Supporting Information: Exploring the Conformation Dependent Reactivity and Dynamics of a Dinucleotide Inhibitor of Ribonuclease A

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Supplementary Information

Definition of *closed* and *open* of the inhibitor from the distance between N (-NH_2) of adenine base and =O of uracil (d_{ee}):

Closed - $d_{ee} \leq 10$ Å

Open - $d_{ee} > 10$ Å

Table S1: Total ground-state energies (Hartree) of the optimized structure of the *open* conformer at the B3LYP/def2-TZVP level with two different dispersion correction methods.

	[B3LYP/def2-TZVP IOP(3/124=40)]	**[B3LYP/def2-TZVP IOP(3/124=30)]**
Total Energy (Hartree)	-3995.3971	-3995.3117

Table S2: Ground state energies of the optimized structures of *closed* and *open* conformers at different levels of theory.

PUA	**B3LYP/def2-TZVP**	**B3LYP/6-31G++(d,p)**	**HF/6-31G**
Closed	-3995.2162	-3994.024	-3975.2169
Open	-3995.1958	-3994.021	-3975.2113

Table S3: Comparison of total energies (Hartree) and global reactivity descriptors (eV) for *closed* conformer with ribose and arabinose units optimized at the B3LYP/def2-TZVP level.

	***Closed* (ribose)**	***Closed* (arabinose)**
Energy (Hartree)	-3995.2148	-3995.2162
Descriptors (eV)		
Electronegativity	3.72	3.88
Chemical Potential	-3.72	-3.88
Global Hardness	2.46	2.49
Global Softness	0.20	0.20
Electrophilicity Index	2.81	3.03
Softness	0.40	0.40

