SOMD/AM1BCC-GAFF-TIP3P/MBAR/C CB8-G3-0 CB8-G3-4 2 -6 Mean ΔG CB8-G3-1 CB8-G3-2 Ref mean ΔG Bias to reference [kcal/mol] -8 CB8-G3-3 -2 ΔG [kcal/mol] -10 -4 -6 **OA-G3-4** OA-G6-4 -14OA-G3-0 OA-G6-0 OA-G3-1 -8 Mean ΔG OA-G6-1 Mean ΔG OA-G3-2 Ref mean ΔG OA-G6-2 Ref mean ΔG -16 OA-G3-3 OA-G6-3 -10 Simulation percentage Simulation percentage Simulation percentage (N energy evaluations: 459,995,400) (N energy evaluations: 419,995,800) (N energy evaluations: 419,995,800) 0.5 20.0 submission var submission var submission var reference var 17.5 reference var reference var 2.0 submission fitted submission fitted submission fitted 0.4 15.0 reference fitted reference fitted reference fitted efficiency 10 submission optimized fitted submission optimized fitted submission optimized fitted 0.3 1.5 0.2 1.0 7.5 5.0

200

Simulation percentage (N energy evaluations: 419,995,800)

300

100

0.1

0.0

0

300

400

2.5

0.0

100

200

0.5

0.0

0

100

200

300

400

400