Supporting Information

Formation Mechanism of NDMA from Ranitidine, TMA and Other Tertiary Amines during Chloramination: A Computational Study

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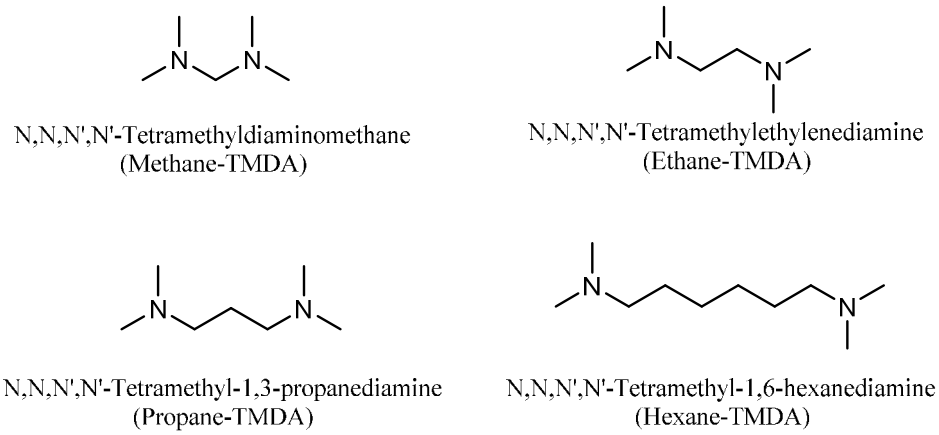
Text SI-1

Experimental Details

A stock solution (4 mM) for each secondary and tertiary amine was prepared in 50 mL methanol and stored in the 65 mL amber glass bottles at 4ºC until use. Each of these model compounds were diluted to 200 nM in distilled and deionized water (DDW).



Chemical Structures of Selected Precursors

Chloramine formation potential (FP) tests were conducted by spiking a pre-calculated volume of monochloramine stock solution which was prepared by mixing diluted sodium hypochlorite and ammonium sulfate solutions at Cl:N mass ratio of 4:1 at pH 9. An initial chloramine concentration of 100 mg/L as Cl_2 was used at pH 7.5 in the presence of 10 mM phosphate buffer. All the nitrosamine FP tests in this study were carried out in 1-L amber glass bottles without headspace in the dark at 21-23^{o}C and for 5 days of contact time.

NDMA was analyzed following US EPA method 521 (US EPA, 2004), consisting

a solid-phase extraction using coconut charcoal tubes followed by GC/MS analysis. Further analytical details can be found elsewhere (Selbes et al., 2013). Measured NDMA concentrations were used to calculate percent molar yield for each amine using the following equation:

$$\text{NDMA Yield (\%)} = \left({[\text{NDMA}]\ (\text{nM}) \Big/ [\text{Amine}]_0\ (\text{nM})} \right) \times 100$$

Concentrations of free chlorine, and mono- and dichloramine as free chlorine were determined following Standard Method 4500-Cl F (APHA/AWWA/WEF, 2005). All samples and blanks were prepared, extracted and analyzed in duplicates. Error bars presented among the data show the variability due to duplicate analysis (n=2).

APHA, AWWA, WEF, 2005. Standard Methods for the Examination of Water and Wastewater, twenty-first ed.. Washington, DC.

Selbes, M., Kim, D., Ates, N., Karanfil, T., 2013. The roles of tertiary amine structure, background organic matter and chloramine species on NDMA formation, Water Res. 47 (2), 945-953.

US EPA, 2004. Method 521: Determination of Nitrosamines in Drinking Water by Solid Phase Extraction and Capillary Column Gas Chromatography with Large Volume Injection and Chemical Tandem Mass Spectrometry (MS/MS). EPA/600/ R-05/054. U.S. Environmental Protection Agency. http://www. epa.gov/microbes/m_521.pdf (accessed on 26.03.12.).

