

Supporting Information

Simulations Reveal Key Role of Arg18 for Promiscuous Activity in HisA Enzyme

Kshatresh Dutta Dubey*, and Warispreet Singh^{b,c}

Department of Chemistry and Center for Informatics, School of Natural Sciences, Shiv Nadar University, Gautam Buddha Nagar, Uttar Pradesh-201314, India

^b Department of Applied Sciences, Northumbria University, Newcastle upon Tyne, NE1 8ST, United Kingdom

^c Hub for Biotechnology in Build Environment, Newcastle upon Tyne, NE1 8ST, United Kingdom

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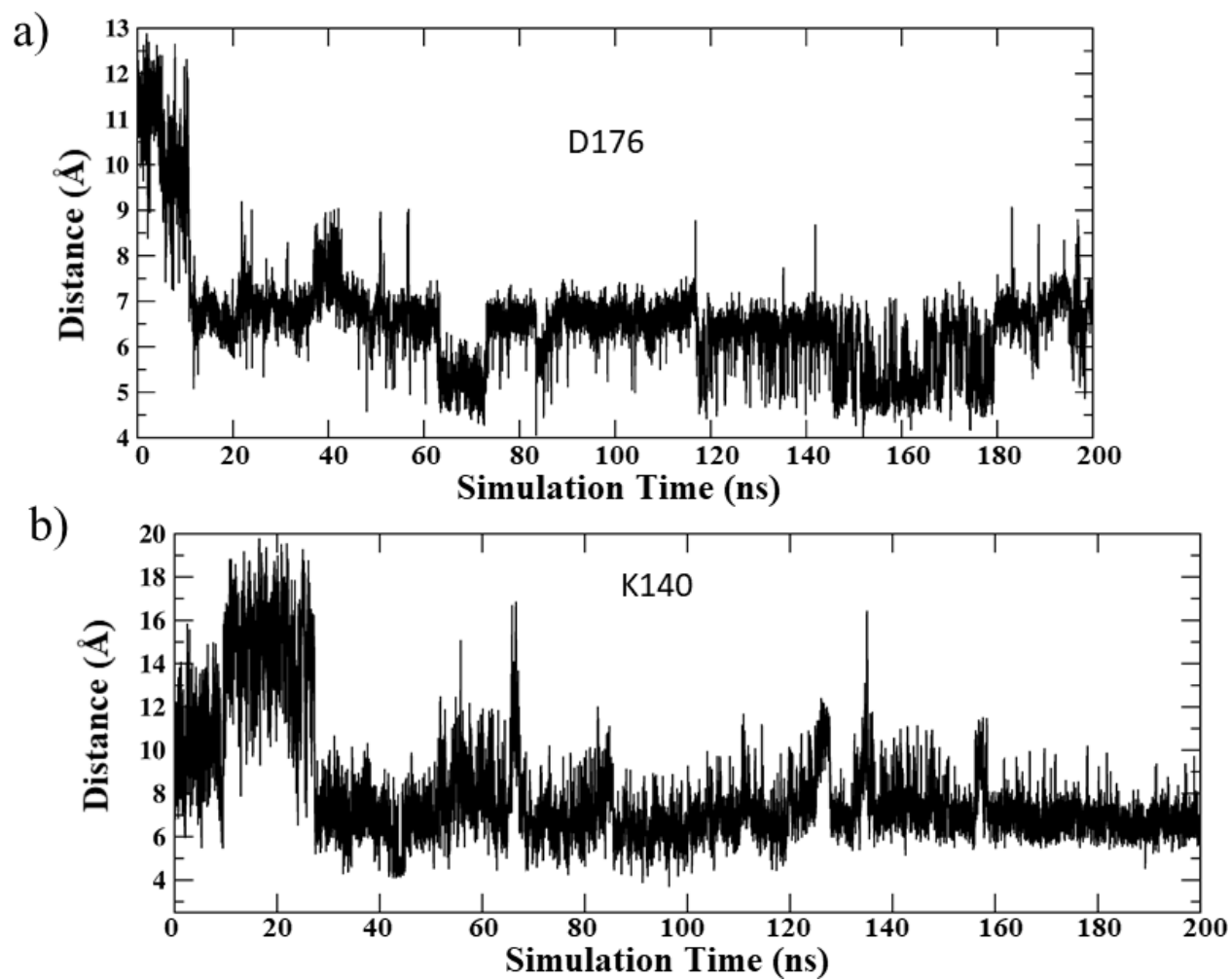


Figure S1. The distance between Asp176 and O of furanose ring is shown in a, while the distance between the K141 to C'OH is shown in b.

