# Supporting Information

## Projector-based embedding eliminates density functional dependence for QM/MM calculations of reactions in enzymes and solution

Kara E. Ranaghan, Darya Shchepanovska, Simon J. Bennie, Narin Lawan[^], Stephen J. Macrae[§], Jolanta Zurek, Frederick R. Manby and Adrian J. Mulholland*

AUTHOR INFORMATION

Centre for Computational Chemistry, School of Chemistry, University of Bristol, Bristol, UK BS8 1TS.

Corresponding Author

*Adrian J Mulholland: Adrian.Mulholland@bristol.ac.uk

Present Addresses

[^] Department of Chemistry, Faculty of Science, Chiang Mai University, Chiang Mai, Thailand 50200.

[§]Southern Water, Worthing, West Sussex, UK.

KEYWORDS: Quantum mechanics / molecular mechanics (QM/MM), Chorismate mutase, enzyme catalysis, projector embedding.

# Contents

## 1.1 Comparison of adiabatic mapping and nudged elastic band methods

As there is often an energy barrier associated with reaction, we need to use some method to drive the reaction of interest. Simple geometric reaction coordinates e.g. bond lengths or a combination of distances, but can have limitations for complicated reactions. The validity of the reaction coordinate used to model the reaction ($r = d$(C2-O17) – $d$(C4-C14)/Å) was tested using NEB methods. [1, 2] Geometries from one the pathway with chorismate only in the QM region were taken for a NEB calculation. The reactant complex and product complex (fully optimized in QoMMMa without reaction coordinate restraints) were used as the end points for the NEB calculation, with 5 additional geometries created between these two endpoints using linear interpolation of Cartesian Coordinates. The seven images were subsequently subjected to NEB optimization and NEB forces were only applied to the QM atoms using a spring force constant of $k$ = 150 kcal/mol Å$^{-2}$. To obtain a more detailed representation of the pathway near the transition state, a second stage of NEB optimization was run. At this stage, 10 different images were used using the same spring force constant. The second and fifth image of the first stage were used as the edge points for NEB (and thus fixed). These points were chosen as they enclose a region of the profile where the reaction coordinate changes more sharply in adiabatic mapping. Images 3 and 4 from the first stage were also included, with additional images created between them, using linear interpolation. Three additional images were added between images 2 (now edge point) and 3, two between images 3 and 4 and one between 4 and 5 (edge point), giving a total of ten images in the second stage simulation. As before, the edge images were fixed and all the other images were free to move. After the second-stage NEB was converged,

the structures were subjected to a climbing-image NEB[1] procedure to obtain the fully optimized profile.

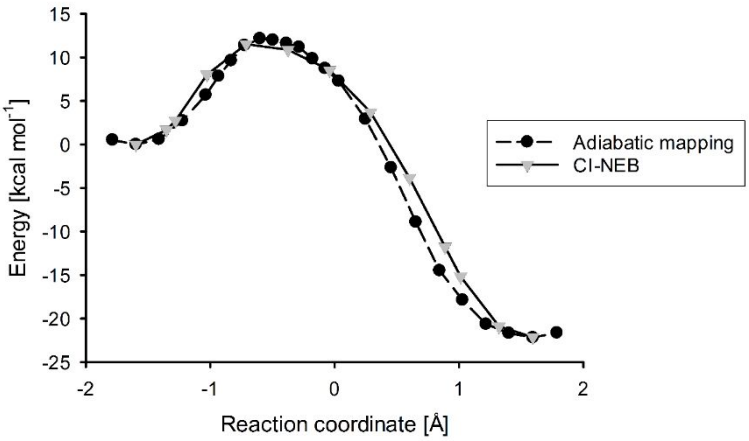


Figure S1. A comparison of potential energy profiles for the conversion of chorismate to prephenate generated using adiabatic mapping and climbing image nudged elastic band (CI-NEB) methods at the B3LYP/6-31G(d)/CHARMM27 level of theory. No reaction coordinate was used in the generation of the CI-NEB profile, the geometric properties were extracted from the images to facilitate comparison. All energies are relative to the reactant ($r$ = −1.8 Å).

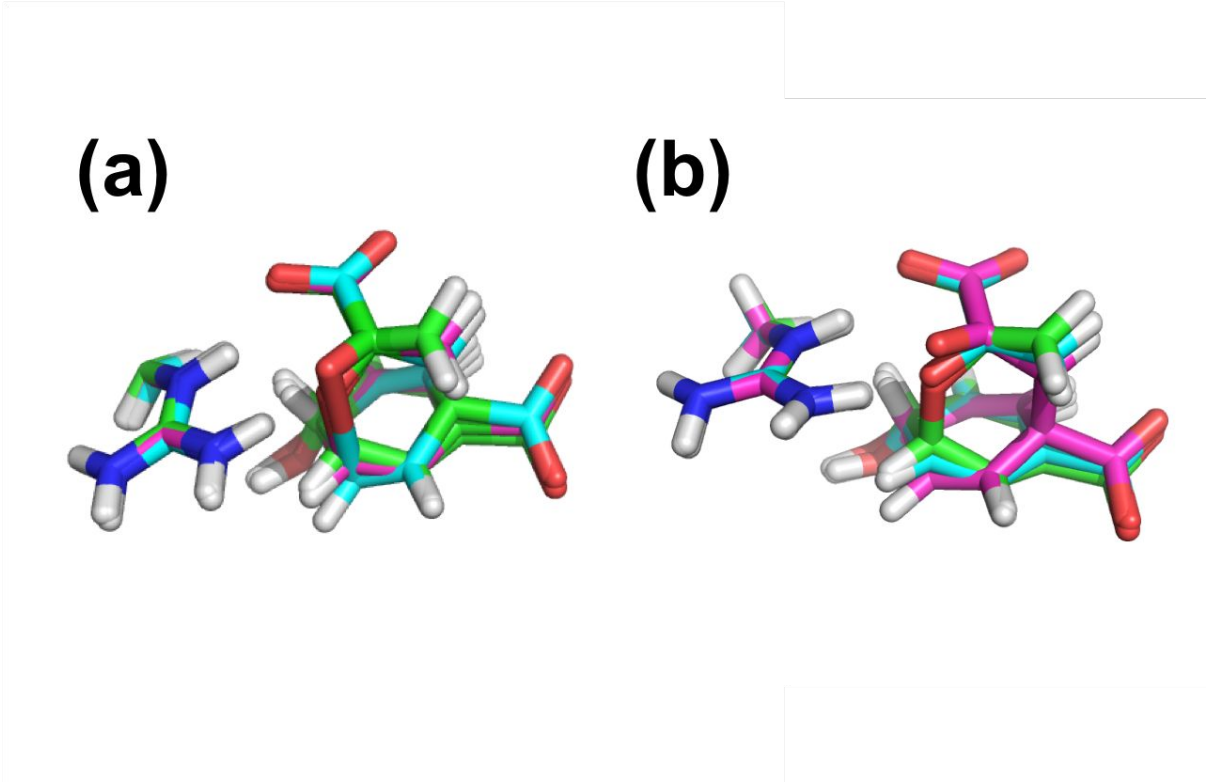


Figure S2. A comparison of the geometry of the arginine sidechain at the reactant (green), TS (cyan) and product (pink) (a) when it is included in QM/MM optimizations at the MM level and (b) when it is included in the QM region in QM/MM calculations at the B3LYP/6-31G(d)/CHARMM27 level of theory. Note that there is very little change in the internal geometry of the arginine sidechain along the path at either level of theory.

