

**Converging ligand-binding free energies obtained with free-energy
perturbations at the quantum mechanical level**

Supplementary material

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Figure S1. Distribution (left) and normality-probability plots (right) for three typical $E_{QM} - E_{MM}$ results: Ligand Hep from the simulation with the host (top; from the Hep→Hx perturbation), ligand Pen without the host (centre; from the Hx→Pen perturbation), and ligand Bz from the simulation with the host (bottom; from the MeBz→Bz perturbation). The plots were constructed by Matlab.

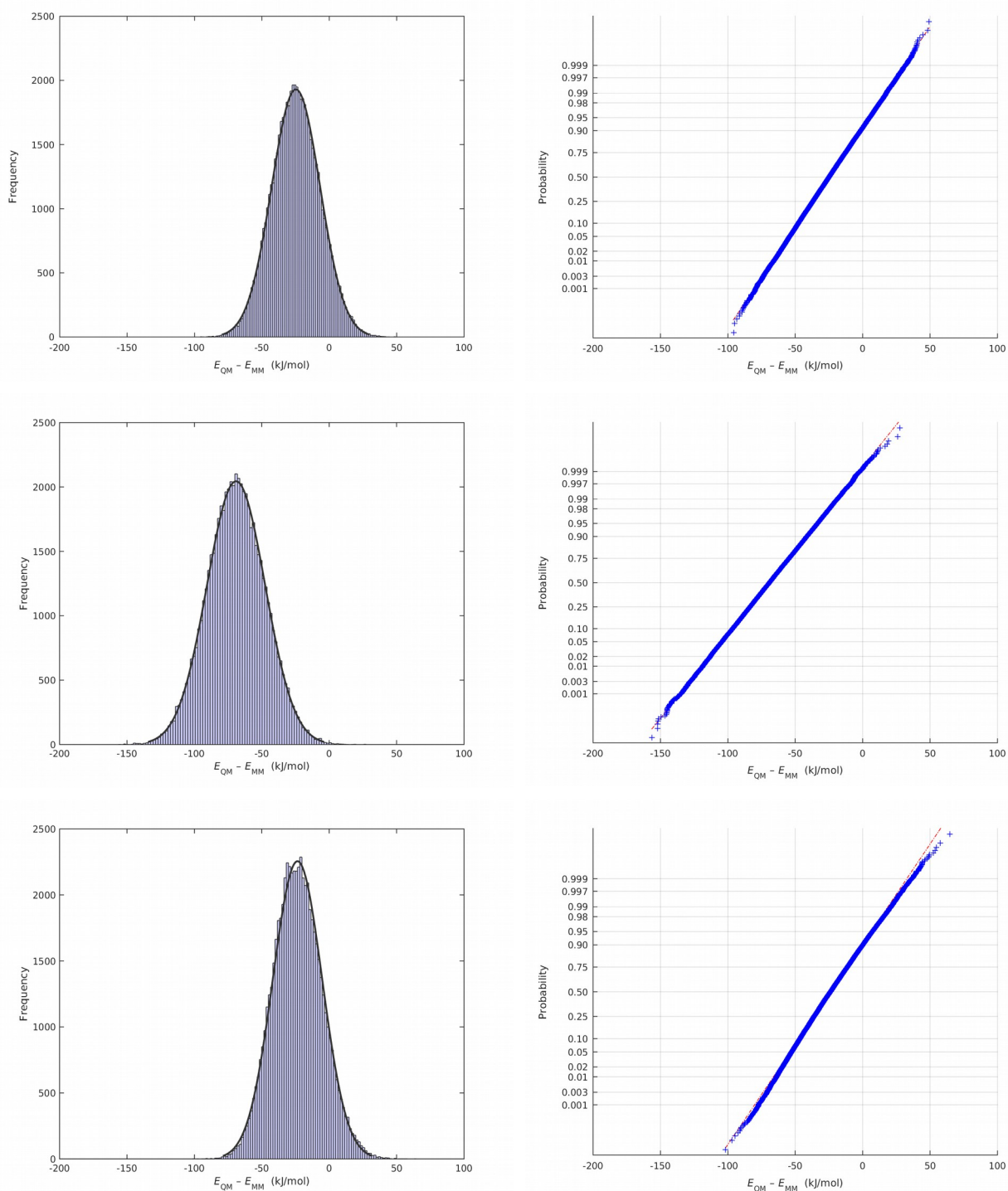


Table S1. AMBER topology file for the NOA host. The third column is the GAFF atom type and the last column is the charge.