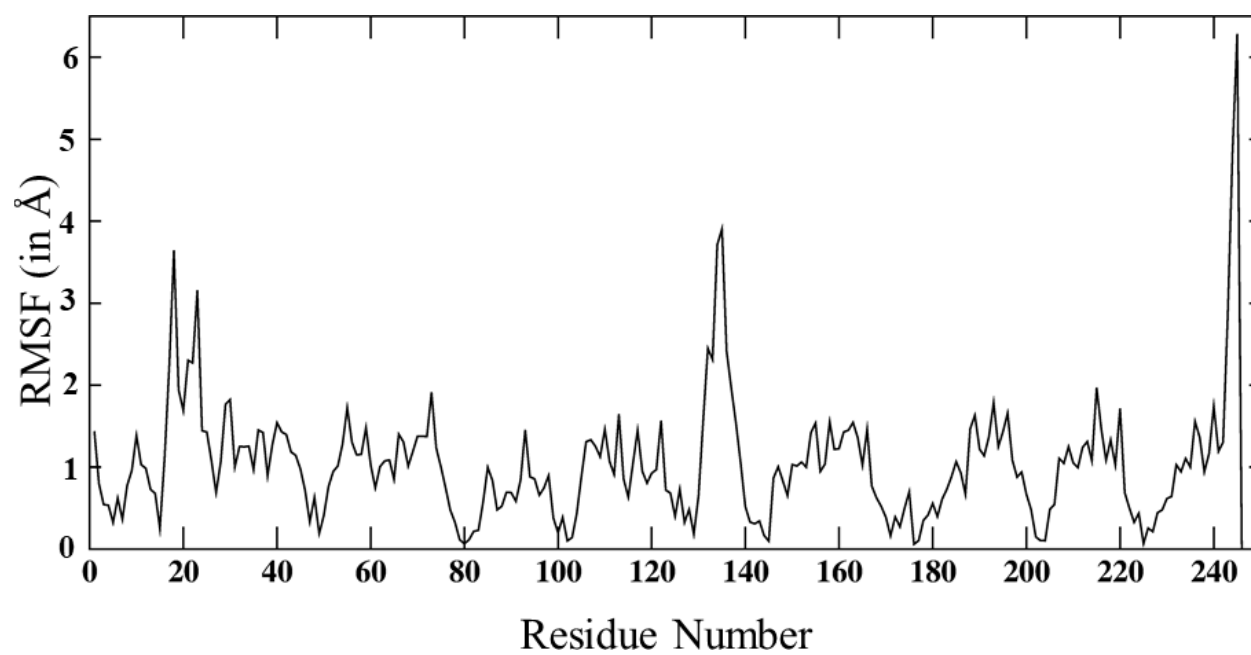


Figure S2. The RMSF for the MD simulations of the substrate bound HisA.

