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Isotopic Effect in Double Proton Transfer Process of Porphycene Investigated by Enhanced QM/MM Method

--Manuscript Draft--

1   **TITLE:**
2   Isotopic Effect in Double Proton Transfer Process of Porphycene Investigated by Enhanced
3   QM/MM Method
4
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22 **KEYWORDS:**
23 isotopic effect, double proton transfer, enhanced sampling, QM/MM, selective integrated
24 tempering sampling, free energy calculation
25

26 **SUMMARY:**
27 A protocol that uses enhanced QM/MM method to investigate the isotopic effect on the double
28 proton transfer process in porphycene is presented here.
29

30 **ABSTRACT:**
31 The single deuterium substitution in porphycene leads to an asymmetric molecular geometry,
32 which may affect the double proton transfer process in the porphycene molecule. In this study,
33 we applied an enhanced QM/MM method called SITS-QM/MM to investigate
34 hydrogen/deuterium (H/D) isotope effects on the double proton transfer in porphycene.
35 Distance changes in SITS-QM/MM molecular dynamics simulations suggested that the
36 deuterium substituted porphycene adopted the stepwise double proton transfer mechanism.
37 The structural analysis and the free energy shifts of double proton transfer process indicated
38 that the asymmetric isotopic substitution subtly compressed the covalent hydrogen bonds and
39 may alter the original transition state location.
40

41 **INTRODUCTION:**
42 The proton transfer process in porphycenes holds potential applications in developing
43 molecular switches, transistors and information storage devices[1,2]. In particular,
44 tautomerization in porphycenes through double proton transfer process has attracted wide

45   interest in the fields of spectroscopy and photophysics[2]. The inner hydrogen atoms of
46   porphycene can migrate from one *trans* isomer to the other equivalent *trans* isomer through
47   double proton transfer process as shown in **Figure 1**. Two mechanisms have been proposed for
48   the double proton transfer process: the concerted and the stepwise mechanism[3,4]. In the
49   concerted double proton transfer process, both proton atoms move to the transition state
50   synchronously in a symmetric way, whereas one proton completes the transfer before the
51   other proton in a stepwise process. Two hydrogen atoms can transfer simultaneously or
52   stepwise depending on the correlation strength between two hydrogen atoms[5].
53
54   Isotopic substitution has been used to detect the structural properties of molecules and rate
55   constants of reaction kinetics[6]. Single deuterium substitution in the inner hydrogen of
56   porphycene leads to an asymmetric shape of the molecule. The hydrogen bond may expand or
57   contract because of mass difference between the hydrogen and deuterium atoms. The isotopic
58   substitution introduces a perturbation in the scaffold of porphycene. The question arises that
59   whether asymmetric structure would affect the proton transfer process. Limbach and
60   coworkers reported that the replacement of hydrogen with deuterium will compress both
61   hydrogen bonds, and the cooperative coupling of two hydrogen bonds in porphycene may favor
62   concerted mechanism[7], whereas Yoshikawa stated the deuteration would make the stepwise
63   mechanism contribute more than the concerted mechanism[8]. Experimental techniques, such as
64   force spectroscopy, have been developed to capture tautomerization details in a single
65   porphycene[9]. However, it is still challenging to determine the atomic details of proton transfer
66   experimentally because of its transient nature.
67
68   Theoretical calculations and simulations can act as complementary tools in elucidating the
69   reaction mechanisms of proton transfer. Among different theoretical methods, molecular
70   dynamics (MD) simulations can monitor dynamic motions of each atom, and has been widely
71   used to reveal complex mechanisms in chemical and enzymatic reactions. However, regular MD
72   simulations tend to suffer from insufficient sampling issue, especially when high energy barrier
73   exists in the process of interest. Therefore, enhanced sampling methods have been developed,
74   which include transition path sampling[10,11], umbrella sampling (US)[12,13], and integrated
75   tempering sampling (ITS)[14,15]. Combination of different enhanced sampling methods can further
76   increase sampling efficiency[16-18]. To harness the enhanced sampling algorithms in simulating
77   chemical reactions, we have implemented the selective integrated tempering sampling (SITS)
78   method with quantum mechanical and molecular mechanical (QM/MM) potentials recently[19].
79   The proposed SITS-QM/MM method combines the advantages from both methods: the SITS
80   method accelerates the sampling and can explore all possible reaction channels without prior
81   knowledge of the reaction mechanism, and QM/MM provides more accurate description of the
82   bond forming and bond breaking process, which cannot be simulated by MM methods solely.
83   The implemented SITS-QM/MM approach has successfully uncovered concerted double proton
84   transfer, uncorrelated and correlated stepwise double proton transfer mechanism in different
85   systems, without pre-defining reaction coordinates[19]. For porphycene, the stepwise but
86   correlated proton transfer character has been reported[19]. The hybrid SITS-QM/MM method
87   was used to investigate the isotopic effect in porphycene in our study, and below are the
88   detailed descriptions of the algorithm and protocol of our method.

89

90 We have implemented SITS method with hybrid QM/MM potentials. The effective potential of
91 SITS was defined to include the potential energy at different temperatures with the weighting
92 factors $\{n_k\}$ to cover wider temperature ranges,
93

$$U'(R) = U_N(R) - \frac{1}{\beta_0} ln \left(\sum_{k=1}^{N} n_k e^{-\beta_k U_E(R)} \right)$$

