Supplementary Information For:

Revisiting the HYDROPHOBE Challenge:

Application of Unrestrained Advanced Sampling to the Calculation of Cavitand Binding Energies

       This document contains an analysis of the convergence of ABF simulations for each of the 26 guests, and expands upon the results in Fig. 2.
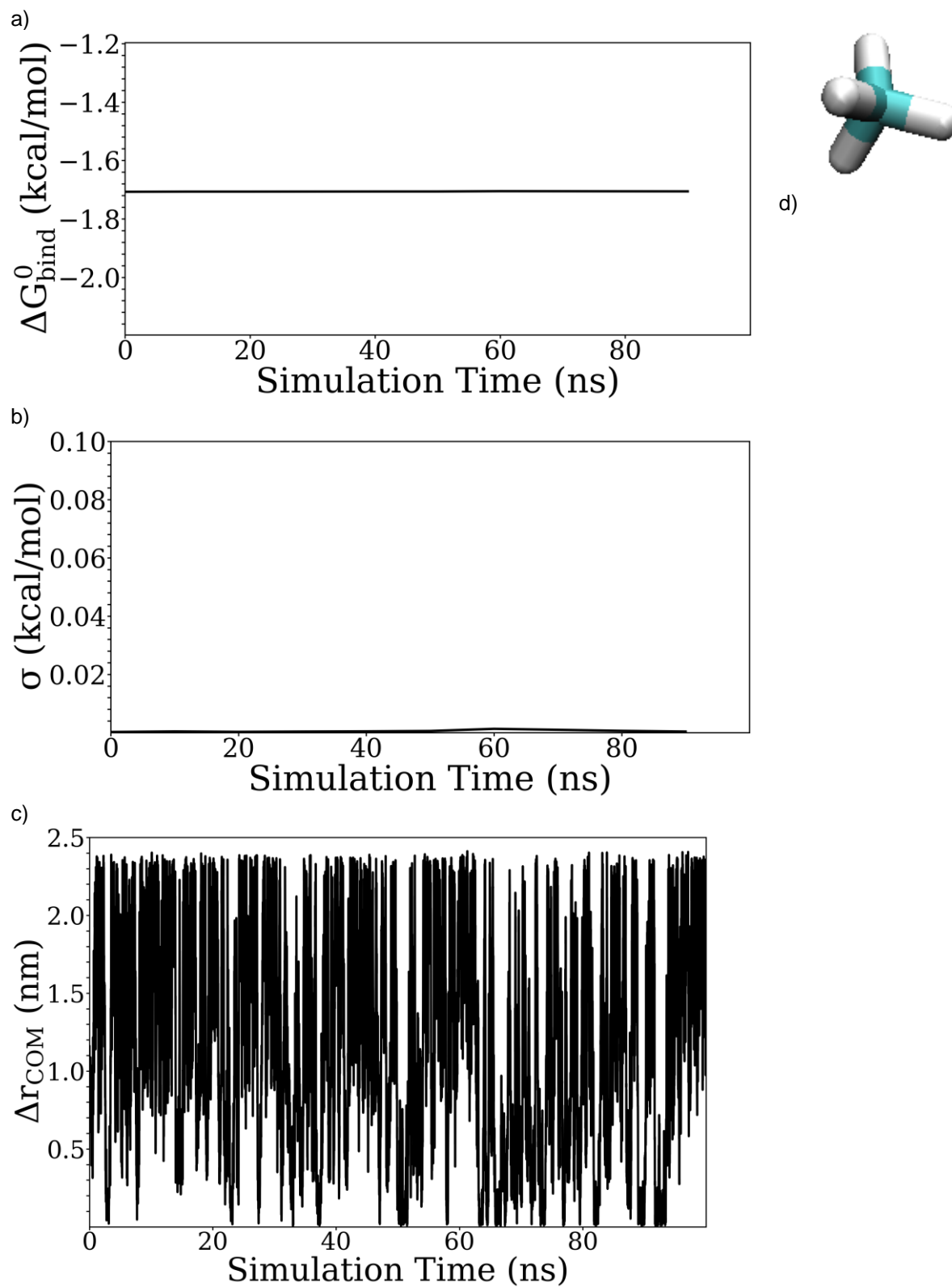
Figure S1. Convergence data for guest 01. Plots include a) $\Delta G^0_{bind}(t)$ over the last 100 ns of simulation, b) $\sigma(t)$ over the last 100 ns of simulation, and c) $\Delta r_{CM}(t)$ over the last 100 ns of simulation. Also included is an image of the guest (d).

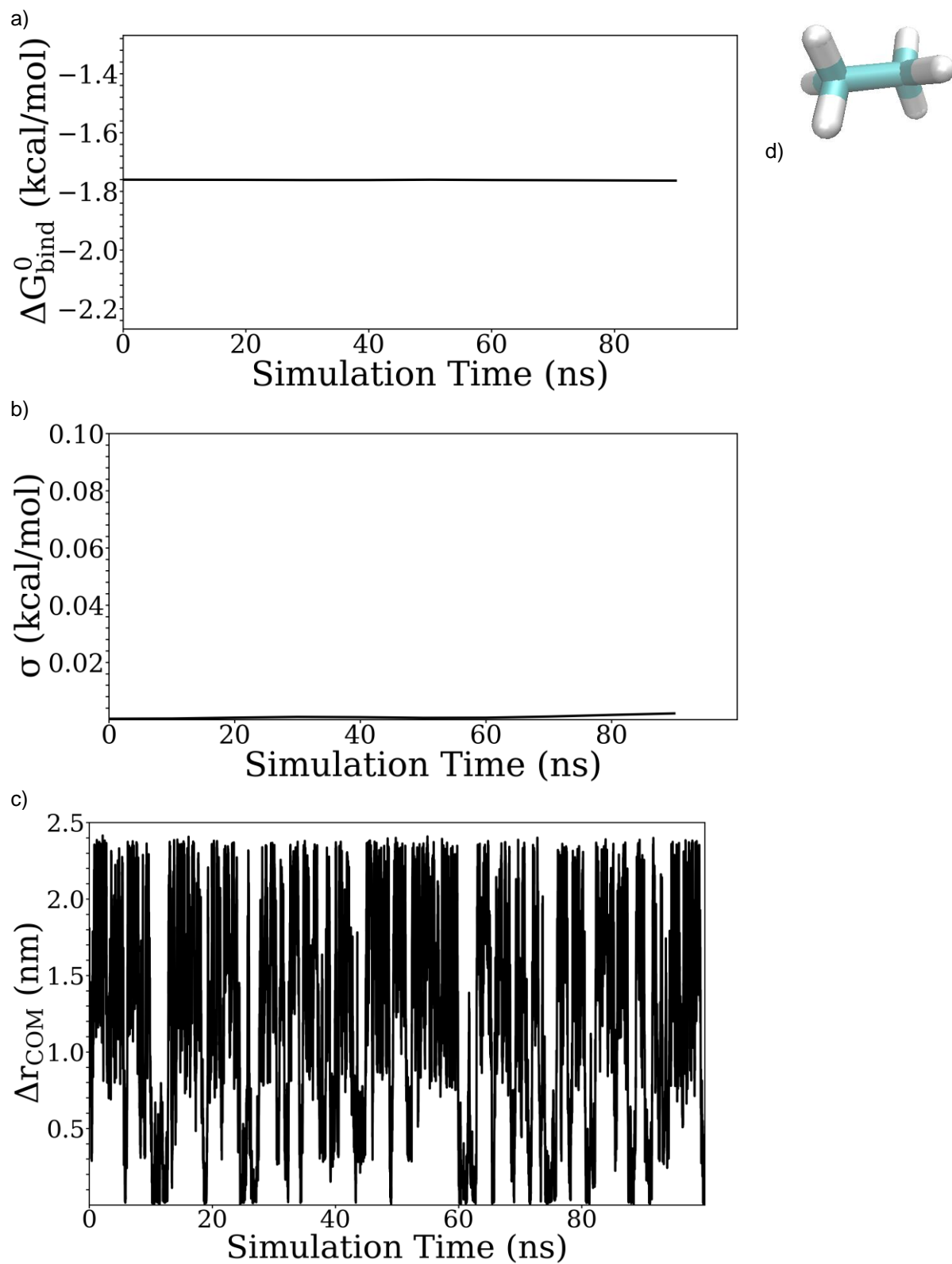Figure S2. Convergence data for guest 02. Plots include a) $\Delta G^0_{bind}(t)$ over the last 100 ns of simulation, b) $\sigma(t)$ over the last 100 ns of simulation, and c) $\Delta r_{CM}(t)$ over the last 100 ns of simulation. Also included is an image of the guest (d).

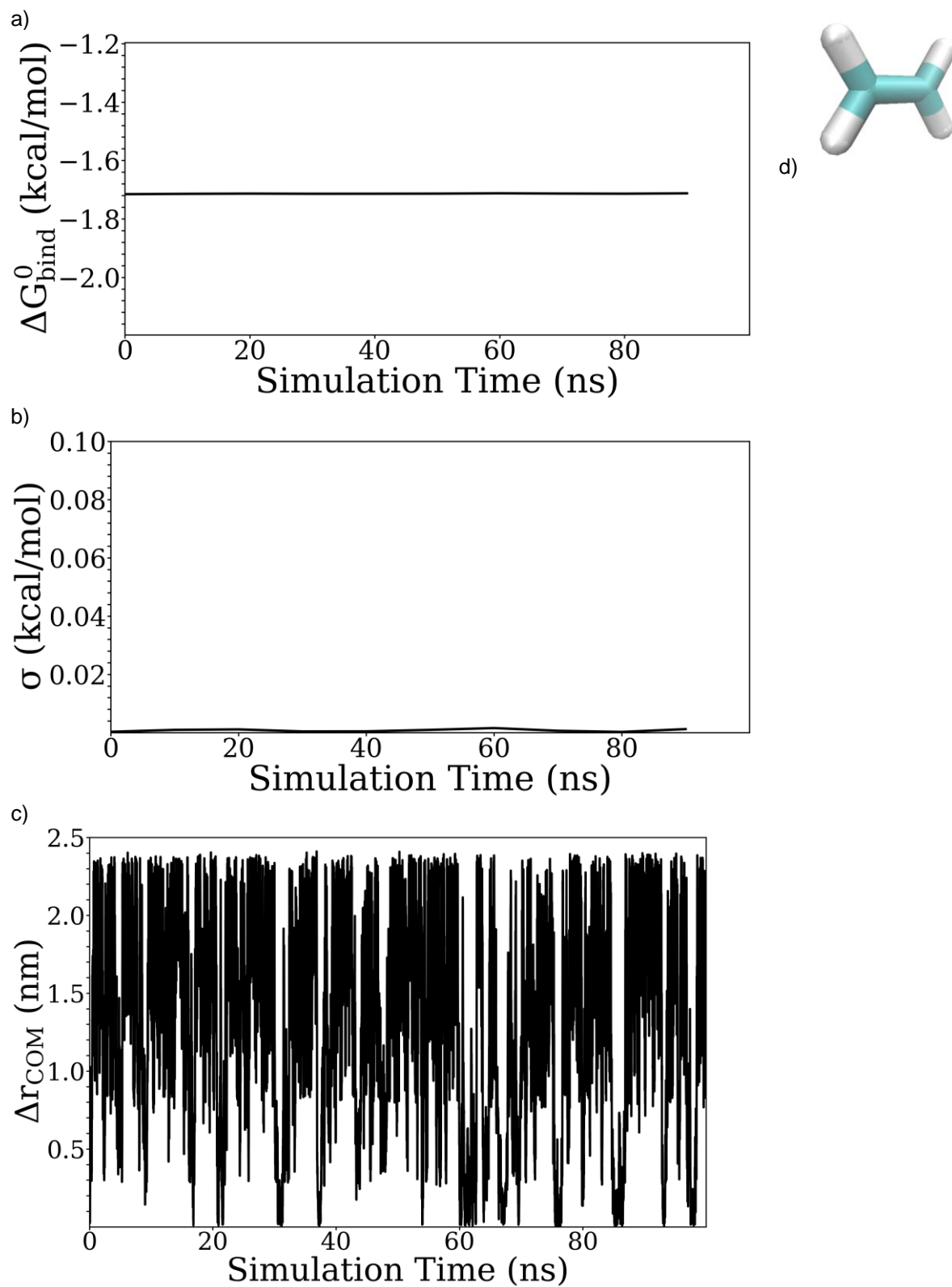Figure S3. Convergence data for guest 03. Plots include a) $\Delta G^0_{bind}(t)$ over the last 100 ns of simulation, b) $\sigma(t)$ over the last 100 ns of simulation, and c) $\Delta r_{CM}(t)$ over the last 100 ns of simulation. Also included is an image of the guest (d).

