Supplementary Information

Origins of halogen effects in bioorthogonal sydnone cycloadditions

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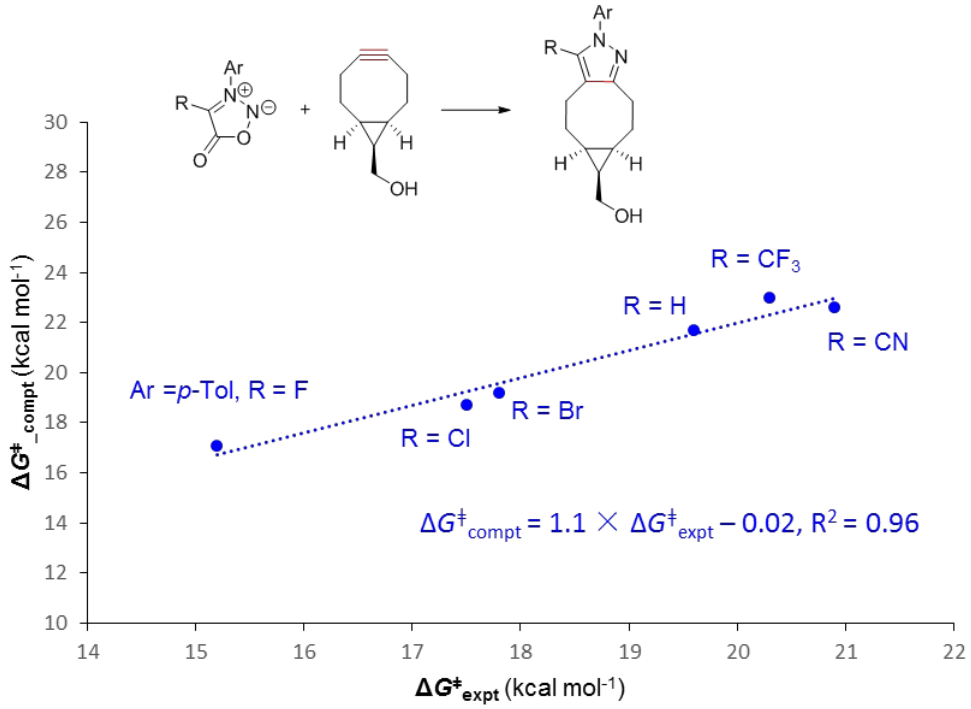
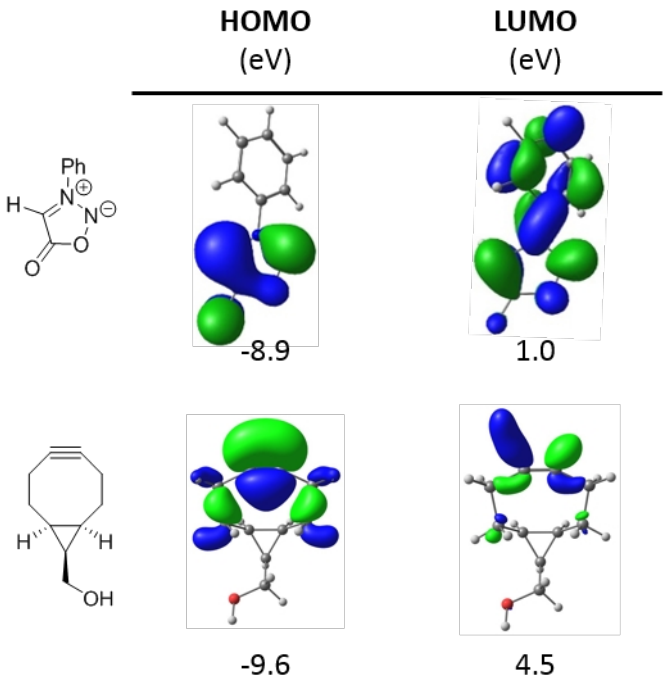
1. Computational details and references

The DFT calculations were performed with Gaussian 09.[1] Geometry optimizations of all the minima and transition structures were carried out at the M06-2X level of theory[2] with the 6-31G(d) basis set. Vibrational frequencies were computed at the same level to verify that optimized structures are energy minima or transition states and to evaluate zero-point vibrational energies (ZPVE) and thermal corrections at 298 K. A quasiharmonic correction was applied during the entropy calculation by setting all positive frequencies that are less than 100 cm^{-1} to 100 cm^{-1}.[3] Solvent effects in water were evaluated at the more accurate M06-2X/6-311+G(d,p) level with the CPCM model,[4] using the gas-phase optimized structures. As shown below (Ar = Ph, expect for R = F), the computed activation free energies using the current method correlate well with those derived from experimentally measured rate constants (for details, see Fig. 1c in the paper) based on the Eyring equation.



