

Supporting Information for The Good, the Bad, and the Ugly: “Hipen,” a new dataset for validating indirect free energy simulations

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This Supporting Information contains dihedral distribution plots and potential energy overlap plots for all 22 molecules in the HiPen set. Additionally, all topology, minimized coordinates, parameters, and necessary input files can be found at <https://zenodo.org/record/2328952>, doi:10.5281/zenodo.2328952.

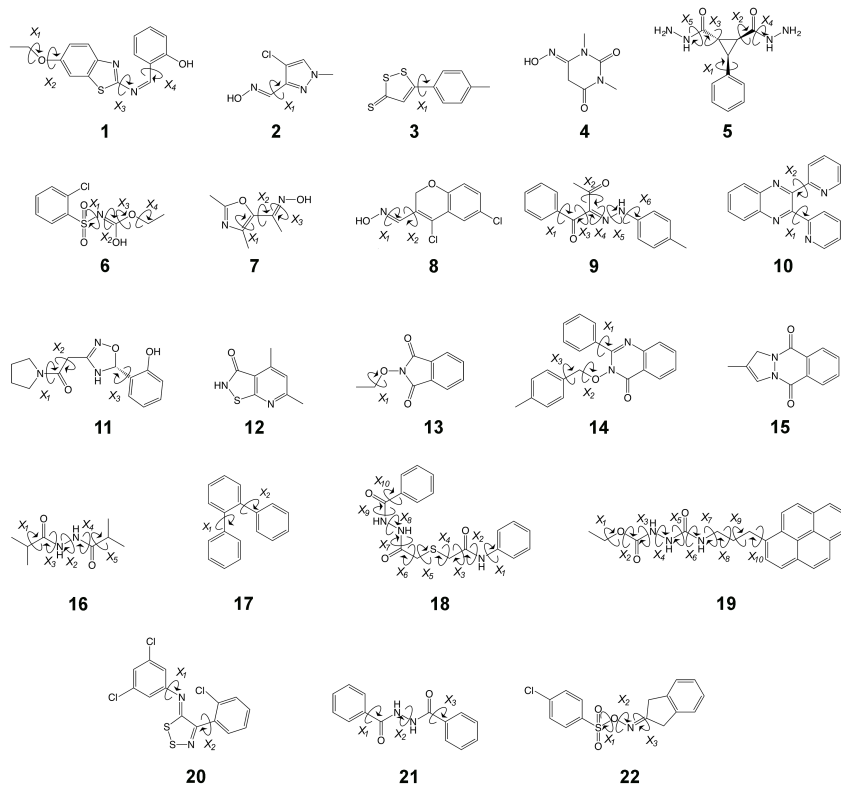
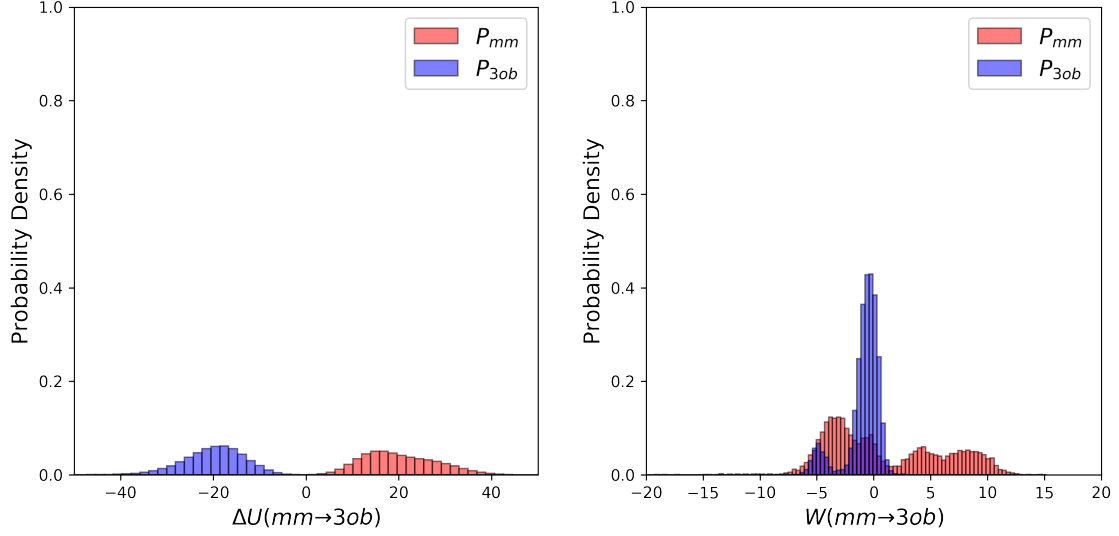
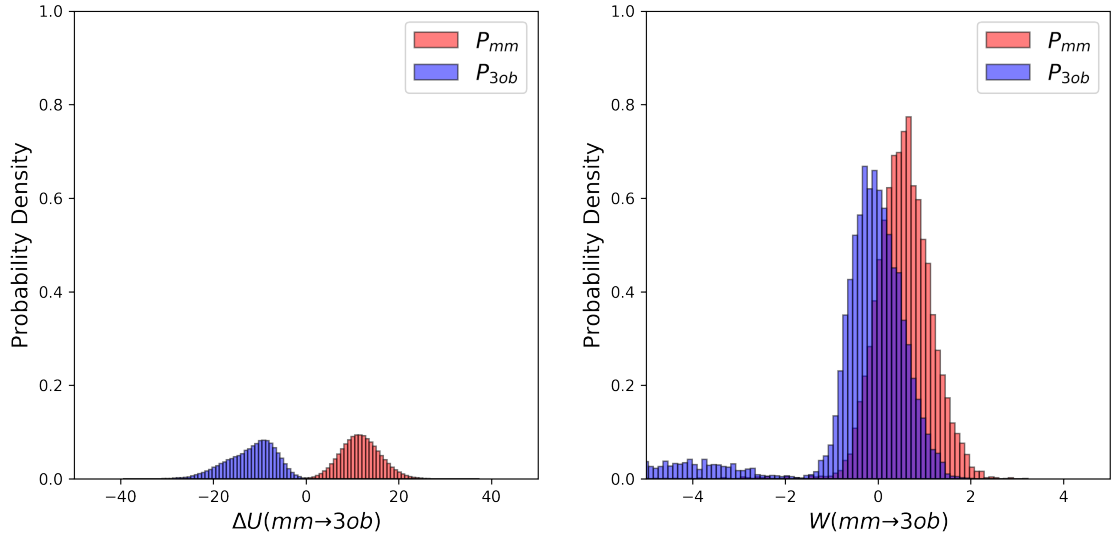


Figure 1: All 22 molecules included in our HiPen testset.



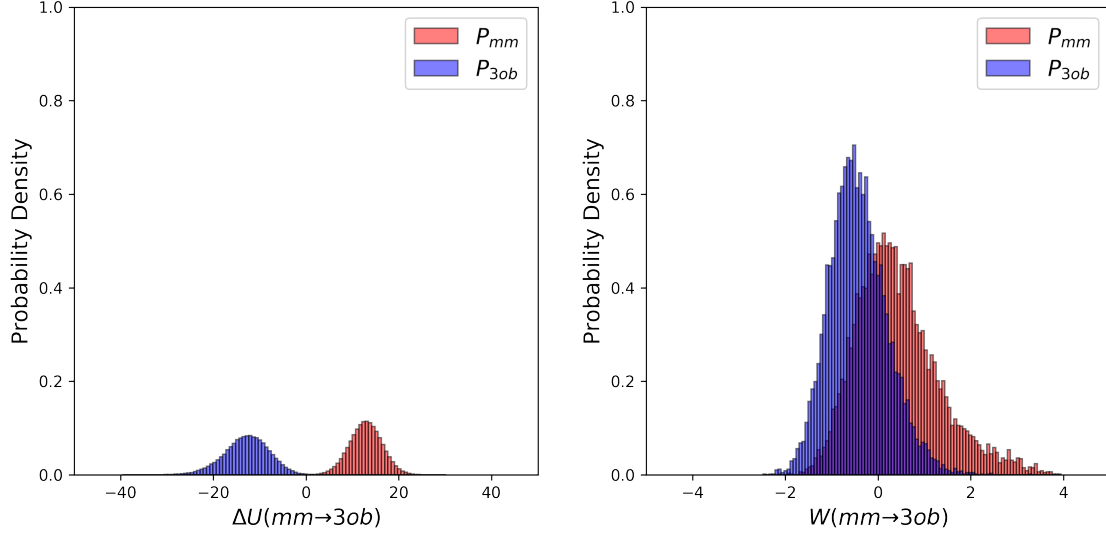
(a) $P_{mm} = p(U^{3ob} - U^{MM})$, $P_{3ob} = -p(U^{MM} - U^{3ob})$ (b) $P_{mm} = p(W^{MM \rightarrow 3ob})$, $P_{3ob} = -p(W^{3ob \rightarrow MM})$

Figure 2: (a) **1**'s potential energy “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\Delta U^{MM \rightarrow 3ob}$ to simplify the x-axis. (b) **1**'s nonequilibrium work “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\overline{W}^{MM \rightarrow 3ob}$ to simplify the x-axis.



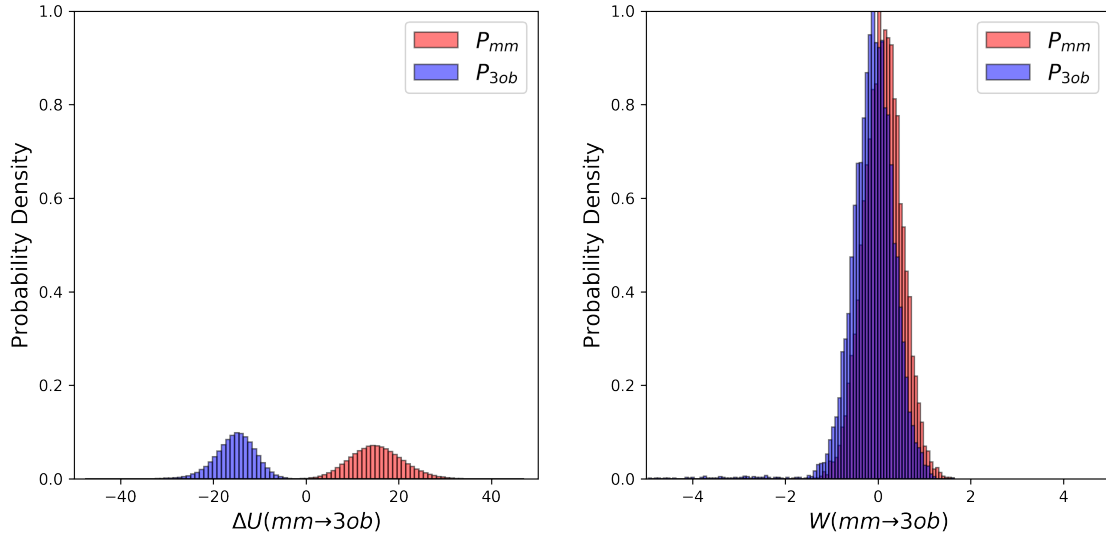
(a) $P_{mm} = p(U^{3ob} - U^{MM})$, $P_{3ob} = -p(U^{MM} - U^{3ob})$ (b) $P_{mm} = p(W^{MM \rightarrow 3ob})$, $P_{3ob} = -p(W^{3ob \rightarrow MM})$

Figure 3: (a) **2**'s potential energy “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\Delta U^{MM \rightarrow 3ob}$ to simplify the x-axis. (b) **2**'s nonequilibrium work “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\overline{W}^{MM \rightarrow 3ob}$ to simplify the x-axis.



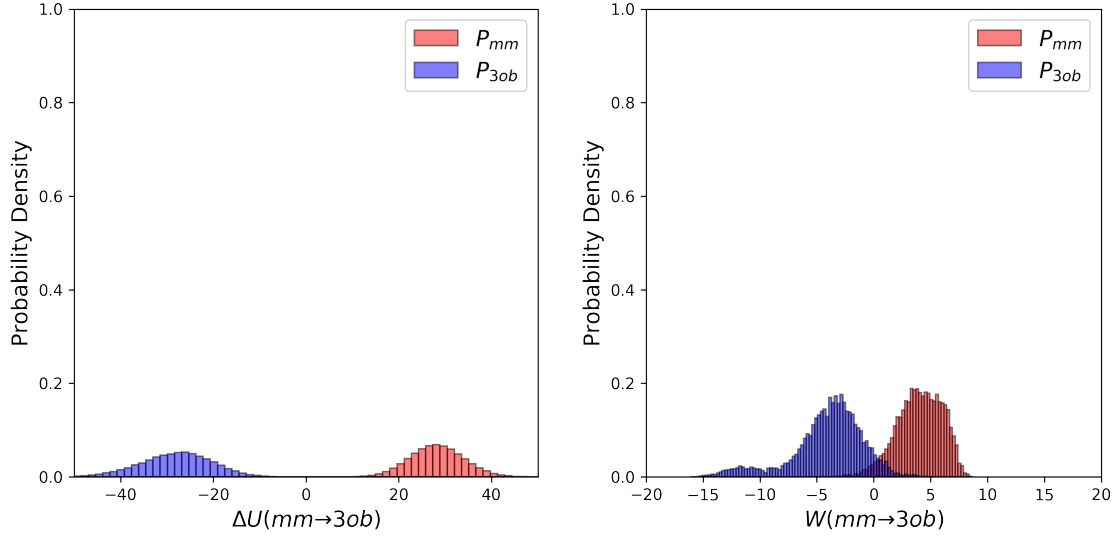
(a) $P_{mm} = p(U^{3ob} - U^{MM})$, $P_{3ob} = -p(U^{MM} - U^{3ob})$ (b) $P_{mm} = p(W^{MM \rightarrow 3ob})$, $P_{3ob} = -p(W^{3ob \rightarrow MM})$

Figure 4: (a) **3**'s potential energy “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\overline{\Delta U^{MM \rightarrow 3ob}}$ to simplify the x-axis. (b) **3**'s nonequilibrium work “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\overline{W^{MM \rightarrow 3ob}}$ to simplify the x-axis.



