Binding of berberine derivates to G-quadruplex: insight from computational study

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DNA Force Field and Ligand Charge Models

Force field is vital for accurate modeling of nucleic structure in all-atom MD simulation. In this study, two force fields OL15 and BSC1 were adopted to carry out simulation for the G-quadruplex systems. Accurate calculation of partial charge of small molecules also plays an important role for accurate calculation of binding free energy, therefore RESP and AM1-BCC were used to calculate the partial charges of the ligand atoms. Overall, four combinations of force field and atomic charge (OL15+AM1-BCC, OL15+RESP, BSC1+AM1-BCC, BSC1+RESP) were examined.

The average values of root-mean-square-deviations (RMSD) of simulated structures with respect to the initial crystal structure were listed in Table S1-2. It can be clearly found that the values of RMSD for G-quadruplex and ligands with the lowest value and best structural stability under the combination of OL15+RESP relative to other three combinations. To further assess the flexibility of the nucleic structure, the root mean square fluctuation (RMSF) of every tetrads in G-quadruplex under four combinations were analyzed in Figure S1. The results showed the fluctuations with nucleic in the combination of OL15 and RESP were generally lower than other combinations for all systems. According the above analysis, the structure of complex was more stable under the combination of OL15+RESP on the whole.

Table S1. The RMSD for G-quadruplex in Tel12-**BER**, Tel12-**4** and Tel12-**L** under four combinations in five simulations. All values are in Å.

	Simulations	BSC1+AM1-BCC	BSC1+RESP	OL15+AM1-BCC	OL15+RESP
TEL12-BER	**No. 1**	2.47 ± 0.31	2.55 ± 0.27	2.66 ± 0.24	2.65 ± 0.27
	No. 2	2.82 ± 0.35	2.57 ± 0.26	2.83 ± 0.34	2.35 ± 0.18
	No. 3	2.70 ±0.27	2.67 ± 0.30	2.69 ± 0.22	2.28 ± 0.16
	No. 4	2.66 ± 0.31	2.51 ± 0.25	2.67 ± 0.25	2.72 ± 0.24
	No. 5	2.73 ± 0.28	2.63 ± 0.28	2.37 ± 0.25	2.69±0.21
	AVE	**2.68**	**2.59**	**2.64**	**2.54**
TEL12-4	**No. 1**	2.61 ± 0.37	2.34 ± 0.31	2.61 ± 0.32	2.10 ± 0.25
	No. 2	2.65 ± 0.31	2.59 ± 0.44	2.44 ± 0.38	2.76 ± 0.26
	No. 3	2.69 ± 0.37	2.63 ± 0.33	2.81 ± 0.37	2.78 ± 0.22
	No. 4	2.64 ± 0.29	2.75 ± 0.37	2.53 ± 0.36	2.37 ± 0.34
	No. 5	2.54 ± 0.32	2.63 ± 0.40	2.33 ± 0.31	2.73 ± 0.25
	AVE	**2.63**	**2.59**	**2.55**	**2.55**
TEL12-L	**No. 1**	2.69 ± 0.31	2.84 ± 0.28	2.73 ± 0.21	2.49 ± 0.29
	No. 2	2.73 ± 0.35	2.87 ± 0.43	2.71 ± 0.25	2.47 ± 0.27
	No. 3	2.31 ± 0.28	2.83 ±0.26	2.75 ± 0.21	2.66 ± 0.22
	No. 4	2.53 ± 0.21	2.51 ± 0.27	2.62 ± 0.19	2.69 ± 0.31
	No. 5	2.79 ± 0.29	2.80 ± 0.39	2.66 ± 0.24	2.58 ± 0.31
	AVE	**2.61**	**2.77**	**2.70**	**2.58**

Table S2. The RMSD for ligands in Tel12-**BER**, Tel12-**4** and Tel12-**L** under four combinations in five simulations. All values are in Å.

