

Supporting Information:

**Comprehensive Evaluation of End-Point Free Energy Techniques in
Carboxylated-Pillar[6]arene Host-guest Binding: IV. The QM treatment, GB models and the
Multi-Trajectory Extension**

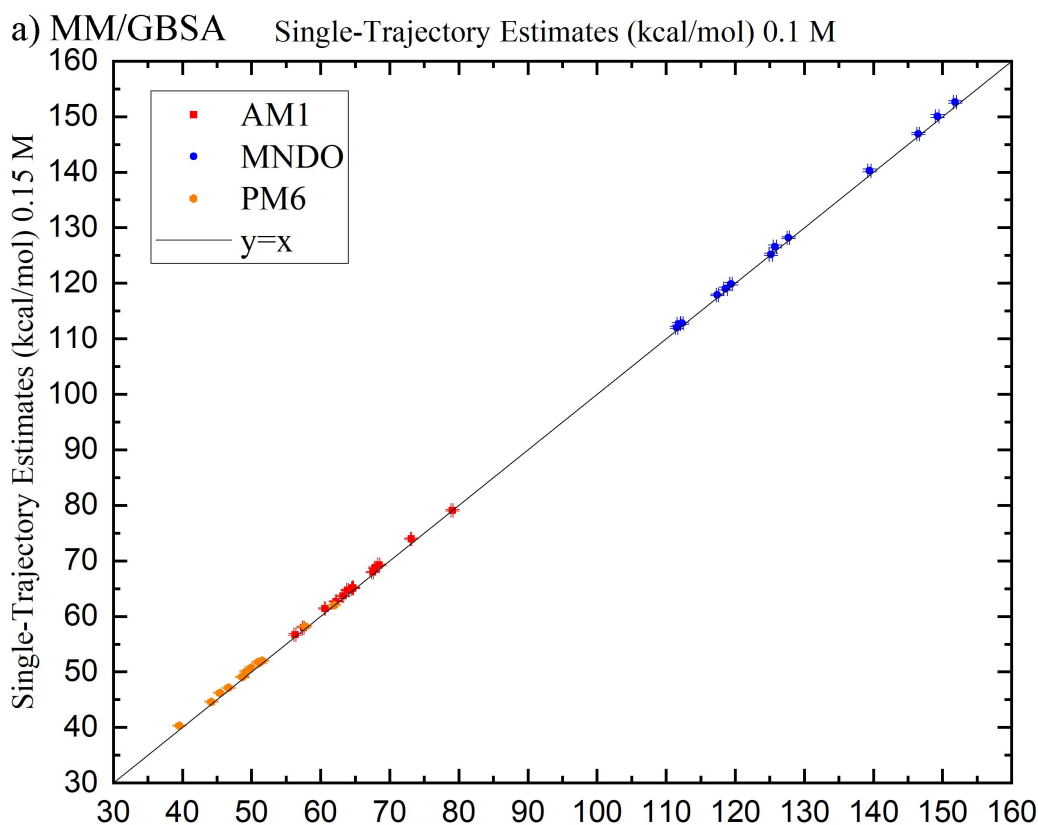
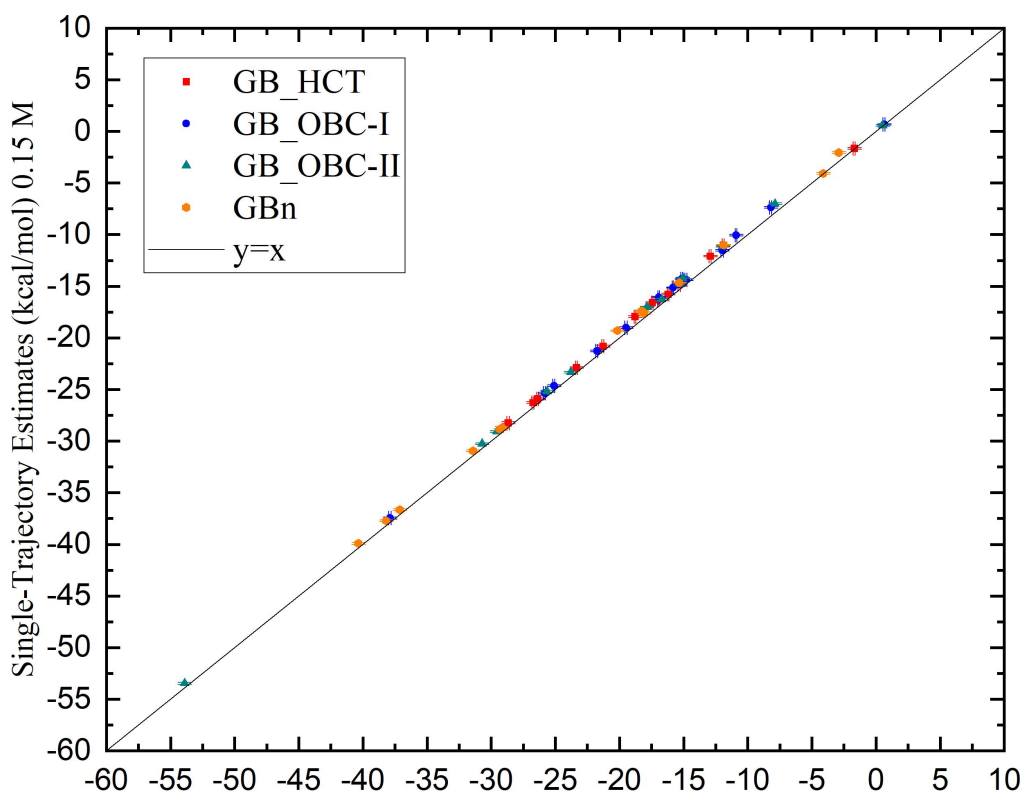
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Figure S1. Comparison between free energy estimates obtained with two salt-concentration conditions (0.1 M and 0.15 M) with a) MM/GBSA and b) QM/GBSA Hamiltonians in the single-trajectory realization. While for MM/GBSA estimates four GB models are employed, in QM/GBSA calculations only the GB^{OBC-II} model is considered.



