

Supporting Information for  
Theoretical Study on the Inhibition Mechanism of the Proteasome by  
Bortezomib

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Communications in Computational Chemistry

## 1. Parameters for boron center

The MOL2 file of Bortezomib (naming Bortezomib as BOZ)

@<TRIPOS>MOLECULE

BOZ

53 54 1 0 0

SMALL

resp

@<TRIPOS>ATOM

1 C1	1.1300	-2.3300	0.4310 ca	1 BOZ	0.258908
2 N1	1.7140	-2.6360	-0.7120 nb	1 BOZ	-0.344143
3 O1	0.1280	-0.6060	1.6900 o	1 BOZ	-0.522484
4 C2	0.9160	-3.2860	1.4140 ca	1 BOZ	0.265001
5 N2	1.2910	-4.5390	1.2450 nb	1 BOZ	-0.530911
6 O2	-0.9250	2.0650	-1.9030 o	1 BOZ	-0.582844
7 C3	1.8750	-4.8390	0.1020 ca	1 BOZ	0.270621
8 N3	0.9500	-0.0560	-0.3310 n	1 BOZ	-0.256326
9 O3	-3.4420	1.7150	2.2420 oh	1 BOZ	-0.790298
10 C4	2.0880	-3.8850	-0.8830 ca	1 BOZ	-0.044584
11 N4	-1.7500	1.3410	0.0590 n	1 BOZ	-0.463789
12 O4	-5.3670	2.0040	0.9680 oh	1 BOZ	-0.790298
13 C5	0.6860	-0.9110	0.6640 c	1 BOZ	0.269248
14 C6	0.6570	1.3640	-0.2430 c3	1 BOZ	0.339886
15 C7	1.7020	2.1870	-1.0040 c3	1 BOZ	-0.467756
16 C8	3.1070	2.0210	-0.4650 ca	1 BOZ	0.297644
17 C9	4.0700	1.3210	-1.1800 ca	1 BOZ	-0.279434
18 C10	5.3560	1.1670	-0.6850 ca	1 BOZ	-0.109084
19 C11	5.7000	1.7160	0.5370 ca	1 BOZ	-0.164480
20 C12	4.7500	2.4230	1.2590 ca	1 BOZ	-0.109084
21 C13	3.4690	2.5740	0.7600 ca	1 BOZ	-0.279434
22 C14	-0.7540	1.6330	-0.7910 c	1 BOZ	0.539010
23 C15	-3.1520	1.5200	-0.2860 c3	1 BOZ	-0.231853
24 C16	-3.6750	0.4320	-1.2540 c3	1 BOZ	-0.230225
25 C17	-3.5060	-1.0340	-0.8240 c3	1 BOZ	0.551342
26 C18	-4.2450	-1.3860	0.4710 c3	1 BOZ	-0.383890
27 C19	-3.9590	-1.9570	-1.9620 c3	1 BOZ	-0.383890
28 B	-4.0330	1.7440	1.0240 b	1 BOZ	0.812127
29 H1	0.4390	-3.0200	2.3360 h4	1 BOZ	0.071819
30 H2	2.1830	-5.8580	-0.0430 h4	1 BOZ	0.067174
31 H3	2.5630	-4.1410	-1.8120 h4	1 BOZ	0.121593
32 H4	1.4020	-0.4150	-1.1430 hn	1 BOZ	0.174729
33 H5	0.6780	1.6220	0.8060 h1	1 BOZ	0.013672
34 H6	1.4030	3.2280	-0.9510 hc	1 BOZ	0.139563

35 H7	1.6620	1.9200	-2.0530 hc	1 BOZ	0.139563
36 H8	3.8180	0.8960	-2.1370 ha	1 BOZ	0.162743
37 H9	6.0860	0.6210	-1.2560 ha	1 BOZ	0.137089
38 H10	6.6970	1.5990	0.9230 ha	1 BOZ	0.138470
39 H11	5.0090	2.8590	2.2070 ha	1 BOZ	0.137089
40 H12	2.7440	3.1330	1.3270 ha	1 BOZ	0.162743
41 H13	-1.5190	0.9810	0.9600 hn	1 BOZ	0.319944
42 H14	-3.2150	2.4550	-0.8400 h2	1 BOZ	0.137404
43 H15	-3.1660	0.5700	-2.2000 hc	1 BOZ	0.047023
44 H16	-4.7320	0.6200	-1.4510 hc	1 BOZ	0.047023
45 H17	-2.4460	-1.2100	-0.6600 hc	1 BOZ	-0.077686
46 H18	-5.3050	-1.1550	0.3960 hc	1 BOZ	0.074963
47 H19	-4.1560	-2.4470	0.6850 hc	1 BOZ	0.074963
48 H20	-3.8430	-0.8580	1.3290 hc	1 BOZ	0.074963
49 H21	-3.4200	-1.7450	-2.8800 hc	1 BOZ	0.074963
50 H22	-3.7890	-3.0000	-1.7100 hc	1 BOZ	0.074963
51 H23	-5.0200	-1.8360	-2.1650 hc	1 BOZ	0.074963
52 H24	-4.0520	1.8720	2.9500 ho	1 BOZ	0.485644
53 H25	-5.7350	2.0220	0.0970 ho	1 BOZ	0.485644

@<TRIPOS>BOND

1	1	2 ar
2	1	4 ar
3	1	13 1
4	2	10 ar
5	3	13 2
6	4	5 ar
7	4	29 1
8	5	7 ar
9	6	22 2
10	7	10 ar
11	7	30 1
12	8	13 1
13	8	14 1
14	8	32 1
15	9	28 1
16	9	52 1
17	10	31 1
18	11	22 1
19	11	23 1
20	11	41 1
21	12	28 1
22	12	53 1
23	14	15 1
24	14	22 1

25	14	33 1
26	15	16 1
27	15	34 1
28	15	35 1
29	16	17 ar
30	16	21 ar
31	17	18 ar
32	17	36 1
33	18	19 ar
34	18	37 1
35	19	20 ar
36	19	38 1
37	20	21 ar
38	20	39 1
39	21	40 1
40	23	24 1
41	23	28 1
42	23	42 1
43	24	25 1
44	24	43 1
45	24	44 1
46	25	26 1
47	25	27 1
48	25	45 1
49	26	46 1
50	26	47 1
51	26	48 1
52	27	49 1
53	27	50 1
54	27	51 1

