

# Supporting Information for

## Comparison of Three Chain-of-States Methods: Nudged Elastic Band and Replica Path with Restraints or Constraints

Peng Tao<sup>\*†</sup>, Milan Hodošček<sup>‡</sup>, Joseph D. Larkin<sup>†</sup>, Yihan Shao<sup>†§</sup>, Bernard R. Brooks<sup>†</sup>

*<sup>†</sup>Laboratory of Computational Biology, National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, Maryland 20892, United States; <sup>‡</sup>Center for Molecular Modeling, National Institute of Chemistry, Hajdrihova 19, SI-1000 Ljubljana, Slovenia; <sup>§</sup>Q-Chem Inc., 5001 Baum Boulevard, Suite 690, Pittsburgh, Pennsylvania 15213, United States*

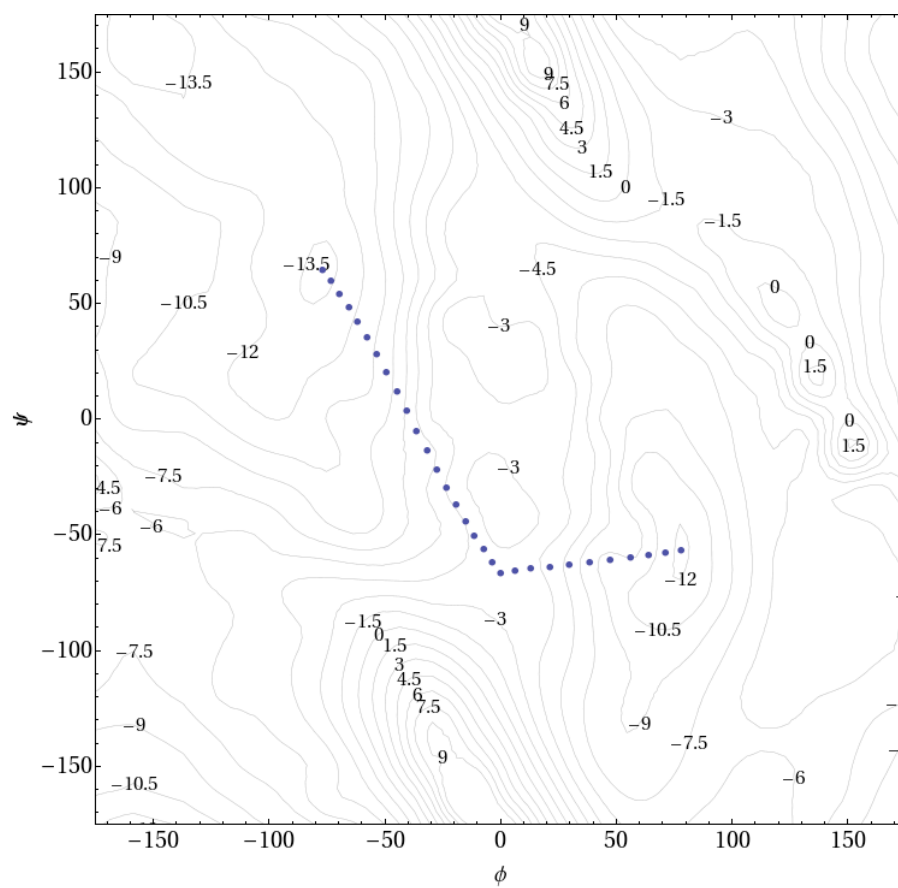


Fig. S1. Plot of initial path for RPATH calculations of alanine dipeptide isomerization