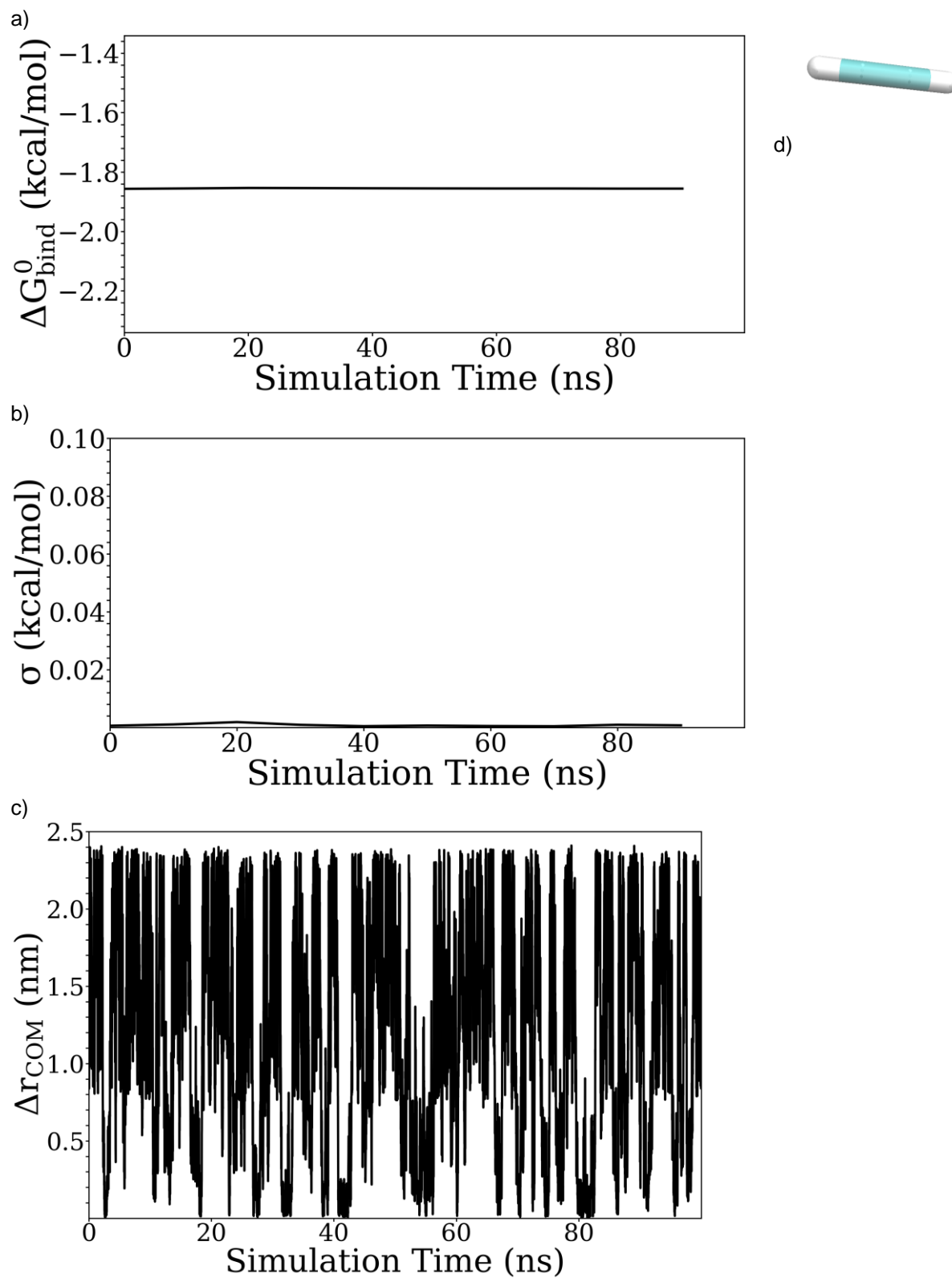Figure S4. Convergence data for guest 04. Plots include a) $\Delta G^0_{bind}(t)$ over the last 100 ns of simulation, b) $\sigma(t)$ over the last 100 ns of simulation, and c) $\Delta r_{CM}(t)$ over the last 100 ns of simulation. Also included is an image of the guest (d).
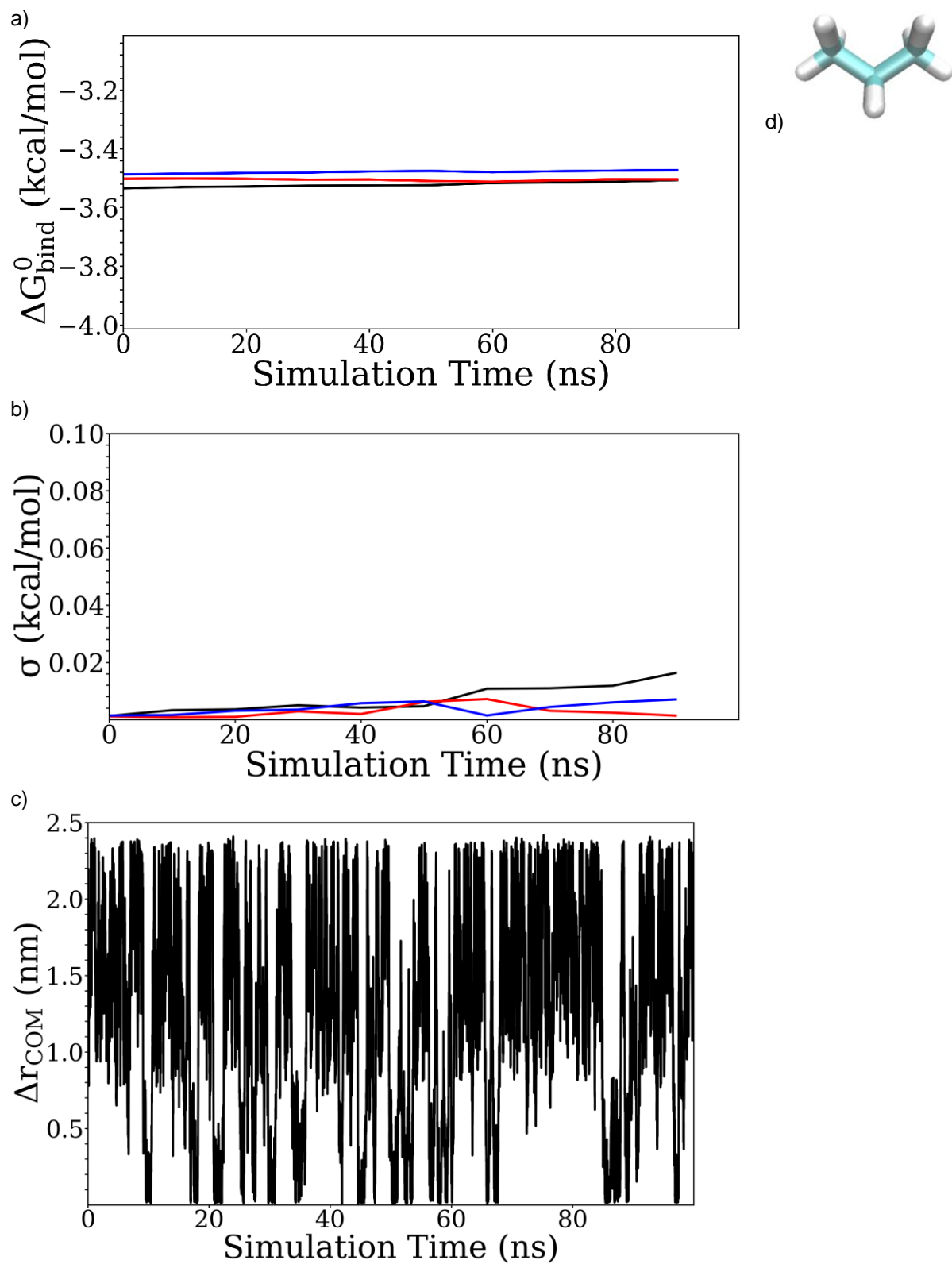
Figure S5. Convergence data for guest 05. Plots include a) $\Delta G_{bind}^0(t)$ over the last 100 ns of simulation (multiple runs), b) $\sigma(t)$ over the last 100 ns of simulation, and c) $\Delta r_{CM}(t)$ over the last 100 ns of simulation. Also included is an image of the guest (d).
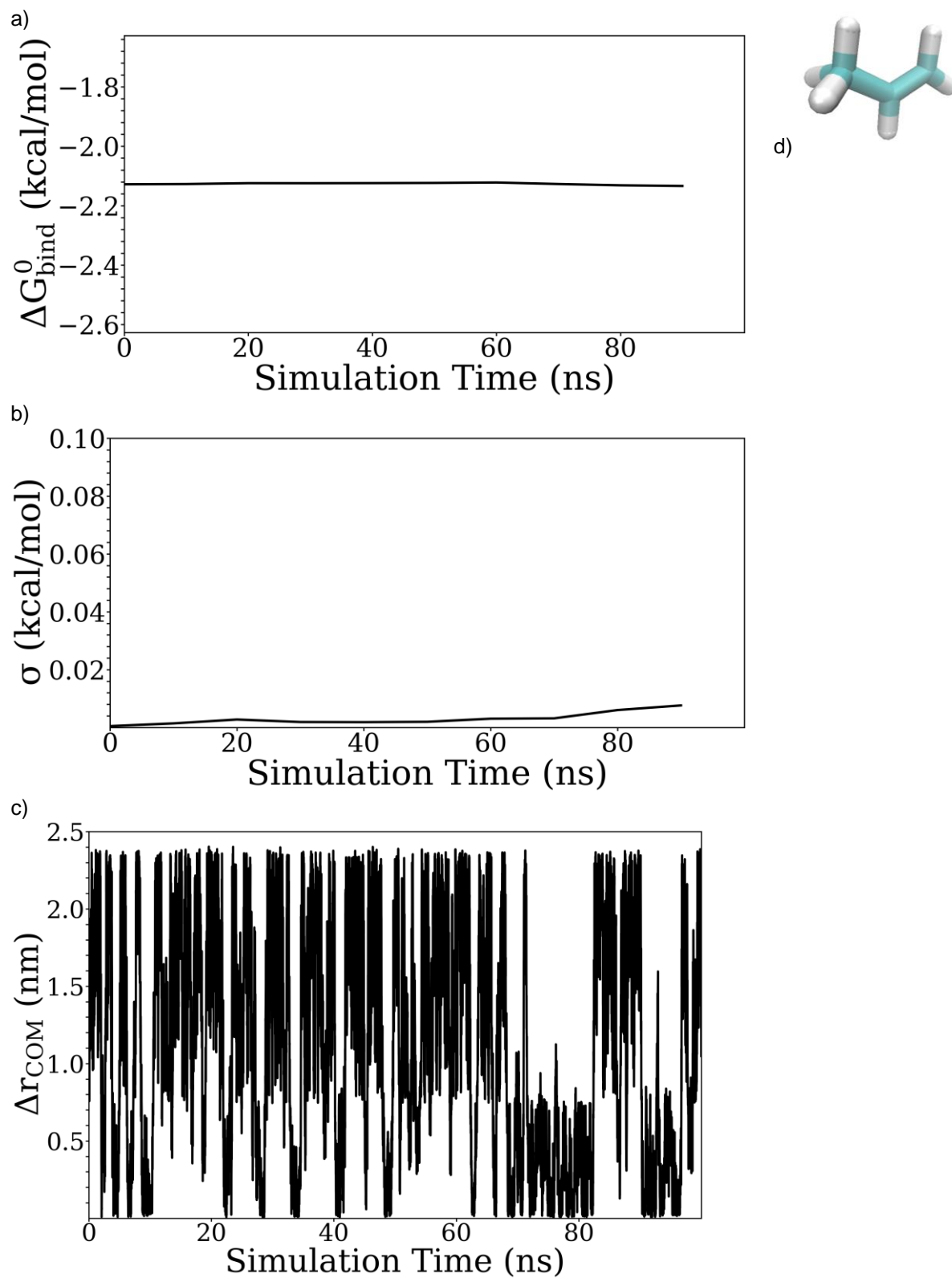
Figure S6. Convergence data for guest 06. Plots include a) $\Delta G^0_{bind}(t)$ over the last 100 ns of simulation, b) $\sigma(t)$ over the last 100 ns of simulation, and c) $\Delta r_{CM}(t)$ over the last 100 ns of simulation. Also included is an image of the guest (d).