@<TRIPOS>SUBSTRUCTURE

1 BOZ                    1 TEMP                    0 \*\*\*\*    \*\*\*\*    0 ROOT

**The FRCMOD file of Bortezomib (naming Bortezomib as BOZ)**

MASS

ca	12.010	0.360
nb	14.010	0.530
o	16.000	0.434
n	14.010	0.530
oh	16.000	0.465
c	12.010	0.616
c3	12.010	0.878
b	10.810	0.360
h4	1.008	0.135
hn	1.008	0.161

h1	1.008	0.135
hc	1.008	0.135
ha	1.008	0.135
h2	1.008	0.135
ho	1.008	0.135

#### BOND

ca-nb	488.00	1.339
ca-ca	461.10	1.398
c-ca	345.90	1.491
c-o	637.70	1.218
ca-h4	341.50	1.089
c-n	427.60	1.379
c3-n	328.70	1.462
hn-n	403.20	1.013
b-oh	457.89	1.366
ho-oh	371.40	0.973
c3-c3	300.90	1.538
c-c3	313.00	1.524
c3-h1	330.60	1.097
c3-ca	321.00	1.516
c3-hc	330.60	1.097
ca-ha	345.80	1.086
b-c3	223.16	1.622
c3-h2	331.70	1.096

#### ANGLE

ca-nb-ca	68.300	117.220
ca-ca-nb	68.800	122.940
ca-ca-h4	48.100	120.340
ca-c-o	68.700	122.600
ca-c-n	67.700	115.250
c-ca-nb	67.700	117.780
h4-ca-nb	51.900	116.030
n-c-o	74.200	123.050
c-ca-ca	64.300	120.330
c3-c-o	67.400	123.200
c3-c3-n	65.900	111.610
c-c3-n	67.000	109.060
h1-c3-n	49.800	108.880
oh-b-oh	94.216	115.969
c3-b-oh	87.651	123.722
c3-c-n	66.800	115.180
b-c3-n	85.681	108.769

h2-c3-n	50.200	107.280
c -n -c3	63.400	120.690
c -n -hn	48.300	117.550
c3-n -hn	45.800	117.680
c3-c3-ca	63.100	112.070
c3-c3-hc	46.300	109.800
c -c3-c3	63.300	111.040
c3-c3-h1	46.400	109.560
c3-ca-ca	63.500	120.770
ca-c3-hc	46.800	110.470
ca-ca-ca	66.600	120.020
ca-ca-ha	48.200	119.880
c -c3-h1	47.000	108.220
c3-c3-c3	62.900	111.510
b -c3-c3	73.535	116.336
c3-c3-h2	46.200	110.220
b -oh-ho	39.065	113.988
b -c3-h2	43.333	105.639
hc-c3-hc	39.400	107.580

#### DIHE

ca-ca-nb-ca	2	9.600	180.000	2.000
h4-ca-nb-ca	2	9.600	180.000	2.000
nb-ca-ca-nb	4	14.500	180.000	2.000
h4-ca-ca-nb	4	14.500	180.000	2.000
o -c -ca-nb	4	4.000	180.000	2.000
n -c -ca-nb	4	4.000	180.000	2.000
o -c -ca-ca	4	4.000	180.000	2.000
n -c -ca-ca	4	4.000	180.000	2.000
ca-c3-c3-n	9	1.400	0.000	3.000
hc-c3-c3-n	9	1.400	0.000	3.000
o -c -c3-n	6	0.000	180.000	2.000
n -c -c3-n	1	1.700	180.000	-1.000
n -c -c3-n	1	2.000	180.000	2.000
c3-c3-c3-n	9	1.400	0.000	3.000
oh-b -c3-n	1	0.155	180.000	2.000
oh-b -c3-n	0	0.000	0.000	0.000
c -ca-nb-ca	2	9.600	180.000	2.000
c -ca-ca-nb	4	14.500	180.000	2.000
c -ca-ca-h4	4	14.500	180.000	2.000
c3-c3-n -c	1	0.500	180.000	-4.000
c3-c3-n -c	1	0.150	180.000	-3.000
c3-c3-n -c	1	0.000	0.000	-2.000
c3-c3-n -c	1	0.530	0.000	1.000

c -c3-n -c	1	0.850	180.000	-2.000
c -c3-n -c	1	0.800	0.000	1.000
h1-c3-n -c	6	0.000	0.000	2.000
ca-c -n -c3	4	10.000	180.000	2.000
o -c -n -c3	4	10.000	180.000	2.000
c3-c3-ca-ca	6	0.000	0.000	2.000
o -c -c3-c3	6	0.000	180.000	2.000
n -c -c3-c3	1	0.100	0.000	-4.000
n -c -c3-c3	1	0.070	0.000	2.000
c3-ca-ca-ca	4	14.500	180.000	2.000
c3-ca-ca-ha	4	14.500	180.000	2.000
ca-ca-ca-ca	4	14.500	180.000	2.000
ca-ca-ca-ha	4	14.500	180.000	2.000
b -c3-n -c	6	0.000	0.000	2.000
h2-c3-n -c	6	0.000	0.000	2.000
c -c3-c3-ca	9	1.400	0.000	3.000
c -c3-c3-hc	9	1.400	0.000	3.000
c3-c -n -c3	1	0.000	0.000	-2.000
c3-c -n -c3	1	1.500	180.000	1.000
c3-c3-c3-c3	1	0.180	0.000	-3.000
c3-c3-c3-c3	1	0.250	180.000	-2.000
c3-c3-c3-c3	1	0.200	180.000	1.000
c3-c3-c3-hc	1	0.160	0.000	3.000
oh-b -c3-c3	1	0.300	180.000	2.000
oh-b -c3-c3	0	0.000	0.000	0.000
b -c3-c3-c3	9	1.400	0.000	3.000
b -c3-c3-hc	9	1.400	0.000	3.000
h4-ca-ca-h4	4	14.500	180.000	2.000
ca-c -n -hn	4	10.000	180.000	2.000
o -c -n -hn	1	2.500	180.000	-2.000
o -c -n -hn	1	2.000	0.000	1.000
c3-c3-n -hn	6	0.000	0.000	2.000
c -c3-n -hn	6	0.000	0.000	2.000
h1-c3-n -hn	6	0.000	0.000	2.000
ca-c3-c3-h1	9	1.400	0.000	3.000
h1-c3-c3-hc	9	1.400	0.000	3.000
o -c -c3-h1	1	0.800	0.000	-1.000
o -c -c3-h1	1	0.000	0.000	-2.000
o -c -c3-h1	1	0.080	180.000	3.000
n -c -c3-h1	6	0.000	180.000	2.000
hc-c3-ca-ca	6	0.000	0.000	2.000
ha-ca-ca-ha	4	14.500	180.000	2.000
c3-c -n -hn	4	10.000	180.000	2.000
b -c3-n -hn	6	0.000	0.000	2.000

