40°C over a 24-hour period.

	Peak Area Counts												
Hours	0	2	4	6	8	10	12	14	16	18	20	22	24
pH10	1506915	1231925	1004993	819183	666530	544920	443694	360769	295081	238486	196694	160180	131011
pH8	1491604	1238032	1038540	872180	729714	610690	511238	428166	357953	300573	252714	211433	177100
pH6	1489405	1463939	1437310	1411642	1381243	1354945	1325908	1299106	1277310	1251252	1222360	1198949	1177264
pH4	1499565	1500782	1501189	1499872	1502654	1504029	1500071	1501548	1498625	1500165	1503767	1499386	1496954
pH2	1494873	1497982	1497982	1499866	1497283	1496278	1499995	1498980	1498745	1500574	1502297	1494084	1499563
0.1N HCL	1494431	1496888	1497755	1498173	1492737	1495760	1494544	1498171	1494589	1498799	1489398	1493578	1494350

	% Remaining														
Hours	0	2	4	6	8	10	12	14	16	18	20	22	24	Rate (k)	$T_{1/2}$
pH10	100.0%	81.8%	66.7%	54.4%	44.2%	36.2%	29.4%	23.9%	19.6%	15.8%	13.1%	10.6%	8.7%	0.101989	6.8
pH8	100.0%	83.0%	69.6%	58.5%	48.9%	40.9%	34.3%	28.7%	24.0%	20.2%	16.9%	14.2%	11.9%	0.088602	7.8
pH6	100.0%	98.3%	96.5%	94.8%	92.7%	91.0%	89.0%	87.2%	85.8%	84.0%	82.1%	80.5%	79.0%	0.009939	69.7
pH4	100.0%	100.1%	100.1%	100.0%	100.2%	100.3%	100.0%	100.1%	99.9%	100.0%	100.3%	100.0%	99.8%	0.000040	>300
pH2	100.0%	100.2%	100.2%	100.3%	100.2%	100.1%	100.3%	100.3%	100.3%	100.4%	100.5%	99.9%	100.3%	-0.000062	>300
0.1N HCL	100.0%	100.2%	100.2%	100.3%	99.9%	100.1%	100.0%	100.3%	100.0%	100.3%	99.7%	99.9%	100.0%	0.000078	>300

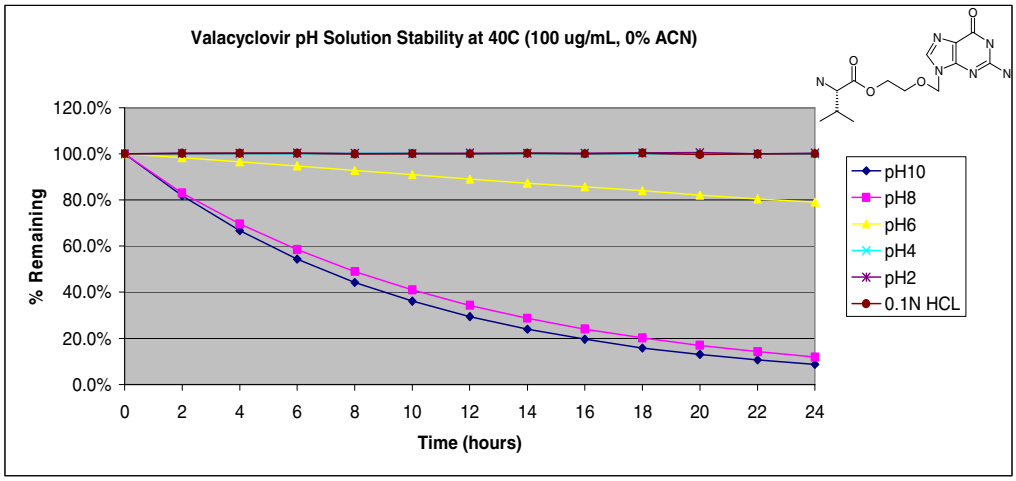


Figure S4: Overlaid chromatogram showing the degradation of cyclopropyl acyclovir (15) in pH 10 buffer stored at 40°C over a 24-hour period.

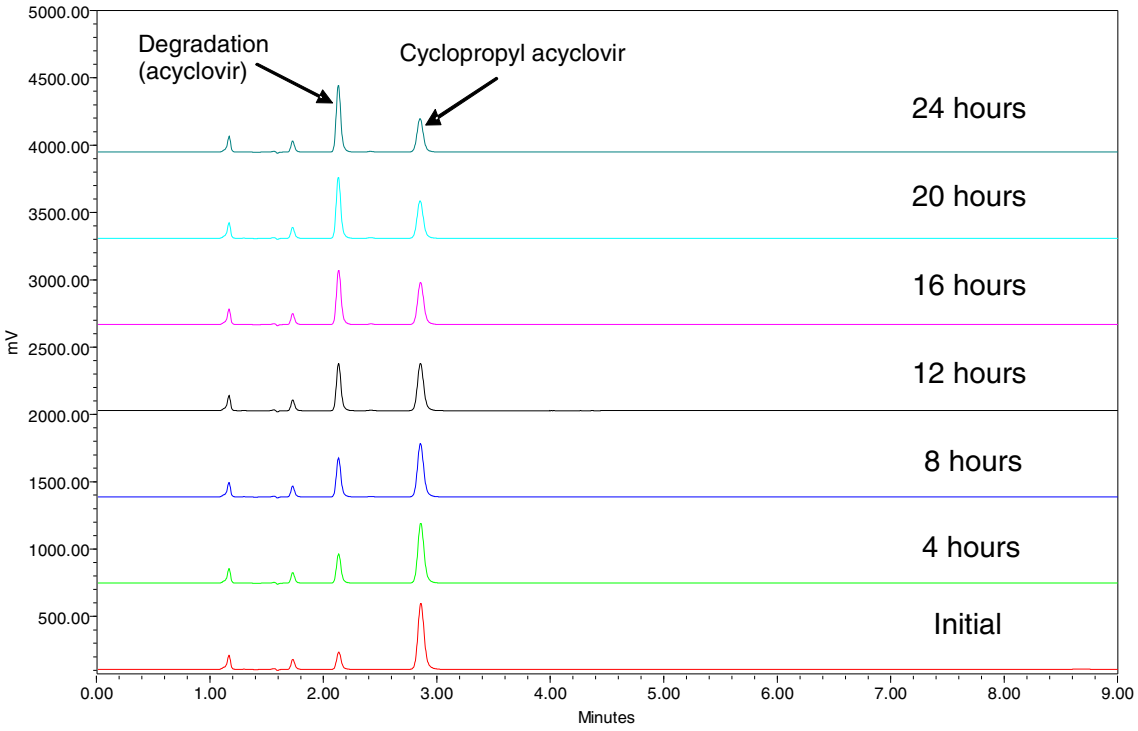


Figure S5: pH Stability Plot – Rate Constant and $t_{1/2}$ Determination:
Plot of raw data showing the degradation rate of cyclopropyl acyclovir in pH1-10 buffers stored at 40°C over a 24-hour period.

