**Supplementary Information**

**Molecular Dynamics Studies on Conformational Thermodynamics of Orai1-Calmodulin Complex**

Lakshmi Maganti, a, $ \* Mahua Ghosh, a\* and J. Chakrabarti a, b \*

a Department of Chemical, Biological and Macromolecular Sciences, S. N. Bose National Centre for Basic Sciences, Sector III, Block JD, Salt Lake, Kolkata 700106, INDIA.

b Unit of Nanoscience and Technology-II and The Thematic Unit of Excellence on Computational Materials Science, S. N. Bose National Centre for Basic Sciences, Sector III, Block JD, Salt Lake, Kolkata 700106, INDIA.

$ Present address: Computational Science Division, Saha Institute of Nuclear Physics

1/AF, Bidhannagar, Kolkata – 700035, INDIA.

**\***corresponding authors

E-mail: lakshmimaganti6@gmail.com, jaydeb@bose.res.in, mahua.ghosh@gmail.com

Table S1. List of interface residues of holoCaM bound to Orai1-CMBD in different domains.

|  |  |  |
| --- | --- | --- |
| **Name** | **Interface Residues/CaM** | **Interface Residues/Orai1-CMBD** |
| holoCaMC/Orai1-CMBD  Crystal structure | E84, I85, A88, V91, F92, I100, L105, M109, L112, E 114, L 116, T 117, E 119, E 120,V 121, E 123, M 124, I 125, E 127, A 128, V 136, F 141, M 144, M 145 | L74,W76,L79,Y80 |
| holoCaMC/Orai1-CMBD  Simulated structure | E84, E85,A 88, V 91, F 92, I 100, L 105, M 109, L 112, E 114, L 116, E 119, E 120, V 121, E 123, M 124, I 125, R 126, E 127, A 128, V 136, F 141, M 144, M 145,T 146 | Q72,L74,W76,R77, L79,Y80, |
| holoCaMN/Orai1-CMBD | A10, E11, F12, E14, A15, F16, S17, L18, F19, L32,V35, M 36, L39, Q41, E47, M51, I52, F68, L69, M71 | L74, T76, L79, R83 |
| holoCaMCN/Orai1-CMBD/N- terminal | E11, F12, E14, A15, F16, L18, F19, L32, M36, Q41, P43,T44 M51, I52,V55, I63, E67, F 68, L69, M71, M72, A73. | L74,W76,L79,Y80, |
| holoCaMCN/Orai1-CMBD/C- terminal | S 81, E 84, I 85, E 87, A 88, F 89, V 91, F 92, I 100, L 105, V 108, L 112, E 114, K 115,T 117, E 120, V 121, E 123, M 124, I 125, E 127, A 128, V 136, F 141, M 144, M145,T 146 | L74, W76, L79, Y80, L81, A84 |

