The N…H hydrogen bond strength in the transition state at the limiting step determines the reactivity of cephalosporins in the active site of L1 metallo-β-lactamase

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Computational protocol

The combined QM/MM method with the electronic embedding scheme was used, wherein the QM subsystem was calculated at the PBE0-D3/6-31G** level of theory,[S1,S2] and the MM subsystem was described by the classical force field parameters: the AMBERforce field[S3] for the protein and TIP3P for H_2O molecules. The QM subsystems were similar to the previously reported ones[S4] and comprised the cephalosporin compound, catalytic OH^- and aspartate, two zinc cations with their coordination spheres, and several molecular moieties that form hydrogen bonds in the active site. The transition states were confirmed by the vibrational analysis and also by forward and backward relaxation of the systems along the reaction coordinate. By the latter, we checked the correctness of intermediates preceding and following the considered transition states. For all the transition states, the electron densities of QM subsystems placed in the electrostatic field of atoms of the MM subsystem were calculated. All the QM/MM calculations were performed using the NWChem program,[S5] and the electron density analysis was carried out in the Multiwfn program[S6] and visualized in the VMD.[S7]

We tested several bonding descriptors including the electron density at the bond critical point, $\rho(r_{BCP})$, the electron localization function (ELF),[S8] and associated core–valence bifurcation (CVB) index, and the potential acting on an electron in the molecule (PAEM).

The ELF is commonly used to extract the information about the spatial electron localization hidden in the electronic kinetic energy density.[S8] The ELF $\eta(r)$ is written as

$$\eta(r) = \left(1 + \left(\frac{D_P(r)}{D_0(r)}\right)^2\right)^{-1} \tag{1},$$

wherein $D_P(r)$ is the Pauli electron kinetic energy density at point r, and $D_0(r)$ is the kinetic energy of a uniform gas with the local electron density of the considered system. The ELF values were in the range of 0–1: $\eta(r) = 1$ corresponding to the total electron pair localization, $\eta(r) = 1/2$ matching a uniform electron gas, and $\eta(r) = 0$ indicating the border between electron pairs and electron shells.

The core–valence bifurcation (CVB)[S9] index for the X–H…Y is written as

$$CVB = \eta_{min}(V(XH), V(Y)) - \eta_{min}(C(Y), V(Y)) \tag{2},$$

wherein $\eta_{min}(V(XH),V(Y))$ is the ELF minimum between the valence regions of X–H group and Y atom and $\eta_{min}(C(Y),V(Y))$ is the ELF minimum between the valence and core regions of Y atom.

The potential acting on an electron in the molecule (PAEM) quantifies the total interaction energy of any one electron with the rest $(n-1)$ electrons of the molecule and with all the nuclei. The PAEM at the point r is written as

$$V_{\text{PAEM}}(r) = -\sum_A \frac{Z_A}{|r-R_A|} + \frac{1}{\rho(r)} \int \frac{\pi(r,r\prime)}{|r-r\prime|}\, dr\prime \qquad (3),$$

wherein $\pi(r,r\prime)$ is the pair electron density,[S10] Z_A is the charge of A nucleus, R_A is the coordinate of A nucleus, and $\rho(r)$ is the one-electron density. It can be further presented as a sum

$$V_{\text{PAEM}}(r) = -V_{\text{ESP}}(r) + V_X(r)/\rho(r) \qquad (4),$$

wherein $V_{\text{ESP}}(r)$ is the electrostatic potential and $V_X(r)$ is the exchange potential. In this work, we have estimated $V_X(r)$ using the PBE scheme.[S11]

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