94

95 where, N is the number of canonical terms, β_k is the inverse temperature, and n_k is the
96 corresponding weighting factor for each canonical component. $U_E(R)$ and $U_N(R)$ represent the
97 enhanced and non-enhanced terms in SITS and are defined as,

$$U_E(R) = U_s + \frac{1}{2} U_{se}$$

98

$$U_N(R) = U_e + \frac{1}{2} U_{se}$$

99

100 U_s, U_{se} and U_e are the potential energy of sub-system, the interaction between sub-system and
101 the environment, and the potential energy of environment. QM/MM potential is expressed as a
102 hybrid summation of three components,
103

$$U = U_{qm} + U_{qm/mm} + U_{mm}$$

104

105

106 where U_{qm}, $U_{qm/mm}$, and U_{mm} are the internal energy term of the QM subsystem, the
107 interaction energy between the QM and MM regions, and the interaction energy within the
108 MM subsystem, respectively. The $U_{qm/mm}$ term can be further divided into three components,
109 which include the electrostatic, van der Waals, and covalent interaction energy terms between
110 the QM and MM atoms,
111

$$U_{qm/mm} = U_{qm/mm}^{ele} + U_{qm/mm}^{vdW} + U_{qm/mm}^{cova}$$

112

113

114 We assign U_{qm}, and $U_{qm/mm}^{ele}$ into one U_s term in SITS,
115

$$U_s = U_{qm} + U_{qm/mm}^{ele}$$

116

117

$$U_{se} = U_{qm/mm}^{vdW} + U_{qm/mm}^{cova}$$

118

119

$$U_e = U_{mm}$$

120

121

122 The full potential of the system was then decomposed into the energy of subsystem U_s, the
123 interaction energy between the subsystem and the environment U_{se}, and the energy of
124 environment U_e. For instance, in the system of the present work, the subsystem is the
125 porphycene, and the environment the water.
126

127 The PMF profile along a collective variable $\tau(R)$ is derived as,

128 $$PMF(\tau) = -k_B T ln(\sum \tau * e^{-(U_0 - U')} \delta\tau)$$

129 The generally used reaction coordinates for each hydrogen transfer of $N1 - H1 \cdots N2$ are $q_1 =$
130 $(r_1 - r_2)/2$ and $q_2 = r_1 + r_2$, where r_1 is the distance of N1-H1 and r_2 is the distance of H1-N2.

131

132 The method has been implemented in the QM/MM MD simulation package QM^{4}D[20]. The
133 complete source code and documentation can be found here: http://www.qm4d.info/.

134

135 Generally, the SITS-QM/MM MD simulations involve four steps: pre-equilibrium (pre-sits);
136 optimization $\{n_k\}$ (opt-sits); production simulation and data analysis.

137

138 **PROTOCOL:**

139

140 **1.   Building model**

141

142 **1.1.   Build porphycene structure:** Open **GaussView** software by double-click the mouse.
143 Then click **Element Fragment** button in the menu of the **GaussView** to choose the needed
144 elements. Construct porphycene. Then click **File** button to save as the pdb file.

145

146 **1.2.   Solvate the model:** Solvate porphycene in a cubic TIP3P[21] water box with an edge length
147 of 38 Å by issuing the command in the linux operating system: **genbox_d -cp prp-vac.pdb -cs**
148 **spc216.gro -o solv.pdb -maxsol 1484 –box 3.8.**

149

150 **1.3.   Build deuterium porphycene:** Issue the following command to generate topology file:
151 **cns < ppi_solv.inp.** Then open **prp-wat.psf** with **vi** command and change the mass of H1 from
152 1.00800 to 2.01600 to replace one intramolecular hydrogen atom of porphycene with
153 deuterium to build single deuterium substituted porphycene.

154

155 **1.4.   Set normal MD simulation parameters:** Input **method scctb**, **integral 0.5 fs**, and **cutoff**
156 **12** in the MD input file by opening it with **vi** command.

157

158 NOTE: Adopt a cutoff distance of 12 Å for calculating both vdW and electrostatic interactions.
159 Simulate the porphycene molecule with DFTB/MIO method[22]. Set the integration time step as
160 0.5 fs for MD simulations. Maintain the temperature of the simulation system at 300 K with
161 Langevin thermostat. Then perform the simulations with QM^{4}D software following the steps
162 below.

163

164 **2.   Pre-sits**

165

166 **2.1. Set up temperature parameters:** Input **templow 260**, **temphigh 1100** and **ntemp 160** in
167 the input file.

168

169 NOTE: The temperature range from 260K to 1100K was spread out by **QM4D** software to 160

170 temperature points during MD simulations. The template input files are included in
171 **Supplementary Files**.

172

173 **2.2. Initiate the pre-sits:** Set **runtype 100** and **step 120,000** in the input file. Then issue the
174 following command: **$PATH/qm4d $INPUTFILE > $OUTPUTFILE**.

175

176 NOTE: The total step is 120,000 but can be adjusted depending on the specific need. The
177 suggested parameters of MD simulations are saved in the **$INPUTFILE**. The same command is
178 also used in the following opt-sits and production simulation steps, with the input file modified
179 accordingly.

180

181 **2.3. Calculating the decomposed energies**

182

183 2.3.1. Extract energy changes: During the pre-sits stage, monitor the energy of each term to
184 calculate the mean values, as shown in **Figure 1**. Use **grep** Linux command to extract the energy
185 as follows:
186 **grep 'SITS-ener0' $INPUTFILE | awk '{a+=$3;b+=$4;c+=$5}END{print a/NR,b/NR,c/NR}**.

187

188 2.3.2. Modify average energies in the MD input file: Calculate the average energies based on
189 the output of the command line above, and modify the line **vshift0 -30801.95; vshift1 -26.88;**
190 **vshift2 -13888.28** in the input file with the newly generated averages.

191

192 NOTE: Numbers -30801.85, -26.88 and -13888.28 are the average energies in the current model
193 system. Please modify the values based on the specific systems.

194

195 **3.   Opt-sits**

196

197 **3.1. Initiate opt-sits:** Set **runtype 0** in the input file. Then initiate the QM^{4}D program by typing
198 the command as shown in step 2.2 to start the optimization step.

199

200 **3.2. Monitoring the energy changes and $\{n_k\}$ values.**

201

202 3.2.1. Plot the energy propagation with "grace" program and make sure the energy fluctuation
203 can cover the lowest and the highest ends of the temperature range.

204

205 3.2.2. After optimization, save the final $\{n_k\}$ values of the opt-sits step into a new file, which is
206 named as nk.dat in this protocol.

207

208 **4.   Running production simulations**

209

210 **4.1. Prepare MD input file:** Set **runtype 1** in the new input file to start the production
211 simulation step. Specify the file name of stored $\{n_k\}$ file as **nkfile nk.dat** in the input file. The
212 number of time steps was set as 6,400,000 in the present systems.

