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

Supplementary Information

Naphthoquinone-dopamine hybrids disrupt α-synuclein fibrils by their intermolecular synergistic interactions with fibrils and displays a better effect on fibril disruption

Yun Zhou†, Yifei Yao†, Zhongyuan Yang, Yiming Tang and Guanghong Wei*

Department of Physics, State Key Laboratory of Surface Physics, Key Laboratory for Computational Physical Sciences (Ministry of Education), Fudan University, Shanghai 200438, People's Republic of China.

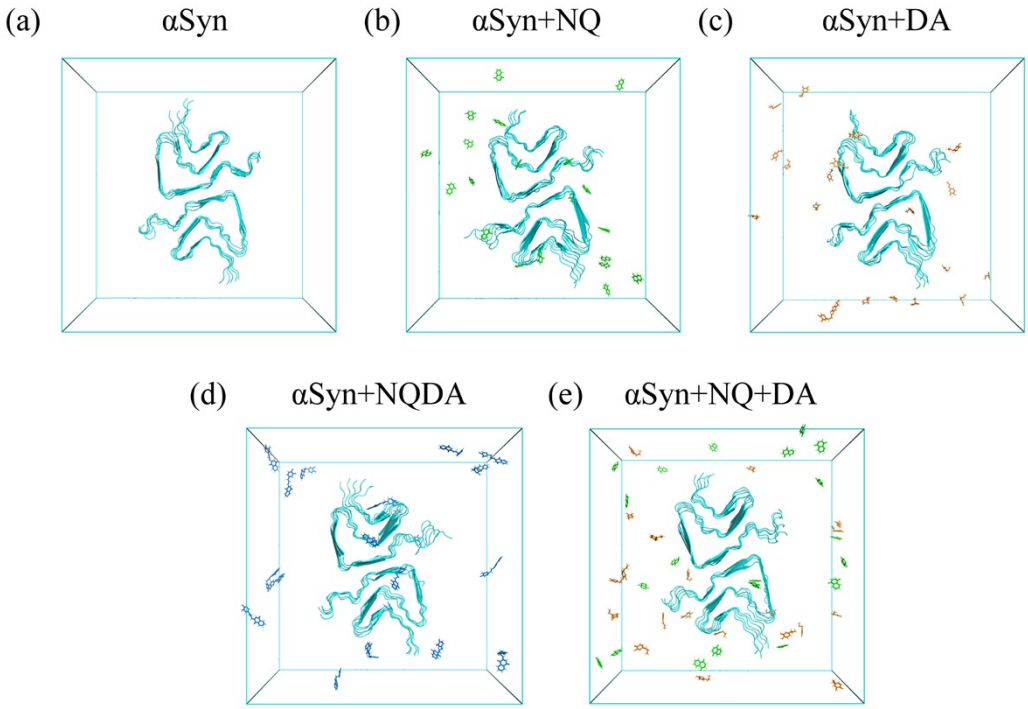

Fig. S1 The initial structure of αSyn system, αSyn+NQDA system, αSyn+NQ system, αSyn+DA system. αSyn fibril is shown in cyan. NQDA molecule is shown in blue. NQ molecule is shown in green. DA molecule is shown in orange. (a) αSyn system. (b) αSyn+NQ system. (c) αSyn+DA system. (d) αSyn+NQDA system. (e) αSyn+NQ+DA system.

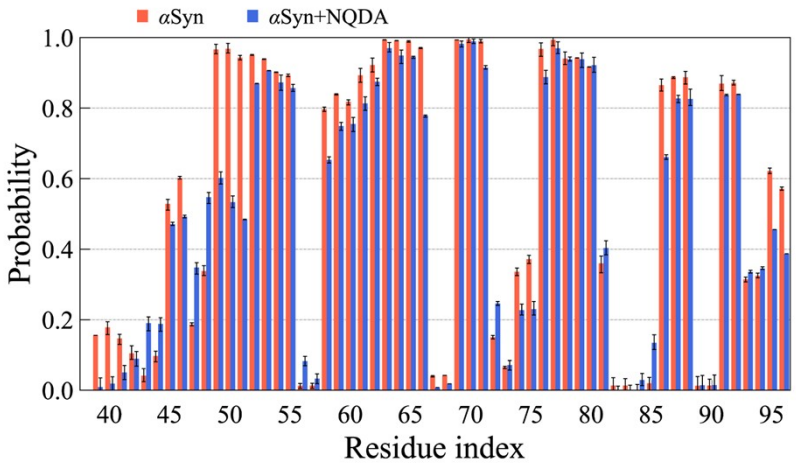

Fig. S2 The β-sheet probabilities of each amino acid residue of αSyn in the absence and presence of NQDA. The error bars are calculated using the bootstrap method.

