Supplementary Information (SI) for Physical Chemistry Chemical Physics.

Thermal Degradation Energetics of Fentanyl and Its Analogues: Furanyl Fentanyl and Ortho-Fluoro Fentanyl

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Materials and Methods

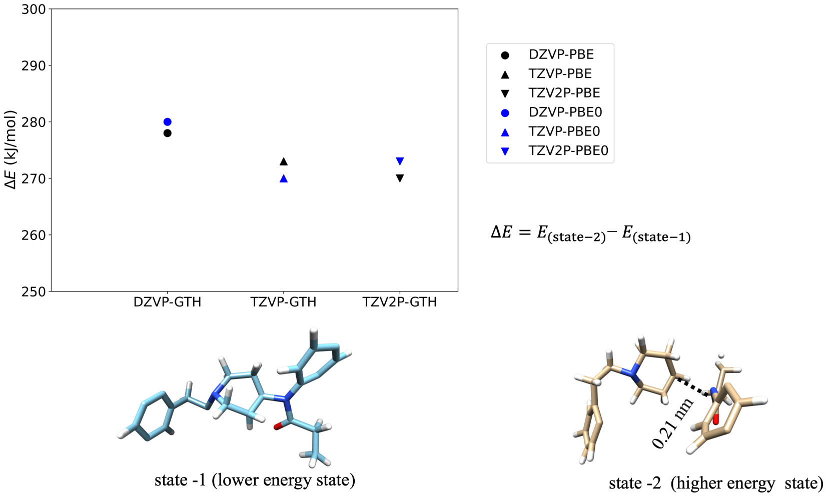
We conducted benchmark simulations using various basis sets with the PBE and PBE0 functionals. The key difference between PBE and PBE0 density functionals lies in their treatment of exchange energy: PBE is a generalized gradient approximation (GGA) functional, while PBE0 is a hybrid functional that includes a contribution of Hartree-Fock exchange.

In this benchmarking study, we compare the single-point energies (SPE) associated with breaking bond B4 of fentanyl molecules. We present the energy change between two states:

a) the state with bond length of 0.15 nm, corresponding to the equilibrium geometry of fentanyl; and b) the state corresponding to the maximum energy value (PMF(R_{max}) for fentanyl along the reaction coordinate, R, with a stretched bond length of 0.21 nm. The energy differences are shown below (Fig. S1).

Specifically, the difference in energy changes ΔE for PBE and PBE0 with the DZVP basis set is 2 kJ/mol, while it is 3 kJ/mol for both TZVP-GTH and TZV2P-GTH (Fig. S1). When comparing the hybrid functional PBE0 with the larger TZVP-GTH basis set to the PBE functional with the smaller DZVP-GTH basis set, the difference is only 5 kJ/mol. These results shows that the energetic trends of bond breaking investigated here are not significantly affected by the choice of the basic set and functional we used in our study. However, the combination of the PBE functional with the DZVP basis set offers higher computational efficiency with minimal impact on the accuracy of the computed energy changes.

Apart from computing the SPE for two different geometries, we also optimized those two different geometries for fentanyl and furanyl fentanyl using PBE and PBE0 functionals with double-zeta basis functions and computed the energy differences. The energy difference for fentanyl between the excited state, E(R_{max}) and the ground state E(R_{eq}) for PBE is 84.541 kJ/mol whereas for PBE0 it is 118.48 kJ/mol. Similarly for furanyl fentanyl, the energy difference for PBE is 144.32 kJ/mol and 174.33 kJ/mol for PBE0. We can see the difference between the absolute values of energy, but the trends are similar.



state -1 (lower energy state)

state -2 (higher energy state)

Figure S1: The plot shows the benchmarking study between PBE and PBE0 functionals with different basis sets, DZVP-GTH , TZVP-GTH, and TZV2P-GTH. The structures show a higher and lower energy state of bond B4, defined by the bond in its equilibrium position (0.15 nm) and a stretched position (0.21 nm) for fentanyl. We computed the energy difference between those two states.