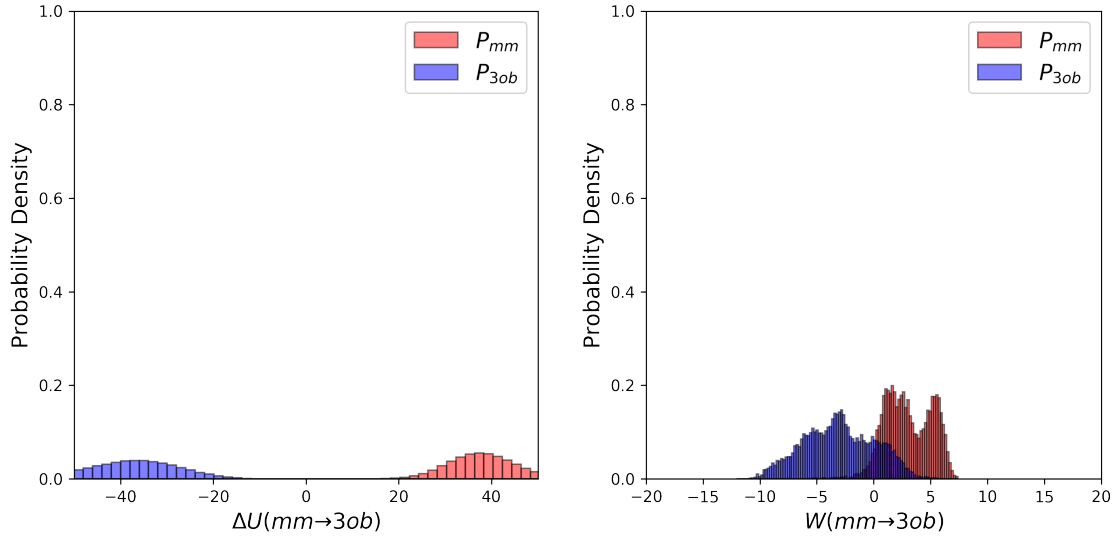
(a) $P_{mm} = p(U^{3ob} - U^{MM})$, $P_{3ob} = -p(U^{MM} - U^{3ob})$ (b) $P_{mm} = p(W^{MM \rightarrow 3ob})$, $P_{3ob} = -p(W^{3ob \rightarrow MM})$

Figure 5: (a) **4**'s potential energy “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\overline{\Delta U^{MM \rightarrow 3ob}}$ to simplify the x-axis. (b) **4**'s nonequilibrium work “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\overline{W^{MM \rightarrow 3ob}}$ to simplify the x-axis.



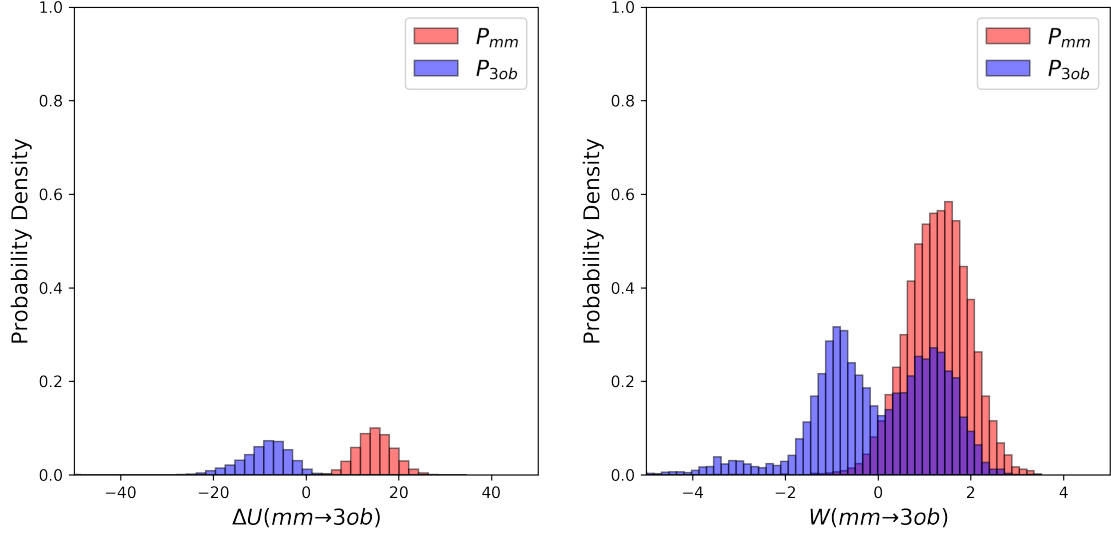
(a) $P_{mm} = p(U^{3ob} - U^{MM})$, $P_{3ob} = -p(U^{MM} - U^{3ob})$ (b) $P_{mm} = p(W^{MM \rightarrow 3ob})$, $P_{3ob} = -p(W^{3ob \rightarrow MM})$

Figure 6: (a) **5**'s potential energy “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\overline{\Delta U^{MM \rightarrow 3ob}}$ to simplify the x-axis. (b) **5**'s nonequilibrium work “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\overline{W^{MM \rightarrow 3ob}}$ to simplify the x-axis.



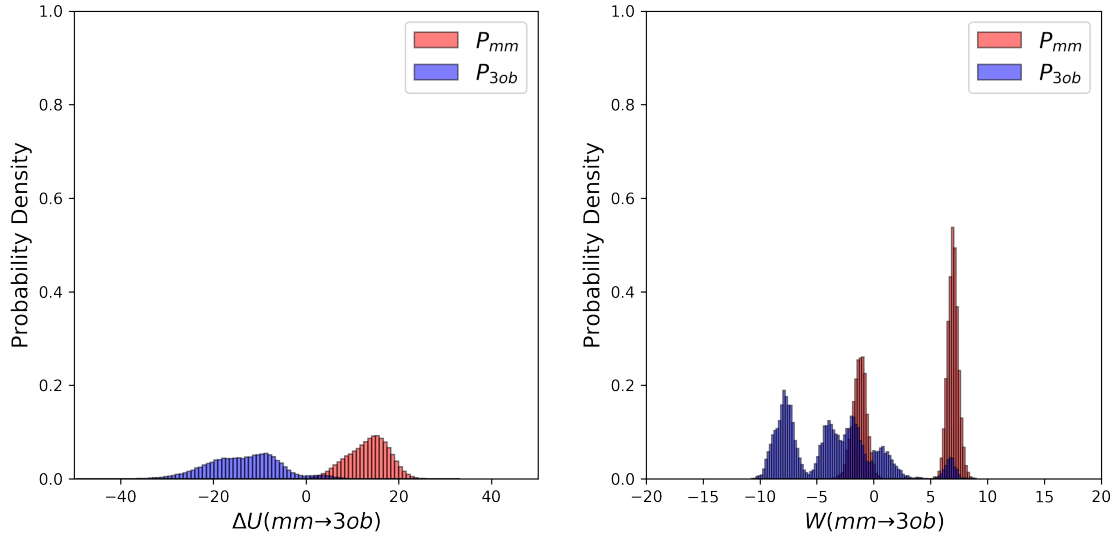
(a) $P_{mm} = p(U^{3ob} - U^{MM})$, $P_{3ob} = -p(U^{MM} - U^{3ob})$ (b) $P_{mm} = p(W^{MM \rightarrow 3ob})$, $P_{3ob} = -p(W^{3ob \rightarrow MM})$

Figure 7: (a) **6**'s potential energy “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\overline{\Delta U^{MM \rightarrow 3ob}}$ to simplify the x-axis. (b) **6**'s nonequilibrium work “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\overline{W^{MM \rightarrow 3ob}}$ to simplify the x-axis.



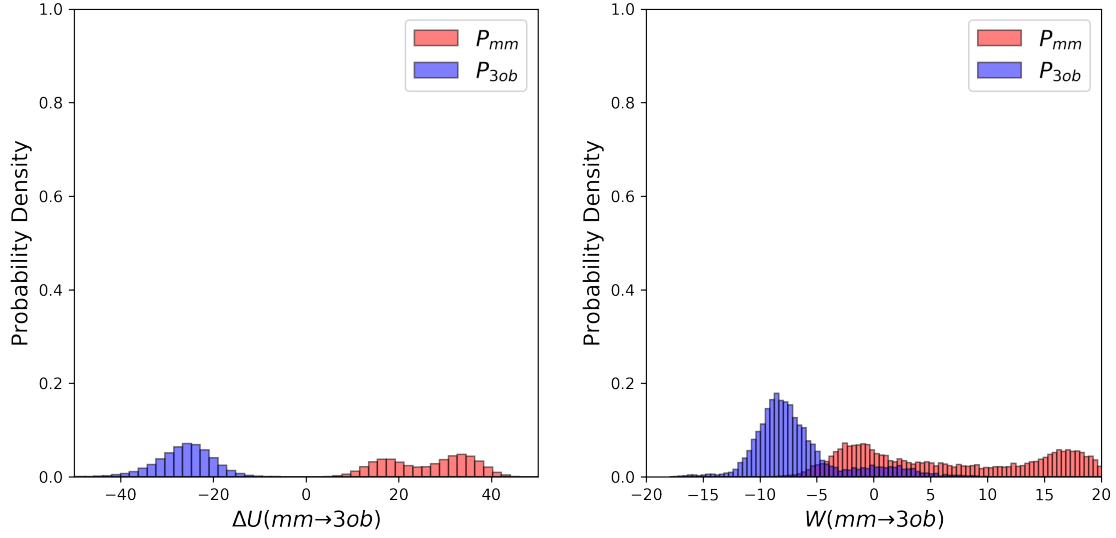
(a) $P_{mm} = p(U^{3ob} - U^{MM})$, $P_{3ob} = -p(U^{MM} - U^{3ob})$ (b) $P_{mm} = p(W^{MM \rightarrow 3ob})$, $P_{3ob} = -p(W^{3ob \rightarrow MM})$

Figure 8: (a) **7**'s potential energy “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\overline{\Delta U^{MM \rightarrow 3ob}}$ to simplify the x-axis. (b) **7**'s nonequilibrium work “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\overline{W^{MM \rightarrow 3ob}}$ to simplify the x-axis.



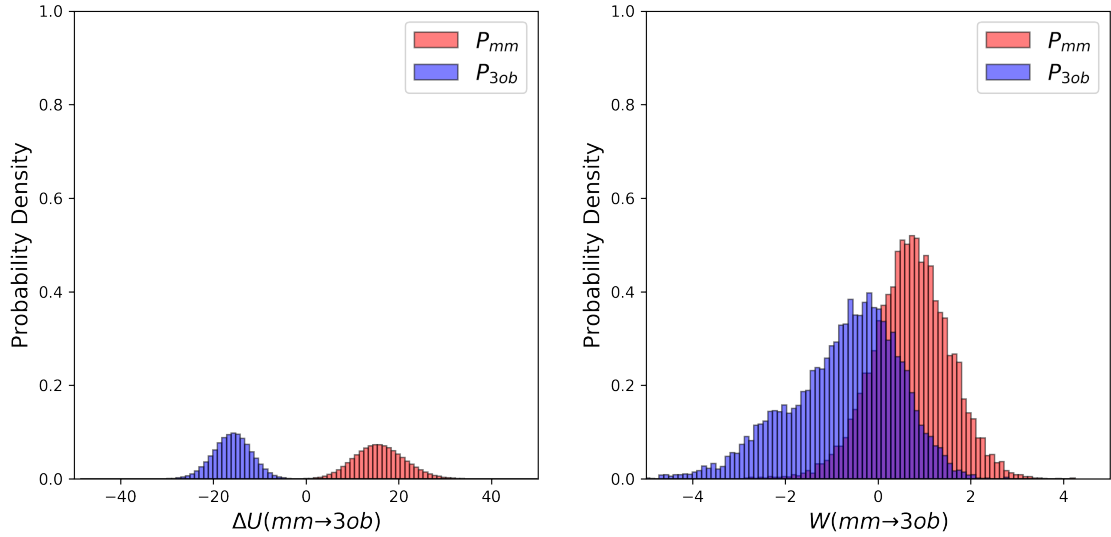
(a) $P_{mm} = p(U^{3ob} - U^{MM})$, $P_{3ob} = -p(U^{MM} - U^{3ob})$ (b) $P_{mm} = p(W^{MM \rightarrow 3ob})$, $P_{3ob} = -p(W^{3ob \rightarrow MM})$

Figure 9: (a) **8**'s potential energy “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\overline{\Delta U^{MM \rightarrow 3ob}}$ to simplify the x-axis. (b) **8**'s nonequilibrium work “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\overline{W^{MM \rightarrow 3ob}}$ to simplify the x-axis.