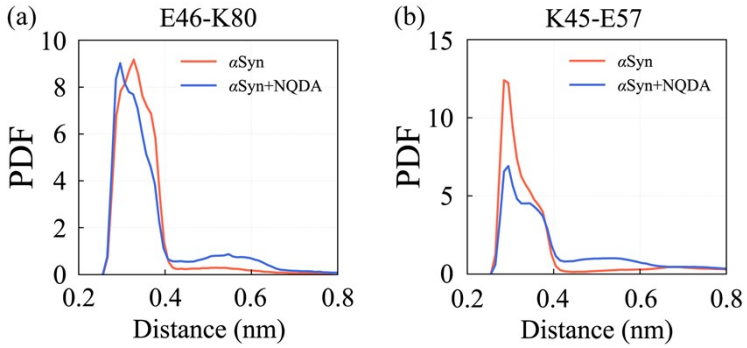

Fig. S3 The probability density function (PDF) of E46-K80 salt-bridge distance (a) and K45-E57 salt-bridge distance (b).

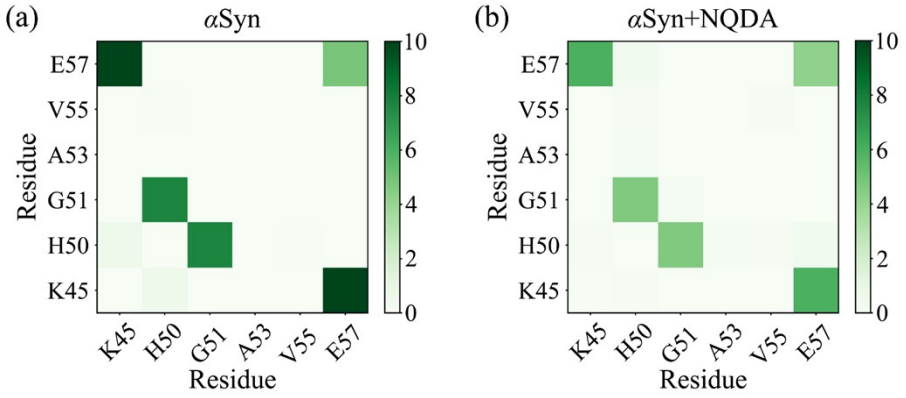

Fig. S4 The H-bond number map among the residues at protofibril interface. (a) H-bond number map of αSyn system. (b) H-bond number map of αSyn+NQDA system.

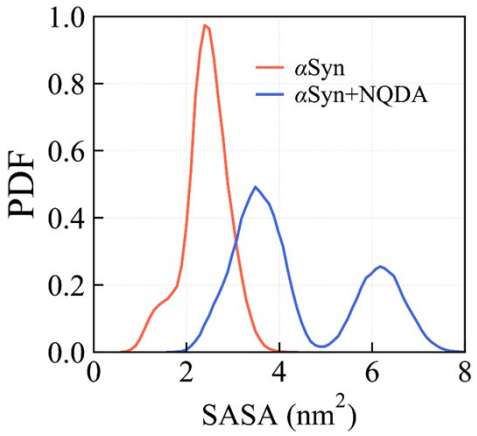

Fig. S5 The probability density function (PDF) of solvent accessible surface area (SASA) of H50 in the absence and presence of NQDA.

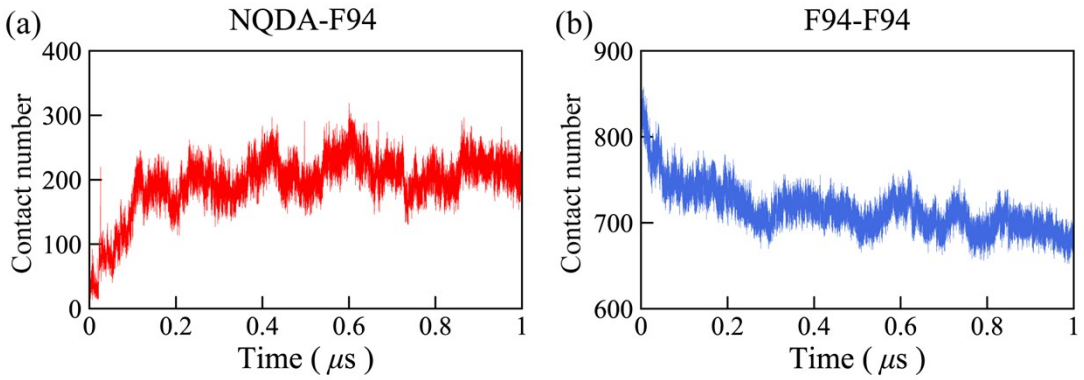

Fig. S6 The contact numbers of (a) NQDA-F94 and (b) F94-F94 as a function of simulation time.