Peak Area Counts													
Hours	0	2	4	6	8	10	12	14	16	18	20	22	24
pH10	981082	941525	892121	840848	791233	745392	700598	660616	622328	587294	554583	524512	494614
pH8	990549	992060	984673	972100	960903	959553	930676	912705	898450	880864	866302	849179	834253
pH6	991508	992364	990021	989406	983295	980522	976043	972338	967948	960370	956167	950538	945016
pH4	990324	1003550	1012492	1016294	1020929	1024136	1025089	1026514	1030839	1030719	1032090	1034018	1034622
pH2	1008300	1030643	1039867	1047438	1051181	1051367	1052777	1050105	1049272	1051112	1049484	1049588	1050829
0.1N HCL	1008516	1030531	1041010	1044280	1047684	1048546	1049081	1050237	1050528	1050523	1046433	1046877	1046983

% Remaining															
Hours	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**Rate (k)**	**$T_{1/2}$**
pH10	100.0%	96.0%	90.9%	85.7%	80.6%	76.0%	71.4%	67.3%	63.4%	59.9%	56.5%	53.5%	50.4%	0.029158	23.8
pH8	100.0%	100.2%	99.4%	98.1%	97.0%	96.9%	94.0%	92.1%	90.7%	88.9%	87.5%	85.7%	84.2%	0.007693	90.1
pH6	100.0%	100.1%	99.9%	99.8%	99.2%	98.9%	98.4%	98.1%	97.6%	96.9%	96.4%	95.9%	95.3%	0.002120	>300
pH4	100.0%	101.3%	102.2%	102.6%	103.1%	103.4%	103.5%	103.7%	104.1%	104.1%	104.2%	104.4%	104.5%	-0.001518	>300
pH2	100.0%	102.2%	103.1%	103.9%	104.3%	104.3%	104.4%	104.1%	104.1%	104.2%	104.1%	104.1%	104.2%	-0.001048	>300
0.1N HCL	100.0%	102.2%	103.2%	103.5%	103.9%	104.0%	104.0%	104.1%	104.2%	104.2%	103.8%	103.8%	103.8%	-0.000959	>300

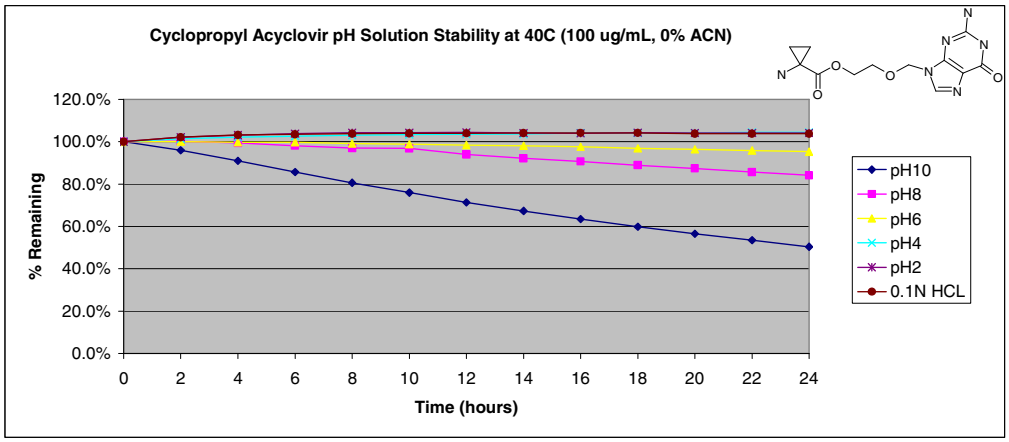
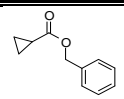
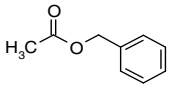
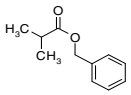
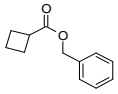
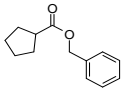
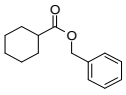
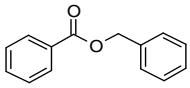
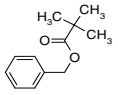
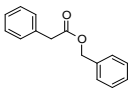
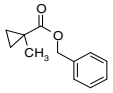
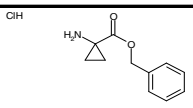
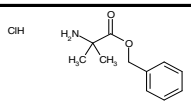
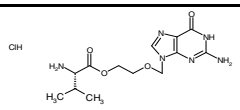
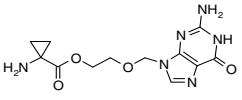


Table S1: Summary of Stability Results

		$t_{1/2}$ at 40C (hours)					
ester	**Structure**	**pH1**	**pH 2**	**pH 4**	**pH 6**	**pH 8**	**pH 10**
3a		180.2	>300	>300	>300	>300	78.7
4a		14.2	255.0	>300	>300	208.0	49.3
5a		32.1	265.5	>300	>300	260.4	40.0
6a		14.1	293.0	>300	>300	287.0	16.0
7a		26.3	>300	>300	>300	>300	43.1
8a		52.4	>300	>300	>300	>300	87.0
9a		>300	>300	>300	>300	>300	55.4
10a		125.7	231.6	267.1	>300	>300	142.4
11a		36.1	>300	>300	>300	>300	12.0
12a		267.5	>300	>300	>300	>300	192.0
13a		>300	>300	>300	>300	266.6	43.1
14a		>300	>300	>300	44.1	11.2	7.8
1 (valacyclovir)		>300	>300	>300	69.7	7.8	6.8
15 (cyclopropyl acyclovir)		>300	>300	>300	>300	90.1	23.8

III. Computed Geometries and Energies

Geometries and energies of the structures for isodesmic reactions computed at CBS-QB3 level.

Methyl formate

C -0.832952 0.431034 0.000012
O -1.301427 -0.672862 0.000002
O 0.474843 0.729510 0.000024
H -1.409510 1.367300 -0.000104
C 1.370780 -0.400426 -0.000021
H 2.372615 0.022143 -0.001439
H 1.212277 -1.012373 0.889264
H 1.210318 -1.013910 -0.887877
CBS-QB3 (0 K)= -228.739234 CBS-QB3 Energy= -228.734649
CBS-QB3 Enthalpy= -228.733705 CBS-QB3 Free Energy= -228.766153

Methane

C 0.000000 0.000000 0.000000
H 0.629587 0.629587 0.629587
H -0.629587 -0.629587 0.629587
H -0.629587 0.629587 -0.629587
H 0.629587 -0.629587 -0.629587
CBS-QB3 (0 K)= -40.409988 CBS-QB3 Energy= -40.407117
CBS-QB3 Enthalpy= -40.406173 CBS-QB3 Free Energy= -40.427305

Methylcyclopropane

C -0.956881 -0.755825 -0.140305
C -0.956877 0.755827 -0.140304
C 0.181065 -0.000002 0.498844
H -1.664719 -1.268056 0.500747
H -0.760982 -1.261041 -1.079781
H -1.664709 1.268063 0.500750
H -0.760978 1.261043 -1.079780
H 0.188265 -0.000003 1.585166
C 1.553851 -0.000001 -0.136660
H 2.128431 0.884581 0.155913
H 2.128416 -0.884602 0.155882
H 1.479335 0.000019 -1.228345
CBS-QB3 (0 K)= -156.861328 CBS-QB3 Energy= -156.856647
CBS-QB3 Enthalpy= -156.855703 CBS-QB3 Free Energy= -156.887880

Ethane

C 0.000000 0.000000 0.765229
H 0.508992 0.882231 1.163787
H 0.509538 -0.881915 1.163787

H -1.018530 -0.000316 1.163787
C 0.000000 0.000000 -0.765229
H 1.018530 -0.000316 -1.163787
H -0.509538 -0.881915 -1.163787
H -0.508992 0.882231 -1.163787
CBS-QB3 (0 K)= -79.630575 CBS-QB3 Energy= -79.627078
CBS-QB3 Enthalpy= -79.626134 CBS-QB3 Free Energy= -79.652006

