MDPI

Article

A New Way to Explore the Mechanism of Catalysis - the Unified Reaction Valley Approach (URVA)

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1. QM/MM computational details

The IRC calculations of the Claisen rearrangement of chorismate to prephenate in explicit aqueous solution (**R3**) were performed using molecular dynamics (MD), followed by the QM/MM calculations using the B3LYP/6-31+G(d,p) level of theory for the QM part,[1,2] and AMBER force field for the MM part.[3,4] First, the chorismate molecule was surrounded by atoms of TIP3P water molecules [5] with a sphere of a radius 20 Å, and applying an external harmonic potential of a force constant 10 kcal/mol/Å^2. MD consisted of 2000 steps of minimisation, 100 ps heating from 0 to 300 K, followed by production dynamics for 2 ns, and followed by annealing dynamics, performed for 200 ps by heating the system to 500 K and cooling to 0 K. The simulations were performed with a constrained TS geometry of the solute with a force constant 1500 kcal/mol/Å^2. Based on the final geometry of the molecular system from MD, the IRC calculations of the reaction **R3** were performed without constraints using the QM/MM method with ONIOM.[6]. The QM part included the chorismate molecule and the MM part included all water molecules. The calculations of the reaction in the protein (**R4**) were performed using the QM/MM method and applying the same level of theory as the reaction in the explicit water solution (**R3**). The initial protein coordinates were taken from the crystal structure of the Arg90Cit (citrulline) mutation of the protein in complexation with a TS analogue.[7] The Arg90Cit mutation was manually replaced back to the original Arg90 structure. The molecular structure was neutralized by six Na^+ ions and minimised at the MM level with a fixed TS geometry.

The following IRC QM/MM calculations were performed without geometry constraints with ONIOM. The calculations of the chemical reaction of chorismate in the protein (**R5**) were performed using the QM/MM method similar as in the reaction **R4**, but with the increased size of the QM part. The QM part in the reaction **R5** included the chorismate molecule and side chains of Arg90, Arg7 and Glu78, which make hydrogen bonds with chorismate. The reaction **R6** was composed of chorsiamte in the original Arg90Cit protein mutation, and the IRC calculations of the reaction **R6** were performed using the same computational protocol and the same level of theory as the reaction **R5**.

2. Summary of reaction videos

Table S1. Description of reaction videos and IRC coordinates files of the chemical reactions discussed in this study

Reaction	File Name		Description
	Movie	Coordinates	
Rh-catalyzed carbonylation	RhCarbonyl-st1.mpg	RhCarbonyl-st1.xyz	**S1**: First reaction step
	RhCarbonyl-st2.mpg	RhCarbonyl-st2.xyz	**S2**: Second reaction step
	RhCarbonyl-st3.mpg	RhCarbonyl-st3.xyz	**S3**: Third reaction step
	RhCarbonyl-st4.mpg	RhCarbonyl-st4.xyz	**S4**: Fourth reaction step
Ti-catalyzed Sharpless epoxidation	Sharpless.mpg	Sharpless.xyz	**S5**: Catalyzed reaction
Au(I)-catalyzed[3,3]-sigmatropic	Claisen-noncat.mpg	Claisen-noncat.xyz	**S6**: Non-catalyzed
rearrangement of allyl acetate	AuClaisen-st1.mpg	AuClaisen-st1.xyz	**S7**: Catalyzed, first reaction step
	AuClaisen-st2.mpg	AuClaisen-st2.xyz	**S8**: Catalyzed, second reaction step
Bacillus subtilis chorismate mutase	Chorism-gas.mpg	Chorism-gas.xyz	**S9**: Reaction **R1**: Gas phase
catalyzed Claisen rearrangement	Chorism-pcm.mpg	Chorism-pcm.xyz	**S10**: Reaction **R2**: Water (PCM)
	Chorism-tip3p .mpg	Chorism-tip3p .xyz	**S11**: Reaction **R3**: Water (TIP3P)
	Chorism-prot1.mpg	Chorism-prot1.xyz	**S12**: Reaction **R4**: BsCM (QM/MM)
	Chorism-prot2.mpg	Chorism-prot2.xyz	**S13**: Reaction **R5**: BsCM (QM_{ext}/MM), part 1
	Chorism-prot3.mpg	Chorism-prot3.xyz	**S14**: Reaction **R5**: BsCM (QM_{ext}/MM), part 2