The frontier molecular orbitals (FMOs) and their energies (see below) were computed at the HF/6-311+G(d,p) level using the M06-2X/6-31G(d) geometries. Kohn-Sham orbitals provide poor estimates of ionization potentials of simple organic molecules, and the medium size 6-31G(d) basis set often gives inaccurate unoccupied orbital eigenvalues.[5] Fragment distortion and interaction energies of transition-state structures were computed at the M06-2X/6-311+G(d,p) level using the M06-2X/6-31G(d) optimized structures. Constrained optimizations with designated distortion angles of sydnones were performed at the M06-2X/6-31G(d) level.



References

(1) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J.*Gaussian 09, revision D.01*; Gaussian Inc., Wallingford, CT, 2013.

(2) (a) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215. (b) Zhao, Y.; Truhlar, D. G. *Acc. Chem. Res.***2008**, *41*, 157.

(3) (a) Zhao, Y.; Truhlar, D. G. *Phys. Chem. Chem. Phys.* **2008**, *10*, 2813. (b) Ribeiro, R. F.; Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2011**, *115*, 14556.

(4) (a) Barone, V.; Cossi, M. *J. Phys. Chem. A* **1998**, *102*, 1995. (b) Cossi, M.; Rega, N.; Scalmani, G.; Barone, V. *J. Comput. Chem.* **2003**, *24*, 669. (c) Takano, Y.; Houk, K. N. *J. Chem. Theory Comput.* **2005**, *1*, 70.

(5) (a) Politzer, P.; Abu-Awwad, F. *Theor. Chem. Acc.* **1998**, *99*, 83. (b) Kar, T.; Angyan, J. G.; Sannigrahi, A. B. *J. Phys. Chem. A* **2000**, *104*, 9953. (c) Zhang, G.; Musgrave, C. B. *J. Phys. Chem. A* **2007**, *111*, 1554.

2. DFT-computed energies and Cartesian coordinates

1

G(water) = -568.166368 Hartree

C	3.547978	0.145023	-0.055818
C	2.915566	-1.068558	-0.317643
C	1.528515	-1.158567	-0.288906
C	0.796660	-0.015890	0.014107
C	1.406337	1.202707	0.287171
C	2.794552	1.276994	0.245676
H	4.630820	0.208391	-0.085644
H	3.502076	-1.949711	-0.555067
H	1.011009	-2.087816	-0.498074
H	0.806637	2.067957	0.549530
H	3.286100	2.220318	0.458528
C	-1.503019	0.851371	-0.344223
H	-1.200172	1.781620	-0.788824
N	-0.635195	-0.097774	0.044382
N	-1.176786	-1.187930	0.492384
O	-2.499556	-0.980168	0.390875
C	-2.800694	0.306536	-0.135163
O	-3.933941	0.670353	-0.299502

2

G(water) = -905.205460 Hartree

C	3.920318	-0.277244	-0.034886
C	3.498525	0.827788	0.701029
C	2.161723	1.210615	0.684822
C	1.272606	0.467044	-0.081315
C	1.669102	-0.634812	-0.828850
C	3.008404	-1.005217	-0.795709
H	4.964243	-0.572699	-0.015233
H	4.208724	1.392623	1.295443
H	1.804508	2.063214	1.251410
H	0.947697	-1.186533	-1.420791
H	3.337721	-1.863363	-1.371441
C	-1.223804	0.123363	-0.042416
N	-0.106200	0.883093	-0.123458
N	-0.335116	2.145051	-0.269396
O	-1.664800	2.276470	-0.281362
C	-2.326914	1.020445	-0.150173
O	-3.520744	0.936331	-0.147313
C	-1.274858	-1.335605	0.223464
F	-0.323466	-1.714821	1.091745
F	-1.095816	-2.081146	-0.886632
F	-2.460711	-1.660803	0.726465

