# Explaining Statin Inhibition Effectiveness of HMG-CoA Reductase by Quantum Biochemistry Computations - Supplementary Information

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## Partial Shielding Effects

When one calculates the interaction energy between an amino acid residue and a ligand, it is important to consider the partial shielding effect caused by the presence of intervening amino acid residues (we note that the data reported previously include this shielding effect).

If the interaction of the statin molecule $S$ with the amino acid residue $R^i$ is shielded by the amino acid residue $R^j$, the total energy between $S$ and $R^i$ is estimated as follows. First, we perform a MFCC calculation to obtain the interaction energy between $S$ and the $R^i$ and $R^j$ residues together (denoted here by $E(S-R^iR^j)$). In this case, $R^i$ and $R^j$ are capped using the same methodology described in the main text of the paper. Afterwards, we calculate the interaction energy between $S$ and $R^j$, without taking into account $R^i$ ($E(S-R^j)$). Finally, we estimated the shielded interaction energy $E'(S-R^i)$ by evaluating the difference between $E(S-R^iR^j)$ and $E(S-R^j)$:

$$E'(S-R^i) = E(S-R^iR^j) - E(S-R^j). \quad (1)$$

In Fig. 1 we present the three possible situations of amino acid shielding observed for the statins complexed with HMGR: R568 shielded by L853, D767 shielded by K691 and R702 by D690. Using the MFCC methodology [1], we have estimated the shielding effect in these three cases. For the R568 interaction, we obtained a maximum decrease for the binding energy of 3.4 kcal/mol for S, 3.2 kcal/mol for F, 1.5 kcal/mol for A, and 0.9 kcal/mol for R when the interaction with L853 is took into account. In the case of D767, a decrease in binding energy of 6.4 kcal/mol was observed for F, 5.2 kcal/mol for S, 4.1 kcal/mol for R and 3.2 kcal/mol for A. The interaction with R702, on the other hand, decreases the binding energy by 3.5 kcal/mol for S, 3.1 kcal/mol for F, 2.3 kcal/mol for A and 1.7 kcal/mol for R. These energy changes due to partial shielding cannot be neglected if we consider that the variation of the total binding energy among the statins is of about 25 kcal/mol.

## References

1 D. W. Zang and J. Z. H. Zhang, *Journal of Chemical Physics*, 2003, **119**, 3599–3605.

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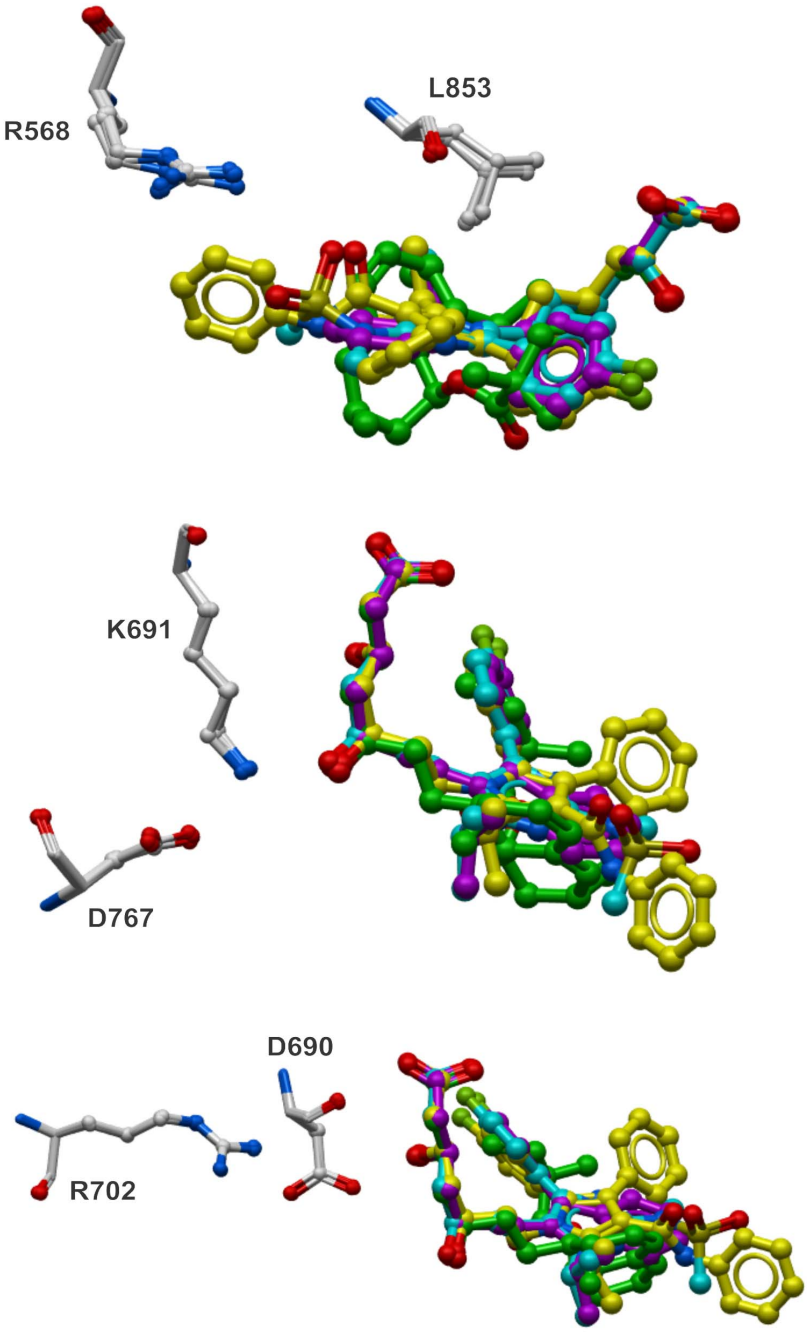


**Fig. 1** Shielded amino acid residues R568, D767, and R702 interacting with atorvastatin, rosuvastatin, simvastatin, and fluvastatin (the molecular structures of the four statins and six amino acid residues are shown superposed).