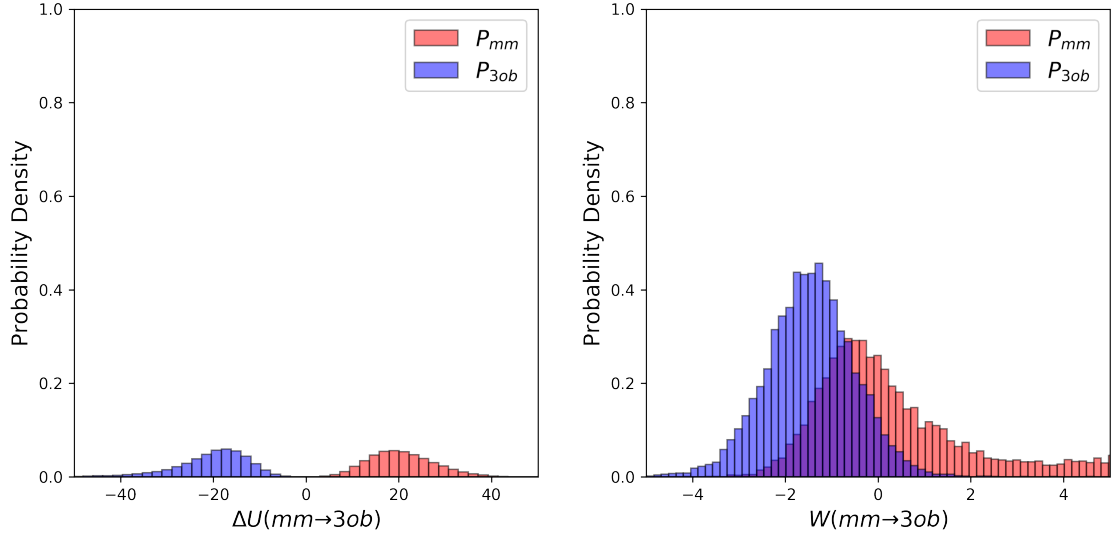
(a) $P_{mm} = p(U^{3ob} - U^{MM})$, $P_{3ob} = -p(U^{MM} - U^{3ob})$ (b) $P_{mm} = p(W^{MM \rightarrow 3ob})$, $P_{3ob} = -p(W^{3ob \rightarrow MM})$

Figure 10: (a) **9**'s potential energy “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\Delta U^{MM \rightarrow 3ob}$ to simplify the x-axis. (b) **9**'s nonequilibrium work “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\overline{W}^{MM \rightarrow 3ob}$ to simplify the x-axis.



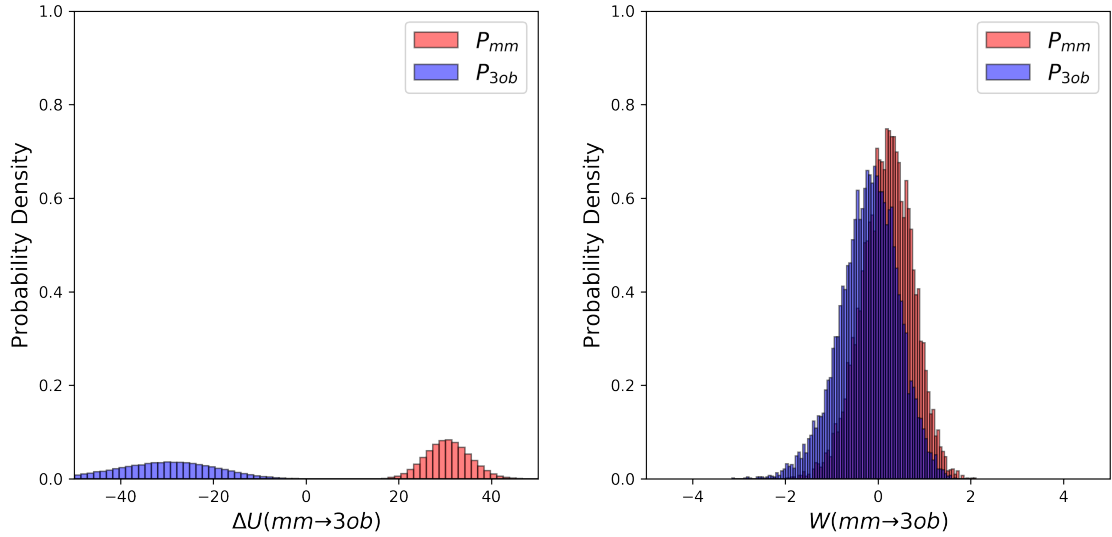
(a) $P_{mm} = p(U^{3ob} - U^{MM})$, $P_{3ob} = -p(U^{MM} - U^{3ob})$ (b) $P_{mm} = p(W^{MM \rightarrow 3ob})$, $P_{3ob} = -p(W^{3ob \rightarrow MM})$

Figure 11: (a) **10**'s potential energy “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\Delta U^{MM \rightarrow 3ob}$ to simplify the x-axis. (b) **10**'s nonequilibrium work “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\overline{W}^{MM \rightarrow 3ob}$ to simplify the x-axis.



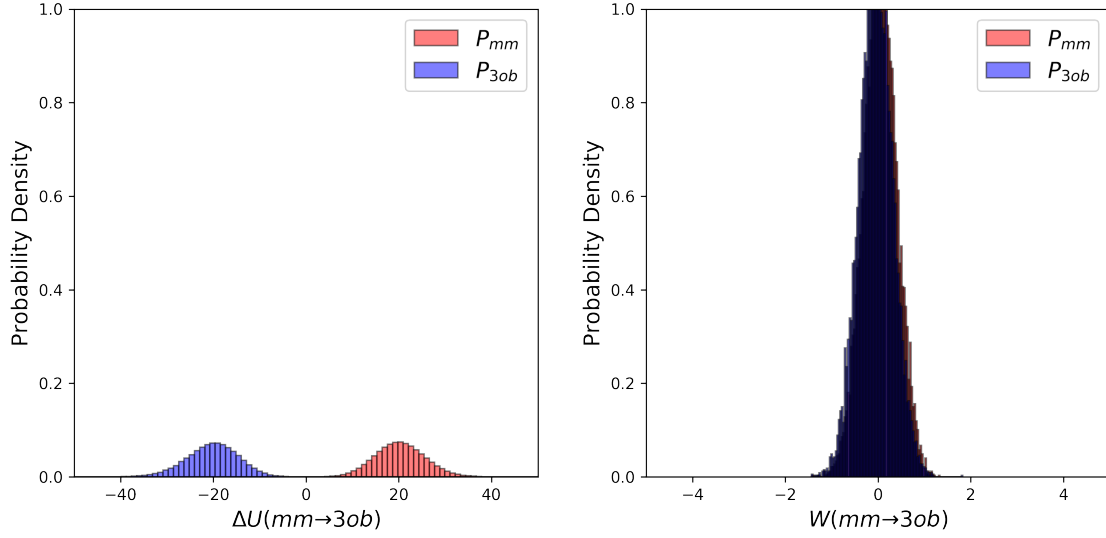
(a) $P_{mm} = p(U^{3ob} - U^{MM})$, $P_{3ob} = -p(U^{MM} - U^{3ob})$ (b) $P_{mm} = p(W^{MM \rightarrow 3ob})$, $P_{3ob} = -p(W^{3ob \rightarrow MM})$

Figure 12: (a) **11**'s potential energy “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\Delta U^{MM \rightarrow 3ob}$ to simplify the x-axis. (b) **11**'s nonequilibrium work “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\overline{W}^{MM \rightarrow 3ob}$ to simplify the x-axis.



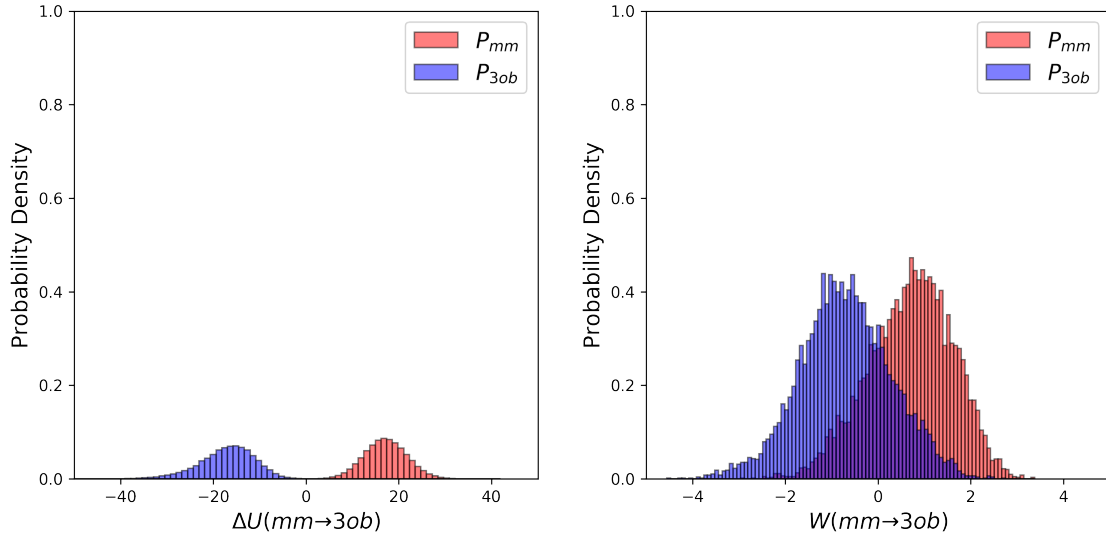
(a) $P_{mm} = p(U^{3ob} - U^{MM})$, $P_{3ob} = -p(U^{MM} - U^{3ob})$ (b) $P_{mm} = p(W^{MM \rightarrow 3ob})$, $P_{3ob} = -p(W^{3ob \rightarrow MM})$

Figure 13: (a) **12**'s potential energy “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\Delta U^{MM \rightarrow 3ob}$ to simplify the x-axis. (b) **12**'s nonequilibrium work “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\overline{W}^{MM \rightarrow 3ob}$ to simplify the x-axis.



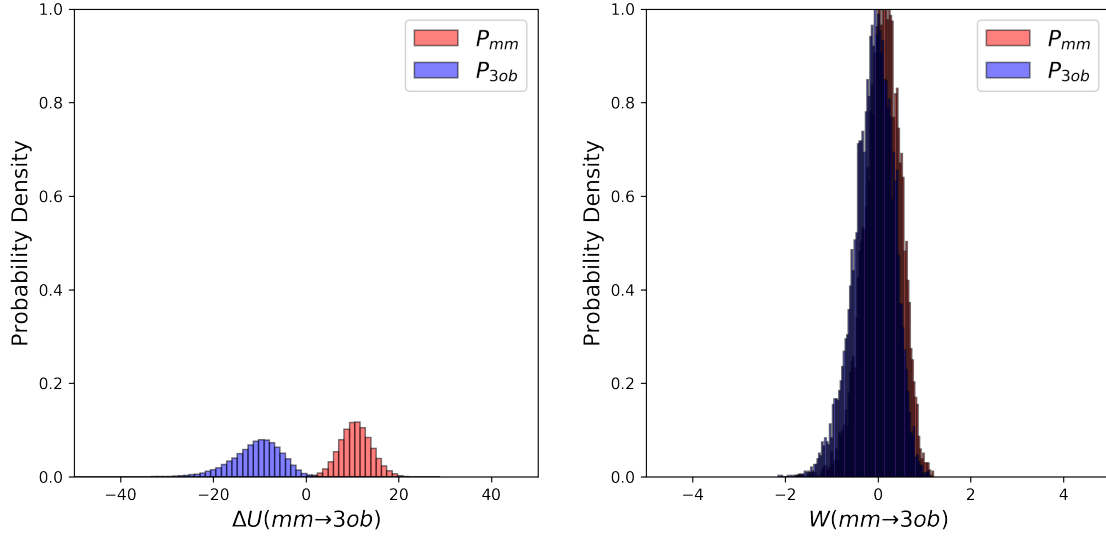
(a) $P_{mm} = p(U^{3ob} - U^{MM})$, $P_{3ob} = -p(U^{MM} - U^{3ob})$ (b) $P_{mm} = p(W^{MM \rightarrow 3ob})$, $P_{3ob} = -p(W^{3ob \rightarrow MM})$

Figure 14: (a) **13**'s potential energy “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\Delta U^{MM \rightarrow 3ob}$ to simplify the x-axis. (b) **13**'s nonequilibrium work “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\overline{W}^{MM \rightarrow 3ob}$ to simplify the x-axis.