3. Browsing file examples

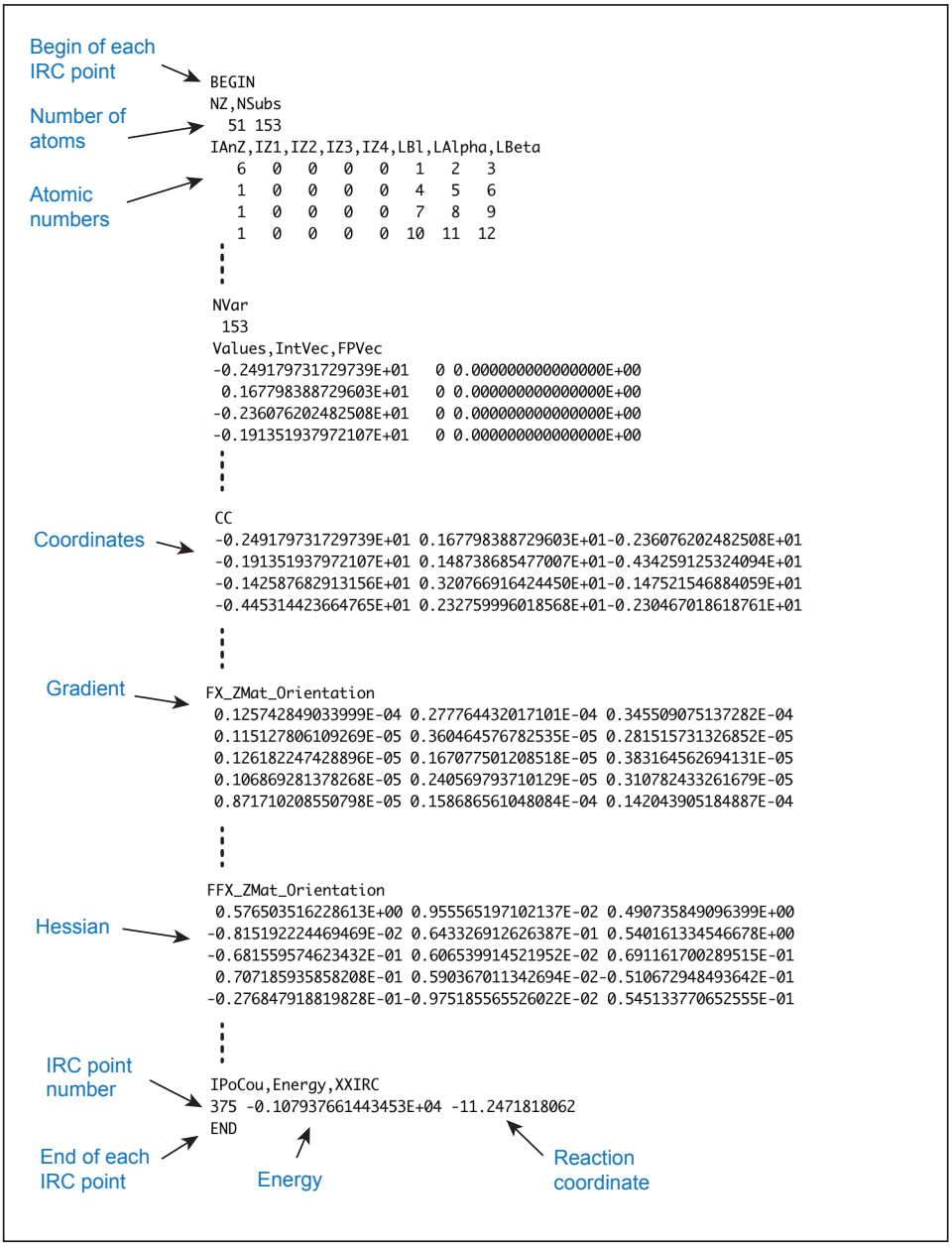

Figure S1. Browsing file *version 1* with storage of the Hessian at one representative IRC point *s*.