b) QM/GBSA Single-Trajectory Estimates (kcal/mol) 0.1 M

Table S1. Single-trajectory end-point estimates of WP6 host-guest binding affinities with the GB^{HCT} model (kcal/mol).

Host	Guest	Exp	MM	±	AM1	±	AM1-DH+	±	MNDO	±	PM6	±	PM6-DH+	±	DFTB2	±	DFTB3	±
WP6	G1	-6.53	-16.2	0.1	50.4	0.2	-10.9	0.1	114.9	0.3	44.4	0.1	17.2	0.1	16.2	0.1	23.3	0.1
	G2	-10.59	-18.8	0.1	65.2	0.1	3.4	0.1	133.3	0.2	50.2	0.1	22.6	0.1	16.9	0.1	24.1	0.1
	G3	-8.03	-26.4	0.1	65.1	0.1	18.2	0.1	117.1	0.2	51.2	0.1	29.8	0.1	5.3	0.1	12.3	0.1
	G4	-6.50	-15.3	0.1	68.5	0.1	24.7	0.1	118.4	0.2	61.1	0.1	40.9	0.1	-	-	-	-
	G5	-5.46	-17.0	0.0	59.1	0.1	-12.2	0.1	143.9	0.2	45.4	0.1	14.8	0.1	21.4	0.0	28.4	0.1
	G6	-8.08	-26.7	0.1	66.3	0.1	12.3	0.1	127.8	0.2	52.8	0.1	28.5	0.1	7.4	0.1	15.1	0.1
	G7	-7.07	-23.3	0.1	63.4	0.1	19.6	0.1	111.7	0.2	49.1	0.1	29.2	0.1	5.5	0.1	11.9	0.1
	G8	-6.04	-1.7	0.1	70.8	0.1	13.6	0.1	116.3	0.2	56.7	0.1	29.2	0.1	30.5	0.1	37.3	0.1
	G9	-6.32	-28.7	0.1	73.7	0.1	12.0	0.1	149.5	0.2	56.0	0.1	28.8	0.1	9.4	0.1	19.6	0.1
	G10	-9.96	-12.9	0.1	61.4	0.1	6.3	0.1	120.5	0.3	45.1	0.1	18.9	0.1	16.3	0.1	22.9	0.1
	G11	-6.26	-21.3	0.1	59.0	0.1	17.4	0.1	109.5	0.2	50.0	0.1	31.0	0.1	3.7	0.1	9.8	0.1
	G12	-11.02	-17.4	0.1	69.4	0.1	-1.2	0.1	143.0	0.2	50.7	0.1	20.1	0.1	19.8	0.1	27.1	0.1
	G13	-8.58	-11.9	0.1	65.2	0.1	15.6	0.1	109.3	0.2	45.0	0.1	19.5	0.1	-	-	-	-
RMSE			19.5		59.8		15.9		135.0		47.9		24.9		23.1		30.0	
MSE			15.1		-58.4		-3.1		-134.2		-45.6		-20.5		-21.6		-28.8	
τ			0.1		-0.1		0.0		-0.1		0.0		-0.1		-0.1		-0.1	
PI			-0.1		-0.2		-0.1		0.0		-0.1		-0.1		0.1		0.1	
Pearson r			-0.2		-0.3		-0.1		-0.2		-0.2		-0.1		0.0		0.0	

