Electronic Supplementary Material (ESI) for RSC Advances.

Electronic Supplementary Information (ESI)†

Kinetics and thermodynamics of enzymatic decarboxylation of α,β-unsaturated acid: A theoretical study

by

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and

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1. Interaction energy calculations

The strength of the intermolecular interaction that was responsible for the transition state formation in acid catalysts (1) and (2) (elementary reactions (**III**) and (**V**), respectively) was approximated using the interaction energy between molecular fragments inside the model molecular cluster ($\Delta E^{Total,A...B}$), which was computed using $\Delta E^{Total,A...B} = E^{Total,AB} - (E^{Total,A} + E^{Total,B})$, where $E^{Total,AB}$ is the total energy of the model molecular cluster and $E^{Total,A}$ and $E^{Total,B}$ are the total energies of the parts of the model molecular cluster that contain molecular fragments A and B, respectively. Because the model molecular clusters that were considered in this work were large and the basis set was restricted, to account for the effect of the basis set superposition error (BSSE), the counterpoise correction was applied, for which $\Delta E^{Total,A...B/CP} = E^{Total,AB} - (E^{Total,A(B)} + E^{Total,B(A)})$, where $E^{Total,A(B)}$ and $E^{Total,B(A)}$ denote the total energy of molecular fragment A computed with the "ghost" basis set (without electrons and nuclei) of molecular fragment B and the total energy of molecular fragment B computed with the "ghost" basis set (without electrons and nuclei) of molecular fragment A, respectively. Because the hypothesized elementary reactions involve covalent bond breaking and formation, to study the characteristic electron density distributions (e.g., π-π and ion-pair characters), the highest occupied molecular orbitals (HOMOs) of the model molecular clusters along the potential energy curves were plotted.

2. Discussion on the elementary reactions

1,3-Dipolar cycloaddition (I)

The associative interactions between the residues, substrate, and cofactor in **React** are represented by the salt bridges between **Glu277** and **Arg173H$^+$** and between **Arg173H$^+$** and **Cin** and by the N–H…O$^-$ H-bond between **Gln190** and **PrFMN** (Table S2†), respectively. Because the aromatic rings are relatively close, the π–π interaction between **Cin** and **PrFMN** could help facilitate 1,3-dipolar cycloaddition. The HOMOs in Fig. S1a† show a significant difference between the electron density distributions in **React** at ε = 1 and 78. At ε = 1, the highest electron density is localized at the salt-bridge network that spans from the COO$^-$ group of **Glu277** to **Arg173H$^+$** to the COO$^-$ group of **Cin**, whereas at ε =78 (Fig. S1b†), the highest electron density

distribution is at the **PrFMN** aromatic rings, thereby indicating higher aromaticity in the high local dielectric environment.

For 1,3-dipolar cycloaddition **(I)**, the potential energy curve in Fig. S1c† reveals that at ε = 1, **React**→**TS1** is a two-step process, in which the formation of π–π stacking (a) occurs first ($\Delta E^{\ddagger}$ = 24 kJ/mol), followed by dipolarophile-iminum pair formation (b) in the transition structure **TS1** (**(**$\Delta E^{\ddagger}$ = 50 kJ/mol). **TS1** is characterized by the α,β-double bond of **Cin** staying exactly above the iminium ion (C_{29}^{PrFMN}–$N_{35}^{PrFMN,+}$–C_{34}^{PrFMN}, 1,3–dipole) of **PrFMN** ($R_{C_{\alpha}^{Cin}-C_{29}^{PrFMN}}$ = 2.78 and $R_{C_{\beta}^{Cin}-C_{34}^{PrFMN}}$ = 3.30 Å).

It appears that pyrrolidine cycloadduct formation (c) and relaxation of π–π stacking (d) occur instantly in **TS1**→**Int1,** thereby leading to the transformation of the enolate anion to a C=O group at the O_{30}^{PrFMN} atom. Fig. S1c† also shows that **Int1** possesses approximately the same stability as **React**. The HOMO plots along the potential energy curve (Fig. S1a†) show electron density redistribution upon pyrrolidine cycloadduct formation and relaxation of the π–π stacking interaction, thereby leading to a considerable increase in the π–character spanning from the enoate group of **Cin** to the heteroaromatic rings (the isoalloxazine ring) of **PrFMN**. The electron density redistribution is due to neutralization of the iminium ion and is accompanied by an increase in the C_{α}^{Cin}–C_{43}^{Cin} bond distance from $R_{C_{\alpha}^{Cin}-C_{43}^{Cin}}$ = 1.54 to 1.58 Å, which reflects a weaker C_{α}^{Cin}–C_{43}^{Cin} covalent bond in **Int1** (precursor for CO_2 elimination) compared with the precursor **React**.

At ε = 78, the potential energy curve is almost the same as that at ε = 1 (Fig. S1c†). The energy barriers for π–π stacking (a)$^{\varepsilon}$ and **TS1$^{\varepsilon}$** formation (b)$^{\varepsilon}$ are slightly different, namely, $\Delta E^{\ddagger}$ = 26 and 48 kJ/mol, respectively. This could be because cycloadduct formation (**React**$^{\varepsilon}$→**TS1**$^{\varepsilon}$→**Int1**$^{\varepsilon}$) does not involve direct charge (proton) transfer. Therefore, the electric field that is induced by the aqueous solvent (ε = 78) does not have a strong influence on the energy barriers. The relative solvation energies ($\Delta E^{Rel,Solv}$) in Fig. S1c†, which were computed with respect to the solvation energy (ΔE^{Solv}) of the precursor **React**, show that because the charges in the active site (e.g., $N_{35}^{PrFMN,+}$ in Fig. S1b†) are not directly hydrated, the stability of **TS1$^{\varepsilon}$** is only slightly increased (~-8 kJ/mol) and that of **Int1$^{\varepsilon}$** is slightly decreased (~6 kJ/mol); the latter is due to the neutralization of the iminium charge ($N_{35}^{PrFMN,+}$) upon pyrrolidine cycloadduct formation.

Decarboxylation (II)

At ε = 1, the structures of the model molecular clusters on the potential energy curve in Fig. S2a† reveal that decarboxylation (**II**) (**Int1→TS2→Int2**) is a three-step process, in which the C_{α}^{Cin}–C_{43}^{Cin} bond extension (a) continues in **Int1→TS2** ($R_{C_{\alpha}^{Cin}-C_{43}^{Cin}}$ = 1.62 Å and $\Delta E^{\ddagger}$ = 60 kJ/mol), followed by CO_2 elimination (b), C_{β}^{Cin}– C_{34}^{PrFMN} dissociation (c) and reorientation of the aromatic ring of **Cin** away from **PrFMN** (d) in **TS2→Int2**, with $R_{C_{\alpha}^{Cin}-C_{43}^{Cin}}$ = 4.52 and $R_{C_{\beta}^{Cin}-C_{34}^{PrFMN}}$ = 3.67 Å, respectively. The potential energy curve in Fig. S2c† shows that at ε = 78, although the consecutive reaction scheme is not different from that at ε = 1, the C_{α}^{Cin}–C_{43}^{Cin} bond extension (a)$^{\varepsilon}$, CO_2 elimination (b)$^{\varepsilon}$ and C_{β}^{Cin}–C_{34}^{PrFMN}dissociation (c)$^{\varepsilon}$ occur readily in **Int1$^{\varepsilon}$→TS2$^{\varepsilon}$** with a significantly lower energy barrier ($\Delta E^{\ddagger}$ = 39 kJ/mol). It appears that the transfer of the negative charge from the COO^{-} group of **Cin** to form the enolate anion (enolization) at the O_{30}^{PrFMN} atom (Fig. S2b†), which accompanies (a)$^{\varepsilon}$, (b)$^{\varepsilon}$ and (c)$^{\varepsilon}$, leads to a decrease in the relative solvation energy (stabilization of **TS2$^{\varepsilon}$**) to $\Delta E^{Rel,Solv}$ = -12 kJ/mol (Fig. S2c†), whereas the substrate moiety reorientation (d)$^{\varepsilon}$ ($R_{C_{\beta}^{Cin}-C_{34}^{PrFMN}}$ = 3.67 Å) results in an increase in $\Delta E^{Rel,Solv}$ to 26 kJ/mol; **Int2$^{\varepsilon}$** (e.g., the aromatic ring of **Cin**) is moderately destabilized by the electric field of the aqueous solvent.

Acid catalyst (1) (III)

The precursor and transition structures of the model molecular clusters on the potential energy curves in Fig. S3a† indicate that at ε = 1, proton transfer from the COOH group of **Glu282** to C_{α}^{Cin} (a) and formation of the pyrrolidine cycloadduct (b) are associated with a low energy barrier; for **Int2b→TS3**, $R_{C_{\alpha}^{Cin}-H_{126}^{Glu282}}$ = 1.10, $R_{C_{\alpha}^{Cin}-C_{29}^{PrFMN}}$ = 1.53 and $R_{C_{\beta}^{Cin}-C_{34}^{PrFMN}}$ = 1.64 Å with $\Delta E^{\ddagger}$ = 42 kJ/mol. The formation of π–π stacking between **Cin** and **PrFMN** (c) is partly responsible for the stability of **Int3**.

The scenario is slightly different at ε = 78 (Figs. S3b† and S3c†), in which proton transfer from the COOH group of **Glu282** to C_{α}^{Cin} (a)$^{\varepsilon}$ instantly produces the transition state (**TS3$^{\varepsilon}$**); for **Int2b$^{\varepsilon}$→TS3$^{\varepsilon}$**, $R_{C_{\alpha}^{Cin}-H_{126}^{Glu282}}$ = 1.26 (shared proton structure), $R_{C_{\alpha}^{Cin}-C_{29}^{PrFMN}}$ = 1.55 and $R_{C_{\beta}^{Cin}-C_{34}^{PrFMN}}$ = 2.31 Å with a considerably higher energy barrier ($\Delta E^{\ddagger}$ = 137 kJ/mol) and destabilized relative solvation energy ($\Delta E^{Rel,Solv}$ = 5 kJ/mol). At ε = 78, acid catalyst (1) is accomplished through the formation of pyrrolidine cycloadduct (b)$^{\varepsilon}$ and π–π stacking intermediate (c)$^{\varepsilon}$ (**Int3$^{\varepsilon}$**).

The increase in $\Delta E^{\ddagger}$ at $\varepsilon = 78$ is opposite the situation in decarboxylation (**II**) because proton transfer in this case leads to an increase in the number of the positive and negative charges (acid-base ion pairs in **TS3$^{\varepsilon}$** with $R_{C_{\alpha}^{Cin}-H_{126}^{Glu282}} = 1.26$ Å), which are partly stabilized by the high local dielectric environment; the "dipolar" interaction $(a)^{\varepsilon}$ in **TS3$^{\varepsilon}$** forms a "dipolar energy trap", which increases $\Delta E^{\ddagger}$ at $\varepsilon = 78$. Analysis of the $O_{125}^{Glu282,-}...H_{126}^{Glu282}-C_{\alpha}^{Cin}$ H-bond and $O_{125}^{Glu282,-}...H_{126}^{Glu282,+}...C_{\alpha}^{Cin}$ ion-pair interaction energies (at (a) and $(a)^{\varepsilon}$ in **TS3** and **TS3$^{\varepsilon}$**, respectively) suggests that with respect to the precursor, the H-bond is strongly destabilized at $\varepsilon = 1$ ($\Delta E^{Rel,H\text{-}bond/CP} = 39$ kJ/mol), whereas at $\varepsilon = 78$, the ion pair is only weakly destabilized ($\Delta E^{Rel,H\text{-}bond/CP,\varepsilon} = 2$ kJ/mol).

Cycloelimination (IV)

To complete the enzymatic reaction cycle, **β–MeSt** and **PrFMN** are formed through cycloelimination (**IV**). In **Int3→TS4→Prod** at $\varepsilon = 1$ (Fig. S4a†), the $C_{\beta}^{Cin}-C_{34}^{PrFMN}$ extension (a) and dissociation (b) ($R_{C_{\beta}^{Cin}-C_{34}^{PrFMN}} = 2.93$ Å) and $C_{\alpha}^{Cin}-C_{29}^{PrFMN}$ dissociation (c) ($R_{C_{\alpha}^{Cin}-C_{29}^{PrFMN}} = 2.69$ Å) occur consecutively in **Int3→TS4** ($\Delta E^{\ddagger} = 81$ kJ/mol, Fig. S4c†), whereas **β–MeSt** leaves the iminium ion **(TS4→Prod)** on a barrierless potential curve ($R_{C_{\alpha}^{Cin}-C_{29}^{PrFMN}} = 3.85$ and $R_{C_{\beta}^{Cin}-C_{34}^{PrFMN}} = 3.90$ Å); the model molecular cluster **Prod** consists of free **β–MeSt** and the regenerated **PrFMN**, **Glu277**, **Arg173H^{+}** and **Gln190,** as in **React**.

