Comparison of QM/MM Methods To Obtain Ligand-Binding Free Energies

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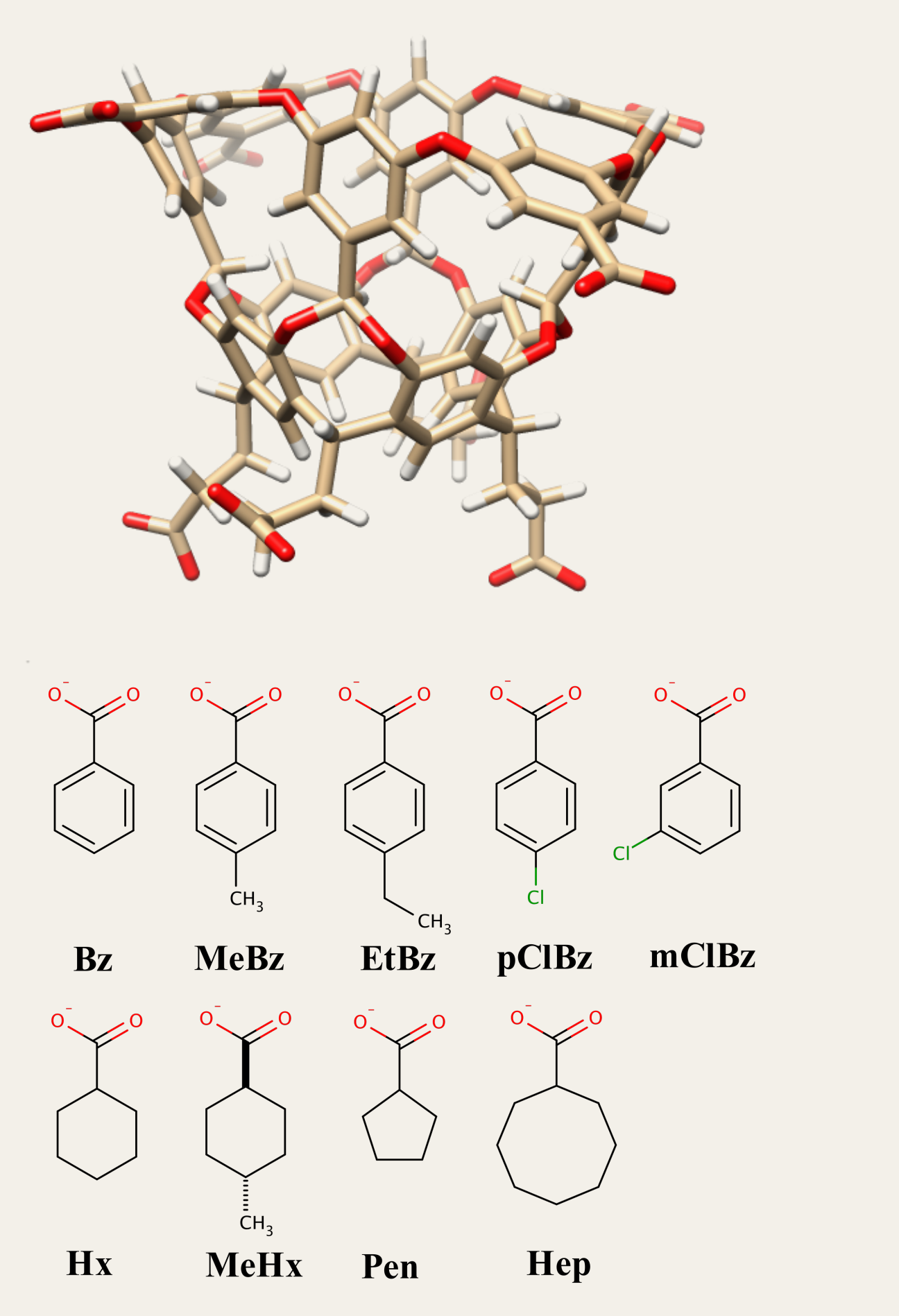

Fig. 1. (Top) Octa-acid deep-cavitand host (OA). (Bottom) Guest molecules that bind to OA.