213

214 **4.2. Initiate production MD simulation:** Issue the following command to start MD simulations:
215 **$PATH/qm4d $INPUTFILE > $OUTPUTFILE**.

217 NOTE: Make sure the $\{n_k\}$ values can be read in by the QM4D software. The simulation time is
218 system dependent so change the simulation step based on specific demands. Select a proper
219 number of time steps to ensure enough simulation time for your own system. This step is likely
220 time consuming, so save restart files to avoid restarting the production from the very beginning
221 once being disrupted.

223 **5.   Data analysis**

225 **5.1. Monitoring the distance changes**

227 5.1.1. Monitor the bond forming and breaking process during the production phase, use the
228 **grep** command to check the distance changes of H1-N1 and H1-N2 along the simulation time.
229 The same operation can be conducted for H2-N3 and H2-N4. Then plot the distance
230 propagation using the accumulated distance value during the production simulations.

232 **5.2. Extracting reaction coordinates**

234 5.2.1. Extract the reaction coordinates and the energy terms from the production output file
235 generated by QM^{4}D by **grep** command:
236 **grep 'dist   1' $OUTPUTFILE | awk '{print $5}' > distance1;**
237 **grep 'ener0' $OUTPUTFILE > ener0.**

239 5.2.2. Organize data in four columns: q_1, q_2, U_0 and U' (U_0 and U' are the output normal energy
240 and weighted energy), and write them into the data file at each time frame.

242 **5.3. Calculating Free energy**

244 5.3.1. Calculate the free energy by issuing the following command:
245 **sits-pmf 300 $INPUTFILE PMF2 [hist_minx hist_maxx num_binsx] [hist_miny hist_maxy**
246 **num_binsy] > $OUTPUTFILE**.

248 NOTE: sits-pmf is the histogram-based analysis method. [hist_minx hist_maxx num_binsx]
249 defines the range and number of bins for the first reaction coordinate. The second reaction
250 coordinates can be set by [hist_miny hist_maxy num_binsy].

252 5.3.2. To project the free energy on the two-dimensional landscape, type the following
253 command:
254 **sits-pmf 300 h1-2d.dat PMF2 -0.6 0.6 24 2.45 4.25 36 > sits-pmf.out**.

256 NOTE: Use a total of 24 bins and 36 bins to cover the distance changes in two selected reaction
257 coordinates, q_1 and q_2, respectively. Save the 2D PMF data for each hydrogen/deuterium to the

258   **sits-pmf.out** file.

259

260   **REPRESENTATIVE RESULTS:**

261   The single deuterium substitution effect on double proton transfer process in porphycene was

262   examined in the current protocol (**Figure 1**). The potential energy of QM sub-system and the

263   water during pre-equilibrium and optimization step were checked to make sure the energy has

264   been broadened to a wider energy range (**Figure 2**). The representative distance and angle

265   changes (**Figure 3** and **Figure 4**), and the projected free energy changes (**Figure 5**) were used to

266   characterize the deuterium substitution effect on the geometry and proton transfer process of

267   porphycene.

268

269   **FIGURE AND TABLE LEGENDS:**

270   **Figure 1. The structures of investigated molecules**. The structures of porphycene (**A**) and

271   deuterated porphycene(**B**).

272

273   **Figure 2. The potential energy changes during MD simulations.** The potential energy changes

274   of QM region (**A**) and environment (**B**) in pre-sits and opt-sits steps.

275

276   **Figure 3. The characteristic distance changes.** (**A**) The distance changes of H1-N1 and H2-N3 for

277   porphycene, and (**B**) the distance changes of D1-N1 and H2-N3 for deuterated porphycene

278   during SIRTS-QM/MM simulations; (**C**) the distribution of distance changes for H1-N1 and H2-

279   N3 for porphycene, and (**D**) D1-N1 and H2-N3 for deuterated porphycene.

280

281   **Figure 4. The hydrogen bond angles during the production MD simulations.** The hydrogen

282   bond angels for (**A**) prophycene and (**B**) deuterated porphycene.

283

284   **Figure 5. The free energy landscape of each hydrogen transfer process that was projected on**

285   **two reaction coordinates (q_1, q_2).** (**A**) and (**B**) are 2D free energy landscapes of H1 and H2

286   transfer in porphycene; (**C**) and (**D**) 2D free energy landscape of D1 and H2 transfer in

287   deuterated porphycene.

288

289   **Supplementary files. Topology file, force field parameter file, coordinates file and input file.**

290

291   **Supplementary movie 1. Porphycene.**

292

293   **DISCUSSION:**

294   The structure of porphycene was shown in **Figure 1**. The electrostatic embedding QM/MM

295   hybrid potential with SITS method was used to describe the chemical reactions in water[23,24].

296   The proton transfer occurs within porphycene[3] and thus porphycene is set as QM region and

297   the reminding water is set as MM region. Herein we adopted DFTB/MIO as our QM method to

298   treat the porphycene by balancing the efficiency and accuracy[22,25]. As a sampling enhancement

299   technique, SITS simulation was shown to broaden the distribution of U_s to high-energy regions

300   and meantime preserve sufficient sampling around the energy region at the temperature of

301   interest. For current case, the energy of U_s in the "opt-sits" step was broadened to wider ranges

302 encompassing the energy of the standard MD simulations in the "pre-sits" step as shown in
303 **Figure 2**. Meantime, the smooth energy changes of U_e indicated that the higher temperature in
304 the QM subsystem would not bring perturbation into the environment. SITS-QM/MM method
305 realized enhanced sampling at the interested QM region without affecting the potential energy
306 of water.