h2-c3-n -hn	6	0.000	0.000	2.000
c3-c3-c3-h2	9	1.400	0.000	3.000
h2-c3-c3-hc	9	1.400	0.000	3.000
oh-b -c3-h2	1	4.166	180.000	2.000
oh-b -c3-h2	0	0.000	0.000	0.000
hc-c3-c3-hc	1	0.150	0.000	3.000
oh-b -oh-ho	1	8.212	180.000	2.000
c3-b -oh-ho	1	8.459	180.000	2.000
oh-b -oh-ho	0	0.000	0.000	0.000
c3-b -oh-ho	0	0.000	0.000	0.000

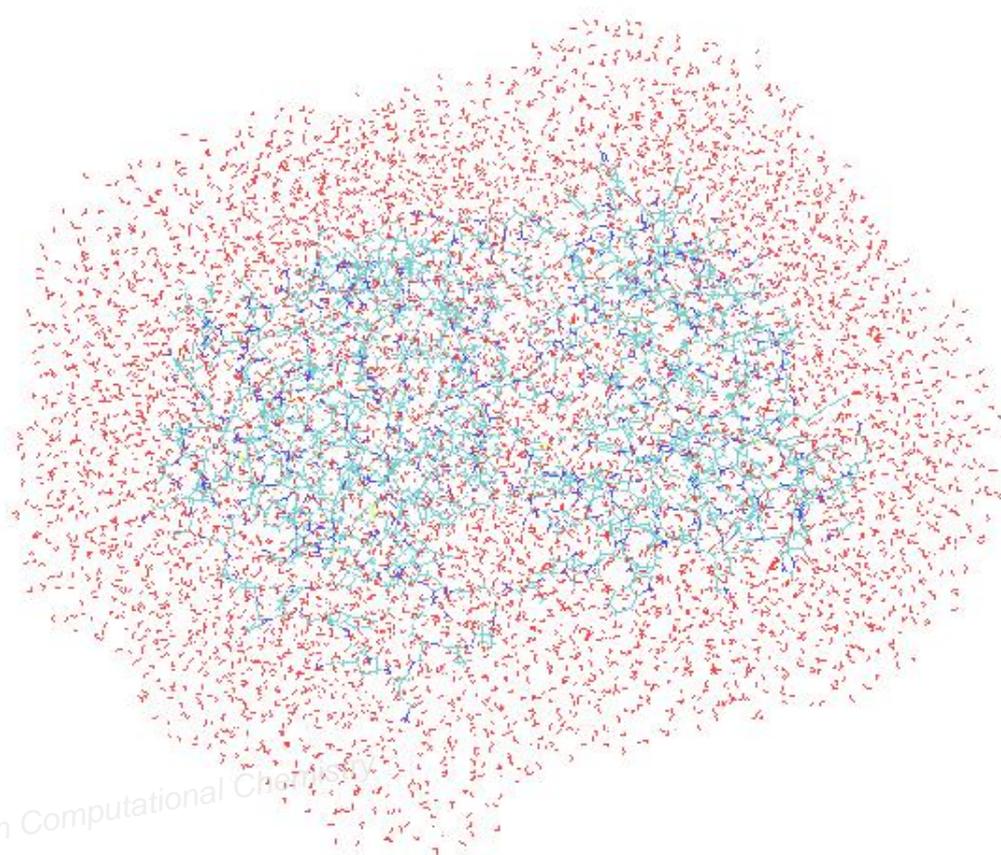
#### IMPROPER

c -ca-ca-nb	1.1	180.0	2.0
ca-h4-ca-nb	1.1	180.0	2.0
c -c3-n -hn	1.1	180.0	2.0
ca-n -c -o	10.5	180.0	2.0
c3-ca-ca-ca	1.1	180.0	2.0
ca-ca-ca-ha	1.1	180.0	2.0
c3-n -c -o	10.5	180.0	2.0