The scenarios are slightly different at $\varepsilon = 78$ (Fig. S4b†), in which the $C_{\beta}^{Cin}-C_{34}^{PrFMN}$ extension $(a)^{\varepsilon}$ takes place first in **Int3$^{\varepsilon}$→TS4$^{\varepsilon}$** ($R_{C_{\beta}^{Cin}-C_{34}^{PrFMN}} = 2.93$ Å) with a comparable energy barrier ($\Delta E^{\ddagger} = 77$ kJ/mol), followed by the $C_{\beta}^{Cin}-C_{34}^{PrFMN}$ $(b)^{\varepsilon}$ and $C_{\alpha}^{Cin}-C_{29}^{PrFMN}$ dissociations $(c)^{\varepsilon}$ ($R_{C_{\beta}^{Cin}-C_{34}^{PrFMN}} = 3.89$ Å and $R_{C_{\alpha}^{Cin}-C_{29}^{PrFMN}} = 3.87$ Å, respectively). Analysis of $\Delta E^{Rel,Solv}$ on the potential energy curve in Fig. S4c† suggests similar stabilization and destabilization effects of the aqueous solvent as in decarboxylation (**II**), in which the transition structure **TS4$^{\varepsilon}$** is stabilized and **Prod$^{\varepsilon}$** is slightly destabilized by the local dielectric environment; **TS4$^{\varepsilon}$→Prod$^{\varepsilon}$** results in **β–MeSt** and **PrFMN**.

Acid catalyst (2) (V)

Based on the potential energy curves that have been discussed up to this point, the highest energy barrier at $\varepsilon = 1$ is for cycloelimination (**IV**) ($\Delta E^{\ddagger} = 81$ kJ/mol), whereas that at $\varepsilon = 78$ is for acid catalyst (1) (**III**) ($\Delta E^{\ddagger} = 137$ kJ/mol)). To complete the discussion on the potential energy

curves of the elementary reactions, the route for generating **Prod** directly from **Int2b** (without the formation of pyrrolidine cycloadduct) is discussed (Fig. S5†). At ε = 1, the proton transfer from the COOH group of **Glu282** to C_{α}^{Cin} (a) instantly leads to C_{α}^{Cin}–C_{29}^{PrFMN} dissociation (b) ($R_{C_{\alpha}^{Cin}-C_{29}^{PrFMN}}$ = 2.95 and $R_{C_{\alpha}^{Cin}-C_{43}^{Cin}}$ = 4.18 Å) and the formation of **β–MeSt** (c) with a slightly lower energy barrier ($\Delta E^{\ddagger}$ = 73 kJ/mol) compared with **Int3→TS4→Prod** ($\Delta E^{\ddagger}$ = 81 kJ/mol), whereas at ε = 78, **Int2b$^{\varepsilon}$ →TS3b$^{\varepsilon}$ →Prod$^{\varepsilon}$** involves a considerably lower energy barrier ($\Delta E^{\ddagger}$ = 47 kJ/mol). Therefore, the direct route at ε = 78 should also be considered in further discussion.

3. Energy barrier calculations

The energy barriers are conducted using the ChemShell and TURBOMOLE software packages. The followings explain the methods to calculate the potential energy barrier ($\Delta E^{\ddagger}$), zero-point correction energy ($\Delta E^{\ddagger,ZPE}$) to $\Delta E^{\ddagger}$, which leads to zero point-corrected energy barrier ($\Delta E^{\ddagger,ZPC}$), using the rate determining elementary reaction **Int3→TS4** in ε = 1 as an example.

Example for the Calculations of the kinetic and thermodynamic properties (Extracted from ChemShell Output):

For the rate determining elementary reaction

Int3→TS4 in ε = 1

1) Model molecular cluster Int3

$E^{Total,Int3}$ = -2680.0803909669999 au

(Total energy of the equilibrium structure Int3)

Thermochemical analysis

Temperature: 300.00 Kelvin

total ZPE ($E^{ZPE,Int3}$) 1.0746681505 au

total E_vib ($E^{Vib,Int3}$) 0.0633498277 au

-T*S -0.1421675356 au

total vibrational energy correction to E_electronic 0.9958504426 au

total ZPE ($E^{ZPE,Int3}$) 2821540.81983 J/mol

total E vib ($E^{Vib,Int3}$) 166324.94857 J/mol

total S vib ($S^{Vib,Int3}$) 1244.20270 J/mol/K

Crossover temperature for tunnelling 1.50197 K

Writing file qts_reactant.txt

Writing Hessian file qts_hessian_rs.txt

Vibrational adiabatic energy of Int3($E^{ZPC,Int3}$ in au)

$$E^{ZPC,Int3} = E^{Total,Int3} + E^{ZPE,Int3}$$

$$= -2680.0803909669999 \text{ au} + 1.07466791273907 \text{ au}$$

$$= -2679.0057230542500 \text{ au}$$

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2) Model molecular cluster TS4

$E^{Total,TS4}$ = -2680.0495493439998 au

(Total energy of the transition structure TS4)

Thermochemical analysis

Temperature: 300.00 Kelvin

total ZPE ($E^{ZPE,TS4}$) 1.0702864713 au

total E vib ($E^{Vib,TS4}$) 0.0627030206 au

-T*S -0.1386259552 au

total vibrational energy correction to E_electronic 0.9943635367 au

total ZPE ($E^{ZPE,TS4}$) 2810036.72294 J/mol

total E vib ($E^{Vib,TS4}$) 164626.75663 J/mol

total S vib($S^{Vib,TS4}$) 1213.20798 J/mol/K

Crossover temperature for tunnelling 6.53993 K

Writing file qts_ts.txt

Writing Hessian file qts_hessian_ts.txt

Vibrational adiabatic energy of **TS4**($E^{ZPC,TS4}$ in au)

$$E^{ZPC,TS4} = E^{Total,TS4} + E^{ZPE,TS4}$$

$$= -2680.0495493439998 \text{ au} + 1.07028623457732 \text{ au}$$

$$= -2678.9792631094100 \text{ au}$$

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3) Int3→TS4

Calculation of the reaction rate based on harmonic TST

Number of zero modes in RS and TS: 6 6

	Reactant	TS
Number of atoms	126	126
Degrees of freedom	378	378

	Hartree	kJ/mol	eV	K
Potential energy Barrier ($\Delta E^{\ddagger}$)	0.03084162	80.97466944	0.83924324	9739.00265146
ZPE Correction ($\Delta E^{\ddagger,ZPE}$)	-0.00436449	-11.45897673	-0.11876392	-1378.19648438
Vibrational adiabatic barrier($\Delta E^{\ddagger,ZPC}$)	0.02647713	69.51569271	0.72047933	8360.80616708
Rotational contr. at start T	0.00000000	0.00000000	0.00000000	0.00000000

Crossover Temperature 6.53992787 K

log_10 of rates in second^-1

Change of log(rate) by the rotational partition function 0.00000000

1000/T	rate classical	quantised vib.	simpl. Wigner	full wigner
5.000000000000	-4.284663602045	-3.280337114370	-3.279573916635	-3.279572976758
3.606060606061	1.611135643271	2.117736273529	2.118133415856	2.118133670221
3.333333333333	2.764661582571	3.187119006740	3.187458371323	3.187458557044
2.696969696970	5.456222107607	5.705103782678	5.705325970245	5.705326049842

Example

Potential energy Barrier ($\Delta E^{\ddagger}$)

$$\Delta E^{\ddagger} = E^{Total,TS4} - E^{Total,Int3}$$

$$= -2680.0495493439998 \text{ au} - (-2680.0803909669999 \text{ au})$$

$$= 0.0308416230 \text{ au}$$

$$= 80.97466944 \text{ kJ/mol (Table 1)}$$

ZPE Correction ($\Delta E^{\ddagger,ZPE}$)

$$\Delta E^{\ddagger,ZPE} = E^{ZPE,TS4} - E^{ZPE,Int3}$$

$$= 2810036.72294 \text{ J/mol} - 2821540.81983 \text{ J/mol}$$

$$= -11.45897673 \text{ kJ/mol (Table 1)}$$

Vibrational adiabatic barrier ($\Delta E^{\ddagger,ZPC}$)

$$\Delta E^{\ddagger,ZPC} = \Delta E^{\ddagger} + \Delta E^{\ddagger,ZPE}$$

$$= 80.97466944 \text{ kJ/mol} + (-11.45897673 \text{ kJ/mol})$$

$$= 69.51569271 \text{ kJ/mol (Table 1)}$$

or

Vibrational adiabatic barrier ($\Delta E^{\ddagger,ZPC}$)

$$\Delta E^{\ddagger,ZPC} = E^{ZPC,TS4} - E^{ZPC,Int3}$$

$$= (-2678.9792631094100 \text{ au}) - (-2679.0057230542500 \text{ au})$$

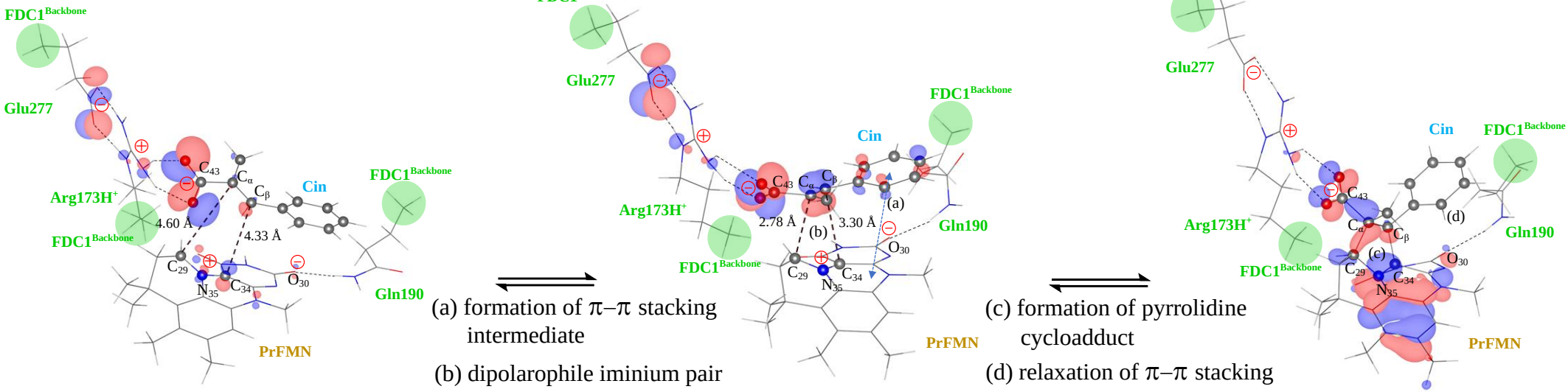
$$= 0.0264599448383 \text{ au}$$

$$= 69.51569271 \text{ kJ/mol (Table 1)}$$

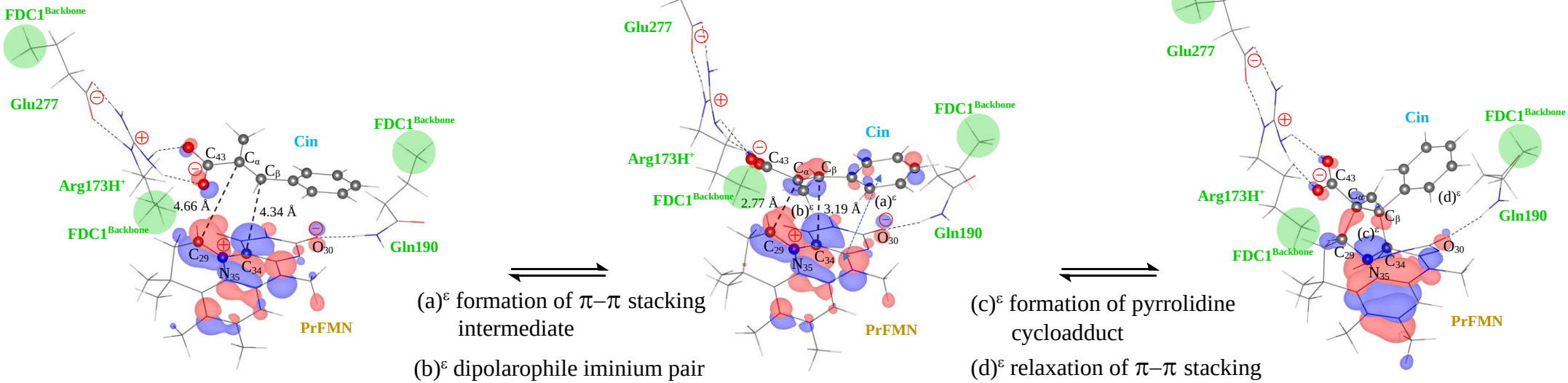
Figure S1 a)–b) Structures of the model molecular clusters involved in 1,3-dipolar cycloaddition **(I)** (Scheme I) obtained using the B3LYP/DZP and NEB methods in ε = 1 and 78, respectively. Distances are in Å and isosurface of HOMO is 0.042.