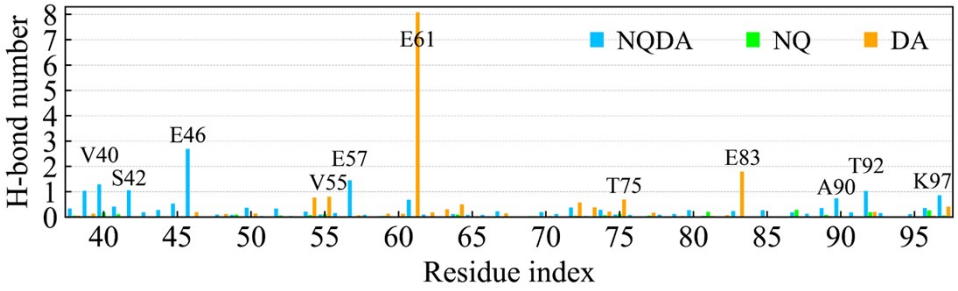

Fig. S7 The H-bond number formed between each residue and NQDA, NQ, or DA molecules.

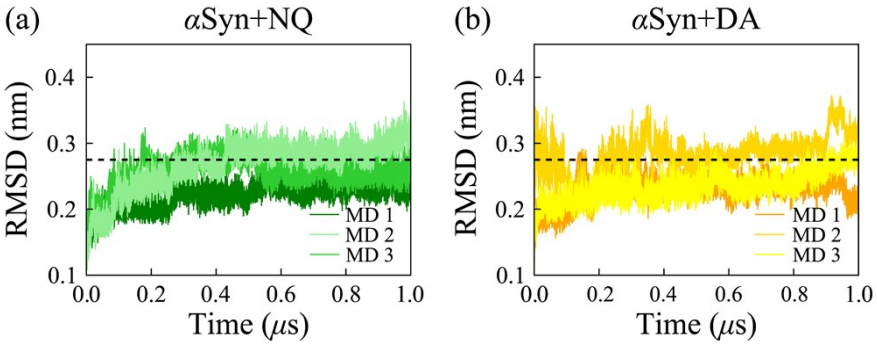

Fig. S8 The backbone root mean square deviation (RMSD) of αSyn fibril in (a) αSyn+NQ, (b) αSyn+DA systems. The dashed line in (a-b) is the average RMSD of αSyn fibril in αSyn system over three MD simulations between 0.6 μs to 1.0 μs.