Table S2. Single-trajectory end-point estimates of WP6 host-guest binding affinities with the GB^{OBC-1} model (kcal/mol).

Host	Guest	Exp	MM	±	AM1	±	AM1-DH+	±	MNDO	±	PM6	±	PM6-DH+	±	DFTB2	±	DFTB3	±
WP6	G1	-6.53	-14.8	0.1	56.0	0.2	-5.4	0.1	118.9	0.3	50.0	0.1	22.7	0.1	19.7	0.1	27.0	0.1
	G2	-10.59	-16.9	0.1	67.6	0.1	5.9	0.1	136.5	0.2	52.0	0.1	24.4	0.1	19.0	0.1	26.9	0.1
	G3	-8.03	-25.1	0.1	69.7	0.1	22.8	0.1	121.4	0.2	56.2	0.1	34.8	0.1	9.4	0.1	16.4	0.1
	G4	-6.50	-12.0	0.1	72.2	0.1	28.5	0.1	124.2	0.2	64.4	0.1	44.3	0.1	-	-	-	-
	G5	-5.46	-15.8	0.0	61.2	0.1	-10.1	0.1	147.7	0.2	45.7	0.1	15.1	0.1	23.2	0.0	31.0	0.1
	G6	-8.08	-25.8	0.1	70.2	0.1	16.2	0.1	131.9	0.2	57.2	0.1	32.9	0.1	11.2	0.1	19.0	0.1
	G7	-7.07	-21.8	0.1	67.2	0.1	23.4	0.1	115.9	0.2	53.4	0.1	33.4	0.1	9.4	0.1	15.8	0.1
	G8	-6.04	0.6	0.1	78.6	0.2	21.3	0.1	122.3	0.2	63.3	0.1	35.8	0.1	32.6	0.1	41.2	0.1
	G9	-6.32	-37.9	0.1	77.1	0.1	15.4	0.1	153.6	0.2	56.4	0.1	29.3	0.1	10.8	0.1	21.1	0.1
	G10	-9.96	-10.9	0.1	64.1	0.1	9.0	0.1	123.3	0.3	47.4	0.1	21.3	0.1	19.0	0.1	26.5	0.1
	G11	-6.26	-19.5	0.1	63.0	0.1	21.5	0.1	114.6	0.2	53.4	0.1	34.4	0.1	7.6	0.1	13.8	0.1
	G12	-11.02	-15.1	0.1	72.2	0.1	1.6	0.1	146.1	0.3	52.6	0.1	21.9	0.1	22.2	0.1	30.1	0.1
	G13	-8.58	-8.2	0.1	68.1	0.1	18.5	0.1	110.9	0.2	48.8	0.1	23.2	0.1	-	-	-	-
RMSE			13.3		76.2		23.6		136.6		61.9		37.2		25.7		33.2	
MSE			9.4		-76.0		-20.7		-136.0		-61.6		-36.5		-24.5		-32.2	
τ			0.0		0.0		0.2		-0.1		0.2		0.3		-0.1		-0.1	
PI			0.0		0.0		0.1		0.0		0.3		0.3		0.1		0.1	
Pearson r			-0.1		-0.1		0.1		-0.1		0.3		0.3		0.0		0.0	

Table S3. Single-trajectory end-point estimates of WP6 host-guest binding affinities with the GB^{OBC-II} model (kcal/mol).