c) Potential energy curves obtained using the B3LYP/DZP and NEB methods in ε = 1 and 78. ΔE^{Rel} = relative total energy with respect to the precursor **React** in ε = 1; $\Delta E^{Rel,\varepsilon}$ = relative total energy with respect to the precursor **React**$^{\varepsilon}$ in ε = 78; $\Delta E^{Rel,Solv}$ = relative solvation energy with respect to the precursor **React**$^{\varepsilon}$; $\Delta E^{\ddagger}$ = energy barrier; (…) and (…)$^{\varepsilon}$ = scenarios in the elementary reactions in ε = 1 and 78, respectively.

a)


FDC1Backbone
Glu277
Arg173H+
FDC1Backbone
4.60 Å
4.33 Å
C43
Cα
Cβ
Cin
FDC1Backbone
C29
N35
C34
O30
Gln190
PrFMN
React
(a) formation of π–π stacking intermediate
(b) dipolarophile iminium pair formation
FDC1Backbone
Glu277
Arg173H+
FDC1Backbone
2.78 Å
(b)
3.30 Å
(a)
Cin
FDC1Backbone
Gln190
PrFMN
TS1
(c) formation of pyrrolidine cycloadduct
(d) relaxation of π–π stacking
FDC1Backbone
Glu277
Arg173H+
FDC1Backbone
(c)
(d)
Cin
FDC1Backbone
Gln190
PrFMN
Int1

b)



React$^{\varepsilon}$

(a)$^{\varepsilon}$ formation of π–π stacking intermediate

(b)$^{\varepsilon}$ dipolarophile iminium pair formation

TS1$^{\varepsilon}$

(c)$^{\varepsilon}$ formation of pyrrolidine cycloadduct

(d)$^{\varepsilon}$ relaxation of π–π stacking

Int1$^{\varepsilon}$

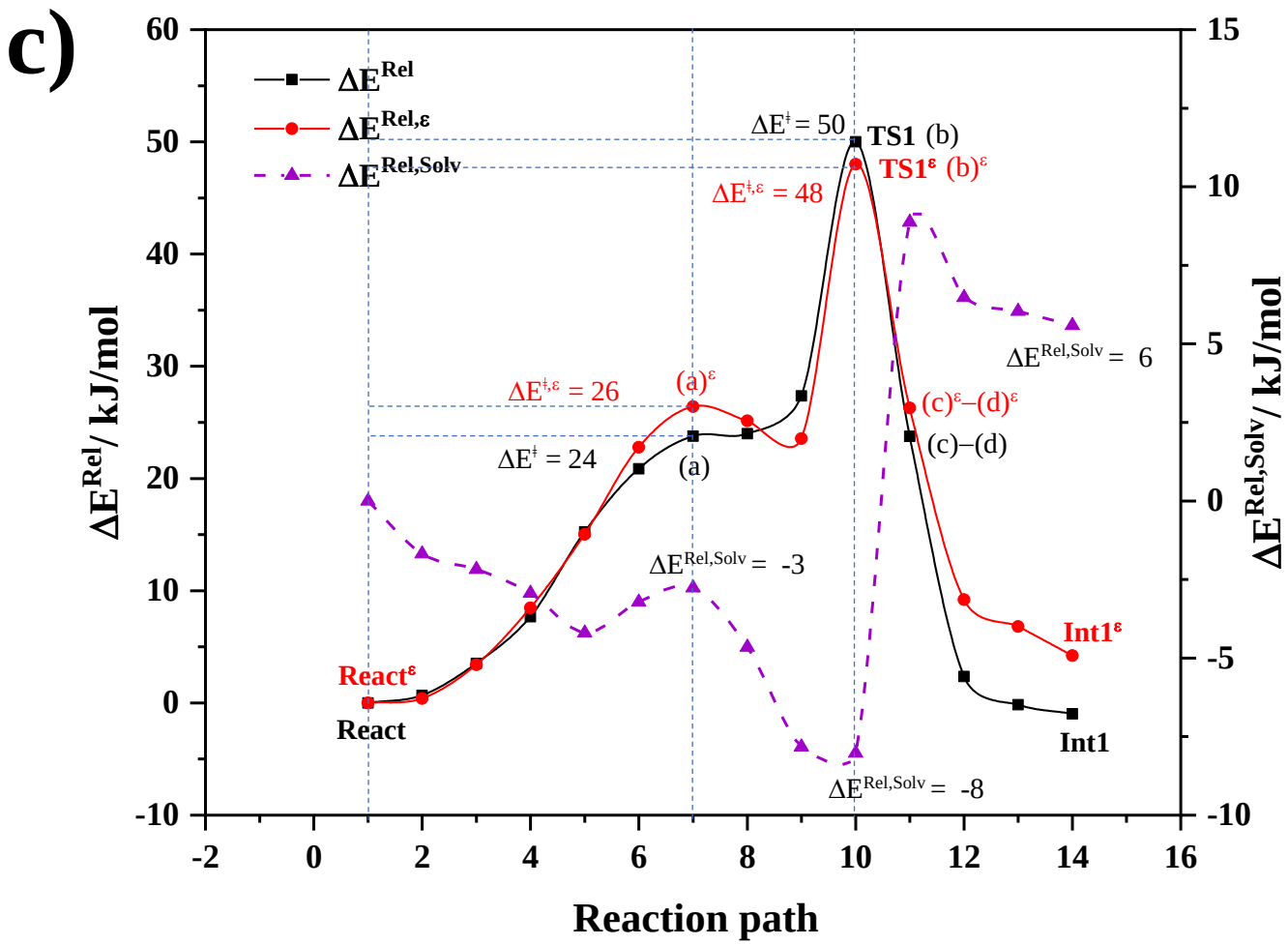
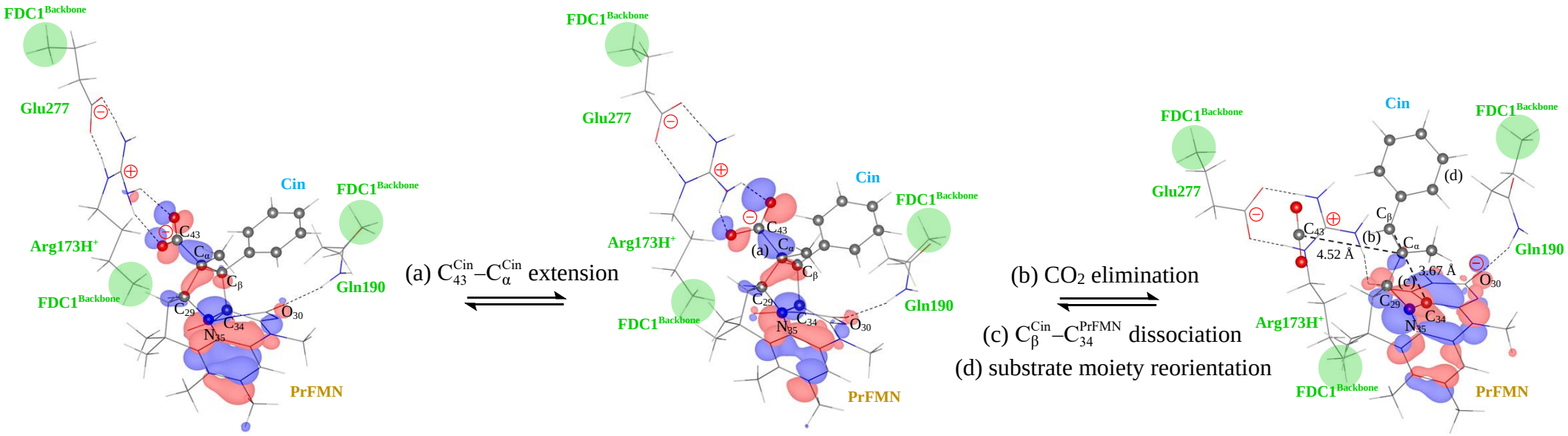

c)
ΔE^Rel
ΔE^Rel,ε
ΔE^Rel,Solv
ΔE‡ = 50
TS1 (b)
TS1ε (b)ε
ΔE‡,ε = 48
ΔE^Rel,Solv = 6
ΔE‡,ε = 26
(a)ε
(c)ε–(d)ε
(c)–(d)
ΔE‡ = 24
(a)
ΔE^Rel,Solv = -3
Int1ε
Reactε
React
Int1
ΔE^Rel,Solv = -8
ΔE^Rel/ kJ/mol
ΔE^Rel,Solv/ kJ/mol
Reaction path
60
50
40
30
20
10
0
-10
15
10
5
0
-5
-10
-2
0
2
4
6
8
10
12
14
16

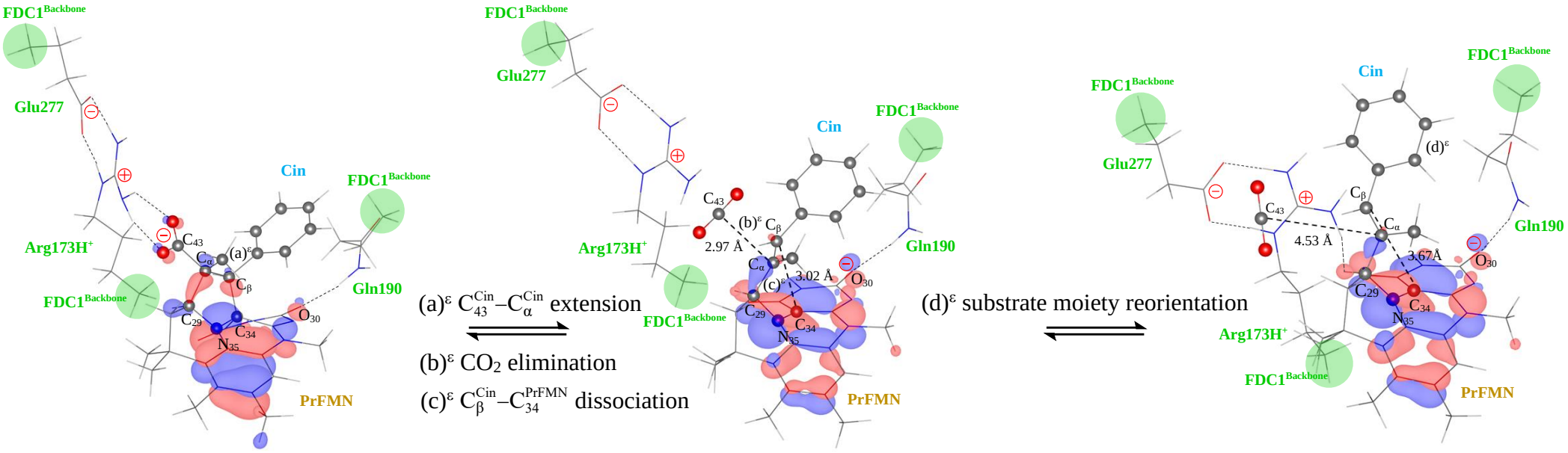
Figure S2 a)–b) Structures of the model molecular clusters involved in decarboxylation **(II)** (Scheme I) obtained using the B3LYP/DZP and NEB methods in ε = 1 and 78, respectively. Distances are in Å and isosurface of HOMO is 0.042.

c) Potential energy curves obtained using the B3LYP/DZP and NEB methods in ε = 1 and 78. ΔE^{Rel} = relative total energy with respect to the precursor **Int1** in ε = 1; $\Delta E^{Rel,\varepsilon}$ = relative total energy with respect to the precursor **Int1$^{\varepsilon}$** in ε = 78; $\Delta E^{Rel,Solv}$ = relative solvation energy with respect to the precursor **Int1$^{\varepsilon}$**; $\Delta E^{\ddagger}$ = energy barrier; (…) and (…)$^{\varepsilon}$ = scenarios in the elementary reactions in ε = 1 and 78, respectively.

a)


FDC1Backbone
Glu277
Arg173H+
FDC1Backbone
Cin
FDC1Backbone
Gln190
PrFMN
C43
Cα
Cβ
C29
N35
C34
O30
Int1
(a) C43Cin–CαCin extension
TS2
(b) CO2 elimination
(c) CβCin–C34PrFMN dissociation
(d) substrate moiety reorientation
4.52 Å
3.67 Å
Int2

b)