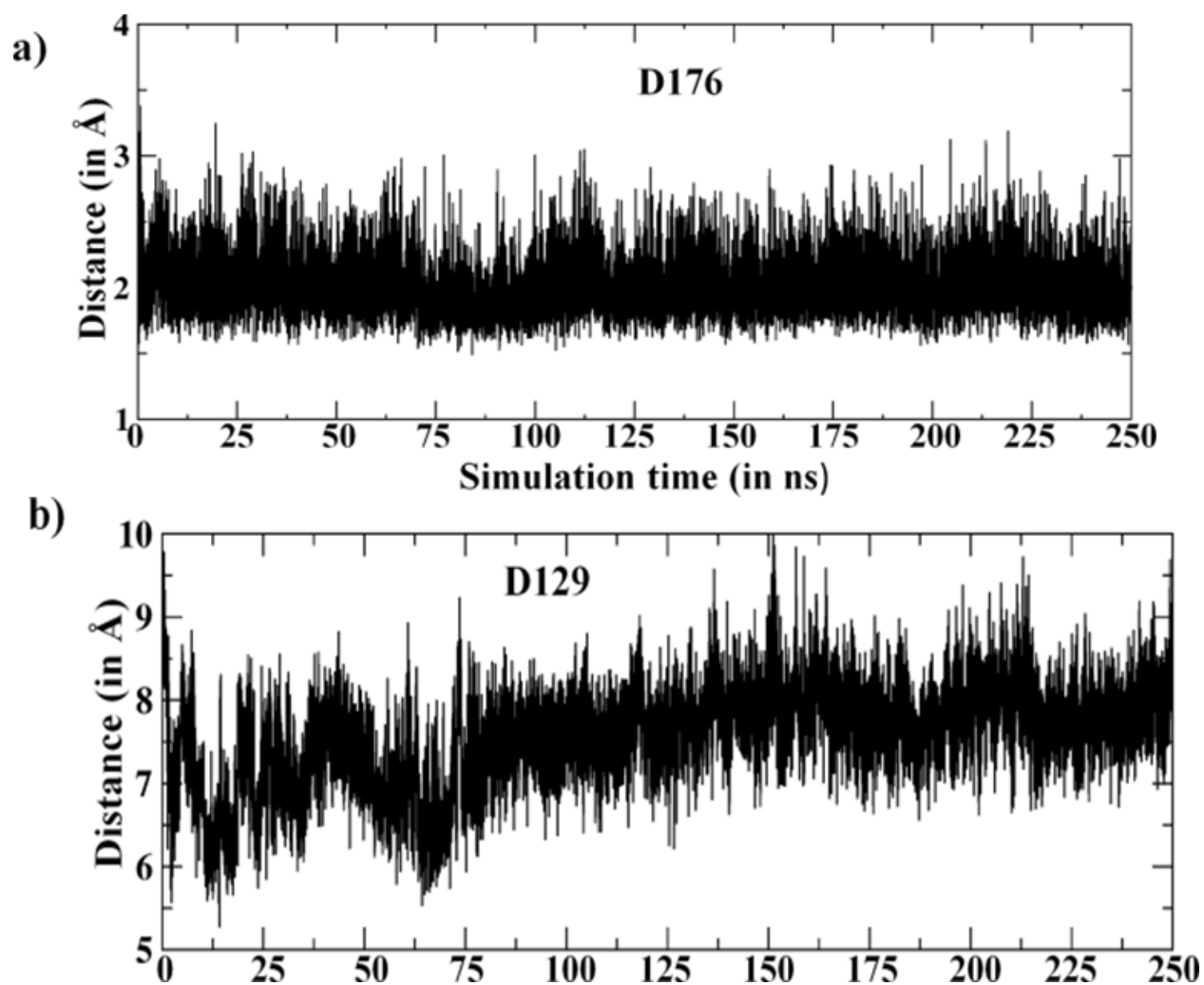


Figure S3. The distances of protonated Asp176 and Asp129 with MD simulations.

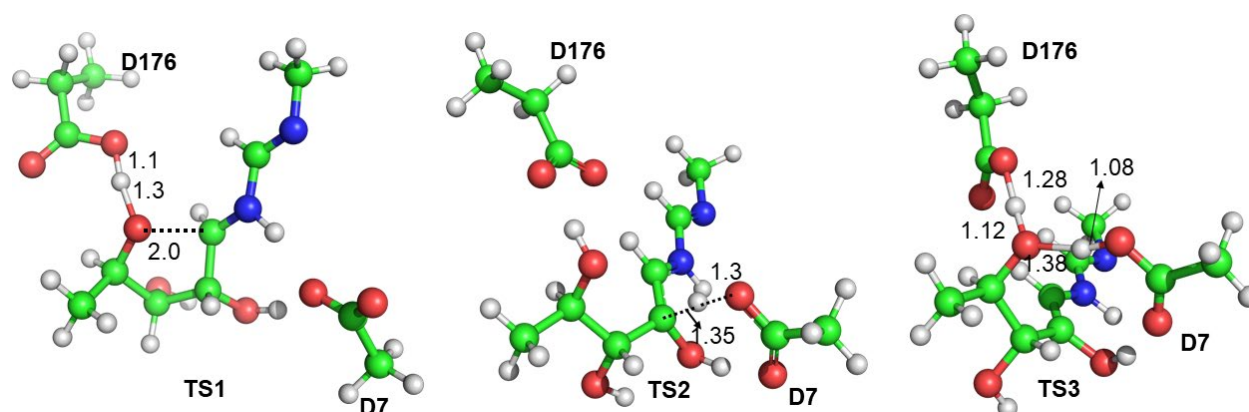


Figure S4: Transition state geometry for different stationary point corresponding to Figure 5 of main text.