#### NONBON

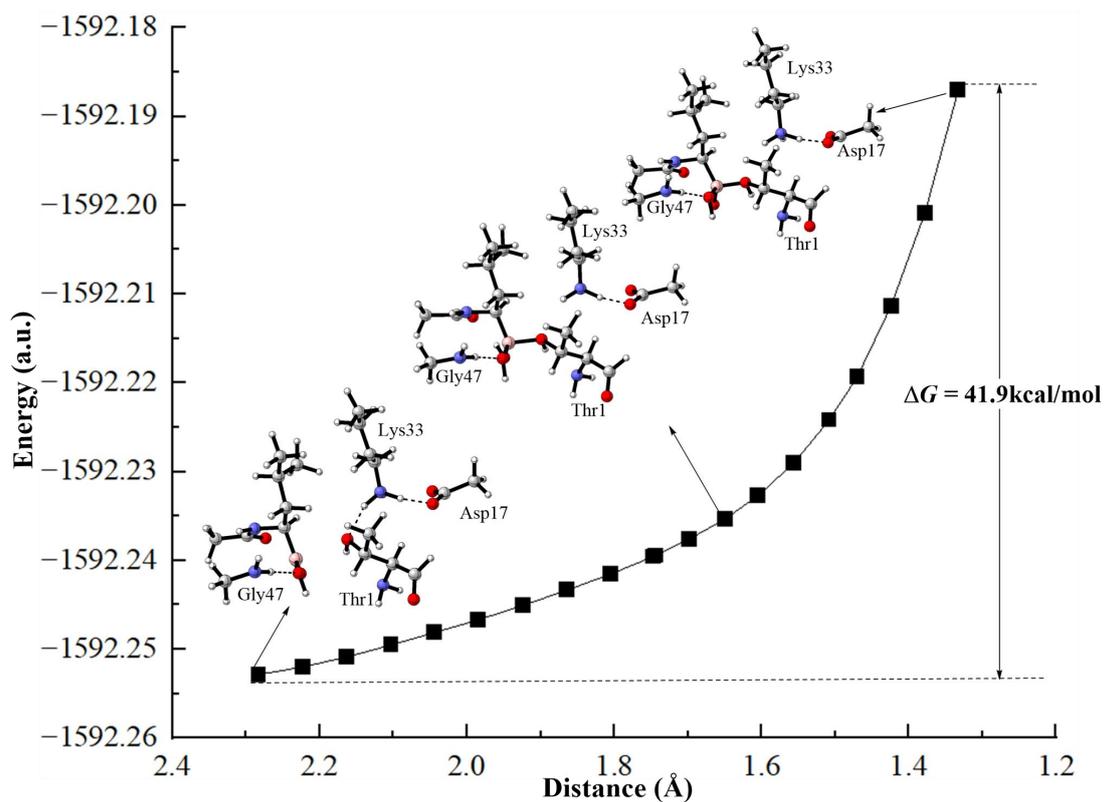
ca	1.9080	0.0860
nb	1.8240	0.1700
o	1.6612	0.2100
n	1.8240	0.1700
oh	1.7210	0.2104
c	1.9080	0.0860
c3	1.9080	0.1094
b	1.9800	0.0340
h4	1.4090	0.0150
hn	0.6000	0.0157
h1	1.3870	0.0157
hc	1.4870	0.0157
ha	1.4590	0.0150
h2	1.2870	0.0157
ho	0.0000	0.0000

## 2. QM/MM calculation model



**Figure S1** The waters within 12 Å of the enzyme-substrate retained in QM/MM calculations.

### 3. Energy scan curve .



**Figure S2** Through QM/MM calculation, the energy scan curve for the distance change of the first step B(bortezomib)  $\rightarrow$  O(Thr1) of the reaction between bortezomib and the 20S proteasome was obtained.

#### 4. Relative energy of the optimized structures

**Table S1** The single-point energies (SPE), free energy correction (FEC), and Gibbs free energies (GFE=SPE+FEC) of the stationary points involved in the enzyme catalytic Cycle computed at the QM/MM[B3LYP-D4/def2-TZVPP:Amber)//QM/MM[B3LYP-D4/def2-SVP:Amber)] theory level.

	SPE(a.u.)	FEC(a.u.)	GFE(a.u.)
ES	-1593.987741	0.586179359	-1593.401562
TS1	-1593.953707	0.582622415	-1593.371085
INT1	-1593.972797	0.586101875	-1593.386695
TS2	-1593.972090	0.583512924	-1593.388577
EP	-1593.984917	0.586093769	-1593.398823

**5. The energy related to TS1 of the 193rd snapshot and the 2146th snapshot**

**Table S2 The single-point energies (SPE), free energy correction (FEC), and Gibbs free energies (GFE=SPE+FEC) of the stationary points involved in the proteasome inhibition reaction computed at the QM/MM[B3LYP-D4/def2-TZVPP:Amber]//QM/MM[B3LYP-D4/def2-SVP:Amber] theory level.**

	SPE(a.u.)	FEC(a.u.)	GFE(a.u.)
ES	-1593.987741	0.586179359	-1593.401562
TS1	-1593.953707	0.582622415	-1593.371085
ES-2146	-1597.974276	0.585199117	-1597.389077
TS1-2146	-1597.936503	0.583221063	-1597.353282

## 6. Cartesian coordinates

### ES

N	38.840037000	28.259069000	59.977603000
H	39.460311000	27.446199000	60.031318000
H	37.970839000	27.906877000	60.398106000
C	39.358438000	29.324260000	60.830248000
C	38.465674000	30.561655000	60.571825000
C	38.666622000	31.759779000	61.487272000
H	38.321376000	31.521544000	62.504726000
H	39.718222000	32.073433000	61.560568000
H	38.071477000	32.611667000	61.130177000
O	38.660682000	30.978926000	59.220439000
H	38.591656000	30.176023000	58.665687000
H	37.420061000	30.222095000	60.685240000
H	40.383328000	29.563479000	60.505375000
C	39.376652000	29.024102000	62.330477000
O	38.486131000	28.335670000	62.804753000
C	44.721835000	30.404032000	61.794291000
H	45.510263000	29.838712000	61.278147000
H	44.503548000	29.931805000	62.764223000
C	43.469947000	30.439143000	60.910489000
O	42.361229000	30.747906000	61.461024000
O	43.622299000	30.227008000	59.688096000
C	41.386498000	36.637793000	60.847077000
H	42.022937000	36.456934000	61.729095000
H	40.345063000	36.493245000	61.184826000
C	41.720253000	35.604939000	59.765805000
H	41.228777000	35.873205000	58.813443000
H	42.810865000	35.581325000	59.574816000
C	41.290648000	34.182154000	60.132681000
H	41.643333000	33.919179000	61.141855000
H	40.189169000	34.128834000	60.155458000
C	41.859942000	33.183688000	59.136124000
H	41.662030000	33.497829000	58.101701000
H	42.949279000	33.112537000	59.263737000
N	41.318833000	31.817234000	59.296758000
H	41.753783000	31.202157000	58.593512000
H	41.610193000	31.388671000	60.240820000
H	40.289921000	31.732474000	59.168753000
N	33.455161000	33.223104000	59.897437000
H	34.219592000	32.569079000	59.696980000
C	32.337304000	33.332496000	59.004216000
H	32.023493000	32.322707000	58.703564000
H	31.469226000	33.821501000	59.471891000