Text SI-2

Calculation Details of Step 2 and Step 1′

The reaction pathways involving oxygen molecule on the singlet and triplet potential energy surfaces (PESs) have been investigated. The graphical representation of the activation free energies for these reactions is demonstrated in Figure S1. The calculation results indicate that there is an intersystem crossing between the singlet and triplet PESs for Step 2. Thus, the most feasible pathway of Step 2 proceeds through $^{3}R \rightarrow {}^{3}TS \rightarrow {}^{1/3}P$, in which the reaction starts from a singlet RMe_2N-NX and a triplet O_2, then proceeds a triplet transition state, finally forms a singlet OONX and tertiary amine from the triplet to singlet PES through the spin-orbit coupling, whereas there is no intersystem crossing for Step 1′ and the most feasible pathway of Step 1 proceeds on the triplet PES through $^{3}R \rightarrow {}^{3}TS \rightarrow {}^{3}P$. Similar to Step 2, the intersystem crossing between the singlet PES and triplet PES occurs in Step 2′.

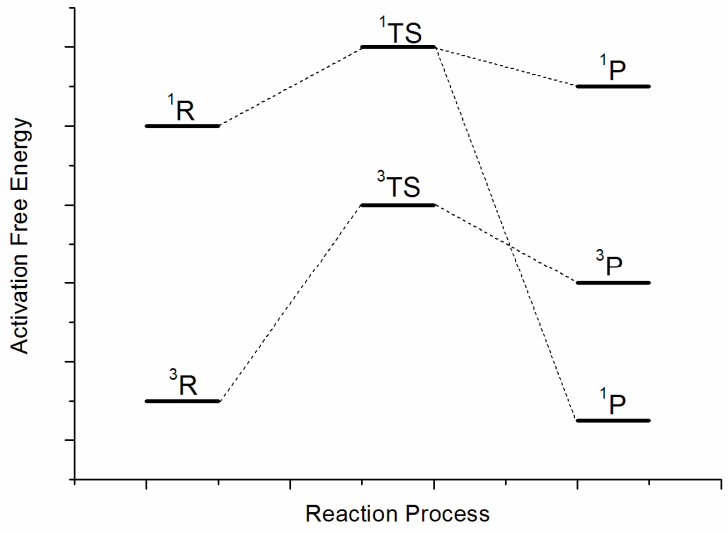


Figure S1. Graphical representation of the activation free energies for the reactions involving oxygen molecule including Step 2 and Step 1′.

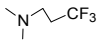
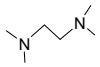
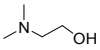
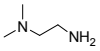
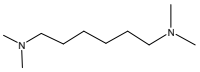
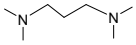
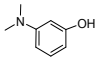
Text SI-3

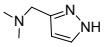
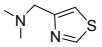
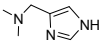
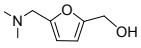
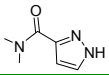
Some Additional Details of Figs. 1-2

In Figs. 1-2, the calculated activation free energies ($\Delta G^{\neq c}$) were obtained from the calculation at the B3LYP/6-311G* level using Gaussian program, whereas predicted activation free energies ($\Delta G^{\neq p}$) were obtained based on the fitting formula from the single-variate linear regression analysis using the statistical software SPSS.

Table SI-1

Table SI-1. Activation Free Energies and Reaction Energies of Step 2 (at 298 K and 1 atm, in kcal/mol Except for ΔS in cal/mol·K) Calculated at the B3LYP/6-311G* Level in the Gas phase

No.	Tertiary Amines Structure	$\Delta G^{\neq}$	ΔH	ΔG	ΔS
1		23.4	-11.0	-9.1	-6.4
2		25.5	-7.9	-6.2	-5.8
3		25.4	-9.4	-7.4	-6.5
4		25.5	-9.1	-7.1	-6.9
5		25.6	-8.2	-5.9	-7.7
6		25.0	-8.9	-7.0	-6.5
7		24.2	-9.0	-7.1	-6.2
8		25.8	-7.3	-5.4	-6.5
9		25.5	-7.5	-5.9	-5.6
10		25.2	-7.4	-6.1	-4.5
11	 C-Model	26.0	-7.2	-5.4	-6.1
12		25.0	-8.2	-6.6	-5.5
13		25.2	-8.3	-6.6	-5.6
14	 D-Model	24.8	-8.9	-7.2	-5.7
15		25.4	-7.4	-6.0	-4.9
16		26.1	-7.0	-5.2	-6.0
17		25.3	-7.5	-5.8	-5.7
18		25.4	-8.4	-6.8	-5.4
19		26.1	-7.9	-5.2	-9.0
20		26.9	-5.3	-4.0	-4.4
21		25.2	-14.0	-10.5	-11.8
22		23.0	-14.5	-11.9	-8.5
23		23.3	-13.9	-11.2	-8.9