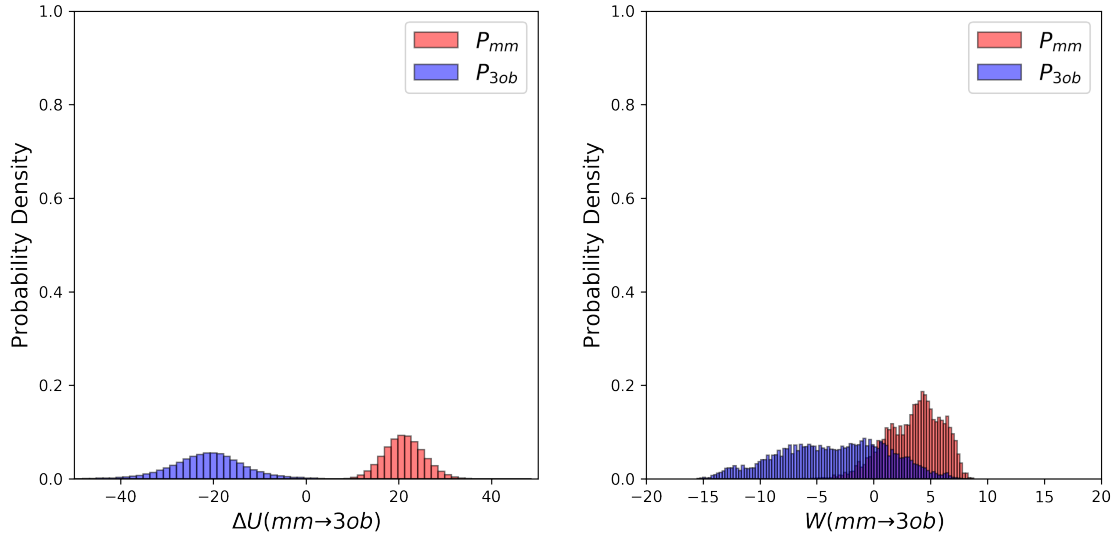
(a) $P_{mm} = p(U^{3ob} - U^{MM})$, $P_{3ob} = -p(U^{MM} - U^{3ob})$ (b) $P_{mm} = p(W^{MM \rightarrow 3ob})$, $P_{3ob} = -p(W^{3ob \rightarrow MM})$

Figure 15: (a) **14**'s potential energy “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\Delta U^{MM \rightarrow 3ob}$ to simplify the x-axis. (b) **14**'s nonequilibrium work “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\overline{W}^{MM \rightarrow 3ob}$ to simplify the x-axis.



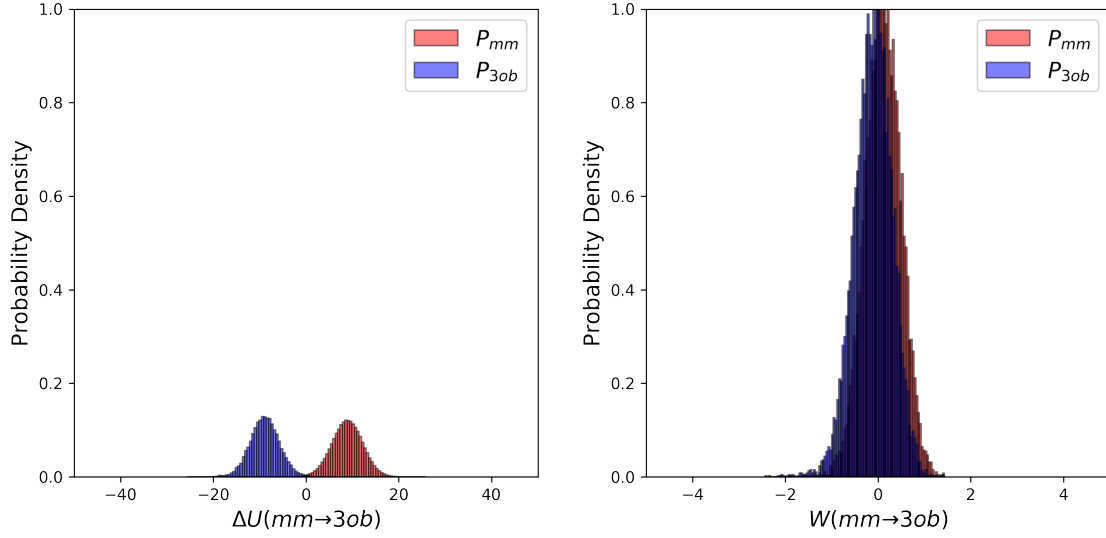
(a) $P_{mm} = p(U^{3ob} - U^{MM})$, $P_{3ob} = -p(U^{MM} - U^{3ob})$ (b) $P_{mm} = p(W^{MM \rightarrow 3ob})$, $P_{3ob} = -p(W^{3ob \rightarrow MM})$

Figure 16: (a) **15**'s potential energy “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\Delta U^{MM \rightarrow 3ob}$ to simplify the x-axis. (b) **15**'s nonequilibrium work “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\overline{W}^{MM \rightarrow 3ob}$ to simplify the x-axis.



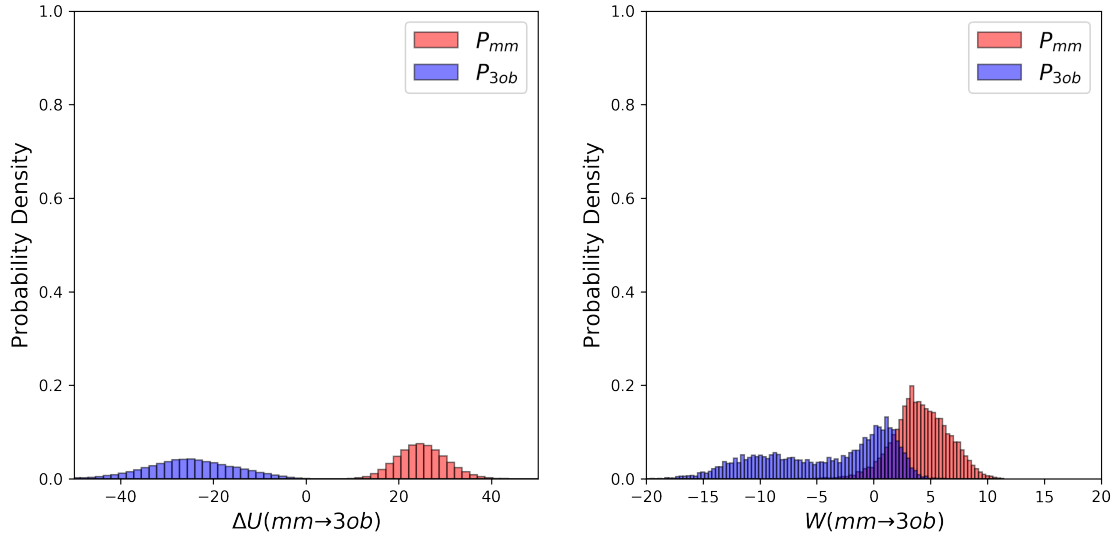
(a) $P_{mm} = p(U^{3ob} - U^{MM})$, $P_{3ob} = -p(U^{MM} - U^{3ob})$ (b) $P_{mm} = p(W^{MM \rightarrow 3ob})$, $P_{3ob} = -p(W^{3ob \rightarrow MM})$

Figure 17: (a) **16**'s potential energy “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\Delta U^{MM \rightarrow 3ob}$ to simplify the x-axis. (b) **16**'s nonequilibrium work “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\overline{W}^{MM \rightarrow 3ob}$ to simplify the x-axis.



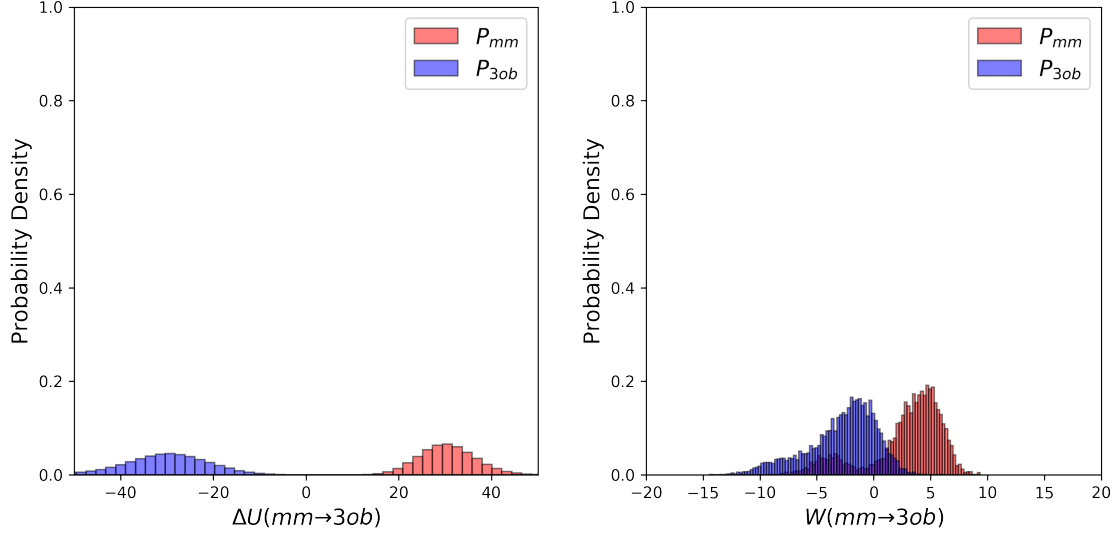
(a) $P_{mm} = p(U^{3ob} - U^{MM})$, $P_{3ob} = -p(U^{MM} - U^{3ob})$ (b) $P_{mm} = p(W^{MM \rightarrow 3ob})$, $P_{3ob} = -p(W^{3ob \rightarrow MM})$

Figure 18: (a) **17**'s potential energy “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\Delta U^{MM \rightarrow 3ob}$ to simplify the x-axis. (b) **17**'s nonequilibrium work “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\overline{W}^{MM \rightarrow 3ob}$ to simplify the x-axis.



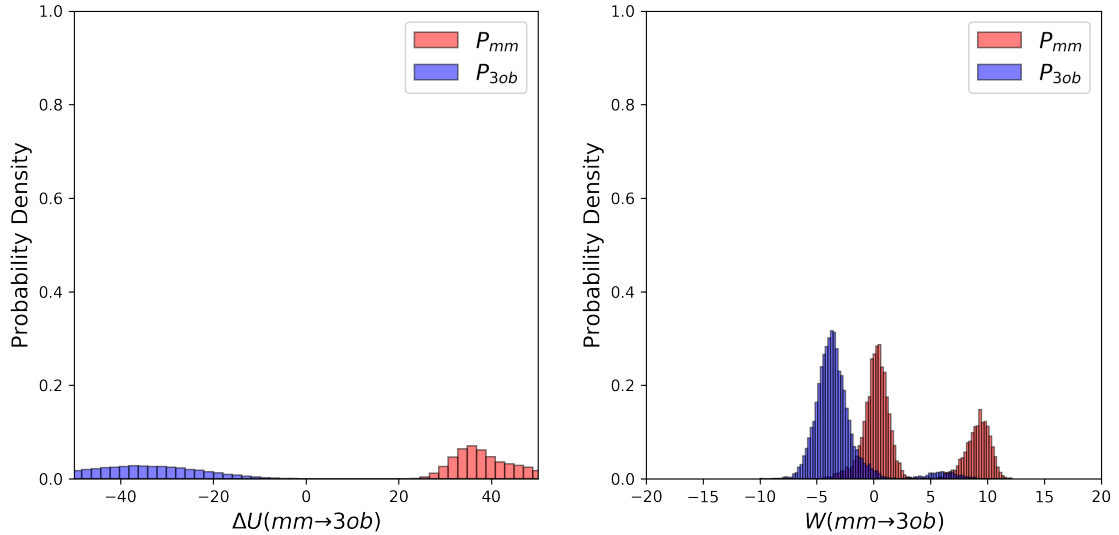
(a) $P_{mm} = p(U^{3ob} - U^{MM})$, $P_{3ob} = -p(U^{MM} - U^{3ob})$ (b) $P_{mm} = p(W^{MM \rightarrow 3ob})$, $P_{3ob} = -p(W^{3ob \rightarrow MM})$

Figure 19: (a) **18**'s potential energy “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\Delta U^{MM \rightarrow 3ob}$ to simplify the x-axis. (b) **18**'s nonequilibrium work “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\overline{W}^{MM \rightarrow 3ob}$ to simplify the x-axis.