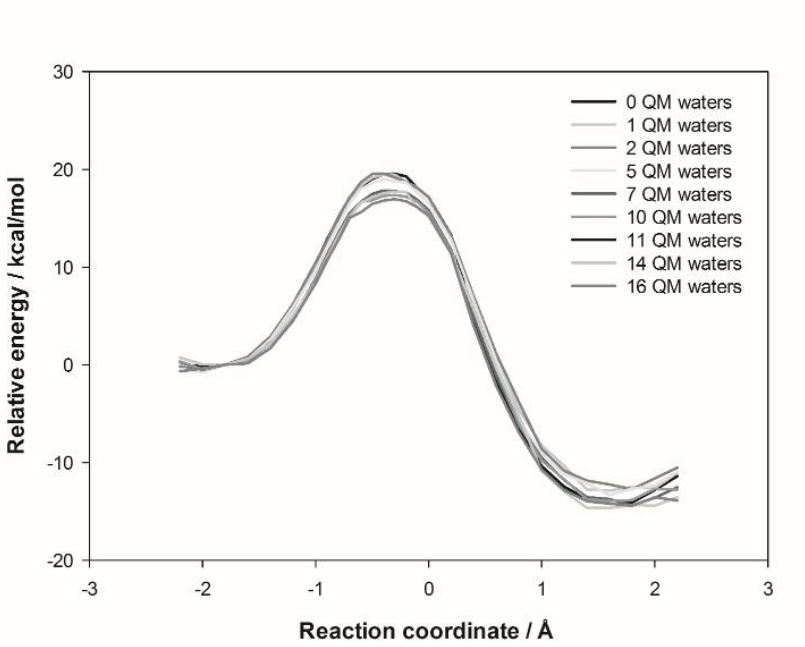


Figure S3. Potential energy profiles for the conversion of chorismate to prephenate in water calculated at the B3LYP/6-31G(d)/CHARMM27 level of theory with chorismate/TS/prephenate and an increasing number of water molecules treated by QM (see Figure 3 for the QM configurations). All energies are relative to the reactant ($r = -1.8$ Å).

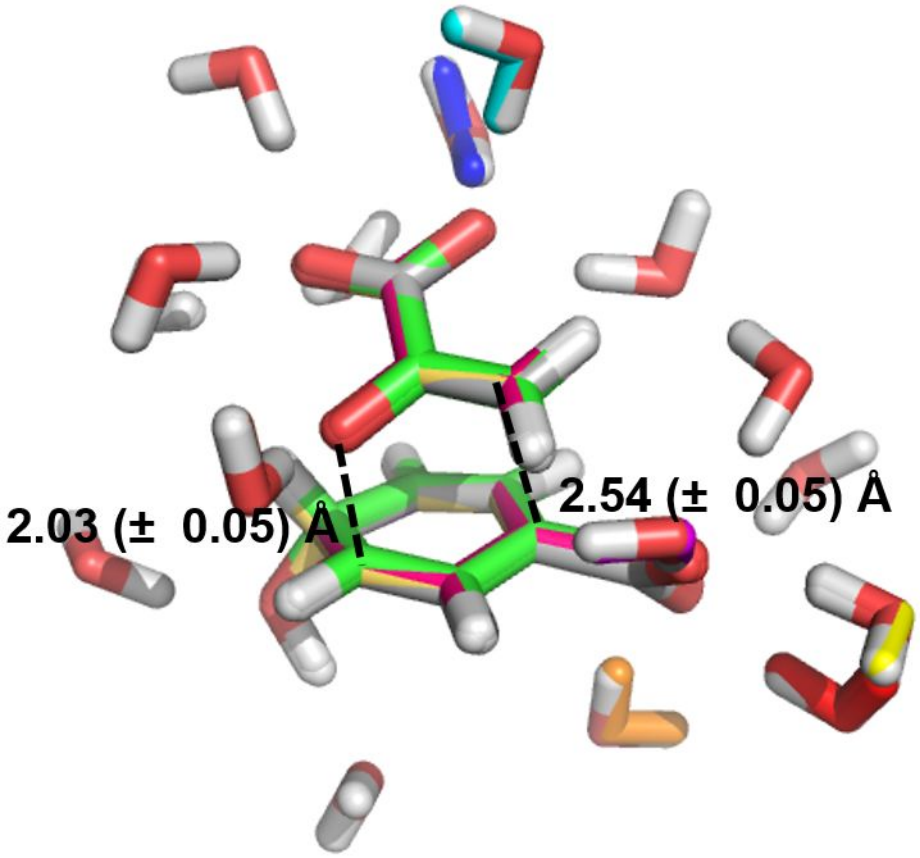


Figure S4. The structure of the approximate TSs for the conversion of chorismate to prephenate in water calculated at the B3LYP/6-31G(d)/CHARMM27 level of theory with chorismate/TS/prephenate and an increasing number of water molecules treated by QM (see Figure 3 for the QM configurations).

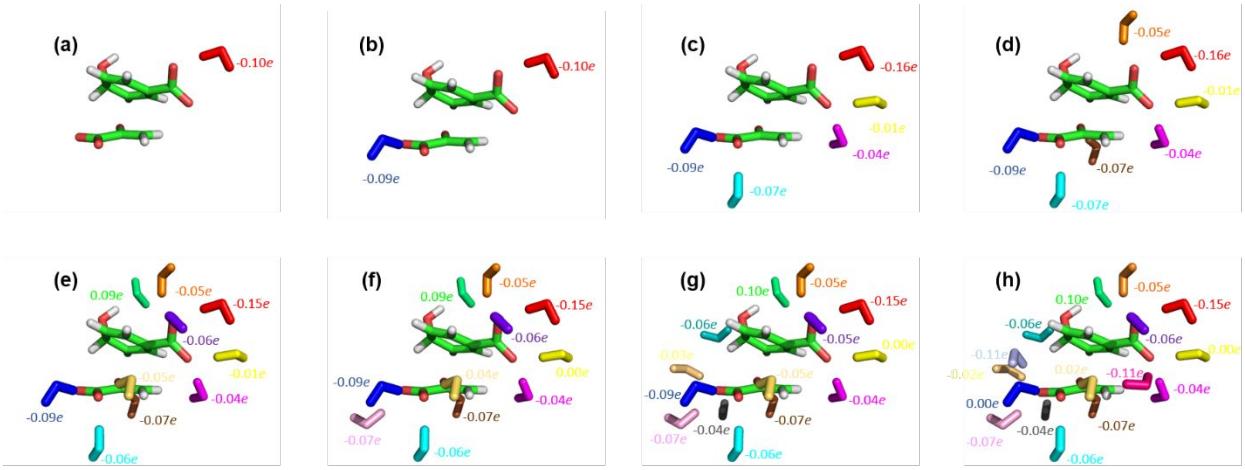


Figure S5. Charge distribution on the water molecules from Mulliken population analysis of the TS in the different water clusters (B3LYP/6-31G(d)/CHARMM27). The overall charge of the system in all models is $-2e$. The water molecules are shown in different colors to aid comparison between different clusters.