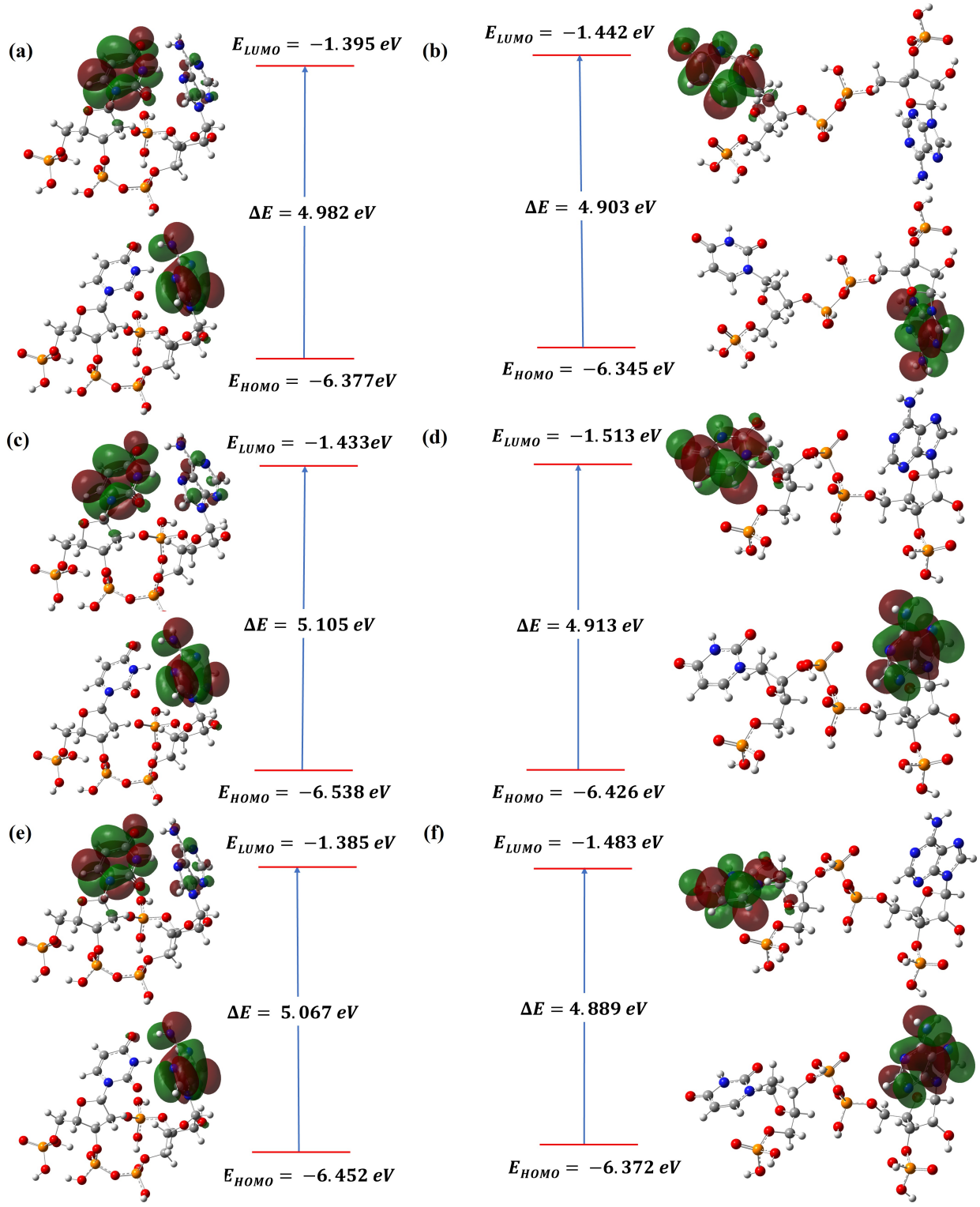

Figure S1: HOMO-LUMO gap for the (a,c,e) *closed* and (b,d,f) *open* conformers of PUA in (a,b) the gas phase (c,d) in water cand (e,f) diethyl ether without dispersion correction terms in the calculation of total energy, E. Also shown the HOMO and LUMO orbitals; green and red lobes represent the negative and positive electron densities, respectively.