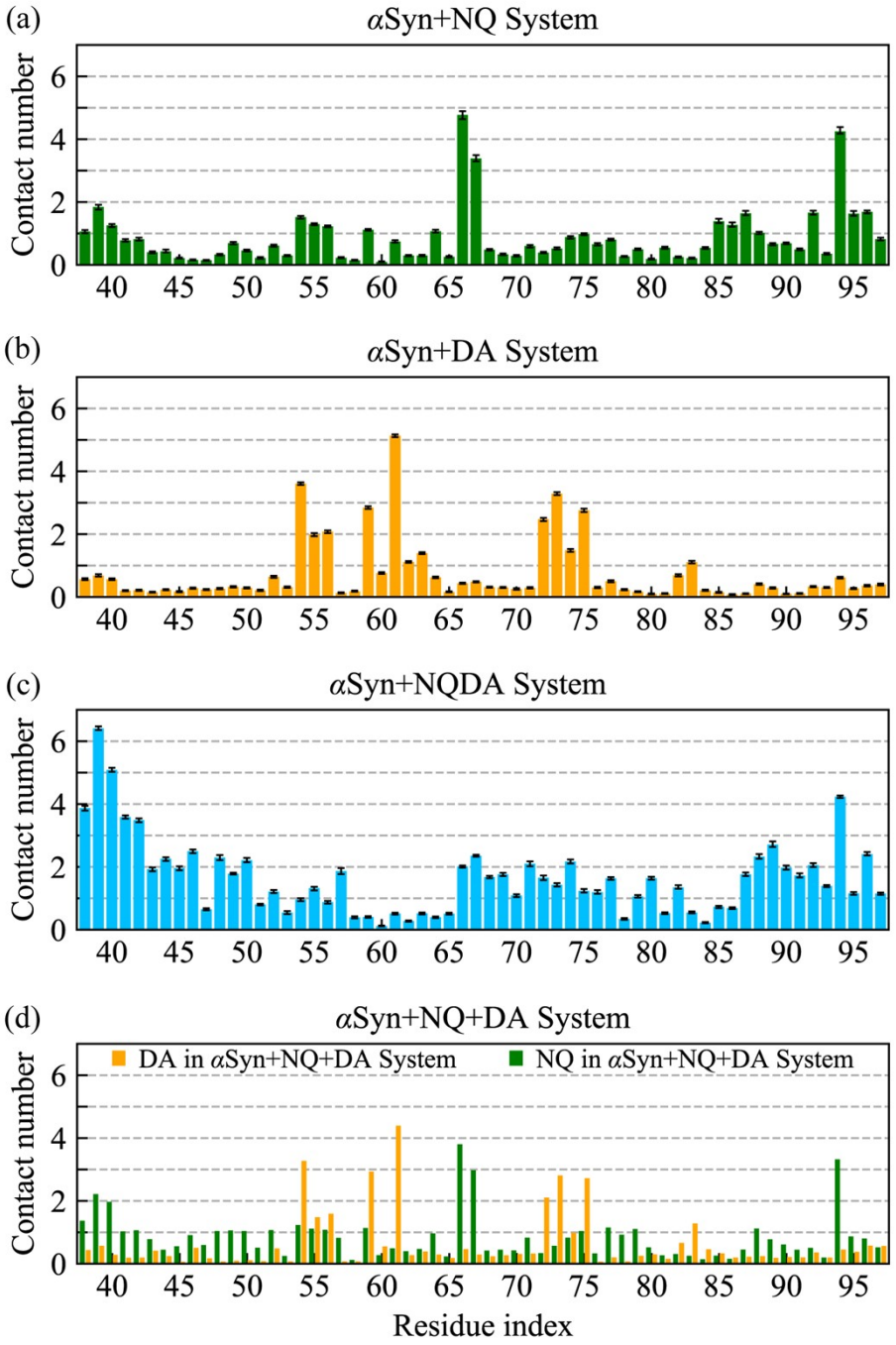

Fig. S9 Contact number between NQDA, NQ, DA or NQ+DA molecules and each residue of αSyn fibril in (a) αSyn+NQ, (b) αSyn+DA, (c) αSyn+NQDA, and (d) αSyn+NQ+DA systems.

Table S1 The binding free energy (predicted by MM-PBSA calculations and the solute dielectric constant ε=9) between αSyn fibril and DA, NQ, or NQDA molecules (kcal/mol)

System	ΔE_{vdW}	ΔE_{elec}	ΔG_{polar}	$\Delta G_{nonpolar}$	$\Delta G_{binding}$
αSyn+DA	-100.31±17.62	393.82±21.35	285.12±53.93	-17.40±2.60	561.24±45.60
αSyn+NQ	-153.25±23.02	-4.68±14.84	72.83±27.25	-17.32±2.68	-102.65±30.50
αSyn+NQDA	-277.69±18.51	-28.63±4.95	162.19±26.36	-30.57±1.98	-174.71±27.05

Table S2 The binding free energy (predicted by MM-PBSA calculations and the solute dielectric constant ε=4) between αSyn fibril and DA, NQ, or NQDA molecules (kcal/mol)

System	ΔE_{vdW}	ΔE_{elec}	ΔG_{polar}	$\Delta G_{nonpolar}$	$\Delta G_{binding}$
αSyn+DA	-100.31±17.62	886.11±48.04	389.16±66.58	-17.40±2.60	1157.56±61.27
αSyn+NQ	-153.50±23.03	-10.53±4.48	96.91±30.10	-17.31±2.69	-84.43±30.71
αSyn+NQDA	-277.70±18.51	-64.42±11.1	232.16±32.74	-30.57±1.9	-140.52±27