	Simulations	BSC1+AM1-BCC	BSC1+RESP	OL15+AM1-BCC	OL15+RESP
TEL12-BER	**No. 1**	0.58 ± 0.10	0.58 ± 0.10	0.58 ± 0.10	0.55 ± 0.10
	No. 2	0.59 ± 0.10	0.61 ± 0.09	0.54 ± 0.11	0.57 ± 0.09
	No. 3	0.59 ± 0.10	0.58 ± 0.10	0.57 ± 0.10	0.56 ± 0.09
	No. 4	0.60 ± 0.40	0.58 ± 0.09	0.56 ± 0.10	0.57 ± 0.10
	No. 5	0.60 ± 0.10	0.59 ± 0.10	0.56 ± 0.10	0.57 ± 0.10
	AVE	**0.59**	**0.59**	**0.56**	**0.56**
TEL12-4	**No. 1**	2.43 ± 0.58	2.33 ± 0.47	2.07 ±0.60	1.42 ± 0.32
	No. 2	2.31 ± 0.57	1.33 ± 0.29	1.56 ±0.49	1.36 ± 0.18
	No. 3	2.55 ± 0.55	2.21 ± 0.69	1.94 ± 0.62	1.36 ± 0.18
	No. 4	2.02 ± 0.70	2.07 ± 0.74	1.79 ± 0.74	1.38 ± 0.17
	No. 5	1.85 ± 0.66	2.00 ± 0.59	2.11 ± 0.60	1.35 ± 0.27
	AVE	**2.23**	**1.99**	**1.89**	**1.38**
TEL12-L	**No. 1**	1.46 ± 0.17	1.38 ± 0.19	2.08 ± 0.61	1.47 ± 0.18
	No. 2	1.44 ± 0.17	1.44 ± 0.17	1.47 ± 0.18	1.47 ± 0.21
	No. 3	1.48 ± 0.20	1.62 ± 0.54	1.46 ± 0.19	1.49 ± 0.18
	No. 4	2.55 ± 0.71	2.28 ± 0.56	1.49 ± 0.19	1.47 ± 0.17
	No. 5	2.25 ± 0.64	1.41 ± 0.18	1.61 ± 0.43	1.48 ± 0.19
	AVE	**1.84**	**1.63**	**1.62**	**1.48**

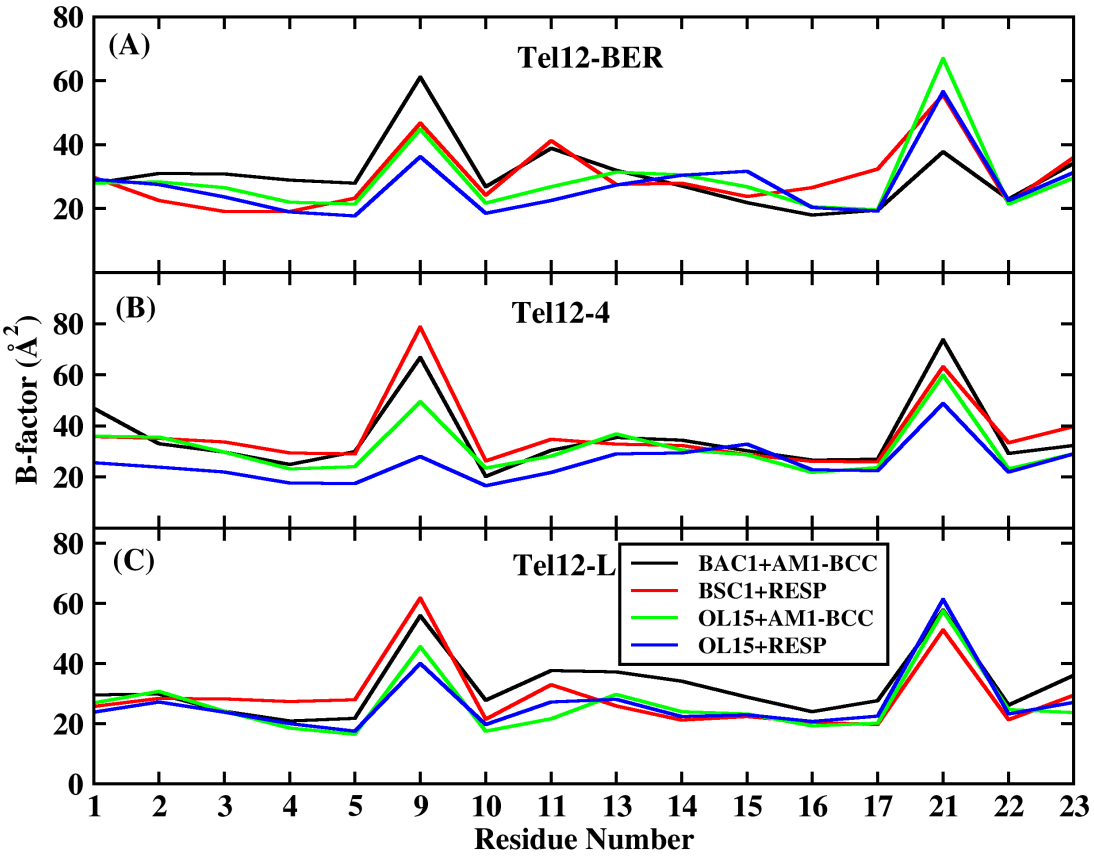


Figure S1. The calculated RMSF of every tetrad in Tel12-**BER**, Tel12-**4** and Tel12-**L** under four combinations. (A). Tel12-**BER** system. (B). Tel12-**4** system. (C). Tel12-**L** system.