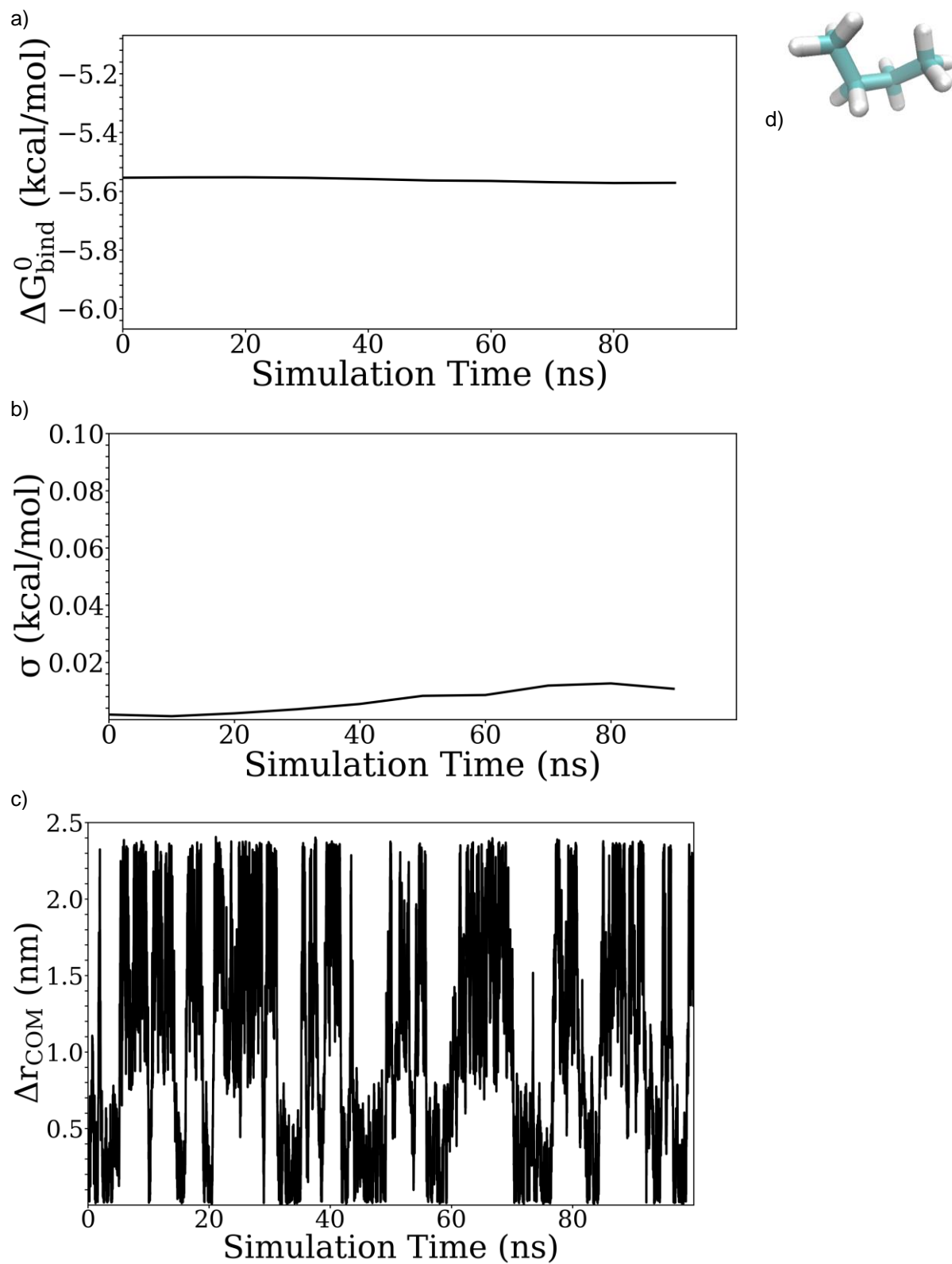Figure S7. Convergence data for guest 07. Plots include a) $\Delta G^0_{bind}(t)$ over the last 100 ns of simulation, b) $\sigma(t)$ over the last 100 ns of simulation, and c) $\Delta r_{CM}(t)$ over the last 100 ns of simulation. Also included is an image of the guest (d).
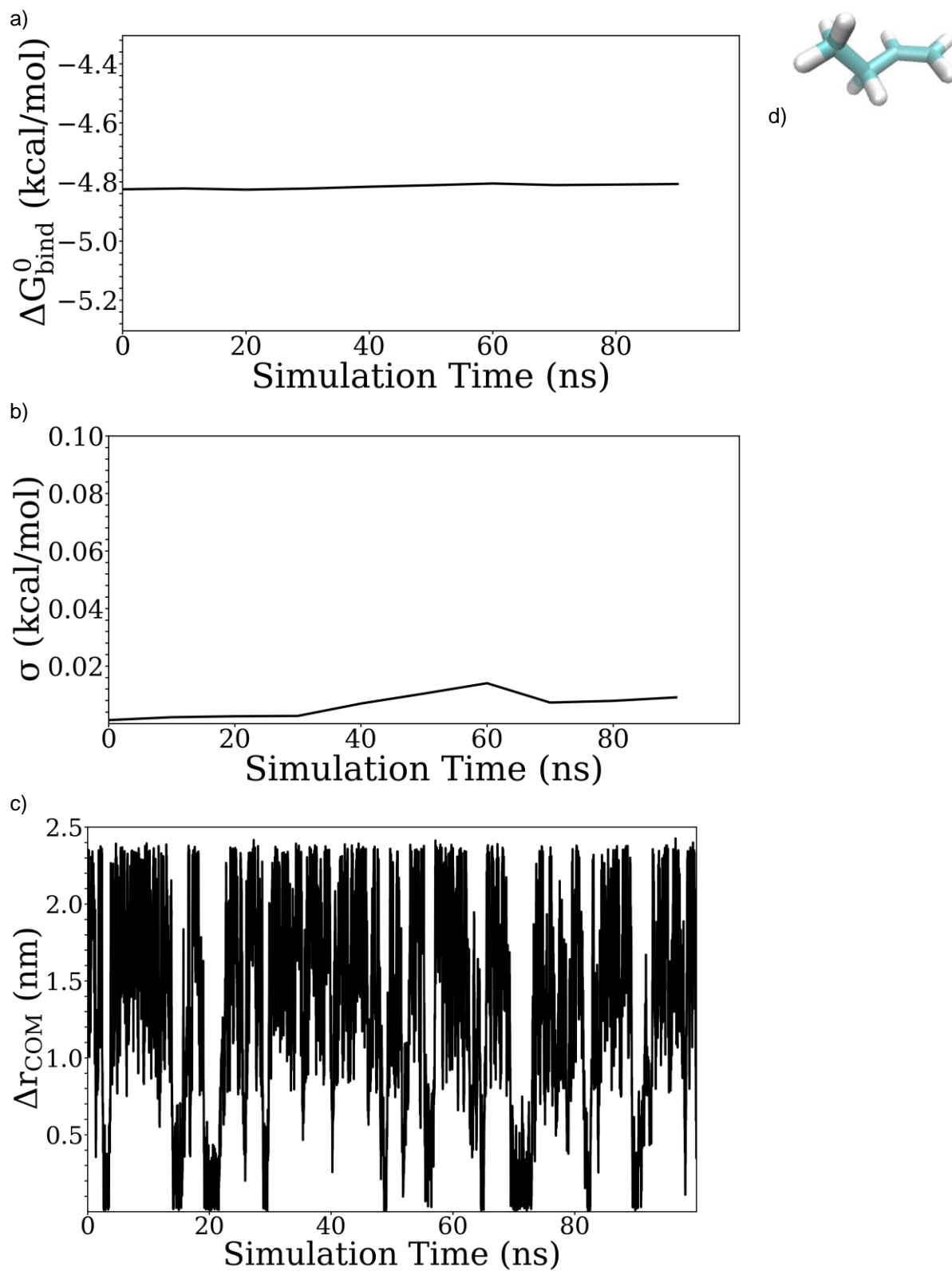
Figure S8. Convergence data for guest 08. Plots include a) $\Delta G_{bind}^0(t)$ over the last 100 ns of simulation, b) $\sigma(t)$ over the last 100 ns of simulation, and c) $\Delta r_{CM}(t)$ over the last 100 ns of simulation. Also included is an image of the guest (d).
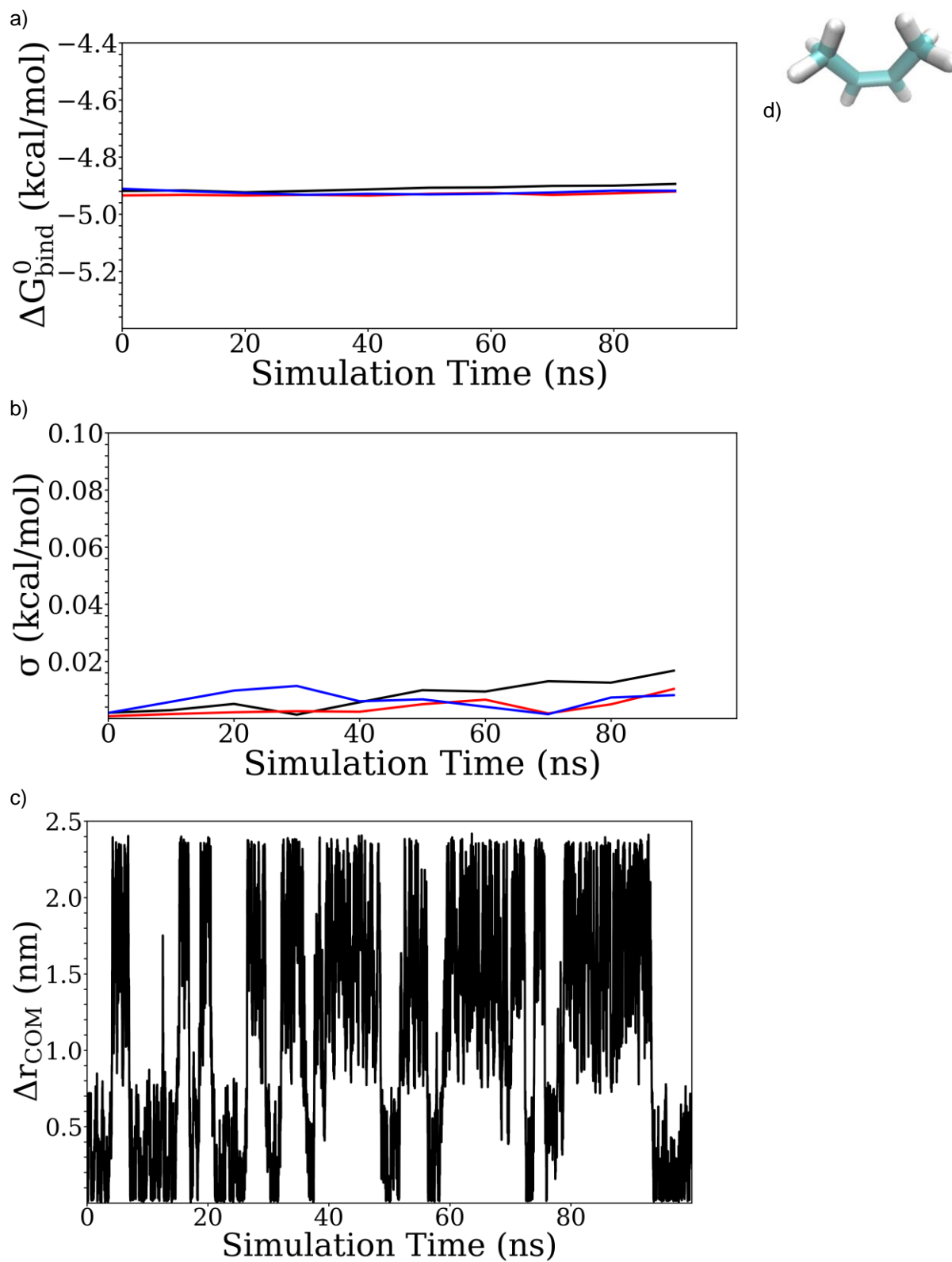
Figure S9. Convergence data for guest 09. Plots include a) $\Delta G_{bind}^0(t)$ over the last 100 ns of simulation (multiple runs), b) $\sigma(t)$ over the last 100 ns of simulation, and c) $\Delta r_{CM}(t)$ over the last 100 ns of simulation. Also included is an image of the guest (d).
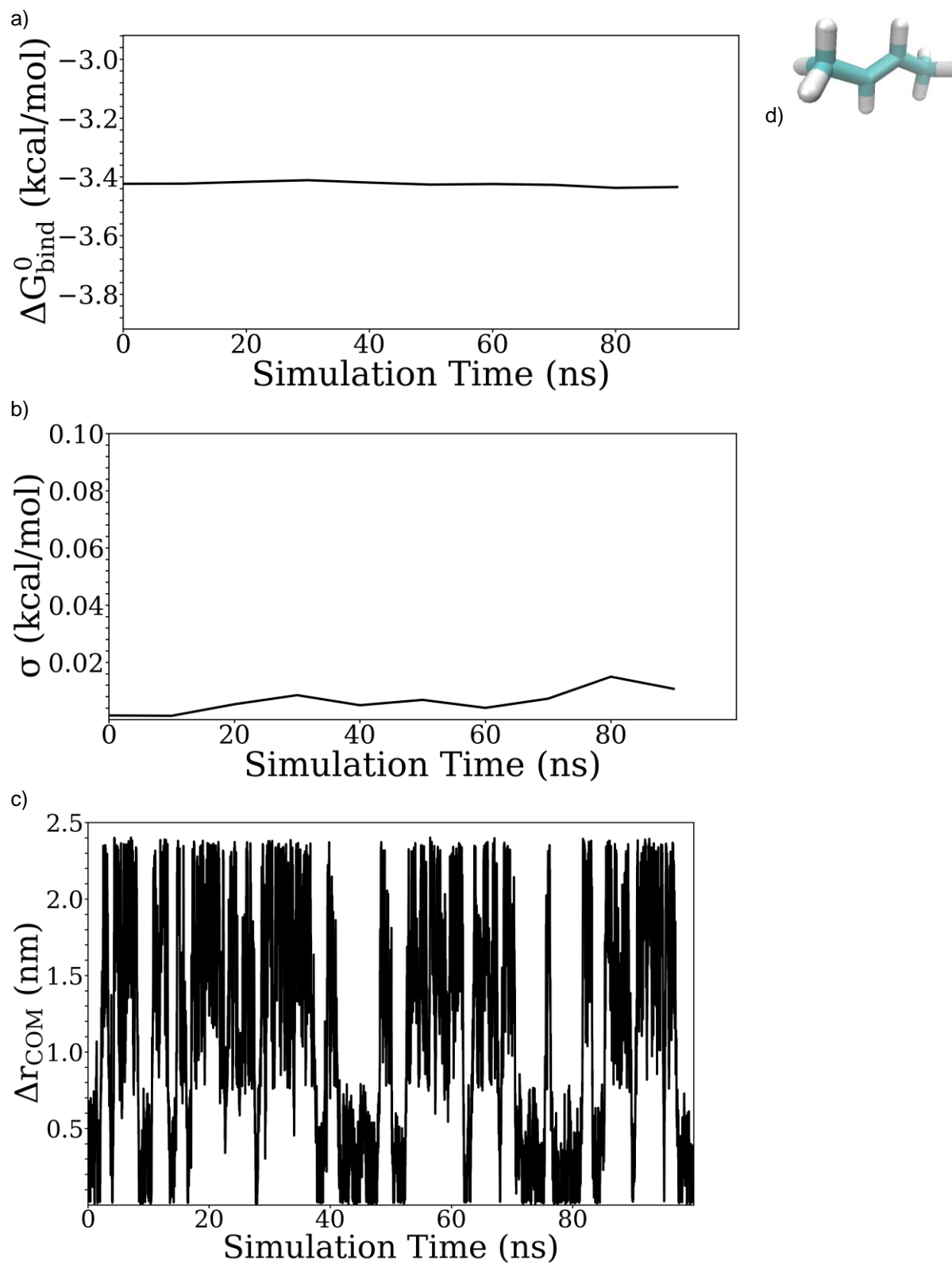
Figure S10. Convergence data for guest 10. Plots include a) $\Delta G_{bind}^0(t)$ over the last 100 ns of simulation, b) $\sigma(t)$ over the last 100 ns of simulation, and c) $\Delta r_{CM}(t)$ over the last 100 ns of simulation. Also included is an image of the guest (d).