The convergence of the free energy profiles for both furanyl fentanyl (Fig. S2) and o-fluoro fentanyl (Fig. S3) along the reaction coordinates was computed by calculating the difference between the minimum (F_{min}, at the equilibrium bond length) and the maximum (F_{max}, at the transition barrier) free energy values in 2 ps intervals (per walker).

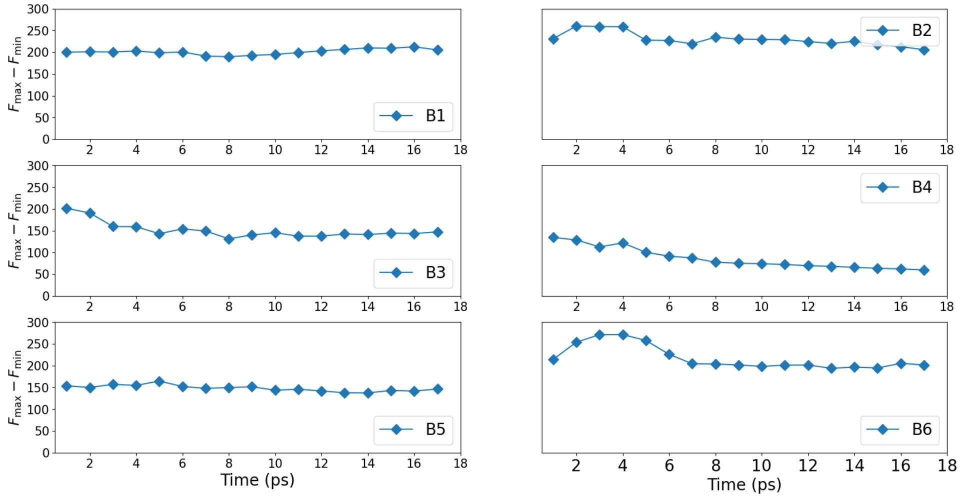


Figure S2: The change in free energy as a function of time throughout the simulation for furanyl fentanyl. The $F_{\max} - F_{\min}$ is the difference in the free energy between the energy barrier and the global minimum at 0 kJ/mol. This quantity is computed in the interval of every 2 picoseconds. The energy converges early, suggesting that the simulation is converged, too.

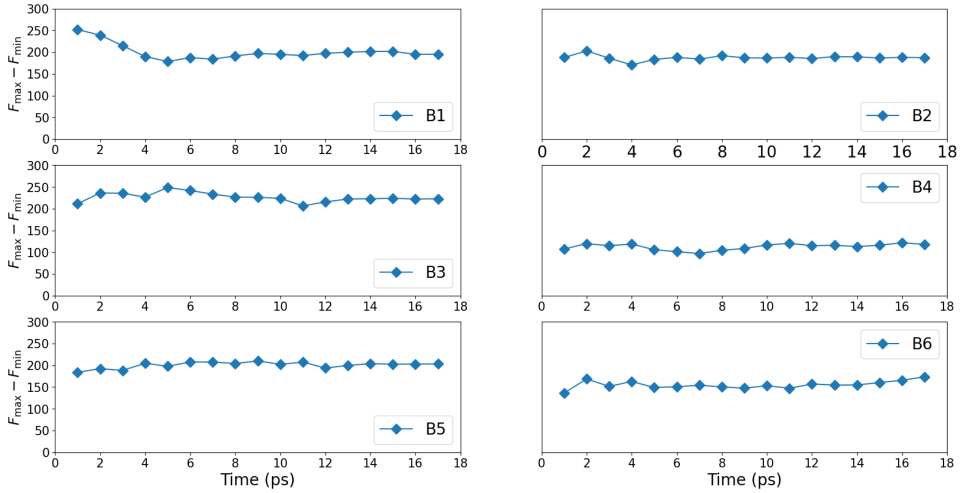


Figure S3: The change in free energy as a function of time throughout the simulation for o-fluoro fentanyl. The $F_{\max} - F_{\min}$ is the difference in the free energy between the energy barrier and the global minima (which is 0 kJ/mol). This quantity is computed in the interval of every 2 picoseconds. The energy converges early, suggesting that the simulation is converged, too.