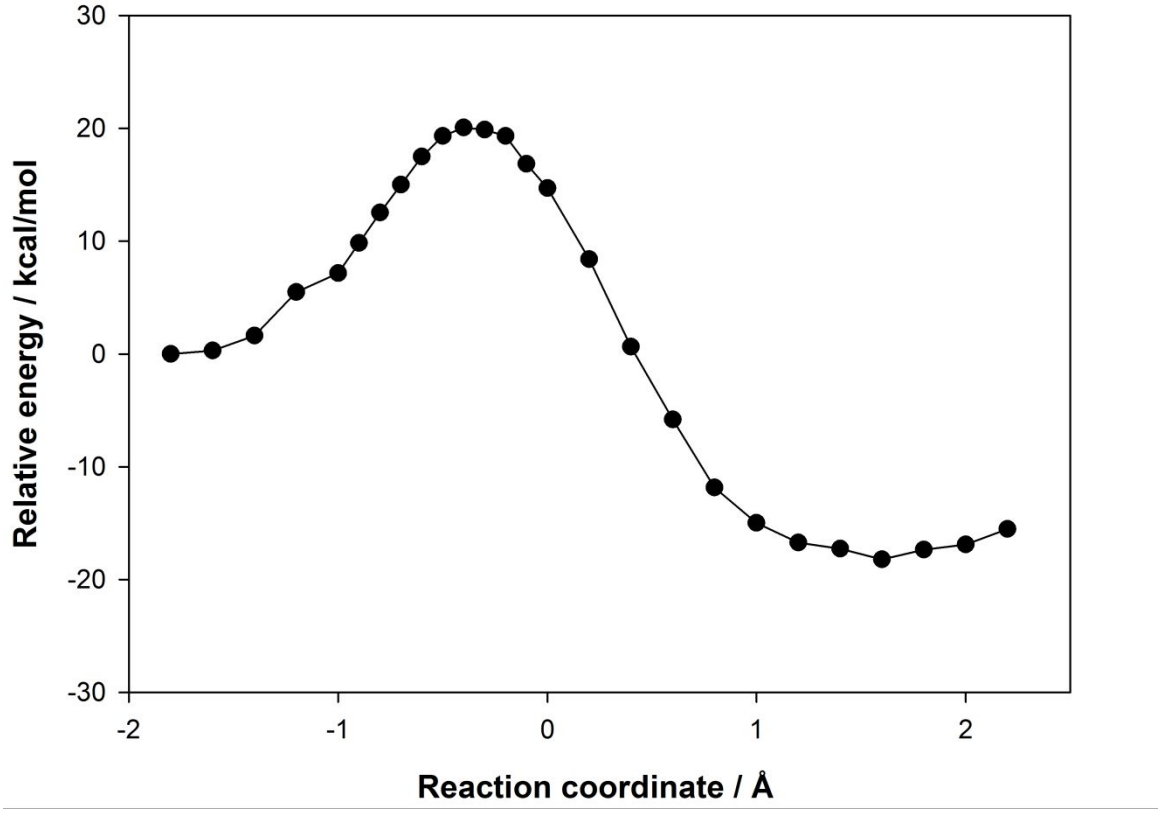


Figure S6. Potential energy profile for the rearrangement of chorismate to prephenate in solution calculated using projector-based embedding of the SCS-MP2 method in B3LYP with 7 of water molecules in sub-system B. A mixed basis set was used for the SCS-MP2 method with oxygen atoms treated by the aug-cc-pVTZ basis and all other atoms by the cc-p-VTZ basis. The geometries are taken from B3LYP/6-31G(d)/CHARMM27 pathway calculations treating chorismate/TS/prephenate and 7 water molecules by QM. All energies are relative to the reactant ($r = -1.8$ Å).

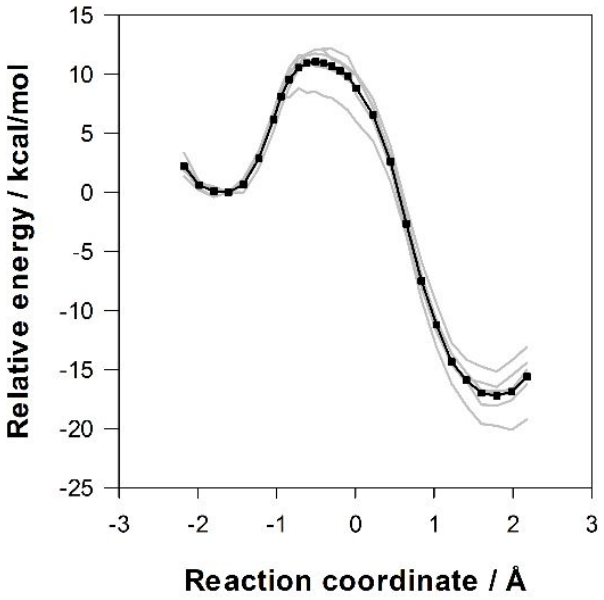


Figure S7. Potential energy profiles for the conversion of chorismate to prephenate generated using adiabatic mapping techniques treating the 24 atoms of chorismate/TS/prephenate by QM in calculations at the B3LYP/6-31G(d)/CHARMM27 level of theory. The individual profiles are shown as grey lines with the average profile shown as black squares. All energies are relative to the reactant ($r = -1.8$ Å).

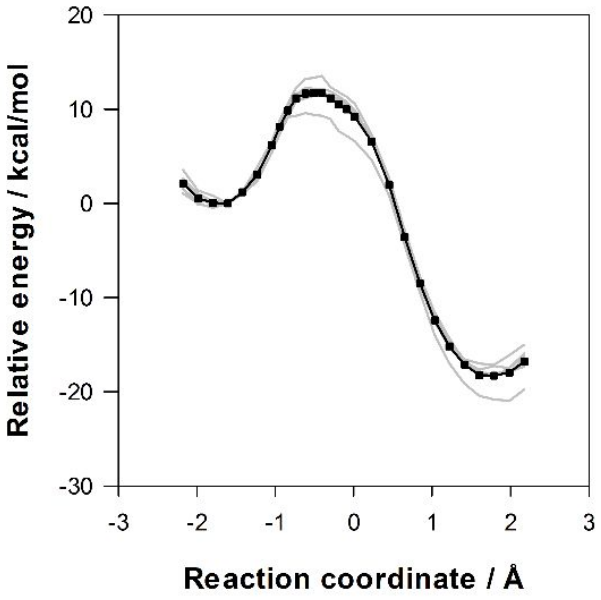


Figure S8. Potential energy profiles for the conversion of chorismate to prephenate generated using adiabatic mapping techniques treating chorismate/TS/prephenate and the sidechain of Arg90 (37 atoms) by QM in calculations at the B3LYP/6-31G(d)/CHARMM27 level of theory. The individual profiles are shown as grey lines with the average profile shown as black squares. All energies are relative to the reactant ($r = -1.8$ Å).