24		23.0	-15.9	-13.8	-7.2
25		23.2	-14.4	-12.5	-6.4
26		27.5	-6.5	-4.2	-7.6
27		23.6	-12.7	-11.4	-4.4
28		27.3	-5.5	-3.5	-6.9
29		27.7	-6.5	-3.8	-9.2
30		26.9	-6.2	-4.1	-7.0
31		24.6	-6.3	-6.3	0.2
32		26.7	-6.3	-5.1	-4.2
33		23.8	-14.0	-11.4	-9.0
34		24.3	-10.7	-8.2	-8.5
35		24.6	-13.5	-10.9	-8.7
36		23.6	-10.6	-8.6	-6.4
37		27.8	-7.0	-4.3	-9.3
38		26.9	-7.1	-4.8	-7.6
39		26.7	-8.2	-6.1	-7.1
40		26.6	-7.3	-5.0	-7.6
41		26.9	-7.6	-6.8	-2.7
42		26.7	-7.3	-4.9	-7.8
43		26.9	-6.9	-4.7	-7.5
44	 R-Model	27.2	-6.7	-4.4	-7.7
45		27.2	-7.4	-3.5	-13.2
46		26.5	-7.8	-5.6	-7.2
47		--	--	--	--

-- means that the transition state has not been found.