308 From distance changes in **Figure 3**, we noticed that H1 transferred from N1 to N2 to form a
309 transit *cis* state, and then initiated a consecutively rapid H2 transfer to arrive the other *trans*
310 state again; and vice versa. The dynamics proton transfer process is shown in **Supplementary**
311 **Movie 1**. Deuterium D1 transfer between N1 and N2 in the single deuterated porphycene
312 invoked the transfer of H2 between N3 and N4. Asynchronous distance changes indicated the
313 stepwise double proton transfer process for both of porphycene and single deuterium
314 substituted porphycene. The similar distance distributions of D1-N1 and H2-N3 suggested that
315 the cooperative effect on two hydrogen bonds[26]. Consistent with previously reported primary
316 geometric isotope effect[26], the distance of D1-N1 is shorter than the distance of H1-N1 (1.048 Å
317 vs. 1.051 Å). As shown in **Figure 3**, we observed around 135, and 65 times of transfer of H or D
318 for porphycene and its isotopomers within 3.2 ns MD simulations, respectively. Deuteriation
319 may exert less effect on the hydrogen bond angles as shown in **Figure 4**. The sufficient sampling
320 on the two reaction channels enabled us to calculate the free energy changes of each proton
321 transfer. The obvious isotopic effect was observed in the 2D free energy landscape. The
322 transition state has been shifted from (0.01 Å, 2.52 Å) to (-0.01 Å, 2.76 Å) as revealed from
323 reaction coordinates (q_1, q_2) (see **Figure 5**). The higher q_2 value means the nonbonded
324 hydrogen bond were expanded. This may come from the asymmetric scaffold of the deuterated
325 porphycene.

327 Both proton transfer processes in porphycene and deuterated porphycene can be captured by
328 SITS-QM/MM MD simulations without pre-defining the reaction coordinates. Moreover, SITS-
329 QM/MM MD simulations revealed the structural difference that was introduced by isotopic
330 effect. The hydrogen bond D1-N1 was shortened in comparison with H1-N1. The transition
331 state has been shifted toward higher q_2 value because of an asymmetric shape caused by
332 deuteration. Though only subtle difference was detected in covalent hydrogen bond, the
333 distance difference may invoke bigger energy difference around the equilibrium bond distance.
334 We are planning to further validate this observation at higher level QM method in the future
335 studies.

337 The feasibility of SITS-QM/MM has been well validated in the double channel of reactions
338 without pre-defining reaction coordinates in the present study. This method holds potential of
339 searching reaction products from known reactant states if no prior reaction mechanism is
340 provided. We have adopted DFTB/MIO method in our current implementation of SITS-QM/MM
341 approach, and gained a better understanding of the isotopic effect. It is worth noting that the
342 implemented approach is able to capture the free energy changes, but may not capture
343 dynamic properties without considering the quantum tunneling effect. Still, this protocol acts as
344 a starting point to investigate the chemical reaction mechanisms in the condensed
345 environment. We expect SITS-QM/MM method to be extended to higher level QM methods