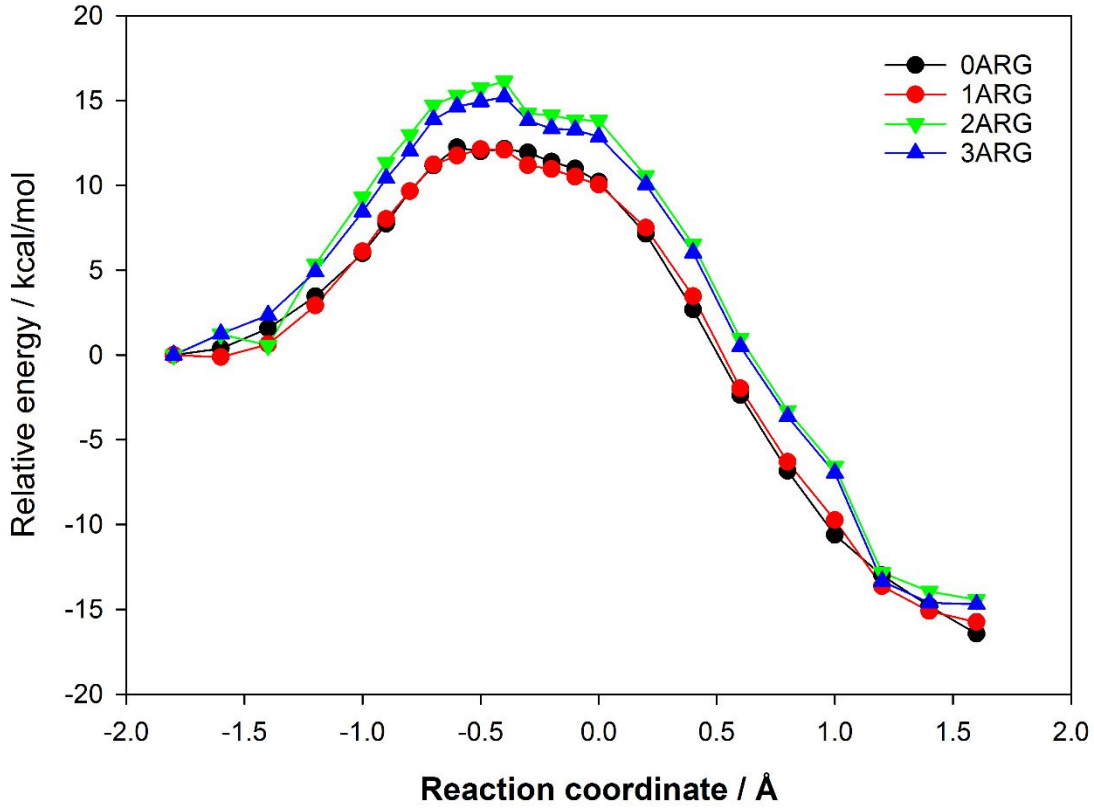


Figure S9. B3LYP/aug-cc-pVDZ//B3LYP/6-31G(d)/CHARMM27 profiles for different QM region sizes (see main text for details). All energies are relative to the reactant ($r = -1.8$ Å).

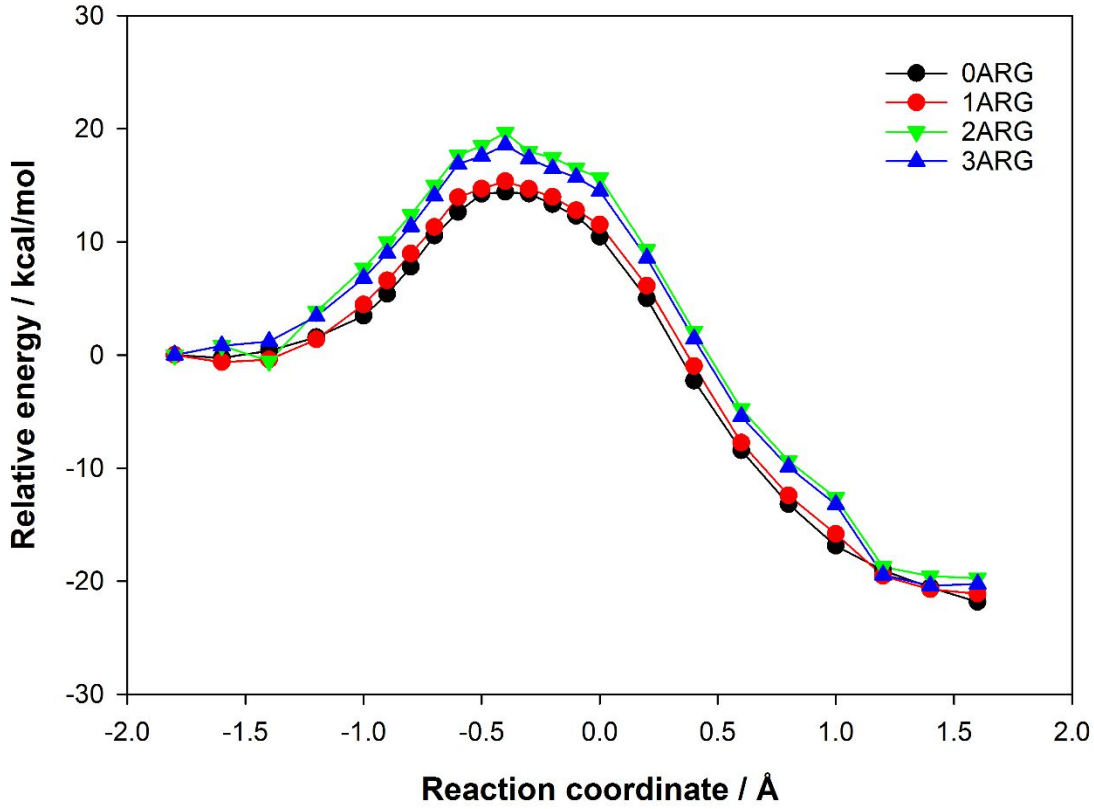


Figure S10. SCS-MP2-in-B3LYP/aug-cc-pVDZ//B3LYP/6-31G(d)/CHARMM27 profiles for different QM region sizes (see main text for details). All energies are relative to the reactant ($r = -1.8$ Å).