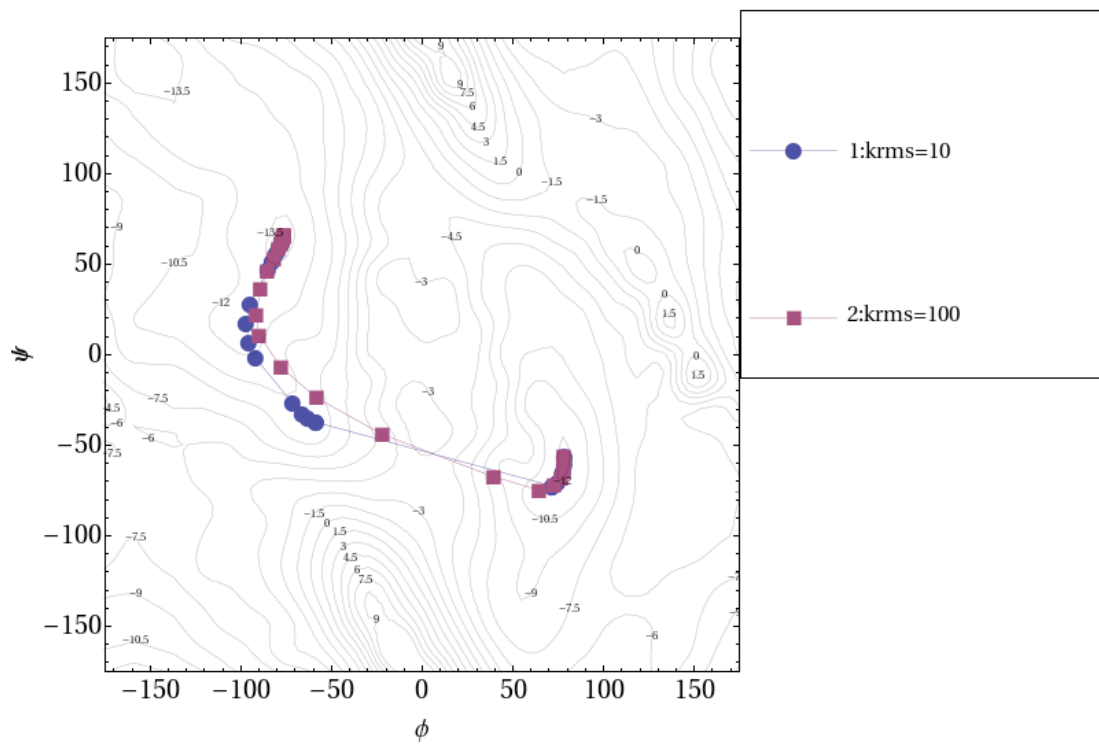


Fig. S2. Reaction pathways of alanine dipeptide isomerization using RPATH/restraint method with force constants  $k_{rms}$  as 10 and 100 kcal $\cdot$ mol $^{-1}\cdot$ Å $^{-2}$