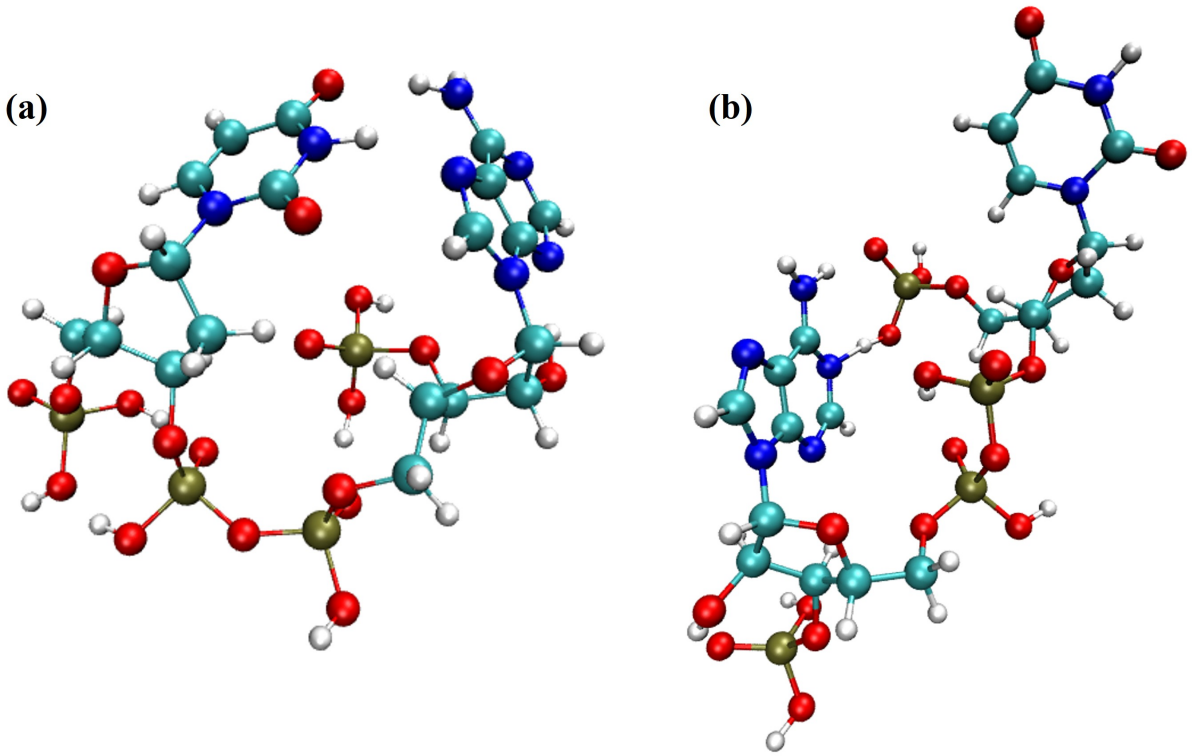

Figure S2: Optimized geometries of (a) *closed* and (b) *open* PUA are presented using the B3LYP/6-31G++(d,p) level.