346 and thus can exploit more complex systems in the future.
347

354 **DISCLOSURES:**
355 The authors have nothing to disclose.
356

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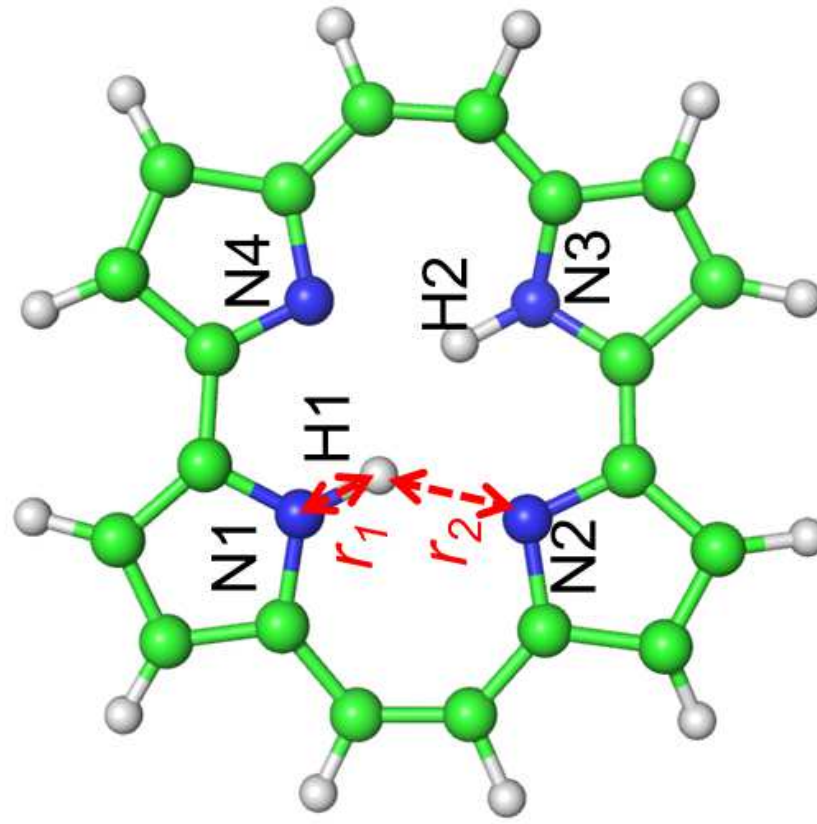
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Figure1