O	36.930846000	31.466077000	54.910809000
O	35.614686000	31.329840000	59.275397000
N	36.051214000	33.001653000	56.320331000
O	36.523467000	30.164335000	57.414842000
C	34.959675000	32.770895000	54.196816000
C	36.067655000	32.334520000	55.137371000
C	36.905815000	32.667996000	57.462755000
C	37.051457000	33.893003000	58.361701000
C	37.776379000	35.070538000	57.693203000
C	37.888870000	36.277225000	58.628856000
C	39.151305000	34.637925000	57.172003000
B	36.354986000	31.324395000	58.113006000
H	34.621843000	33.750040000	54.583377000
H	35.196148000	33.530322000	56.559419000
H	37.891167000	32.405334000	57.048006000
H	37.604085000	33.604668000	59.270570000
H	36.046792000	34.221118000	58.684853000
H	37.169907000	35.369475000	56.825738000
H	36.902490000	36.571592000	59.023548000
H	38.535215000	36.057138000	59.493501000
H	38.311205000	37.148773000	58.099249000
H	39.646162000	33.986168000	57.905130000
H	39.075748000	34.073382000	56.230405000
H	39.805946000	35.502970000	56.996384000
H	35.305890000	30.434405000	59.572908000
H	36.908543000	30.363415000	56.532497000
H	40.179920000	29.478534000	62.910408000
H	35.308068000	32.942832000	53.178421000
H	34.063567000	32.151199000	54.228989000
H	33.660233000	33.967602000	60.532765000
H	32.544834000	33.850868000	58.068112000
H	45.093993000	31.404646000	62.014149000
H	41.509610000	37.675776000	60.538042000

**TS1**

N	38.851265000	28.673701000	59.953062000
H	39.546534000	28.017430000	59.596093000
H	38.039310000	28.134219000	60.297520000
C	39.395258000	29.560059000	61.005188000
C	38.466798000	30.817531000	60.801105000
C	38.812644000	31.998426000	61.692700000
H	38.546992000	31.761270000	62.735651000
H	39.879399000	32.260505000	61.676900000
H	38.228023000	32.879120000	61.395932000

O	38.519920000	31.029721000	59.431843000
H	38.586683000	29.586014000	59.252997000
H	37.445841000	30.480668000	61.093840000
H	40.416521000	29.818845000	60.701038000
C	39.383865000	29.066274000	62.425755000
O	38.506171000	28.314485000	62.815066000
C	44.650687000	30.406997000	61.786457000
H	45.425338000	29.834905000	61.256200000
H	44.444754000	29.933499000	62.758948000
C	43.383500000	30.456022000	60.919977000
O	42.286705000	30.781034000	61.485151000
O	43.516333000	30.227784000	59.698571000
C	41.367375000	36.653354000	60.829257000
H	42.017433000	36.455697000	61.697908000
H	40.330722000	36.518331000	61.184782000
C	41.666647000	35.625341000	59.732576000
H	41.174720000	35.915220000	58.786795000
H	42.754873000	35.575371000	59.534115000
C	41.196600000	34.215880000	60.098648000
H	41.556013000	33.945417000	61.103848000
H	40.095376000	34.200987000	60.135786000
C	41.713901000	33.195730000	59.097007000
H	41.502847000	33.508708000	58.065231000
H	42.804640000	33.095521000	59.197961000
N	41.142624000	31.840474000	59.278263000
H	41.533525000	31.229496000	58.546305000
H	41.485452000	31.426506000	60.195672000
H	40.085418000	31.746505000	59.224643000
N	33.528848000	33.151485000	59.964266000
H	34.315565000	32.518033000	59.770751000
C	32.430144000	33.250914000	59.044723000
H	32.150488000	32.238766000	58.718565000
H	31.537484000	33.706075000	59.501215000
O	37.098332000	31.481986000	55.005471000
O	35.747118000	31.280093000	59.416882000
N	36.167762000	32.889829000	56.514446000
O	36.744517000	30.068570000	57.618975000
C	35.079816000	32.765598000	54.379557000
C	36.207688000	32.301326000	55.293065000
C	37.073101000	32.600344000	57.629288000
C	37.145712000	33.838041000	58.521326000
C	37.703747000	35.083650000	57.821347000
C	37.806508000	36.279696000	58.770538000
C	39.048623000	34.780798000	57.155536000

B	36.640861000	31.239748000	58.345927000
H	34.760912000	33.743339000	54.786438000
H	35.325497000	33.437484000	56.751400000
H	38.063150000	32.401155000	57.189283000
H	37.760806000	33.605714000	59.404551000
H	36.128149000	34.066839000	58.884121000
H	36.985918000	35.341690000	57.029850000
H	36.839645000	36.485961000	59.256720000
H	38.542200000	36.098401000	59.570323000
H	38.109050000	37.192639000	58.228302000
H	39.648578000	34.121790000	57.796093000
H	38.921671000	34.264783000	56.191923000
H	39.626408000	35.699388000	56.985004000
H	35.408660000	30.392659000	59.688308000
H	37.174251000	30.258932000	56.762243000
H	40.176958000	29.509422000	63.027993000
H	35.391147000	32.945785000	53.350638000
H	34.181714000	32.149989000	54.429615000
H	33.708804000	33.903784000	60.598013000
H	32.643911000	33.793869000	58.124087000
H	45.039036000	31.401820000	62.004583000
H	41.497389000	37.692504000	60.527046000