Table S1. The CHARMM27 atom types used and partial atomic charges used for chorismate.

| Atom | Type | Charge / e |
|---|---|---|
| C | CT1 | 0.693 |
| C1 | CT1 | 0.542 |
| C2 | CE1 | −0.386 |
| C3 | CE1 | −0.035 |
| C4 | CE1 | −0.465 |
| C5 | CE1 | −0.025 |
| H | HA | −0.139 |
| H1 | HA1 | 0.131 |
| H2 | HA1 | 0.132 |
| H3 | HA1 | 0.087 |
| O | OH1 | −0.762 |
| H4 | H | 0.36 |
| H5 | HA | 0.006 |
| C6 | CC | 0.849 |
| O1 | OC | −0.817 |
| O2 | OC | −0.829 |
| O3 | OS | −0.578 |
| C7 | CE1 | 0.267 |
| C8 | CC | 0.81 |
| C9 | CE2 | −0.555 |
| H6 | HA2 | 0.147 |
| H7 | HA2 | 0.19 |
| O4 | OC | −0.818 |
| O5 | OC | −0.805 |

Table S2. A comparison of partial atomic charges in different sized clusters of chorismate/TS/prephenate and water molecules from Mulliken population analysis[3] used in the B3LYP/6-31G(d)/CHARMM27 QM/MM calculations at the reactant (R), transition state (TS) and product (P). All charges are given in atomic units (*e*), see Figure 1 in the main text for atom numbering.

| | **0 QM water** | | | **1 QM water** | | | **2 QM waters** | | |
|---|---|---|---|---|---|---|---|---|---|
| | **R** | **TS** | **P** | **R** | **TS** | **P** | **R** | **TS** | **P** |
| C1 | 0.056 | −0.100 | −0.159 | 0.056 | −0.084 | −0.155 | 0.057 | −0.083 | −0.156 |
| C2 | 0.080 | 0.073 | 0.077 | 0.080 | 0.075 | 0.073 | 0.079 | 0.077 | 0.073 |
| C3 | −0.197 | −0.090 | −0.095 | −0.195 | −0.093 | −0.092 | −0.197 | −0.094 | −0.091 |
| C4 | 0.119 | 0.021 | −0.093 | 0.124 | 0.026 | −0.091 | 0.124 | 0.023 | −0.093 |
| C5 | −0.143 | −0.137 | −0.140 | −0.142 | −0.139 | −0.138 | −0.144 | −0.140 | −0.138 |
| C6 | −0.121 | −0.089 | −0.091 | −0.119 | −0.086 | −0.091 | −0.120 | −0.088 | −0.092 |
| H7 | 0.171 | 0.179 | 0.159 | 0.173 | 0.181 | 0.160 | 0.175 | 0.182 | 0.160 |
| H8 | 0.150 | 0.156 | 0.146 | 0.153 | 0.160 | 0.149 | 0.153 | 0.161 | 0.151 |
| H9 | 0.154 | 0.165 | 0.156 | 0.157 | 0.164 | 0.157 | 0.159 | 0.166 | 0.158 |
| H10 | 0.135 | 0.137 | 0.124 | 0.136 | 0.136 | 0.126 | 0.138 | 0.138 | 0.128 |
| O11 | −0.753 | −0.759 | −0.778 | −0.752 | −0.760 | −0.777 | −0.752 | −0.759 | −0.776 |
| H12 | 0.476 | 0.481 | 0.484 | 0.478 | 0.483 | 0.484 | 0.479 | 0.483 | 0.484 |
| H13 | 0.164 | 0.187 | 0.166 | 0.165 | 0.188 | 0.168 | 0.164 | 0.187 | 0.167 |
| C14 | 0.534 | 0.564 | 0.611 | 0.553 | 0.581 | 0.630 | 0.553 | 0.583 | 0.630 |
| O15 | −0.771 | −0.738 | −0.741 | −0.709 | −0.685 | −0.681 | −0.708 | −0.684 | −0.679 |
| O16 | −0.750 | −0.753 | −0.775 | −0.741 | −0.746 | −0.770 | −0.739 | −0.744 | −0.769 |
| O17 | −0.606 | −0.605 | −0.523 | −0.604 | −0.602 | −0.521 | −0.604 | −0.602 | −0.517 |
| C18 | 0.329 | 0.401 | 0.428 | 0.329 | 0.395 | 0.428 | 0.334 | 0.401 | 0.436 |
| C19 | 0.569 | 0.560 | 0.556 | 0.569 | 0.565 | 0.559 | 0.577 | 0.575 | 0.571 |
| C20 | −0.360 | −0.399 | −0.340 | −0.363 | −0.398 | −0.342 | −0.361 | −0.399 | −0.343 |
| H21 | 0.166 | 0.142 | 0.146 | 0.167 | 0.143 | 0.147 | 0.170 | 0.145 | 0.148 |
| H22 | 0.155 | 0.160 | 0.168 | 0.156 | 0.162 | 0.171 | 0.158 | 0.164 | 0.174 |
| O23 | −0.771 | −0.775 | −0.750 | −0.771 | −0.776 | −0.752 | −0.717 | −0.721 | −0.701 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| O24 | −0.787 | −0.781 | −0.736 | −0.785 | −0.783 | −0.737 | −0.772 | −0.772 | −0.731 |
| SUM | **−2.000** | **−2.000** | **−2.000** | **−1.886** | **−1.895** | **−1.892** | **−1.793** | **−1.801** | **−1.806** |
| O | | | | −0.987 | −0.981 | −0.987 | −0.989 | −0.983 | −0.985 |
| H | | | | 0.448 | 0.451 | 0.452 | 0.449 | 0.452 | 0.452 |
| H | | | | 0.425 | 0.425 | 0.427 | 0.426 | 0.426 | 0.426 |
| O | | | | | | | −0.982 | −0.983 | −0.981 |
| H | | | | | | | 0.430 | 0.428 | 0.430 |
| H | | | | | | | 0.460 | 0.461 | 0.464 |
| SUM | | | | **−0.114** | **−0.105** | **−0.108** | **−0.207** | **−0.199** | **−0.194** |