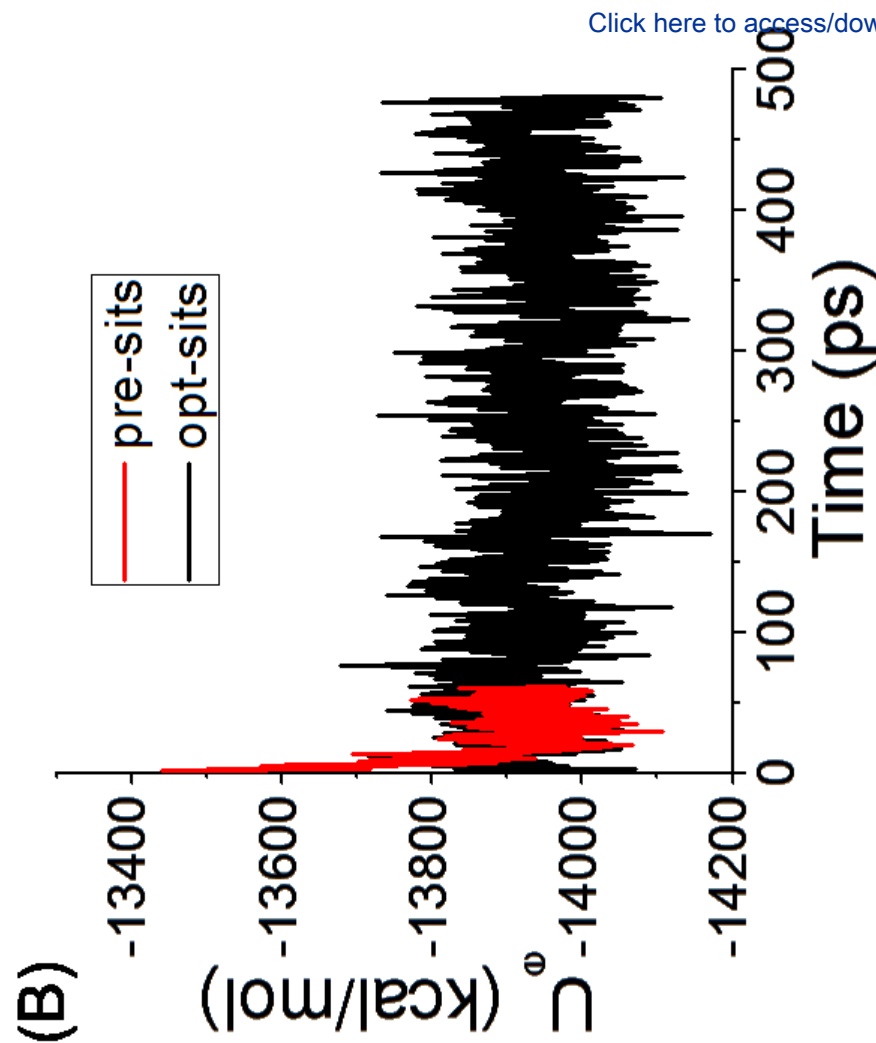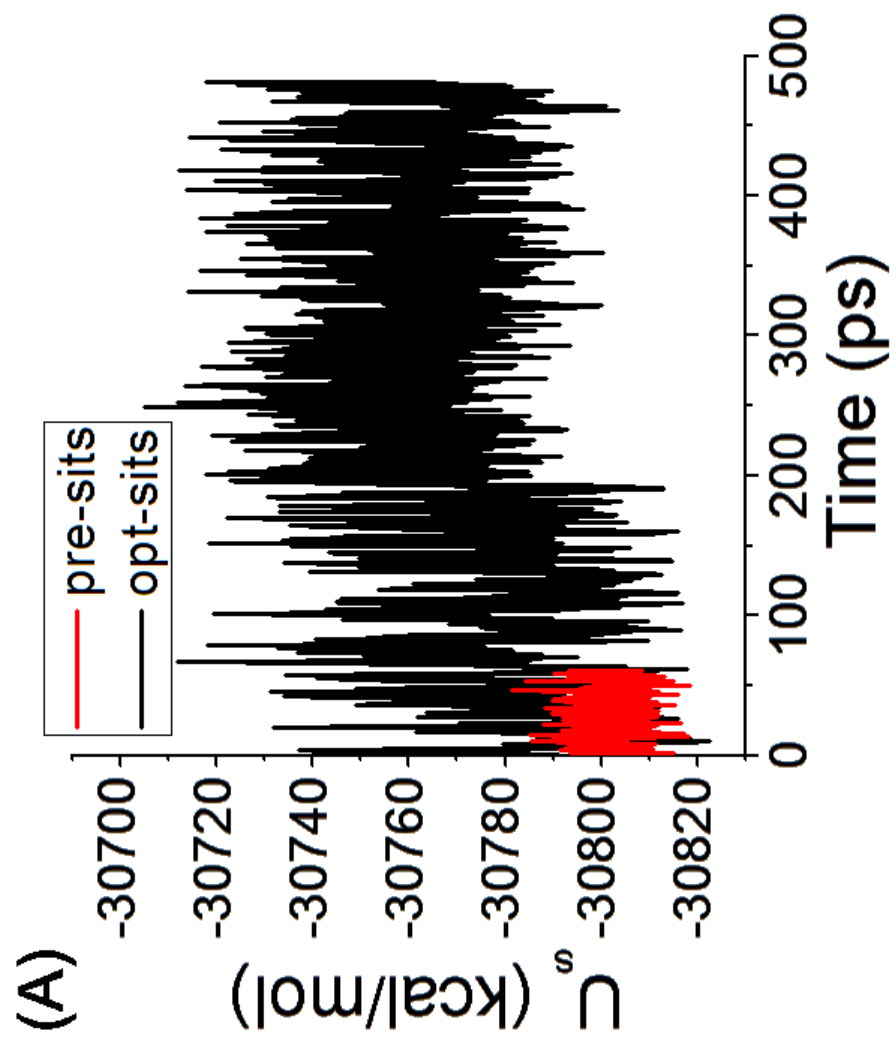
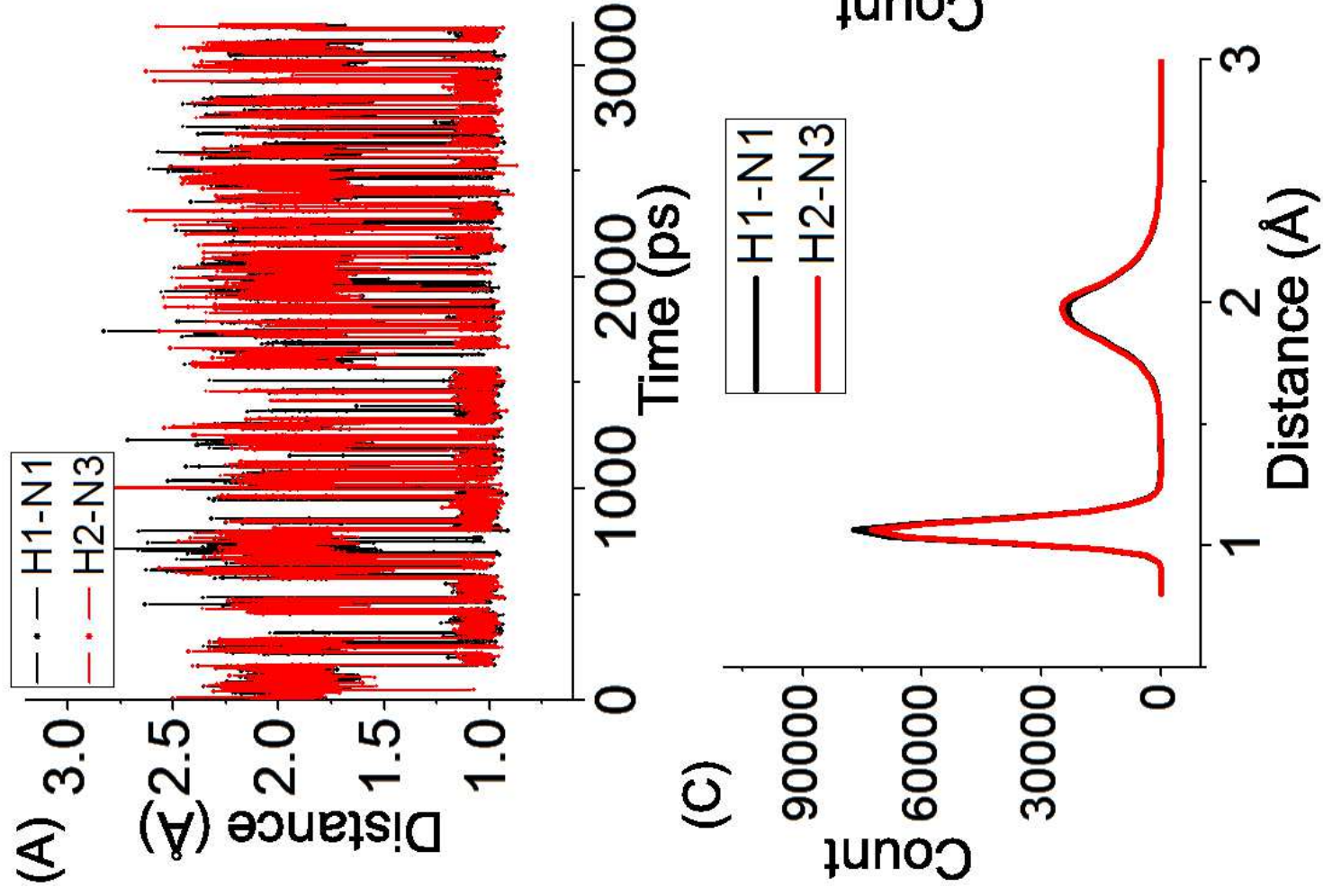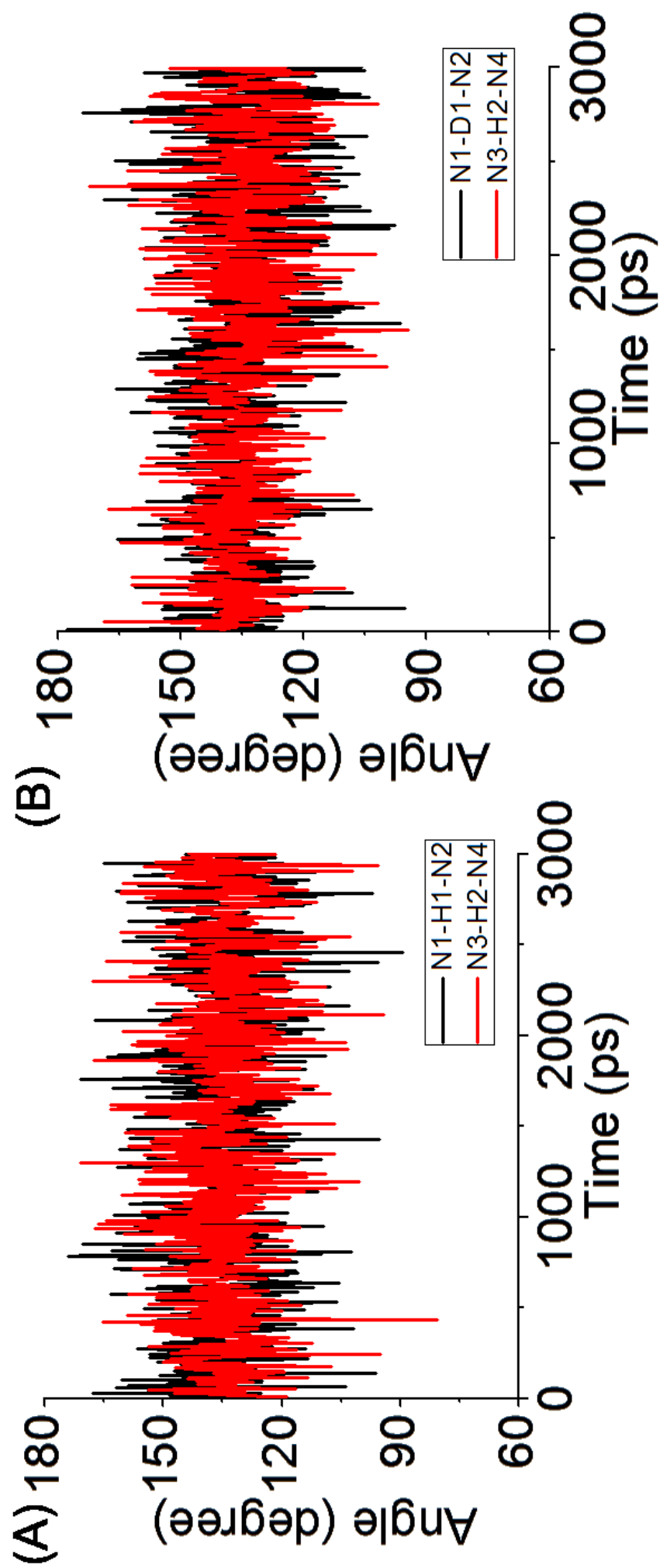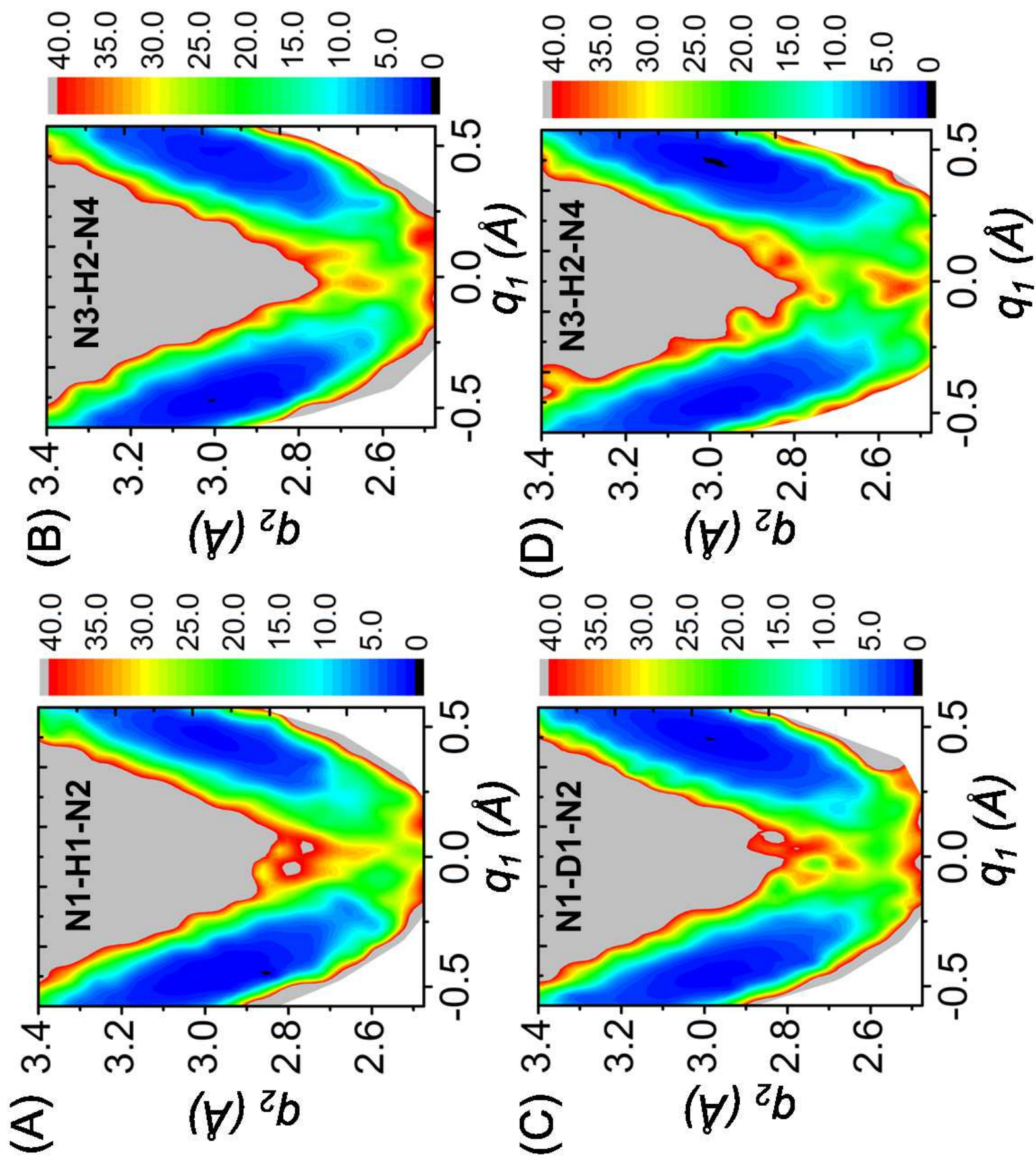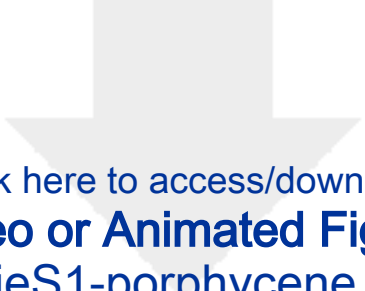Figure2