FDC1Backbone
Glu277
Cin
FDC1Backbone
Arg173H+
C43
Cα
(a)ε
Cβ
FDC1Backbone
Gln190
C29
C34
O30
N35
PrFMN
Int1ε
(a)ε C_{43}^{Cin}–C_{α}^{Cin} extension
(b)ε CO_2 elimination
(c)ε C_{β}^{Cin}–C_{34}^{PrFMN} dissociation
FDC1Backbone
Glu277
Cin
FDC1Backbone
C43
(b)ε Cβ
2.97 Å
Arg173H+
Cα
(c)ε
3.02 Å
O30
Gln190
FDC1Backbone
C29
C34
N35
PrFMN
TS2ε
(d)ε substrate moiety reorientation
FDC1Backbone
Cin
FDC1Backbone
Glu277
(d)ε
Cβ
C43
Cα
4.53 Å
Gln190
3.67Å
O30
C29
C34
N35
Arg173H+
FDC1Backbone
PrFMN
Int2ε

c)

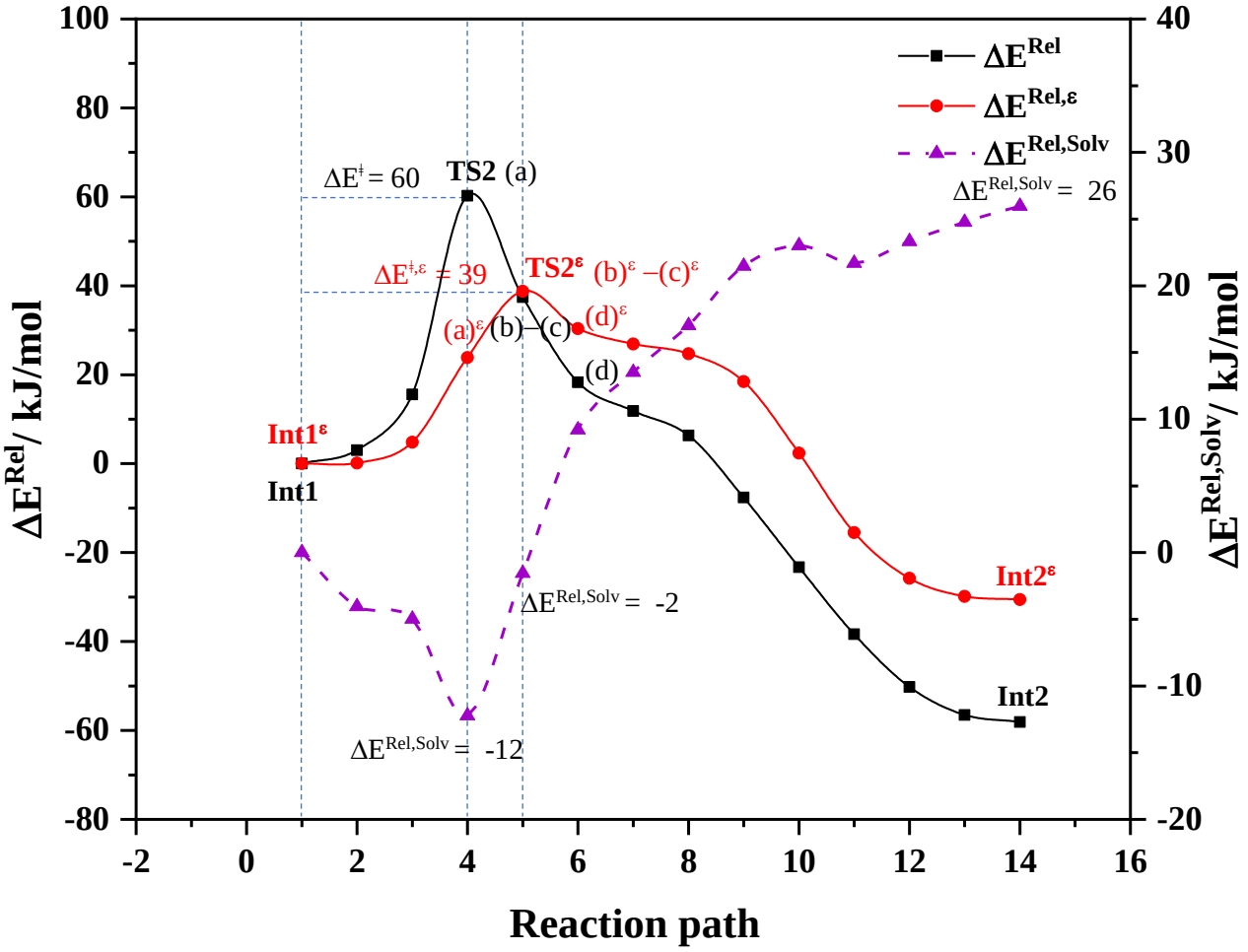
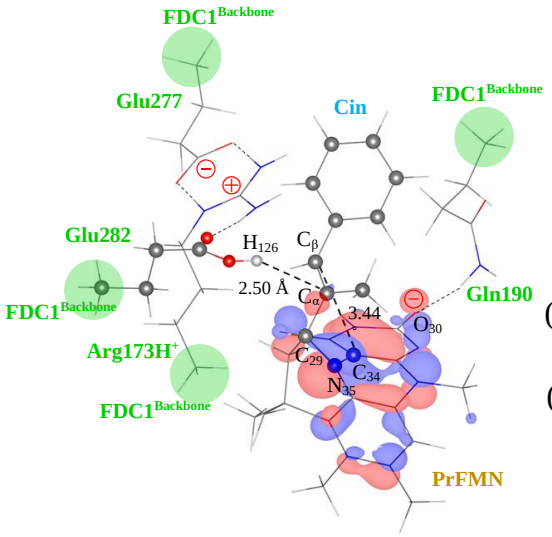

ΔE^Rel
ΔE^Rel,ε
ΔE^Rel,Solv
ΔE^‡ = 60
TS2 (a)
ΔE^Rel,Solv = 26
ΔE^‡,ε = 39
TS2^ε (b)^ε –(c)^ε
(d)^ε
(a)^ε (b)–(c)
(d)
Int1^ε
Int1
ΔE^Rel,Solv = -2
Int2^ε
Int2
ΔE^Rel,Solv = -12
ΔE^Rel/ kJ/mol
ΔE^Rel,Solv/ kJ/mol
Reaction path
100
80
60
40
20
0
-20
-40
-60
-80
40
30
20
10
0
-10
-20
-2
0
2
4
6
8
10
12
14
16

Figure S3 a)–b) Structures of the model molecular clusters involved in acid catalyst (1) (**III)** (Scheme I) obtained using the B3LYP/DZP and NEB methods in ε = 1 and 78, respectively. Distances are in Å and isosurface of HOMO is 0.042.

c) Potential energy curves obtained using the B3LYP/DZP and NEB methods in ε = 1 and 78. The calculations of the H-bond interaction energies ($\Delta E^{Rel,H\text{-}bond}$, $\Delta E^{Rel,H\text{-}bond/CP}$, $\Delta E^{Rel,H\text{-}bond,\varepsilon}$ and $\Delta E^{Rel,H\text{-}bond/CP,\varepsilon}$) are explained in the text. ΔE^{Rel} = relative total energy with respect to the precursor **Int2b** in ε = 1; $\Delta E^{Rel,\varepsilon}$ = relative total energy with respect to the precursor **Int2b$^{\varepsilon}$** in ε = 78; $\Delta E^{Rel,Solv}$ = relative solvation energy with respect to the precursor **Int2b$^{\varepsilon}$**; $\Delta E^{\ddagger}$ = energy barrier; (…) and (…)$^{\varepsilon}$ = scenarios in the elementary reactions in ε = 1 and 78, respectively.

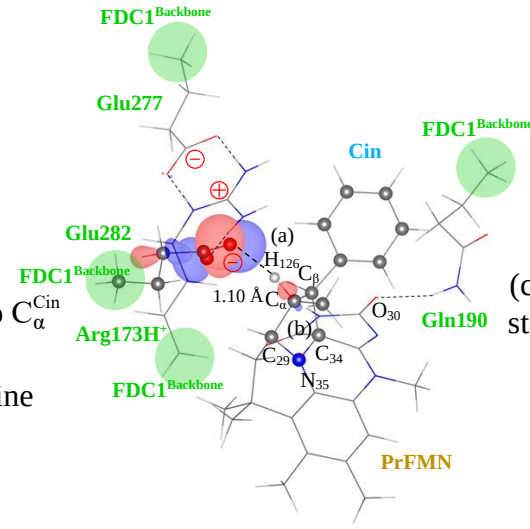
a)



Int2b

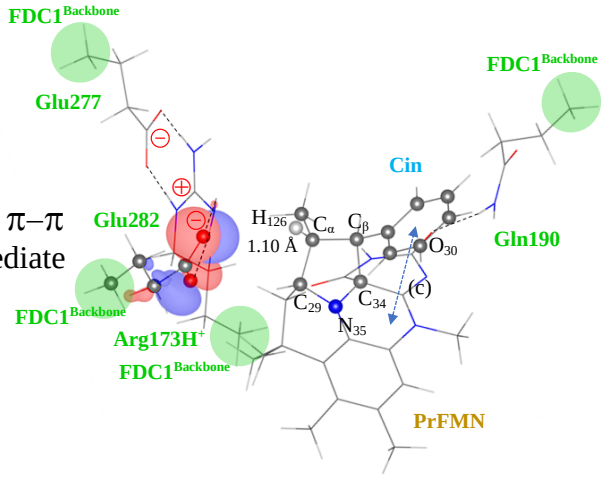
(a) Glu282 protonation to C_{α}^{Cin}

(b) formation of pyrrolidine cycloadduct TS



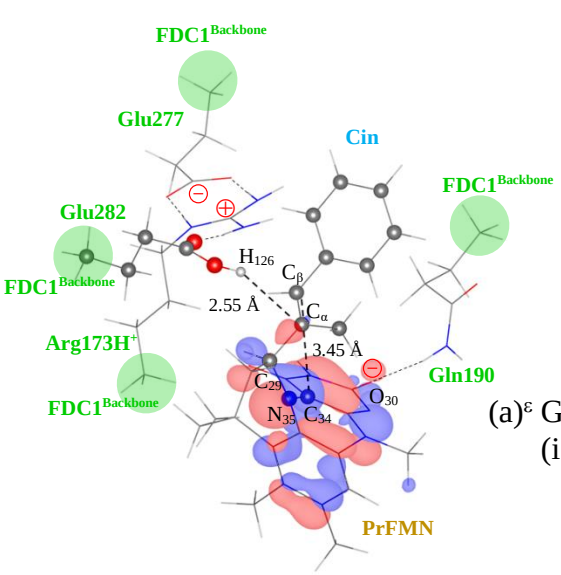
TS3

(c) formation of π–π stacking intermediate



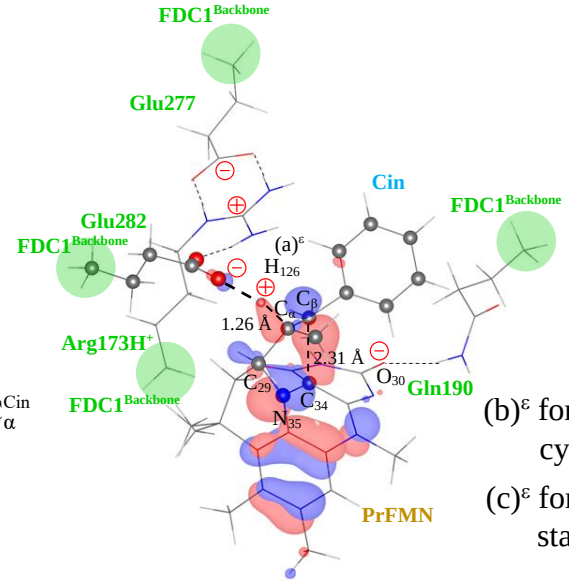
Int3

b)



Int2b$^{\varepsilon}$

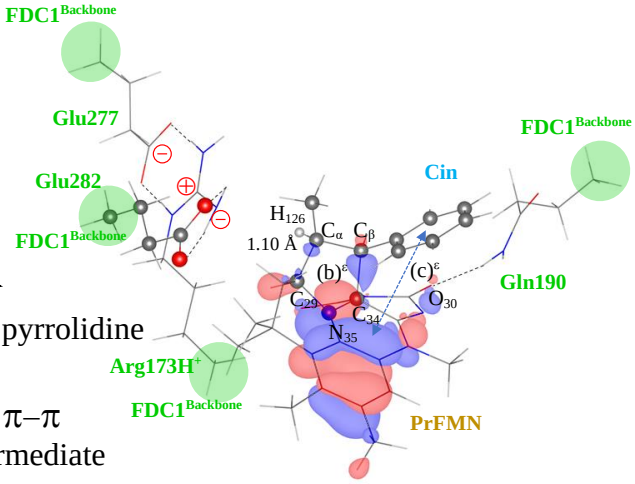
(a)$^{\varepsilon}$ Glu282 protonation to C_{α}^{Cin} (ion-pair interaction)