**INT1**

N	38.592305000	28.671785000	60.063046000
H	39.259918000	27.954916000	59.763254000
H	37.835748000	28.154670000	60.547307000
C	39.228422000	29.628214000	61.001756000
C	38.318706000	30.894663000	60.978370000
C	38.685650000	31.956009000	62.001044000
H	38.451375000	31.628685000	63.027114000
H	39.752195000	32.226082000	61.961193000
H	38.094296000	32.856088000	61.789441000
O	38.356550000	31.397931000	59.687503000
H	38.162257000	29.224771000	59.182577000
H	37.294755000	30.542560000	61.212826000
H	40.221868000	29.872577000	60.608982000
C	39.334954000	29.087183000	62.414327000
O	38.481028000	28.315479000	62.817319000
C	44.561050000	30.411276000	61.777070000
H	45.332256000	29.822813000	61.258489000
H	44.334606000	29.945345000	62.748972000
C	43.309138000	30.478407000	60.887752000
O	42.201711000	30.805342000	61.434856000

O	43.460656000	30.260006000	59.669057000
C	41.311101000	36.689619000	60.847044000
H	41.948750000	36.486202000	61.723691000
H	40.268716000	36.570389000	61.191817000
C	41.605274000	35.656463000	59.756099000
H	41.115818000	35.948530000	58.809410000
H	42.692644000	35.597770000	59.555621000
C	41.129534000	34.249652000	60.122895000
H	41.524055000	33.958389000	61.109251000
H	40.029077000	34.242306000	60.198423000
C	41.598661000	33.246854000	59.082254000
H	41.329315000	33.573375000	58.067431000
H	42.692919000	33.143122000	59.122110000
N	41.027429000	31.894982000	59.279360000
H	41.352381000	31.291705000	58.509404000
H	41.416284000	31.458888000	60.173922000
H	39.972998000	31.864343000	59.311099000
N	33.626030000	33.064730000	60.005532000
H	34.439900000	32.459589000	59.815619000
C	32.543570000	33.142392000	59.064052000
H	32.303269000	32.126386000	58.718279000
H	31.626492000	33.560300000	59.508101000
O	37.416889000	31.631334000	55.036938000
O	35.901093000	31.242604000	59.484464000
N	36.277232000	32.650905000	56.705509000
O	37.385608000	29.925555000	58.072558000
C	35.263801000	32.743529000	54.525522000
C	36.420924000	32.269582000	55.410186000
C	37.278266000	32.539362000	57.761296000
C	37.206752000	33.822548000	58.603560000
C	37.509672000	35.123558000	57.862987000
C	37.452678000	36.327930000	58.804471000
C	38.860135000	35.071039000	57.155362000
B	37.143940000	31.252368000	58.738941000
H	34.961253000	33.718177000	54.954116000
H	35.435286000	33.198345000	56.935398000
H	38.261509000	32.476577000	57.258286000
H	37.881140000	33.728704000	59.467996000
H	36.180684000	33.893734000	59.001235000
H	36.721219000	35.233651000	57.104022000
H	36.488233000	36.372998000	59.332928000
H	38.247037000	36.270608000	59.567238000
H	37.580915000	37.277031000	58.255358000
H	39.624037000	34.650612000	57.823983000

H	38.833446000	34.446002000	56.249866000
H	39.187886000	36.082510000	56.880652000
H	35.543719000	30.357839000	59.702627000
H	37.915284000	30.065963000	57.261658000
H	40.157922000	29.504714000	62.994378000
H	35.538329000	32.935042000	53.488206000
H	34.362104000	32.134657000	54.590981000
H	33.771198000	33.823607000	60.640359000
H	32.759992000	33.704405000	58.155553000
H	44.970210000	31.397577000	61.995850000
H	41.459552000	37.725013000	60.540470000

**TS2**

N	38.572844000	28.648773000	60.057874000
H	39.244829000	27.913267000	59.819994000
H	37.814518000	28.148264000	60.551284000
C	39.198834000	29.617625000	60.986484000
C	38.299715000	30.891858000	60.998247000
C	38.670445000	31.927797000	62.047622000
H	38.434073000	31.582169000	63.066700000
H	39.738806000	32.193294000	62.012511000
H	38.084751000	32.835538000	61.852645000
O	38.331327000	31.471325000	59.731405000
H	38.093397000	29.245203000	59.043138000
H	37.273173000	30.541117000	61.219353000
H	40.190305000	29.868930000	60.591596000
C	39.327347000	29.088526000	62.408477000
O	38.475951000	28.323390000	62.829971000
C	44.560315000	30.410126000	61.778631000
H	45.331296000	29.820542000	61.260965000
H	44.330721000	29.944082000	62.749713000
C	43.310429000	30.481831000	60.887297000
O	42.204332000	30.814612000	61.433399000
O	43.462389000	30.263695000	59.668663000
C	41.296027000	36.689042000	60.850441000
H	41.929877000	36.485358000	61.729746000
H	40.252212000	36.571385000	61.191407000
C	41.593186000	35.654498000	59.761874000
H	41.105379000	35.944675000	58.813635000
H	42.680849000	35.596404000	59.563037000
C	41.120029000	34.247351000	60.129881000
H	41.515426000	33.957587000	61.116369000
H	40.019447000	34.236542000	60.205923000
C	41.592784000	33.244835000	59.090438000

H	41.321847000	33.568130000	58.074767000
H	42.687339000	33.144537000	59.130386000
N	41.024876000	31.892593000	59.292941000
H	41.345697000	31.286852000	58.523554000
H	41.418525000	31.456907000	60.189764000
H	39.972898000	31.871565000	59.333267000
N	33.634754000	33.059182000	59.998811000
H	34.444222000	32.449900000	59.809637000
C	32.549181000	33.132263000	59.060688000
H	32.305615000	32.114372000	58.723120000
H	31.634726000	33.555639000	59.504752000
O	37.455232000	31.650144000	55.014215000
O	35.899268000	31.217999000	59.447499000
N	36.273574000	32.593853000	56.697022000
O	37.494029000	29.898556000	58.126133000
C	35.288623000	32.737594000	54.504290000
C	36.441459000	32.255984000	55.390892000
C	37.283046000	32.518356000	57.747204000
C	37.192835000	33.812945000	58.572467000
C	37.485045000	35.108919000	57.823358000
C	37.399137000	36.313374000	58.762468000
C	38.847272000	35.070166000	57.138322000
B	37.172988000	31.272178000	58.773468000
H	34.991134000	33.712365000	54.936319000
H	35.429387000	33.138552000	56.925895000
H	38.264671000	32.463373000	57.240706000
H	37.863767000	33.738586000	59.440639000
H	36.164458000	33.874647000	58.965865000
H	36.705368000	35.202923000	57.053105000
H	36.426589000	36.345051000	59.277125000
H	38.183057000	36.263189000	59.536435000
H	37.525105000	37.264968000	58.217626000
H	39.606074000	34.667605000	57.823996000
H	38.844889000	34.437300000	56.237675000
H	39.163908000	36.084325000	56.861368000
H	35.559125000	30.336371000	59.705744000
H	38.078161000	30.027522000	57.344964000
H	40.157968000	29.498661000	62.982868000
H	35.564760000	32.931479000	53.467842000
H	34.382078000	32.135289000	54.563194000
H	33.782362000	33.819415000	60.631449000
H	32.765170000	33.686568000	58.147363000
H	44.970102000	31.395978000	61.998258000
H	41.447408000	37.723862000	60.543362000