QM-MM geometry for Reactant:

C	35.034258000	30.586889000	25.109385000
H	35.253086000	30.794656000	24.057577000
H	35.398076000	31.419730000	25.725579000
C	35.705066000	29.272018000	25.562693000
O	36.434464000	28.664880000	24.762165000
O	35.441848000	28.919585000	26.774074000
C	36.387782000	24.829941000	35.136690000
H	36.962003000	25.594984000	34.605668000
C	35.928194000	23.721231000	34.174996000
H	36.807210000	23.253086000	33.712613000
H	35.372265000	22.945683000	34.709697000
C	35.031630000	24.234174000	33.060021000
O	33.882282000	23.859254000	32.886449000
O	35.648905000	25.140531000	32.297180000
H	35.056471000	25.471956000	31.554095000
C	32.260654000	24.890628000	29.873695000
C	32.781161000	26.237673000	30.354194000
O	34.238663000	26.221399000	30.274935000
C	32.325401000	27.449581000	29.515320000
O	31.850250000	28.490907000	30.369116000
C	33.600032000	27.900336000	28.790701000
O	33.535995000	29.261710000	28.460691000
C	34.698223000	27.535227000	29.800537000
N	36.000410000	27.467395000	29.238826000
C	37.111454000	27.542349000	30.039719000
N	38.310801000	27.607558000	29.605231000
H	32.523119000	24.724078000	28.822164000
H	31.168024000	24.856611000	29.973098000
H	32.489575000	26.406892000	31.398352000
H	31.532928000	27.170997000	28.806350000
H	32.094099000	29.321065000	29.915169000
H	33.756609000	27.286472000	27.893274000
H	34.242552000	29.380639000	27.738721000
H	34.669476000	28.217375000	30.662378000
H	36.876292000	27.518667000	31.117338000
H	36.097445000	27.712164000	28.242882000
H	33.947182000	30.530819000	25.252948000
H	37.020239000	24.409992000	35.928102000
H	35.529693000	25.317776000	35.614418000
H	32.686441000	24.084932000	30.478903000
C	39.363756000	27.684897000	30.594208000
H	39.943732000	28.608671000	30.455680000
H	38.998811000	27.664332000	31.639926000
H	40.065226000	26.848158000	30.464201000

QM-MM geometry for IM1:

C	5.781771000	-0.528790000	-0.976712000
H	6.094057000	-0.918514000	-1.949578000
H	6.046177000	-1.246675000	-0.190399000
C	4.271979000	-0.275410000	-0.948194000
O	3.569769000	-0.565082000	-1.928758000
O	3.830177000	0.241150000	0.160764000
C	-5.576929000	-2.215240000	-0.825038000
H	-6.096846000	-1.420452000	-0.278686000
C	-4.169064000	-2.434174000	-0.267585000
H	-4.211908000	-2.758708000	0.781575000
H	-3.663906000	-3.249246000	-0.805550000
C	-3.234162000	-1.207394000	-0.327855000
O	-2.079598000	-1.362881000	0.173362000
O	-3.678030000	-0.153256000	-0.864419000
H	-2.631156000	1.158795000	-1.072414000
C	-2.659194000	3.483953000	0.648908000
C	-1.738438000	2.331087000	0.236924000
O	-1.982771000	1.922852000	-1.098520000
C	-0.260990000	2.731508000	0.338227000
O	0.065066000	2.937121000	1.710059000
C	0.743011000	1.709701000	-0.276478000
O	2.018702000	2.190356000	0.081894000
C	0.424314000	0.303771000	0.108641000
N	1.304278000	-0.562560000	0.500940000
C	0.919199000	-1.898713000	0.802514000
N	1.801295000	-2.706851000	1.216408000
H	-2.529191000	4.332451000	-0.035444000
H	-2.443537000	3.815883000	1.671547000
H	-1.908768000	1.489465000	0.925646000
H	-0.100604000	3.664716000	-0.225282000
H	1.039390000	2.978532000	1.736581000
H	0.581317000	1.726949000	-1.369148000
H	2.744505000	1.510316000	-0.024883000
H	-0.611190000	-0.055203000	0.013971000
H	-0.147886000	-2.100402000	0.647446000
H	2.355777000	-0.323918000	0.483321000
H	6.320490000	0.401027000	-0.757424000
H	-6.176048000	-3.134498000	-0.752466000
H	-5.539057000	-1.907769000	-1.875549000
H	-3.703521000	3.156625000	0.592512000
C	1.364833000	-4.062150000	1.503207000
H	1.610784000	-4.299887000	2.545567000

H	0.288999000	-4.230391000	1.339782000
H	1.935154000	-4.755029000	0.872357000

QM-MM geometry for IM2:

C	3.586816000	0.531502000	-3.146563000
H	3.527900000	-0.563022000	-3.169734000
H	4.613601000	0.837082000	-2.937249000
C	2.658616000	1.058508000	-2.070123000
O	1.390140000	0.844460000	-2.368109000
O	3.073822000	1.611011000	-1.054761000
C	-4.560581000	-2.064347000	-2.041476000
H	-5.106644000	-1.114019000	-2.044584000
C	-3.830866000	-2.274295000	-0.712685000
H	-4.544706000	-2.325613000	0.120880000
H	-3.309677000	-3.242823000	-0.711580000
C	-2.779406000	-1.200792000	-0.347897000
O	-2.247160000	-1.299586000	0.787254000
O	-2.536867000	-0.312415000	-1.227178000
H	-1.393578000	0.767145000	-1.035108000
C	-1.644114000	3.522457000	0.025065000
C	-0.935907000	2.194163000	0.302254000
O	-0.696449000	1.507453000	-0.928362000
C	0.417670000	2.396814000	0.996346000
O	0.219654000	3.287988000	2.127458000
C	1.114433000	1.137800000	1.427164000
O	2.477349000	1.311174000	1.728185000
C	0.548623000	-0.063847000	1.616540000
N	1.261655000	-1.174468000	2.057151000
C	0.719982000	-2.426686000	2.179934000
N	1.407074000	-3.429568000	2.591953000
H	-1.019426000	4.161720000	-0.612544000
H	-1.856510000	4.058126000	0.956199000
H	-1.581426000	1.572298000	0.935502000
H	1.074483000	2.916408000	0.279753000
H	0.993403000	3.169907000	2.701187000
H	0.717801000	1.144263000	-1.680193000
H	2.915048000	1.520046000	0.876733000
H	-0.500969000	-0.254378000	1.402114000
H	-0.338052000	-2.473440000	1.889413000
H	2.243433000	-1.056001000	2.282555000
H	3.273777000	0.895509000	-4.130734000
H	-5.279279000	-2.875865000	-2.229605000
H	-3.851922000	-2.026680000	-2.875609000
H	-2.584509000	3.326270000	-0.502179000
C	0.712834000	-4.700257000	2.673961000
H	0.753962000	-5.086870000	3.703084000
H	-0.347933000	-4.648958000	2.370571000
H	1.212152000	-5.445103000	2.036789000

QM-MM geometry for RC for extended calculations (when R15 is included in QM region):

C	35.544624067	28.650968808	24.578261485
H	35.783471394	27.686978921	24.114149358
H	36.411800484	29.323812879	24.457305719
C	35.313199922	28.440330160	26.092264280
O	35.709089227	27.316507754	26.551152752

O	34.815893494	29.369072127	26.754121028
C	33.123841901	25.271808540	26.782091491
H	33.985950781	25.816467347	26.376718161
H	32.312001678	26.011881642	26.888054993
N	33.413642367	24.677972688	28.067215094
H	32.653375619	24.227382283	28.612233836
C	34.614278763	24.511100647	28.636717915
N	35.729174240	25.037870336	28.086796893
H	35.629006662	25.888144296	27.497600816
H	36.589548920	25.069695385	28.655545827
N	34.668926906	23.733233034	29.720840105
H	33.756097007	23.429424730	30.116391068
H	35.471604680	23.814063406	30.345470107
C	35.698535486	22.187286608	34.190707165
H	34.623144397	22.430779914	34.163988382
C	36.510521183	23.493827528	34.063853584
H	36.323066485	24.111167251	34.955252638
H	37.590611512	23.286246837	33.997981060
C	36.136341820	24.317232078	32.844593162
O	36.709082961	24.179478863	31.766505252
O	35.147643145	25.151055538	33.056671251
H	34.906812376	25.730985588	32.263288740
C	32.022252453	26.042570983	31.072833841
C	32.896439908	27.237845460	31.397027396
O	34.339904054	26.919257747	31.245713945
C	32.665565460	28.500954442	30.518812452
O	32.329826536	29.645425240	31.251458816
C	33.993141819	28.636443462	29.747833638
O	34.305488126	29.905510115	29.905510115
C	34.986808844	28.109834742	30.791200752
N	36.307099104	27.870971959	30.306677405
C	37.348939834	28.679501161	30.616912362
N	38.400981727	28.734391016	29.876609773
H	32.757909428	27.539261403	32.448198596
H	31.822508761	28.333556230	29.829784932
H	33.044541932	29.885999953	31.882523451
H	34.000605963	27.901659875	28.920962445
H	34.550549666	29.784102239	28.322279586
H	35.081737906	28.842263291	31.612518724
H	37.195290823	29.247291365	31.551497814
H	36.423395131	27.301390751	29.469670148
O	38.044334685	25.571046468	29.625464812
H	37.878482261	25.328065441	30.549589051
H	38.874817463	26.095951303	29.610726397
O	38.412770317	27.647225169	27.201873984
H	37.488739362	27.469228064	26.936611452
H	38.364415909	28.055212497	28.093425774
H	34.684993966	29.076066450	24.060192741
H	32.792676108	24.524012451	26.061537978
H	35.882352311	21.704668870	35.150581445
H	35.883825504	21.536689533	33.336038695
H	31.961461338	25.895325858	29.994552592
H	31.013432669	26.245610544	31.432173121
H	32.335946635	25.099878121	31.521156566
H	39.183701837	29.236986821	30.243650679