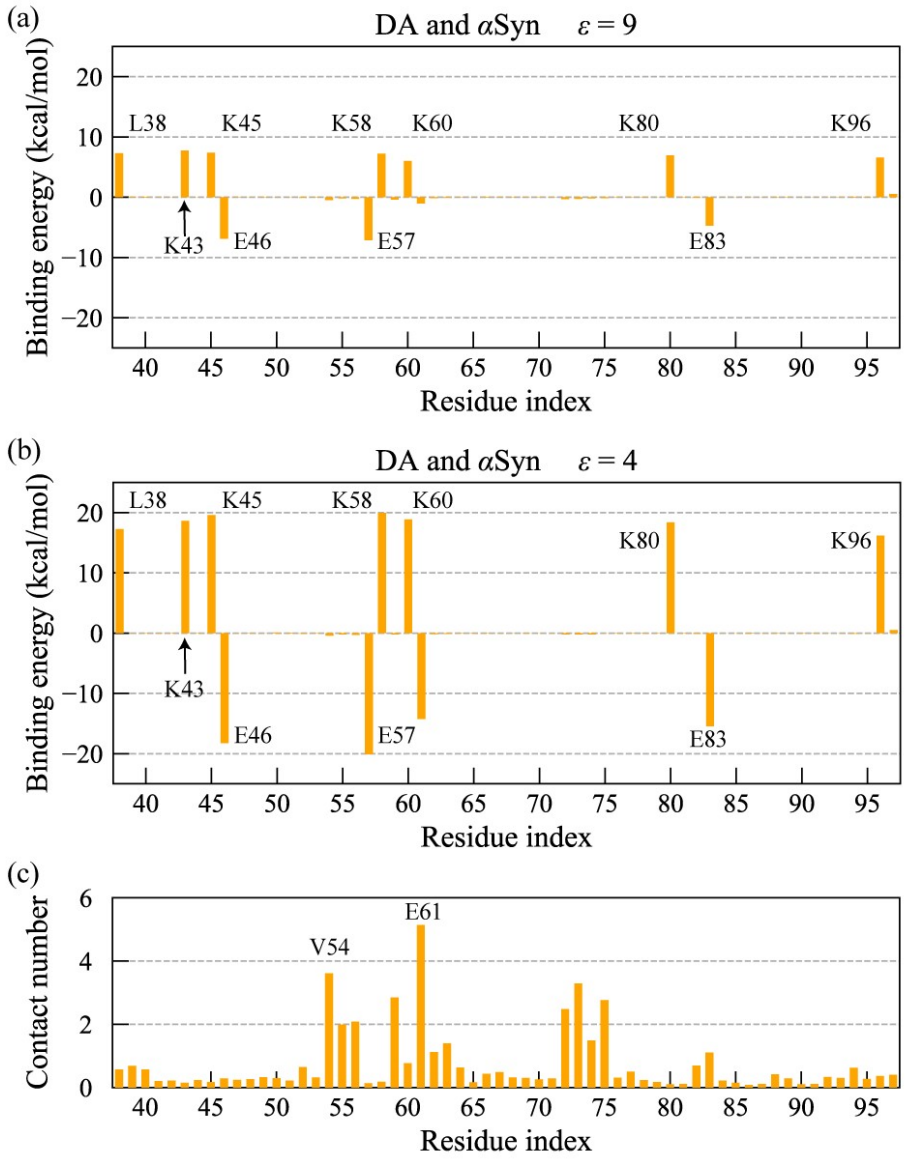

Fig. S10 Comparison of binding free energy using a solute dielectric constant ε=9 (a) or (b) ε=4 (predicted by MM-PBSA calculations) with (c) contact number between DA molecules and each residue of αSyn fibril.