3

G(water) = -660.403694 Hartree

C	3.686665	0.087938	0.010237
C	3.128506	-1.028953	-0.607962
C	1.752468	-1.224852	-0.588086
C	0.962693	-0.285941	0.066304
C	1.495096	0.832650	0.696321
C	2.873383	1.013952	0.658999
H	4.760899	0.238533	-0.015037
H	3.763337	-1.747368	-1.115254
H	1.290041	-2.079857	-1.068649
H	0.852643	1.540240	1.208509
H	3.308972	1.880796	1.143770
C	-1.442058	0.432726	-0.058963
N	-0.460102	-0.496399	0.100059
N	-0.894422	-1.690704	0.301896
O	-2.228703	-1.611536	0.269560
C	-2.680364	-0.278936	0.045711
O	-3.840884	-0.004711	-0.015782
C	-1.222215	1.790526	-0.360152
N	-1.037510	2.910386	-0.595956

4

G(water) = -3141.738523 Hartree

C	-3.933694	-0.293501	0.017804
C	-3.504042	0.775169	-0.765394
C	-2.171030	1.170629	-0.738217
C	-1.292393	0.477689	0.085053
C	-1.699055	-0.585252	0.883451
C	-3.034229	-0.970323	0.838723
H	-4.974352	-0.599866	-0.010452
H	-4.205069	1.302607	-1.403442
H	-1.807551	1.997204	-1.338448
H	-0.985952	-1.095072	1.521879
H	-3.371537	-1.797136	1.454517

C	1.191643	0.155139	0.051073
N	0.079089	0.906038	0.126910
N	0.303977	2.181338	0.256220
O	1.646709	2.299723	0.251657
C	2.295938	1.055335	0.125409
O	3.490250	0.942272	0.095507
Br	1.269957	-1.658990	-0.247734

5

G(water) = -1027.764330 Hartree

C	3.749916	0.123391	-0.004560
C	3.189408	-0.941609	-0.705911
C	1.816154	-1.157061	-0.669888
C	1.030785	-0.290688	0.080935
C	1.567487	0.772618	0.796855
C	2.942069	0.975895	0.744962
H	4.821706	0.289341	-0.040370
H	3.819696	-1.604479	-1.288982
H	1.350177	-1.975408	-1.207288
H	0.925307	1.414861	1.389604
H	3.381943	1.799147	1.297682
C	-1.386936	0.351465	-0.040247
N	-0.385681	-0.529600	0.129147
N	-0.782611	-1.747901	0.361381
O	-2.129325	-1.685642	0.330449
C	-2.603777	-0.385471	0.076857
O	-3.771052	-0.117316	-0.000900
Cl	-1.220495	1.985381	-0.464397

6

G(water) = -667.393467 Hartree

C	-3.652036	0.121226	0.022093
C	-3.060801	-1.073267	0.428143
C	-1.678590	-1.216477	0.399292
C	-0.912618	-0.147012	-0.051205
C	-1.478723	1.053196	-0.466105
C	-2.863112	1.179237	-0.422383
H	-4.731495	0.227898	0.051846
H	-3.675605	-1.896907	0.775083
H	-1.191008	-2.132169	0.713940
H	-0.853818	1.864487	-0.820871
H	-3.323597	2.107230	-0.744203
C	1.444796	0.616457	0.153661
N	0.513486	-0.305349	-0.095530
N	1.006236	-1.477866	-0.407191
O	2.349672	-1.303921	-0.336576
C	2.720730	0.000757	0.012995
O	3.861443	0.363310	0.130350
F	1.147852	1.848017	0.526013

7

G(water) = -464.350532 Hartree

C	-2.171276	1.102073	-0.191485
C	-2.505821	-0.056504	-0.265075
C	0.380967	0.453103	0.918845
C	-2.272848	-1.503935	-0.282820
C	-0.015176	-1.005509	0.799918
C	-0.732813	-1.663626	-0.367904
H	-2.656800	-1.976334	0.629293
H	0.269401	0.843415	1.929777
H	-0.335164	-1.432053	1.750387
H	-2.754310	-1.999982	-1.131895
H	-0.476595	-2.731090	-0.389519
H	-0.411543	-1.234844	-1.322202
C	-1.213345	2.201808	-0.039467
H	-1.338451	2.700114	0.929225
H	-1.323125	2.967647	-0.814095
C	0.183705	1.536065	-0.129004
H	0.296939	1.127790	-1.138607
H	0.969357	2.290093	-0.003355
C	1.443643	-0.607918	0.782281
H	2.019833	-0.829063	1.677351
C	2.272990	-0.671465	-0.471170
H	2.825955	-1.622426	-0.498818
H	1.638135	-0.638706	-1.366778
O	3.162958	0.433455	-0.445830
H	3.752543	0.363251	-1.208848