Table S2. Conformational thermodynamic changes (kJ mol-1) of interface residues in holoCAMC/Orai1-CMBD complex with respect to holoCaM.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Residue |  |  |  |  |  |  |
| E 84 | -0.50 | -0.73 | -0.07 | -3.19 | -1.23 | -3.26 |
| I 85 | -0.48 | 0.15 | 0.64 | -3.01 | -0.34 | -2.37 |
| A 88 | -0.20 | 0.00 | -0.45 | 0.00 | -0.20 | -0.45 |
| V91 | -0.68 | 0.06 | -0.82 | 0.20 | -0.62 | -0.61 |
| F 92 | 0.68 | -0.50 | 0.95 | -1.22 | 0.17 | -0.27 |
| I 100 | 0.08 | -1.23 | 0.20 | -5.82 | -1.16 | -5.62 |
| L 105 | -0.81 | -0.34 | 0.06 | -3.13 | -1.15 | -3.07 |
| M 109 | -0.40 | -0.06 | -0.54 | -2.33 | -0.46 | -2.87 |
| L 112 | -0.49 | -0.60 | -0.02 | -0.92 | -1.09 | -0.93 |
| E 114 | -0.46 | 1.81 | -3.21 | 0.49 | 1.35 | -2.71 |
| E 116 | -0.08 | -0.48 | -1.30 | -2.61 | -0.56 | -3.91 |
| T 117 | -0.18 | 0.12 | 0.21 | 0.50 | -0.06 | 0.29 |
| E 119 | -0.08 | -0.57 | -0.16 | -3.29 | -0.65 | -3.45 |
| E 120 | 0.61 | -1.46 | 0.87 | -6.14 | -0.85 | -5.27 |
| V121 | -0.76 | -0.80 | -0.74 | -3.59 | -1.56 | -4.33 |
| E 123 | 0.40 | -1.02 | 0.06 | -7.65 | -0.62 | -7.59 |
| M 124 | -0.38 | -0.76 | -1.10 | -5.85 | -1.14 | -6.95 |
| I125 | -0.78 | -0.03 | -0.70 | 0.41 | -0.81 | -0.29 |
| E 127 | -0.05 | -0.48 | 0.22 | -4.31 | -0.53 | -4.09 |
| A 128 | 1.02 | 0.00 | 0.98 | 0.00 | 1.02 | 0.98 |
| V 136 | -0.70 | -0.41 | 0.57 | -5.37 | -1.11 | -4.80 |
| F 141 | -0.15 | -0.20 | -1.05 | -4.04 | -0.35 | -5.09 |
| M 144 | -0.81 | -0.20 | -0.49 | -0.80 | -1.01 | -1.29 |
| M 145 | -0.45 | -0.14 | -0.05 | -0.12 | -0.59 | -0.17 |

Table S3. Conformational thermodynamic changes (kJ mol-1) of interface residues in holoCAMN/Orai1-CMBD complex with respect to holoCaM.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Residue |  |  |  |  |  |  |
| A 10 | 0.17 | 0.00 | 0.44 | 0.00 | 0.17 | 0.44 |
| E 11 | -1.80 | 0.47 | -8.06 | 1.36 | -1.33 | -7.06 |
| F 12 | -0.05 | 0.42 | -0.10 | 1.12 | 0.37 | 1.02 |
| E 14 | 0.53 | 0.85 | 0.34 | 5.15 | 1.39 | 5.49 |
| A 15 | 0.08 | 0.00 | 0.03 | 0.00 | 0.08 | 0.03 |
| F 16 | -0.14 | 0.35 | -0.19 | 3.79 | 0.21 | 3.60 |
| S 17 | 1.20 | -0.01 | -2.03 | 0.55 | 1.10 | -1.48 |
| L 18 | 0.48 | -0.76 | 0.68 | 0.05 | -0.29 | 0.73 |
| F 19 | -1.98 | 0.22 | -2.03 | 0.55 | 1.76 | 1.48 |
| V 35 | 0.11 | -0.08 | 0.07 | 0.09 | 0.03 | 0.17 |
| M 36 | 0.37 | 0.58 | 0.63 | 5.44 | 0.95 | 6.08 |
| L 39 | -0.07 | -0.23 | -0.13 | 1.27 | -0.30 | 1.14 |
| Q 41 | -0.94 | 0.42 | -2.46 | 1.11 | -0.52 | -1.35 |
| E 47 | -0.49 | 0.15 | -0.62 | 2.04 | -0.34 | 1.41 |
| M 51 | 0.25 | 1.00 | 0.03 | 7.38 | 1.25 | 7.41 |
| F 68 | -0.04 | 0.96 | 0.24 | 9.07 | 0.92 | 9.31 |
| L 69 | -0.51 | 0.35 | -2.18 | 0.44 | -0.16 | -1.74 |
| M 71 | 0.39 | 0.95 | 0.15 | 2.05 | 1.34 | 2.20 |