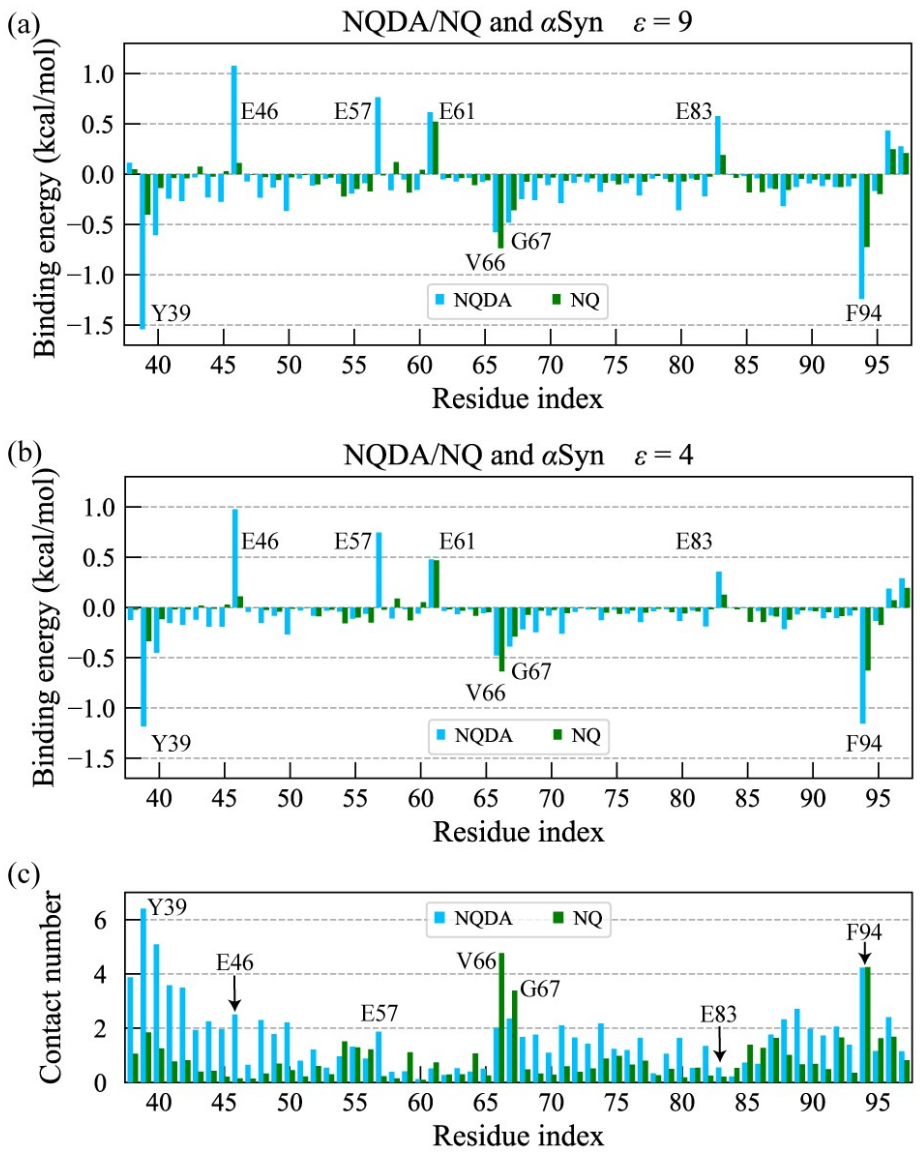

Fig. S11 Comparison of binding free energy using a solute dielectric constant (a) ε=9 or (b) ε=4 (predicted by MM-PBSA calculations) with (c) contact number between NQDA/NQ molecules and each residue of αSyn fibril.

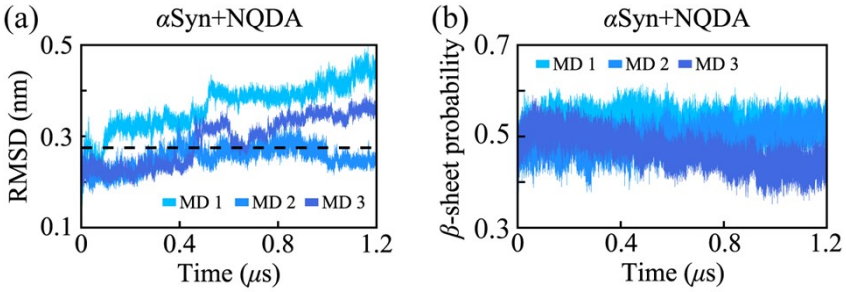

Fig. S12 The time evolution of (a) backbone RMSD values and (b) β-sheets probability of αSyn fibril in αSyn+NQDA system. The dashed line denotes the average RMSD of αSyn fibril over the last 0.4 μs of three MD runs.

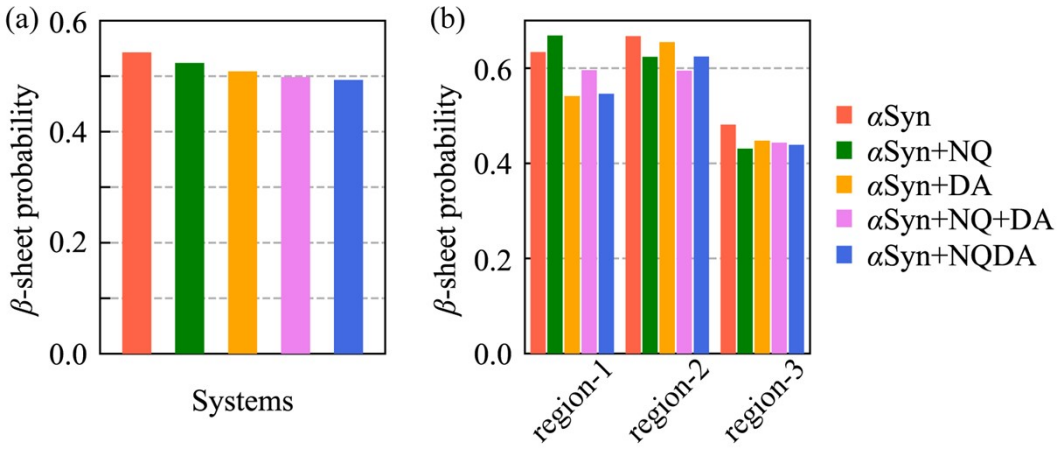

Fig. S13 The β-sheet probability of (a) fibril and (b) each of the three regions (region-1 (residues 45-57), region-2 (residues 58-83), region-3 (residues 84-96)) in αSyn, αSyn+NQ, αSyn+DA, αSyn+NQDA, and αSyn+NQ+DA systems.

