Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.

Supplementary Information

A new, double-inversion mechanism of the $F^- + CH_3Cl$ S_N2 reaction in aqueous solution

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Table S1. Harmonic vibrational frequencies (in cm^{-1}) of the stationary points (reactant complex (RC), transition state of the abstraction-induced inversion (TS_1), intermediate complex (INC), transition state of the Walden inversion (TS_2), product complex (PS)) along the NEB reaction path obtained at the DFT/MM level of theory.

	RC	**TS_1**	**INC**	**TS_2**	**PC**
1	278	589i	271	381i	240
2	380	153	456	327	372
3	734	262	748	334	418
4	826	298	780	583	977
5	1143	702	1116	1024	1265
6	1218	806	1162	1118	1291
7	1466	885	1450	1239	1505
8	1526	1236	1531	1432	1521
9	1559	1528	1557	1502	1530
10	3173	3242	3194	3202	3166
11	3260	3399	3290	3399	3269
12	3305	3503	3321	3540	3300

Table S2. Cartesian coordinates (Å) of 19 snapshots of QM solute along the NEB reaction path obtained at the DFT/MM level of theory.

Snapshot 1			
C	-0.074	0.183	0.165
H	0.651	0.912	0.489
H	-1.054	0.499	0.482
H	-0.085	0.083	-0.902
Cl	0.252	-1.341	0.941
F	-0.626	0.503	-2.598
Snapshot 2			
C	-0.141	0.045	0.197
H	0.635	0.765	0.394
H	-1.124	0.414	0.426
H	-0.126	-0.219	-0.841
Cl	0.178	-1.350	1.241
F	-0.468	0.721	-2.492
Snapshot 3			
C	-0.184	-0.109	0.120
H	0.635	0.570	0.204
H	-1.169	0.285	0.278
H	-0.149	-0.280	-0.959
Cl	0.072	-1.216	1.498
F	-0.402	0.952	-2.257

Snapshot 4			
C	-0.191	-0.205	0.114
H	0.655	0.440	0.126
H	-1.177	0.199	0.225
H	-0.175	0.131	-1.127
Cl	0.070	-1.077	1.701
F	-0.256	1.065	-2.058
Snapshot 5			
C	-0.182	-0.354	0.259
H	0.682	0.229	-0.031
H	-1.167	0.085	0.147
H	-0.201	0.556	-1.231
Cl	0.079	-0.965	1.905
F	-0.328	1.025	-2.039
Snapshot 6			
C	-0.190	-0.148	0.354
H	0.715	-0.124	-0.215
H	-1.203	-0.179	0.006
H	-0.201	0.764	-1.117
Cl	0.062	-0.790	1.974
F	-0.298	1.051	-2.013
Snapshot 7			
C	-0.203	-0.054	0.270
H	0.666	-0.418	-0.263
H	-1.134	-0.479	-0.080
H	-0.224	0.933	-0.955
Cl	0.000	-0.689	1.970
F	-0.252	1.197	-1.910
Snapshot 8			
C	-0.208	-0.084	0.086
H	0.677	-0.549	-0.297
H	-1.130	-0.582	-0.147
H	-0.232	0.857	-0.535
Cl	-0.035	-0.412	1.888
F	-0.253	1.398	-1.942
Snapshot 9			
C	-0.226	-0.217	0.037
H	0.678	-0.702	-0.280
H	-1.124	-0.761	-0.197
H	-0.264	0.730	-0.481
Cl	-0.165	-0.153	1.812
F	-0.170	1.728	-1.810
Snapshot 10			
C	-0.258	-0.290	-0.025

H	0.660	-0.806	-0.242
H	-1.112	-0.904	-0.253
H	-0.301	0.645	-0.547
Cl	-0.271	0.093	1.716
F	-0.040	2.062	-1.608
Snapshot 11			
C	-0.241	-0.191	-0.035
H	0.766	-0.499	-0.251
H	-0.942	-0.938	-0.367
H	-0.431	0.754	-0.501
Cl	-0.371	0.044	1.718
F	0.068	1.942	-1.708
Snapshot 12			
C	-0.229	-0.092	-0.060
H	0.831	-0.147	-0.237
H	-0.726	-0.948	-0.483
H	-0.599	0.815	-0.495
Cl	-0.463	-0.020	1.693
F	0.018	1.956	-1.723
Snapshot 13			
C	-0.225	0.016	-0.093
H	0.833	0.191	-0.167
H	-0.508	-0.880	-0.625
H	-0.795	0.849	-0.446
Cl	-0.532	-0.109	1.681
F	0.098	1.895	-1.797
Snapshot 14			
C	-0.204	0.146	-0.324
H	0.827	0.270	-0.090
H	-0.466	-0.781	-0.815
H	-0.918	0.924	-0.319
Cl	-0.548	-0.162	1.868
F	0.160	1.568	-1.809
Snapshot 15			
C	-0.184	0.294	-0.369
H	0.792	0.540	-0.032
H	-0.309	-0.654	-0.866
H	-1.019	0.936	-0.279
Cl	-0.622	-0.261	1.779
F	0.161	1.449	-1.851
Snapshot 16			
C	-0.118	0.437	-0.650
H	0.767	0.493	-0.038
H	-0.305	-0.597	-0.931