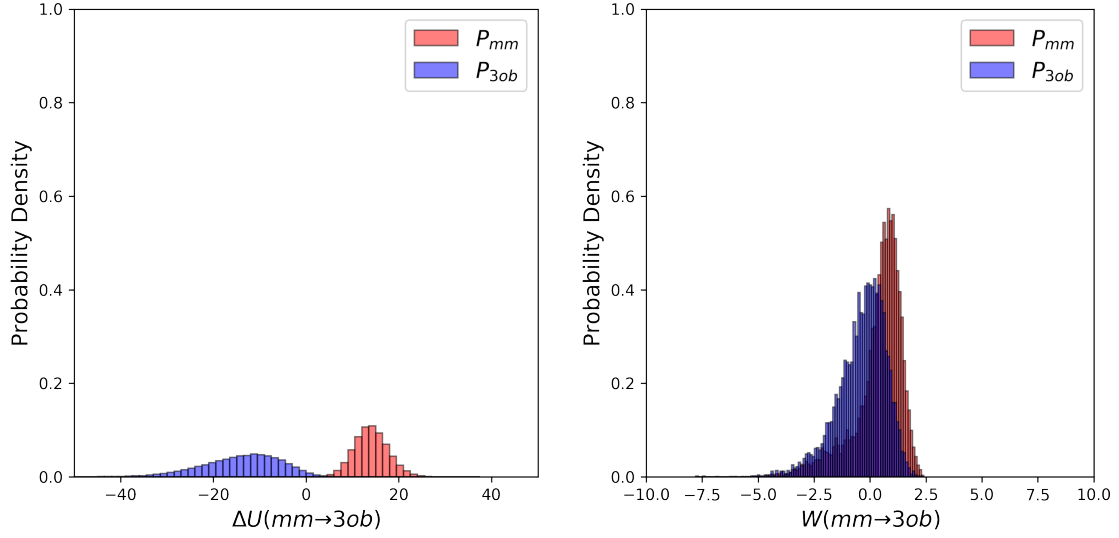
(a) $P_{mm} = p(U^{3ob} - U^{MM})$, $P_{3ob} = -p(U^{MM} - U^{3ob})$ (b) $P_{mm} = p(W^{MM \rightarrow 3ob})$, $P_{3ob} = -p(W^{3ob \rightarrow MM})$

Figure 20: (a) **19**'s potential energy “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\Delta U^{MM \rightarrow 3ob}$ to simplify the x-axis. (b) **19**'s nonequilibrium work “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\overline{W}^{MM \rightarrow 3ob}$ to simplify the x-axis.



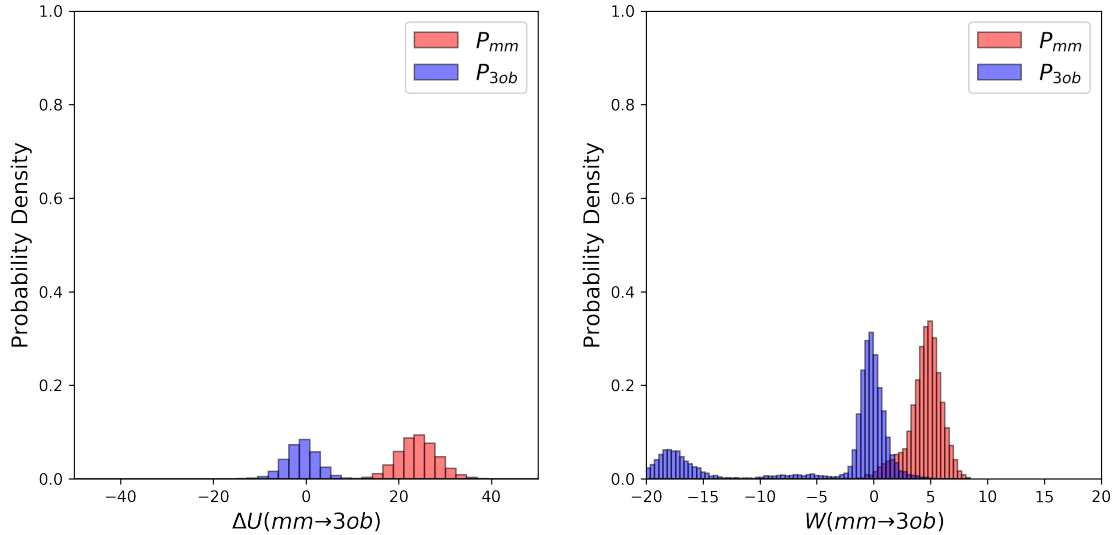
(a) $P_{mm} = p(U^{3ob} - U^{MM})$, $P_{3ob} = -p(U^{MM} - U^{3ob})$ (b) $P_{mm} = p(W^{MM \rightarrow 3ob})$, $P_{3ob} = -p(W^{3ob \rightarrow MM})$

Figure 21: (a) **20**'s potential energy “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\Delta U^{MM \rightarrow 3ob}$ to simplify the x-axis. (b) **20**'s nonequilibrium work “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\overline{W}^{MM \rightarrow 3ob}$ to simplify the x-axis.



(a) $P_{mm} = p(U^{3ob} - U^{MM})$, $P_{3ob} = -p(U^{MM} - U^{3ob})$ (b) $P_{mm} = p(W^{MM \rightarrow 3ob})$, $P_{3ob} = -p(W^{3ob \rightarrow MM})$

Figure 22: (a) **21**'s potential energy “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\Delta U^{MM \rightarrow 3ob}$ to simplify the x-axis. (b) **21**'s nonequilibrium work “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\overline{W}^{MM \rightarrow 3ob}$ to simplify the x-axis.



(a) $P_{mm} = p(U^{3ob} - U^{MM})$, $P_{3ob} = -p(U^{MM} - U^{3ob})$ (b) $P_{mm} = p(W^{MM \rightarrow 3ob})$, $P_{3ob} = -p(W^{3ob \rightarrow MM})$

Figure 23: (a) **22**'s potential energy “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\Delta U^{MM \rightarrow 3ob}$ to simplify the x-axis. (b) **22**'s nonequilibrium work “forward” (P_{mm}) and “backward” (P_{3ob}) distributions plotted as “offset” from the $\overline{W}^{MM \rightarrow 3ob}$ to simplify the x-axis.

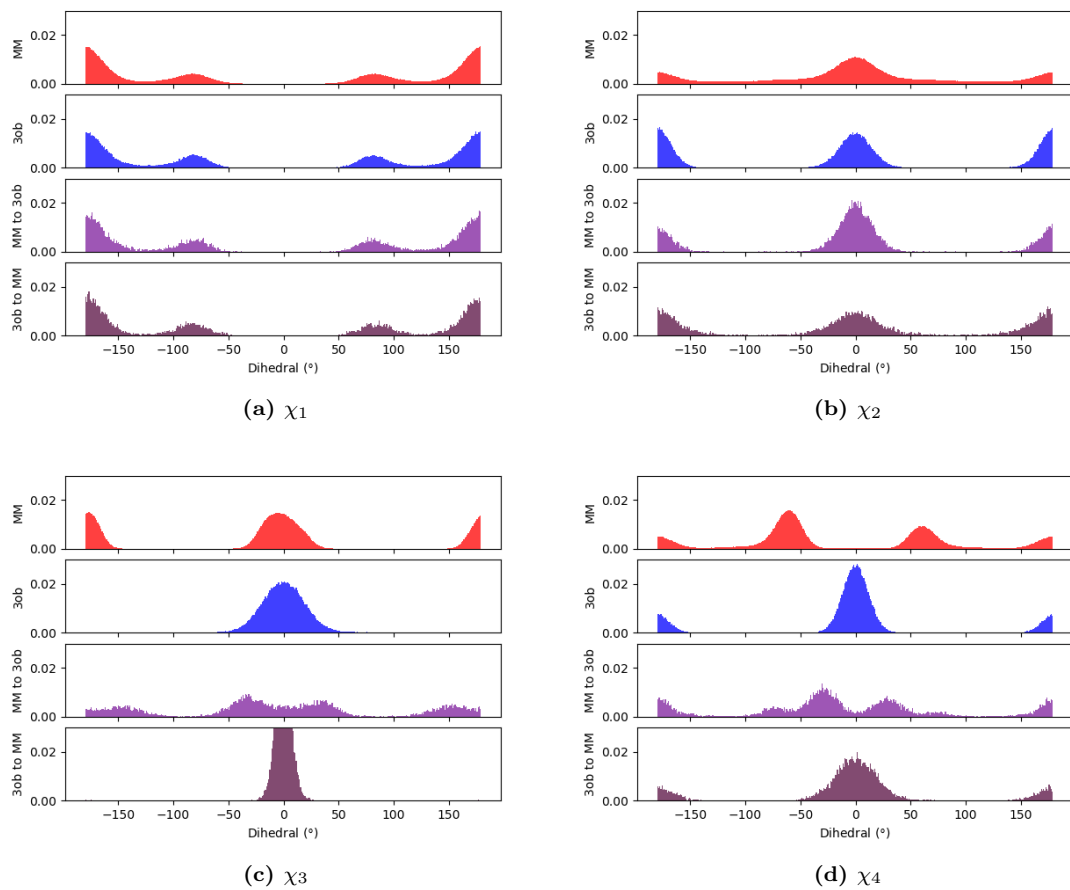


Figure 24: Dihedral distributions of molecule 1.

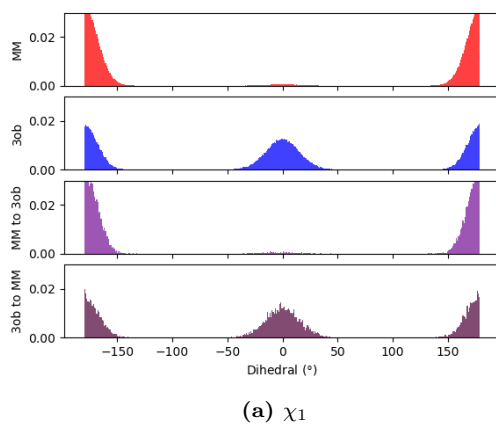
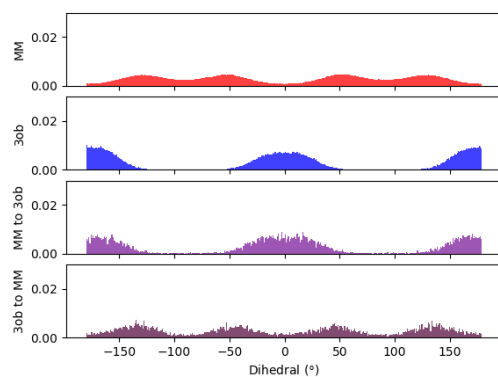


Figure 25: Dihedral distributions of molecule 2.



(a) χ_1

Figure 26: Dihedral distributions of molecule **3**.

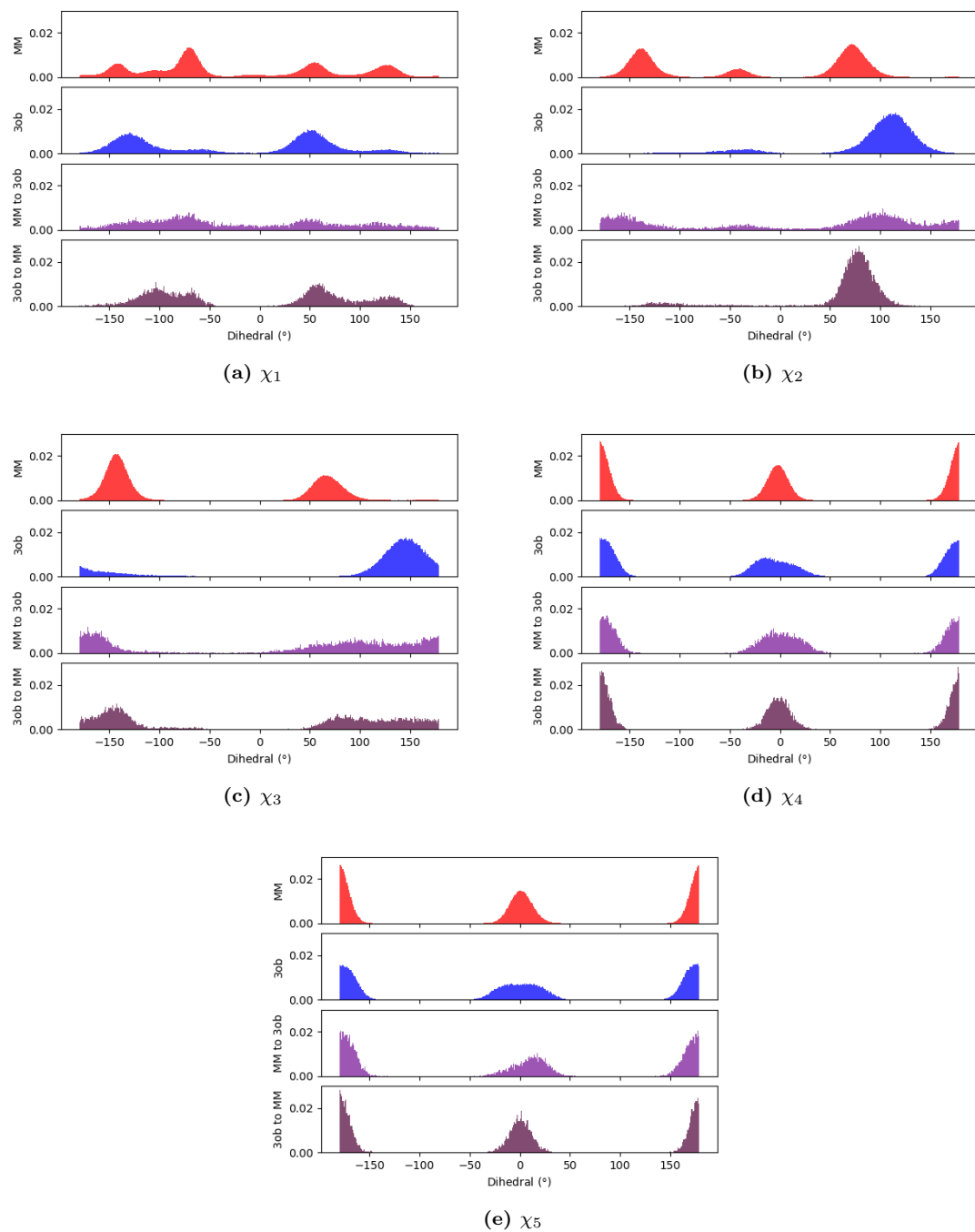


Figure 27: Dihedral distributions of molecule 5.