Host	Guest	Exp	MM	±	AM1	±	AM1-DH+	±	MNDO	±	PM6	±	PM6-DH+	±	DFTB2	±	DFTB3	±
WP6	G1	-6.53	-16.7	0.1	56.3	0.1	-5.0	0.1	118.6	0.3	48.7	0.1	21.4	0.1	18.7	0.1	25.6	0.1
	G2	-10.59	-17.9	0.1	67.9	0.1	6.1	0.1	139.4	0.2	50.0	0.1	22.4	0.1	17.2	0.1	25.6	0.1
	G3	-8.03	-29.6	0.1	64.6	0.1	17.7	0.1	117.4	0.2	51.2	0.1	29.7	0.1	6.3	0.1	13.1	0.1
	G4	-6.50	-15.3	0.1	63.2	0.1	19.5	0.1	119.4	0.2	57.7	0.1	37.6	0.1	-	-	-	-
	G5	-5.46	-17.9	0.0	60.6	0.1	-10.7	0.1	151.8	0.2	39.5	0.1	8.9	0.1	19.9	0.0	28.2	0.1
	G6	-8.08	-30.7	0.1	64.7	0.1	10.7	0.1	127.7	0.2	51.5	0.1	27.2	0.1	7.7	0.1	15.3	0.1
	G7	-7.07	-25.6	0.1	62.2	0.1	18.4	0.1	112.3	0.2	48.7	0.1	28.7	0.1	6.5	0.1	12.8	0.1
	G8	-6.04	0.5	0.1	79.0	0.2	21.8	0.1	125.1	0.2	62.0	0.1	34.5	0.1	32.0	0.1	41.2	0.1
	G9	-6.32	-53.9	0.1	67.5	0.1	5.9	0.1	146.5	0.2	44.2	0.1	17.0	0.1	3.4	0.1	13.4	0.1
	G10	-9.96	-12.0	0.1	63.9	0.1	8.8	0.1	125.7	0.3	45.4	0.1	19.3	0.1	17.7	0.1	25.7	0.1
	G11	-6.26	-23.8	0.1	57.5	0.1	15.9	0.1	111.5	0.2	46.7	0.1	27.7	0.1	4.5	0.1	10.4	0.1
	G12	-11.02	-15.1	0.1	73.1	0.1	2.5	0.1	149.2	0.3	51.0	0.1	20.3	0.1	21.0	0.1	29.3	0.1
	G13	-8.58	-7.9	0.1	68.4	0.1	18.8	0.1	111.8	0.2	49.2	0.1	23.7	0.1	-	-	-	-
RMSE			18.3		73.3		20.3		135.9		57.7		33.0		23.6		31.1	
MSE			12.7		-73.0		-17.8		-135.1		-57.4		-32.2		-21.8		-29.6	
τ			0.0		-0.3		0.2		-0.1		-0.2		0.2		-0.1		-0.2	
PI			-0.1		-0.2		0.0		0.0		0.0		0.1		0.1		0.1	
Pearson r			-0.2		-0.3		0.0		-0.2		0.0		0.1		-0.1		-0.1	

Table S4. Single-trajectory end-point estimates of WP6 host-guest binding affinities with the GBn model (kcal/mol).