Figure SI-1

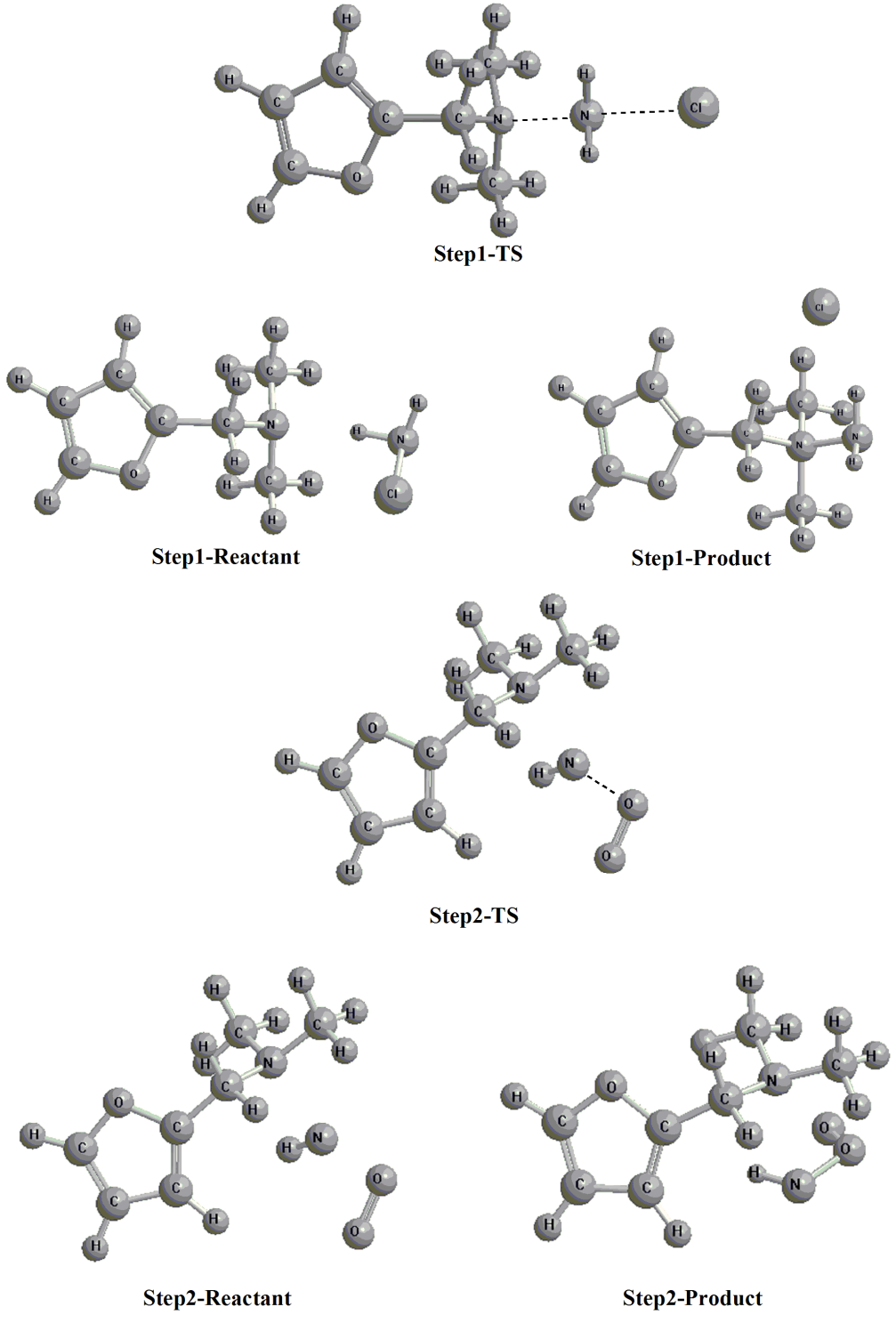


Figure SI-1. Structures of reactants, transition states and products in Steps 1 and 2 for chloramination of ranitidine