Abstract

We have compared two approaches to calculate relative binding free energies employing molecular dynamics simulations at the combined quantum-mechanical/molecular mechanics (QM/MM) level. As a test case, we study the binding of nine cyclic carboxylate ligands to the octa-acid deep-cavitand host system. In the first approach, we perform direct alchemical QM/MM free energy perturbation (FEP). In the second, reference-potential approach, we convert the ligands with FEP at the molecular mechanics (MM) level and then perform also MM→QM/MM FEP for each ligand. We show that the two approaches give identical results within statistical uncertainty. For the reference-potential approach, the MM→QM/MM perturbation converges in terms of energies, uncertainties, and overlap measures with two intermediate states, giving a precision of 0.5–0.9 kJ/mol for all eight transformations considered. On the other hand, the QM/MM-FEP approach requires 17–18 intermediate states, showing that the reference-potential approach is more effective.

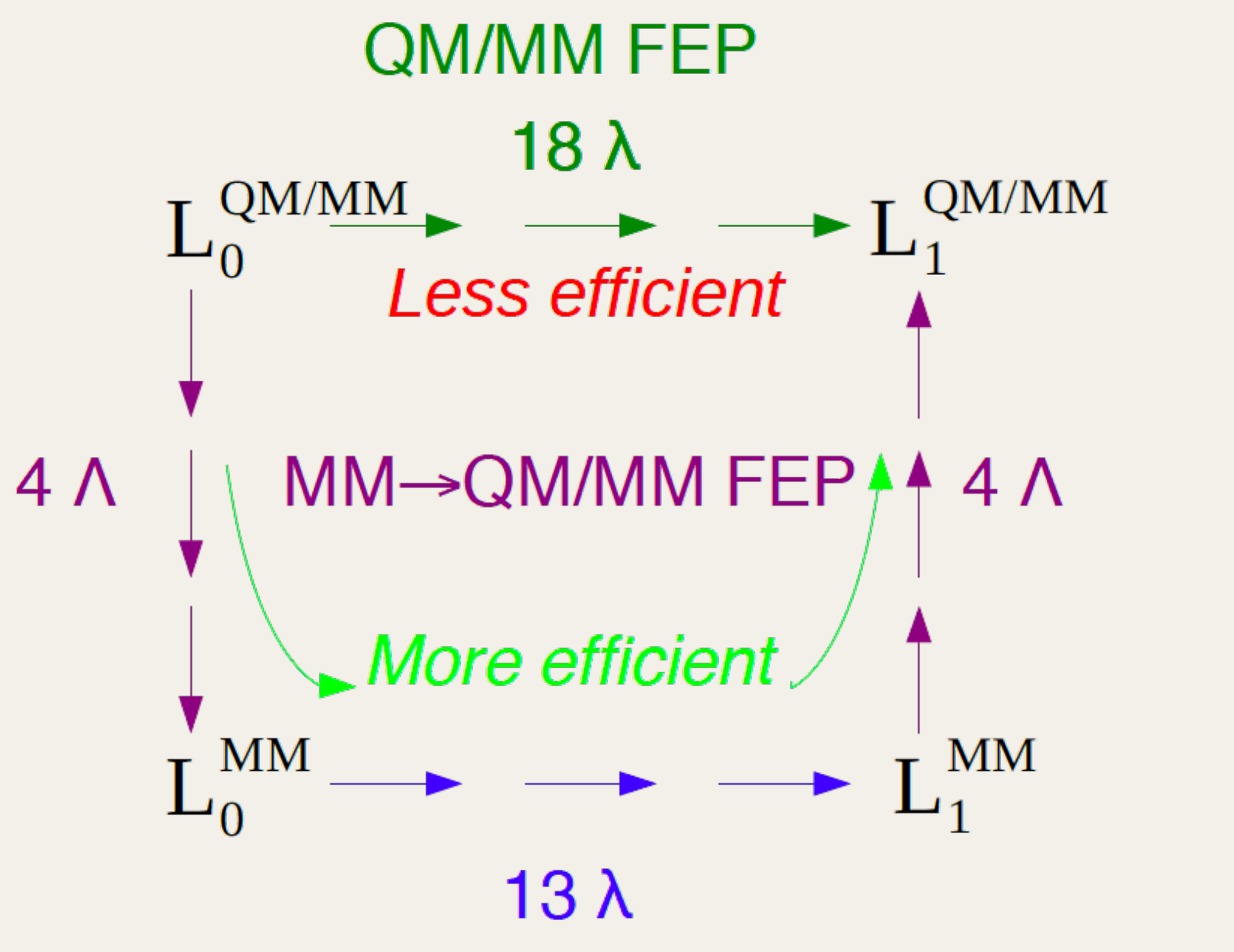

Fig. 2. Thermodynamic cycle for the full QM/MM FEP (direct) and reference-potential QM/MM FEP methods.