Isobutane

C 0.000099 -0.000244 -0.372425
H 0.000228 -0.000173 -1.470328
C -1.379344 -0.482580 0.095787
H -1.596093 -1.489432 -0.273142
H -1.430845 -0.511036 1.189849
H -2.174116 0.181578 -0.256611
C 0.271618 1.435765 0.095801
H 0.283792 1.491718 1.189908
H 1.238911 1.796742 -0.266051
H -0.498345 2.124994 -0.263395
C 1.107656 -0.953027 0.095870
H 0.936619 -1.970550 -0.267632
H 2.089224 -0.629397 -0.262796
H 1.150446 -0.993926 1.189998
CBS-QB3 (0 K)= -158.084558 CBS-QB3 Energy= -158.078791
CBS-QB3 Enthalpy= -158.077847 CBS-QB3 Free Energy= -158.112239

Methylcyclobutane

C -0.500462 1.082959 0.067737
C 0.507898 0.000000 -0.414435
C -0.500463 -1.082960 0.067738
C -1.612708 0.000001 0.063036
H -0.266326 1.413993 1.084208
H -0.640673 1.965124 -0.560995
H 0.542637 -0.000001 -1.509579
H -0.266328 -1.413996 1.084208
H -0.640676 -1.965123 -0.560997
H -2.323076 0.000002 0.891930
H -2.174167 0.000000 -0.874484
C 1.922265 0.000000 0.144523
H 2.479709 -0.883776 -0.182700
H 2.479708 0.883777 -0.182700
H 1.910007 0.000000 1.239518
CBS-QB3 (0 K)= -196.090202 CBS-QB3 Energy= -196.084660
CBS-QB3 Enthalpy= -196.083716 CBS-QB3 Free Energy= -196.118423

Methylcyclopentane

C 0.114982 1.200808 0.533874
C -0.856341 0.001069 0.545452
C 0.114054 -1.199366 0.536814

C 1.270173 -0.779854 -0.403278
C 1.273385 0.777350 -0.402123
H -0.365400 2.130832 0.217445
H 0.495980 1.364709 1.547316
H -1.462314 0.002427 1.457515
H 0.497264 -1.359149 1.550115
H -0.367363 -2.130483 0.225181
H 2.225154 -1.193131 -0.070948
H 1.102829 -1.160610 -1.414033
H 2.228559 1.185742 -0.064331
H 1.112936 1.160506 -1.413055
C -1.802731 -0.000018 -0.662822
H -2.447833 -0.883735 -0.656010
H -2.447750 0.883763 -0.657517
H -1.253199 -0.000798 -1.609187
CBS-QB3 (0 K)= -235.344891 CBS-QB3 Energy= -235.338321
CBS-QB3 Enthalpy= -235.337376 CBS-QB3 Free Energy= -235.375285

Methylcyclohexane

C 0.293945 1.262639 0.168651
C 1.019900 -0.000003 -0.328487
C 0.293941 -1.262641 0.168656
C -1.194643 -1.267412 -0.209080
C -1.906512 0.000001 0.284117
C -1.194641 1.267413 -0.209080
H 0.787321 -2.155867 -0.230559
H 0.968006 -0.000005 -1.427244
H 0.390281 1.317489 1.262000
H 0.787322 2.155862 -0.230576
H -1.289147 -1.331632 -1.300927
H -1.682940 -2.159381 0.197056
H -2.951510 0.000005 -0.042861
H -1.923616 0.000000 1.381873
H -1.289151 1.331640 -1.300925
H -1.682931 2.159382 0.197066
H 0.390271 -1.317482 1.262006
C 2.497857 0.000000 0.073856
H 3.015221 -0.884005 -0.311286
H 3.015216 0.884012 -0.311278
H 2.606569 -0.000005 1.163859
CBS-QB3 (0 K)= -274.581553 CBS-QB3 Energy= -274.574312
CBS-QB3 Enthalpy= -274.573368 CBS-QB3 Free Energy= -274.612208

Toluene

C 0.193957 -1.199991 -0.008844
C 0.912353 0.000295 -0.011813
C 0.193618 1.200176 -0.008849
C -1.199377 1.202776 0.002126

C -1.901749 -0.000191 0.008390
C -1.198874 -1.203046 0.002119
H 0.732225 -2.142685 -0.017559
H 0.731542 2.143044 -0.017565
H -1.736134 2.145182 0.001795
H -2.985879 -0.000422 0.013879
H -1.735383 -2.145596 0.001780
C 2.422598 0.000121 0.009414
H 2.801166 -0.016544 1.037549
H 2.828781 -0.876089 -0.501740
H 2.828533 0.892263 -0.473391
CBS-QB3 (0 K)= -271.020445 CBS-QB3 Energy= -271.014184
CBS-QB3 Enthalpy= -271.013240 CBS-QB3 Free Energy= -271.051035

1b

C -0.326295 0.116594 -0.000109
O -0.438935 1.320224 -0.000005
O -1.379275 -0.730013 -0.000025
C -2.675776 -0.106665 0.000041
H -3.392018 -0.925344 -0.000238
H -2.802259 0.514511 0.888130
H -2.802114 0.515019 -0.887708
C 0.959473 -0.625365 -0.000037
C 2.125509 0.002742 -0.745733
C 2.125424 0.002719 0.745818
H 0.873508 -1.703415 -0.000054
H 1.919517 0.941005 -1.244809
H 2.789898 -0.672270 -1.270605
H 2.789754 -0.672309 1.270743
H 1.919379 0.940967 1.244901
CBS-QB3 (0 K)= -345.211719 CBS-QB3 Energy= -345.204269
CBS-QB3 Enthalpy= -345.203325 CBS-QB3 Free Energy= -345.243615

2b

C 0.462552 0.179540 0.000001
O 0.290194 1.371485 0.000003
O -0.548766 -0.719242 0.000023
C -1.874869 -0.161669 -0.000018
H -2.549758 -1.014768 -0.001094
H -2.033052 0.451993 0.888337
H -2.032301 0.453726 -0.887291
C 1.799054 -0.519448 -0.000007
H 1.884085 -1.160611 0.880168
H 1.884057 -1.160654 -0.880153
H 2.595126 0.221832 -0.000033
CBS-QB3 (0 K)= -267.977056 CBS-QB3 Energy= -267.970809
CBS-QB3 Enthalpy= -267.969865 CBS-QB3 Free Energy= -268.007051

3b

C -0.329077 0.506985 -0.015717
O -0.929324 1.552207 -0.047283
O -0.946190 -0.697274 0.021462
C -2.383966 -0.662968 0.020674
H -2.700963 -1.703157 0.051179
H -2.754749 -0.122514 0.893047
H -2.755068 -0.174403 -0.881647
C 1.184566 0.359913 -0.011827
C 1.669227 -0.395032 -1.260993
C 1.670619 -0.313133 1.282756
H 1.561410 1.385058 -0.045047
H 1.339937 0.099544 -2.178549
H 2.761699 -0.434220 -1.274265
H 1.288392 -1.418445 -1.268322
H 1.342588 0.239698 2.166911
H 1.289553 -1.333809 1.356737
H 2.763088 -0.351821 1.297166
CBS-QB3 (0 K)= -346.429724 CBS-QB3 Energy= -346.420952
CBS-QB3 Enthalpy= -346.420008 CBS-QB3 Free Energy= -346.463465