Host	Guest	Exp	MM	±	AM1	±	AM1-DH+	±	MNDO	±	PM6	±	PM6-DH+	±	DFTB2	±	DFTB3	±
WP6	G1	-6.53	-29.3	0.1	34.6	0.1	-26.7	0.1	115.6	0.3	22.2	0.1	-5.1	0.1	7.5	0.1	14.0	0.1
	G2	-10.59	-18.3	0.1	55.2	0.1	-6.6	0.1	139.7	0.2	44.9	0.1	17.4	0.1	22.9	0.1	32.7	0.1
	G3	-8.03	-37.1	0.1	39.5	0.1	-7.4	0.1	110.1	0.1	26.1	0.1	4.7	0.1	-3.5	0.1	3.8	0.1
	G4	-6.50	-18.1	0.1	71.0	0.1	27.2	0.1	126.7	0.2	56.1	0.1	35.9	0.1	-	-	-	-
	G5	-5.46	-15.3	0.0	50.2	0.1	-21.1	0.1	152.2	0.2	37.7	0.1	7.0	0.1	26.7	0.1	37.0	0.1
	G6	-8.08	-38.2	0.1	38.7	0.1	-15.4	0.1	121.3	0.1	22.6	0.1	-1.7	0.1	-3.6	0.1	4.3	0.1
	G7	-7.07	-31.4	0.1	41.0	0.1	-2.8	0.1	107.4	0.1	26.7	0.1	6.8	0.1	-1.3	0.1	5.4	0.1
	G8	-6.04	-4.1	0.1	63.1	0.1	5.9	0.1	133.6	0.2	62.3	0.1	34.8	0.1	31.9	0.1	46.9	0.1
	G9	-6.32	-40.3	0.1	39.7	0.1	-22.0	0.1	137.5	0.2	19.6	0.1	-7.6	0.1	-5.9	0.1	4.9	0.1
	G10	-9.96	-11.9	0.1	56.2	0.1	1.1	0.1	126.0	0.2	46.3	0.1	20.1	0.1	24.6	0.1	33.1	0.1
	G11	-6.26	-29.2	0.1	40.6	0.1	-1.0	0.2	105.4	0.1	28.4	0.1	9.5	0.1	-2.6	0.1	3.0	0.1
	G12	-11.02	-20.2	0.1	58.7	0.1	-11.9	0.1	150.2	0.2	44.4	0.1	13.7	0.1	24.3	0.1	34.9	0.1
	G13	-8.58	-2.9	0.1	70.2	0.1	20.6	0.1	117.9	0.2	55.6	0.1	30.0	0.1	-	-	-	-
RMSE			19.5		59.8		15.9		135.0		47.9		24.9		24.0		32.4	
MSE			15.1		-58.4		-3.1		-134.2		-45.6		-20.5		-18.8		-27.8	
τ			0.1		-0.1		0.0		-0.1		0.0		-0.1		0.1		-0.1	
PI			-0.1		-0.2		-0.1		0.0		-0.1		-0.1		-0.1		0.0	
Pearson r			-0.2		-0.3		-0.1		-0.2		-0.2		-0.1		-0.3		-0.3	

Table S5. Three-trajectory end-point estimates of WP6 host-guest binding affinities with the GB^{HCT} model (kcal/mol).

Host	Guest	Exp	MM	±	AM1	±	AM1-DH+	±	MNDO	±	PM6	±	PM6-DH+	±	DFTB2	±	DFTB3	±
WP6	G1	-6.53	-99.0	0.3	98.4	0.5	59.0	0.5	105.5	0.7	179.3	0.5	162.6	0.5	-85.0	0.5	-86.5	0.5
	G2	-10.59	-111.5	0.2	111.6	0.5	70.8	0.4	126.6	0.6	186.4	0.4	169.1	0.4	-93.6	0.4	-94.4	0.4
	G3	-8.03	-100.1	0.2	104.7	0.4	72.2	0.4	114.3	0.5	171.3	0.3	156.9	0.3	-79.7	0.4	-78.8	0.4
	G4	-6.50	-89.6	0.2	111.7	0.4	83.4	0.4	116.3	0.5	183.5	0.3	170.9	0.3	-	-	-	-
	G5	-5.46	-101.5	0.3	107.2	0.5	62.6	0.5	132.0	0.7	177.2	0.4	159.0	0.4	-81.2	0.5	-82.6	0.5
	G6	-8.08	-103.0	0.2	106.8	0.4	67.8	0.4	123.7	0.5	177.0	0.3	160.0	0.3	-81.4	0.4	-80.3	0.4
	G7	-7.07	-98.7	0.2	99.2	0.4	69.4	0.4	105.6	0.5	167.5	0.4	154.5	0.4	-81.3	0.4	-81.0	0.5
	G8	-6.04	-91.3	0.2	120.0	0.5	83.2	0.4	111.8	0.6	191.5	0.4	174.2	0.4	-74.1	0.4	-75.4	0.5
	G9	-6.32	-105.3	0.1	118.9	0.4	73.3	0.4	148.1	0.5	184.2	0.3	164.6	0.3	-74.9	0.4	-72.3	0.4
	G10	-9.96	-102.6	0.2	106.1	0.5	73.6	0.4	108.8	0.7	179.0	0.4	163.9	0.4	-91.0	0.4	-92.5	0.4
	G11	-6.26	-91.8	0.2	99.9	0.4	73.9	0.4	106.8	0.5	165.7	0.3	154.2	0.3	-78.3	0.4	-78.3	0.4
	G12	-11.02	-110.6	0.2	115.3	0.5	68.8	0.4	131.9	0.6	186.2	0.4	167.0	0.4	-91.7	0.4	-93.2	0.4
	G13	-8.58	-99.2	0.2	114.2	0.5	85.0	0.4	104.5	0.5	179.7	0.4	164.1	0.4	-	-	-	-
RMSE			92.8		116.7		80.6		126.6		187.0		171.0		75.3		75.7	
MSE			92.6		-116.5		-80.3		-125.9		-186.8		-170.9		75.2		75.4	
τ			0.5		-0.1		0.1		0.0		-0.1		-0.2		0.6		0.5	
PI			0.7		0.0		0.0		0.0		-0.1		-0.1		0.8		0.7	
Pearson r			0.7		-0.2		0.0		-0.1		-0.2		-0.2		0.9		0.8	