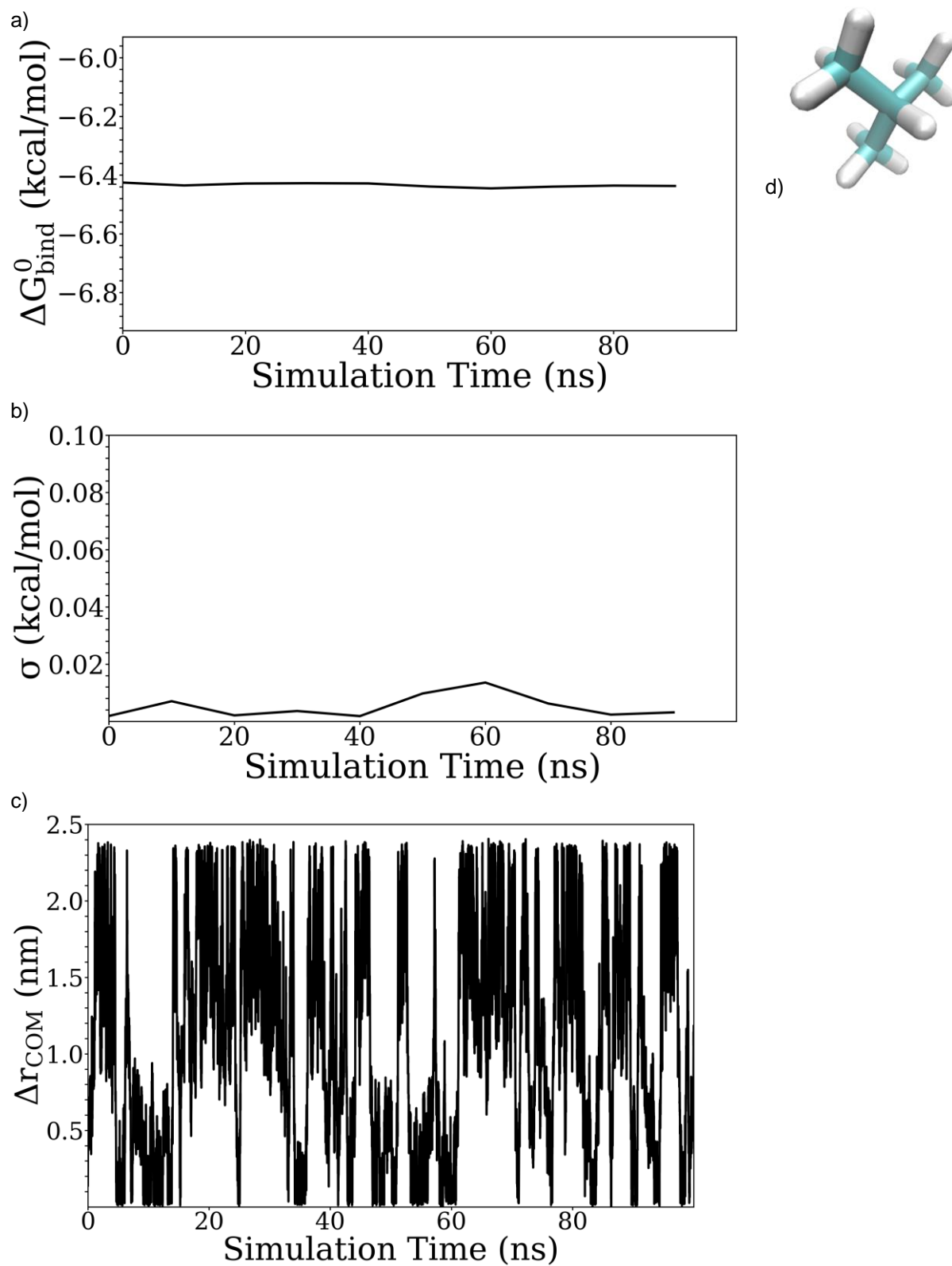
Figure S11. Convergence data for guest 11. Plots include a) $\Delta G^0_{bind}(t)$ over the last 100 ns of simulation, b) $\sigma(t)$ over the last 100 ns of simulation, and c) $\Delta r_{CM}(t)$ over the last 100 ns of simulation. Also included is an image of the guest (d).

Figure S12. Convergence data for guest 12. Plots include a) $\Delta G^0_{bind}(t)$ over the last 100 ns of simulation, b) $\sigma(t)$ over the last 100 ns of simulation, and c) $\Delta r_{CM}(t)$ over the last 100 ns of simulation. Also included is an image of the guest (d).
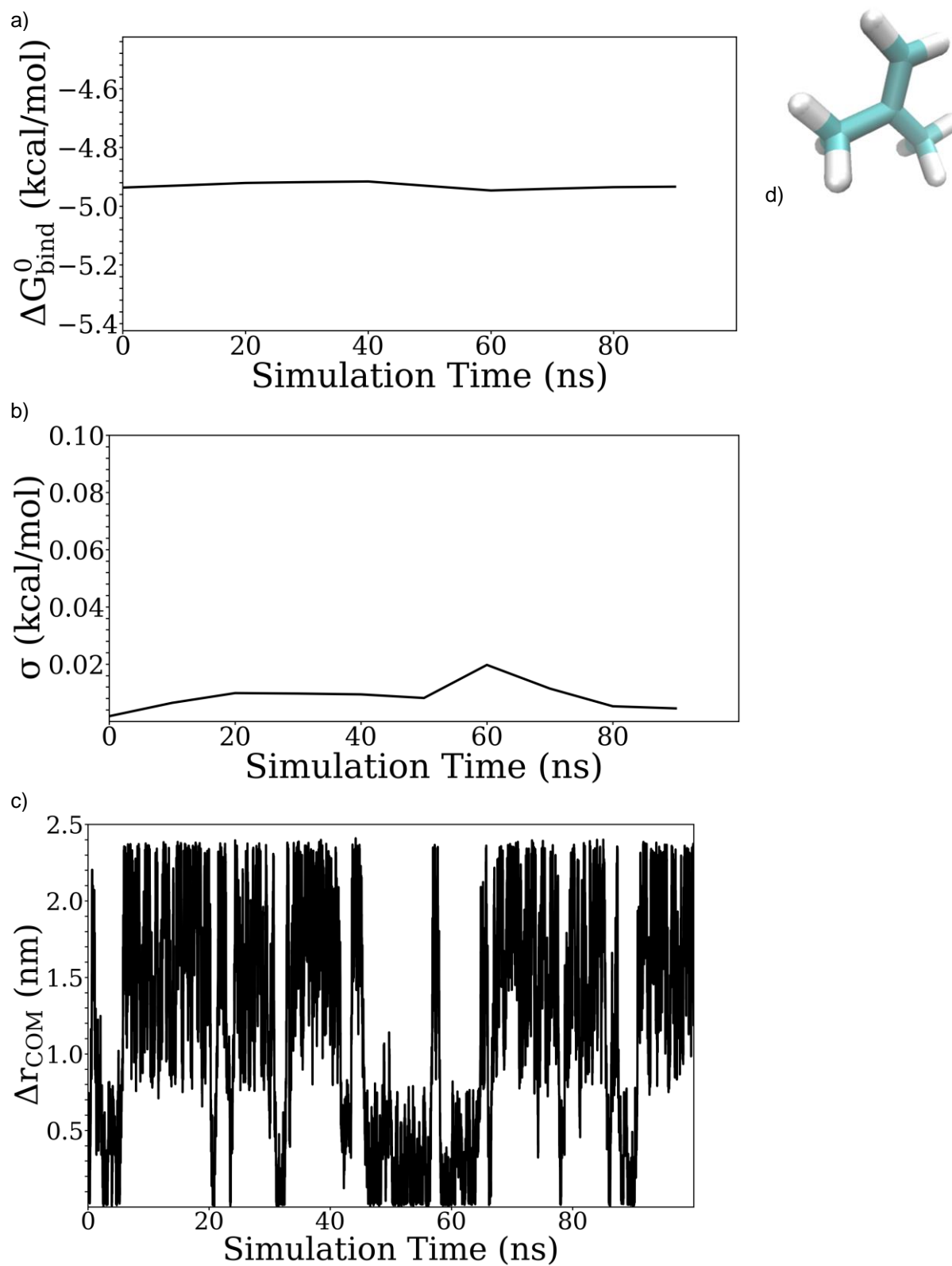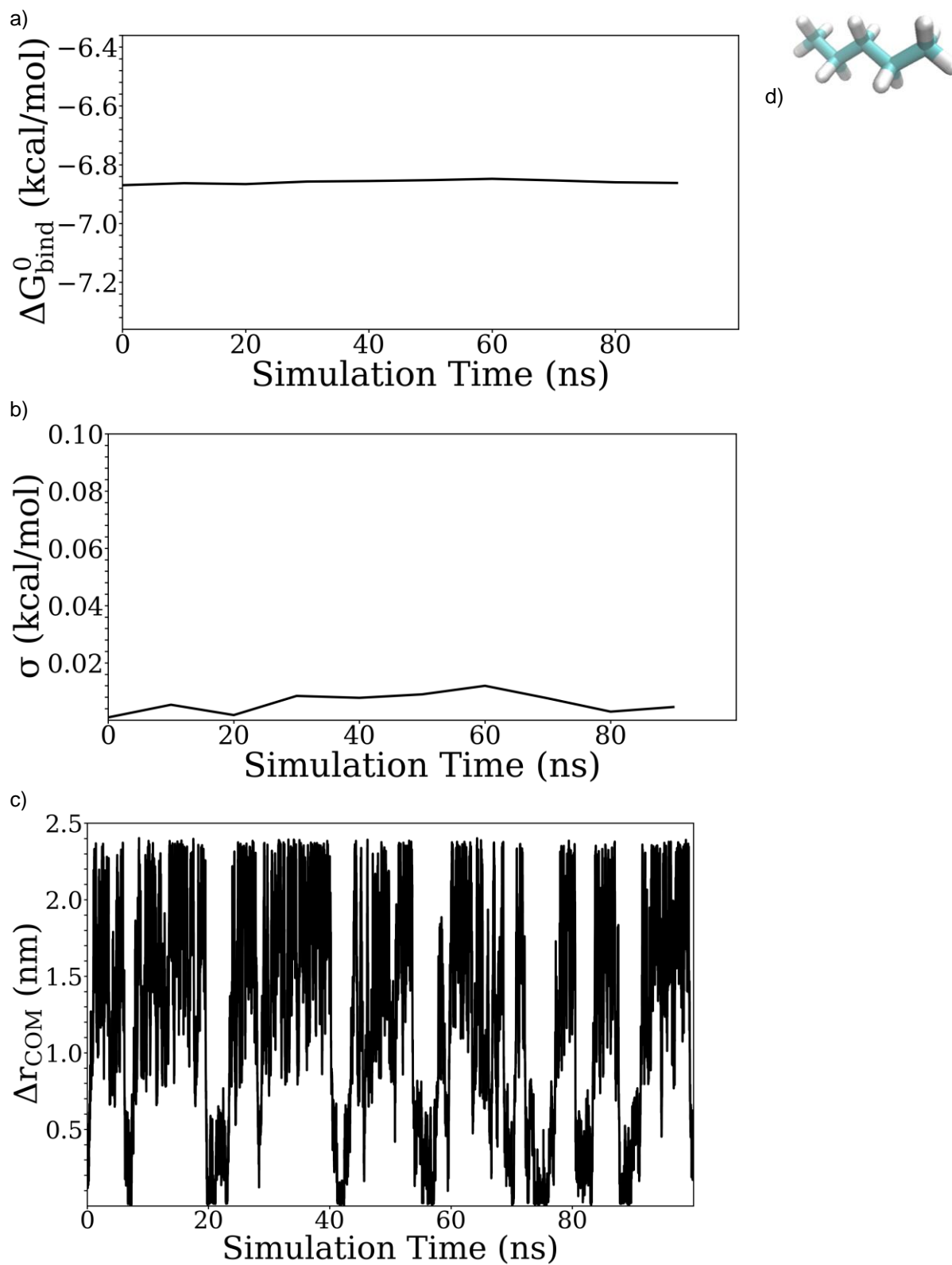
Figure S13. Convergence data for guest 13. Plots include a) $\Delta G_{bind}^0(t)$ over the last 100 ns of simulation, b) $\sigma(t)$ over the last 100 ns of simulation, and c) $\Delta r_{CM}(t)$ over the last 100 ns of simulation. Also included is an image of the guest (d).