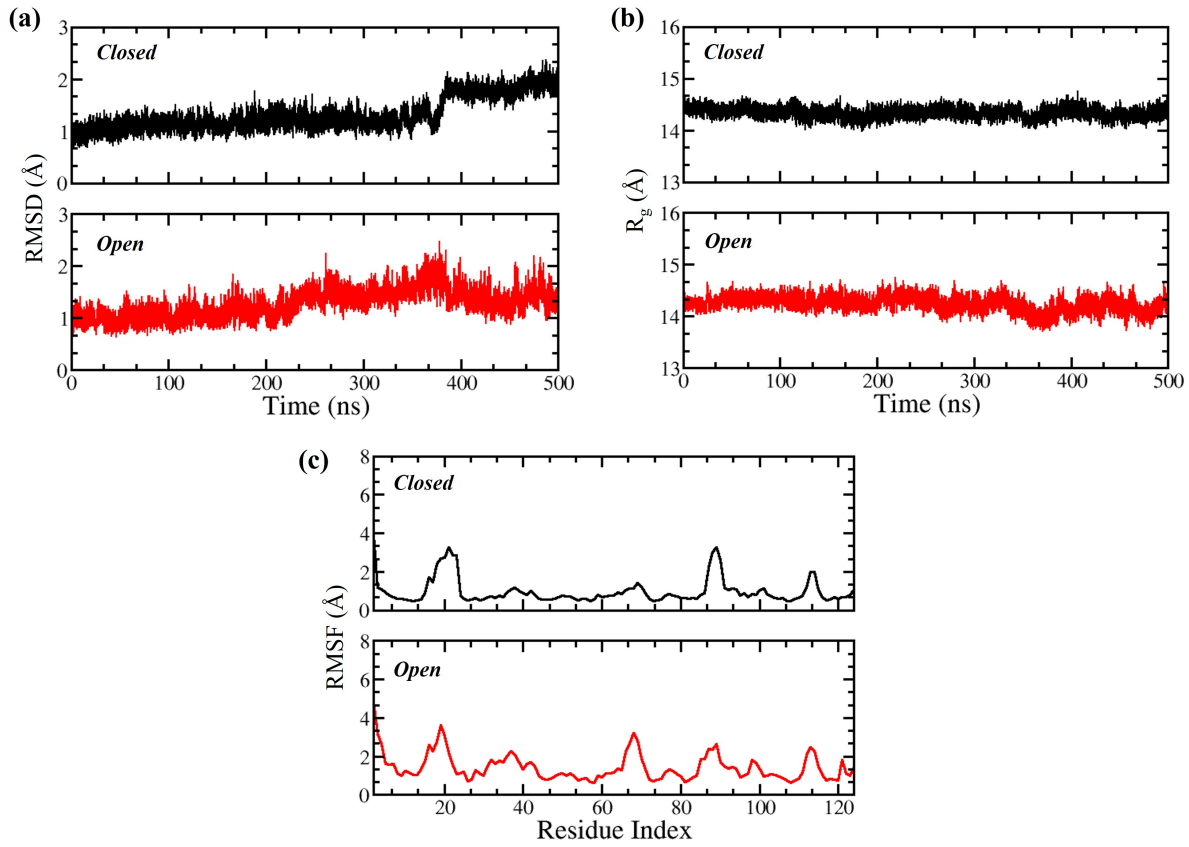

Figure S3: (a) Root mean square deviation (RMSD), radius of gyration (R_g) and root mean square fluctuations (RMSF) of backbone atoms (N, C_α, C) calculated for the 500 ns MD trajectories for both *closed* and *open* inhibitor-bound RNases.

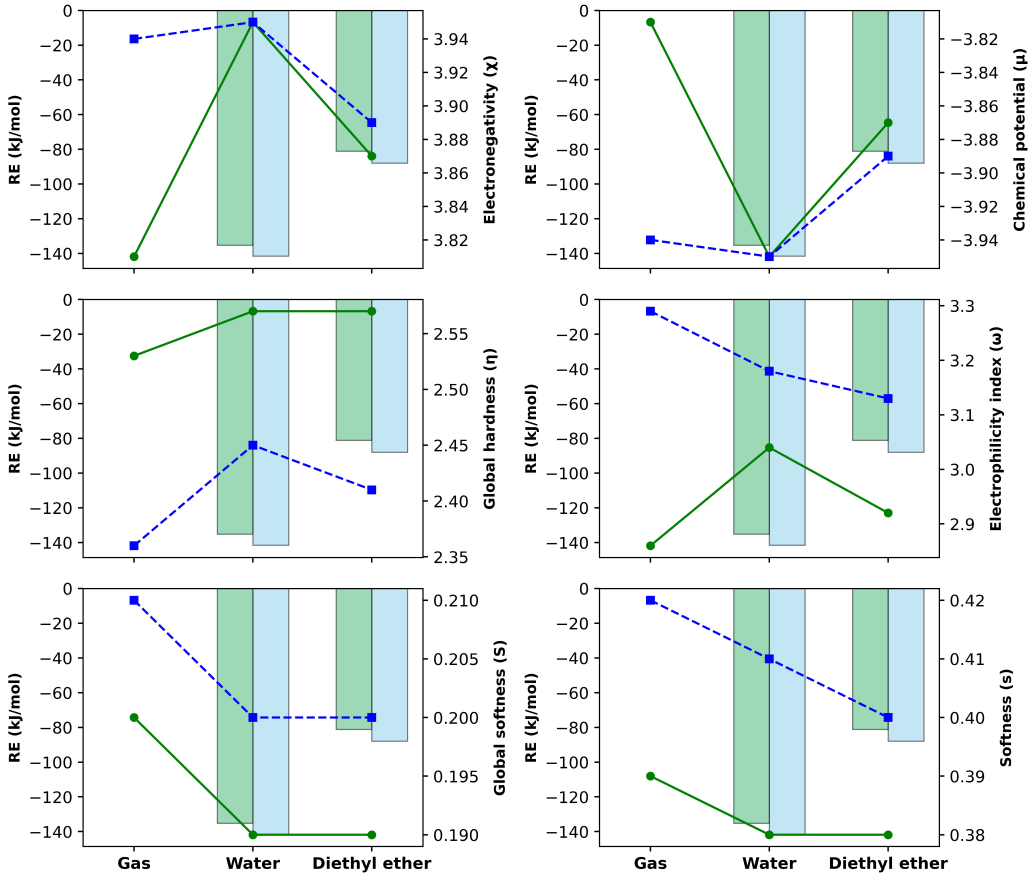

Figure S4: Comparison between the changes in the relative energy (kJ/mol) of the inhibitor and electronic descriptors including (a) electronegetivity (χ), (b) chemical potential (μ), (c) global hardness (η), (d) electrophilicity index (ω), (e) global softness (S) and (f) softness (s) (in eV) values in the gas and solvent phase considered, respectively, for the *closed* (shown in green) and *open* conformer (shown in blue).