Figure SI-2

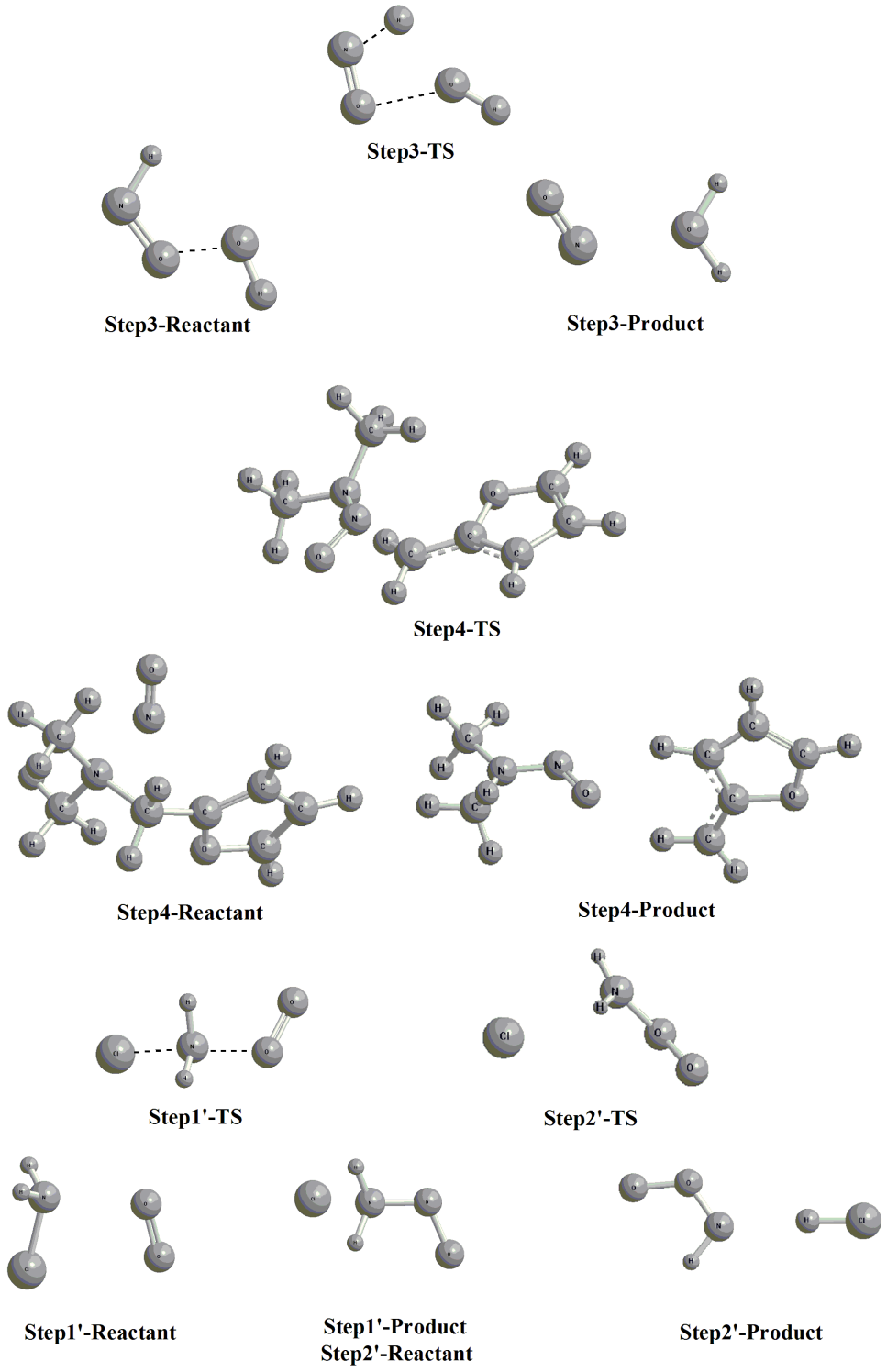


Figure SI-2. Structures of reactants, transition states and products in Steps 3 and 4 as well as Steps 1' and 2' for chloramination of ranitidine

Figure SI-3

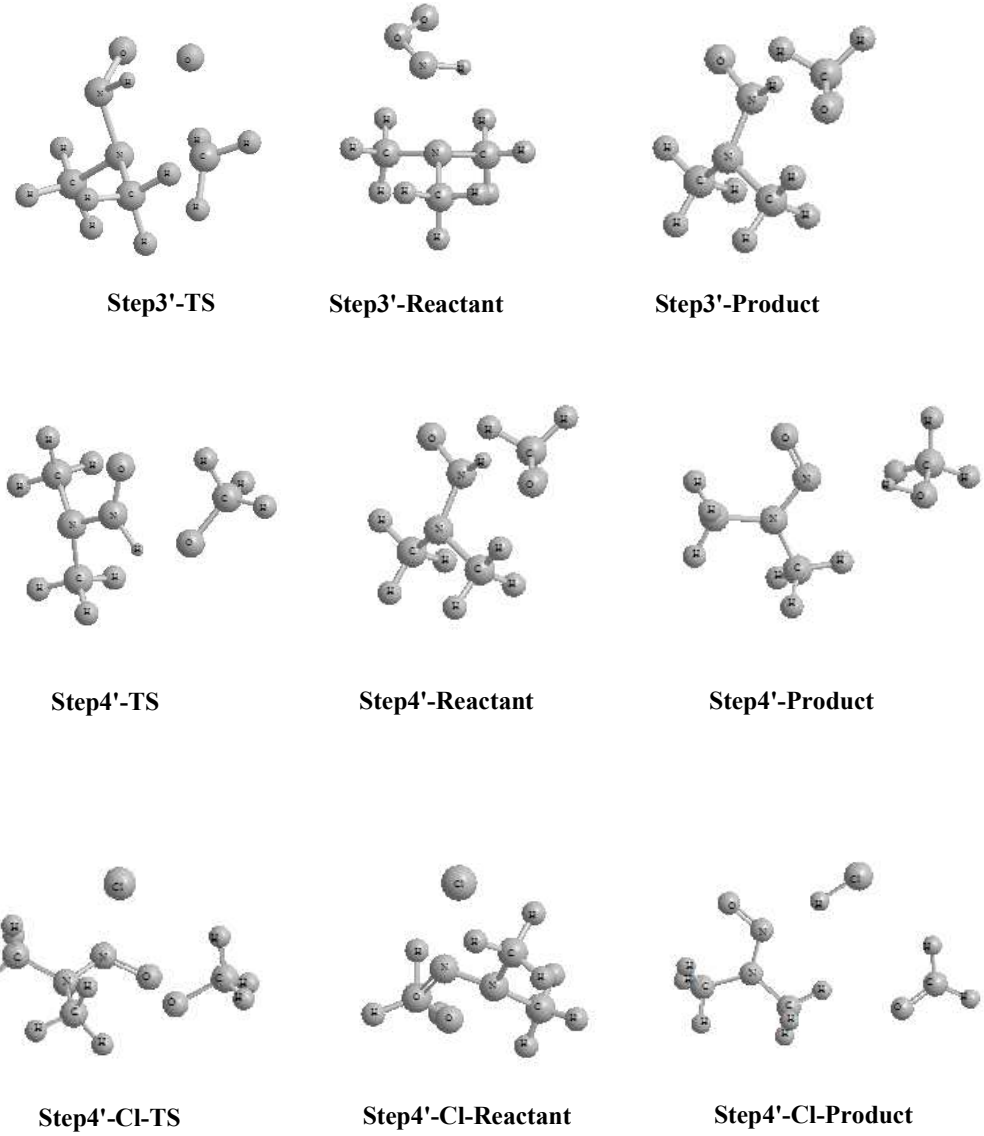


Figure SI-3. Structures of reactants, transition states and products in Steps 3' and 4' for chloramination of TMA