| | **5 QM waters** | | | **7 QM waters** | | | **10 QM waters** | | |
|---|---|---|---|---|---|---|---|---|---|
| | **R** | **TS** | **P** | **R** | **TS** | **P** | **R** | **TS** | **P** |
| C1 | 0.054 | −0.094 | −0.159 | 0.046 | −0.094 | −0.156 | 0.047 | −0.095 | −0.160 |
| C2 | 0.079 | 0.077 | 0.077 | 0.083 | 0.080 | 0.074 | 0.086 | 0.078 | 0.078 |
| C3 | −0.194 | −0.093 | −0.097 | −0.189 | −0.092 | −0.093 | −0.191 | −0.097 | −0.099 |
| C4 | 0.124 | 0.032 | −0.091 | 0.112 | 0.016 | −0.097 | 0.113 | 0.028 | −0.094 |
| C5 | −0.142 | −0.137 | −0.138 | −0.142 | −0.139 | −0.139 | −0.146 | −0.140 | −0.144 |
| C6 | −0.122 | −0.094 | −0.097 | −0.123 | −0.094 | −0.098 | −0.129 | −0.104 | −0.107 |
| H7 | 0.177 | 0.185 | 0.164 | 0.180 | 0.189 | 0.165 | 0.177 | 0.187 | 0.161 |
| H8 | 0.159 | 0.163 | 0.153 | 0.164 | 0.169 | 0.157 | 0.162 | 0.168 | 0.153 |
| H9 | 0.162 | 0.172 | 0.162 | 0.162 | 0.172 | 0.164 | 0.163 | 0.173 | 0.162 |
| H10 | 0.141 | 0.143 | 0.130 | 0.143 | 0.144 | 0.132 | 0.147 | 0.149 | 0.136 |
| O11 | −0.752 | −0.757 | −0.774 | −0.752 | −0.759 | −0.774 | −0.769 | −0.775 | −0.791 |
| H12 | 0.479 | 0.484 | 0.484 | 0.482 | 0.487 | 0.486 | 0.441 | 0.444 | 0.446 |
| H13 | 0.166 | 0.190 | 0.168 | 0.170 | 0.192 | 0.171 | 0.164 | 0.188 | 0.165 |
| C14 | 0.539 | 0.563 | 0.611 | 0.547 | 0.568 | 0.612 | 0.545 | 0.565 | 0.619 |
| O15 | −0.689 | −0.664 | −0.659 | −0.646 | −0.624 | −0.619 | −0.605 | −0.584 | −0.588 |
| O16 | −0.633 | −0.636 | −0.652 | −0.634 | −0.635 | −0.653 | −0.629 | −0.630 | −0.648 |
| O17 | −0.604 | −0.609 | −0.523 | −0.572 | −0.555 | −0.476 | −0.574 | −0.567 | −0.482 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| C18 | 0.336 | 0.406 | 0.438 | 0.337 | 0.393 | 0.435 | 0.334 | 0.397 | 0.436 |
| C19 | 0.581 | 0.580 | 0.568 | 0.583 | 0.584 | 0.571 | 0.579 | 0.577 | 0.553 |
| C20 | −0.373 | −0.406 | −0.351 | −0.373 | −0.407 | −0.351 | −0.372 | −0.413 | −0.361 |
| H21 | 0.172 | 0.146 | 0.150 | 0.173 | 0.150 | 0.151 | 0.176 | 0.148 | 0.149 |
| H22 | 0.152 | 0.160 | 0.173 | 0.158 | 0.169 | 0.179 | 0.158 | 0.166 | 0.176 |
| O23 | −0.672 | −0.677 | −0.658 | −0.672 | −0.677 | −0.660 | −0.623 | −0.628 | −0.607 |
| O24 | −0.766 | −0.765 | −0.711 | −0.762 | −0.762 | −0.718 | −0.756 | −0.756 | −0.703 |
| SUM | **−1.624** | **−1.632** | **−1.634** | **−1.527** | **−1.524** | **−1.537** | **−1.504** | **−1.522** | **−1.552** |
| O | −0.891 | −0.886 | −0.888 | −0.891 | −0.885 | −0.886 | −0.889 | −0.885 | −0.886 |
| H | 0.426 | 0.426 | 0.427 | 0.425 | 0.425 | 0.427 | 0.427 | 0.427 | 0.428 |
| H | 0.447 | 0.452 | 0.452 | 0.450 | 0.452 | 0.452 | 0.450 | 0.453 | 0.452 |
| O | −0.929 | −0.934 | −0.937 | −0.929 | −0.934 | −0.937 | −0.929 | −0.935 | −0.937 |
| H | 0.437 | 0.438 | 0.436 | 0.437 | 0.437 | 0.435 | 0.437 | 0.438 | 0.436 |
| H | 0.455 | 0.454 | 0.452 | 0.456 | 0.456 | 0.454 | 0.456 | 0.455 | 0.453 |
| O | −1.009 | −1.005 | −1.007 | −0.986 | −0.994 | −0.976 | −0.985 | -0.997 | -0.971 |
| H | 0.419 | 0.423 | 0.423 | 0.458 | 0.460 | 0.454 | 0.458 | 0.460 | 0.452 |
| H | 0.425 | 0.424 | 0.423 | 0.476 | 0.471 | 0.473 | 0.475 | 0.470 | 0.473 |
| O | −0.980 | −0.980 | −0.974 | −1.008 | −1.005 | −1.009 | −1.008 | −1.001 | −1.006 |
| H | 0.473 | 0.474 | 0.477 | 0.421 | 0.423 | 0.423 | 0.422 | 0.425 | 0.424 |
| H | 0.443 | 0.438 | 0.435 | 0.425 | 0.424 | 0.424 | 0.428 | 0.427 | 0.427 |
| O | −0.985 | −0.986 | −0.982 | −0.926 | −0.919 | −0.923 | −0.869 | −0.865 | −0.859 |
| H | 0.430 | 0.430 | 0.430 | 0.426 | 0.421 | 0.424 | 0.475 | 0.478 | 0.478 |
| H | 0.463 | 0.463 | 0.467 | 0.446 | 0.449 | 0.449 | 0.481 | 0.481 | 0.473 |
| O | | | | −0.979 | −0.978 | −0.973 | −0.928 | −0.924 | −0.930 |
| H | | | | 0.474 | 0.474 | 0.476 | 0.427 | 0.422 | 0.427 |
| H | | | | 0.443 | 0.438 | 0.435 | 0.446 | 0.451 | 0.452 |
| O | | | | −0.985 | −0.984 | −0.982 | −0.964 | −0.957 | −0.955 |
| H | | | | 0.430 | 0.429 | 0.430 | 0.471 | 0.472 | 0.473 |
| H | | | | 0.464 | 0.464 | 0.467 | 0.433 | 0.429 | 0.427 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| O | | | | | | | −0.978 | −0.977 | −0.968 |
| H | | | | | | | 0.473 | 0.474 | 0.475 |
| H | | | | | | | 0.443 | 0.438 | 0.433 |
| O | | | | | | | −0.982 | −0.985 | −0.981 |
| H | | | | | | | 0.430 | 0.430 | 0.431 |
| H | | | | | | | 0.465 | 0.464 | 0.467 |
| O | | | | | | | −0.974 | −0.973 | −0.967 |
| H | | | | | | | 0.469 | 0.472 | 0.475 |
| H | | | | | | | 0.444 | 0.454 | 0.456 |
| SUM | **−0.376** | **−0.368** | **−0.366** | **−0.473** | **−0.476** | **−0.463** | **−0.496** | **−0.478** | **−0.448** |