**EP**

N	38.702471000	28.317223000	59.905571000
H	39.376127000	27.548568000	59.972635000
H	37.869113000	27.912716000	60.351511000
C	39.169803000	29.411847000	60.752719000
C	38.187076000	30.610151000	60.627976000
C	38.412353000	31.724630000	61.652726000
H	38.182425000	31.391621000	62.677246000
H	39.452133000	32.087676000	61.648581000
H	37.760674000	32.578460000	61.428918000
O	38.255590000	31.154700000	59.323146000
H	38.143422000	29.921948000	57.314852000
H	37.180180000	30.191362000	60.802566000
H	40.159085000	29.725729000	60.389691000
C	39.293116000	29.047072000	62.244350000
O	38.453043000	28.304477000	62.730754000
C	44.568806000	30.421296000	61.744105000
H	45.345081000	29.830743000	61.235709000
H	44.322187000	29.951562000	62.709175000
C	43.332086000	30.500794000	60.835539000
O	42.223203000	30.835303000	61.370267000
O	43.498436000	30.287476000	59.617030000
C	41.343891000	36.623029000	60.868976000
H	41.986423000	36.440658000	61.745538000
H	40.305003000	36.489819000	61.219098000
C	41.654395000	35.583319000	59.786099000
H	41.190851000	35.880801000	58.828960000
H	42.745029000	35.517658000	59.610947000
C	41.157372000	34.176808000	60.135250000
H	41.539577000	33.866048000	61.120211000
H	40.055981000	34.185355000	60.206023000
C	41.617768000	33.174480000	59.086995000
H	41.374686000	33.519236000	58.070958000
H	42.709120000	33.049611000	59.141216000
N	41.029350000	31.825777000	59.258803000
H	41.402531000	31.214977000	58.516914000
H	41.395446000	31.388590000	60.181098000
H	39.986899000	31.785567000	59.210162000
N	33.578237000	33.092364000	59.921319000
H	34.387698000	32.493132000	59.708602000
C	32.498062000	33.188352000	58.980378000
H	32.273339000	32.181927000	58.597890000
H	31.574337000	33.578367000	59.435411000
O	36.966417000	31.400138000	55.157500000

O	35.788927000	31.256126000	59.115919000
N	36.239443000	32.968897000	56.610222000
O	37.196324000	30.193151000	57.352816000
C	35.045429000	32.800153000	54.521966000
C	36.157708000	32.333234000	55.433418000
C	37.239242000	32.747346000	57.664145000
C	37.222673000	33.964568000	58.589847000
C	37.631893000	35.286842000	57.933018000
C	37.641182000	36.447749000	58.927072000
C	38.983713000	35.170666000	57.235676000
B	37.066382000	31.359780000	58.490220000
H	34.731409000	33.780577000	54.919910000
H	35.441973000	33.578399000	56.858942000
H	38.223404000	32.688002000	57.162653000
H	37.878572000	33.764968000	59.451767000
H	36.197591000	34.074199000	58.981383000
H	36.869433000	35.499406000	57.170310000
H	36.675301000	36.533980000	59.445900000
H	38.420261000	36.312099000	59.694083000
H	37.830360000	37.405912000	58.413525000
H	39.704216000	34.654309000	57.882706000
H	38.918170000	34.600514000	56.297129000
H	39.393147000	36.164225000	57.009591000
H	35.539756000	30.383873000	59.489313000
H	37.080179000	30.628893000	56.404682000
H	40.105753000	29.493713000	62.817237000
H	35.359856000	32.968128000	53.491924000
H	34.152321000	32.177276000	54.571463000
H	33.709061000	33.826150000	60.587964000
H	32.711161000	33.791047000	58.097533000
H	44.978223000	31.404873000	61.974369000
H	41.472004000	37.658751000	60.554437000

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N	38.802787000	28.233921000	60.005241000
H	39.467542000	27.457268000	60.064541000
H	37.969659000	27.848901000	60.472035000
C	39.304307000	29.339849000	60.820362000
C	38.383712000	30.554806000	60.555257000
C	38.564668000	31.752649000	61.475748000
H	38.240084000	31.501649000	62.496942000
H	39.610289000	32.089364000	61.534011000
H	37.947345000	32.592646000	61.128325000
O	38.574158000	30.991311000	59.213182000