TS3$^{\varepsilon}$

(b)$^{\varepsilon}$ formation of pyrrolidine cycloadduct

(c)$^{\varepsilon}$ formation of π–π stacking intermediate



Int3$^{\varepsilon}$

c)

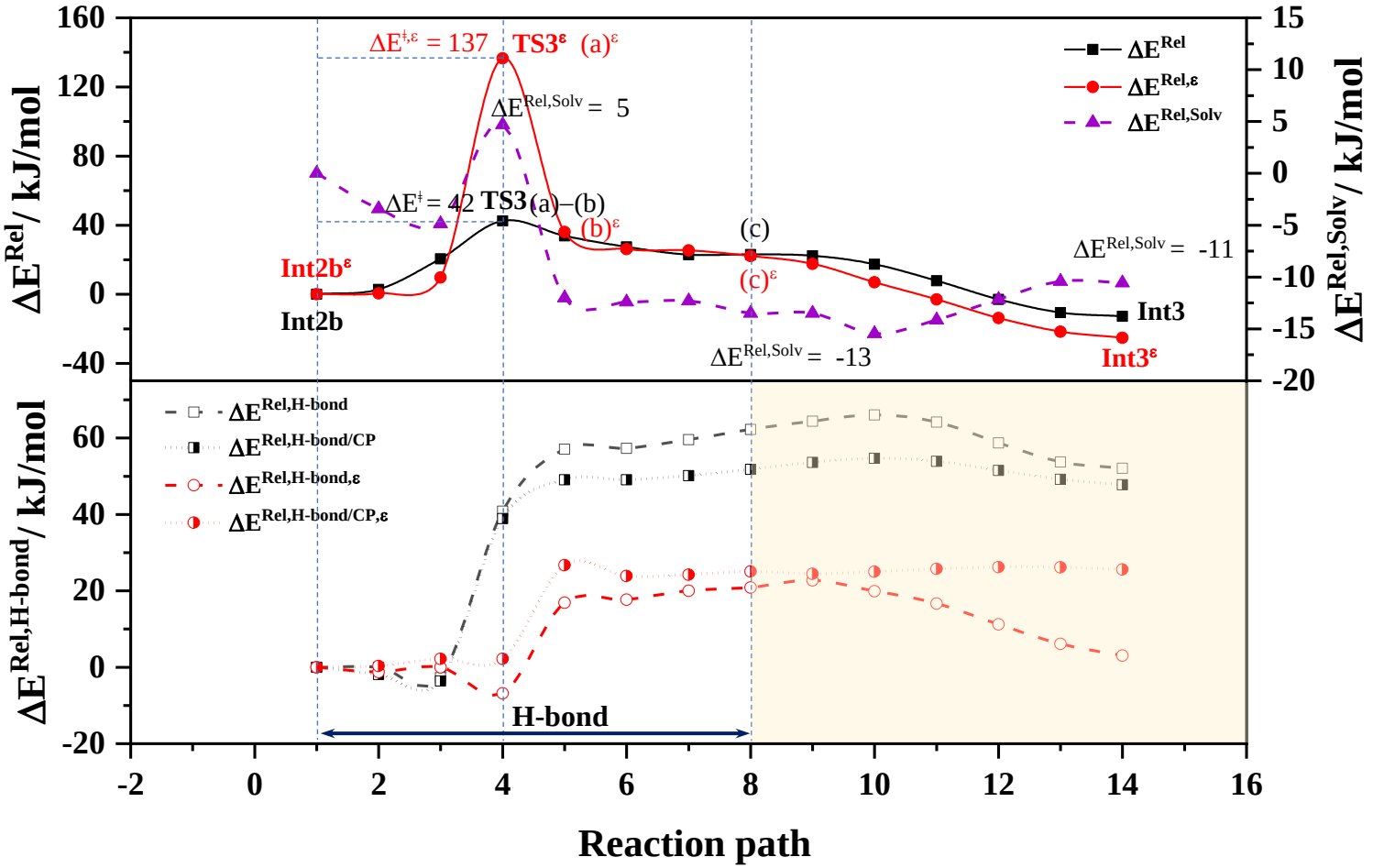
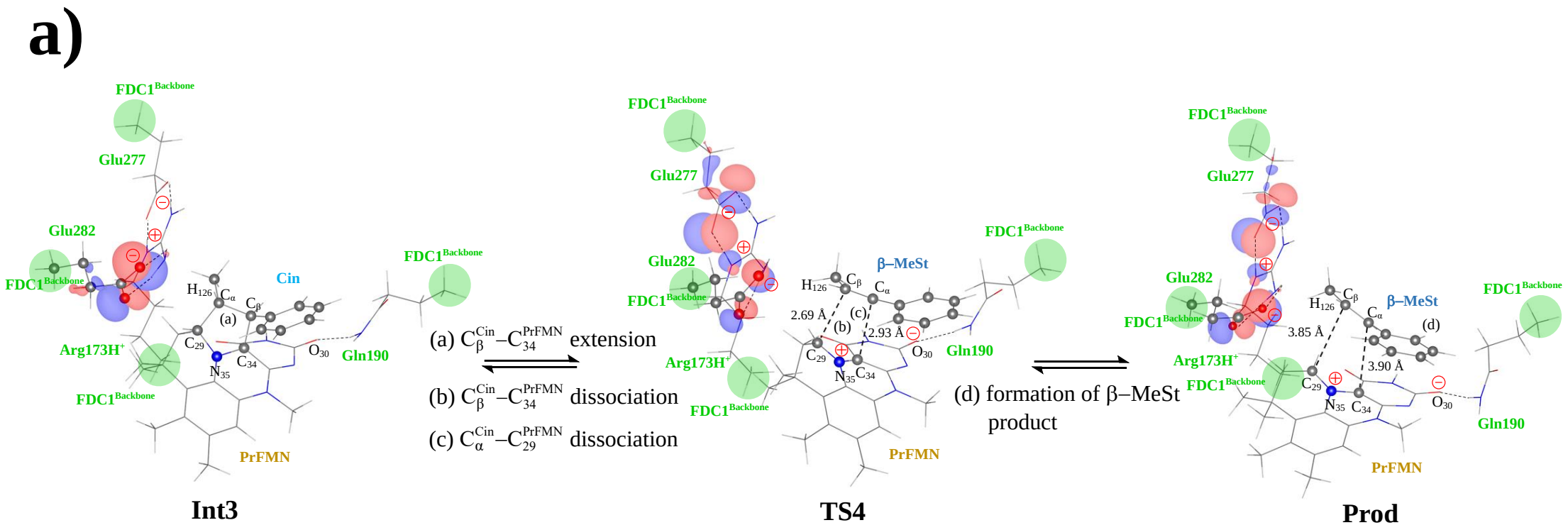
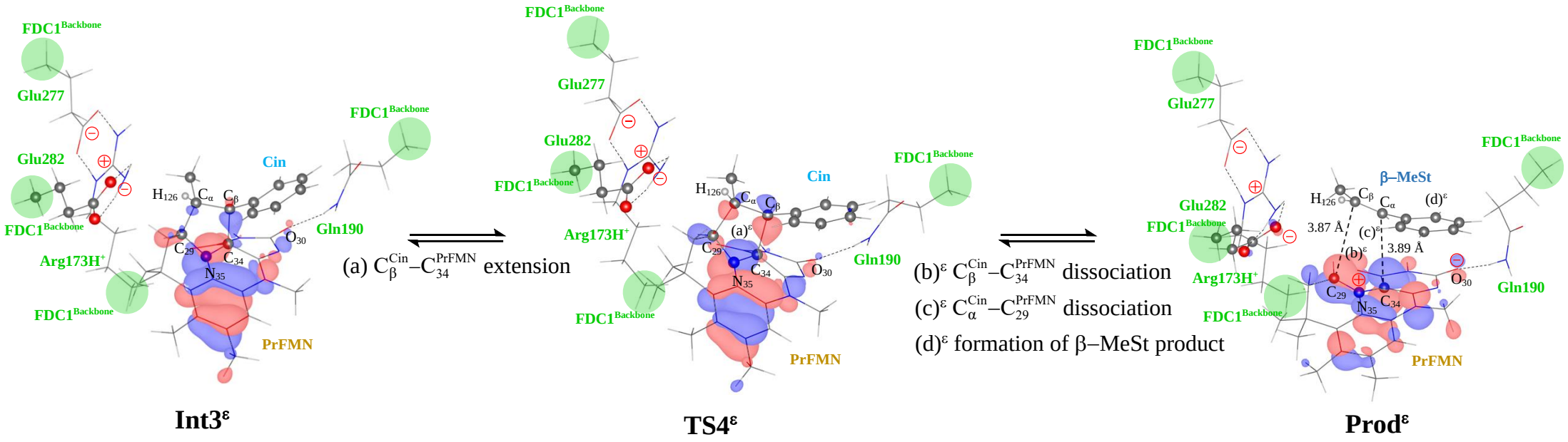

ΔE‡,ε = 137
TS3ε
(a)ε
ΔERel,Solv = 5
ΔE‡ = 42
TS3
(a)–(b)
(b)ε
(c)
(c)ε
Int2bε
Int2b
ΔERel,Solv = -11
Int3
Int3ε
ΔERel,Solv = -13
ΔERel
ΔERel,ε
ΔERel,Solv
ΔERel,H-bond
ΔERel,H-bond/CP
ΔERel,H-bond,ε
ΔERel,H-bond/CP,ε
H-bond
ΔERel / kJ/mol
ΔERel,Solv / kJ/mol
ΔERel,H-bond / kJ/mol
Reaction path

Figure S4 a)–b) Structures of the model molecular clusters involved in cycloelimination (**IV**) (Scheme I) obtained using the B3LYP/DZP and NEB methods in ε = 1 and 78, respectively. Distances are in Å and the isosurface of HOMO is 0.042.

c) Potential energy curves obtained using the B3LYP/DZP and NEB methods in ε = 1 and 78. ΔE^{Rel} = relative total energy with respect to the precursor **Int3** in ε = 1; $\Delta E^{Rel,\varepsilon}$ = relative total energy with respect to the precursor **Int3$^{\varepsilon}$** in ε = 78; $\Delta E^{Rel,Solv}$ = relative solvation energy with respect to the precursor **Int3$^{\varepsilon}$**; $\Delta E^{\ddagger}$ = energy barrier; (…) and (…)$^{\varepsilon}$ = scenarios in the elementary reactions in ε = 1 and 78, respectively.


a)
FDC1Backbone
Glu277
Glu282
FDC1Backbone
Cin
H126
Cα
Cβ
(a)
C29
N35
C34
O30
Gln190
FDC1Backbone
Arg173H+
FDC1Backbone
PrFMN
Int3
(a) Cβ^Cin–C34^PrFMN extension
(b) Cβ^Cin–C34^PrFMN dissociation
(c) Cα^Cin–C29^PrFMN dissociation
FDC1Backbone
Glu277
Glu282
FDC1Backbone
β–MeSt
H126
Cβ
Cα
2.69 Å
(b)
(c)
2.93 Å
C29
N35
C34
O30
Gln190
FDC1Backbone
Arg173H+
FDC1Backbone
PrFMN
TS4
(d) formation of β–MeSt product
FDC1Backbone
Glu277
Glu282
FDC1Backbone
β–MeSt
H126
Cβ
Cα
(d)
3.85 Å
3.90 Å
C29
N35
C34
O30
FDC1Backbone
Gln190
Arg173H+
FDC1Backbone
PrFMN
Prod

b)


FDC1Backbone
Glu277
Glu282
FDC1Backbone
Arg173H+
FDC1Backbone
Cin
FDC1Backbone
Gln190
H126
Cα
Cβ
C29
C34
N35
O30
PrFMN
Int3ε
(a) Cβ^Cin–C34^PrFMN extension
TS4ε
(a)ε
(b)ε Cβ^Cin–C34^PrFMN dissociation
(c)ε Cα^Cin–C29^PrFMN dissociation
(d)ε formation of β–MeSt product
β–MeSt
(b)ε
(c)ε
(d)ε
3.87 Å
3.89 Å
Prodε

c)