H	-0.996	0.891	-0.235
Cl	-0.570	-0.280	1.986
F	0.154	1.276	-1.770
Snapshot 17			
C	-0.075	0.545	-0.747
H	0.704	0.700	-0.017
H	-0.089	-0.486	-1.065
H	-1.043	0.824	-0.371
Cl	-0.678	-0.335	2.016
F	0.182	1.360	-1.837
Snapshot 18			
C	-0.044	0.613	-0.805
H	0.621	0.911	-0.010
H	0.145	-0.402	-1.116
H	-1.071	0.729	-0.504
Cl	-0.674	-0.248	2.039
F	0.166	1.463	-1.889
Snapshot 19			
C	-0.022	0.713	-0.849
H	0.554	1.096	-0.024
H	0.344	-0.259	-1.144
H	-1.073	0.697	-0.624
Cl	-0.749	-0.242	2.093
F	0.164	1.595	-1.941

Table S3. Charge distributions along the NEB reaction path.

	q (CH_3)	q (Cl)	q (F)
1	0.30	-0.28	-1.02
2	0.33	-0.32	-1.02
3	0.17	-0.19	-0.98
4	0.09	-0.24	-0.85
5	-0.21	-0.31	-0.48
6	-0.18	-0.29	-0.53
7	-0.08	-0.36	-0.56
8	0.26	-0.31	-0.95
9	0.31	-0.32	-1.00
10	0.29	-0.27	-1.02
11	0.29	-0.28	-1.01
12	0.34	-0.30	-1.03
13	0.36	-0.33	-1.04
14	0.61	-0.69	-0.92
15	0.64	-0.82	-0.83
16	0.53	-1.08	-0.45
17	0.41	-1.05	-0.36
18	0.45	-1.03	-0.42
19	0.43	-1.03	-0.41

Table S4. The free energies of (with respect to the reactant complex energy, -376092.8 kcal/mol, as a reference point) E_{qm} + $E_{qm/mm}$, water contribution E_{mm}, and total potential of mean force along the reaction path at the CCSD(T)/MM level of theory.

	$E_{qm} + E_{qm/mm}$ (kcal/mol)	E_{mm} (kcal/mol)	E_{total} (kcal/mol)
1	0	0	0
2	0.8	-0.4	0.4
3	9.8	4.4	14.2
4	30.4	28.2	58.6
5	34.1	36.7	70.8
6	37.8	37.3	75.1
7	15.4	41.6	57.0
8	3.9	15.3	19.2
9	2.2	2.1	4.3
10	0.3	-2.1	-1.8
11	1.5	-0.8	0.7
12	2.1	0.1	2.2
13	5.0	-1.6	3.4

14	9.9	18.3	28.3
15	2.5	23.1	25.6
16	-19.9	17.5	-2.4
17	-25.1	18.9	-6.2
18	-27.3	21.0	-6.4
19	-28.7	20.0	-8.7

Methods

Computational procedures. First, the estimated transition state 1 (TS_1) ($FH\cdots CH_2Cl^-$) was embedded in water, QM and MM regions are optimized using a multi-region optimization protocol. Then the solute region was fixed and the solvent MM region was equilibrated using molecular dynamics simulation for 120 picoseconds at 298 K, where the fixed QM region was represented by the ESP charges obtained from the previous optimization step. After that, the whole system was optimized again and the optimized structure was used to search the saddle point of abstraction-induced inversion, and it was confirmed using a numerical frequency calculation with one imaginary frequency. Then the reactant state and the intermediate complex were identified by optimizing displacements of the TS_1 along the imaginary frequency mode. So the first segment of nudged elastic band (NEB) reaction path,[1]

the abstraction-induced inversion mechanism, can be established using the obtained reactant complex, TS_1 and intermediate complex. Ten NEB snapshots were used to construct this segment of the reaction path.

Second, the obtained intermediate complex from above step was used to search the final product complex with a C-Cl bond-breaking and C-F bond-formation procedure.[2] This final product complex was optimized and equilibrated as we did to the initial TS_1. Based on the intermediate complex and the final product complex, a NEB reaction path was constructed and the back-side attack transition state 2 (TS_2) was identified. Ten NEB snapshots were used to construct this segment of the reaction path. The whole reaction path has 19 NEB points along the reaction path in all.

The molecular dynamics simulation was used to equilibrate the solvent for 120 picoseconds and the whole NEB reaction path was then optimized. This step is repeated until the final NEB reaction path was converged. Finally, the PMF was calculated with the DFT/MM and CCSD(T)/MM levels of theory according to $\Delta W_{AB}^{CC} = (\Delta W_{AA}^{CC\leftarrow DFT} + \Delta W_{BB}^{CC\leftarrow DFT}) + (\Delta W_{AA}^{DFT\leftarrow ESP} + \Delta W_{BB}^{DFT\leftarrow ESP}) + \Delta W_{AB}^{ESP}$.

1 G. Henkelman, B. P. Uberuaga and H. Jónsson, *J. Chem. Phys.*, 2000, **113**, 9901-9904.

2 J. Zhang, Y. Xu, J. Chen and D. Wang, *Phys. Chem. Chem. Phys.*, 2014, **16**, 7611-7617.