In order to explore the reason why the G-quadruplex systems were more stable with OL15 and RESP, the absolute value of ligand charge under AM1-BCC and RESP method was plotted Figure S2 and we noticed that the RESP charges were higher than AM1-BCC charges overall. In theory, RESP charge was more accurate compared with semi-empirical AM1-BCC charge method. To further compare the two charge methods, the average charge was calculated (Table S3). The average charge obtained by AM1-BCC for all ligands were smaller than that of RESP method, demonstrating RESP charge were higher than AM1-BCC charge. We speculated that stronger charges may produce higher interaction under the combination of OL15 and RESP. Therefore, the interaction energy for all systems in four combination was calculated (Figure S3). It was obvious that the interaction between G-quadruplex and ligand was higher and more stable with the combination of OL15 and RESP.

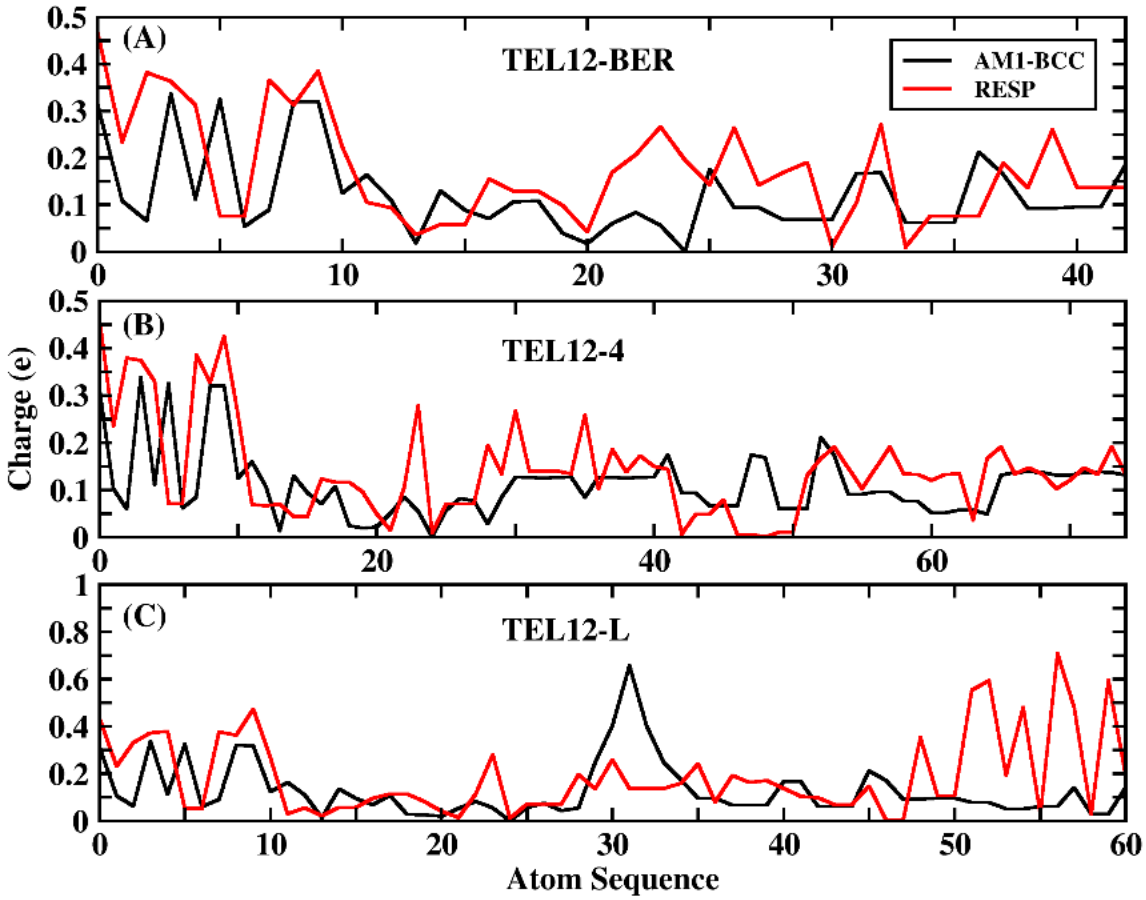


Figure S2. The absolute value of ligand charge under AM1-BCC and RESP method. (A). Tel12-**BER** system. (B). Tel12-**4** system. (C). Tel12-**L** system.