H	38.480433000	30.220601000	58.621266000
H	37.344215000	30.193117000	60.664766000
H	40.317680000	29.596684000	60.476516000
C	39.353130000	29.062272000	62.325982000
O	38.463692000	28.387347000	62.821792000
C	44.651759000	30.465416000	61.774522000
H	45.441235000	29.917551000	61.240548000
H	44.440165000	29.963616000	62.731575000
C	43.405083000	30.518864000	60.881693000
O	42.288728000	30.800937000	61.423821000
O	43.568105000	30.342119000	59.653033000
C	41.459511000	36.567618000	60.877800000
H	42.111535000	36.319451000	61.731854000
H	40.419117000	36.465219000	61.234833000
C	41.708914000	35.570070000	59.744390000
H	41.197743000	35.892710000	58.819629000
H	42.786335000	35.516508000	59.503192000
C	41.246172000	34.152886000	60.083885000
H	41.607147000	33.859872000	61.082981000
H	40.143227000	34.119817000	60.114950000
C	41.784774000	33.169158000	59.059364000
H	41.566536000	33.499268000	58.033587000
H	42.876282000	33.084995000	59.160350000
N	41.234456000	31.805154000	59.216633000
H	41.520877000	31.395900000	60.166723000
H	40.203620000	31.728227000	59.096619000
H	41.678359000	31.182260000	58.527805000
N	33.409907000	33.275939000	59.866031000
H	34.192604000	32.649356000	59.654443000
C	32.292294000	33.352324000	58.968743000
H	32.003558000	32.334076000	58.667604000
H	31.413530000	33.823065000	59.434970000
O	36.743884000	31.223010000	54.913134000
O	35.532649000	31.336128000	59.159117000
N	35.952158000	32.897634000	56.217045000
O	36.507214000	30.087788000	57.372135000
C	34.820656000	32.525145000	54.120145000
C	35.913421000	32.144964000	55.092222000
C	36.852505000	32.605280000	57.342001000
C	36.994253000	33.820110000	58.254980000
C	37.630533000	35.052024000	57.598350000
C	37.714484000	36.230640000	58.572466000
C	38.999487000	34.737872000	56.985841000
B	36.306707000	31.283295000	58.023490000

H	34.212925000	33.327186000	54.566550000
H	35.099402000	33.434779000	56.454896000
H	37.831549000	32.352670000	56.906640000
H	37.598202000	33.525903000	59.129053000
H	35.996536000	34.098001000	58.640167000
H	36.962403000	35.335969000	56.774494000
H	38.067529000	37.144668000	58.066954000
H	36.729148000	36.451082000	59.016707000
H	38.403332000	36.012610000	59.405069000
H	38.914887000	34.088595000	56.101512000
H	39.512413000	35.660691000	56.676379000
H	39.637964000	34.226585000	57.722389000
H	35.204443000	30.431675000	59.423898000
H	36.874574000	30.300831000	56.474399000
H	40.169068000	29.506983000	62.895669000
H	35.267541000	32.904848000	53.201349000
H	34.175326000	31.686062000	53.860231000
H	33.576538000	34.009286000	60.525127000
H	32.490688000	33.866808000	58.028523000
H	45.023230000	31.459876000	62.021757000
H	41.634416000	37.605561000	60.594692000

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N	38.745513000	28.663413000	59.936897000
H	39.484297000	28.040936000	59.606695000
H	37.976575000	28.087630000	60.327003000
C	39.240264000	29.629758000	60.940811000
C	38.229575000	30.801647000	60.726087000
C	38.544772000	32.035936000	61.547338000
H	38.385256000	31.801451000	62.612249000
H	39.581899000	32.378044000	61.436950000
H	37.874543000	32.862751000	61.284772000
O	38.237246000	30.940496000	59.328709000
H	38.402314000	29.542747000	59.201298000
H	37.236735000	30.429177000	61.050434000
H	40.235363000	29.942115000	60.607323000
C	39.308442000	29.160018000	62.375544000
O	38.462780000	28.395602000	62.803305000
C	44.481574000	30.486492000	61.731622000
H	45.257473000	29.904603000	61.211925000
H	44.239715000	29.997519000	62.688427000
C	43.247916000	30.572084000	60.818551000
O	42.130167000	30.889538000	61.344061000
O	43.418235000	30.370261000	59.596201000

C	41.436050000	36.563097000	60.829902000
H	42.104437000	36.283724000	61.661527000
H	40.403051000	36.468930000	61.209459000
C	41.639821000	35.586854000	59.668305000
H	41.134656000	35.950156000	58.755290000
H	42.712932000	35.497539000	59.420245000
C	41.116224000	34.187288000	59.990072000
H	41.488748000	33.862694000	60.975468000
H	40.015278000	34.213935000	60.046946000
C	41.573152000	33.191810000	58.939698000
H	41.328610000	33.533153000	57.924618000
H	42.663163000	33.058098000	58.994662000
N	40.983040000	31.839192000	59.112812000
H	41.317954000	31.442085000	60.047269000
H	39.941973000	31.776279000	59.037281000
H	41.391511000	31.220118000	58.397912000
N	33.481277000	33.161679000	59.970146000
H	34.292381000	32.563244000	59.755768000
C	32.385123000	33.237960000	59.044824000
H	32.132548000	32.221151000	58.709681000
H	31.481386000	33.674253000	59.498751000
O	36.907097000	31.207436000	55.042491000
O	35.714711000	31.299323000	59.374633000
N	36.083051000	32.744560000	56.491484000
O	36.709912000	29.998451000	57.590431000
C	34.942696000	32.507280000	54.367584000
C	36.053692000	32.084114000	55.313798000
C	37.069524000	32.522249000	57.557728000
C	37.153958000	33.774647000	58.427073000
C	37.562070000	35.060168000	57.701190000
C	37.650624000	36.249343000	58.661542000
C	38.854741000	34.887368000	56.900335000
B	36.743641000	31.180908000	58.387002000
H	34.342398000	33.301974000	54.836580000
H	35.247953000	33.302812000	56.735107000
H	38.036557000	32.348460000	57.056464000
H	37.855953000	33.588495000	59.255697000
H	36.164474000	33.943577000	58.885922000
H	36.751922000	35.254473000	56.986599000
H	37.867741000	37.188726000	58.125899000
H	36.703537000	36.384160000	59.209412000
H	38.439827000	36.099528000	59.417378000
H	38.706947000	34.255264000	56.012001000
H	39.248269000	35.859191000	56.570853000

H	39.627088000	34.411123000	57.522733000
H	35.346446000	30.408665000	59.584894000
H	37.050855000	30.236697000	56.698809000
H	40.127210000	29.594617000	62.948964000
H	35.372739000	32.900339000	53.446371000
H	34.296932000	31.675078000	54.087411000
H	33.628346000	33.912495000	60.614054000
H	32.593988000	33.781965000	58.123683000
H	44.893448000	31.464472000	61.980585000
H	41.620130000	37.604314000	60.565233000

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