Table S6. Three-trajectory end-point estimates of WP6 host-guest binding affinities with the GB^{OBC-I} model (kcal/mol).

Host	Guest	Exp	MM	±	AM1	±	AM1-DH+	±	MNDO	±	PM6	±	PM6-DH+	±	DFTB2	±	DFTB3	±
WP6	G1	-6.53	-97.3	0.3	110.9	0.5	71.5	0.5	114.5	0.7	193.6	0.5	176.8	0.5	-82.2	0.5	-83.9	0.5
	G2	-10.59	-108.8	0.2	122.4	0.5	81.6	0.4	135.9	0.6	198.6	0.4	181.3	0.4	-91.4	0.4	-91.9	0.4
	G3	-8.03	-98.5	0.2	115.8	0.4	83.3	0.4	123.2	0.5	184.5	0.4	170.1	0.4	-76.1	0.4	-75.3	0.4
	G4	-6.50	-86.1	0.2	121.9	0.4	93.6	0.4	126.6	0.5	195.0	0.4	182.4	0.3	-	-	-	-
	G5	-5.46	-99.8	0.3	116.7	0.5	72.1	0.5	140.9	0.7	186.6	0.4	168.4	0.4	-79.6	0.5	-80.8	0.5
	G6	-8.08	-101.8	0.2	117.4	0.4	78.4	0.4	132.6	0.5	190.0	0.3	173.0	0.3	-78.0	0.4	-77.0	0.4
	G7	-7.07	-96.9	0.2	109.4	0.4	79.6	0.4	114.4	0.5	180.1	0.4	167.1	0.4	-77.9	0.4	-77.8	0.5
	G8	-6.04	-88.5	0.2	135.1	0.5	98.3	0.4	123.1	0.6	207.0	0.4	189.7	0.4	-72.2	0.5	-72.3	0.5
	G9	-6.32	-114.0	0.1	128.4	0.4	82.9	0.4	156.5	0.5	192.9	0.3	173.3	0.3	-74.0	0.4	-71.5	0.4
	G10	-9.96	-100.0	0.2	116.6	0.5	84.2	0.4	117.3	0.7	191.1	0.4	176.1	0.4	-88.5	0.4	-89.7	0.4
	G11	-6.26	-89.9	0.2	110.0	0.4	83.9	0.4	116.0	0.5	176.7	0.4	165.2	0.4	-74.9	0.4	-75.1	0.4
	G12	-11.02	-107.5	0.2	126.1	0.5	79.6	0.4	140.8	0.7	198.2	0.4	179.0	0.4	-89.3	0.4	-90.6	0.4
	G13	-8.58	-94.8	0.2	125.2	0.5	95.9	0.4	112.0	0.6	193.3	0.4	177.7	0.4	-	-	-	-
RMSE			91.3		127.7		91.5		135.6		199.3		183.3		72.8		73.0	
MSE			91.0		-127.4		-91.2		-134.9		-199.1		-183.1		72.6		72.8	
τ			0.4		-0.1		0.1		0.0		-0.2		-0.2		0.6		0.5	
PI			0.4		0.0		0.0		0.1		-0.2		-0.2		0.8		0.7	
Pearson r			0.5		-0.1		0.0		0.0		-0.3		-0.2		0.8		0.8	

Table S7. Three-trajectory end-point estimates of WP6 host-guest binding affinities with the GB^{OBC-II} model (kcal/mol).