QM-MM geometry for TS for extended calculations (when R15 is included in QM region):

C	35.506879741	28.622444352	24.711580352
H	35.694875054	27.601622348	24.363702363
H	36.419308261	29.215752722	24.543294676
C	35.248531517	28.616175180	26.234041515
O	35.745310968	27.637412936	26.888969689
O	34.635731734	29.566145419	26.738346766
C	33.106181726	25.313489566	26.795525665
H	33.976927926	25.846598005	26.397501926

H	32.299390607	26.056785493	26.881971563
N	33.373321112	24.740769063	28.091262519
H	32.611542205	24.288209659	28.635887743
C	34.569118086	24.557018752	28.658249928
N	35.686712719	25.068081920	28.092225041
H	35.572763043	25.930185187	27.545617745
H	36.528207079	25.138489746	28.682108927
N	34.625995182	23.774296410	29.725904653
H	33.711075064	23.464432311	30.113750567
H	35.427245774	23.858855555	30.354692668
C	35.659066719	22.255444733	34.158960070
H	34.582374421	22.478570504	34.124256721
C	36.437858117	23.576290042	34.015759837
H	36.220580988	24.198607633	34.892133289
H	37.520708886	23.390545890	33.970728969
C	36.072826748	24.384134839	32.770983110
O	36.670480752	24.170979997	31.708749996
O	35.135430816	25.247989229	32.934817110
H	34.816945649	25.869879653	32.057981919
C	31.968967149	25.948033610	31.165680385
C	32.951380853	27.078556624	31.422967636
O	34.294631574	26.683549371	31.120712003
C	32.613321671	28.347895601	30.592516728
O	32.289343686	29.474378444	31.358105010
C	33.802410886	28.609465692	29.667945395
O	33.828503240	29.912281751	29.184299665
C	35.070164268	28.391884542	30.456013736
N	36.228993954	28.269809651	29.786802305
C	37.404270933	28.734270026	30.329492070
N	38.459511157	28.842785922	29.631707821
H	32.895791701	27.385235124	32.483352257
H	31.722308180	28.170417883	29.971763887
H	33.041345149	29.724328487	31.933791865
H	33.810676889	27.860219099	28.853664966
H	34.171891204	29.858815971	28.250784145
H	35.148487887	28.883529582	31.428342720
H	37.294346795	29.039234234	31.383116027
H	36.195787953	27.994623368	28.786090270
O	37.886728181	25.755040014	29.646020653
H	37.732270390	25.336714931	30.509331822
H	38.807476115	26.083563890	29.642136981
O	38.519327791	27.541221466	27.012117843
H	37.571835642	27.437546188	26.810179828
H	38.517584324	28.012301020	27.864889527
H	34.682543860	29.043644931	24.136143502
H	32.783215897	24.557171522	26.080163358
H	35.845921930	21.773761367	35.118717021
H	35.856380388	21.600037719	33.310681755
H	31.843199463	25.819075216	30.090683008
H	30.997483479	26.216528372	31.580646866
H	32.268810387	24.987947160	31.585674649
H	39.227863889	29.275063423	30.103663945

QM-MM geometry for IM1 for extended calculations (when R15 is included in QM region):

C	35.685511100	28.368050800	24.229108300
H	35.698488300	27.464251100	23.618172000
H	36.562263500	28.997579100	24.010933600
C	35.784114600	27.911865300	25.667214900
O	35.672364700	26.745396700	25.994558700
O	36.124713300	28.871900100	26.514854500
C	32.961737500	24.959433200	26.989286900
H	33.831853800	25.540258700	26.661366600
H	32.137688000	25.677708600	27.132882200
N	33.194334800	24.238570100	28.217787600