4b

C 0.718917 0.162728 -0.008445
O 0.896076 1.354676 -0.092220
O 1.728782 -0.732971 0.051872
C 3.056233 -0.178137 0.009652
H 3.730367 -1.029878 0.067190
H 3.210766 0.373293 -0.919099
H 3.215689 0.496663 0.852132
C -0.630894 -0.502788 0.039925
C -1.651537 0.056827 1.078491
C -1.646493 -0.109499 -1.077209
H -0.513233 -1.583185 0.123222
C -2.760498 -0.042478 -0.000743
H -1.414661 1.094631 1.319098
H -1.777084 -0.511240 2.001647
H -1.408457 0.879174 -1.473316
H -1.767854 -0.812634 -1.902796
H -3.473640 0.780722 -0.065760
H -3.315120 -0.981106 0.070449
CBS-QB3 (0 K)= -384.436824 CBS-QB3 Energy= -384.428297
CBS-QB3 Enthalpy= -384.427352 CBS-QB3 Free Energy= -384.471478

5b

C 1.043200 0.297532 0.015113
O 1.304087 1.196722 0.776345
O 1.977622 -0.549868 -0.473202
C 3.322177 -0.329103 -0.011368
H 3.928032 -1.085655 -0.505297

H 3.660823 0.672023 -0.282597
H 3.378720 -0.439676 1.072819
C -0.337294 -0.074994 -0.481421
C -1.003246 -1.135016 0.437192
C -1.336147 1.111026 -0.508072
H -0.224836 -0.510683 -1.477200
C -2.497329 -0.962631 0.136770
H -0.804785 -0.887539 1.485937
H -0.625492 -2.142390 0.251674
C -2.676063 0.565478 0.059025
H -1.450767 1.487787 -1.526941
H -0.952418 1.930291 0.100697
H -2.733854 -1.423748 -0.828885
H -3.138702 -1.430314 0.887889
H -3.535941 0.854740 -0.549112
H -2.846250 0.966579 1.062440
CBS-QB3 (0 K)= -423.692916 CBS-QB3 Energy= -423.683384
CBS-QB3 Enthalpy= -423.682440 CBS-QB3 Free Energy= -423.729317

6b

C 1.374232 -0.332469 0.070197
O 1.741067 -1.175584 0.851077
O 2.221145 0.538300 -0.527319
C 3.605374 0.416854 -0.155219
H 4.128827 1.182002 -0.724397
H 3.730696 0.581988 0.916171
H 3.983818 -0.575221 -0.406440
C -0.059915 -0.071043 -0.349379
C -0.945743 -1.305652 -0.126748
C -0.610923 1.157157 0.416028
H -0.041019 0.183926 -1.415534
C -2.409122 -1.021007 -0.491330
H -0.870990 -1.604084 0.923855
H -0.563506 -2.147465 -0.711834
C -2.074955 1.433069 0.047886
H -0.534741 0.962792 1.493091
H 0.010375 2.030983 0.202719
C -2.957346 0.196475 0.265766
H -3.020345 -1.904261 -0.281189
H -2.487928 -0.839496 -1.571266
H -2.449629 2.277235 0.635518
H -2.130191 1.736889 -1.005380
H -3.985275 0.406270 -0.046760
H -2.997404 -0.033583 1.338178
CBS-QB3 (0 K)= -462.928153 CBS-QB3 Energy= -462.917779
CBS-QB3 Enthalpy= -462.916835 CBS-QB3 Free Energy= -462.964930

7b

C 1.233548 0.395833 -0.000363
O 1.724700 1.500367 -0.000745
O 1.969804 -0.737406 0.000341
C 3.394969 -0.550871 0.000318
H 3.819641 -1.552324 -0.002252
H 3.708582 0.002424 -0.886250
H 3.709037 -0.002157 0.889620
C -0.231753 0.121569 0.000052
C -1.100979 1.217433 0.000423
C -0.750676 -1.177755 -0.000153
C -2.476225 1.016198 0.000369
H -0.678168 2.214379 0.000712
C -2.127971 -1.374744 -0.000289
H -0.072998 -2.020983 -0.000293
C -2.991262 -0.279989 -0.000054
H -3.147224 1.867577 0.000585
H -2.528545 -2.382050 -0.000481
H -4.064261 -0.436597 -0.000221
CBS-QB3 (0 K)= -459.367911 CBS-QB3 Energy= -459.359021
CBS-QB3 Enthalpy= -459.358077 CBS-QB3 Free Energy= -459.402403

B3LYP/6-31+G(d) optimized structures and energies for the tetrahedral (negatively charged and neutral) intermediates, transition structures and reactants.

Water

O 0.000000 0.000000 0.117266
H 0.000000 0.771292 -0.469066
H 0.000000 -0.771292 -0.469066
Sum of electronic and thermal Enthalpies= -76.397695
Sum of electronic and thermal Free Energies= -76.419134
(Polarized solute)-Solvent (kcal/mol) = -12.52

Hydroxide

O 0.000000 0.000000 0.108319
H 0.000000 0.000000 -0.866552
Sum of electronic and thermal Enthalpies= -75.785045
Sum of electronic and thermal Free Energies= -75.804622
(Polarized solute)-Solvent (kcal/mol) = -100.82

1b

C -0.326935 0.118221 -0.000007
O -0.444352 1.330454 0.000195
O -1.383317 -0.729280 -0.000132
C -2.683699 -0.112222 -0.000090
H -3.394722 -0.938971 -0.000915
H -2.811654 0.507205 0.891733
H -2.811106 0.508563 -0.891037
C 0.960425 -0.621603 -0.000091

C 2.133664 -0.000181 -0.746732
C 2.133608 -0.000439 0.746857
H 0.872746 -1.702848 -0.000277
H 1.939245 0.941898 -1.250850
H 2.792708 -0.684459 -1.273890
H 2.792612 -0.684899 1.273828
H 1.939153 0.941465 1.251287
Sum of electronic and thermal Enthalpies= -345.657166
Sum of electronic and thermal Free Energies= -345.697283
(Polarized solute)-Solvent (kcal/mol) = -10.45

1b – anionic tetrahedral intermediate

C 2.486826 -0.683684 0.031683
O 1.198748 -0.729336 -0.527489
C 0.259052 0.270111 0.074161
C -1.073062 -0.109537 -0.595729
C -2.353783 0.357701 0.041951
C -1.968852 -1.108502 0.087097
O 0.277032 0.343715 1.362032
O 0.672375 1.565902 -0.558088
H 3.039969 -1.552695 -0.353632
H 3.028521 0.234382 -0.257606
H 2.447271 -0.731778 1.130016
H -1.040625 -0.133495 -1.683738
H -1.611097 -1.490760 1.040269
H -2.527035 -1.818286 -0.523998
H -3.177984 0.665810 -0.601734
H -2.246128 0.919182 0.967246
H 0.800777 2.108852 0.236559

Sum of electronic and thermal Enthalpies= -421.484946
Sum of electronic and thermal Free Energies= -421.528326
(Polarized solute)-Solvent (kcal/mol) = -75.72

1b – neutral tetrahedral intermediate

C 2.554346 -0.576078 -0.045544
O 1.203694 -0.745527 -0.474365
C 0.279483 0.198055 -0.031198
C -1.063060 -0.180962 -0.618003
C -2.341997 0.406923 -0.060113
C -2.029416 -1.059164 0.129217
O 0.181357 0.239468 1.381103
O 0.717148 1.474066 -0.491178
H 3.117437 -1.379953 -0.523954
H 2.956462 0.391801 -0.364395
H 2.640651 -0.682452 1.043597