Table S4. Conformational thermodynamic changes (kJ mol-1) of destabilized and disordered N-terminal residues in holoCaMCN/Orai1-CMBD complex.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Residue |  |  |  |  |  |  |
| T 5 | -0.17 | 0.00 | -2.65 | -1.57 | -0.17 | -4.22 |
| E 7 | 0.19 | 0.04 | 0.32 | 0.22 | 0.23 | 0.56 |
| I 9 | -0.25 | -0.81 | -0.90 | -1.25 | -1.06 | -2.15 |
| A 10 | -1.03 | 0.00 | -0.91 | 0.00 | -1.03 | -0.91 |
| A 15 | -0.92 | 0.00 | -0.79 | 0.00 | -0.92 | -0.79 |
| I 27 | -0.40 | -0.50 | -0.32 | -0.54 | -0.90 | -0.86 |
| K 30 | -0.31 | -0.24 | -0.11 | -0.12 | -0.55 | -0.23 |
| L32 | -1.72 | 0.50 | -3.76 | -0.10 | -1.22 | -3.86 |
| T 34 | 0.34 | 0.44 | -0.13 | 4.28 | 0.78 | 4.15 |
| V 35 | -2.52 | 2.00 | -3.95 | 0.45 | -0.52 | -3.50 |
| R 37 | 0.39 | 0.17 | -1.35 | 3.86 | 0.56 | 2.51 |
| T44 | -0.68 | 0.98 | 0.20 | -0.07 | 0.30 | 0.13 |
| Q 49 | 0.47 | 0.14 | -0.05 | 2.53 | 0.61 | 2.48 |
| M51 | -1.10 | 0.01 | -7.32 | -0.20 | -1.09 | -7.52 |
| N 53 | -0.13 | -0.35 | 0.08 | 1.17 | -0.47 | 1.25 |
| V 55 | -0.12 | -0.59 | -0.46 | -0.56 | -0.71 | -1.02 |
| D 56 | -0.83 | -0.53 | 0.70 | -0.14 | -1.36 | 0.56 |
| D 58 | 0.03 | 0.32 | -0.21 | 0.46 | 0.35 | -0.25 |
| D 64 | 0.26 | 0.01 | 0.18 | -0.40 | 0.27 | -0.22 |
| F 65 | -0.73 | -0.02 | -1.68 | -0.75 | -0.75 | -2.43 |
| E 67 | -0.70 | 1.49 | -0.27 | -3.44 | 0.79 | -3.71 |

Table S5. Conformational thermodynamic changes (kJ mol-1) of destabilized and disordered N-terminal residues in holoCaMN/Orai1-CMBD complex.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Residue |  |  |  |  |  |  |
| T 5 | -2.75 | 0.34 | -2.06 | 2.38 | -2.41 | 0.32 |
| E 7 | 0.09 | 0.05 | -0.07 | 2.11 | 0.14 | 2.04 |
| I 9 | -0.32 | 0.83 | -1.00 | 2.97 | 0.51 | 1.97 |
| A 10 | 0.17 | 0.00 | 0.44 | 0.00 | 0.17 | 0.44 |
| A 15 | 0.60 | 0.00 | 0.30 | 0.00 | 0.60 | 0.30 |
| I 27 | -0.23 | 1.90 | -0.23 | 0.73 | 1.67 | 0.50 |
| K 30 | -0.68 | -0.96 | 0.52 | 5.58 | -1.64 | 6.10 |
| L32 | -0.05 | 0.89 | 1.06 | 2.20 | 0.84 | 3.26 |
| T 34 | 0.02 | 0.82 | -0.09 | 4.24 | 0.84 | 4.15 |
| V 35 | 0.29 | 0.70 | 0.32 | 0.37 | 0.99 | 0.69 |
| R 37 | -0.51 | 0.39 | 2.60 | 1.24 | -0.12 | 3.84 |
| T44 | 1.86 | 0.26 | 2.60 | 1.23 | 2.12 | 3.83 |
| Q 49 | 0.11 | 0.12 | 0.21 | 1.27 | 0.24 | 1.58 |
| M51 | 0.15 | 1.65 | 0.03 | 7.38 | 1.80 | 7.41 |
| N 53 | 0.18 | 0.21 | 0.60 | 1.90 | 0.39 | 2.50 |
| V 55 | -0.67 | 0.59 | -0.62 | 3.08 | -0.07 | 2.46 |
| D 56 | -0.30 | 0.51 | -0.30 | 0.65 | 0.21 | 0.35 |
| D 58 | 0.76 | 1.18 | -0.14 | 7.87 | 1.94 | 7.73 |
| D 64 | -0.08 | 0.57 | -0.02 | 0.64 | 0.49 | 0.62 |
| F 65 | 0.32 | 0.61 | 0.32 | 4.43 | 0.93 | 4.75 |
| E 67 | 0.05 | 2.12 | 0.11 | 4.30 | 2.17 | 4.41 |