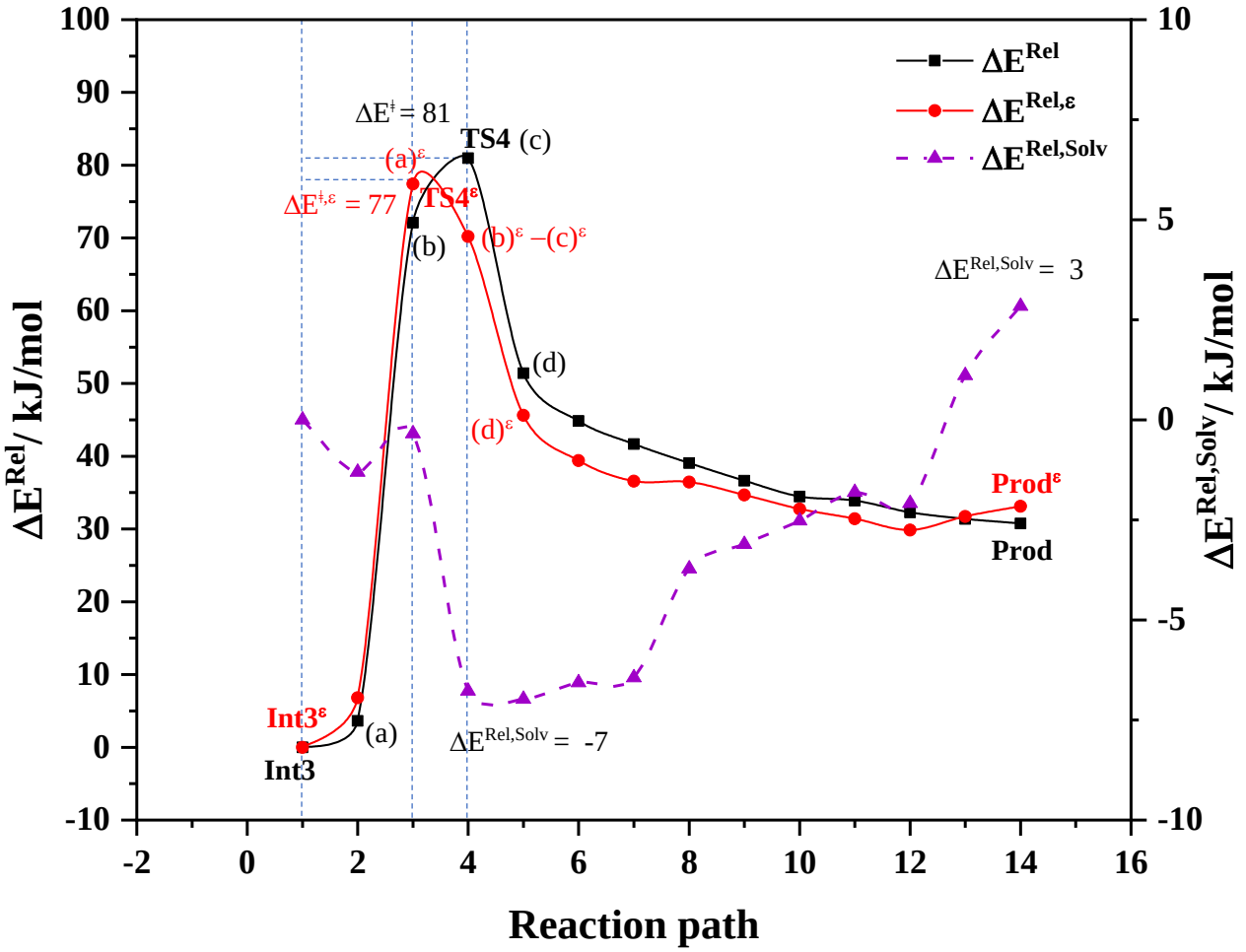
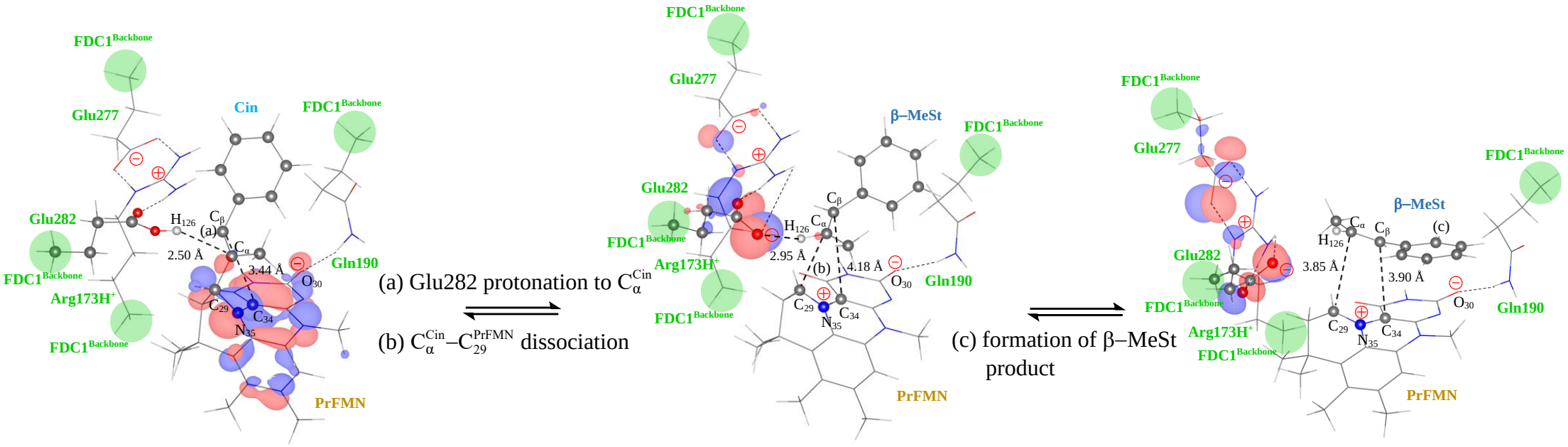

ΔE‡ = 81
TS4 (c)
(a)ε
ΔE‡,ε = 77
TS4ε
(b)ε –(c)ε
(b)
(d)
(d)ε
ΔERel,Solv = 3
Prodε
Prod
Int3ε
(a)
Int3
ΔERel,Solv = -7
ΔERel
ΔERel,ε
ΔERel,Solv
ΔERel/ kJ/mol
ΔERel,Solv/ kJ/mol
Reaction path
100
90
80
70
60
50
40
30
20
10
0
-10
10
5
0
-5
-10
-2
0
2
4
6
8
10
12
14
16

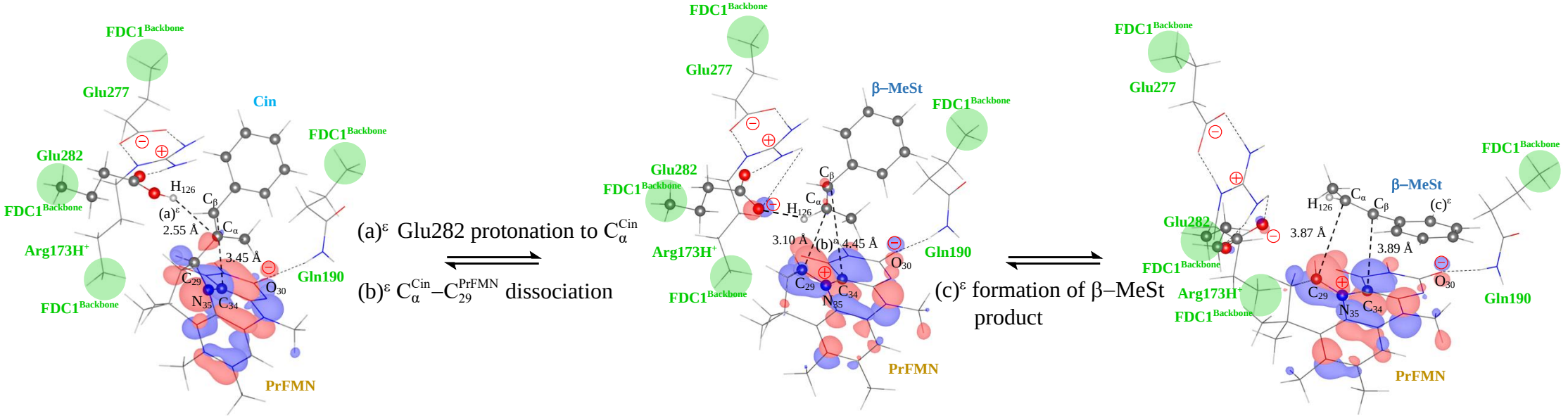
Figure S5 a)–b) Structures of the model molecular clusters involved in acid catalyst (2) (**V**) (Scheme I) obtained using the B3LYP/DZP and NEB methods in ε = 1 and 78, respectively. Distances are in Å and isosurface of HOMO is 0.042.

c) Potential energy curves obtained using the B3LYP/DZP and NEB methods in ε = 1 and 78. The calculations of the H-bond interaction energies ($\Delta E^{Rel,H\text{-}bond}$, $\Delta E^{Rel,H\text{-}bond/CP}$, $\Delta E^{Rel,H\text{-}bond,\varepsilon}$ and $\Delta E^{Rel,H\text{-}bond/CP,\varepsilon}$) are explained in the text. ΔE^{Rel} = relative total energy with respect to the precursor **Int2b** in ε = 1; $\Delta E^{Rel,\varepsilon}$ = relative total energy with respect to the precursor **Int2b$^{\varepsilon}$** in ε = 78; $\Delta E^{Rel,Solv}$ = relative solvation energy with respect to the precursor **Int2b$^{\varepsilon}$**; $\Delta E^{\ddagger}$ = energy barrier; (…) and (…)$^{\varepsilon}$ = scenarios in the elementary reactions in ε = 1 and 78, respectively.

a)


FDC1Backbone
Glu277
Cin
FDC1Backbone
Glu282
FDC1Backbone
Arg173H+
FDC1Backbone
PrFMN
Gln190
H126
Cβ
(a)
Cα
2.50 Å
3.44 Å
O30
C29
C34
N35
Int2b
(a) Glu282 protonation to Cα^Cin
(b) Cα^Cin–C29^PrFMN dissociation
FDC1Backbone
Glu277
β–MeSt
FDC1Backbone
Glu282
FDC1Backbone
Arg173H+
FDC1Backbone
PrFMN
Gln190
Cβ
H126
Cα
2.95 Å
(b)
4.18 Å
O30
C29
C34
N35
TS3b
(c) formation of β–MeSt product
FDC1Backbone
Glu277
FDC1Backbone
β–MeSt
Glu282
FDC1Backbone
Arg173H+
FDC1Backbone
PrFMN
Gln190
Cα
Cβ
(c)
H126
3.85 Å
3.90 Å
O30
C29
C34
N35
Prod

b)



Int2b$^{\varepsilon}$ **TS3b$^{\varepsilon}$** **Prod$^{\varepsilon}$**

c)