Figure S14. Convergence data for guest 14. Plots include a) $\Delta G^0_{bind}(t)$ over the last 100 ns of simulation, b) $\sigma(t)$ over the last 100 ns of simulation, and c) $\Delta r_{CM}(t)$ over the last 100 ns of simulation. Also included is an image of the guest (d).
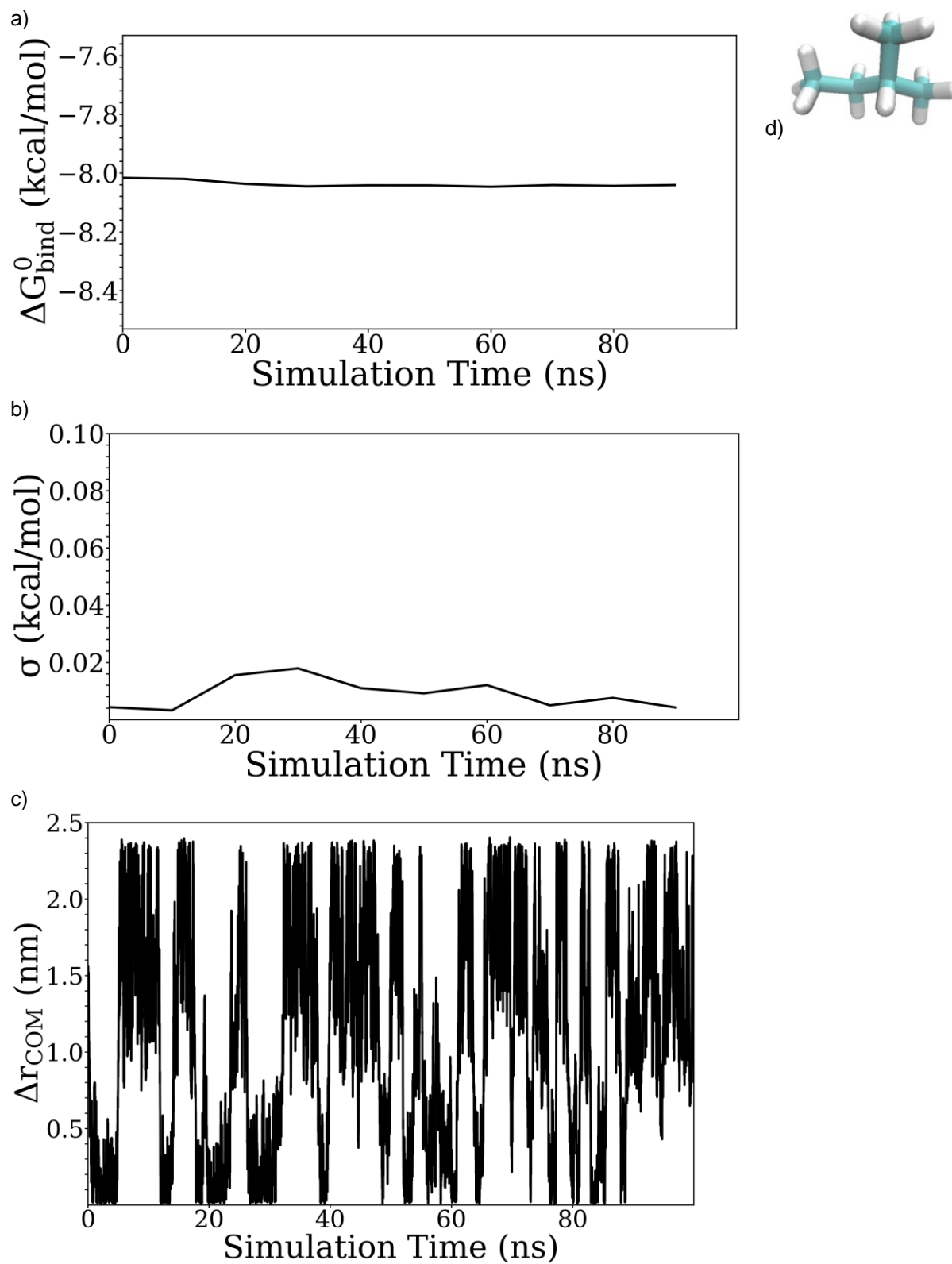
Figure S15. Convergence data for guest 15. Plots include a) $\Delta G^0_{bind}(t)$ over the last 100 ns of simulation, b) $\sigma(t)$ over the last 100 ns of simulation, and c) $\Delta r_{CM}(t)$ over the last 100 ns of simulation. Also included is an image of the guest (d).
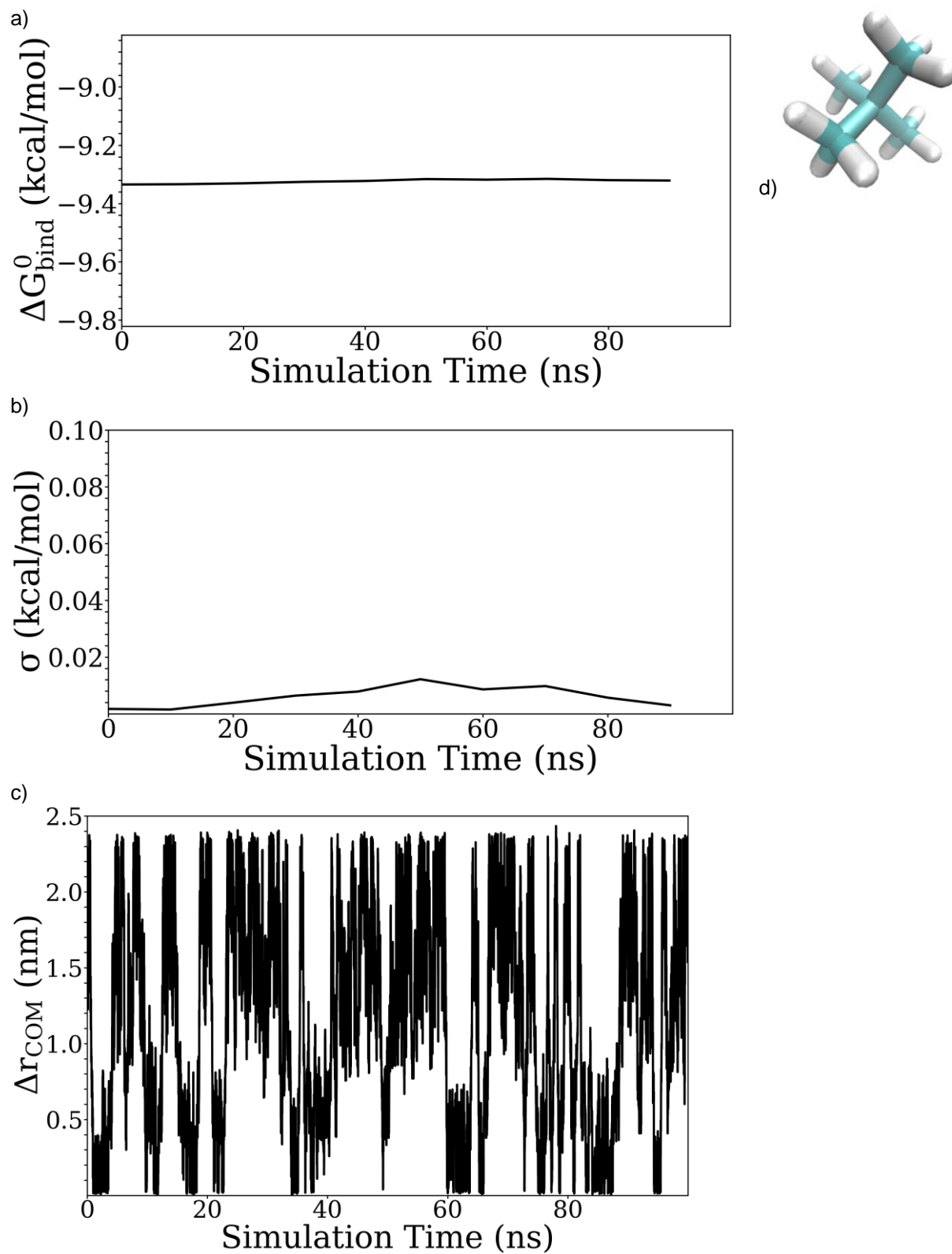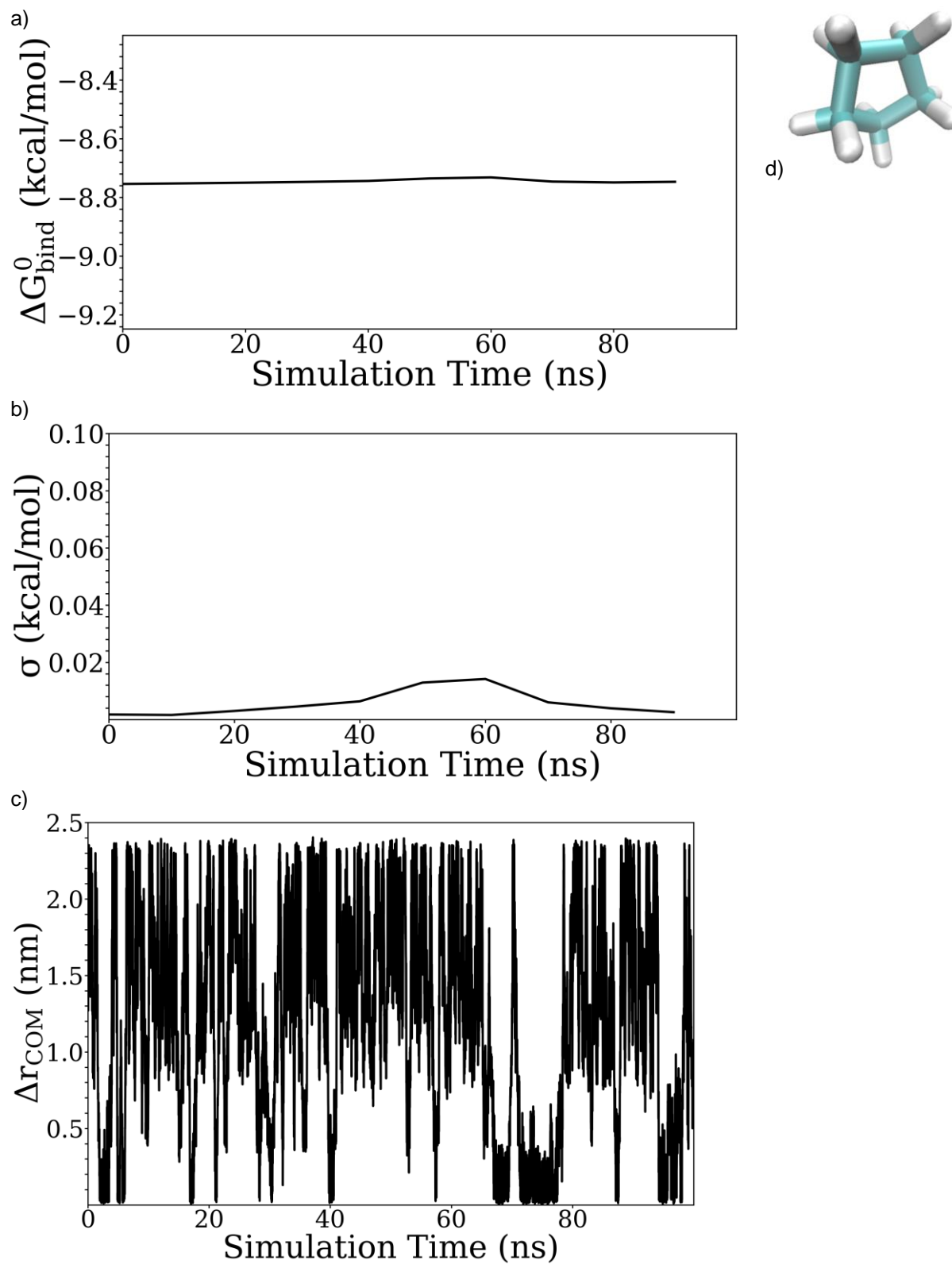
Figure S16. Convergence data for guest 16. Plots include a) $\Delta G^0_{bind}(t)$ over the last 100 ns of simulation, b) $\sigma(t)$ over the last 100 ns of simulation, and c) $\Delta r_{CM}(t)$ over the last 100 ns of simulation. Also included is an image of the guest (d).

Figure S17. Convergence data for guest 17. Plots include a) $\Delta G^0_{bind}(t)$ over the last 100 ns of simulation (multiple runs), b) $\sigma(t)$ over the last 100 ns of simulation, and c) $\Delta r_{CM}(t)$ over the last 100 ns of simulation. Also included is an image of the guest (d).