Table S3. The average charge for three ligands.

Ligands	$Mean_{AM1-BCC}$ (e)	$Mean_{RESP}$ (e)
BER	0.12	0.17
4	0.11	0.14
L	0.12	0.19

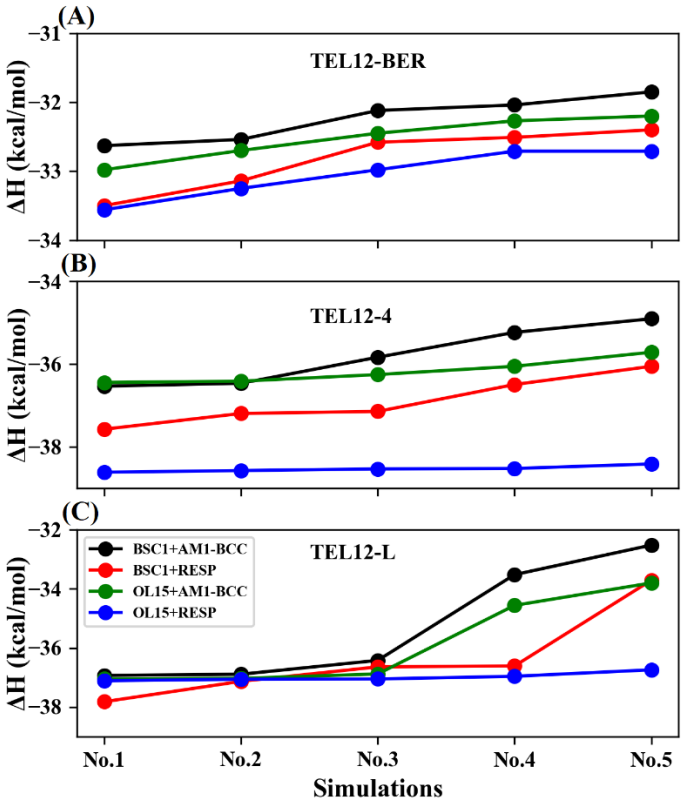
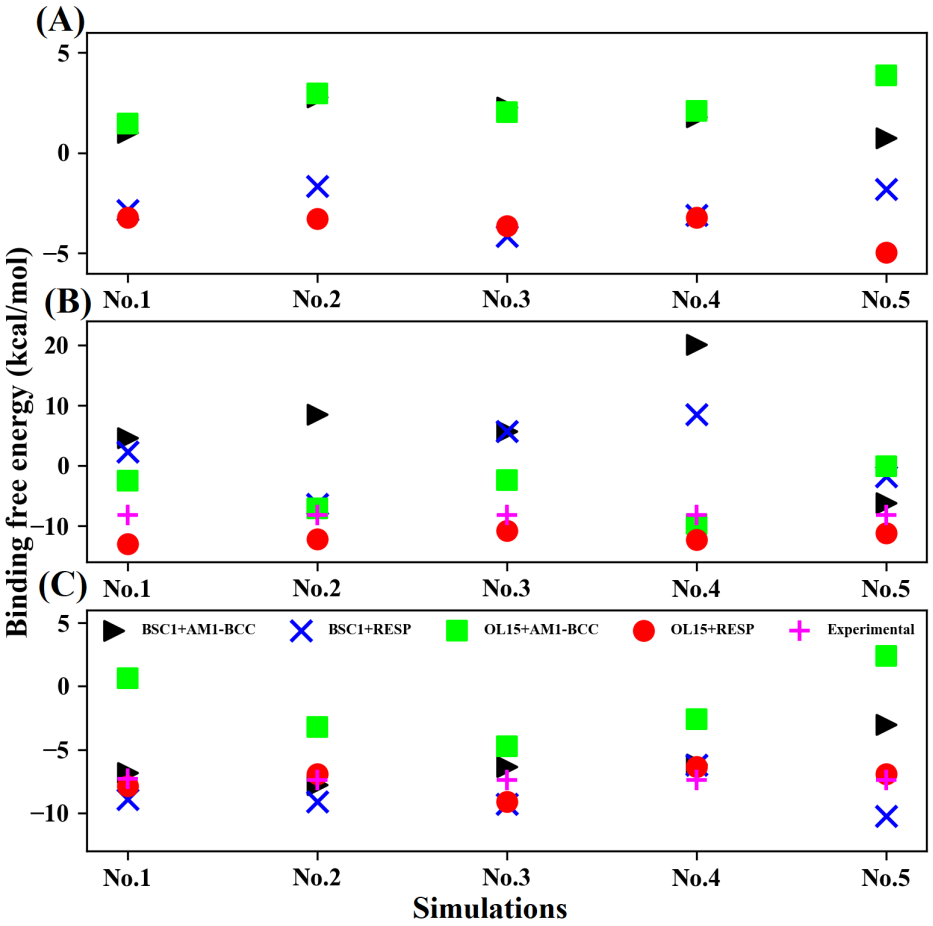