H	32.381136200	24.011008600	28.822676100
C	34.367467600	24.062305100	28.826764600
N	35.510114500	24.572832800	28.268327000
H	35.393386500	25.436306400	27.737655000
H	36.287596700	24.676207700	28.921253800
N	34.456479900	23.280768900	29.893470900
H	33.598216400	23.042899700	30.437526600
H	35.320957900	23.368034600	30.444941500
C	35.876497200	22.137353700	34.089622600
H	34.816865500	22.448223200	34.077435600
C	36.731421800	23.397473700	33.840582200
H	36.618853500	24.073081300	34.703919300
H	37.799720000	23.147901000	33.727612700
C	36.250512700	24.169851700	32.596210200
O	36.849292100	23.920130100	31.490471700
O	35.277160000	24.930072100	32.735562800
H	34.557498000	25.512766900	31.281858500
C	31.872059800	26.143720300	31.454059400
C	33.194705600	26.865594600	31.089958900
O	34.113247700	25.952787900	30.513249800
C	32.878172600	28.089055800	30.177428600
O	32.148173500	29.035026800	30.942406300
C	33.863706900	28.950726900	29.356877500
O	33.150654500	29.497104900	28.325940400
C	35.143762000	29.364399300	29.541940600
N	36.104670700	28.624289000	30.295080800
C	37.227726500	29.297158200	30.678428600
N	38.384641800	28.973626400	30.216299600
H	33.662121100	27.289112200	32.003725100
H	32.176065200	27.726736100	29.407704500
H	32.724888500	29.322183700	31.686442800
H	36.622392300	28.449896700	27.248510600
H	33.749232300	29.983182800	27.741033800
H	35.557108600	30.099008800	28.837886800
H	37.010084000	30.131519700	31.363531600
H	36.281150400	27.658873900	29.998433700
O	37.687031600	25.815073200	29.857639500
H	37.376602500	25.157137200	30.552844900
H	38.566846600	26.130514600	30.131006100
O	37.966289900	27.648460100	27.886958200
H	37.690981400	26.816117000	28.326239400
H	38.271219100	28.157573100	28.696285300
H	34.797713600	28.920954200	23.922219600
H	32.686439000	24.304682600	26.162498200
H	36.039998200	21.674814500	35.062963300
H	35.995429500	21.442092300	32.558639000
H	31.287647000	25.976848000	30.549248700
H	31.256929700	26.745141600	32.123368500
H	32.062687200	25.153787800	31.868501300
H	39.201947000	29.468603300	30.511227600

QM-MM geometry for TS2 for extended calculations (when R15 is included in QM region):

C	35.5100778	28.4573246	24.7829074
H	35.7074181	27.4820959	24.3142760
H	36.4505820	29.0301743	24.7140160
C	35.2422371	28.1698027	26.2817241
O	36.1571235	27.5240526	26.8910963
O	34.1956283	28.5307474	26.8631162
C	33.0820328	25.0696397	26.8861460
H	33.9353151	25.6422834	26.5059569
H	32.2747538	25.8001452	27.0584616
N	33.3911228	24.3612859	28.1016058
H	32.6164317	24.1053458	28.7513879
C	34.5959091	24.2336082	28.6598081

