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# Insight into the excited-state double proton transfer mechanisms of Doxorubicin in acetonitrile solvent

## Supplementary Information

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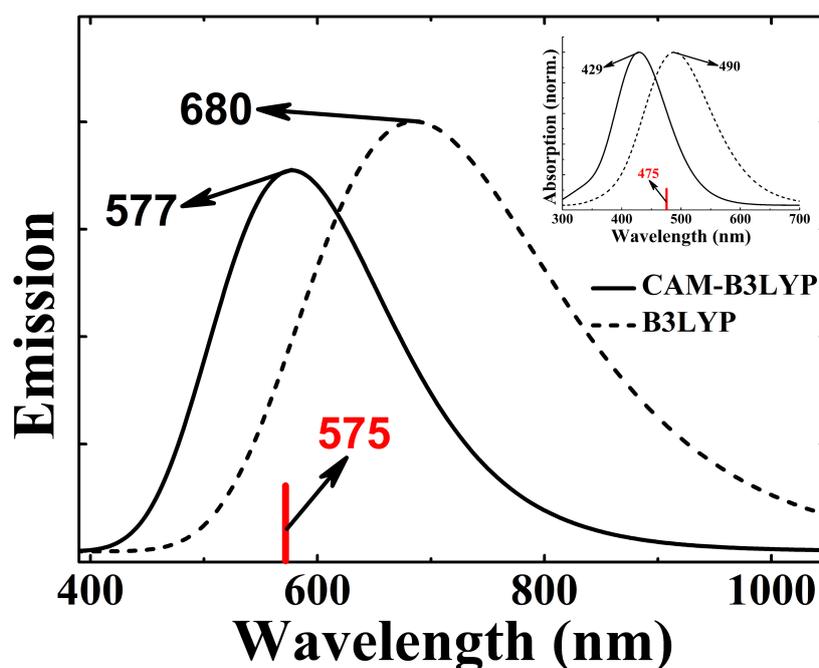


Figure S1: Simulated emission spectra of DXR-D form calculated by using the B3LYP (dashed line) and CAM-B3LYP (solid line) functionals. The inset shows the simulated absorption of DXR. The vertical lines denote the corresponding peaks observed experimentally.

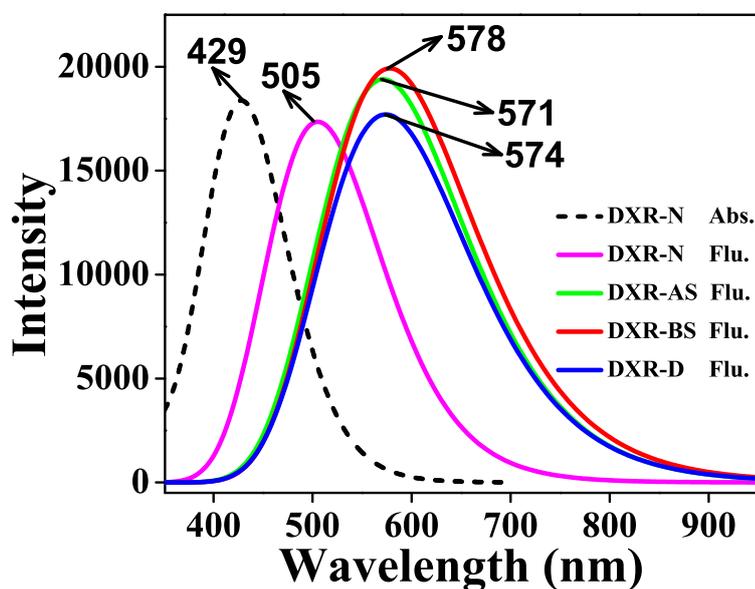


Figure S2: The absorption and fluorescence spectra of DXR in acetonitrile solvent based on the  $\omega$ B97XD functional.