Introduction

One of the largest challenges of computational chemistry is to accurately predict the binding affinities of small molecules to biological macromolecules. If such affinities could reliably be predicted this would revolutionise drug discovery [1,2]. FEP simulations should in principle give the correct results, provided that the energy function is perfect and the sampling is infinite. If only the ligand is treated with a cheap semiempirical QM method, a full FEP could be performed with the combined QM/MM potential. Only a few applications with such an approach have been presented, but often with impressive results [3]. However, it has been more common to employ more accurate QM methods (e.g. density functional theory or coupled-cluster calculations) and reference-potential methods [4-6]. In these, the phase space is still sampled with MM methods and these simulations are then used to perform a FEP in the method space, from the MM to the QM/MM potential. The prime problem with these approaches is to properly converge the MM→QM/MM perturbation. Here we try to improve the convergence by doing the QM/MM MD simulations. We do FEP calculations with up to seven intermediate states in the MM→QM/MM perturbations. Moreover, we compare the accuracy and efficiency of reference-potential calculations with full QM/MM FEP simulations of the same systems.

Methods

We have studied the relative binding free energy of nine cyclic carboxylate ligands to the octa-acid deep-cavity host, originally involved in the SAMPL4 competition. The octa-acid host and the nine ligands are shown in Fig. 1. Eight ligand transformations were considered: MeBz→Bz, EtBz→MeBz, pClBz→Bz, mClBz→Bz, Hx→Bz, MeHx→Hx, Hx→Pen, and Hep→Hx (Fig. 1).

MM

The host and guest molecules were parameterized using the GAFF force field with HF/6-31G* RESP charges. Amber 14 was used for MD simulations with the explicit water model TIP3P. For 8 perturbations with a coupling parameter expansion of 13 λ-values at the MM level of theory, Particle Mesh Ewald MD was performed with production runs of 10 ns/λ.

SQM/MM

The energy function $E(\Lambda) = (1 - \Lambda)\,E_{MM} + \Lambda\,E_{QM/MM}$ is used in method space between MM and QM/MM levels of theory where E_{MM} is the MM energy, $E_{QM/MM}$ is the QM/MM energy, where a coupling parameter Λ is used (to separate it from the λ-coordinate used to alchemically transform L_0 to L_1 in Fig. 3). We employed the semiempirical PM6-DH+ hamiltonian for the QM calculations.