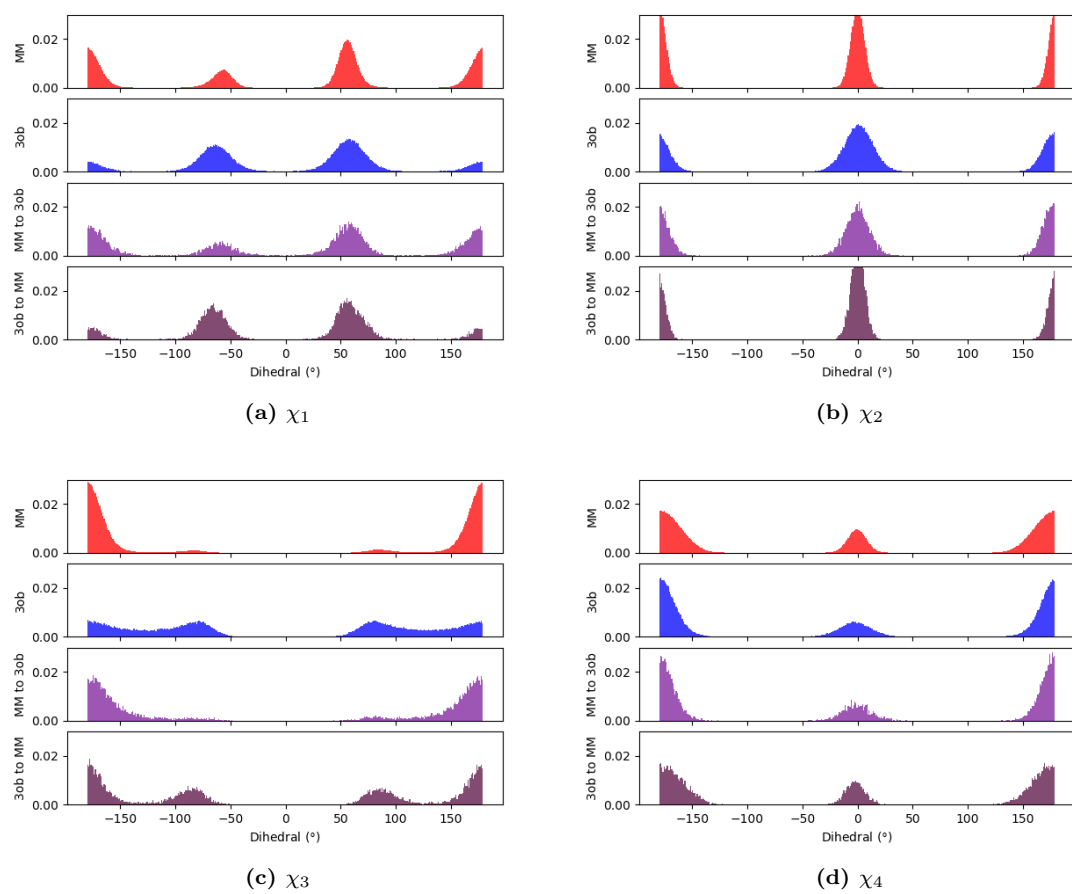


Figure 28: Dihedral distributions of molecule **6**.

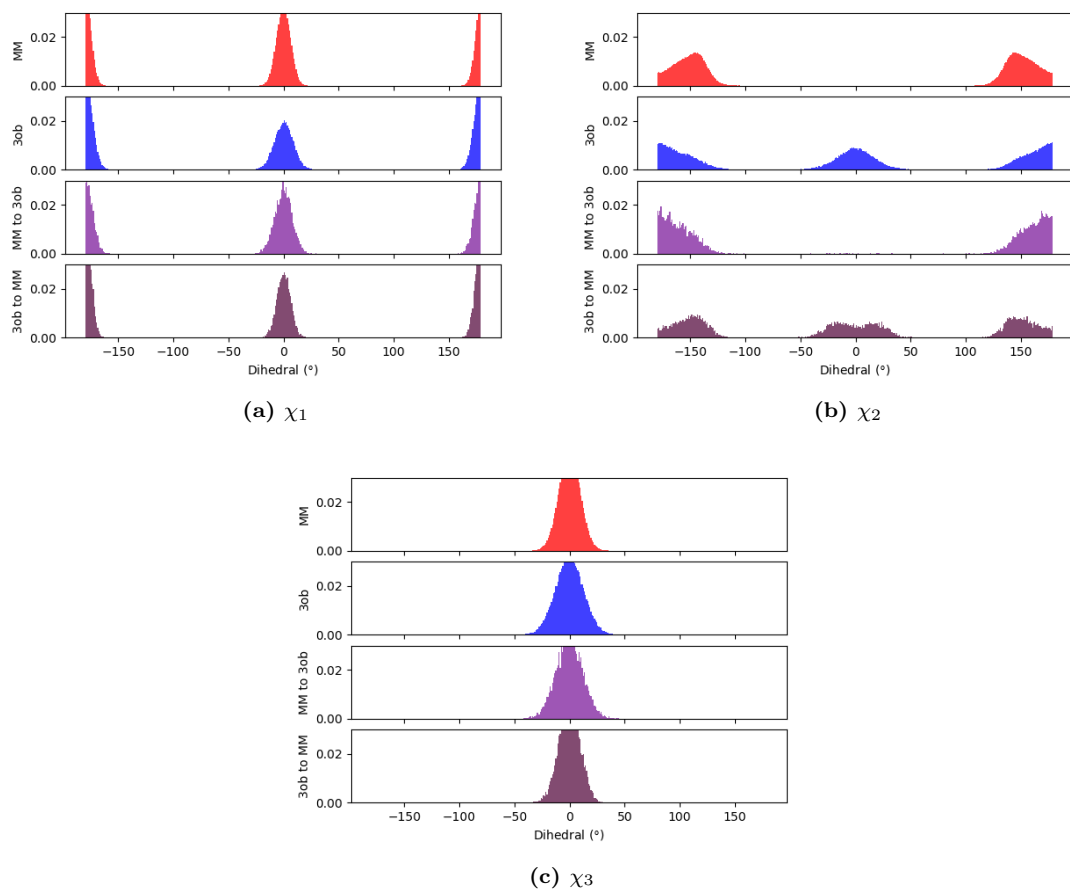


Figure 29: Dihedral distributions of molecule 7.

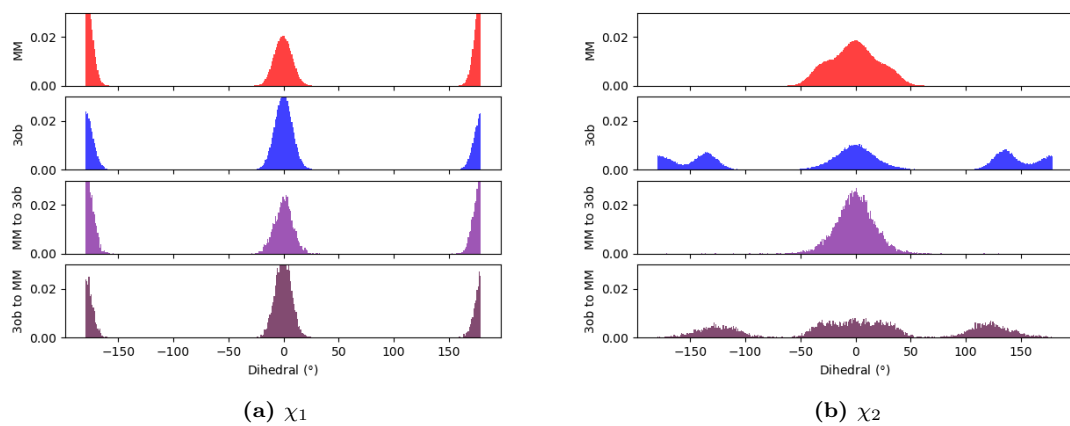


Figure 30: Dihedral distributions of molecule 8.

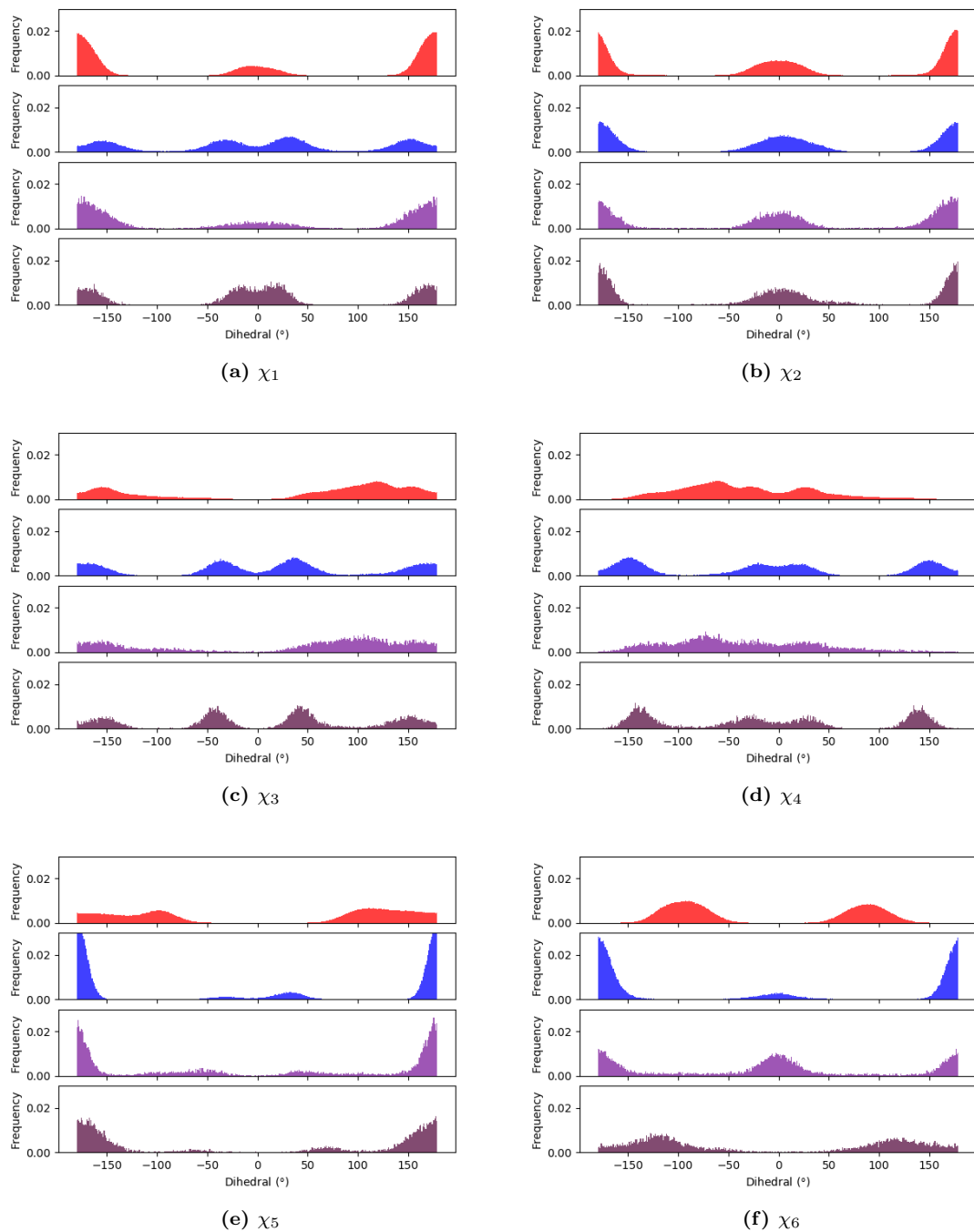


Figure 31: Dihedral distributions of molecule **9**.