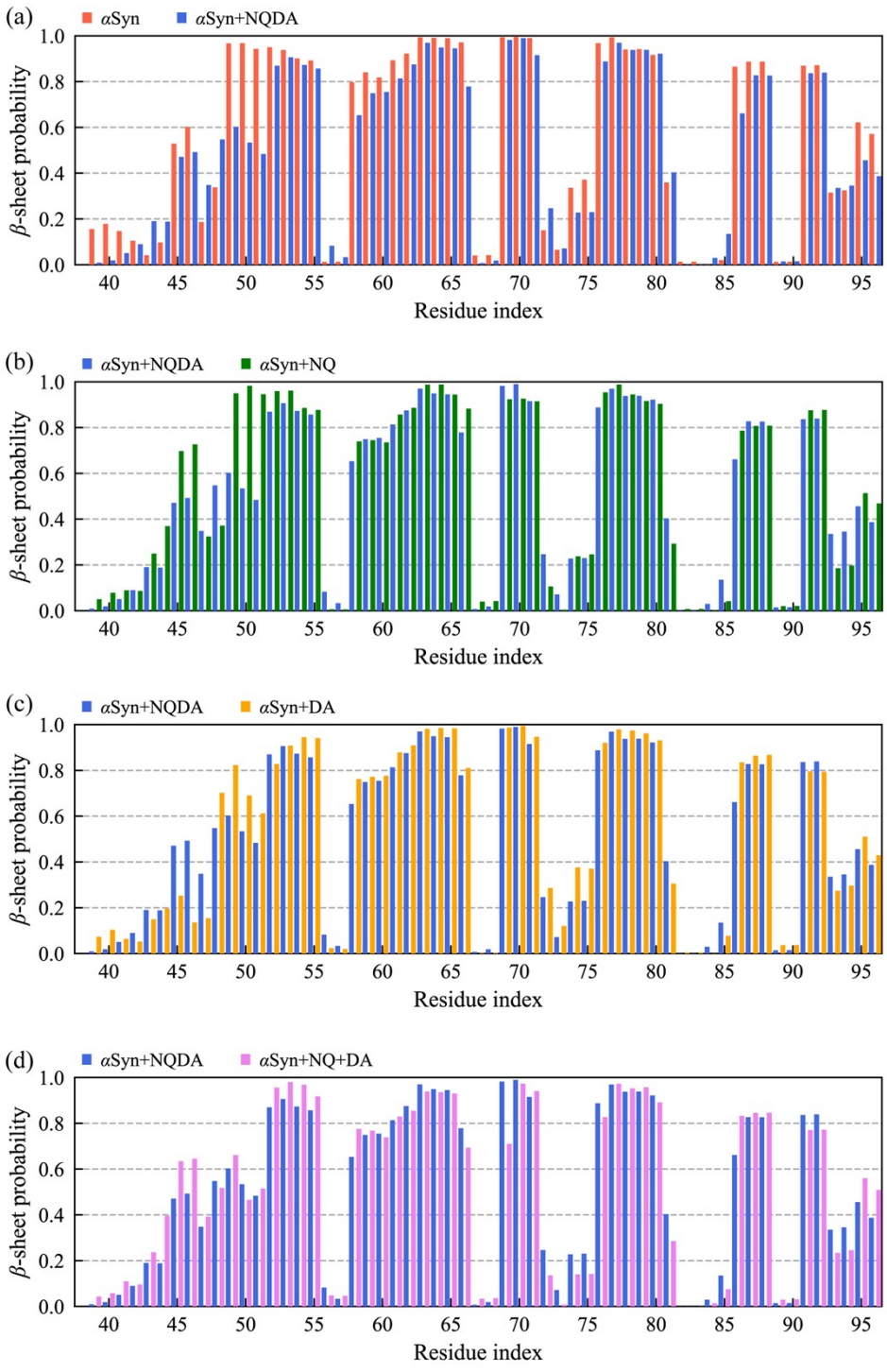

Fig. S14 Comparisons of β-sheet probability of each residue in αSyn+NQDA system with that in the other four systems: (a) αSyn with αSyn+NQDA system, (b) αSyn+NQ with αSyn+NQDA system, (c) αSyn+NQ with αSyn+NQDA system, and (d) αSyn+NQ+DA with αSyn+NQDA system.