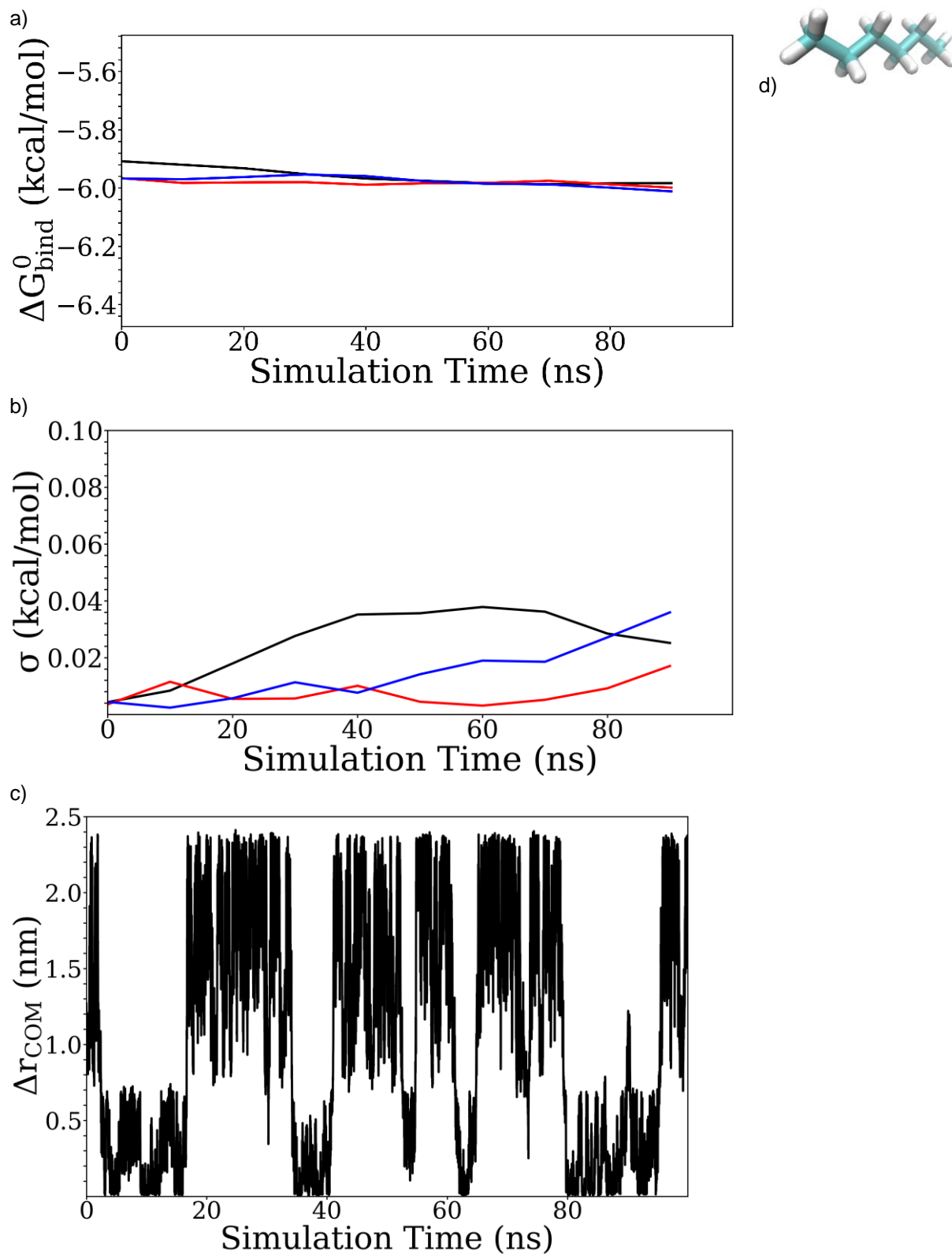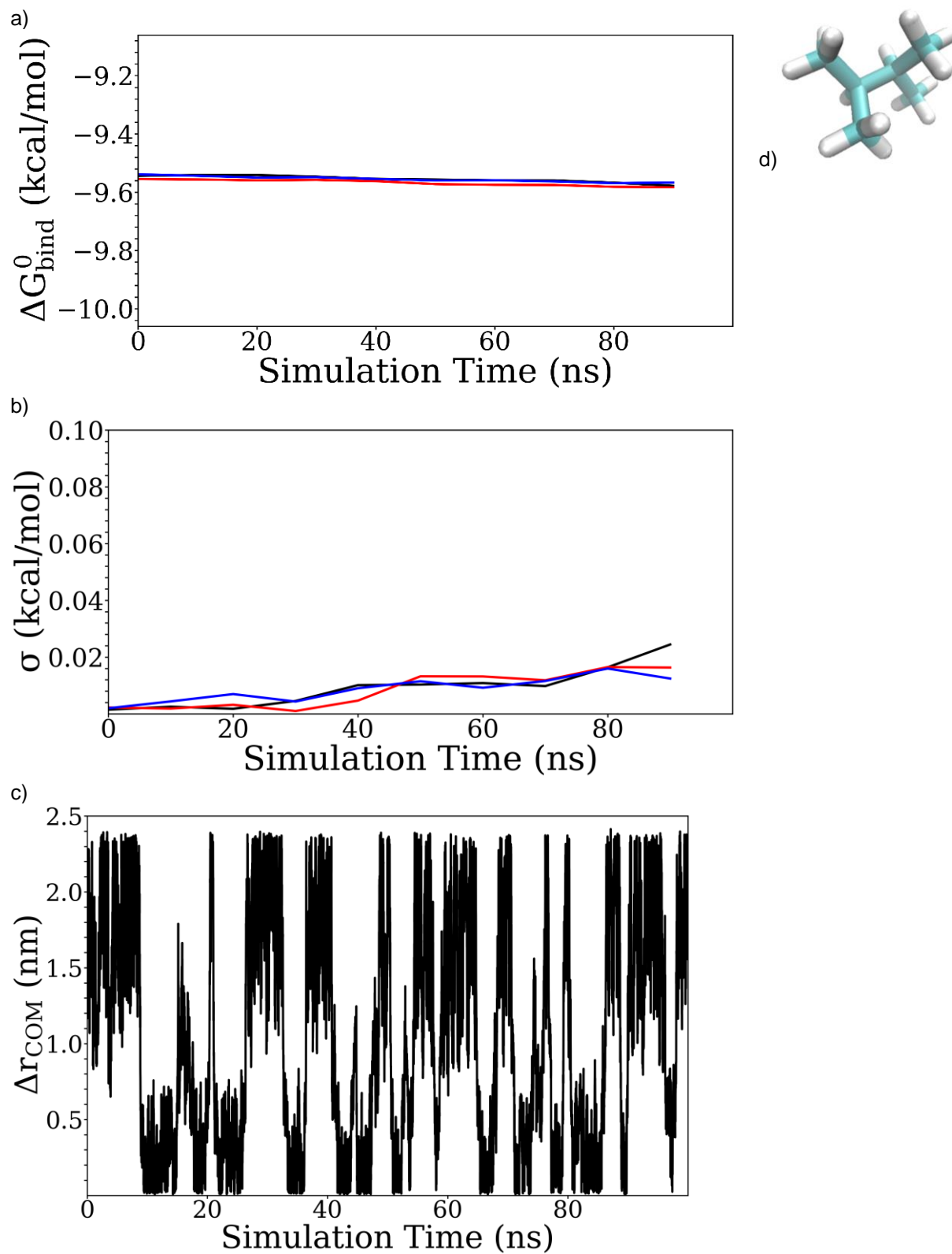
Figure S18. Convergence data for guest 18. Plots include a) $\Delta G^0_{bind}(t)$ over the last 100 ns of simulation (multiple runs), b) $\sigma(t)$ over the last 100 ns of simulation, and c) $\Delta r_{CM}(t)$ over the last 100 ns of simulation. Also included is an image of the guest (d).

Figure S19. Convergence data for guest 19. Plots include a) $\Delta G^0_{bind}(t)$ over the last 100 ns of simulation, b) $\sigma(t)$ over the last 100 ns of simulation, and c) $\Delta r_{CM}(t)$ over the last 100 ns of simulation. Also included is an image of the guest (d).
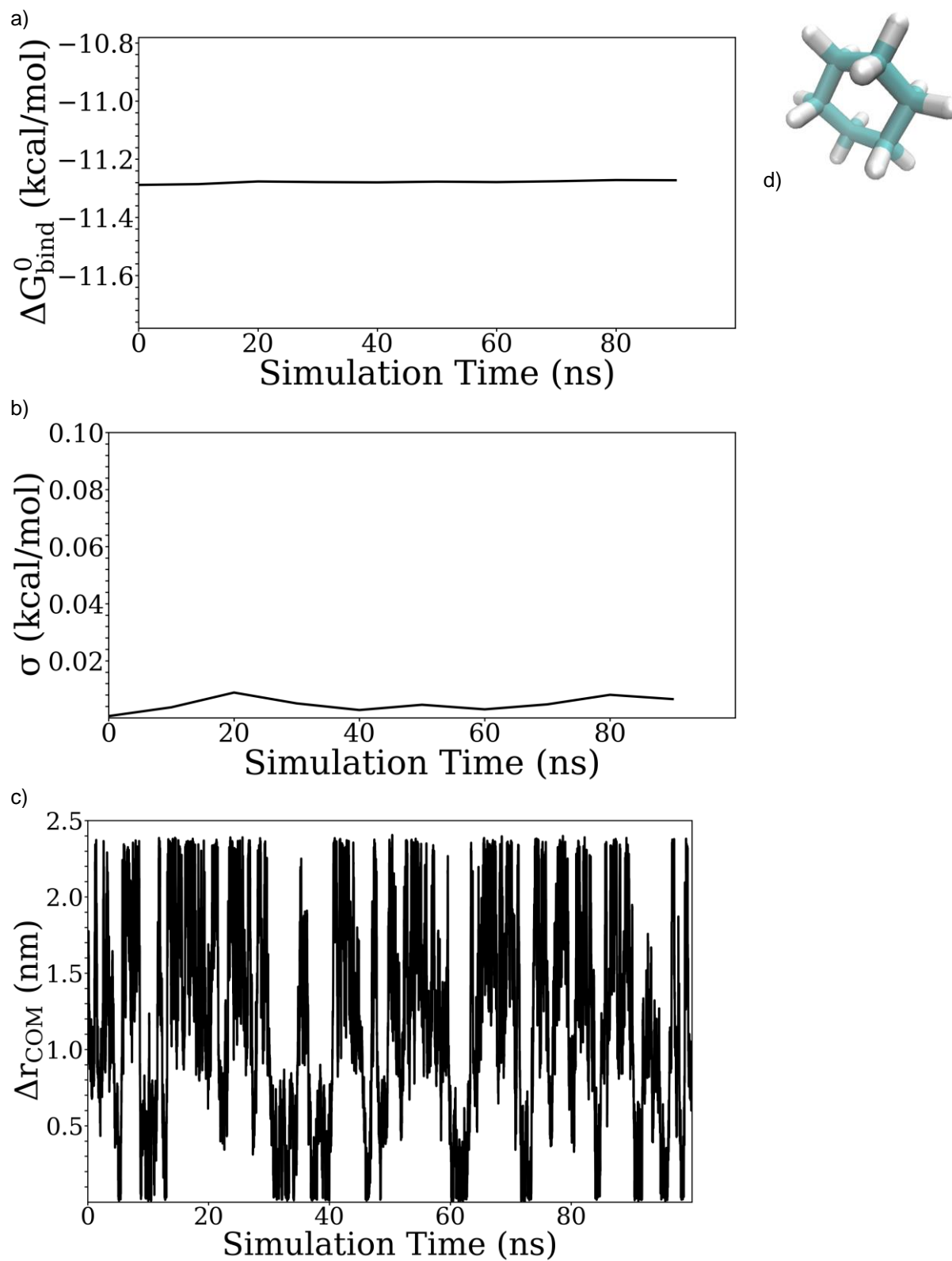
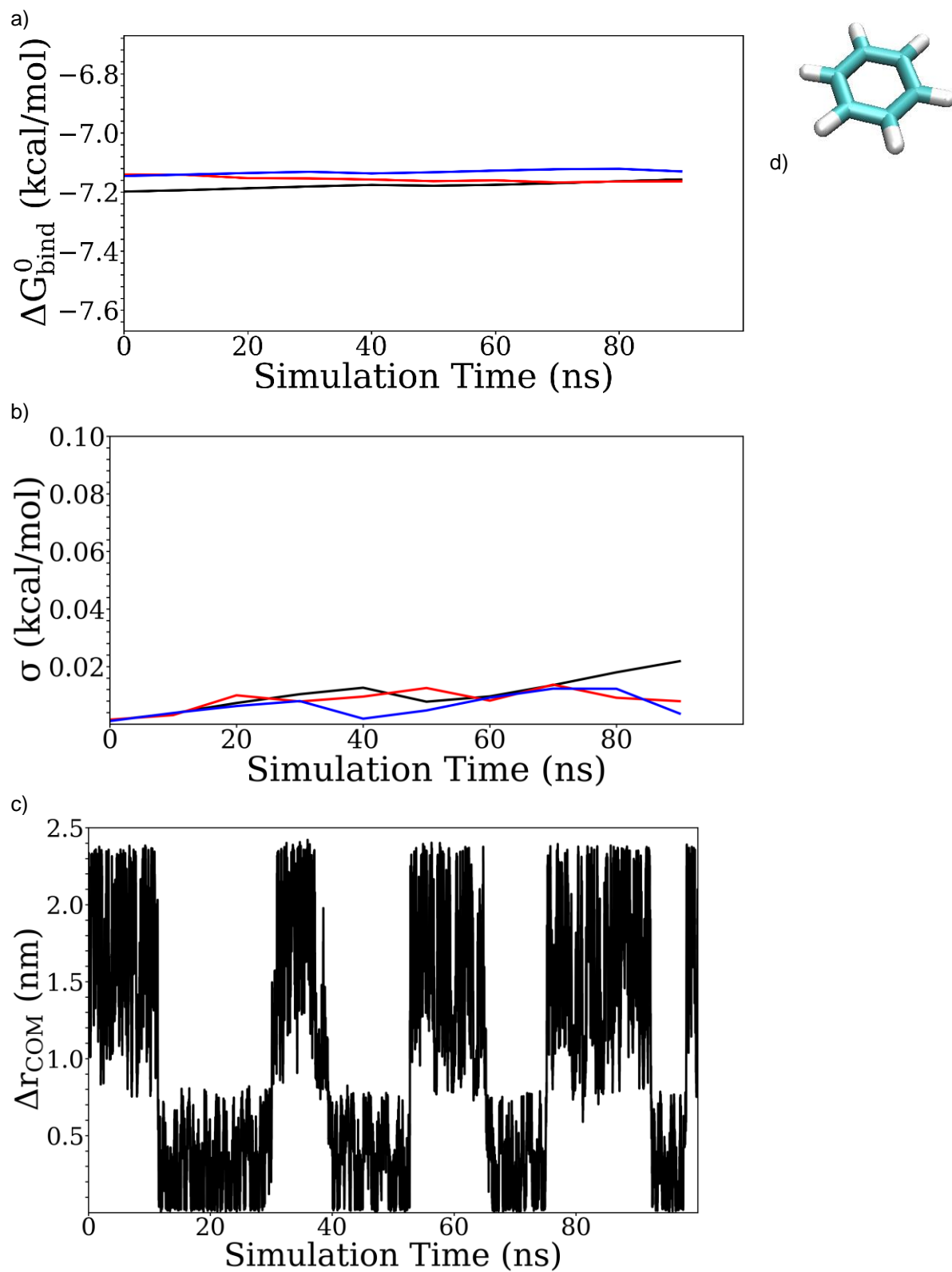Figure S20. Convergence data for guest 20. Plots include a) $\Delta G^0_{bind}(t)$ over the last 100 ns of simulation (multiple runs), b) $\sigma(t)$ over the last 100 ns of simulation, and c) $\Delta r_{CM}(t)$ over the last 100 ns of simulation. Also included is an image of the guest (d).