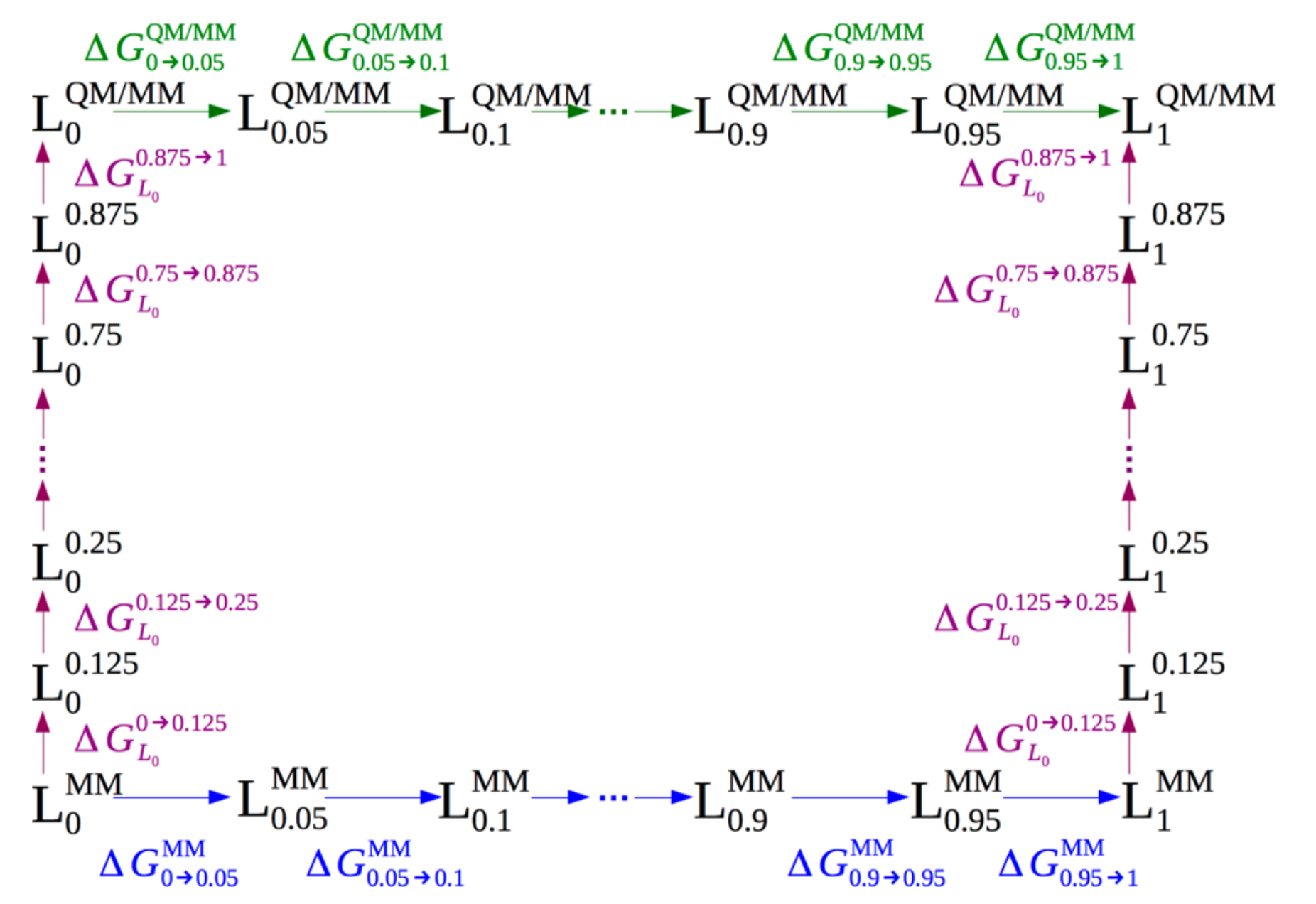

Fig. 3. Thermodynamic cycle employed to study the relative free-energy for the binding of two ligands (L0 and L1) to OA.

Reference-potential	**Full QM/MM FEP**
13 λ-values at MM level	**17-18 λ-values at QM/MM level**
2, 3, 4, 5, 9 Λ in method space	**Only H→ Cl perturbations**
8 perturbations	**2 perturbations**

Results

Both methods agree within statistical uncertainty validating the reference-potential method. However, the reference-potential method is ~4 times more effective (Fig. 5). The SQM/MM energies perform slightly worse than MM energies in reproducing experimental binding energies, with a mean average deviation (MAD) of 4.7 ± 0.2 kJ/mol with 4 Λ compared to the MAD 3.6 ± 0.2 kJ/mol at the MM level. The r^2 is slightly worse than MM (Fig. 7), probably owing to the limited accuracy of the PM6-DH+ hamiltonian.

The QM/MM free-energies converge with a precision of 1 kJ/mol for all perturbations for both the reference-potential method and the direct method. With 4Λ values the precision was on average 0.6 kJ/mol for all calculations (Fig. 4).