H -1.003381 -0.312035 -1.695012
H -1.743816 -1.380394 1.125724
H -2.589293 -1.790683 -0.447191
H -3.118032 0.691075 -0.766201
H -2.270288 1.038766 0.821244
H -0.046934 2.072591 -0.462625
H 0.843466 0.874588 1.698195
Sum of electronic and thermal Enthalpies= -422.032801
Sum of electronic and thermal Free Energies= -422.076354

1b – TS1

C 0.234298 -0.061487 0.189377
O 0.291172 -0.122984 1.427756
O 1.178001 -0.717193 -0.605562
O 0.832682 1.873819 -0.364273
H 0.642244 2.276577 0.499343
C 2.498752 -0.661448 -0.087829
H 3.139691 -1.148262 -0.832585
H 2.782855 0.389474 0.039952
H 2.577153 -1.190247 0.871815
C -1.067763 0.002693 -0.565059
C -2.297496 0.460669 0.157593
C -2.153943 -1.001792 -0.201768
H -2.767431 -1.412272 -1.003372
H -1.933531 -1.695269 0.606750
H -3.013347 1.069495 -0.392019
H -2.161632 0.732046 1.201476
H -0.963926 0.277512 -1.608612
Sum of electronic and thermal Enthalpies= -421.468332
Sum of electronic and thermal Free Energies= -421.511839
(Polarized solute)-Solvent (kcal/mol) = -81.15

1b – TS2

C 2.446447 -0.964528 0.157729
O 1.598543 -0.367470 -0.745311
C 0.014342 0.635433 0.222467
O 0.484357 1.782366 -0.439881
C -1.039382 -0.105686 -0.562433
C -2.481838 0.000455 -0.086366
C -1.715826 -1.296279 0.052164
O 0.095844 0.541051 1.445532
H -0.872487 -0.121781 -1.634090
H -1.380332 -1.572965 1.048201
H -1.974489 -2.128674 -0.600313
H -3.268684 0.070628 -0.836676
H -2.661720 0.575031 0.819298

H 2.551085 -2.065554 -0.005344
H 3.485535 -0.555564 0.126818
H 2.095541 -0.830509 1.206476
H 1.253134 1.365442 -0.908449
Sum of electronic and thermal Enthalpies= -421.479227
Sum of electronic and thermal Free Energies= -421.523053
(Polarized solute)-Solvent (kcal/mol) = -70.85

2b

C 0.464505 0.175608 -0.000015
O 0.294475 1.377638 0.000007
O -0.553310 -0.717754 0.000023
C -1.881479 -0.161367 -0.000015
H -2.553864 -1.019742 -0.000805
H -2.037540 0.451561 0.891815
H -2.036996 0.452832 -0.891054
C 1.802507 -0.522998 -0.000005
H 1.892422 -1.165636 0.882547
H 1.892397 -1.165715 -0.882501
H 2.601063 0.220172 -0.000043
Sum of electronic and thermal Enthalpies= -268.304767
Sum of electronic and thermal Free Energies= -268.341745
(Polarized solute)-Solvent (kcal/mol) = -10.55

2b – neutral tetrahedral intermediate

C -2.008944 0.178017 0.005434
H -2.124078 -0.497684 -0.848291
H -2.738942 0.986671 -0.066568
H -2.184138 -0.364830 0.945117
O -0.731711 0.813321 0.000611
C 0.392981 -0.010634 0.003462
O 0.303700 -0.837265 -1.151502
H 1.071511 -1.431286 -1.151012
O 0.483641 -0.834140 1.152225
C 1.616909 0.890966 -0.004419
H 1.581755 1.538153 -0.883775
H 2.528873 0.286213 -0.029530
H 1.628374 1.505868 0.899233
H -0.214072 -1.508531 1.097294
Sum of electronic and thermal Enthalpies= -344.684835
Sum of electronic and thermal Free Energies= -344.724179

3b

C 0.329577 0.501956 -0.010736
O 0.930072 1.558630 -0.033318
O 0.955752 -0.698332 0.015031

C 2.394705 -0.662771 0.014583
H 2.709886 -1.706501 0.037335
H 2.763300 -0.166913 -0.887476
H 2.762902 -0.128142 0.894373
C -1.185491 0.357674 -0.008253
C -1.678517 -0.325531 1.281225
C -1.677220 -0.383077 -1.266075
H -1.562820 1.385718 -0.031679
H -1.339280 0.211399 2.174744
H -2.774642 -0.343812 1.295692
H -1.317587 -1.357663 1.342764
H -1.336805 0.112761 -2.182596
H -1.316533 -1.417034 -1.280331
H -2.773337 -0.401703 -1.280981
Sum of electronic and thermal Enthalpies= -346.873471
Sum of electronic and thermal Free Energies= -346.917014
(Polarized solute)-Solvent (kcal/mol) = -9.90

3b – neutral tetrahedral intermediate

C -2.227603 -0.103631 -1.017630
O -0.806364 -0.112316 -0.900966
C -0.263924 0.049911 0.370605
C 1.272695 0.008988 0.251733
C 1.816906 1.201167 -0.549904
O -0.609153 1.286375 0.971047
C 1.757210 -1.326962 -0.329393
O -0.781906 -1.001782 1.179171
H -2.437702 -0.307959 -2.069462
H -2.685069 -0.879189 -0.394765
H -2.645052 0.881009 -0.764556
H -0.416587 -0.893350 2.072351
H 1.640198 0.097549 1.285201
H 2.852386 -1.370431 -0.298153
H 1.363046 -2.180458 0.231370
H 1.441472 -1.433266 -1.372586
H 2.913137 1.171246 -0.562942
H 1.463464 1.162896 -1.586094
H 1.503512 2.154349 -0.114779
H -1.545124 1.242536 1.227936

Sum of electronic and thermal Enthalpies= -423.253454
Sum of electronic and thermal Free Energies= -423.299155

4b

C 0.721222 0.167678 -0.011489
O 0.908965 1.364208 -0.125128

O 1.730414 -0.732159 0.070001
C 3.063998 -0.191472 0.013996
H 3.728528 -1.052455 0.092680
H 3.221750 0.334571 -0.931429
H 3.228652 0.501883 0.843214
C -0.633436 -0.489615 0.053316
C -1.659495 0.091380 1.075882
C -1.651880 -0.134977 -1.075425
H -0.518394 -1.570674 0.166943
C -2.767771 -0.058253 0.000077
H -1.438434 1.142195 1.287257
H -1.776212 -0.452172 2.019124
H -1.428966 0.848944 -1.499681
H -1.762211 -0.863221 -1.885547
H -3.497729 0.752745 -0.087618
H -3.307848 -1.006656 0.097932
Sum of electronic and thermal Enthalpies= -384.940876
Sum of electronic and thermal Free Energies= -384.984835
(Polarized solute)-Solvent (kcal/mol) = -9.79