TS_1

G(water) = -1032.482276 Hartree

C	3.949836	-2.949105	0.377423
C	4.233973	-2.231799	-0.783585
C	3.705174	-0.960165	-0.968521
C	2.883829	-0.423201	0.019237

C	2.573548	-1.132760	1.175346	C	3.803284	3.078141	0.287868
C	3.121588	-2.399643	1.352396	C	3.280518	1.950487	0.909914
H	4.372071	-3.938665	0.519659	C	2.510934	1.066296	0.159898
H	4.878555	-2.659488	-1.544536	C	2.244533	1.286997	-1.187856
H	3.918313	-0.376949	-1.857591	C	2.785353	2.413540	-1.798444
H	1.891876	-0.708571	1.905206	H	3.976036	4.186327	-1.548716
H	2.886937	-2.962905	2.249634	H	4.407775	3.774336	0.859909
C	1.861715	1.702970	0.761486	H	3.458736	1.743539	1.959536
H	2.222899	1.706399	1.778015	H	1.620279	0.595964	-1.742702
N	2.344597	0.876567	-0.180969	H	2.589316	2.594871	-2.850044
N	1.750375	1.100833	-1.351956	C	1.505853	-1.219334	0.285403
O	1.368668	2.423972	-1.285745	N	1.948919	-0.062361	0.829327
C	1.332377	2.843620	0.035306	N	1.227215	0.225687	1.910281
O	0.929635	3.923506	0.374006	O	0.822411	-0.997356	2.397619
C	-0.204944	0.387380	-0.614384	C	0.868062	-1.940435	1.383601
C	-0.230904	0.824643	0.545385	O	0.446008	-3.054795	1.498685
C	-2.531370	-1.343925	-0.175349	C	-0.584828	-0.315278	-0.061075
C	-0.995580	1.099907	1.779598	C	-0.599074	0.539180	0.840767
C	-2.621539	-0.763500	1.218951	C	-3.511619	-0.634925	0.100118
C	-2.468900	0.707891	1.554809	C	-1.305459	1.556943	1.637327
H	-0.579450	0.535668	2.626021	C	-3.527021	0.440764	1.162181
H	-2.034971	-2.312562	-0.219933	C	-2.734244	1.732058	1.090021
H	-2.188157	-1.402304	1.988215	H	-1.330589	1.232558	2.685952
H	-0.920495	2.162808	2.040279	H	-3.538303	-1.649607	0.494356
H	-3.047966	0.939288	2.458257	H	-3.576826	0.052258	2.178622
H	-2.860461	1.340443	0.752130	H	-0.760570	2.507647	1.617348
C	-0.834777	-0.300551	-1.752641	H	-3.249004	2.509183	1.669399
H	-0.325736	-1.256037	-1.934796	H	-2.660393	2.098467	0.061025
H	-0.719219	0.293685	-2.666014	C	-1.313214	-1.084251	-1.092821
C	-2.325592	-0.532452	-1.439430	H	-1.323626	-2.145476	-0.808932
H	-2.815696	0.443748	-1.362008	H	-0.809484	-1.024625	-2.062544
H	-2.805754	-1.054933	-2.274556	C	-2.751135	-0.542670	-1.206971
C	-3.846977	-1.351854	0.559688	H	-2.703546	0.493183	-1.560727
H	-4.177193	-2.318854	0.930942	H	-3.295836	-1.106637	-1.972810
C	-4.986140	-0.497270	0.073990	C	-4.765554	0.165854	0.342082
H	-5.773453	-0.464301	0.842185	H	-5.570817	-0.359665	0.848959
H	-4.659636	0.536948	-0.099861	C	-5.265427	1.120241	-0.708307
O	-5.470978	-1.079604	-1.125647	H	-6.057604	1.752599	-0.280539
H	-6.237770	-0.569327	-1.419917	H	-4.464727	1.790637	-1.049573
---				O	-5.762594	0.343568	-1.786806
Ts_2				H	-6.171892	0.942566	-2.425921
G(water) = -1369.519846 Hartree				C	2.182401	-1.909439	-0.861141
---				F	3.428251	-1.447925	-1.031611
C	3.560488	3.308063	-1.065166	F	1.534367	-1.723825	-2.026106