Initial coordinates (x, y, z) of the ***closed*** conformation

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C   0.25642003    7.85323445   -0.52674367
C  -0.20882654    6.86697389    0.26227668
H   3.47442632    7.48568185    0.06069500
H  -0.42849202    8.48005613   -1.08632680
H  -1.26118802    6.67216485    0.34150515
N   0.73058042    6.07823661    1.00953302
N   2.49033746    7.32528564    0.13217930
C   2.04046032    6.35221237    0.95579905
O   2.84035652    5.73312603    1.67554063
C   1.64819148    8.08210513   -0.60933950
O   2.11181825    8.97911874   -1.35693170
C   0.23974550    5.00925828    1.84013757
O  -1.18278366    4.83196900    1.47615464
C   0.90543834    3.63605816    1.55596986
H   0.42108411    5.25706768    2.87543437
C  -1.40702571    3.45870209    1.18047420
C  -0.05005965    2.99690670    0.59214102
H   0.88265754    3.02682264    2.43432601
H   1.93585997    3.69206901    1.22129238
H  -1.61713421    2.86030270    2.04846107
H   0.07874087    3.35263017   -0.41586870
O   0.25040407    1.58021072    0.66075194
P  -0.02155229    0.32552996   -0.49482470
O  -0.36995802    0.98165940   -1.87409141
O  -1.12347125   -0.84927886   -0.00197007
O   1.31965595   -0.71592319   -0.54279389
H  -1.98477791   -0.54721792   -0.04575378
C  -2.56557059    3.37959315    0.17518892
H  -2.34500111    3.97456077   -0.70239529
H  -3.47907682    3.74370381    0.58792348
O  -2.65047214    2.03109072   -0.10117228
```

P	-3.59866529	1.33431365	-1.31221400
O	-5.04387109	1.89101989	-1.40446275
O	-2.85120050	1.53282400	-2.85926340
O	-3.61353985	-0.29816168	-0.72665987
H	-4.28161475	-0.79932019	-1.17022474
H	-1.94819366	1.25643256	-2.76020846
P	2.98304790	-0.62622182	-0.84902134
O	3.34052924	-0.08330636	-2.24918831
O	3.29544175	-2.29152380	-0.68009822
O	3.80843636	0.33060736	0.36324682
H	2.74484808	-2.55137751	0.09663159
C	5.18535181	0.82039040	0.30011491
H	5.88606162	0.15871258	-0.17711849
H	5.48210078	0.96600899	1.30898427
C	5.15148154	2.15858015	-0.39995560
O	6.34736494	2.86364891	0.06482126
C	5.23105161	2.19616081	-1.95833680
H	4.21065917	2.60908515	-0.11800972
C	6.89992129	3.64925578	-0.98145754
H	4.95777094	1.25819320	-2.44538207
H	7.93737088	3.84449621	-0.81891319
O	4.38255881	3.20590643	-2.48432685
P	2.65027665	2.75528548	-2.65380543
O	2.15038939	2.14764754	-1.32121748
O	2.30121053	1.61912011	-3.94015687
O	1.80328769	4.16635460	-3.06644736
H	2.66228371	0.74350216	-3.76649837
H	2.08779666	4.38601119	-3.94888984
C	6.49897243	5.82880207	-2.13615878
C	5.46832519	5.58099780	-0.22721094
C	5.77058030	6.90324941	-1.93923280
H	5.16849098	5.13219856	0.68529116
C	5.75213715	7.93944028	-2.87499461

C	7.35626868	6.74129590	-4.05826999
N	6.28809883	4.97897525	-1.11660223
N	5.10599884	6.76243928	-0.66040692
N	7.31534090	5.70828694	-3.18335322
N	6.59708605	7.83931406	-3.90702587
N	4.93917587	9.00866133	-2.80746401
H	5.01594180	9.72939146	-3.50817279
H	4.24999903	9.10062546	-2.07847294
H	8.01456303	6.68753264	-4.91810148