4b – anionic tetrahedral intermediate

C -2.743953 -0.873686 0.008448
O -1.547104 -0.571685 -0.661210
C -0.603217 0.361966 0.166722
O -0.687281 0.243753 1.425477
C 0.761776 0.048945 -0.492210
C 1.985145 0.851728 0.030679
C 2.820855 -0.458511 0.014111
C 1.486495 -1.252179 -0.053144
O -1.015279 1.718281 -0.318485
H -3.147627 -1.807240 -0.414551
H -2.560401 -1.002141 1.085044
H -3.507169 -0.081106 -0.113336
H 0.682610 0.107349 -1.586392
H 1.786244 1.198078 1.050739
H 2.342737 1.694940 -0.574560
H 1.131294 -1.543224 0.941587
H 1.437512 -2.117162 -0.727280
H 3.487783 -0.650064 0.867713
H 3.408197 -0.560478 -0.909663
H -1.306474 1.568671 -1.233191

Sum of electronic and thermal Enthalpies= -460.768709
Sum of electronic and thermal Free Energies= -460.815101
(Polarized solute)-Solvent (kcal/mol) = -74.04

4b – neutral tetrahedral intermediate

C -2.777824 -0.795452 -0.033844
O -1.453031 -0.712255 -0.562121
C -0.616129 0.277328 -0.010134
O -0.645672 0.279402 1.389722
C 0.788435 -0.019210 -0.523698
C 1.957323 0.891703 -0.063412
C 2.848563 -0.377378 0.044576
C 1.557018 -1.241977 0.049119
O -1.065102 1.577093 -0.387175
H -3.290971 -1.546092 -0.638697
H -2.761323 -1.116801 1.013134
H -3.306434 0.162497 -0.118986
H 0.735034 -0.076040 -1.618015
H 1.751503 1.329474 0.918277
H 2.276239 1.685600 -0.746859
H 1.225105 -1.475053 1.065332
H 1.549294 -2.158959 -0.548174
H 3.508662 -0.454471 0.914916
H 3.445926 -0.537282 -0.860431
H -1.185583 1.584139 -1.350724
H -1.181329 1.038974 1.671176

Sum of electronic and thermal Enthalpies= -461.322329
Sum of electronic and thermal Free Energies= -461.368445

4b – TS1

C -0.597064 -0.001077 0.224222
C 0.763093 -0.011571 -0.448255
O -1.479202 -0.766889 -0.553193
O -0.738501 0.059409 1.457732
C 1.696483 -1.234051 -0.150303
C 1.860971 0.905728 0.135976
H 0.634921 0.145566 -1.521466
C 2.890229 -0.246926 -0.041245
H 1.449551 -1.680035 0.820480
H 1.751997 -2.028534 -0.905841
H 3.618245 -0.414919 0.765272
H 3.440189 -0.165175 -0.988902
H 1.652540 1.111089 1.191691
H 2.040091 1.850314 -0.387556
C -2.821131 -0.739569 -0.096857
H -3.398803 -1.346841 -0.804008
H -2.912367 -1.158093 0.914405
H -3.181885 0.296087 -0.100330
O -1.121580 1.840382 -0.535713

H -1.135703 2.292124 0.324417
Sum of electronic and thermal Enthalpies= -460.757917
Sum of electronic and thermal Free Energies= -460.803964
(Polarized solute)-Solvent (kcal/mol) = -78.56

4b – TS2

C -0.438487 0.779570 0.188874
O -0.715942 0.721852 1.392479
O -0.791845 1.908999 -0.547197
H -1.563515 2.270658 -0.079257
C 0.748957 0.095590 -0.446208
C 1.181796 -1.272094 0.124562
C 2.667389 -0.822910 0.017306
C 2.171507 0.645588 -0.082151
H 2.661225 1.306588 -0.808849
H 2.162811 1.138337 0.897447
H 3.341158 -1.075925 0.847779
H 3.133446 -1.160109 -0.918430
H 0.862147 -2.155905 -0.435961
H 0.597893 0.052052 -1.526807
H 0.852985 -1.367431 1.164838
O -1.781766 -0.584754 -0.811034
C -2.551786 -1.254275 0.098593
H -3.653777 -1.149720 -0.089088
H -2.388781 -0.893571 1.142986
H -2.365414 -2.362559 0.125506

Sum of electronic and thermal Enthalpies= -460.761503
Sum of electronic and thermal Free Energies= -460.808748
(Polarized solute)-Solvent (kcal/mol) = -75.47

5b

C -1.190166 -1.212335 -0.086108
C -0.336405 0.048803 -0.363537
C -2.663861 -0.732082 -0.185681
C -1.170582 1.170949 0.294744
H -0.266959 0.227942 -1.442575
C -2.617789 0.822077 -0.104233
H -3.265262 -1.161381 0.623248
H -3.123943 -1.058099 -1.125369
H -1.040940 1.114583 1.382684
H -0.864906 2.172750 -0.028331
H -3.347852 1.228612 0.604406
H -2.848448 1.259495 -1.083759
H -0.967425 -1.567407 0.926355
C 1.064863 -0.051438 0.199117

O 1.337204 -0.271154 1.363716
O 2.008998 0.139765 -0.753440
C 3.376661 0.070104 -0.308092
H 3.980021 0.240140 -1.200381
H 3.572080 0.839711 0.443590
H 3.587816 -0.913230 0.120657
H -0.960129 -2.028475 -0.780002
Sum of electronic and thermal Enthalpies= -424.252744
Sum of electronic and thermal Free Energies= -424.300002
(Polarized solute)-Solvent (kcal/mol) = -9.77

5b – anionic tetrahedral intermediate

C 1.528632 1.134138 -0.099313
C 2.872201 0.386095 -0.142987
C 2.499689 -1.013146 0.380503
C 1.101830 -1.292342 -0.227828
C 0.477246 0.098002 -0.558873
C -0.900065 0.308882 0.132027
O -1.385527 1.645212 -0.332754
O -0.944172 0.210204 1.417878
O -1.766120 -0.670944 -0.610733
C -3.042668 -0.826156 -0.046842
H -3.514745 -1.689562 -0.538168
H -2.980718 -1.006786 1.036374
H -3.679047 0.061670 -0.215570
H 0.323837 0.187287 -1.642185
H 1.299037 1.422021 0.935534
H 1.516481 2.043407 -0.711882
H 1.191332 -1.900963 -1.138405
H 0.458884 -1.835714 0.470503
H 3.235877 0.314512 -1.181151
H 3.664595 0.871908 0.446510
H 3.245049 -1.782714 0.130247
H 2.422581 -0.975605 1.475963
H -1.637799 2.041931 0.516972
Sum of electronic and thermal Enthalpies= -500.085174
Sum of electronic and thermal Free Energies= -500.133605
(Polarized solute)-Solvent (kcal/mol) = -73.56

5b – neutral tetrahedral intermediate

C -2.667405 -1.010336 -0.134330
C -2.828852 0.484215 0.208353
C -1.503351 1.153210 -0.250961
C -0.499818 -0.009888 -0.504746
C -1.169798 -1.266331 0.093623
C 0.918204 0.273874 0.002915

O 1.421571 1.401036 -0.658399
O 1.675440 -0.888518 -0.255838
C 3.092077 -0.769344 -0.124644
O 0.983902 0.598460 1.387739
H 3.489867 -1.774595 -0.279595
H 3.500060 -0.094351 -0.885270
H 3.378009 -0.417144 0.874789
H -0.389138 -0.165193 -1.584759
H -0.978662 -1.331216 1.176169
H -0.803166 -2.193242 -0.357154
H -1.641949 1.739316 -1.165070
H -1.120292 1.839735 0.509991
H -2.915656 -1.187849 -1.190370
H -3.312757 -1.662540 0.466011
H -3.711999 0.933134 -0.260266
H -2.951944 0.598762 1.293539
H 0.816183 -0.214217 1.891867
H 1.947801 1.909191 -0.019161