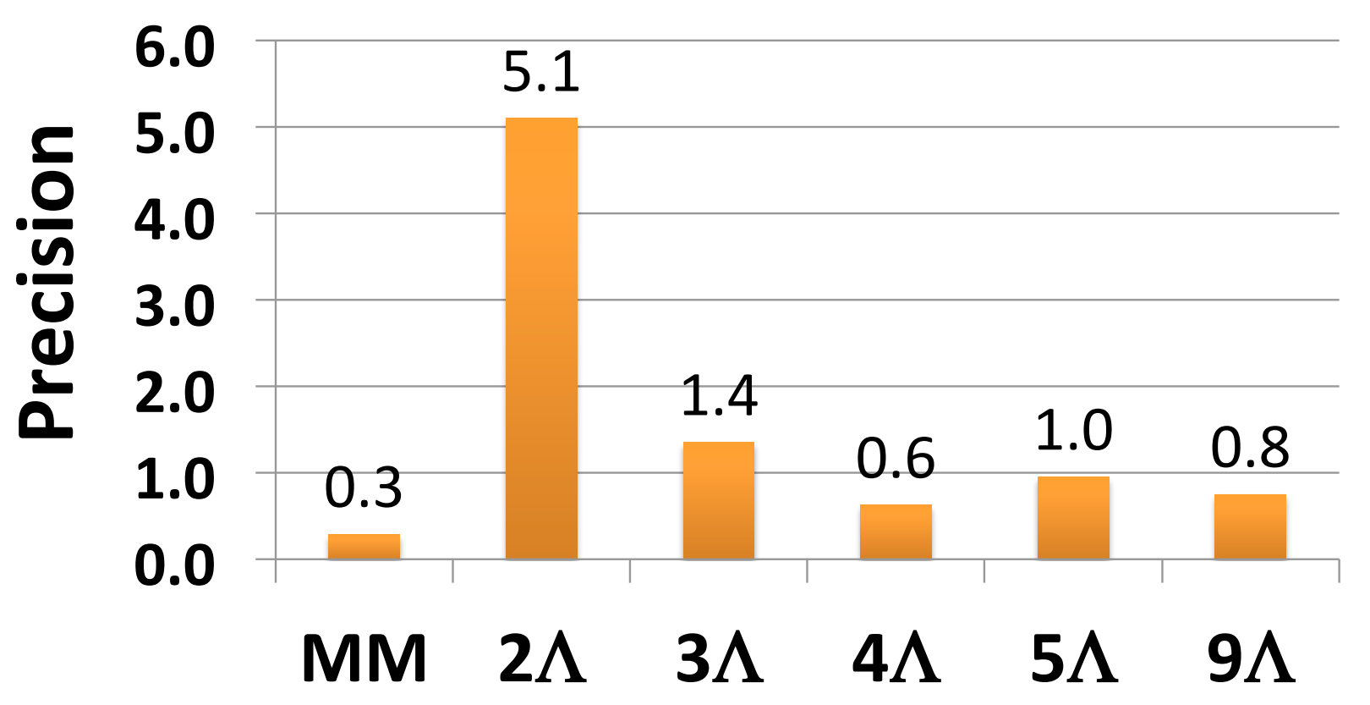

Fig. 4. The average precision of the QM/MM free-energies for OA in Λ–parameter. Unit: kJ/mol.

	Ref.-pot. 4 Λ	**Direct 17-18 λ**	**Δ**
pClBz → Bz	23.3 ± 0.5	23.2 ± 0.9	0.1
mClBz → Bz	9.4 ± 0.5	11.3 ± 0.8	1.9

Fig. 5. Comparison of the reference-potential method and the direct method. Unit: kJ/mol