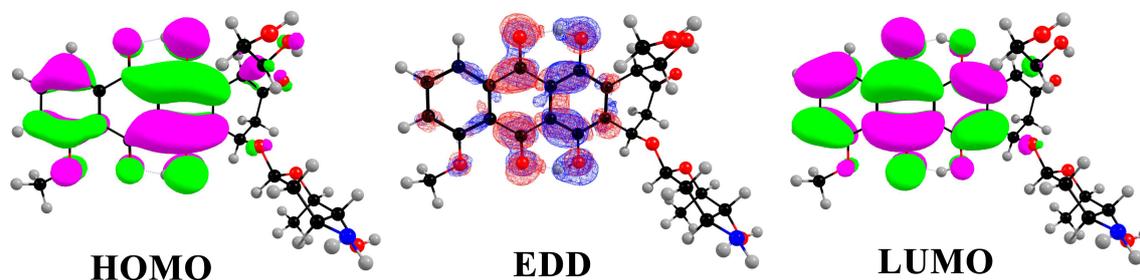


Figure S3: Calculated electron-density difference (EDD) map between  $S_0$  and  $S_1$  states and the HOMO-LUMO maps of DXR-N in acetonitrile solvent at the  $\omega$ B97XD/6-311+G(d,p) level. In the EDD maps, from  $S_0$  to  $S_1$ , the regions with increasing electron density are shown in red, whereas the regions with decreasing density are shown in blue.

Whether it is the SPT or the DPT processes, we can clearly see that there exists high barriers ( $> 5$  kcal/mol) in the  $S_0$  state. Upon electronic excitation, the SPT and DPT potential energy barriers dramatically decrease. However, compared with the SPT

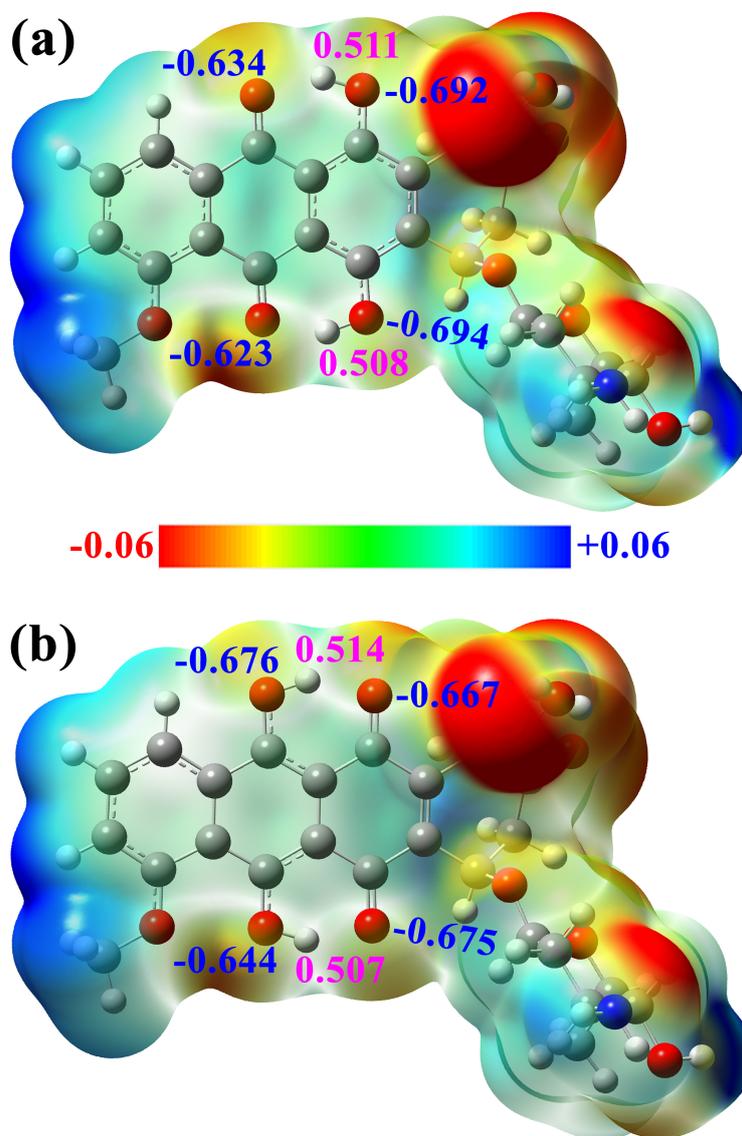


Figure S4: ESP of (a) DXR-N and (b) DXR-D forms, and NPA charges of the selected atoms are given in blue and magenta fonts.

process, the energy barrier of the DPT process is slightly higher ( $< 2$  kcal/mol), which is little convincing to rule out the DPT mechanism.

