Catalysis of Carboxypeptidase A: Promoted-water vs Nucleophilic Pathways

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Support information:

1. Stationary point structures along the promoted-water pathway for the ester substrate

The structures of six stationary points along the promoted-water pathway for the ester substrate identified by DFT full optimization at the B3LYP/6-31G(d) level of theory are displayed in Fig. S1. The key internuclear distances are listed in Table S1.

2. Stationary point structures along the nucleophilic pathway for an ester substrate

The structures of six stationary points along the nucleophilic pathway for the ester substrate identified by DFT full optimization at the B3LYP/6-31G(d) level of theory are displayed in Fig. S2. The key internuclear distances are listed in Table S2.

3. Full citations of Refs 57 and 85.

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Table S1. Key geometric parameters of stationary points for the promoted-water pathway obtained at the B3LYP/6-31G(d) level of theory with the truncated active-site model.

Distance (Å)	Truncated Model					
	ES	TS1	TI1	TI2	TS3	EP
$O_w \cdots C_6$	3.55	1.84	1.43	1.41	1.34	1.25
$H_1 \cdots O_{\varepsilon2}(E270)$	1.04	1.00	0.99	1.00	1.22	1.83
$Zn \cdots N_{\delta1}(H69)$	2.01	2.11	2.02	2.05	2.03	2.05
$Zn \cdots O_{\varepsilon2}(E72)$	1.95	1.95	1.95	1.97	1.95	1.95
$Zn \cdots N_{\delta1}(H196)$	2.06	2.04	2.02	2.04	2.03	2.01
$O_w \cdots Zn$	1.94	2.06	3.05	3.04	3.22	3.12
$Zn \cdots O_7$	4.02	2.37	1.97	1.93	1.95	1.99
$O_7 \cdots H_{21}(R127)$	1.89	1.82	1.88	1.99	2.59	4.18
$O_7 \cdots H_{11}(R127)$	2.60	3.38	3.62	3.69	3.91	4.93
$O_{12} \cdots H_{11}(R127)$	4.39	1.85	1.83	1.77	1.86	1.94
$O_{13} \cdots H_{22}(N144)$	-	-	-	-	-	-
$O_{12} \cdots H_{21}(R145)$	1.68	1.67	1.72	1.68	1.68	1.69
$O_{13} \cdots H_{11}(R145)$	1.70	1.71	1.69	1.68	1.69	1.71
$O_{12} \cdots H_{\eta}(Y248)$	-	-	-	-	-	-
$O_7 \cdots H_{\eta}(Y248)$	-	-	-	-	-	-
$C_5 \cdots C_6$	1.52	1.53	1.55	1.56	1.54	1.53
$C_6 \cdots O_7$	1.22	1.27	1.35	1.34	1.29	1.27
$C_6 \cdots O_9$	1.33	1.36	1.45	1.48	1.89	4.00
$H_1 \cdots O_9$	-	-	-	1.77	1.21	0.98

Table S2. Key geometric parameters of stationary points for the nucleophilic pathway obtained at the B3LYP/6-31G(d) level of theory with the truncated active-site model.

Distance (Å)	Truncated Model					
	ES	TS1	AE1	AE2	TS2	EP
$C_5 \cdots C_6$	1.52	1.54	1.55	1.55	1.54	1.53
$C_6 \cdots O_7$	1.24	1.29	1.34	1.32	1.29	1.28
$C_6 \cdots O_9$	1.31	1.35	1.40	1.42	1.88	5.72
$C_6 \cdots O_{\varepsilon 2}$	3.01	1.82	1.51	1.51	1.36	1.24
$O_w \cdots C_\delta$ (E270)	-	-	-	3.47	1.77	1.34
$H_2 \cdots O_9$	-	-	-	1.99	1.18	0.97
$H_2 \cdots O_w$	-	-	-	0.97	1.25	2.01
$O_{\varepsilon 2} \cdots C_\delta$ (E270)	-	-	-	1.34	1.50	3.68
$Zn \cdots N_{\delta 1}$(H69)	2.01	2.07	2.03	2.03	2.03	2.03
$Zn \cdots O_{\varepsilon 2}$(E72)	1.93	1.95	1.95	1.94	1.94	1.94
$Zn \cdots N_{\delta 1}$(H196)	2.00	2.06	2.03	2.02	2.01	2.02
$Zn \cdots O_7$	2.01	1.99	1.94	1.94	1.96	1.98
$O_{12} \cdots H11$(R127)	1.86	1.87	1.79	1.84	1.86	1.94
$O_{12} \cdots H21$(R145)	1.73	1.71	1.69	1.69	1.73	1.84
$O_{13} \cdots H11$(R145)	1.67	1.67	1.67	1.67	1.66	1.84

Fig. S1. Stationary point structures of the promoted-water pathway for the ester substrate obtained at the B3LYP/6-31G(d) level of theory.
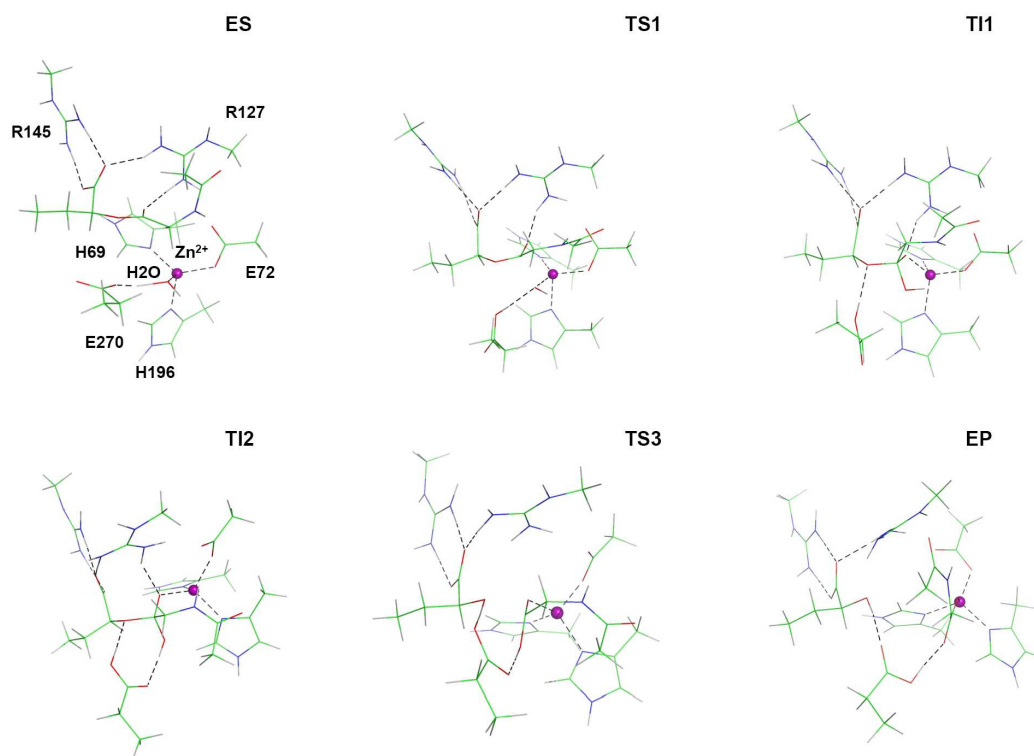
Fig. S2. Stationary point structures of the nucleophilic pathway for the ester substrate obtained at the B3LYP/6-31G(d) level of theory.