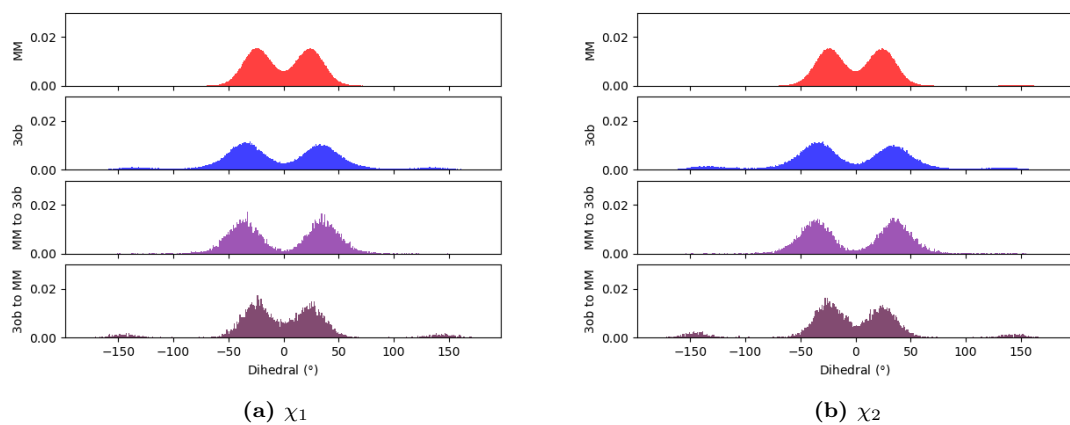


Figure 32: Dihedral distributions of molecule 10.

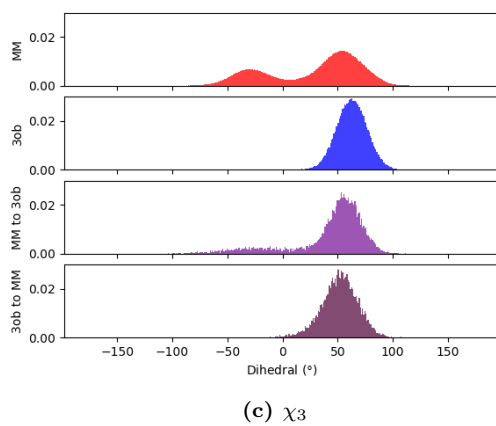
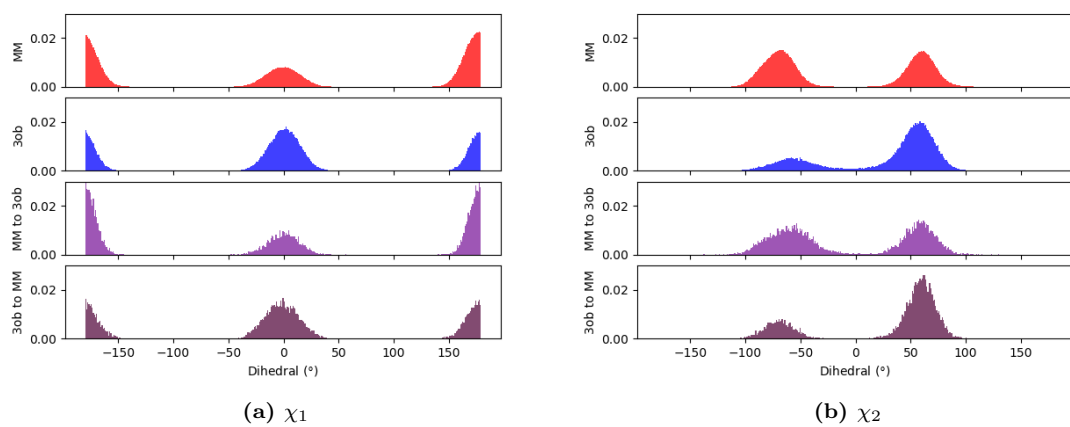
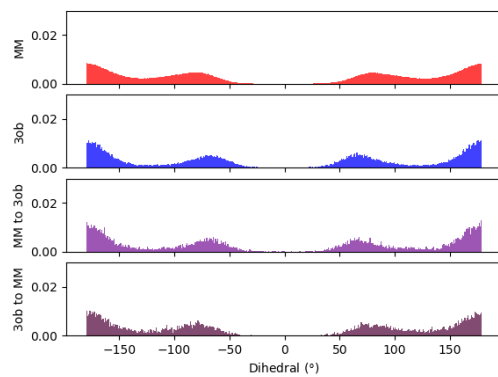
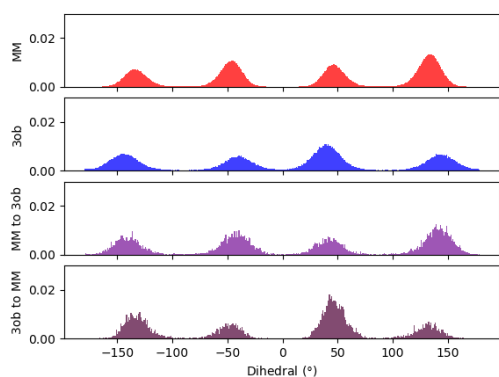


Figure 33: Dihedral distributions of molecule 11.

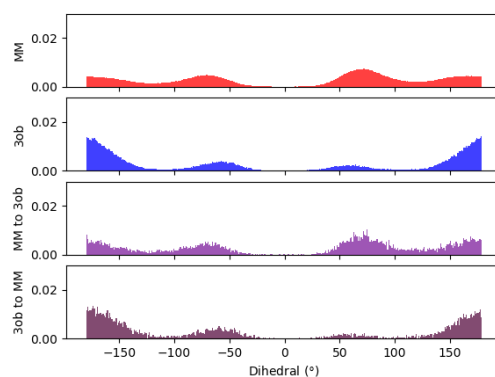


(a) χ_1

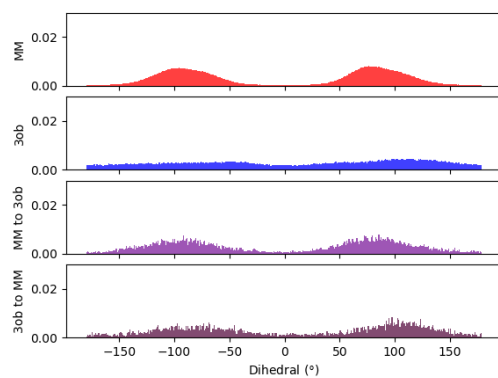
Figure 34: Dihedral distributions of molecule 13.



(a) χ_1



(b) χ_2



(c) χ_3

Figure 35: Dihedral distributions of molecule 14.

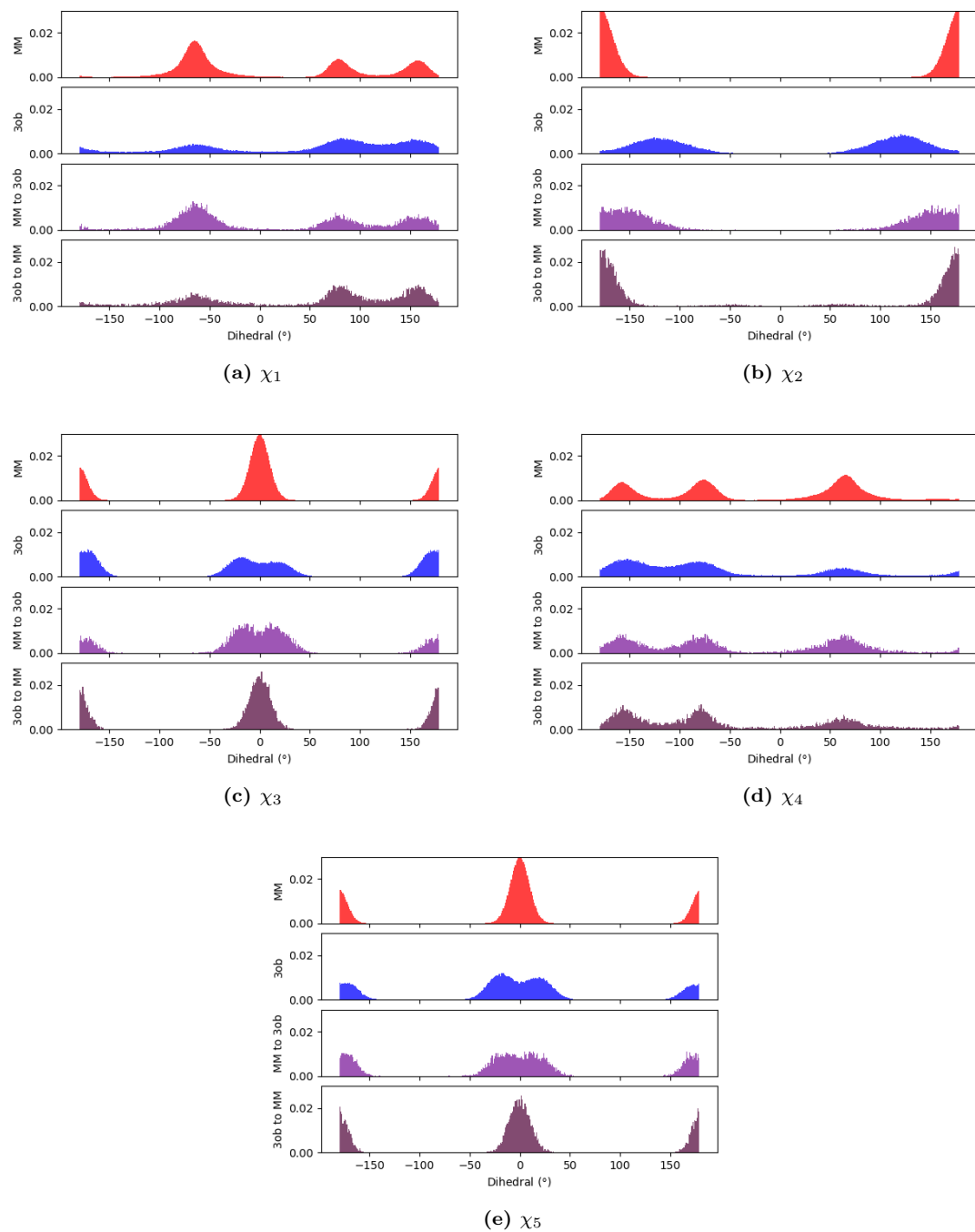


Figure 36: Dihedral distributions of molecule 16.

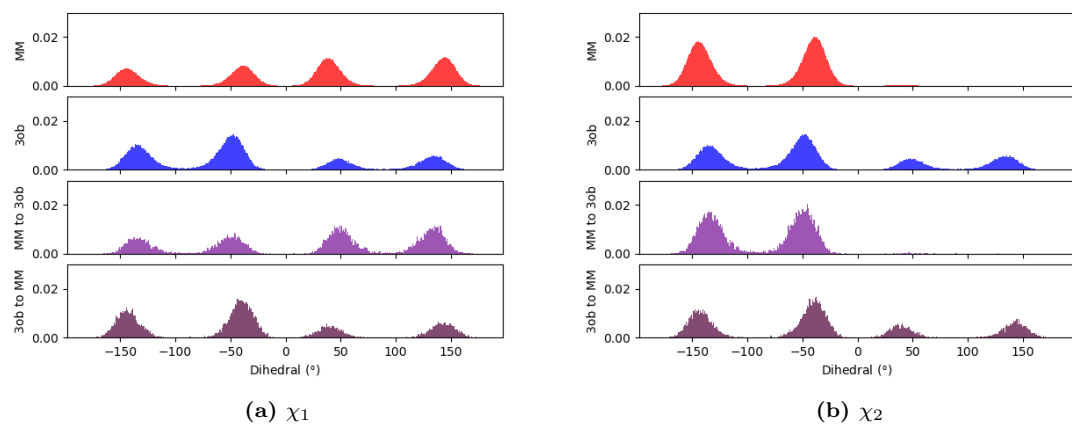


Figure 37: Dihedral distributions of molecule 17.