| | **11 QM waters** | | | **14 QM waters** | | | **16 QM waters** | | |
|---|---|---|---|---|---|---|---|---|---|
| | **R** | **TS** | **P** | **R** | **TS** | **P** | **R** | **TS** | **P** |
| C1 | 0.046 | −0.103 | −0.158 | 0.048 | −0.105 | −0.160 | 0.048 | −0.103 | −0.155 |
| C2 | 0.086 | 0.078 | 0.077 | 0.079 | 0.073 | 0.073 | 0.076 | 0.069 | 0.070 |
| C3 | −0.191 | −0.090 | −0.095 | −0.193 | −0.092 | −0.100 | −0.194 | −0.095 | −0.097 |
| C4 | 0.112 | 0.019 | −0.096 | 0.111 | 0.019 | −0.093 | 0.113 | 0.022 | −0.098 |
| C5 | −0.148 | −0.141 | −0.146 | −0.147 | −0.137 | −0.138 | −0.144 | −0.135 | −0.139 |
| C6 | −0.129 | −0.105 | −0.109 | −0.130 | −0.106 | −0.112 | −0.136 | −0.108 | −0.111 |
| H7 | 0.178 | 0.187 | 0.161 | 0.181 | 0.190 | 0.162 | 0.182 | 0.190 | 0.161 |
| H8 | 0.162 | 0.168 | 0.153 | 0.164 | 0.170 | 0.156 | 0.166 | 0.173 | 0.155 |
| H9 | 0.164 | 0.175 | 0.164 | 0.168 | 0.178 | 0.166 | 0.166 | 0.175 | 0.163 |
| H10 | 0.147 | 0.150 | 0.137 | 0.149 | 0.150 | 0.137 | 0.148 | 0.148 | 0.135 |
| O11 | −0.770 | −0.777 | −0.791 | −0.725 | −0.735 | −0.749 | −0.724 | −0.734 | −0.747 |
| H12 | 0.442 | 0.444 | 0.446 | 0.445 | 0.447 | 0.451 | 0.445 | 0.447 | 0.452 |
| H13 | 0.164 | 0.188 | 0.164 | 0.162 | 0.184 | 0.162 | 0.160 | 0.183 | 0.161 |
| C14 | 0.545 | 0.570 | 0.618 | 0.546 | 0.571 | 0.620 | 0.551 | 0.574 | 0.622 |
| O15 | −0.605 | −0.585 | −0.587 | −0.604 | −0.584 | −0.588 | −0.602 | −0.581 | −0.584 |
| O16 | −0.629 | −0.629 | −0.649 | −0.628 | −0.629 | −0.648 | −0.598 | −0.597 | −0.611 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| O17 | −0.575 | −0.563 | −0.473 | −0.574 | −0.560 | −0.460 | −0.575 | −0.563 | −0.461 |
| C18 | 0.342 | 0.409 | 0.439 | 0.342 | 0.410 | 0.441 | 0.348 | 0.417 | 0.441 |
| C19 | 0.589 | 0.578 | 0.558 | 0.592 | 0.576 | 0.557 | 0.601 | 0.586 | 0.570 |
| C20 | −0.371 | −0.415 | −0.358 | −0.369 | −0.416 | −0.364 | −0.374 | −0.423 | −0.363 |
| H21 | 0.177 | 0.148 | 0.147 | 0.178 | 0.149 | 0.148 | 0.178 | 0.152 | 0.152 |
| H22 | 0.160 | 0.168 | 0.178 | 0.162 | 0.170 | 0.179 | 0.163 | 0.171 | 0.182 |
| O23 | −0.626 | −0.626 | −0.606 | −0.627 | −0.626 | −0.607 | −0.628 | −0.629 | −0.612 |
| O24 | −0.717 | −0.709 | −0.669 | −0.649 | −0.638 | −0.609 | −0.623 | −0.611 | −0.585 |
| SUM | **−1.446** | **−1.463** | **−1.495** | **−1.319** | **−1.340** | **−1.377** | **−1.253** | **−1.271** | **−1.298** |
| O | −0.888 | −0.885 | −0.886 | −0.958 | −0.950 | −0.948 | −0.958 | −0.949 | −0.949 |
| H | 0.427 | 0.427 | 0.428 | 0.454 | 0.456 | 0.457 | 0.454 | 0.457 | 0.456 |
| H | 0.450 | 0.453 | 0.452 | 0.435 | 0.433 | 0.431 | 0.436 | 0.432 | 0.431 |
| O | −0.929 | −0.934 | −0.936 | −0.888 | −0.885 | −0.885 | −0.892 | −0.888 | −0.888 |
| H | 0.437 | 0.438 | 0.436 | 0.427 | 0.427 | 0.427 | 0.432 | 0.432 | 0.433 |
| H | 0.456 | 0.456 | 0.454 | 0.451 | 0.453 | 0.453 | 0.450 | 0.452 | 0.452 |
| O | −0.986 | −0.997 | −0.975 | −0.927 | −0.932 | −0.935 | −0.924 | −0.931 | −0.934 |
| H | 0.458 | 0.461 | 0.455 | 0.437 | 0.438 | 0.436 | 0.437 | 0.438 | 0.435 |
| H | 0.476 | 0.470 | 0.474 | 0.456 | 0.455 | 0.454 | 0.456 | 0.455 | 0.454 |
| O | −1.009 | −1.002 | −1.007 | −0.952 | −0.952 | −0.944 | −0.955 | −0.955 | −0.951 |
| H | 0.422 | 0.425 | 0.424 | 0.486 | 0.486 | 0.483 | 0.486 | 0.486 | 0.483 |
| H | 0.428 | 0.428 | 0.428 | 0.425 | 0.425 | 0.424 | 0.426 | 0.427 | 0.430 |
| O | −0.869 | −0.865 | −0.860 | −0.990 | −1.001 | −0.976 | −0.982 | −0.990 | −0.995 |
| H | 0.475 | 0.479 | 0.478 | 0.459 | 0.462 | 0.452 | 0.425 | 0.434 | 0.437 |
| H | 0.481 | 0.481 | 0.473 | 0.475 | 0.470 | 0.475 | 0.437 | 0.447 | 0.444 |
| O | −0.928 | −0.925 | −0.929 | −1.008 | −1.002 | −1.006 | −0.990 | −1.001 | −0.979 |
| H | 0.427 | 0.423 | 0.426 | 0.422 | 0.425 | 0.424 | 0.459 | 0.462 | 0.455 |
| H | 0.446 | 0.451 | 0.451 | 0.428 | 0.427 | 0.427 | 0.475 | 0.470 | 0.474 |
| O | −0.964 | −0.957 | −0.954 | −0.867 | −0.862 | −0.857 | −1.008 | −1.001 | −1.006 |
| H | 0.471 | 0.472 | 0.473 | 0.477 | 0.480 | 0.481 | 0.422 | 0.426 | 0.425 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| H | 0.433 | 0.429 | 0.427 | 0.482 | 0.482 | 0.474 | 0.429 | 0.428 | 0.428 |
| O | −0.973 | −0.976 | −0.975 | −0.928 | −0.926 | −0.931 | −0.866 | −0.863 | −0.855 |
| H | 0.431 | 0.434 | 0.434 | 0.427 | 0.423 | 0.427 | 0.477 | 0.481 | 0.478 |
| H | 0.476 | 0.475 | 0.479 | 0.447 | 0.451 | 0.451 | 0.482 | 0.482 | 0.473 |
| O | −0.978 | −0.976 | −0.970 | −0.963 | −0.957 | −0.953 | −0.928 | −0.925 | −0.933 |
| H | 0.475 | 0.475 | 0.476 | 0.472 | 0.473 | 0.472 | 0.427 | 0.423 | 0.428 |
| H | 0.443 | 0.438 | 0.435 | 0.433 | 0.429 | 0.426 | 0.447 | 0.452 | 0.453 |
| O | −0.983 | −0.986 | −0.981 | −0.957 | −0.954 | −0.943 | −0.966 | −0.960 | −0.957 |
| H | 0.433 | 0.432 | 0.433 | 0.475 | 0.474 | 0.476 | 0.473 | 0.473 | 0.473 |
| H | 0.466 | 0.465 | 0.468 | 0.455 | 0.449 | 0.437 | 0.432 | 0.428 | 0.425 |
| O | −0.972 | −0.972 | −0.965 | −0.973 | −0.978 | −0.976 | −0.953 | −0.949 | −0.937 |
| H | 0.470 | 0.473 | 0.476 | 0.433 | 0.435 | 0.435 | 0.476 | 0.475 | 0.477 |
| H | 0.444 | 0.454 | 0.455 | 0.477 | 0.476 | 0.481 | 0.454 | 0.450 | 0.440 |
| O | | | | −0.976 | −0.974 | −0.969 | −0.922 | −0.923 | −0.919 |
| H | | | | 0.475 | 0.475 | 0.476 | 0.414 | 0.411 | 0.404 |
| H | | | | 0.442 | 0.438 | 0.434 | 0.402 | 0.403 | 0.410 |
| O | | | | −0.982 | −0.984 | −0.982 | −0.975 | −0.980 | −0.980 |
| H | | | | 0.433 | 0.433 | 0.433 | 0.432 | 0.434 | 0.435 |
| H | | | | 0.467 | 0.466 | 0.469 | 0.479 | 0.478 | 0.482 |
| O | | | | −0.974 | −0.973 | −0.965 | −0.974 | −0.973 | −0.965 |
| H | | | | 0.471 | 0.473 | 0.475 | 0.475 | 0.476 | 0.474 |
| H | | | | 0.444 | 0.454 | 0.456 | 0.441 | 0.437 | 0.434 |
| O | | | | | | | −0.914 | −0.917 | −0.915 |
| H | | | | | | | 0.439 | 0.438 | 0.439 |
| H | | | | | | | 0.473 | 0.474 | 0.476 |
| O | | | | | | | −0.913 | −0.922 | −0.920 |
| H | | | | | | | 0.479 | 0.480 | 0.481 |
| H | | | | | | | 0.448 | 0.458 | 0.461 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| SUM | **−0.554** | **−0.537** | **−0.505** | **−0.681** | **−0.660** | **−0.623** | **−0.747** | **−0.729** | **−0.702** |