Figure3

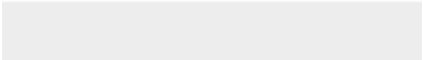Figure4

Figure5

Supplemental Movie
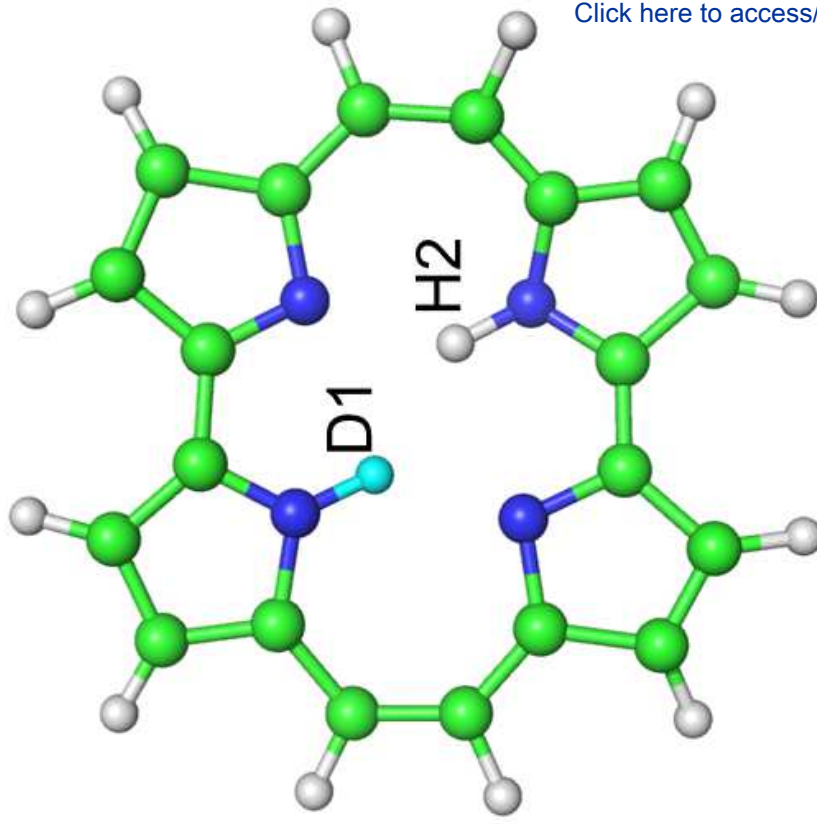
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Video or Animated Figure
MovieS1-porphycene.mp4