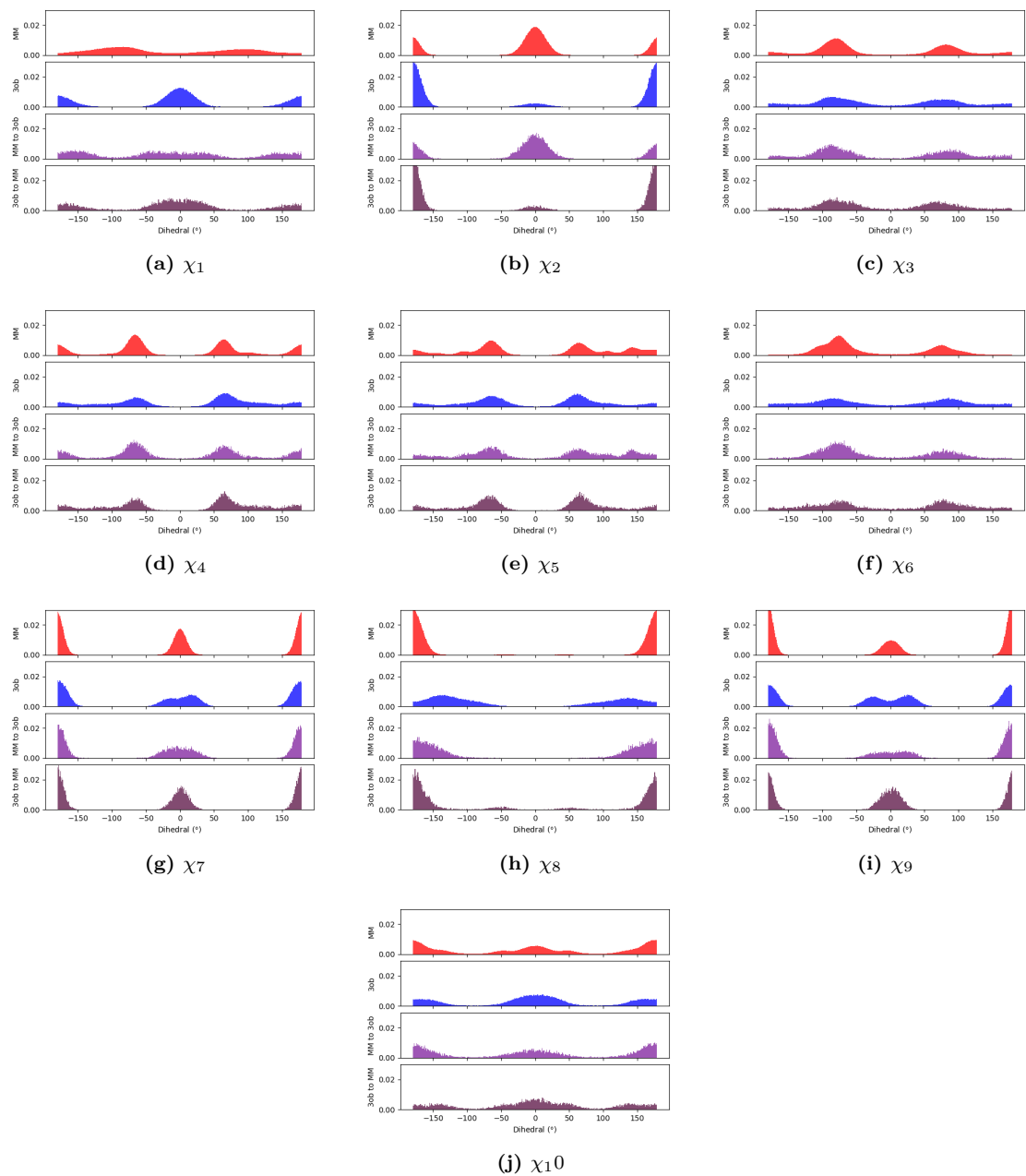


Figure 38: Dihedral distributions of molecule 18.

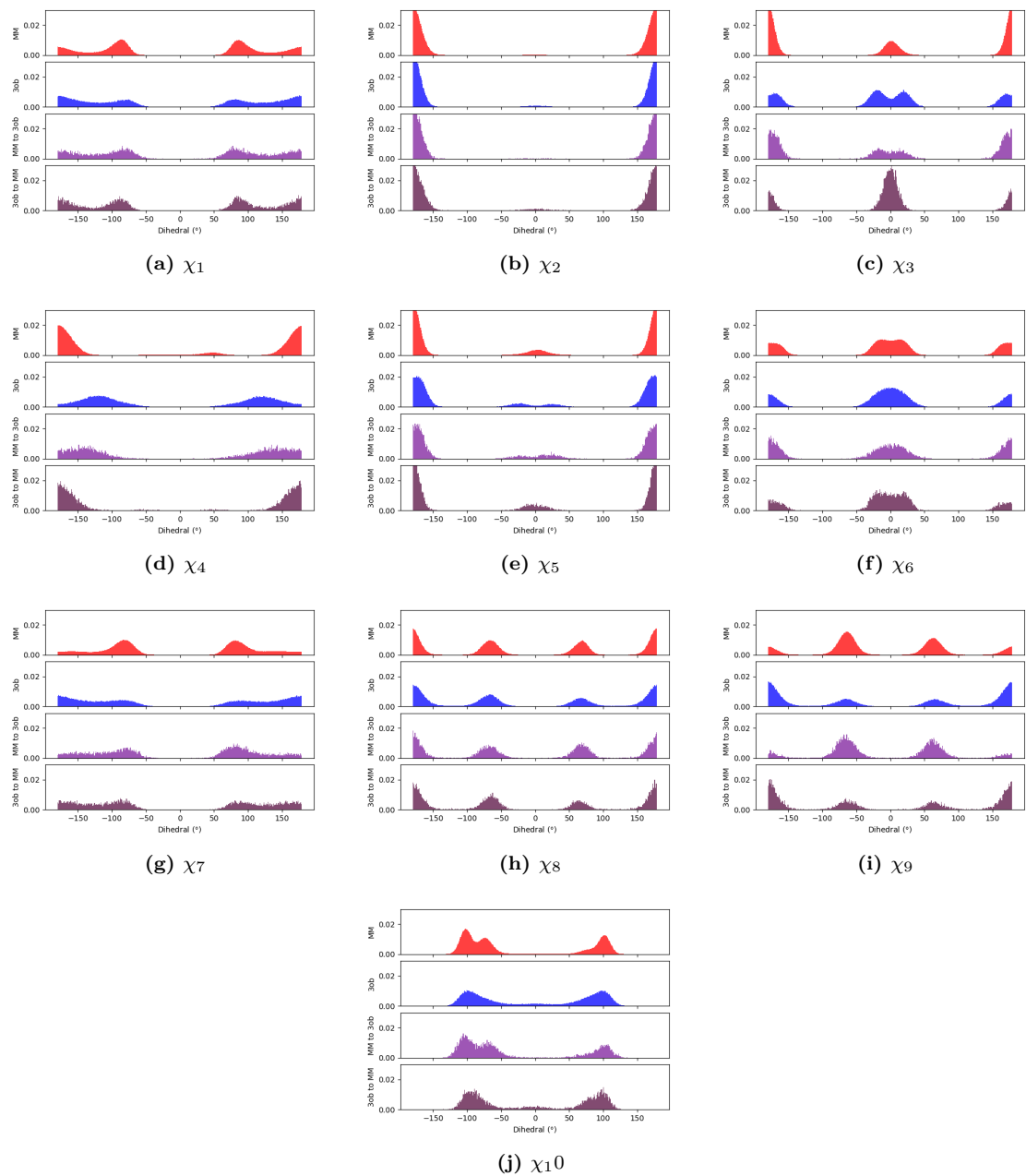


Figure 39: Dihedral distributions of molecule 19.

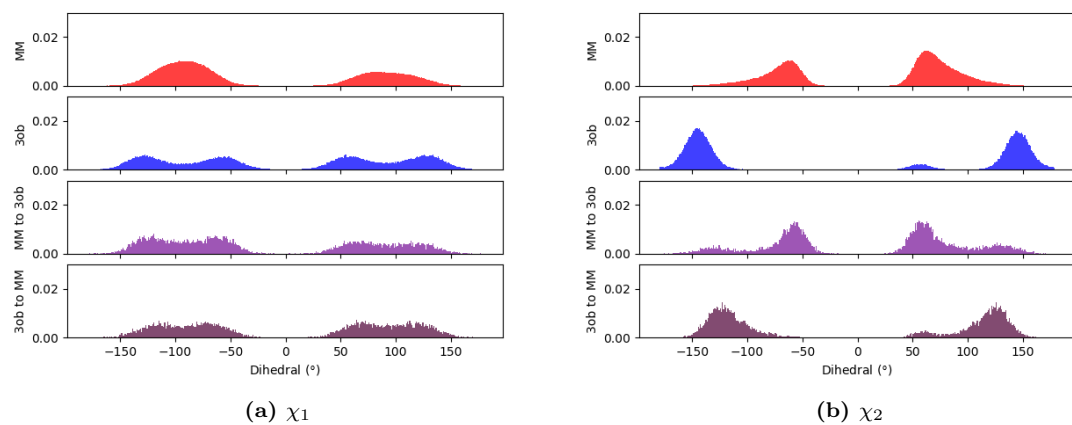


Figure 40: Dihedral distributions of molecule **20**.

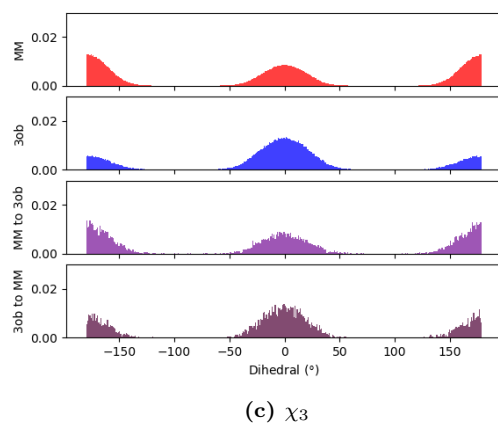
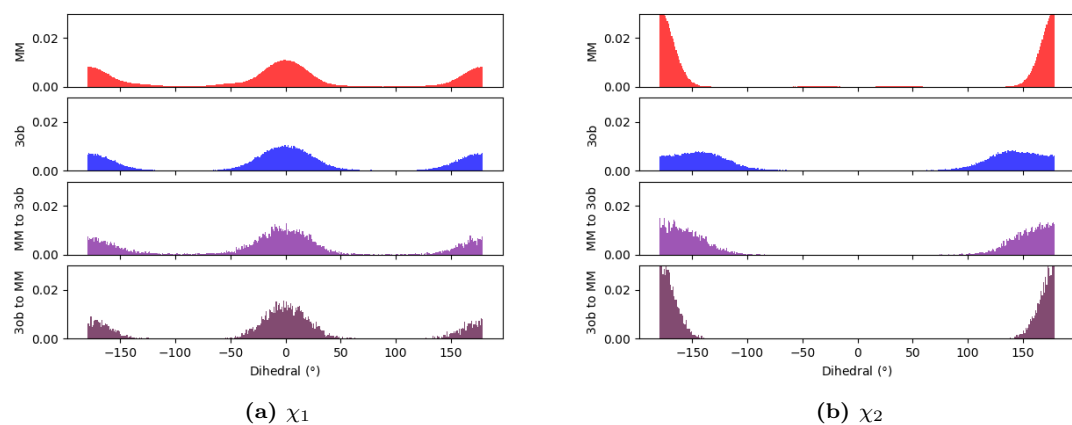


Figure 41: Dihedral distributions of molecule **21**.

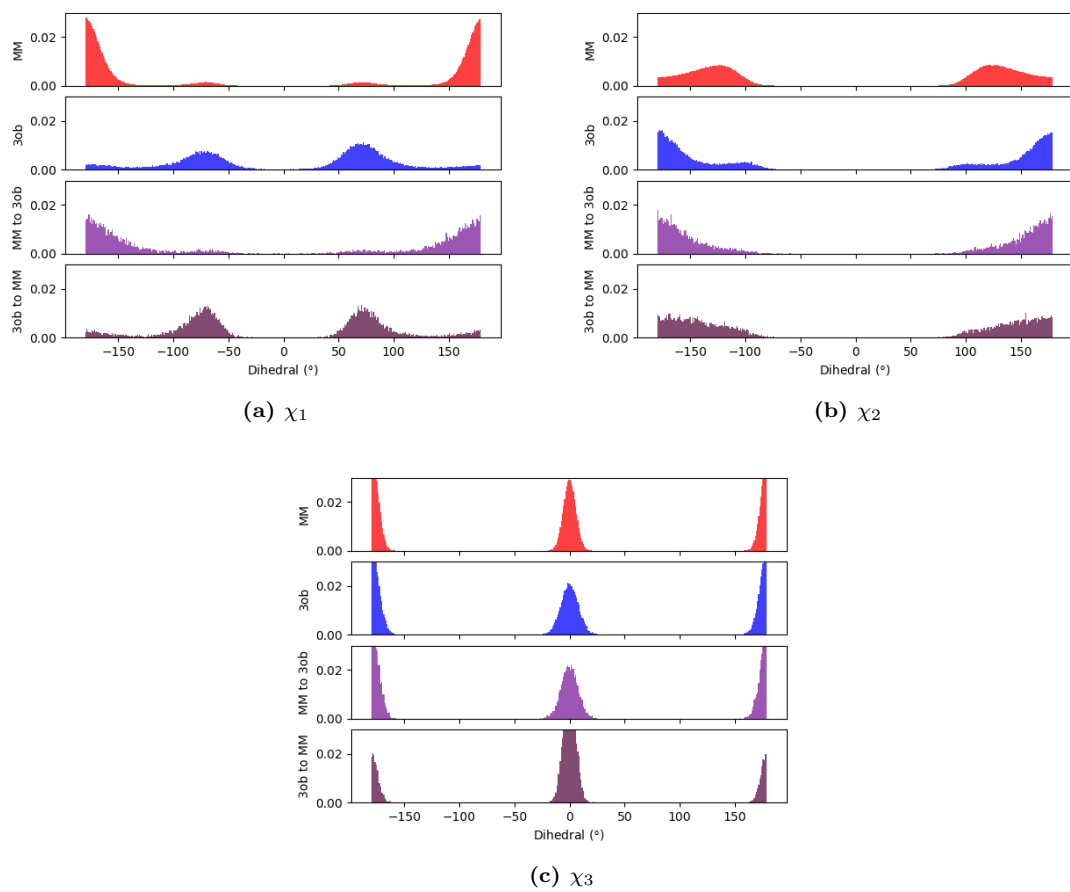


Figure 42: Dihedral distributions of molecule **22**.