Standard orientation of Step 1- TS

Cartesian coordinates of all the transition states optimized at the B3LYP/6-311G* level:

Standard orientation of Step1-TS

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	7	0	0.487490	0.342712	0.459366
2	7	0	2.263622	0.152973	0.187120
3	6	0	-0.307716	-0.455069	-0.529125
4	1	0	0.035830	-1.487605	-0.451446
5	1	0	-0.032906	-0.086759	-1.520072
6	6	0	0.290967	1.799429	0.334509
7	1	0	1.029683	2.292975	0.962404
8	1	0	0.451640	2.096854	-0.701703
9	1	0	-0.719117	2.085140	0.632969
10	17	0	4.548437	-0.388555	-0.514262
11	1	0	2.286597	0.395815	-0.802995
12	1	0	2.306050	-0.865651	0.201511
13	6	0	0.318404	-0.114648	1.849721
14	1	0	0.520203	-1.184876	1.904855
15	1	0	1.043384	0.409965	2.468127
16	1	0	-0.696794	0.078300	2.202930
17	6	0	-1.784891	-0.419527	-0.354052
18	6	0	-2.682319	-1.295603	0.178939
19	8	0	-2.443957	0.691107	-0.814262
20	6	0	-3.974399	-0.694695	0.042379
21	1	0	-2.455486	-2.260981	0.606778
22	6	0	-3.769112	0.503129	-0.562806
23	1	0	-4.923946	-1.106544	0.347955
24	1	0	-4.420309	1.302059	-0.877553

Standard orientation of Step 2- TS

Cartesian coordinates of all the transition states optimized at the B3LYP/6-311G* level:

Standard orientation of Step2-TS

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.250787	1.636790	1.410196
2	1	0	-1.145592	1.697138	2.030331
3	1	0	0.313132	2.576246	1.505447
4	7	0	-0.649681	1.381213	0.026415
5	6	0	-1.554039	2.406612	-0.490769
6	1	0	-1.059532	3.386295	-0.552899
7	1	0	-1.901953	2.110520	-1.479462
8	1	0	-2.420851	2.482072	0.164681
9	6	0	0.480816	1.144175	-0.900106
10	1	0	0.034728	0.893504	-1.863209
11	1	0	1.061698	2.070343	-1.023749
12	7	0	-1.812665	-0.268114	-0.193607
13	8	0	-3.256837	-1.289233	0.186089
14	8	0	-2.826099	-2.469140	0.133541
15	1	0	0.373771	0.821965	1.774538
16	6	0	1.405072	0.054591	-0.479771
17	6	0	1.350052	-1.304652	-0.546596
18	8	0	2.585445	0.440493	0.105768
19	6	0	2.565880	-1.792741	0.031444
20	1	0	0.528361	-1.880214	-0.944387
21	6	0	3.273412	-0.695387	0.405348
22	1	0	2.868943	-2.822617	0.144682
23	1	0	4.236359	-0.548493	0.866759
24	1	0	-1.295151	-0.731745	0.565951

Standard orientation of Step 3- TS

Cartesian coordinates of all the transition states optimized at the B3LYP/6-311G* level:

Standard orientation of Step3-TS

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	7	0	-0.993763	0.436338	0.000037
2	1	0	-0.082969	1.162300	0.000135
3	8	0	-0.552378	-0.601053	-0.000004
4	8	0	1.170542	0.103340	-0.000138
5	1	0	2.094002	-0.234968	0.000739

Standard orientation of Step4-TS

Cartesian coordinates of all the transition states optimized at the B3LYP/6-311G* level:

Standard orientation of Step4-TS

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-1.154955	-1.257041	-1.223603
2	1	0	-1.962384	-1.628729	-1.859694
3	1	0	-0.642136	-2.103436	-0.767320
4	7	0	-1.688987	-0.375687	-0.179820
5	6	0	-2.759025	-0.906646	0.673683
6	1	0	-2.462890	-1.890447	1.035020
7	1	0	-2.936403	-0.238256	1.513621
8	1	0	-3.687652	-0.997340	0.103091
9	6	0	0.041720	0.083753	1.228179
10	1	0	-0.463939	0.991912	1.525592
11	1	0	-0.219422	-0.829320	1.746362
12	7	0	-1.854795	0.961238	-0.679458
13	8	0	-2.681956	1.591244	-0.104552
14	1	0	-0.458879	-0.685262	-1.835248
15	6	0	1.247641	0.168289	0.577817
16	6	0	1.967059	1.238691	0.020514
17	8	0	1.994020	-0.992934	0.402254
18	6	0	3.160581	0.718603	-0.474516
19	1	0	1.638989	2.268099	-0.000908
20	6	0	3.116855	-0.642483	-0.211940
21	1	0	3.966716	1.248253	-0.958290
22	1	0	3.818702	-1.439805	-0.409701

Standard orientation of Step1'-TS

Cartesian coordinates of all the transition states optimized at the B3LYP/6-311G* level:

Standard orientation of Step1′-TS

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	7	0	0.197310	-0.004980	0.266878
2	1	0	0.349753	1.003334	0.203367
3	8	0	1.664953	-0.543649	-0.119955
4	8	0	2.505321	0.395845	-0.107302
5	1	0	0.149678	-0.266804	1.252128
6	17	0	-2.073105	0.028280	-0.088563

Standard orientation of Step2'-TS

Cartesian coordinates of all the transition states optimized at the B3LYP/6-311G* level:

Standard orientation of Step2′-TS

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	7	0	0.493966	0.786050	0.282599
2	1	0	-0.236956	1.257557	-0.264590
3	8	0	1.453211	0.264028	-0.419088
4	8	0	2.076054	-0.719247	0.140449
5	1	0	0.270982	0.298000	1.151850
6	17	0	-1.866230	-0.200950	-0.037432

Standard orientation of Step3'-TS

Cartesian coordinates of all the transition states optimized at the B3LYP/6-311G* level:

Standard orientation of Step3′-TS

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.345323	1.655929	0.367263
2	1	0	0.906636	1.593766	1.286892
3	1	0	-0.672296	2.026734	0.527764
4	7	0	-0.649237	-0.080164	-0.025617
5	6	0	-1.288793	-0.476006	1.235101
6	1	0	-1.774908	0.392975	1.681767
7	1	0	-2.028212	-1.263464	1.061385
8	1	0	-0.514106	-0.843036	1.903678
9	6	0	-1.610070	0.267560	-1.072963
10	1	0	-2.224889	-0.597717	-1.341577
11	1	0	-2.260897	1.065169	-0.711886
12	1	0	-1.073344	0.624950	-1.952330
13	7	0	0.216558	-1.135507	-0.459309
14	1	0	0.434290	-0.904562	-1.433468
15	8	0	1.451707	-0.914650	0.193387
16	8	0	1.887699	0.354155	-0.242003
17	1	0	0.842467	2.213948	-0.415226

Standard orientation of Step4'-TS

Cartesian coordinates of all the transition states optimized at the B3LYP/6-311G* level:

Standard orientation of Step4′-TS

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	2.371880	0.140754	0.561336
2	1	0	3.350619	0.224021	0.055979
3	1	0	2.093591	-0.939843	0.499493
4	7	0	-1.230369	0.003646	-0.225227
5	6	0	-1.646336	-0.723886	0.969070
6	1	0	-2.673532	-0.438833	1.190841
7	1	0	-1.598738	-1.792681	0.778677
8	1	0	-1.000983	-0.477454	1.820720
9	6	0	-1.389348	1.455372	-0.212372
10	1	0	-2.442083	1.677068	-0.039965
11	1	0	-0.754024	1.905550	0.552076
12	1	0	-1.107423	1.862258	-1.184265
13	7	0	-0.052001	-0.413719	-0.757167
14	1	0	0.483399	0.275727	-1.311926
15	8	0	0.352613	-1.560648	-0.618276
16	8	0	1.408704	0.933481	-0.010218
17	1	0	2.518054	0.358589	1.634879