Host	Guest	Exp	MM	±	AM1	±	AM1-DH+	±	MNDO	±	PM6	±	PM6-DH+	±	DFTB2	±	DFTB3	±
WP6	G1	-6.53	-108.6	0.3	82.4	0.5	42.9	0.5	92.2	0.7	163.9	0.5	147.2	0.5	-90.7	0.5	-92.7	0.5
	G2	-10.59	-119.5	0.2	92.9	0.5	52.2	0.4	116.1	0.6	167.2	0.4	149.9	0.4	-101.0	0.4	-101.0	0.4
	G3	-8.03	-111.2	0.2	85.3	0.4	52.8	0.4	99.9	0.5	154.0	0.3	139.5	0.3	-85.7	0.4	-85.2	0.4
	G4	-6.50	-97.7	0.2	87.2	0.4	59.0	0.4	102.3	0.5	162.8	0.3	150.2	0.3	-	-	-	-
	G5	-5.46	-111.1	0.3	88.3	0.5	43.7	0.5	123.3	0.7	153.1	0.4	134.9	0.4	-90.4	0.5	-91.0	0.5
	G6	-8.08	-115.2	0.2	85.6	0.4	46.5	0.4	108.5	0.5	158.0	0.3	141.0	0.3	-88.2	0.4	-87.5	0.4
	G7	-7.07	-109.1	0.2	78.9	0.4	49.2	0.4	91.4	0.5	149.7	0.4	136.6	0.4	-87.3	0.4	-87.4	0.5
	G8	-6.04	-98.1	0.2	106.6	0.5	69.8	0.4	103.8	0.6	177.4	0.4	160.0	0.4	-80.4	0.5	-79.8	0.5
	G9	-6.32	-138.5	0.1	92.3	0.4	46.7	0.4	129.3	0.5	154.1	0.3	134.5	0.3	-88.1	0.4	-85.9	0.4
	G10	-9.96	-110.7	0.2	87.2	0.5	54.8	0.4	97.1	0.7	160.3	0.4	145.3	0.4	-97.4	0.4	-98.1	0.4
	G11	-6.26	-102.2	0.2	79.9	0.4	53.8	0.4	94.2	0.5	145.6	0.3	134.0	0.3	-84.4	0.4	-84.7	0.4
	G12	-11.02	-117.4	0.2	97.2	0.5	50.7	0.4	121.1	0.7	167.3	0.4	148.1	0.4	-98.3	0.4	-99.3	0.4
	G13	-8.58	-104.0	0.2	97.0	0.5	67.8	0.4	91.1	0.6	165.4	0.4	149.8	0.4	-	-	-	-
RMSE			103.8		97.4		61.4		113.9		167.9		151.9		82.5		82.6	
MSE			103.3		-97.0		-60.8		-113.1		-167.6		-151.6		82.4		82.5	
τ			0.4		-0.2		0.0		0.1		-0.4		-0.3		0.5		0.6	
PI			0.2		-0.1		0.0		0.1		-0.3		-0.3		0.8		0.7	
Pearson r			0.2		-0.2		-0.1		-0.1		-0.3		-0.3		0.8		0.8	

Table S8. Three-trajectory end-point estimates of WP6 host-guest binding affinities with the GBn model (kcal/mol).