Table S6.List of disordered and destabilized residues in N-terminal domain of CaM in holoCaMC/Orai1-CMBD complex with respect to holoCaM with their conformational changes (kJ mol-1) (Red color: residues common in initial simulation and average of three independent simulations, bold: residues used for docking).

|  |  |  |
| --- | --- | --- |
| Residue |  |  |
| **I9** | 0.17 | 1.93 |
| **A10** | 0.19 | 1.63 |
| E14 | 0.64 | 2.31 |
| **A15** | 0.17 | 0.37 |
| F16 | 0.30 | 1.66 |
| S17 | 0.12 | 0.41 |
| **I27** | 0.15 | 2.37 |
| K30 | 1.34 | 4.95 |
| **L32** | 0.67 | 2.35 |
| T34 | 0.40 | 1.28 |
| **V35** | 0.47 | 1.62 |
| R37 | 1.11 | 9.76 |
| N42 | 0.35 | 2.47 |
| Q49 | 0.64 | 1.45 |
| M51 | 0.29 | 1.31 |
| **V55** | 1.19 | 3.45 |
| D58 | 1.15 | 2.47 |
| D64 | 0.18 | 1.02 |
| **F65** | 1.16 | 6.33 |
| P66 | 0.10 | 0.63 |
| E67 | 1.26 | 5.83 |

Table S7. List of Destabilized and disordered residues along with their conformational thermodynamic changes (kJ mol-1) for N terminal domain of CaM in holoCaMC/Orai1-CMBD complex with respect to holoCaM using GROMACS data.

|  |  |  |
| --- | --- | --- |
| **Residue** |  |  |
| D 20 | 0.40 | 2.06 |
| D 22 | 0.09 | 0.7 |
| K30 | 0.23 | 1.52 |
| L32 | 0.70 | 0.38 |
| T34 | 0.34 | 1.66 |
| V 35 | 0.20 | 1.85 |
| S 38 | 0.20 | 0.08 |
| L 39 | 0.29 | 1.92 |
| G 40 | 0.27 | 2.47 |
| E 41 | 0.63 | 6.00 |
| P 43 | 0.90 | 4.77 |
| E 45 | 0.51 | 2.72 |
| N 53 | 0.46 | 1.24 |
| V 55 | 1.66 | 1.15 |
| D 56 | 1.30 | 3.97 |
| A 57 | 0.50 | 0.68 |
| G59 | 0.77 | 1.81 |
| N60 | 6.53 | 2.69 |
| I63 | 6.52 | 2.69 |
| F 65 | 0.28 | 2.78 |
| E 67 | 0.13 | 2.16 |

Table S8. Total conformational thermodynamic changes (kJmol-1) for complexes using GROMACS data.

|  |  |  |
| --- | --- | --- |
| **Name** |  |  |
| HoloCAMC/Orai1-CMBD | - 35.56 | - 76.13 |
| HoloCAMN/Orai1-CMBD | -5.46 | 60.30 |
| HoloCAMCN/Orai1-CMBD | -57.72 | -198.50 |

Figure S1.Destabilized and disordered residues in N-terminal domain of holoCaMC/Orai1-CMBD: (a) from single simulation run and (b) averaged over four independent simulations (pink, common residues).