The calculated PECs verify the proposed ESIDPT mechanism at the wB97XD/6-311+G(d,p) level.

All the TS structures on the  $S_1$ -PESs are found based on CIS/6-311+G(d,p) method.

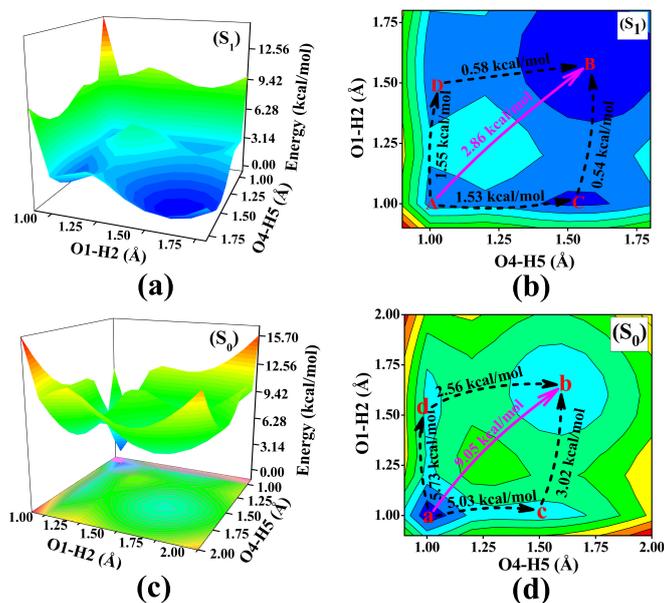


Figure S5: The 3D PESs and PES projections of DXR system in ACN solvent at B3LYP/6-311+G(d,p) level (a) (b) in the  $S_1$  state; (c) (d) in the  $S_0$  state.

Herein, we choose the CIS method rather than TDDFT, since it has second order derivative, which is relatively easy to search TS structure than TDDFT (TDDFT can only solve the first order derivative in excited states.).

Table S1: The imaginary frequencies ( $\text{cm}^{-1}$ ) for  $\text{TS}_1$ ,  $\text{TS}_2$ ,  $\text{TS}_3$  and  $\text{TS}_4$  structures along with stepwise ESIDPT paths ( $A \rightarrow C \rightarrow B$  and  $A \rightarrow D \rightarrow B$ ) based on CIS/6-311+G(d,p) level

	$\text{TS}_1$	$\text{TS}_2$	$\text{TS}_3$	$\text{TS}_4$
frequency	-1419	-1604	-1279	-1627

In this table, we provide all the imaginary frequencies of DXR along with stepwise ESIDPT paths ( $A \rightarrow C \rightarrow B$  and  $A \rightarrow D \rightarrow B$ ) in acetonitrile solvent. It is worth noting that all TS structures are confirmed to be only one imaginary frequency and its vibrational eigenvector points to the correct direction.