H	7.35242228	1.93897277	-2.22244699
O	6.68720042	3.43716459	-3.31533642
C	6.64235672	2.73897730	-2.19599574
H	7.60264585	3.59014898	-3.56060249

Initial coordinates (x, y, z) of the *open* conformation

O	38.08700000	-5.00200000	20.55400000
O	37.93800000	-4.11900000	22.85000000
P	39.72200000	-9.83800000	19.90400000
O	40.66100000	-9.11700000	20.83300000
N	37.24000000	-5.70400000	16.31500000
C	37.53400000	-4.36300000	16.14600000
N	38.28300000	-3.57000000	16.94600000
C	38.36500000	-2.31800000	16.44400000
N	37.81800000	-1.81700000	15.31300000
C	37.07700000	-2.63900000	14.53500000
N	36.54700000	-2.14300000	13.41700000
C	36.91000000	-3.98700000	14.95700000
N	36.22500000	-5.06000000	14.40500000
C	36.44400000	-6.04500000	15.24500000
C	37.36300000	-6.18600000	20.81100000
C	37.49400000	-7.11500000	19.64500000

O	36.82100000	-6.53900000	18.48500000
C	37.67100000	-6.64700000	17.36200000
C	39.08000000	-6.53100000	17.94500000
O	40.08100000	-7.02200000	17.06400000
C	38.93600000	-7.38000000	19.21000000
O	39.03200000	-8.76600000	18.89000000
O	39.87800000	1.83500000	22.39300000
C	40.56200000	0.78600000	23.10700000
C	39.58000000	0.04700000	23.98400000
O	38.86400000	1.01100000	24.79400000
C	37.47500000	0.91800000	24.53500000
C	37.35000000	0.26200000	23.17400000
C	38.50900000	-0.71100000	23.20100000
O	38.13000000	-1.87400000	23.92500000
P	40.24900000	2.19400000	20.84300000
O	40.66200000	3.63800000	20.74800000
N	36.90800000	2.27200000	24.56000000
C	37.46500000	3.30200000	23.80200000
C	35.76600000	2.47900000	25.33400000
O	35.26600000	1.61600000	26.02900000
N	35.23300000	3.74500000	25.24100000
C	35.70400000	4.79700000	24.46300000
O	35.00400000	5.79500000	24.33800000
C	36.91300000	4.52100000	23.72400000
H	36.81800000	-1.23600000	13.09500000
H	36.03900000	-7.02600000	15.11000000
H	37.83800000	-6.66400000	21.64200000
H	36.33100000	-5.91000000	20.87100000
H	37.06200000	-8.03700000	19.97400000
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H	39.68200000	-7.14700000	19.94100000

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H	36.43800000	-0.29800000	23.15000000
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H	38.83000000	-1.02200000	22.22900000
H	38.36900000	3.11200000	23.26100000
H	37.36400000	5.28100000	23.12100000
O	38.88100000	1.92600000	19.85300000
O	41.53600000	1.19700000	20.31900000
H	39.16800000	1.68700000	18.96800000
H	42.37300000	1.61400000	20.53800000
O	36.25700000	-2.18900000	21.96500000
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H	41.07700000	-5.05700000	22.00800000
H	35.87800000	-2.67800000	12.90000000
H	38.94300000	-1.62700000	17.02100000
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H	38.91700000	-11.18800000	21.47600000
H	34.41900000	3.92800000	25.79300000
H	36.91000000	-1.86200000	21.34100000
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O	39.52200000	-3.27900000	21.30800000
P	38.99200000	-4.35600000	21.68700000
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