```

0      0      2
noa.dat
NOA, with RESP charges, 5/3-14
noa.dat
  OAO INT      1
CHANGE OMIT DU  BEG
0.00000
  1 DUMM DU M 0.0000 0.0000 .0000 .0000
  2 DUMM DU M 0.0000 1.0000 .0000 .0000
  3 DUMM DU M 1.0000 1.0000 .0000 .0000
  4 C55 ca M -1.5220 3.2080 -4.2130 -0.137304
  5 H28 ha E -0.9350 3.9470 -3.6740 0.077201
  6 C42 ca M -2.4280 2.4090 -3.5740 -0.011167
  7 C56 ca S -3.2280 1.6060 -4.2980 -0.137304
  8 H29 ha E -4.1010 1.1070 -3.8840 0.077201
  9 C9 c3 M -2.6020 2.4590 -2.0300 0.114807
10 O3 os E -2.3830 3.7840 -1.5580 -0.224878
11 H19 h2 E -1.7860 1.8200 -1.6630 0.135169
12 O1 os M -3.8870 1.8990 -1.6480 -0.224878
13 C3 ca M -3.9100 1.1440 -0.5370 0.066965
14 C1 ca M -3.8090 -0.1940 -0.7940 -0.182589
15 H1 ha E -3.7770 -0.4960 -1.8380 0.203172
16 C4 ca M -3.5960 -1.0770 0.2820 0.066965
17 O2 os E -3.5150 -2.4080 -0.0920 -0.224878
18 C5 ca M -3.5760 -0.6530 1.6280 0.062476
19 C7 c3 3 -3.4220 -1.7270 2.6740 -0.029682
20 H12 hc E -4.0350 -1.4450 4.1080 0.057240
21 C32 ca S -1.9080 -2.1060 2.8250 0.062476
22 C31 ca S -1.0700 -1.3980 3.6830 -0.311116
23 H56 ha E -1.4800 -0.5880 4.2800 0.175692
24 H4 hc E -4.0520 -2.5450 2.3190 0.057240
25 C2 ca M -3.6140 0.7180 1.8500 -0.311116
26 H2 ha E -3.5190 1.1430 2.8460 0.175692
27 C6 ca M -3.8150 1.6430 0.7650 0.062476
28 C8 c3 M -3.5870 3.1110 1.0700 -0.029682
29 H13 hc E -4.2140 3.7790 2.3520 0.057240
30 H3 hc E -4.0610 3.5940 0.2130 0.057240
31 C10 ca M -2.1180 3.3410 0.8270 0.062476
32 C15 ca S -1.2000 3.2470 1.8990 -0.311116
33 H5 ha E -1.4830 2.7760 2.8370 0.175692
34 C14 ca M -1.6790 3.8550 -0.3830 0.066965
35 C17 ca M -0.3540 4.2700 -0.5020 -0.182589
36 H6 ha E -0.0230 4.5760 -1.4910 0.203172
37 C13 ca M 0.5180 4.3050 0.5390 0.066965
38 O4 os S 1.9160 4.5440 0.3420 -0.224878
39 C34 c3 3 2.7380 3.3120 0.0870 0.114807
40 C41 ca B 3.7170 3.4890 -1.0630 -0.011167
41 C50 ca S 4.9700 2.8340 -1.1090 -0.137304
42 H25 ha E 5.2320 2.2220 -0.2500 0.077201
43 C51 ca S 3.2900 4.1570 -2.1870 -0.137304
44 H26 ha E 2.3190 4.6440 -2.1600 0.077201
45 O5 os E 3.3430 2.9830 1.3450 -0.224878
46 H18 h2 E 2.1180 2.4680 -0.2510 0.135169
47 C16 ca M 0.0690 3.7170 1.7650 0.062476
48 C18 c3 M 0.9430 3.6670 3.0350 -0.029682
49 H14 hc E 0.2660 4.1450 4.3360 0.057240
50 H7 hc E 1.7670 4.3580 2.8390 0.057240
51 C19 ca M 1.6220 2.2760 2.9700 0.062476
52 C23 ca S 1.0540 1.2190 3.7130 -0.311116