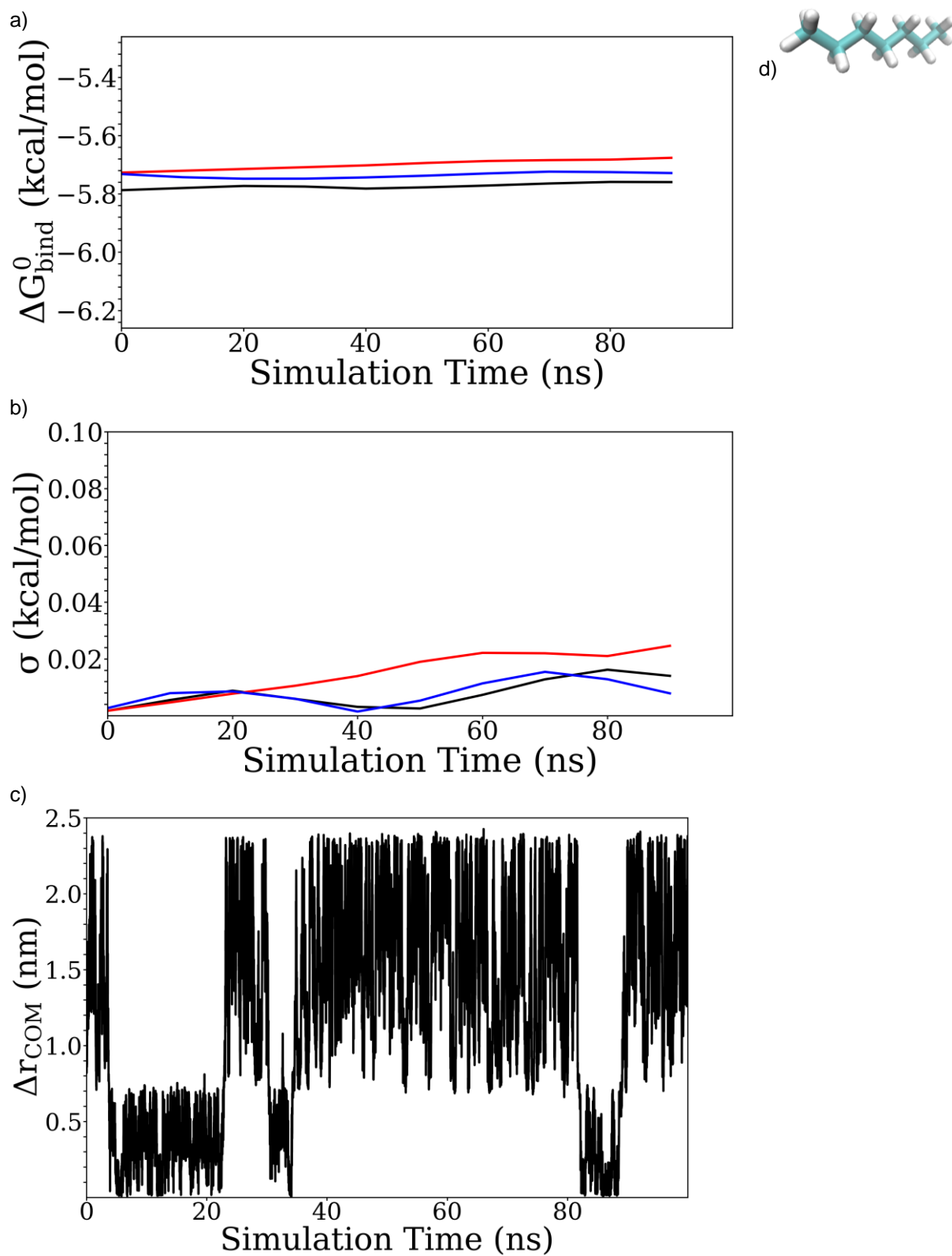
Figure S21. Convergence data for guest 21. Plots include a) $\Delta G^0_{bind}(t)$ over the last 100 ns of simulation (multiple runs), b) $\sigma(t)$ over the last 100 ns of simulation, and c) $\Delta r_{CM}(t)$ over the last 100 ns of simulation. Also included is an image of the guest (d).

Figure S22. Convergence data for guest 22. Plots include a) $\Delta G^0_{bind}(t)$ over the last 100 ns of simulation, b) $\sigma(t)$ over the last 100 ns of simulation, and c) $\Delta r_{CM}(t)$ over the last 100 ns of simulation. Also included is an image of the guest (d).
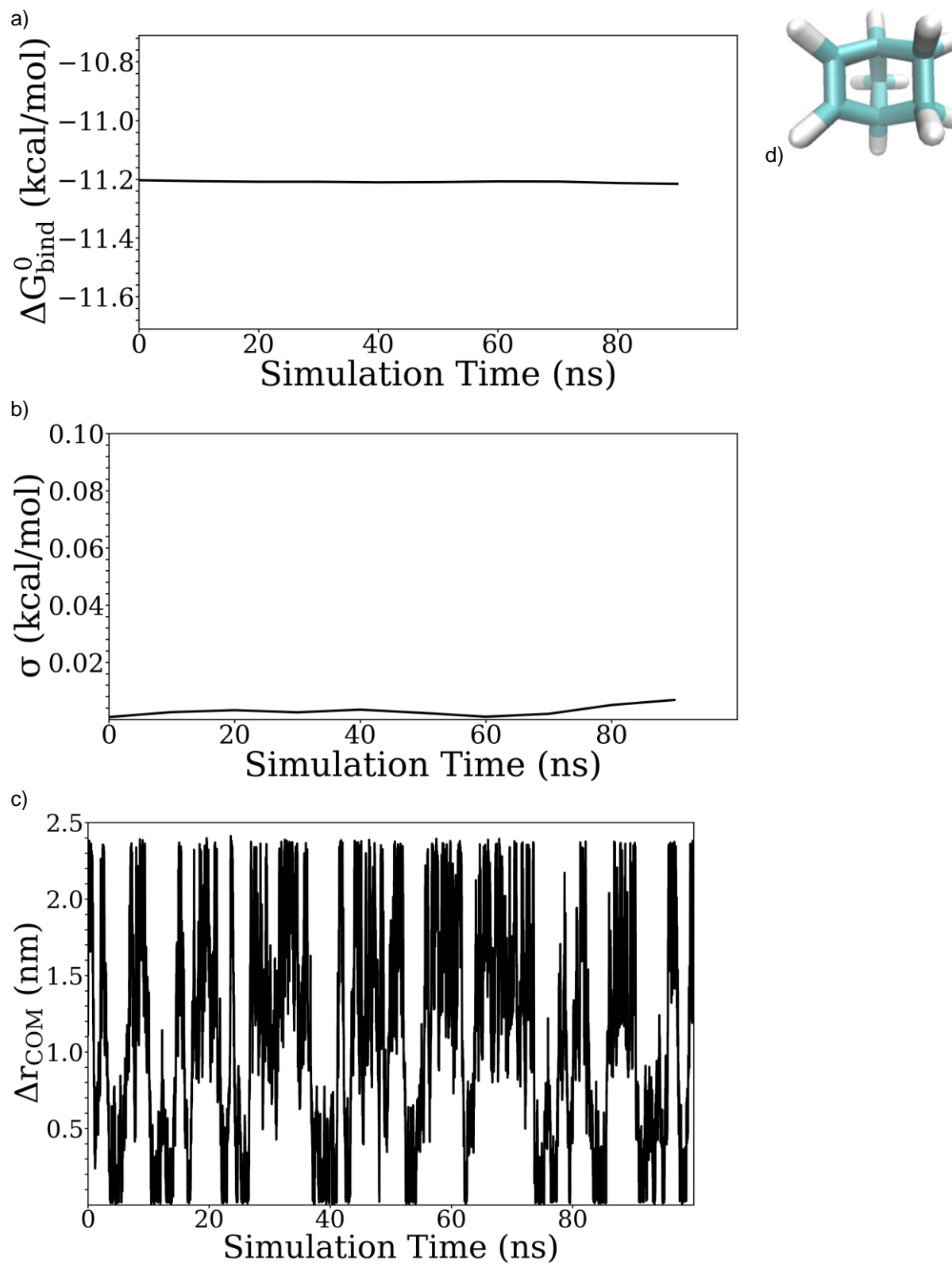
Figure S23. Convergence data for guest 23. Plots include a) $\Delta G_{bind}^0(t)$ over the last 100 ns of simulation, b) $\sigma(t)$ over the last 100 ns of simulation, and c) $\Delta r_{CM}(t)$ over the last 100 ns of simulation. Also included is an image of the guest (d).