Name of Material/ Equipment	Company	Catalog Number	Comments/Description
operating system	CentOS Linux release 6.0		
QM4D software	http://www.qm4d.info/		in-house program
Computer desktop	HP		

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Author(s): Zhihui Tu, Jian Yin, Liangxu Xie

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Article Title: Isotopic Effect in Double Proton Transfer Process of Porphycene Investigated by Enhanced QM/MM method

Signature: *Liangxu Xie*

Date: 26/03/2019

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Editorial comments:

Reply: Thanks for the comments to improve our manuscript.

*The manuscript has been modified and the updated manuscript, **60040_R1.docx**, is attached and located in your Editorial Manager account. **Please use the updated version to make your revisions.***

1. Step 1.1, 1.2: Is a software being used in this step? If yes, a step-wise description of software usage must be included in the step. Please mention what button is clicked on in the software, or which menu items need to be selected to perform the step. If not, please add more details to the steps. Please ensure you answer the "how" question, i.e., how is the step performed?

Reply: We thank editor for the detailed comments. The model either can be downloaded from PubChem (https://pubchem.ncbi.nlm.nih.gov/compound/Porphycene) or be built manually by "GaussView" software. Here we would like to add the following approach in our revised manuscript. To make sure the readers can follow the steps, we changed Step 1.1 and step 1.2 thoroughly as follows. Hope the step-wise description can ensure the readers to reproduce the results.

We have changed from

*"**1.1 Build model**: Solvate porphycene in a cubic TIP3P[21] water box with an edge length of 38 Å. Replace one intramolecular hydrogen atom of porphycene with deuterium to build single deuterium substituted porphycene."*

To

"

*"**1.1 Build porphycene structure**: Open "GaussView" software by double-click the mouse. Then click "Element Fragment" button in the menu of the "GaussView" to choose the needed elements. Single-click mouse to construct porphycene. Then click "File" button to save as the pdb file.*

1.2 Solvate the model*: Solvate porphycene in a cubic TIP3P water box with an edge length of 38 Å by issuing the command in the linux operating system.*

"genbox_d -cp prp-vac.pdb -cs spc216.gro -o solv.pdb -maxsol 1484 –box 3.8"

1.3 Build deuterium porphycene*: Issue the following command to generate topology file.*

"cns < ppi_solv.inp"

Then open "prp-wat.psf" with "vi" command and change the mass of H1 from 1.00800 to 2.01600" to replace one intramolecular hydrogen atom of porphycene with deuterium to build single deuterium substituted porphycene.

"

We have added the follows at line 151-152 in the revised manuscript,

"Input "method scctb", "integral 0.5 fs", and "cutoff 12" in the MD input file by opening it with "vi" command."

2. 2.1: Please write this step in the imperative tense.

Reply 2: We have changed Step 2.1 from

*"****2.1 Set up temperature parameters:*** *QM4D reads the molecular dynamics parameters from the input file. For SITS simulations, the temperature range was evenly spread out from 260K to 1100K by 160 temperature points. The input files are supplied as the supporting materials."*

to

"2.1 Set up temperature parameters: *Input "templow 260","temphigh 1100" and "ntemp 160" in the input file.*

NOTE: The temperature range from 260K to 1100K was spread out by "QM4D" software to 160 temperature points during MD simulations. The template input files are supplied as the supporting materials."

3. 5.2.2: Please write this step in the imperative tense.

Reply 3: We have changed Step 2.2 from

"Set "runtype 100" in the input file to start the equilibrium simulations. The total step is 120,000 but can be adjusted depending on the specific needs."

To

"Set "runtype 100" and "step 120,000" in the input file. Then issue the following command,

$PATH/qm4d $INPUTFILE > $OUTPUTFILE

NOTE: The total step is 120,000 but can be adjusted depending on the specific needs."

4. 5.3.3: Please write this step in the imperative tense.

Reply 4: Step 5.3.3 is not a single step. It explains the command of Step 5.3.2. We are sorry for the misleading and replace "5.3.3" with a "NOTE" word.

5. For in-text referencing, please add the reference number before a comma or period.

Reply 5: Thanks for the reminding. We have moved the reference number before the period accordingly.

6. Figure 2: Please add a short description of the figure in Figure Legend.

Reply 6: Thanks for the comments. We have added a short description of Figure 2 as follows,

"Figure 2. The potential energy changes during MD simulations. The potential energy changes of QM region (A) and environment (B) in pre-sitsand opt-sits steps."
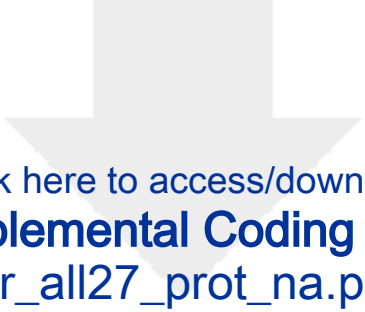
7. Figure 4: Please add a short description of the figure in Figure Legend.

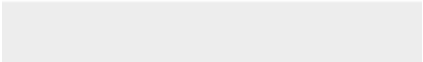**Reply 7: Thanks for the comments. We have added a short description of Figure 4 as follows,**

"Figure 4. The hydrogen bond angles during the production MD simulations. The hydrogen bond angels for (A) prophycene; and (B) deuterated porphycene.**"**

topology file

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