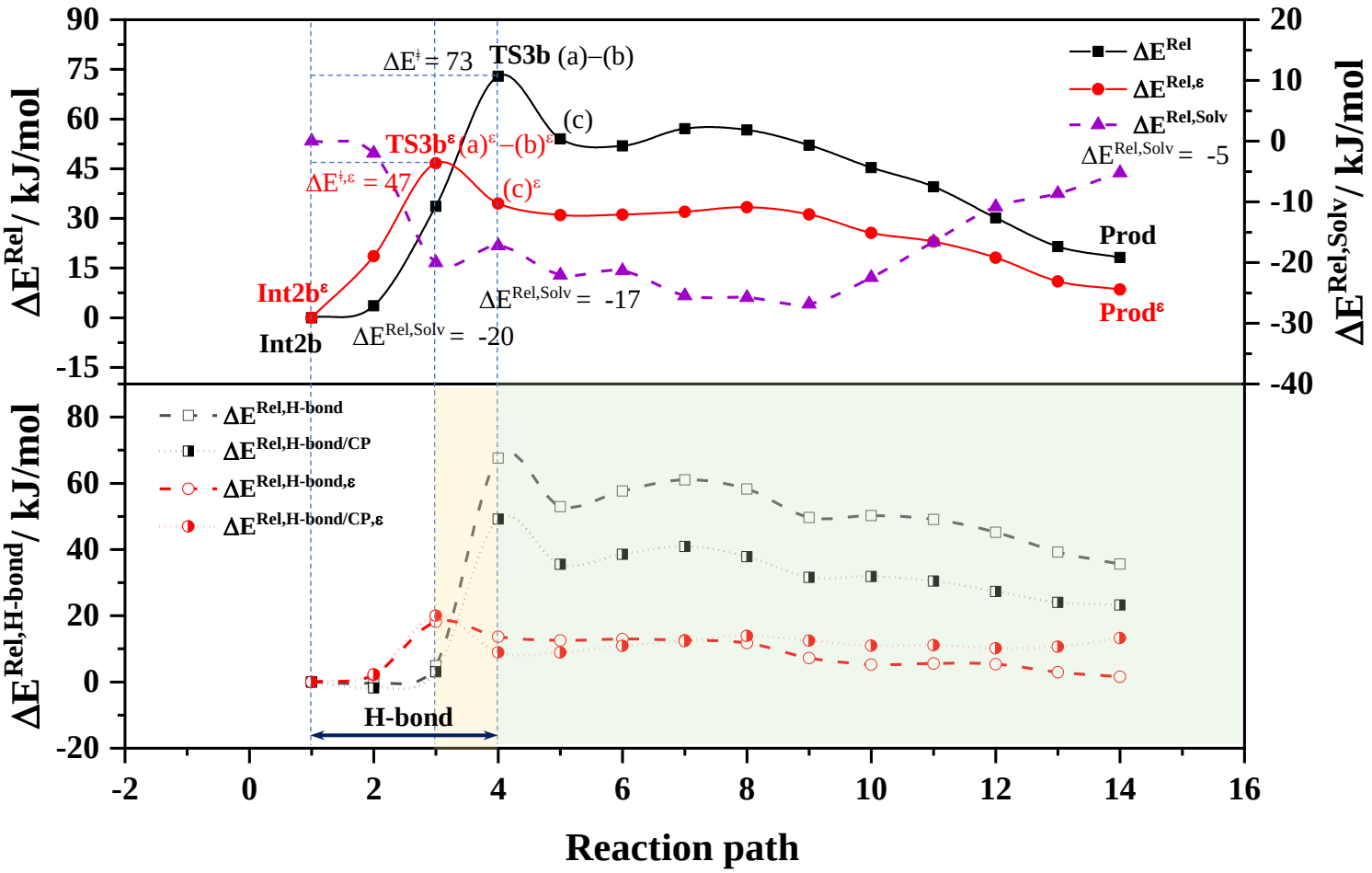
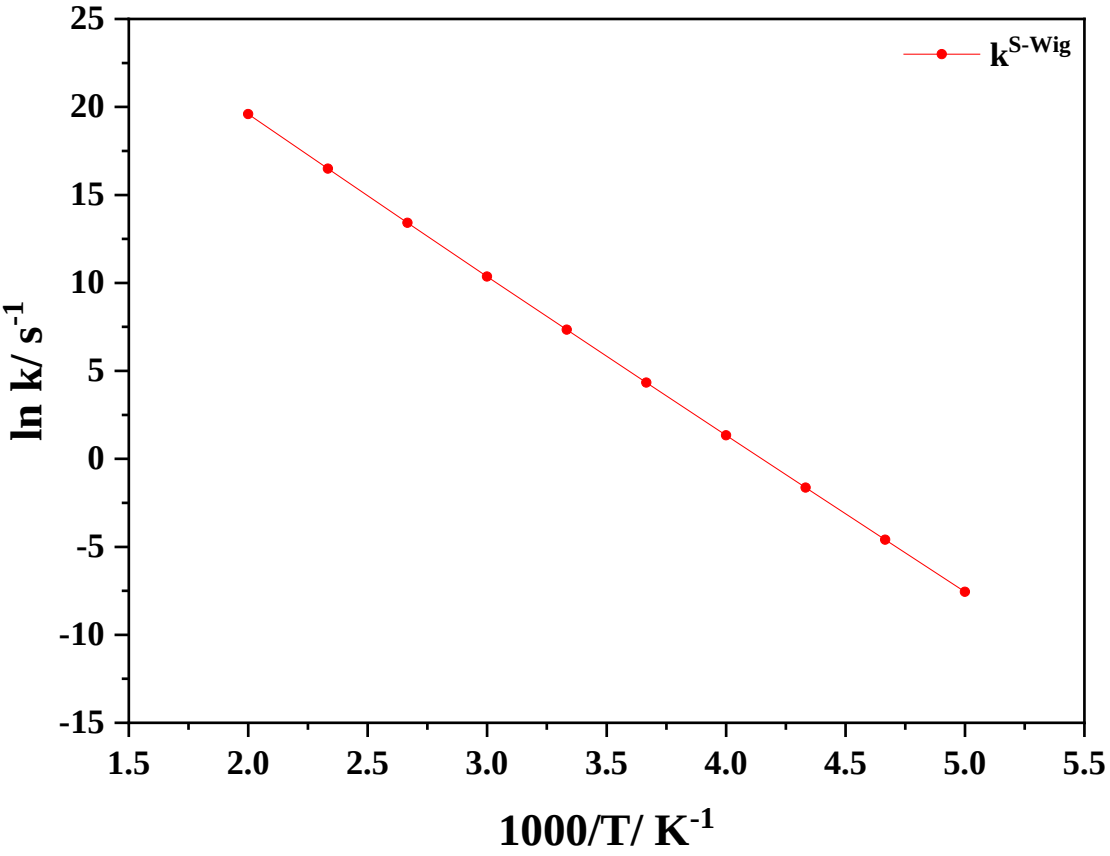

ΔE‡ = 73
TS3b (a)–(b)
(c)
TS3b^ε (a)^ε–(b)^ε
ΔE‡,ε = 47
(c)^ε
Int2b^ε
Int2b
ΔE^Rel,Solv = -20
ΔE^Rel,Solv = -17
ΔE^Rel,Solv = -5
Prod
Prod^ε
ΔE^Rel
ΔE^Rel,ε
ΔE^Rel,Solv
ΔE^Rel,H-bond
ΔE^Rel,H-bond/CP
ΔE^Rel,H-bond,ε
ΔE^Rel,H-bond/CP,ε
H-bond
ΔE^Rel/ kJ/mol
ΔE^Rel,Solv/ kJ/mol
ΔE^Rel,H-bond/ kJ/mol
Reaction path

Figure S6 Example of $\Delta H^{\ddagger}$ obtained from the slope of linear relationship between ln $k^{S\text{-}Wig}(T)$ and 1000/T.

Cycloelimination

(Int3→TS4)



Slope = -9.04133±0.02485

ΔH = –slope×R

= 9.04133×8.314

= 75.17 kJ/mol

Table S1 Equilibrium structures, total energies in ε = 1 and 78 (E^{Total} and $E^{Total,\varepsilon}$, respectively), and solvation energies (ΔE^{Solv}) of the substrate, cofactor and residues, obtained from B3LYP/DZP geometry optimizations. E^{Total} and $E^{Total,\varepsilon}$ are in au and ΔE^{Solv} in kJ/mol. Spheres are the CH_3 groups substituting backbone atoms of the **FDC1** enzyme.

Table S1

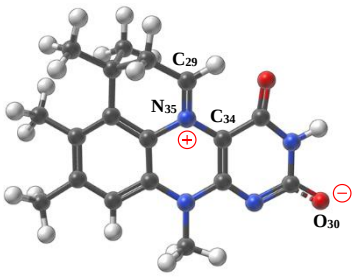
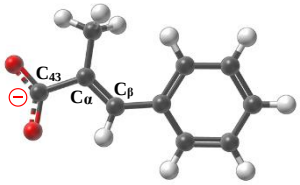
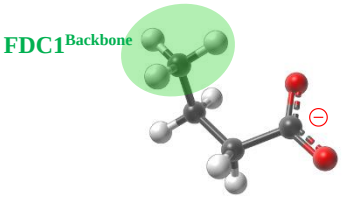
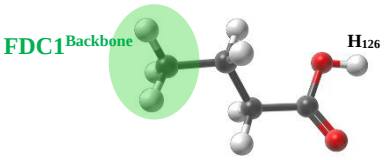
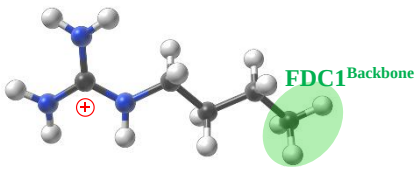
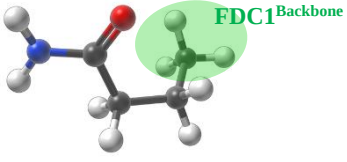
Monomer	E^{Total}	$E^{Total,\varepsilon}$	ΔE^{Solv}
 **PrFMN^{iminium} (Prenylated flavin mononucleotide)**	-1066.743684	-1066.774864	-81.9
 **Cin (α-methylcinnamate)**	-536.630165	-536.730934	-264.6
 **Glu277 (Glutamate role 277 in FDC1)**	-306.937339	-307.042215	-275.3
 **Glu282 (Glutamic acid role 282 in FDC1)**	-307. 514128	-307.524709	-27.8
 **Arg173H^{+} (Arginine role 173 in FDC1)**	-362.766189	-362.857665	-240.2
 **Gln190 (Glutamine role 190 in FDC1)**	-287.647484	-287.661320	-36.3

Table S1 (Cont.)

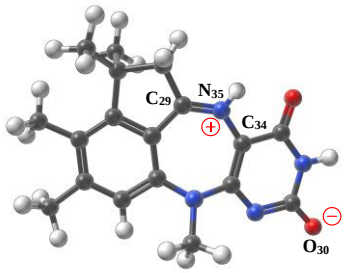
Monomer	E^{Total}	$E^{Total,\varepsilon}$	ΔE^{Solv}
 **$PrFMN^{ketimine}$ (Prenylated flavin mononucleotide)**	-1066.7564177	-1066.789252	-86.25

Table S2 Equilibrium structures, total energies in ε = 1 and 78 (E^{Total} and $E^{Total,\varepsilon}$, respectively), and solvation energies (ΔE^{Solv}) of the six model molecular clusters, obtained from B3LYP/DZP geometry optimizations. Spheres are the CH_3 groups substituting backbone atoms of the **FDC1** enzyme. E^{Total} and $E^{Total,\varepsilon}$ are in au and ΔE^{Solv} in kJ/mol. […] = values computed in ε = 78.

Table S2

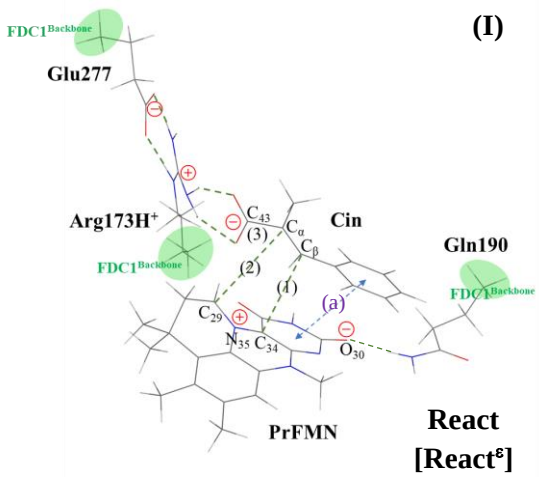
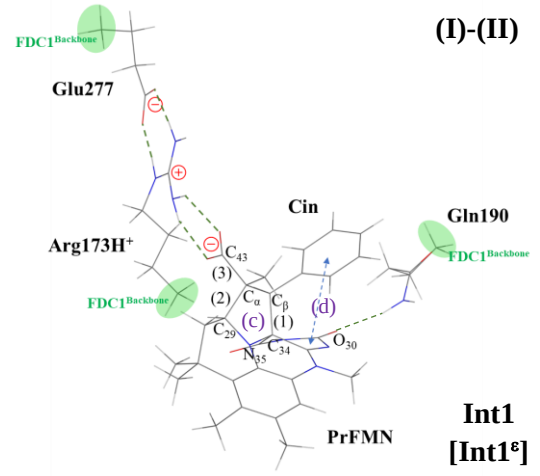
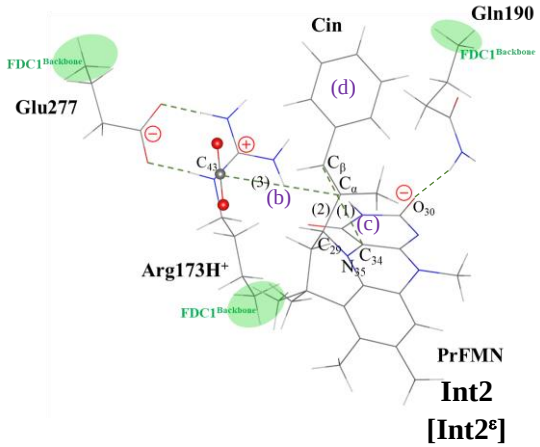
Model molecular cluster	E^{Total}	ΔE^{Solv}	R
	-2561.033273 [-2561.125954]	-243.3	(1) $R_{C_\beta^{Cin}-C_{34}^{PrFMN}}$ = 4.33 [4.34] (2) $R_{C_\alpha^{Cin}-C_{29}^{PrFMN}}$ = 4.60 [4.66] (3) $R_{C_\alpha^{Cin}-C_{43}^{Cin}}$ = 1.54 [1.53] (a) formation of π–π stacking intermediate
	-2561.033539 [-2561.123699]	-236.7	(1) $R_{C_\beta^{Cin}-C_{34}^{PrFMN}}$ = 1.64 [1.64] (2) $R_{C_\alpha^{Cin}-C_{29}^{PrFMN}}$ = 1.56 [1.56] (3) $R_{C_\alpha^{Cin}-C_{43}^{Cin}}$ = 1.58 [1.57] (c) formation of pyrrolidine cycloadduct (d) relaxation of π–π stacking
	-2561.055668 [-2561.135336]	-209.2	(1) $R_{C_\beta^{Cin}-C_{34}^{PrFMN}}$ = 3.67 [3.67] (2) $R_{C_\alpha^{Cin}-C_{29}^{PrFMN}}$ = 1.53 [1.53] (3) $R_{C_\alpha^{Cin}-C_{43}^{Cin}}$ = 4.52 [4.53] (b) CO_2 elimination (c) $C_\beta^{Cin}-C_{34}^{PrFMN}$ dissociation (d) substrate moiety reorientation

Table S2 (Cont.)