Host	Guest	Exp	MM	±	AM1	±	AM1-DH+	±	MNDO	±	PM6	±	PM6-DH+	±	DFTB2	±	DFTB3	±
WP6	G1	-6.53	-95.5	0.3	93.7	0.5	54.3	0.5	115.7	0.7	180.4	0.5	163.6	0.47	-81.6	0.5	-80.2	0.5
	G2	-10.59	-93.3	0.2	113.8	0.4	73.0	0.4	143.9	0.6	205.8	0.4	188.5	0.37	-74.2	0.4	-69.0	0.4
	G3	-8.03	-97.0	0.2	89.3	0.4	56.8	0.4	116.5	0.5	166.8	0.4	152.4	0.37	-78.0	0.4	-73.8	0.4
	G4	-6.50	-78.0	0.2	123.9	0.4	95.6	0.4	133.4	0.5	199.2	0.4	186.6	0.35	-	-	-	-
	G5	-5.46	-83.6	0.3	110.5	0.5	66.0	0.5	150.3	0.7	192.5	0.4	174.4	0.42	-63.7	0.5	-59.0	0.5
	G6	-8.08	-100.0	0.2	89.8	0.4	50.8	0.4	126.8	0.5	168.5	0.3	151.5	0.36	-81.1	0.4	-76.9	0.4
	G7	-7.07	-92.9	0.2	87.0	0.4	57.3	0.5	110.4	0.5	165.9	0.4	152.8	0.40	-77.6	0.4	-74.0	0.4
	G8	-6.04	-76.6	0.2	123.9	0.4	87.2	0.4	138.7	0.6	220.3	0.4	203.0	0.38	-59.6	0.4	-49.8	0.5
	G9	-6.32	-102.0	0.1	95.6	0.4	50.0	0.4	145.9	0.5	169.8	0.3	150.2	0.34	-78.7	0.4	-72.4	0.4
	G10	-9.96	-84.4	0.2	113.0	0.4	80.5	0.4	124.7	0.7	204.3	0.4	189.2	0.37	-70.0	0.4	-66.4	0.4
	G11	-6.26	-85.8	0.2	91.3	0.4	65.3	0.4	111.4	0.5	164.3	0.4	152.7	0.39	-74.1	0.4	-71.7	0.4
	G12	-11.02	-95.2	0.2	117.3	0.4	70.7	0.4	150.0	0.7	205.0	0.4	185.8	0.36	-73.5	0.4	-68.3	0.4
	G13	-8.58	-73.9	0.2	130.4	0.5	101.1	0.4	123.4	0.6	213.1	0.4	197.5	0.36	-	-	-	-
RMSE			81.8		114.9		79.4		138.6		197.7		181.7		66.4		62.0	
MSE			81.4		-113.8		-77.6		-137.8		-196.6		-180.7		66.1		61.5	
τ			0.2		-0.1		-0.1		0.0		-0.2		-0.1		0.1		0.1	
PI			0.3		-0.2		-0.1		0.0		-0.2		-0.2		0.4		0.4	
Pearson r			0.2		-0.3		-0.2		-0.2		-0.4		-0.3		0.2		0.2	

Table S9. Comparison between quality metrics computed with all guest molecules and without G4 and G13 (the two guests with convergence problems or with elements unsupported for DFTB Hamiltonians) in the single- and three-trajectory realizations for all post-processing Hamiltonians except DFTB. The GB^{OBC-II} implicit solvent model is used here. The inclusion/exclusion of G4 and G13 perturbs the results in a Hamiltonian-dependent manner, but the magnitudes of variations of the quality metrics are generally insignificant.

Single Trajectory	all guests						without G4 and G13					
	MM	AM1	AM1-DH+	MNDO	PM6	PM6-DH+	MM	AM1	AM1-DH+	MNDO	PM6	PM6-DH+
RMSE	18.3	73.3	20.3	135.9	57.7	33.0	19.7	73.3	18.9	138.1	57.1	31.9
MSE	12.7	-73.0	-17.8	-135.1	-57.4	-32.2	14.3	-73.0	-16.1	-137.3	-56.8	-31.1
τ	0.0	-0.3	0.2	-0.1	-0.2	0.2	0.0	-0.3	0.2	-0.2	-0.3	0.1
PI	-0.1	-0.2	0.0	0.0	0.0	0.1	0.0	-0.2	0.0	-0.1	-0.1	-0.1
Pearson r	-0.2	-0.3	0.0	-0.2	0.0	0.1	-0.2	-0.3	0.0	-0.2	-0.1	0.0

Three Trajectory	all guests						without G4 and G13					
	MM	AM1	AM1-DH+	MNDO	PM6	PM6-DH+	MM	AM1	AM1-DH+	MNDO	PM6	PM6-DH+
RMSE	103.8	97.4	61.4	113.9	167.9	151.9	105.6	96.9	59.4	115.5	167.2	150.8
MSE	103.3	-97.0	-60.8	-113.1	-167.6	-151.6	105.1	-96.5	-59.0	-114.8	-166.9	-150.6
τ	0.4	-0.2	0.0	0.1	-0.4	-0.3	0.5	-0.2	-0.1	-0.1	-0.4	-0.4
PI	0.2	-0.1	0.0	0.1	-0.3	-0.3	0.3	0.0	0.1	0.0	-0.2	-0.3
Pearson r	0.2	-0.2	-0.1	-0.1	-0.3	-0.3	0.2	-0.2	-0.1	-0.1	-0.3	-0.3