53 H8 ha E 0.1680 1.3470 4.3280 0.175692
54 C22 ca M 2.7970 2.0530 2.2300 0.066965
55 C25 ca M 3.4100 0.8020 2.2740 -0.182589
56 H9 ha E 4.2770 0.6000 1.6510 0.203172
57 C21 ca M 2.9540 -0.1560 3.1840 0.066965
58 O6 os S 3.5260 -1.3650 2.9920 -0.224878
59 C38 c3 3 2.8680 -2.3720 2.1430 0.114807
60 C40 ca B 3.7410 -3.0970 1.1560 -0.011167
61 C45 ca S 4.6920 -2.4430 0.4170 -0.137304

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62	H22	ha	E	4.8000	-1.3670	0.5280	0.077201
63	C46	ca	S	3.7040	-4.5050	0.9540	-0.137304
64	H23	ha	E	3.0520	-5.1060	1.5820	0.077201
65	O7	os	E	2.0630	-3.1990	3.0450	-0.224878
66	H20	h2	E	2.1440	-1.8390	1.5090	0.135169
67	C24	ca	M	1.8100	0.0410	3.8860	0.062476
68	C26	c3	M	1.2020	-1.0390	4.7470	-0.029682
69	H15	hc	E	0.5170	-0.7400	6.1700	0.057240
70	H10	hc	E	2.0710	-1.6340	5.0360	0.057240
71	C28	ca	M	0.2870	-1.7610	3.8000	0.062476
72	C30	ca	M	0.7650	-2.8410	3.0580	0.066965
73	C33	ca	M	-0.0940	-3.5100	2.1790	-0.182589
74	H11	ha	E	0.2760	-4.3380	1.5800	0.203172
75	C29	ca	M	-1.3960	-3.1670	2.0210	0.066965
76	O8	os	M	-2.2010	-3.7230	1.1090	-0.224878
77	C39	c3	M	-2.2460	-3.0170	-0.1190	0.114807
78	H21	h2	E	-1.4410	-2.2680	-0.1360	0.135169
79	C43	ca	M	-2.1220	-3.8470	-1.3610	-0.011167
80	C61	ca	S	-2.8770	-3.6480	-2.4770	-0.137304
81	H32	ha	E	-3.5880	-2.8250	-2.4940	0.077201
82	C60	ca	M	-1.1610	-4.8870	-1.5080	-0.137304
83	H31	ha	E	-0.4580	-5.0240	-0.6910	0.077201
84	C63	ca	M	-1.0570	-5.6870	-2.6250	0.170479
85	O16	os	E	-0.0010	-6.5630	-2.7380	-0.295814
86	C59	ca	M	-1.7870	-5.3340	-3.7420	-0.166592
87	H33	ha	E	-1.5690	-5.8270	-4.6860	0.155458
88	C62	ca	M	-2.6680	-4.2930	-3.7170	0.170479
89	O15	os	M	-3.2710	-3.9870	-4.9160	-0.295814
90	C77	ca	M	-4.0610	-2.9060	-5.1440	0.129911
91	C74	ca	S	-3.4630	-1.7490	-5.6080	-0.125196
92	H37	ha	E	-2.3900	-1.5760	-5.6390	0.161643
93	C73	ca	M	-5.3960	-3.1620	-5.3070	-0.070243
94	H39	ha	E	-5.8020	-4.1500	-5.1040	0.152216
95	C76	ca	M	-6.2480	-2.1320	-5.6650	-0.271146
96	H78	ha	E	-7.7260	-2.3950	-5.6970	0.175048
97	C75	ca	M	-5.6930	-0.8190	-5.9550	-0.070243
98	H38	ha	E	-6.2600	0.0840	-6.1660	0.152216
99	C65	ca	M	-4.3320	-0.6840	-5.8620	0.129911
100	O13	os	M	-3.8470	0.5350	-6.3550	-0.295814
101	C57	ca	M	-2.9710	1.3190	-5.6770	0.170479
102	C54	ca	M	-1.8770	1.9370	-6.2420	-0.166592
103	H30	ha	E	-1.5790	1.6560	-7.2490	0.155458
104	C58	ca	M	-1.1840	2.8990	-5.5540	0.170479
105	O14	os	M	-0.2710	3.6030	-6.3370	-0.295814