Sum of electronic and thermal Enthalpies= -500.633382
Sum of electronic and thermal Free Energies= -500.682684

5b – TS1

C -0.482359 0.003530 -0.417062
C -1.418153 1.150504 0.045926
C -1.267671 -1.296888 -0.097099
C 0.890316 0.034101 0.249145
H -0.318754 0.069080 -1.496121
C -2.809640 0.511018 0.317974
H -1.460712 1.927910 -0.722884
H -1.008959 1.612206 0.949277
C -2.736889 -0.897181 -0.309053
H -3.642211 1.107902 -0.080270
H -2.977622 0.414011 1.400425
H -2.953871 -0.842190 -1.387163
H -3.454761 -1.604640 0.132069
H -1.106484 -1.575251 0.954709
H -0.947727 -2.142416 -0.717839
O 1.722539 -0.872524 -0.416039
O 1.056803 0.274465 1.454739
C 3.077031 -0.827783 0.003703
H 3.614570 -1.553674 -0.617830
H 3.467481 0.183144 -0.162788
H 3.179744 -1.096430 1.063546
O 1.531537 1.738709 -0.796391
H 1.606461 2.311347 -0.014812

Sum of electronic and thermal Enthalpies= -500.068380
Sum of electronic and thermal Free Energies= -500.117361
(Polarized solute)-Solvent (kcal/mol) = -78.55

5b – TS2

C -0.454218 0.189322 -0.594789
C -0.823254 -1.251833 -0.166198
C -2.360460 -1.279319 -0.057467
C -2.698790 0.128996 0.460606
C -1.747416 1.042497 -0.339018
C 0.739212 0.738150 0.179217
O 0.888953 0.611157 1.404536
O 2.076566 -0.550127 -0.735510
C 2.743752 -1.309892 0.188974
O 1.193535 1.908529 -0.442931
H 2.493313 -2.403187 0.139871
H 3.857011 -1.256302 0.077414
H 2.523303 -0.989823 1.233814
H -0.185299 0.219399 -1.653063
H -0.377192 -1.444444 0.816230
H -0.416942 -1.992409 -0.861391
H -2.210542 1.310914 -1.299905
H -1.525288 1.979576 0.182963
H -2.817928 -1.428391 -1.049120
H -2.732490 -2.081982 0.595277
H -3.758698 0.398772 0.343156
H -2.456451 0.189724 1.530516
H 1.941821 2.194155 0.107530
Sum of electronic and thermal Enthalpies= -500.074212
Sum of electronic and thermal Free Energies= -500.123358
(Polarized solute)-Solvent (kcal/mol) = -74.02

6b

C -1.374641 -0.212205 0.167048
O -1.703503 -0.757933 1.202398
O -2.268545 0.340391 -0.689002
C -3.651004 0.266665 -0.292975
H -4.207278 0.755620 -1.093414
H -3.961947 -0.776121 -0.186935
H -3.803471 0.785776 0.657248
C 0.051907 -0.026832 -0.314736
C 0.689589 1.183071 0.414778
C 0.888804 -1.302202 -0.091740
H 0.013628 0.201960 -1.387632
C 2.150596 1.385441 -0.016096

H 0.643860 1.003961 1.498099
H 0.104849 2.089801 0.213133
C 2.349919 -1.093810 -0.519652
H 0.842682 -1.571197 0.971380
H 0.446704 -2.139998 -0.646769
C 2.984865 0.111748 0.190914
H 2.586788 2.223021 0.544014
H 2.179229 1.671037 -1.078649
H 2.927687 -2.004208 -0.313148
H 2.393901 -0.937749 -1.608533
H 4.010218 0.267991 -0.169353
H 3.059331 -0.100816 1.268146
Sum of electronic and thermal Enthalpies= -463.545154
Sum of electronic and thermal Free Energies= -463.593459
(Polarized solute)-Solvent (kcal/mol) = -9.87

6b – anionic tetrahedral intermediate

C -0.784312 1.206484 0.300671
C -2.245223 1.463453 -0.113150
C -3.145804 0.254378 0.190452
C -2.582385 -1.029876 -0.441280
C -1.123060 -1.274998 -0.022971
C -0.220068 -0.072908 -0.342938
C 1.266097 -0.388761 0.018070
O 1.366228 -0.351763 1.515426
O 1.753064 -1.484972 -0.455035
O 1.972955 0.860323 -0.424253
C 3.372257 0.748894 -0.383704
H 3.784438 1.644015 -0.871969
H 3.751570 0.709986 0.653090
H 3.717178 -0.151214 -0.913418
H -0.216641 0.065479 -1.436504
H -1.082822 -1.465785 1.060406
H -0.715530 -2.164128 -0.517038
H -0.723519 1.104480 1.393813
H -0.154540 2.060740 0.028849
H -3.212236 -1.891660 -0.167997
H -2.637324 -0.940774 -1.539125
H -2.637183 2.361159 0.391527
H -2.285395 1.672959 -1.195216
H -4.174107 0.439680 -0.159467
H -3.204762 0.118396 1.282574
H 1.827887 -1.192025 1.670467

Sum of electronic and thermal Enthalpies= -539.376542
Sum of electronic and thermal Free Energies= -539.426365

(Polarized solute)-Solvent (kcal/mol) = -73.50

6b – neutral tetrahedral intermediate

C 2.293237 -1.445372 -0.180288
C 3.169510 -0.237942 0.184938
C 2.582766 1.064020 -0.380935
C 1.122590 1.269337 0.054299
C 0.247395 0.060577 -0.327436
C 0.831866 -1.242314 0.254604
C -1.230747 0.275494 0.054340
O -1.711587 1.432350 -0.572118
O -1.928162 -0.877389 -0.360447
C -3.353626 -0.795975 -0.356784
O -1.436787 0.498225 1.446295
H -3.707854 -1.794886 -0.620479
H -3.740325 -0.524223 0.633693
H -3.706108 -0.074289 -1.101728
H 0.243519 -0.031023 -1.423430
H 1.081767 1.413997 1.143357
H 0.716133 2.178162 -0.401967
H 0.800222 -1.199168 1.355947
H 0.222250 -2.098558 -0.052128
H 3.188527 1.923505 -0.064276
H 2.633683 1.035993 -1.480319
H 2.692798 -2.360605 0.276523
H 2.325035 -1.601214 -1.269418
H 4.194090 -0.386832 -0.181491
H 3.236983 -0.158150 1.281066
H -1.277834 -0.339868 1.910131
H -2.268552 1.904728 0.068256

Sum of electronic and thermal Enthalpies= -539.925462
Sum of electronic and thermal Free Energies= -539.975374

6b – TS1

C 0.224339 0.030306 -0.255068
C 1.055027 1.206730 0.275370
C 0.890128 -1.313763 0.124490
C -1.216904 0.078622 0.267641
H 0.168953 0.101038 -1.348390
C 2.516001 1.140283 -0.197993
H 1.020227 1.195795 1.374757
H 0.572473 2.131040 -0.056965
C 3.177720 -0.198303 0.170068
H 3.093588 1.975185 0.228391
H 2.550861 1.266426 -1.292561