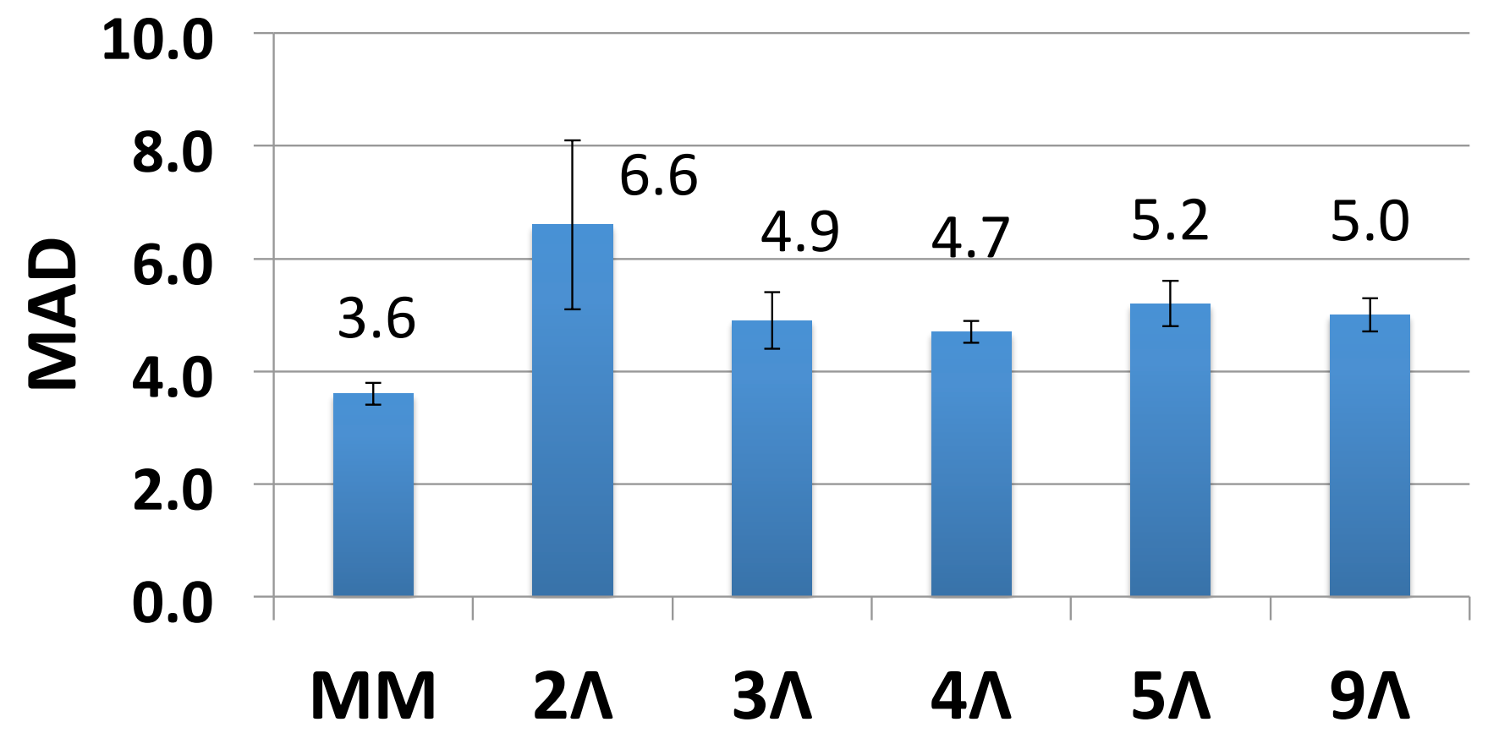

Fig. 6. MAD in Λ–parameter employing QM/MM sampling. Unit: kJ/mol.