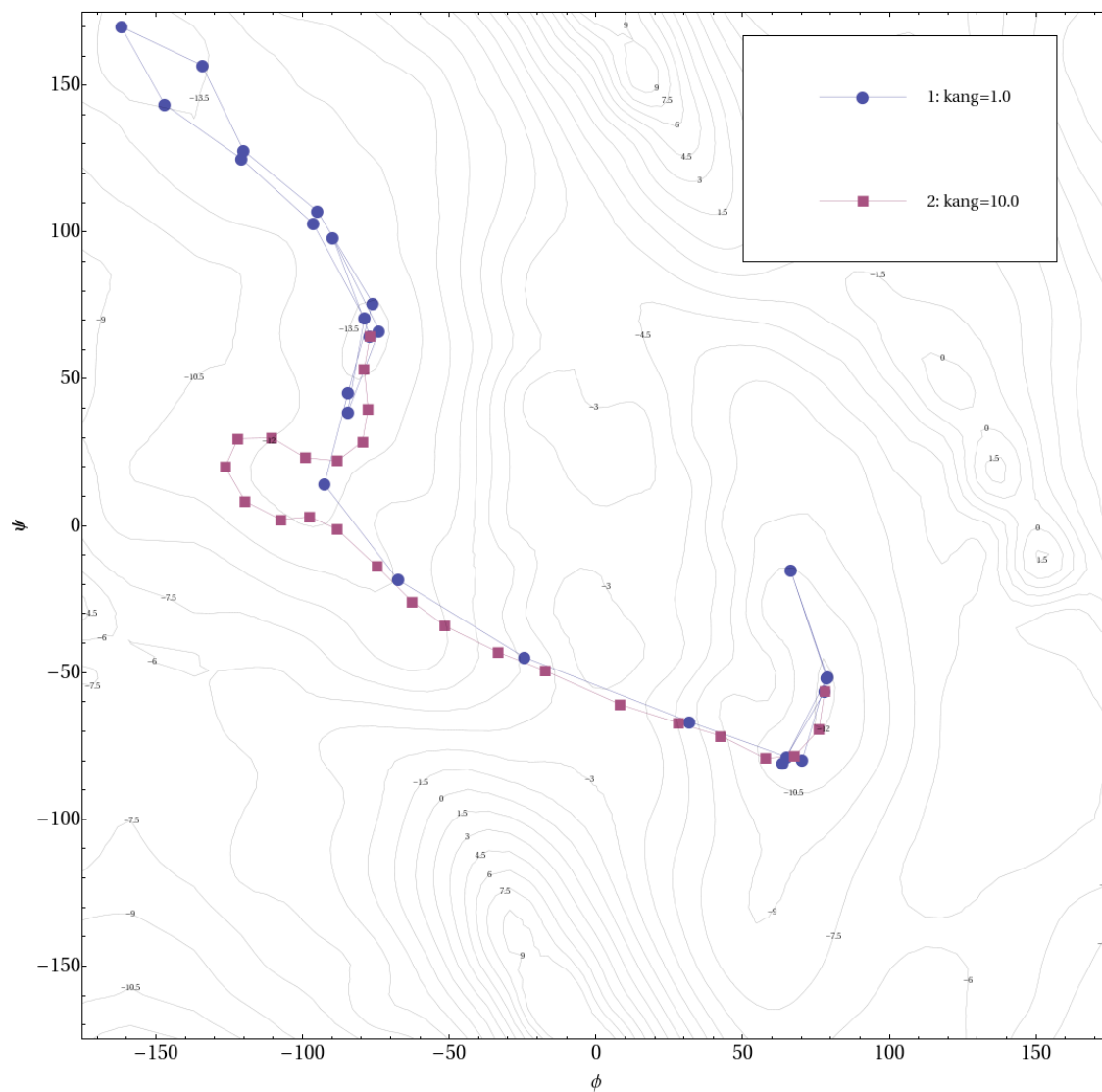


Fig. S3. Reaction pathways of alanine dipeptide isomerization using RPATH/restraint method with force constants  $k_{ang}$  as 1.0 and 10.0 kcal•mol<sup>-1</sup>•Å<sup>-2</sup>, force constants  $k_{rms}$  is in both calculations 100000 kcal•mol<sup>-1</sup>•Å<sup>-2</sup> in both calculations.

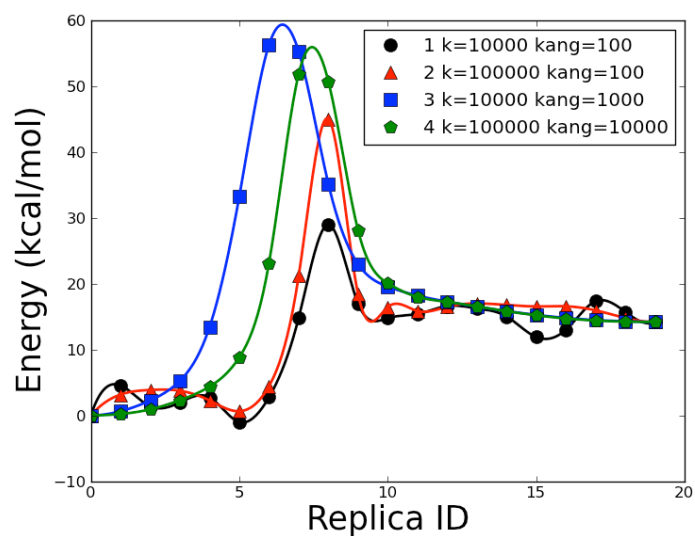


Fig. S4. Energetic profile of  $\beta$ -alanine intramolecular condensation reaction using RPATH/restraint method with 20 replicas and additional weighting factor on migration hydrogen. Four calculations with different force constant  $k$  and angle force  $k_{ang}$  in  $\text{kcal}\cdot\text{mol}^{-1}\cdot\text{\AA}^{-2}$ . All the calculations are done at B3PW91/6-31g(d,p) level of theory.

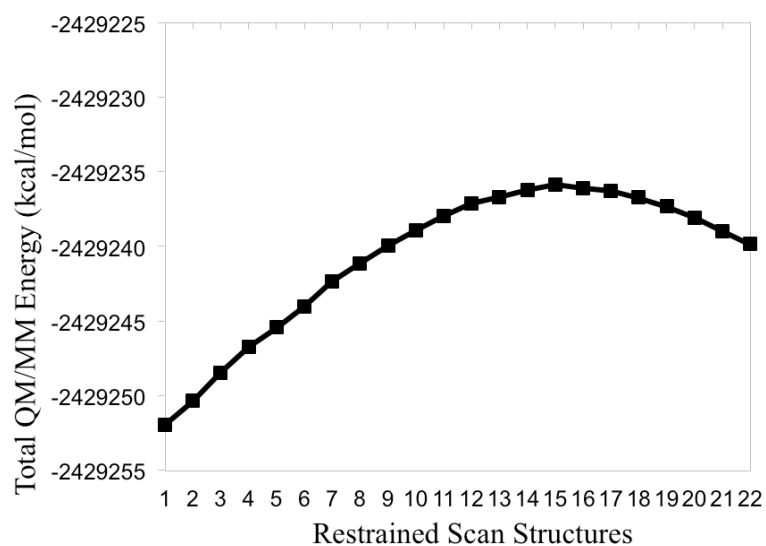


Fig. S5. The energetic profile for the restrained scan between replica 17 and 19 from the pathway 4 using RPATH/constraint (Fig. 24). The breaking C–H and C–S bonds, and forming O–H bond were restrained simultaneously to ensure the concerted reaction mechanism. The highest energy structure is referred as estimated TS, and leads to a barrier as 33.85 kcal/mol.