C 2.351043 -1.385221 -0.350815
H 4.206118 -0.244849 -0.221953
H 3.255203 -0.270688 1.267035
H 2.810727 -2.335276 -0.035189
H 2.373289 -1.379124 -1.452817
H 0.856444 -1.427803 1.219197
H 0.312822 -2.144947 -0.298683
O -1.969452 -0.861742 -0.460343
O -1.492792 0.311107 1.457841
C -3.350103 -0.867333 -0.144856
H -3.808272 -1.634262 -0.781091
H -3.521225 -1.110354 0.912467
H -3.778536 0.117094 -0.369409
O -1.783592 1.719924 -0.803140
H -2.029478 2.258479 -0.032674
Sum of electronic and thermal Enthalpies= -539.362326
Sum of electronic and thermal Free Energies= -539.412016
(Polarized solute)-Solvent (kcal/mol) = -77.39

6b – TS2

C -1.310472 -1.286462 0.075870
C -0.219099 -0.242089 -0.259673
C -0.586156 1.124672 0.334070
C -1.977407 1.591728 -0.123107
C -3.065250 0.552879 0.197264
C -2.703423 -0.824338 -0.382912
C 1.147507 -0.722152 0.229358
O 2.196425 0.653269 -0.870865
C 3.051502 1.374404 -0.078153
O 1.531682 -0.622174 1.405351
O 1.533283 -1.847136 -0.518971
H 2.807984 2.469252 -0.034745
H 3.045677 1.015480 0.976529
H 4.115770 1.321152 -0.421196
H -0.147042 -0.144661 -1.350176
H -1.321123 -1.451309 1.164543
H -1.058168 -2.247771 -0.387968
H -0.559724 1.053336 1.431275
H 0.185961 1.841334 0.037988
H -3.465828 -1.567387 -0.100513
H -2.719361 -0.763489 -1.483230
H -2.228240 2.555812 0.345485
H -1.962239 1.769633 -1.210646
H -4.043938 0.885322 -0.183226
H -3.166380 0.464773 1.291124
H 2.402319 -2.085003 -0.155667

Sum of electronic and thermal Enthalpies= -539.367501
Sum of electronic and thermal Free Energies= -539.417867
(Polarized solute)-Solvent (kcal/mol) = -73.78

7b

C -1.235229 0.394488 -0.000051
O -1.730494 1.507041 -0.000111
O -1.976546 -0.738358 0.000035
C -3.403044 -0.553280 -0.000052
H -3.823874 -1.559310 -0.000728
H -3.715717 -0.003422 0.891723
H -3.715496 -0.002269 -0.891182
C 0.230932 0.122559 -0.000003
C 1.103608 1.221203 -0.000040
C 0.751797 -1.180688 0.000071
C 2.483182 1.018681 -0.000007
H 0.684399 2.222462 -0.000097
C 2.133241 -1.378823 0.000108
H 0.075548 -2.028528 0.000102
C 3.000035 -0.281344 0.000070
H 3.155180 1.872833 -0.000040
H 2.533413 -2.389323 0.000160
H 4.075735 -0.438689 0.000100

Sum of electronic and thermal Enthalpies= -459.993930
Sum of electronic and thermal Free Energies= -460.038045
(Polarized solute)-Solvent (kcal/mol) = -10.97

7b – anionic tetrahedral intermediate

C -2.365646 -1.317208 0.063018
C -3.178311 -0.206950 -0.203633
C -2.589194 1.055510 -0.330247
C -1.204002 1.203261 -0.191696
C -0.387057 0.101250 0.075004
C -0.983530 -1.161830 0.200859
C 1.136315 0.320773 0.240903
O 1.481837 -0.278590 1.573154
O 1.698001 -0.655128 -0.740527
C 3.089515 -0.525824 -0.906950
O 1.564577 1.529179 0.137815
H -0.716572 2.170374 -0.284693
H -0.351147 -2.019598 0.410182
H -3.210477 1.926636 -0.538298

H -2.813812 -2.305604 0.164440
H -4.255920 -0.326685 -0.310162
H 3.373179 -1.170272 -1.750673
H 3.368329 0.514585 -1.126670
H 3.641218 -0.854250 -0.009324
H 1.901346 0.487225 1.998111

Sum of electronic and thermal Enthalpies= -535.826534
Sum of electronic and thermal Free Energies= -535.874674
(Polarized solute)-Solvent (kcal/mol) = -75.72

7b – neutral tetrahedral intermediate

C -2.653883 -0.991661 -0.067795
C -3.199903 0.296213 -0.029220
C -2.352491 1.404800 0.016507
C -0.964121 1.232101 0.024891
C -0.416659 -0.054463 -0.012064
C -1.270047 -1.165483 -0.058864
C 1.089196 -0.298970 0.023500
O 1.467629 -1.109830 -1.054269
O 1.728014 0.949393 0.006396
C 3.146497 0.932609 -0.156084
O 1.476221 -1.041784 1.179593
H -0.304924 2.092197 0.050647
H -0.844209 -2.163625 -0.095039
H -2.768549 2.408915 0.041462
H -3.306716 -1.860016 -0.108443
H -4.278525 0.432243 -0.038361
H 3.466290 1.972228 -0.060906
H 3.631458 0.329445 0.621061
H 3.420118 0.555531 -1.147549
H 2.132783 -1.739370 -0.728486
H 1.205838 -0.540662 1.966631

Sum of electronic and thermal Enthalpies= -536.368874
Sum of electronic and thermal Free Energies= -536.418235

7b – TS1

C -3.166142 -0.292464 -0.085316
C -2.278523 -1.376941 -0.037525
C -0.900213 -1.163869 -0.044517
C -0.380526 0.138728 -0.097564
C -1.270902 1.218366 -0.155839
C -2.653422 1.007042 -0.142573
C 1.099508 0.418638 -0.137358
O 1.772575 -0.663019 -0.701478

C 3.185296 -0.585763 -0.570730
O 1.554047 1.568756 -0.218992
H -0.207133 -1.995045 0.020963
H -0.855052 2.220883 -0.203756
H -2.666923 -2.393331 0.015235
H -3.331499 1.858948 -0.181861
H -4.242064 -0.460928 -0.075332
H 3.580790 -1.514699 -0.997100
H 3.589975 0.276727 -1.115922
H 3.437755 -0.508479 0.492863
O 1.353922 -0.201199 1.852886
H 1.439344 0.697197 2.214122

Sum of electronic and thermal Enthalpies= -535.810892
Sum of electronic and thermal Free Energies= -535.858616
(Polarized solute)-Solvent (kcal/mol) = -80.68

7b – TS2

C -3.059906 -0.192142 0.427549
C -2.402938 1.031013 0.605418
C -1.072062 1.182326 0.209184
C -0.372035 0.113482 -0.369140
C -1.041081 -1.105555 -0.556712
C -2.369751 -1.260935 -0.156631
C 1.057053 0.245689 -0.833882
O 1.821857 0.134582 1.183128
C 2.661887 -0.943088 1.333688
O 1.575268 -0.622531 -1.531139
H -0.555104 2.125538 0.348956
H -0.493503 -1.923665 -1.015218
H -2.929995 1.869884 1.058050
H -2.870665 -2.217162 -0.302491
H -4.096641 -0.310603 0.738863
H 2.332659 -1.641168 2.140334
H 2.734805 -1.544330 0.397384
H 3.708640 -0.652496 1.589405
O 1.572963 1.538509 -0.780987
H 2.002095 1.464775 0.119856

Sum of electronic and thermal Enthalpies= -535.821847
Sum of electronic and thermal Free Energies= -535.869931
(Polarized solute)-Solvent (kcal/mol) = -70.87