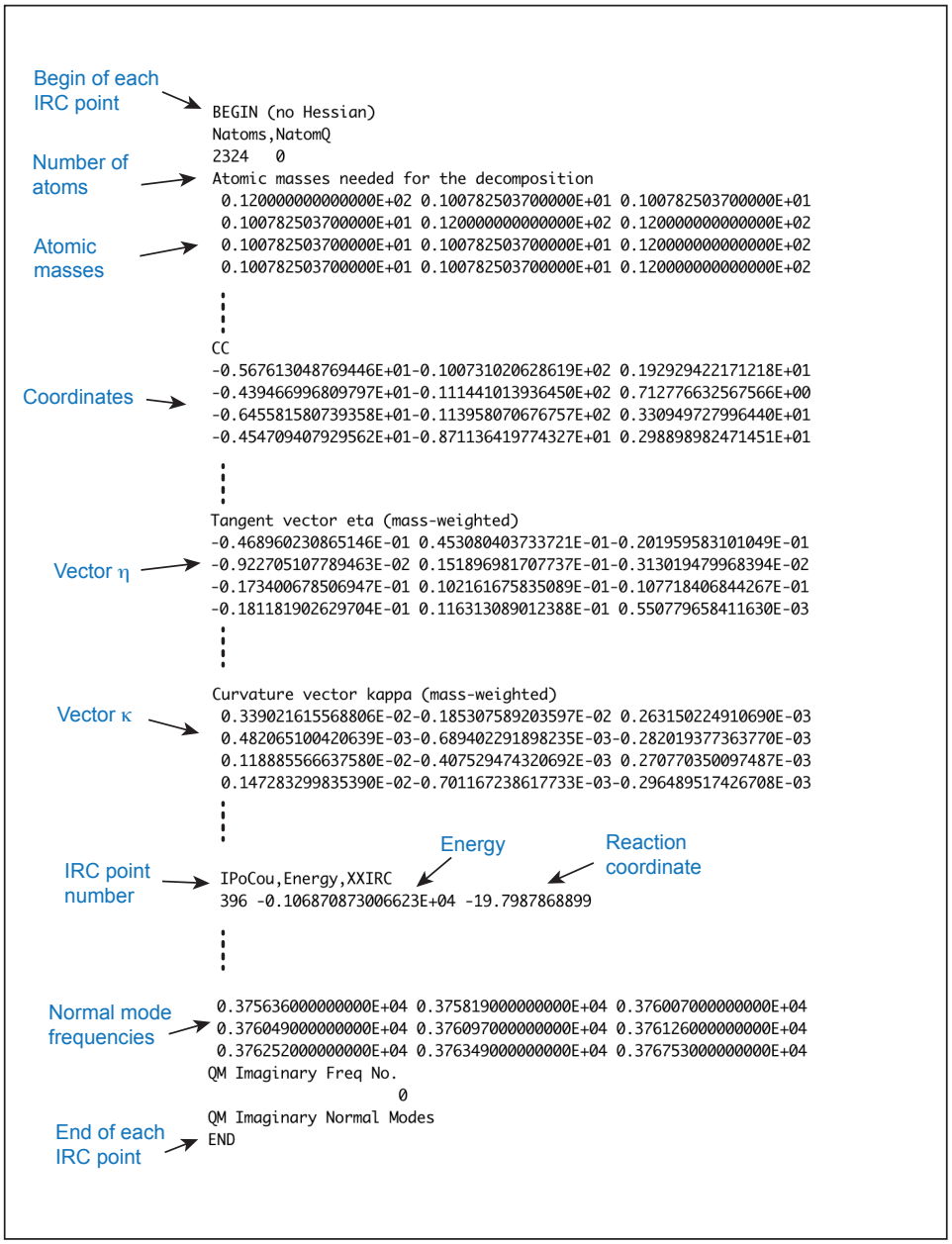

Figure S2. Browsing file *version 2* with storage of reaction path direction $\boldsymbol{\eta}(s)$ and reaction path curvature $\boldsymbol{\kappa}(s)$ instead of gradient and Hessian at one representative IRC point s.

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