N	35.6943060	24.8332225	28.1171994
H	35.5418585	25.7162060	27.6208593
H	36.4878672	24.9932315	28.7587505
N	34.7338429	23.3990336	29.6917902
H	33.8566471	23.1598720	30.1762414
H	35.5473908	23.5628929	30.3105757
C	35.7908272	22.2138955	34.0980664
H	34.7334618	22.5285924	34.1036169
C	36.6479581	23.4733763	33.8513027
H	36.5331294	24.1438737	34.7192868
H	37.7166755	23.2265195	33.7379143
C	36.1636454	24.2501857	32.6071179
O	36.8500378	24.1120278	31.5368068
O	35.1018428	24.8914005	32.7175291
H	34.1620365	25.2498305	31.2893588
C	31.5224295	26.1630740	31.5429076
C	32.9165861	26.6919017	31.1268003
O	33.6399369	25.6288825	30.5394894
C	32.7748922	28.0210568	30.2755842
O	32.2545094	29.0299465	31.1073704
C	33.8909589	28.7110479	29.3792497
O	33.3409764	29.9564502	28.8866968
C	35.1350456	29.2612271	29.9671371
N	36.2979469	28.7966880	29.5970606
C	37.4866987	29.2179743	30.2154306
N	38.5871238	29.0984629	29.6077188
H	33.4696990	27.0127482	32.0374900
H	32.0022631	27.8435140	29.5045544
H	32.8719076	29.1617575	31.8584658
H	34.1303321	28.1993768	28.3830678
H	33.4954540	29.8894189	27.9228607
H	35.1012654	30.0257763	30.7550722
H	37.3122289	29.6508016	31.2154949
H	36.3525369	28.1111838	28.8024295
O	37.5902382	26.0553639	29.8348634
H	37.3655712	25.4269999	30.5764704
H	38.5593492	26.1292377	29.8102839
O	38.8281006	27.4818792	27.0291424
H	37.8763300	27.3765634	26.8173465
H	38.8166002	27.9493959	27.8806877
H	34.7188520	28.9391193	24.2085357
H	32.7612747	24.3860433	26.1000942
H	35.9721233	21.7359240	35.0607409
H	35.8957750	21.5327316	33.2536323
H	30.9166364	25.9924601	30.6529791
H	30.9955107	26.8785173	32.1742273
H	31.6366015	25.1872367	32.0148965
H	39.3608604	29.5160506	30.0840848

N	34.4949668	23.4396855	29.8998695
H	33.6349289	23.1674434	30.4250367
H	35.3698792	23.4869044	30.4446318
C	35.8527943	22.1771941	34.0750679
H	34.7844328	22.4574069	34.0476335
C	36.6824212	23.4590576	33.8531219
H	36.5157759	24.1336464	34.7082810
H	37.7599505	23.2295547	33.7909130
C	36.2620745	24.2220335	32.5788627
O	36.8599193	23.8839453	31.4941836
O	35.3491425	25.0593303	32.6649139
H	34.6862941	25.8010343	31.1727476
C	31.9758188	26.1153108	31.3644564
C	33.1972659	27.0248092	31.1156753
O	34.2660094	26.3517450	30.4660275
C	32.7916487	28.2756707	30.3021848
O	32.3345019	29.3222283	31.1324638
C	33.7661208	28.8753777	29.2970675
O	33.0430926	29.4020612	28.2648993
C	35.1030364	29.0669605	29.3157322
N	36.0861069	28.4586689	30.1403327
C	37.1513121	29.2260067	30.5035120
N	38.3537156	28.9025312	30.1702459
H	33.5833321	27.4061157	32.0828819
H	31.9223817	28.0055050	29.6808670
H	32.9988253	29.4888496	31.8423274
H	37.2777780	28.2536004	26.9965740
H	33.6370794	29.8339624	27.6334137
H	35.5139171	29.6320723	28.4625685
H	36.8484440	30.1155064	31.0803634
H	36.2889511	27.4711684	29.9567022
O	37.8037482	25.7056123	29.8658665
H	37.4827968	25.0461834	30.5576966
H	38.6605495	26.0636793	30.1668936
O	38.2305667	27.4830905	27.9084302
H	37.8968185	26.6638991	28.3373051
H	38.4175864	28.0264106	28.7439094
H	34.8992647	28.9139187	23.8892142
H	32.7116894	24.3979597	26.1749971
H	36.0133051	21.7151242	35.0491289
H	36.0007219	21.4850498	33.2461404
H	31.4508143	25.9506341	30.4235425
H	31.2785122	26.6034531	32.0452998
H	32.2459117	25.1240010	31.7283545
H	39.1527199	29.4180266	30.4798084

QM-MM geometry for IM2 for extended calculations (when R15 is included in QM region):

C	35.8009035	28.3484740	24.1245587
H	35.6976012	27.4228432	23.5528419
H	36.6763043	28.9121293	23.7716894
C	36.0381172	27.9365150	25.5629339
O	35.6070061	26.8981665	26.0394387
O	36.8542618	28.7503576	26.2018338
C	33.0024098	25.0807489	26.9733378
H	33.8719662	25.6473017	26.6221063
H	32.1856933	25.8113240	27.0995778
N	33.2358456	24.3963002	28.2221232
H	32.4238575	24.1107884	28.8027695
C	34.4100469	24.2043328	28.8225314
N	35.5540848	24.6949659	28.2448388
H	35.4401901	25.5607079	27.7151193
H	36.3457195	24.7835466	28.8828566