106	C71	ca	M	0.4830	4.5680	-5.7770	0.129911
107	C70	ca	S	1.8070	4.3690	-5.3040	-0.125196
108	H35	ha	E	2.2100	3.3690	-5.4340	0.161643
109	C68	ca	M	-0.0980	5.8230	-5.7250	-0.070243
110	H36	ha	E	-1.1120	5.9550	-6.0950	0.152216
111	C72	ca	M	0.6450	6.9110	-5.2020	-0.271146
112	H91	ha	E	0.0390	8.2950	-5.3010	0.175048
113	C69	ca	M	1.9590	6.6470	-4.7050	-0.070243
114	H34	ha	E	2.5290	7.4240	-4.2020	0.152216
115	C64	ca	M	2.5180	5.3940	-4.7170	0.129911
116	O11	os	M	3.8140	5.1790	-4.2690	-0.295814
117	C52	ca	M	4.1400	4.3350	-3.2140	0.170479
118	C49	ca	M	5.3730	3.6990	-3.1920	-0.166592
119	H27	ha	E	5.9960	3.9250	-4.0530	0.155458
120	C53	ca	M	5.8060	2.9660	-2.1720	0.170479
121	O12	os	M	6.9260	2.1980	-2.4430	-0.295814
122	C89	ca	M	7.1340	1.1040	-1.6430	0.129911
123	C86	ca	S	6.6520	-0.1000	-2.0110	-0.125196
124	H43	ha	E	6.1020	-0.1680	-2.9460	0.161643
125	C85	ca	M	8.0540	1.1990	-0.5600	-0.070243
126	H45	ha	E	8.4490	2.1800	-0.3090	0.152216
127	C88	ca	M	8.3250	0.1190	0.2670	-0.271146
128	H90	ha	E	8.9880	0.2140	1.6550	0.175048
129	C87	ca	M	7.7270	-1.0940	-0.1070	-0.070243
130	H44	ha	E	7.8830	-1.9790	0.5050	0.152216
131	C67	ca	M	6.8860	-1.2180	-1.1970	0.129911
132	O10	os	M	6.3190	-2.4960	-1.3660	-0.295814
133	C48	ca	M	5.4160	-3.0580	-0.5800	0.170479

134	C44	ca	M	5.1650	-4.3950	-0.9060	-0.166592
135	H24	ha	E	5.6610	-4.9270	-1.7140	0.155458
136	C47	ca	M	4.2660	-5.1190	-0.1630	0.170479
137	O9	os	M	4.1460	-6.4310	-0.3410	-0.295814
138	C83	ca	M	2.9300	-6.9620	-0.4970	0.129911
139	C79	ca	M	2.3990	-7.8210	0.3850	-0.070243
140	H42	ha	E	3.0780	-8.2120	1.1390	0.152216
141	C82	ca	M	1.1080	-8.2640	0.3810	-0.271146
142	H84	ha	E	0.6290	-9.2780	1.4400	0.175048
143	C81	ca	M	0.2650	-7.7360	-0.6370	-0.070243
144	H41	ha	E	-0.7330	-8.1450	-0.7710	0.152216
145	C66	ca	M	0.7510	-6.9350	-1.6650	0.129911
146	C80	ca	M	2.0660	-6.4710	-1.4940	-0.125196
147	H40	ha	E	2.3850	-5.6980	-2.1880	0.161643

LOOP

C58	C55
C57	C56
C14	O3
C6	C3
C39	O2
C29	C32
C28	C31
C16	C15
C53	C50
C52	C51
C22	O5
C24	C23
C48	C45
C47	C46
C30	O7
C62	C61
C66	O16
C65	C74
C64	C70
C67	C86
C80	C83

IMPROPER

C58	C42	C55	H28
C9	C55	C42	C56
C57	C42	C56	H29
C1	C6	C3	O1
C3	C4	C1	H1
C1	C5	C4	O2
C7	C4	C5	C2
C7	C29	C32	C31
C28	C32	C31	H56
C5	C6	C2	H2
C8	C3	C6	C2
C8	C15	C10	C14
C10	C16	C15	H5
C10	C17	C14	O3
C14	C13	C17	H6
C17	C16	C13	O4
C34	C50	C41	C51
C53	C41	C50	H25
C52	C41	C51	H26
C18	C15	C16	C13