Table S3. A comparison of distances involved in hydrogen bonds between Arg90 and chorismate at the reactant (R), transition state (TS) and product (P) with chorismate/TS/prephenate only as the QM region and chorismate/TS/prephenate and Arg90 treated by QM. See Figure 1 in the main text for atom numbering.

| | **R** | | **TS** | | **P** | |
|---|---|---|---|---|---|---|
| | *d*(HH11 – O17) / Å | | *d*(HH11 – O17) / Å | | *d*(HH11 – O17) / Å | |
| | Arg90 MM | Arg90 QM | Arg90 MM | Arg90 QM | Arg90 MM | Arg90 QM |
| 1 | 1.72 | 1.90 | 1.69 | 1.78 | 1.74 | 1.90 |
| 2 | 1.74 | 1.91 | 1.68 | 1.78 | 1.7 | 1.86 |
| 3 | 1.78 | 1.89 | 1.70 | 1.78 | 1.75 | 1.87 |
| 4 | 1.79 | 1.95 | 1.75 | 1.85 | 1.77 | 1.96 |
| 5 | 1.77 | 1.85 | 1.69 | 1.74 | 1.77 | 1.87 |
| 6 | 1.74 | 1.91 | 1.68 | 1.8 | 1.75 | 1.89 |
| **AVERAGE** | **1.76** | **1.90** | **1.70** | **1.79** | **1.75** | **1.89** |
| | **(0.03)** | **(0.03)** | **(0.03)** | **(0.04)** | **(0.03)** | **(0.04)** |
| | **R** | | **TS** | | **P** | |
| | *d*(HE1 – O24) / Å | | *d*(HE1 – O24) / Å | | *d*(HE1 – O24) / Å | |
| | Arg90 MM | Arg90 QM | Arg90 MM | Arg90 QM | Arg90 MM | Arg90 QM |
| 1 | 1.87 | 1.93 | 1.96 | 1.99 | 2.00 | 2.07 |
| 2 | 1.81 | 1.84 | 1.9 | 1.9 | 1.85 | 1.96 |
| 3 | 1.99 | 1.93 | 2.11 | 2.05 | 2.12 | 2.07 |
| 4 | 1.95 | 2.01 | 2.06 | 2.08 | 2.1 | 2.17 |
| 5 | 1.8 | 1.83 | 1.89 | 1.88 | 1.86 | 1.92 |
| 6 | 1.81 | 1.87 | 1.86 | 1.90 | 1.87 | 1.98 |
| **AVERAGE** | **1.87** | **1.90** | **1.96** | **1.97** | **1.97** | **2.03** |
| | **(0.08)** | **(0.07)** | **(0.10)** | **(0.09)** | **(0.12)** | **(0.09)** |

Table S4. A comparison of (average) partial atomic charges of the oxygen atoms of chorismate from Mulliken population analysis[3] used in the B3LYP/6-31G(d)/CHARMM27 QM/MM calculations at the reactant (R), transition state (TS) and product (P) with chorismate/TS/prephenate only as the QM region and chorismate/TS/prephenate and Arg90 treated by QM. All charges are given in atomic units (*e*), see Figure 1 in the main text for atom numbering.

| | **Mulliken Population B3LYP/6-31G(d)/CHARMM27** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **ATOM NAME** | | **R** | | | **TS** | | | **P** | |
| | **CHO** | **CHO + Arg90** | **Diff** | **CHO** | **CHO + Arg90** | **Diff** | **CHO** | **CHO + Arg90** | **Diff** |
| O11 | −0.73 | −0.73 | 0.00 | −0.74 | −0.73 | 0.00 | −0.76 | −0.73 | 0.00 |
| O15 | −0.73 | −0.74 | −0.01 | −0.72 | −0.74 | −0.01 | −0.74 | −0.74 | −0.01 |
| O16 | −0.67 | −0.66 | 0.00 | −0.66 | −0.65 | 0.01 | −0.65 | −0.65 | 0.01 |
| O17 | −0.64 | −0.59 | 0.05 | −0.67 | −0.59 | 0.07 | −0.55 | −0.59 | 0.07 |
| O23 | −0.77 | −0.75 | 0.01 | −0.79 | −0.77 | 0.02 | −0.75 | −0.77 | 0.02 |
| O24 | −0.72 | −0.67 | 0.05 | −0.72 | −0.68 | 0.04 | −0.69 | −0.68 | 0.04 |

# REFERENCES


1. Henkelman, G.; Uberuaga, B. P.; Jonsson, H., A Climbing Image Nudged Elastic Band Method For Finding Saddle Points and Minimum Energy Paths. *J. Chem. Phys.* **2000,** *113* (22), 9901-9904.
2. Sheppard, D.; Terrell, R.; Henkelman, G., Optimization Methods for Finding Minimum Energy Paths. *J. Chem. Phys.* **2008,** *128* (13).
3. Mulliken, R. S., ELECTRONIC POPULATION ANALYSIS ON LCAO-MO MOLECULAR WAVE FUNCTIONS .1. *Journal of Chemical Physics* **1955,** *23* (10), 1833-1840.