Figure S3. The interaction energy under four combinations from five simulations. (A). Tel12-**BER** system. (B). Tel12-**4** system. (C). Tel12-**L** system.

Furthermore, the binding free energy for all systems under four combinations were calculated (Figure S4). It was clear that the calculated energy under the combination of OL15 and RESP were in good agreement with experimental results while results calculated by other combinations were away from the experimental values. Therefore, the following analyses were based on the trajectories obtained from the combination of OL15 and RESP.



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75 **Figure S4.** The binding free energy for all systems under four combinations in five

76 simulations. (A). Tel12-**BER** system. (B). Tel12-**4** system. (C). Tel12-**L** system.

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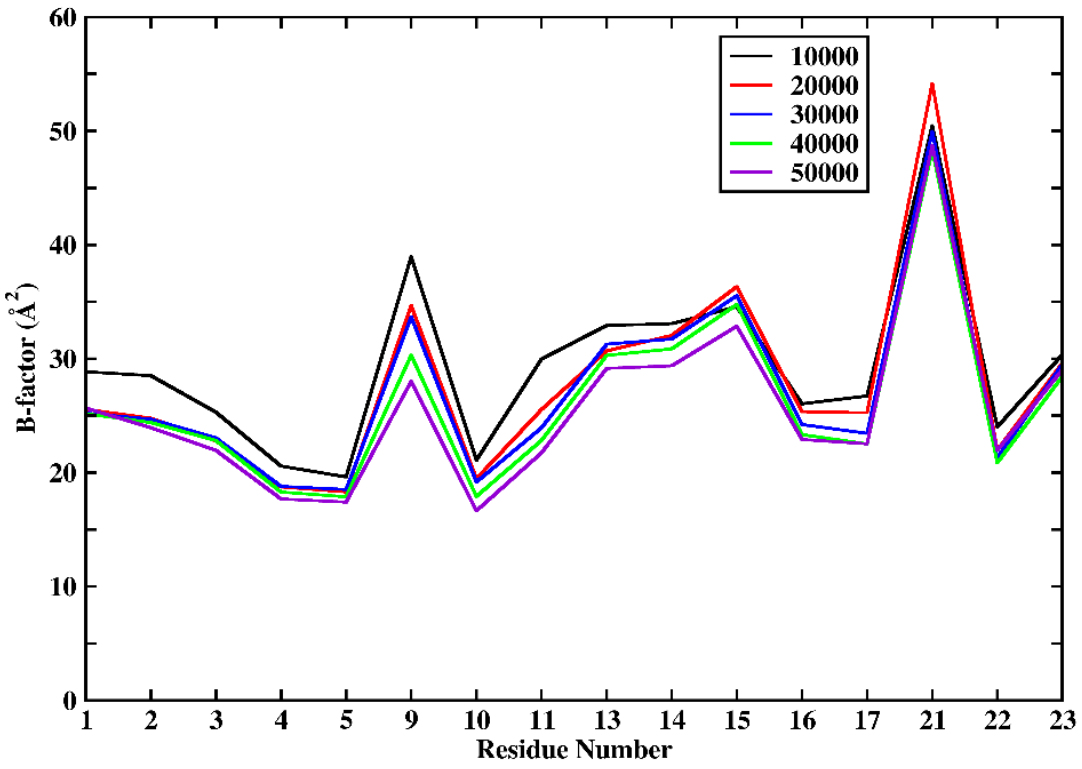

Figure S5. The calculated B-factor of every tetrad in Tel12-**4** system under different frames.