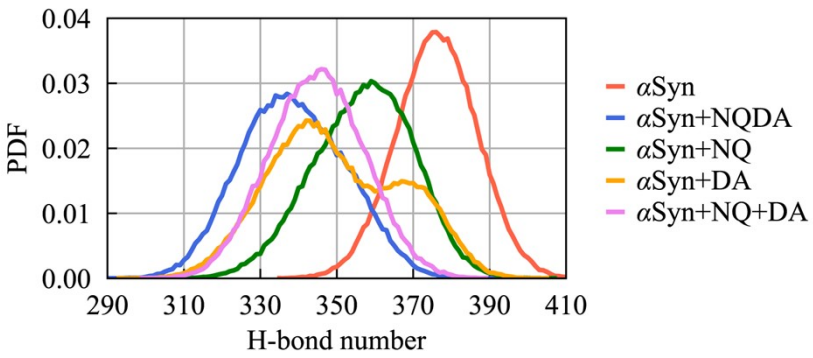

Fig. S15 The PDF of total H-bond number in αSyn, αSyn+NQDA, αSyn+NQ, αSyn+DA, and αSyn+NQ+DA systems.

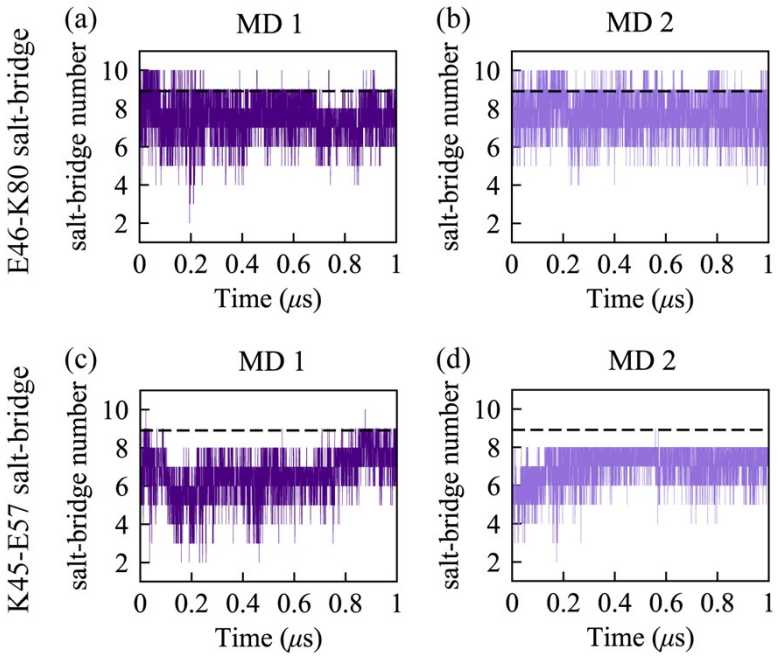

Fig. S16 The time evolution of E46-K80 (a-b) and K45-E57 (c-d) salt-bridge number in two MD simulations of αSyn+NQ+DA systems. The dashed line denotes the average salt-bridge number of αSyn fibril without small molecules over the last 0.4 μs of all MD runs.

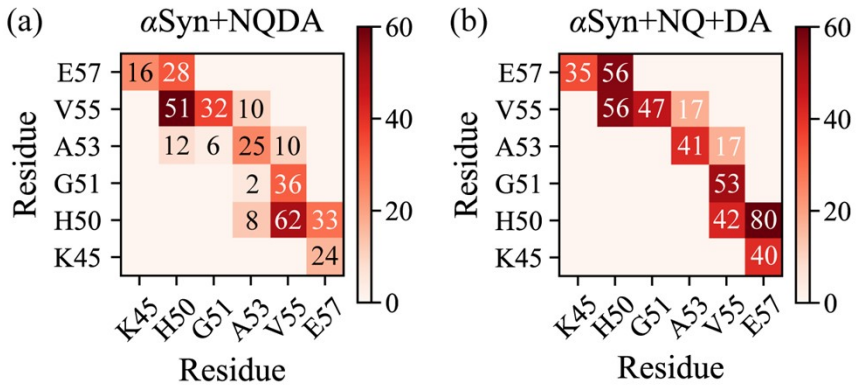

Fig. S17 The Contact number of the protofibril interface residues in (a) αSyn+NQDA and (b) αSyn+NQ+DA systems.