F	2.246097	-3.221153	-0.656751

TS_3

G(water) = -1124.718223 Hartree

C	3.391914	-3.336284	0.585102
C	3.747775	-2.849936	-0.671741
C	3.362257	-1.573234	-1.061103
C	2.612688	-0.799365	-0.178645
C	2.232798	-1.274011	1.073165
C	2.638393	-2.550028	1.452321
H	3.702913	-4.330670	0.888512
H	4.336031	-3.461761	-1.347557
H	3.633484	-1.165581	-2.029007
H	1.622767	-0.666406	1.732249
H	2.353357	-2.931104	2.427234
C	1.847545	1.550792	0.165539
N	2.209936	0.498006	-0.610548
N	1.536653	0.550812	-1.757668
O	1.310407	1.894651	-1.968612
C	1.386519	2.578912	-0.767300
O	1.115073	3.735907	-0.636742
C	-0.374167	0.210267	-0.854150
C	-0.325619	0.861025	0.202456
C	-2.735141	-1.272583	0.075276
C	-0.973076	1.417502	1.406169
C	-2.710022	-0.427626	1.330987
C	-2.474575	1.070857	1.360050
H	-0.512191	1.008824	2.315567
H	-2.279809	-2.255140	0.192041
H	-2.251502	-0.925710	2.184918
H	-0.830091	2.504327	1.444608
H	-2.969429	1.502521	2.239113
H	-2.902689	1.558619	0.478800
C	-1.123122	-0.648351	-1.788817
H	-0.667375	-1.646877	-1.811349
H	-1.051631	-0.249296	-2.806759
C	-2.592057	-0.731123	-1.334345
H	-3.036233	0.266706	-1.416741
H	-3.155433	-1.376817	-2.017274
C	-3.997971	-1.069572	0.872066
H	-4.337822	-1.927987	1.445802
C	-5.132367	-0.273690	0.285184
H	-5.877790	-0.065974	1.066940
H	-4.780945	0.694805	-0.095311
O	-5.694446	-1.050556	-0.760357
H	-6.471830	-0.585141	-1.097637
C	2.335602	1.799656	1.473768
N	2.671083	1.995953	2.564738

TS_4

G(water) = -3606.058527 Hartree

C	2.974865	3.677285	-0.938938
C	3.322740	3.437201	0.389007
C	2.977136	2.235087	0.994015
C	2.277336	1.286553	0.253845
C	1.903012	1.515928	-1.066879
C	2.268108	2.719652	-1.661568
H	3.252815	4.614430	-1.410671
H	3.870090	4.184529	0.953869
H	3.236562	2.018440	2.024526
H	1.332095	0.772502	-1.610850
H	1.987353	2.912481	-2.691796
C	1.655479	-1.128326	0.369156
N	1.907540	0.076550	0.911114
N	1.221898	0.217149	2.045914
O	1.035074	-1.075594	2.498639
C	1.220679	-1.973667	1.472331
O	1.038704	-3.155751	1.561559
C	-0.758187	0.212090	0.958863
C	-0.560706	-0.633089	0.079095
C	-3.186995	1.181729	-0.337105
C	-1.054107	-1.492559	-1.014160
C	-2.984363	0.111687	-1.388777
C	-2.583849	-1.324736	-1.106176
H	-0.579726	-1.218642	-1.966599
H	-2.836732	2.167936	-0.638938
H	-2.529319	0.483946	-2.306430
H	-0.790547	-2.540686	-0.824636
H	-2.972556	-1.974285	-1.901074
H	-3.013164	-1.679538	-0.164031
C	-1.633823	1.152187	1.674421
H	-1.294123	2.181773	1.503793
H	-1.580562	0.978806	2.754844
C	-3.075164	0.962799	1.159477
H	-3.407342	-0.044939	1.430812
H	-3.749503	1.660567	1.668920