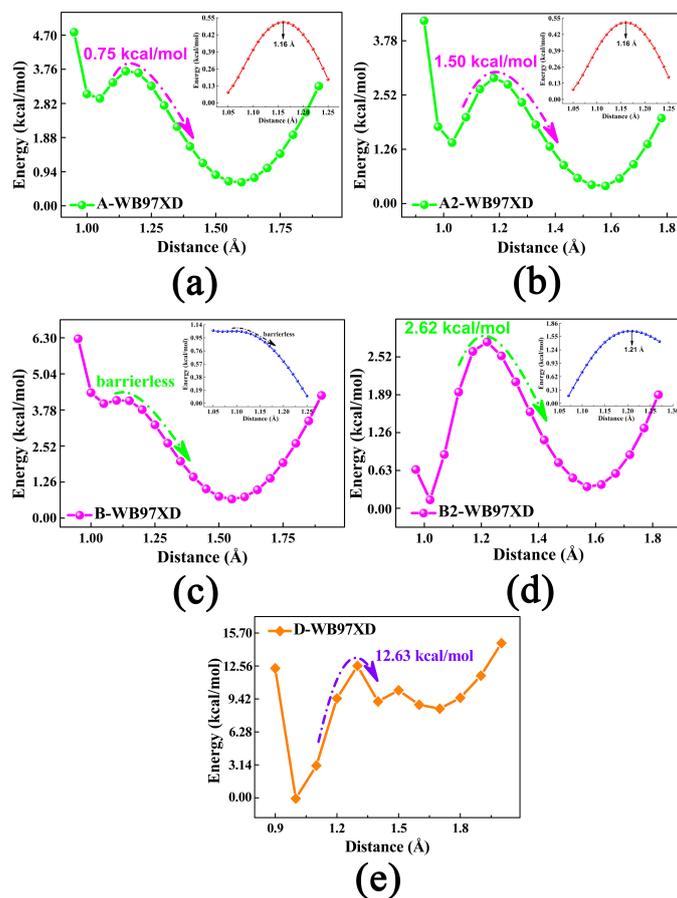


Figure S6: The excited-state PECs of DXR system in ACN solvent at  $\omega$ B97XD/6-311+G(d,p) level. (a) (b) The stepwise single proton ( $H_2$ ) transfer processes; (c) (d) the stepwise single proton ( $H_5$ ) transfer processes; (e) the synchronous double proton ( $H_2$  and  $H_5$ ) transfer process. Inset: the PECs around inflection points along smaller step size (i.e.,  $0.01 \text{ \AA}$ ).

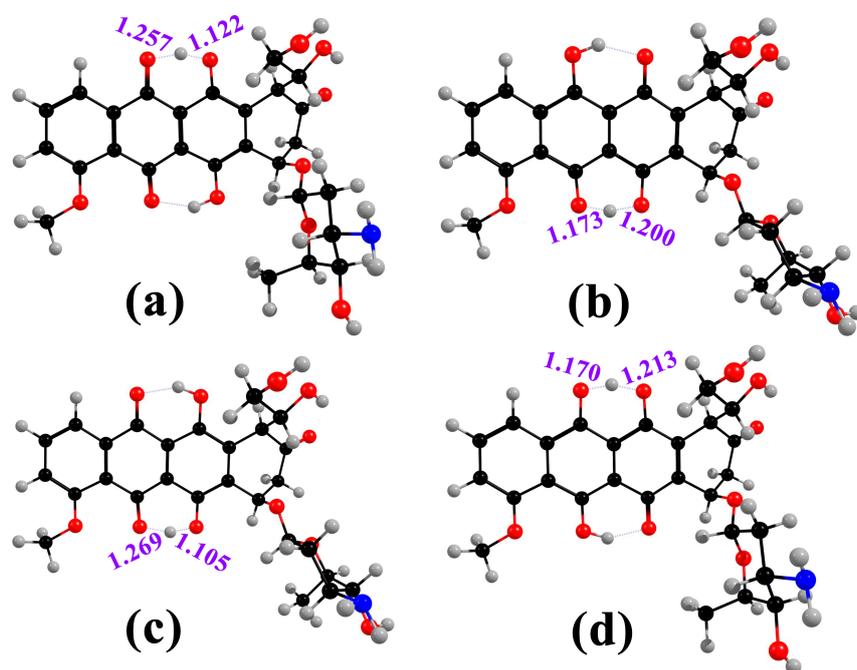


Figure S7: The transition state (TS<sub>1</sub> (a), TS<sub>2</sub> (b), TS<sub>3</sub> (c) and TS<sub>4</sub> (d)) structures of DXR on the S<sub>1</sub>-PESs in acetonitrile solvent.