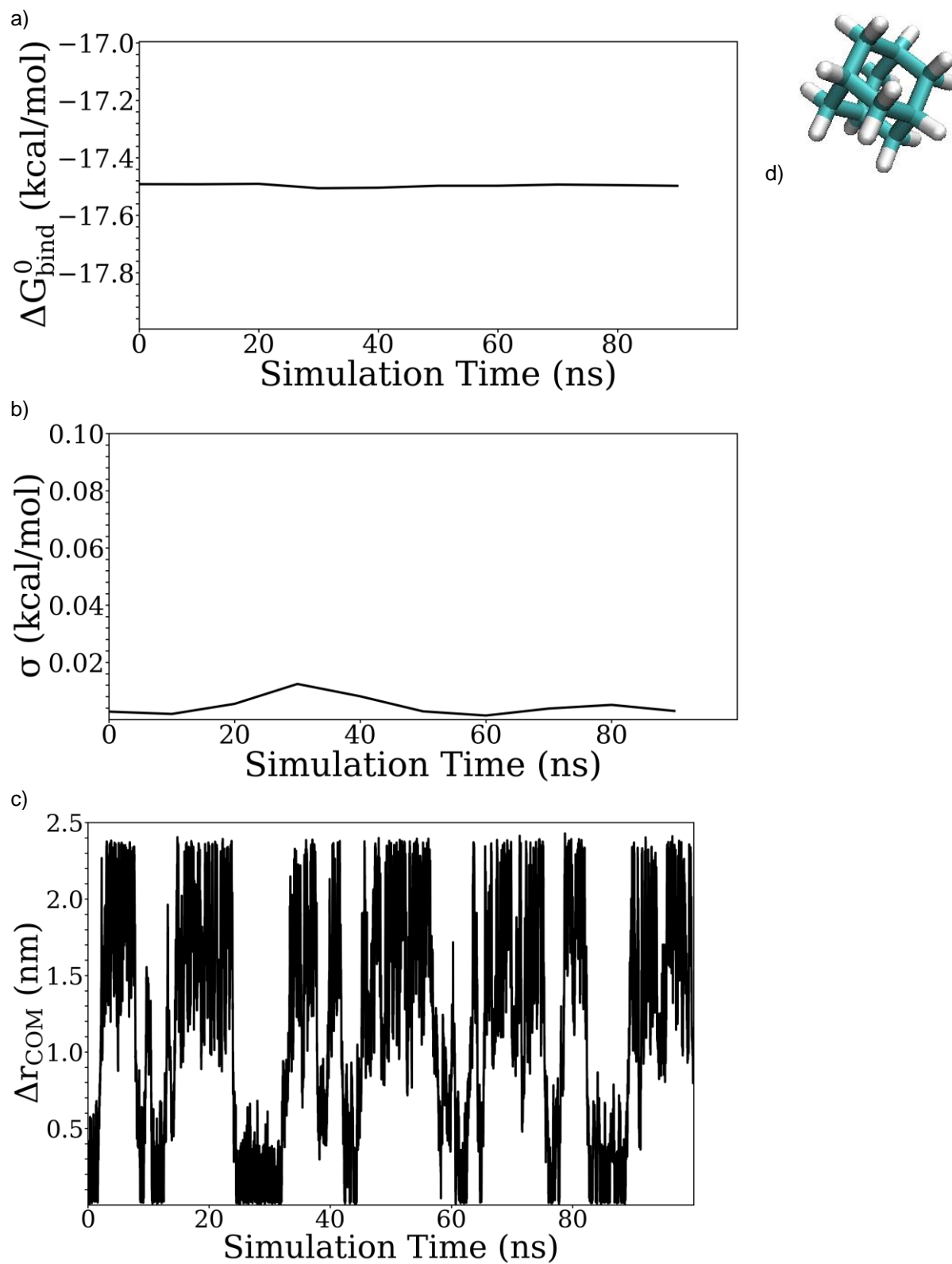
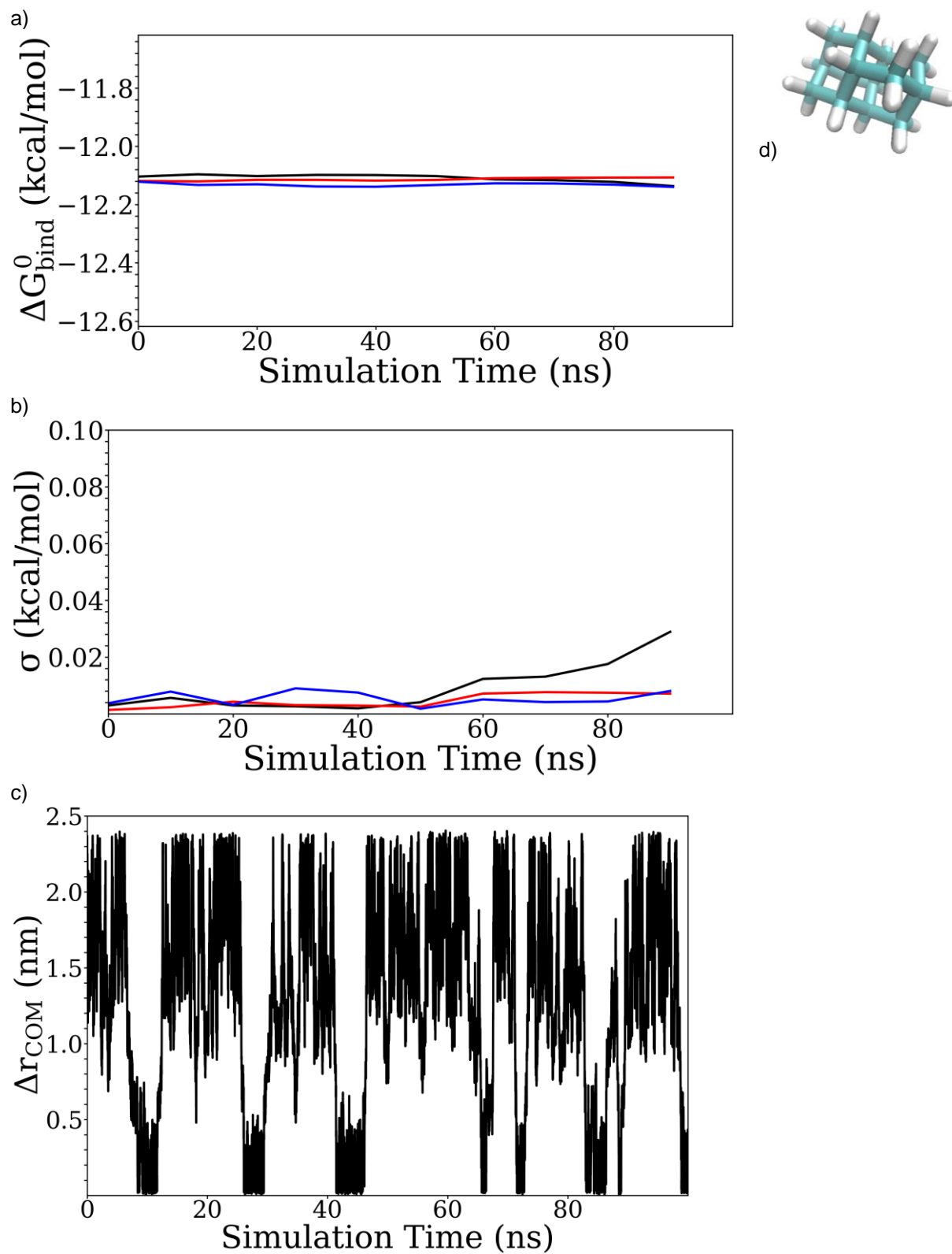Figure S24. Convergence data for guest 24. Plots include a) $\Delta G^0_{bind}(t)$ over the last 100 ns of simulation (multiple runs), b) $\sigma(t)$ over the last 100 ns of simulation, and c) $\Delta r_{CM}(t)$ over the last 100 ns of simulation. Also included is an image of the guest (d).
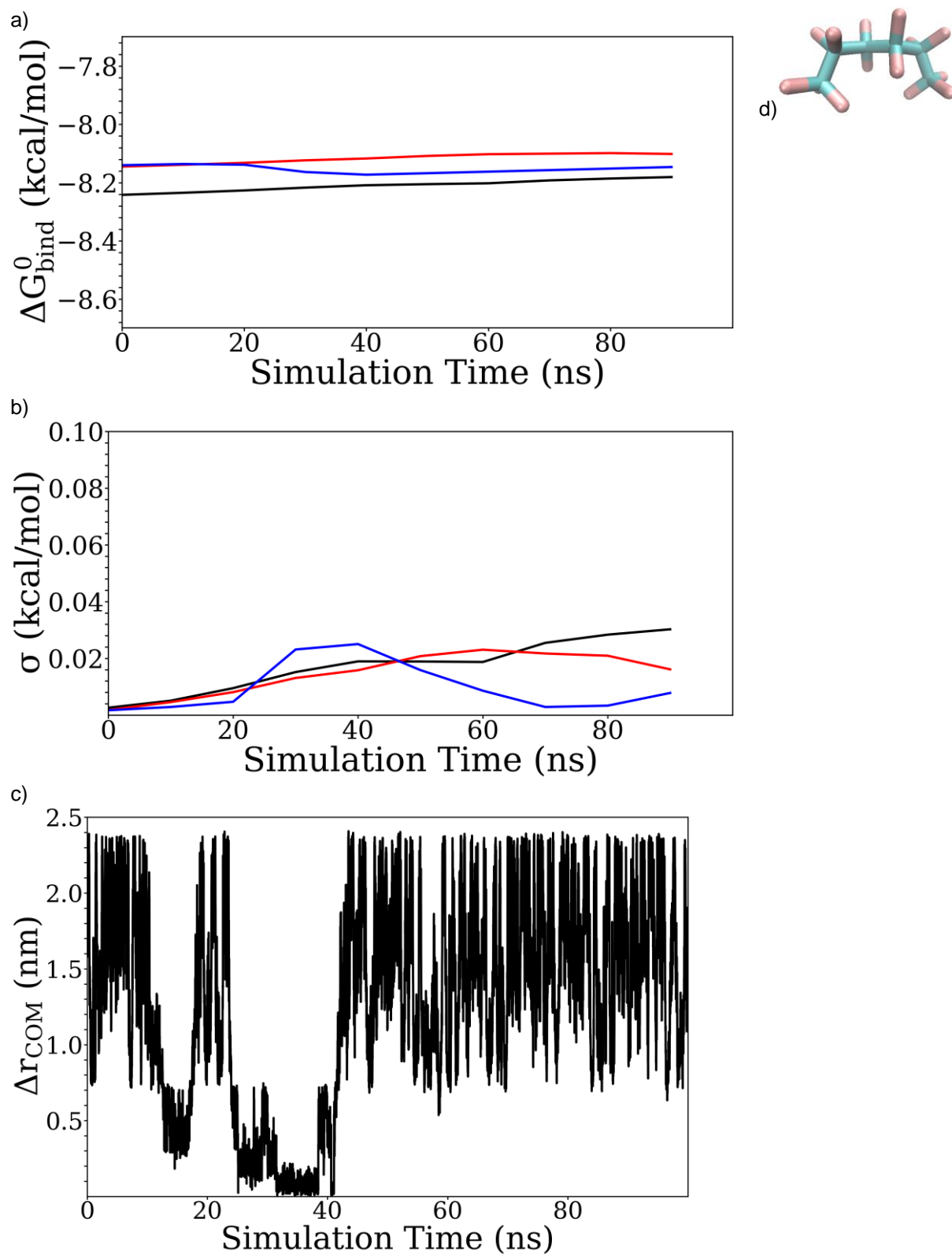
Figure S25. Convergence data for guest 25. Plots include a) $\Delta G_{bind}^0(t)$ over the last 100 ns of simulation (multiple runs), b) $\sigma(t)$ over the last 100 ns of simulation, and c) $\Delta r_{CM}(t)$ over the last 100 ns of simulation. Also included is an image of the guest (d).

Figure S26. Convergence data for guest 26. Plots include a) $\Delta G_{bind}^0(t)$ over the last 100 ns of simulation, b) $\sigma(t)$ over the last 100 ns of simulation, and c) $\Delta r_{CM}(t)$ over the last 100 ns of simulation. Also 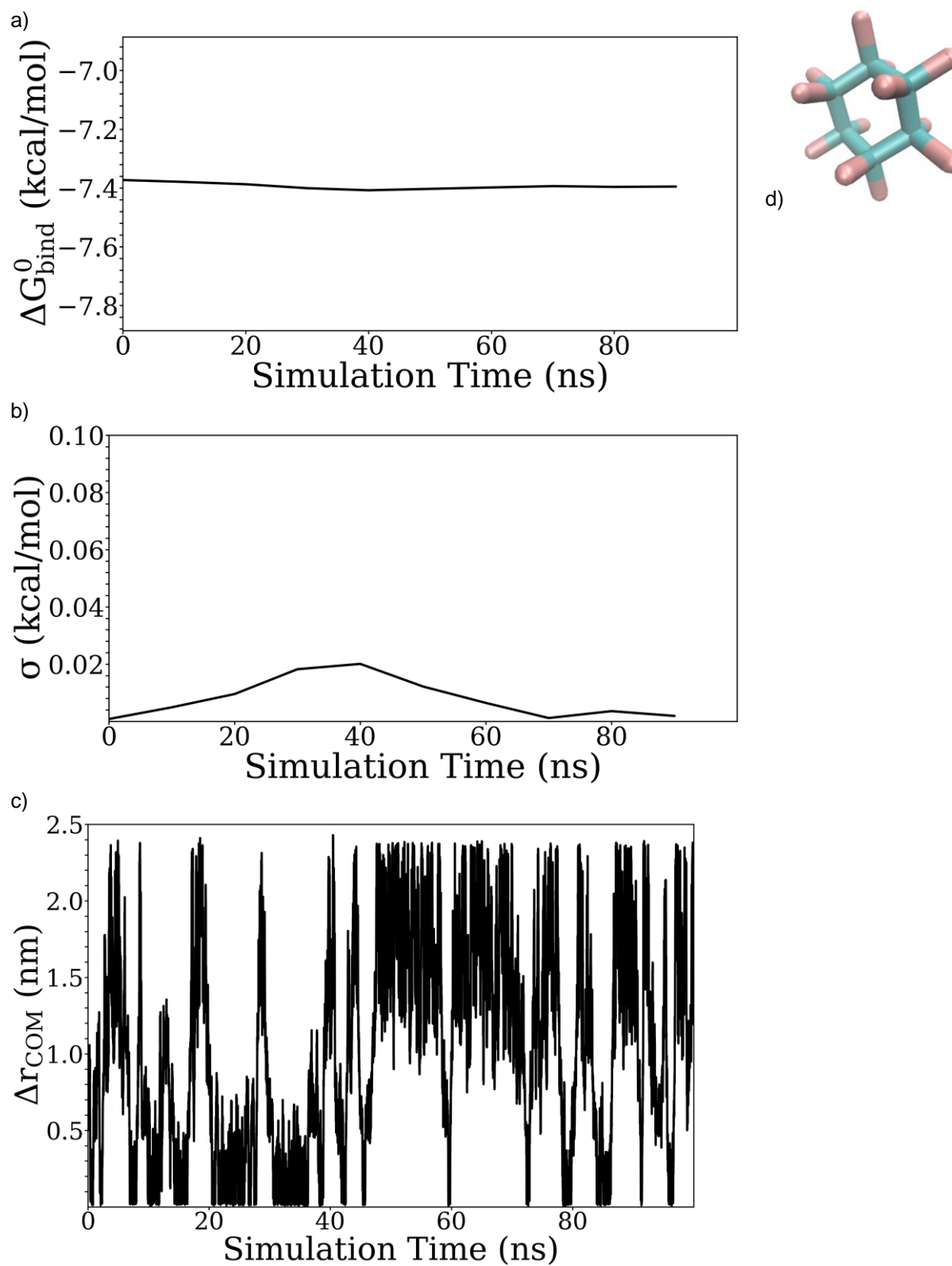included is an image of the guest (d).