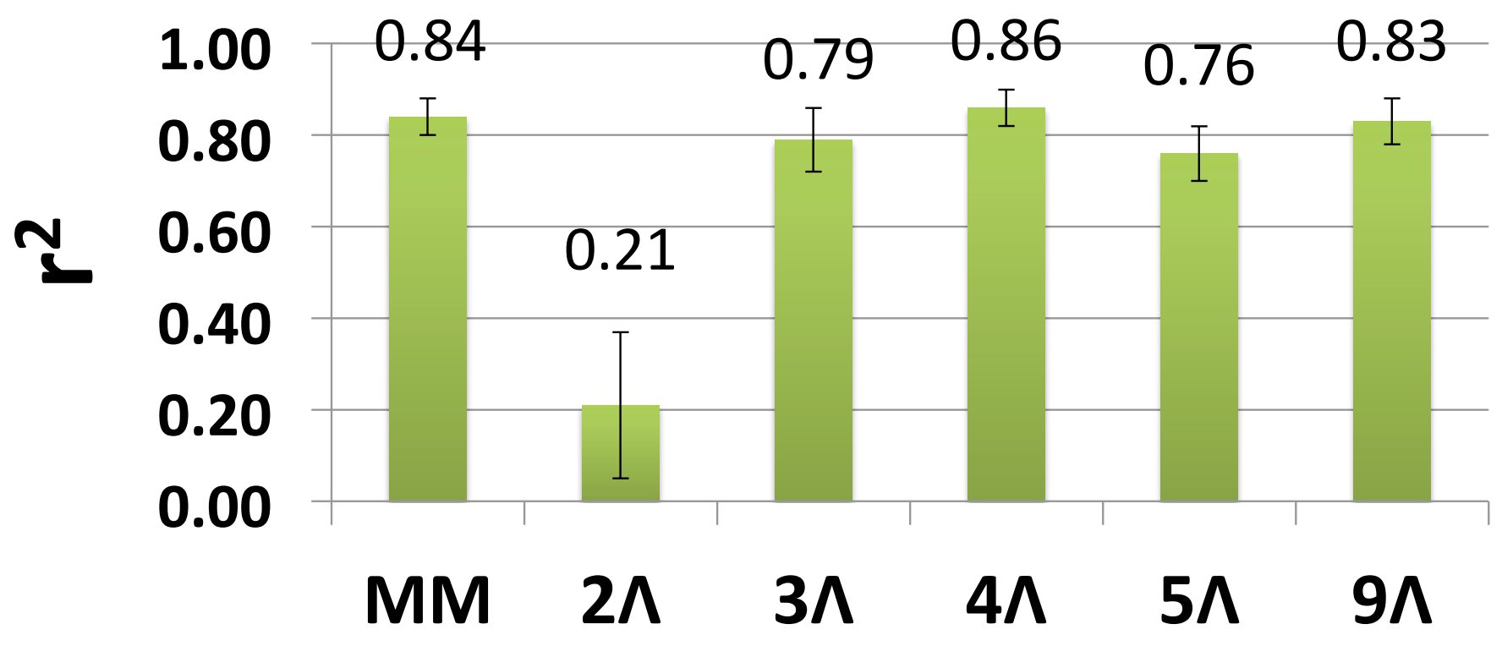

Fig. 7. Comparison of the correlation R^2 with experiment in Λ–parameter of the SQM/MM results for OA. Unit: kJ/mol.

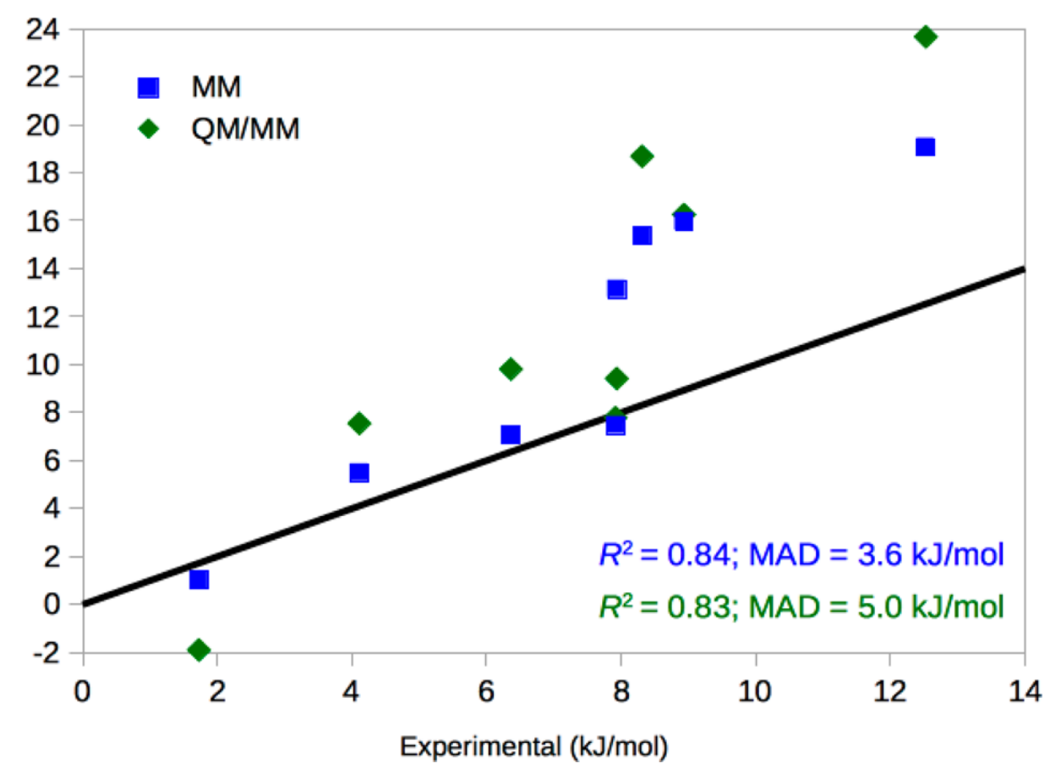

Fig. 8. Comparison of the MM and SQM/MM correlation R^2 to experimental binding energies.

Conclusions

A convergence of the binding free-energy to 0.6 kJ/mol for the reference-potential method with 4Λ has been obtained. The present accuracy for SQM/MM is slightly worse than MM. The direct and reference-potential method agrees to within 0.1–1.9 kJ/mol for the QM/MM binding affinity, with the reference-potential being 4 times more efficient. A 4Λ reference-potential method is recommended for converged QM/MM energies.

J. Chem. Theory Comput., **2017**, *13* (5), pp 2245–2253

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