C	-4.363769	0.669875	-1.127427
H	-4.760653	1.347443	-1.879279
C	-5.437919	-0.128171	-0.439088
H	-6.095999	-0.585357	-1.193041
H	-5.005679	-0.945935	0.153350
O	-6.161445	0.766036	0.391739
H	-6.896707	0.279535	0.788621
Br	2.424747	-1.823874	-1.160761

TS_5

G(water) = -1492.085078 Hartree

C	3.444975	3.360323	-0.609158
C	3.861258	2.844167	0.616583
C	3.445028	1.580695	1.019729
C	2.606977	0.851799	0.181471
C	2.165898	1.357230	-1.037689
C	2.599885	2.619058	-1.431231
H	3.778029	4.344397	-0.922928
H	4.516602	3.423540	1.258456
H	3.756129	1.151561	1.966091
H	1.484665	0.779313	-1.651992
H	2.265836	3.026343	-2.379783
C	1.802594	-1.488275	-0.121121
N	2.165782	-0.429183	0.626713
N	1.517874	-0.451047	1.791229
O	1.235691	-1.787791	2.002971
C	1.322044	-2.489488	0.821720
O	1.046223	-3.649830	0.696961
C	-0.468029	-0.084069	0.828570
C	-0.392835	-0.770478	-0.197018
C	-2.868661	1.299309	-0.104980
C	-1.028742	-1.375150	-1.383606
C	-2.825645	0.417387	-1.334765
C	-2.540387	-1.073344	-1.328999
H	-0.592066	-0.970195	-2.306849
H	-2.449573	2.292884	-0.259473
H	-2.394119	0.906969	-2.207697
H	-0.852746	-2.457754	-1.401400
H	-3.034957	-1.542207	-2.189393
H	-2.940092	-1.550921	-0.428967
C	-1.208881	0.788018	1.752536
H	-0.781088	1.798791	1.732400
H	-1.110573	0.425882	2.781795
C	-2.688641	0.814312	1.320933
H	-3.099879	-0.192999	1.446870
H	-3.260749	1.468282	1.988786
C	-4.131422	1.027272	-0.880849
H	-4.509449	1.854672	-1.476160
C	-5.230201	0.206652	-0.261859
H	-5.967031	-0.061382	-1.033800
H	-4.837330	-0.731571	0.152219
O	-5.824849	0.995980	0.756161
H	-6.574349	0.504552	1.118698
Cl	2.468784	-1.887526	-1.638989

TS_6

G(water) = -1131.717418 Hartree

C	-4.162726	-2.901770	-0.376032
C	-4.458972	-2.135857	0.750243
C	-3.838507	-0.907481	0.944898
C	-2.915510	-0.468601	0.000508
C	-2.595678	-1.223552	-1.124085
C	-3.234999	-2.445024	-1.308519
H	-4.654505	-3.857540	-0.525506
H	-5.181079	-2.492203	1.477419
H	-4.053734	-0.288080	1.808611
H	-1.855186	-0.866725	-1.830636
H	-2.996914	-3.044582	-2.180829
C	-1.649907	1.539697	-0.691312
N	-2.269927	0.781487	0.217462
N	-1.768050	1.013758	1.430887
O	-1.227955	2.286375	1.334099
C	-1.079723	2.666154	0.022154
O	-0.571791	3.690159	-0.347292
F	-1.984843	1.543587	-1.967869
C	0.371047	0.445498	-0.348289
C	0.276711	0.066762	0.820153
C	3.289691	0.532434	-0.163841
C	0.815156	-0.525263	2.050827
C	3.161794	0.044388	1.263113
C	2.230683	-1.056964	1.738459
H	0.851787	0.238260	2.838233
H	3.437087	1.608395	-0.245167
H	3.248587	0.841455	2.000617
H	0.170718	-1.330273	2.420565
H	2.651228	-1.521141	2.639979

H	2.132375	-1.848053	0.988025
C	1.178439	0.649076	-1.567998
H	1.305992	1.725358	-1.745168
H	0.680790	0.242176	-2.456741
C	2.545827	-0.032739	-1.358301
H	2.379747	-1.109578	-1.244016
H	3.167134	0.095443	-2.252246
C	4.433562	-0.203745	0.485855
H	5.293479	0.402183	0.759914
C	4.821983	-1.573687	0.000568
H	5.508663	-2.037068	0.724750
H	3.944186	-2.229362	-0.079785
O	5.447407	-1.417042	-1.263645
H	5.784550	-2.279550	-1.541333