C18	C23	C19	C22
C19	C24	C23	H8
C19	C25	C22	O5
C22	C21	C25	H9
C25	C24	C21	O6
C38	C45	C40	C46
C48	C40	C45	H22
C47	C40	C46	H23
C26	C23	C24	C21
C26	C30	C28	C31
C28	C33	C30	O7
C30	C29	C33	H11

C33	C32	C29	O8
C39	C61	C43	C60
C43	C62	C61	H32
C43	C63	C60	H31
C60	C59	C63	O16
C63	C62	C59	H33
C61	C59	C62	O15
C74	C73	C77	O15
C77	C65	C74	H37
C77	C76	C73	H39
H78	C73	C76	C75
C76	C65	C75	H38
C74	C75	C65	O13
C54	C56	C57	O13
C57	C58	C54	H30
C54	C55	C58	O14
C70	C68	C71	O14
C71	C64	C70	H35
C71	C72	C68	H36
H91	C68	C72	C69
C72	C64	C69	H34
C70	C69	C64	O11
C49	C51	C52	O11
C52	C53	C49	H27
C49	C50	C53	O12
C86	C85	C89	O12
C89	C67	C86	H43
C89	C88	C85	H45
H90	C85	C88	C87
C88	C67	C87	H44
C86	C87	C67	O10
C44	C45	C48	O10
C48	C47	C44	H24
C44	C46	C47	O9
C79	C80	C83	O9
C83	C82	C79	H42
H84	C79	C82	C81
C82	C66	C81	H41
C81	C80	C66	O16
C83	C66	C80	H40

DONE
STOP

Table S2. $\Delta G_{MM \rightarrow QM}$ energy estimates (kJ/mol) for the various simulations involving the same ligand with or without the host, employing all 60 000 snapshots. The reported values for the individual simulations are ssEAc estimates with bootstrapped error estimates. The error estimate of the averages are the standard deviation divided by the square root of the number of instances (2 or 4). The $\Delta \Delta G_{MM \rightarrow QM}$ results in Table 3 in the main article are obtained from the difference of $\Delta G_{MM \rightarrow QM}$ values for the two ligands and for the simulations with and without host (for example, the $\Delta \Delta G_{MM \rightarrow QM}$ results for Hx \rightarrow Bz is $-91.51 - (-85.11) - (-162.42 - (-171.53)) = -15.51$ kJ/mol). Deviating values are marked in bold face.

Ligand	Simulation	with host	without host
Bz	MeBz \rightarrow Bz	-90.18 \pm 0.38	-156.98 \pm 0.60
	pClBz \rightarrow Bz	-90.81 \pm 0.39	-161.59 \pm 0.61
	mClBz \rightarrow Bz	-90.11 \pm 0.39	-162.36 \pm 0.62
	Hx \rightarrow Bz	-91.51 \pm 0.38	-162.42 \pm 0.62
	Average	-90.65 \pm 0.33	-160.84 \pm 1.30
MeBz	MeBz \rightarrow Bz	-89.04 \pm 0.37	-169.58 \pm 0.60
	EtBz \rightarrow MeBz	-89.04 \pm 0.37	-164.25 \pm 0.61
	Average	-89.04 \pm 0.00	-166.92 \pm 2.67
Hx	Hx \rightarrow Bz	-85.11 \pm 0.39	-171.53 \pm 0.56
	MeHx \rightarrow Hx	-82.37 \pm 0.39	-163.15 \pm 0.51
	Pen \rightarrow Hx	-84.49 \pm 0.39	-172.84 \pm 0.55
	Hep \rightarrow Hx	-84.19 \pm 0.38	-171.49 \pm 0.54
	Average	-84.04 \pm 0.59	-169.75 \pm 2.22