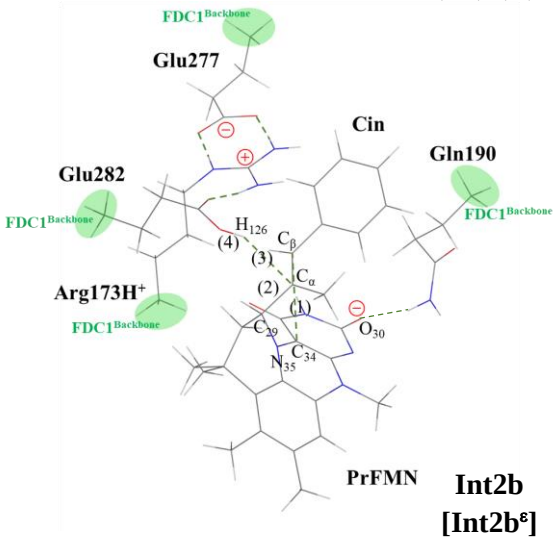
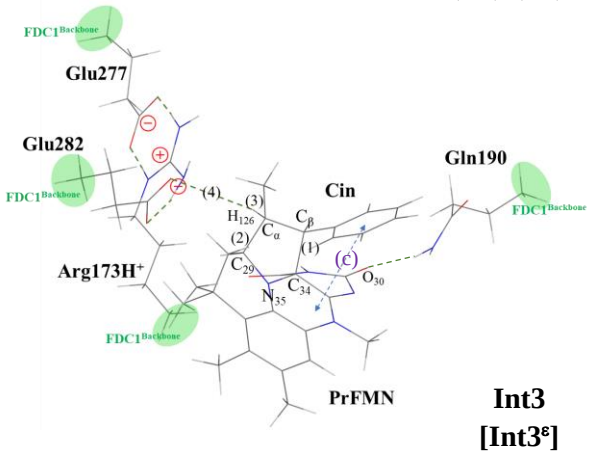
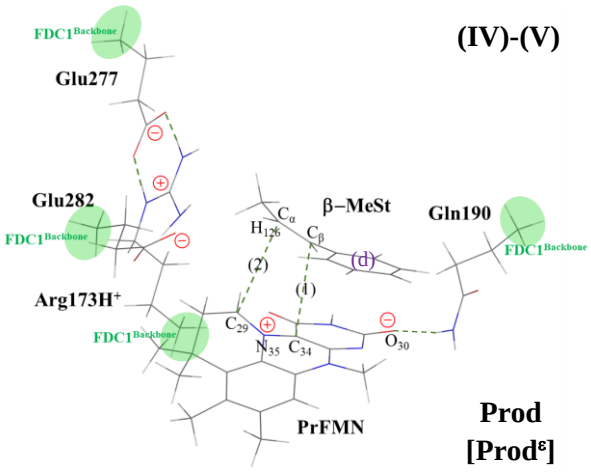
Model molecular cluster	E^{Total}	ΔE^{Solv}	R
(III)-(V)  **Int2b** **[Int2b$^\varepsilon$]**	-2680.075573 [-2680.159207]	-219.6	(1) $R_{C_\beta^{Cin}-C_{34}^{PrFMN}}$ = 3.44 [3.45] (2) $R_{C_\alpha^{Cin}-C_{29}^{PrFMN}}$ = 1.53 [1.53] (3) $R_{C_\alpha^{Cin}-H_{126}^{Glu282}}$ = 2.50 [2.55] (4) $R_{O_{125}^{Glu282}-H_{126}^{Glu282}}$ = 0.99 [0.99]
(III)-(IV)  **Int3** **[Int3$^\varepsilon$]**	-2680.080391 [-2680.168887]	-232.3	(1) $R_{C_\beta^{Cin}-C_{34}^{PrFMN}}$ = 1.60 [1.60] (2) $R_{C_\alpha^{Cin}-C_{29}^{PrFMN}}$ = 1.57 [1.57] (3) $R_{C_\alpha^{Cin}-H_{126}^{Glu282}}$ = 1.10 [1.10] (4) $R_{O_{125}^{Glu282}-H_{126}^{Glu282}}$ = 3.89 [4.00] (c) formation of π–π stacking intermediate
(IV)-(V)  **Prod** **[Prod$^\varepsilon$]**	-2680.068672 [-2680.156268]	-230.0	(1) $R_{C_\beta^{Cin}-C_{34}^{PrFMN}}$ = 3.90 [3.89] (2) $R_{C_\alpha^{Cin}-C_{29}^{PrFMN}}$ = 3.85 [3.87] (d) formation of β–MeSt product

Table S3 The residue-to-residue distances (Å) on the potential energy curves obtained based on the B3LYP/DZP and NEB methods and their average values. The distances are approximated using the distances between the carbon atoms of the CH_3 groups substituting the atoms of the **FDC1** backbone (Scheme I).

a)–b) for elementary reactions **(I)**–**(V)** in ε = 1 and 78, respectively. The averages are made per elementary reaction.

c)–d) the average residue-to-residue distances made per each model molecular cluster on the optimized reaction paths (**I**)→(**II**) and (**III**)→(**V**), in ε = 1 and 78, respectively.

SD = standard deviation computed based on Eqns. (1)–(2); Structure number = structure on the optimized reaction path; * = transition structure.

e) An example for the calculations of the average residue-to-residue distances ($R_{C_R^{Arg173H^+}-C_R^{Glu277}}$ in Tables S3a† and S3c†) and their SD, Eqns. (1) and (2), respectively.

Table S3a

Elementary reaction (ε = 1)	Structure number	Distance (Å)			
		$R_{C_R^{Arg173H^+}-C_R^{Glu277}}$	$R_{C_R^{Arg173H^+}-C_R^{Gln190}}$	$R_{C_R^{Glu277}-C_R^{Gln190}}$	$R_{C_R^{Arg173H^+}-C_R^{Glu282}}$
1,3-dipolar cycloaddition (I)	1	9.61	12.02	18.01	–
	2	9.73	11.85	17.83	–
	3	9.86	11.69	17.67	–
	4	9.90	11.43	17.40	–
	5	10.08	11.21	17.25	–
	6	10.28	11.00	17.13	–
	7	10.48	10.84	17.02	–
	8	10.65	10.74	16.89	–
	9	10.76	10.70	16.78	–
	10*	10.81	10.71	16.78	–
	11	10.80	10.72	16.78	–
	12	10.79	10.77	16.84	–
	13	10.91	10.69	16.55	–
	14	11.01	10.56	16.23	–
Average±SD		10.41±0.48	11.07±0.49	17.08±0.50	–
Decarboxylation (II)	1	11.01	10.56	16.23	–
	2	11.00	10.74	16.01	–
	3	11.01	10.90	15.82	–
	4*	11.04	10.95	15.70	–
	5	11.07	10.87	15.78	–
	6	11.08	10.97	15.62	–
	7	11.07	11.09	15.40	–
	8	11.07	11.23	15.18	–
	9	11.05	11.32	15.01	–
	10	11.01	11.45	14.81	–
	11	10.96	11.59	14.58	–
	12	10.89	11.74	14.34	–
	13	10.81	10.88	14.10	–
	14	10.72	12.00	13.87	–
Average±SD		10.99±0.11	11.16±0.41	15.18±0.74	–

Table S3a (Cont.)

Elementary reaction (ε = 1)	Structure number	Distance (Å)			
		$R_{C_R^{\zeta Arg173H^+}-C_R^{\zeta Glu277}}$	$R_{C_R^{\zeta Arg173H^+}-C_R^{\zeta Gln190}}$	$R_{C_R^{Glu277}-C_R^{Gln190}}$	$R_{C_R^{\zeta Arg173H^+}-C_R^{\zeta Glu282}}$
Acid catalyst (1) (III)	1	10.86	11.79	10.23	7.61
	2	10.84	12.11	11.07	7.94
	3	10.82	12.41	11.51	8.06
	4*	10.81	12.59	11.74	8.07
	5	10.79	12.78	12.08	8.43
	6	10.78	12.98	12.83	8.76
	7	10.78	13.13	13.41	8.99
	8	10.77	13.24	13.87	9.16
	9	10.76	13.33	14.26	9.31
	10	10.75	13.39	14.62	9.45
	11	10.74	13.45	14.98	9.61
	12	10.73	13.51	15.40	9.78
	13	10.73	13.60	15.93	9.97
	14	10.74	13.72	16.56	10.21
Average±SD		10.78±0.04	13.00±0.59	13.46±1.94	8.95±0.83
Cycloelimination (IV)	1	10.74	13.72	16.56	10.21
	2	10.74	13.65	16.53	10.32
	3	10.74	13.63	16.52	10.34
	4*	10.73	13.63	16.52	10.34
	5	10.73	13.62	16.51	10.37
	6	10.73	13.57	16.50	10.48
	7	10.72	13.52	16.48	10.57
	8	10.71	13.47	16.46	10.66
	9	10.69	13.42	16.43	10.73
	10	10.68	13.37	16.41	10.79
	11	10.66	13.33	16.39	10.82
	12	10.65	13.29	16.37	10.86
	13	10.63	13.24	16.35	10.90
	14	10.62	13.20	16.33	10.95
Average±SD		10.70±0.04	13.48±0.17	16.45±0.07	10.60±0.25

Table S3a (Cont.)

Elementary reaction (ε = 1)	Structure number	Distance (Å)			
		$R_{C_R^{Arg173H^+}-C_R^{Glu277}}$	$R_{C_R^{Arg173H^+}-C_R^{Gln190}}$	$R_{C_R^{Glu277}-C_R^{Gln190}}$	$R_{C_R^{Arg173H^+}-C_R^{Glu282}}$
Acid catalyst (2) (V)	1	10.86	11.79	10.23	7.61
	2	10.82	11.97	11.05	8.12
	3	10.81	12.15	11.68	8.53
	4*	10.80	12.25	11.85	8.66
	5	10.79	12.38	12.14	8.88
	6	10.78	12.54	12.84	9.29
	7	10.77	12.67	13.39	9.66
	8	10.74	12.76	13.79	9.88
	9	10.71	12.85	14.21	10.04
	10	10.69	12.92	14.58	10.18
	11	10.67	12.97	14.91	10.31
	12	10.65	13.02	15.27	10.84
	13	10.63	13.10	15.73	10.70
	14	10.62	13.20	16.33	10.95
Average±SD		10.74±0.08	12.61±0.44	13.43±1.86	9.55±0.57

Table S3b

Elementary reaction (ε = 78)	Structure number	Distance (Å)			
		$R_{C_R^{Arg173H^+}-C_R^{Glu277}}$	$R_{C_R^{Arg173H^+}-C_R^{Gln190}}$	$R_{C_R^{Glu277}-C_R^{Gln190}}$	$R_{C_R^{Arg173H^+}-C_R^{Glu282}}$
1,3-dipolar cycloaddition (I)	1	9.63	12.02	18.02	–
	2	9.76	11.84	17.85	–
	3	9.86	11.62	17.61	–
	4	9.99	11.43	17.44	–
	5	10.13	11.25	17.30	–
	6	10.29	11.08	17.19	–
	7	10.47	10.92	17.06	–
	8	10.62	10.80	16.93	–
	9	10.73	10.75	16.81	–
	10*	10.71	10.78	16.88	–
	11	10.72	10.78	16.85	–
	12	10.77	10.77	16.79	–
	13	10.92	10.66	16.49	–
	14	10.04	10.55	16.25	–
Average±SD		10.33±0.43	11.09±0.47	17.11±0.50	–
Decarboxylation (II)	1	10.04	10.55	16.23	–
	2	10.99	10.77	16.01	–
	3	10.98	10.91	15.86	–
	4	11.07	10.84	15.88	–
	5*	11.07	10.84	15.86	–
	6	11.09	10.83	15.78	–
	7	11.09	10.97	15.55	–
	8	11.11	11.13	15.31	–
	9	11.15	11.22	15.20	–
	10	11.14	11.36	15.01	–
	11	11.09	11.52	14.75	–
	12	10.98	10.71	14.26	–
	13	10.86	10.87	14.18	–
	14	10.74	12.01	13.89	–
Average±SD		10.96±0.29	11.04±0.38	15.27±0.75	–

Table S3b (Cont.)

Elementary reaction (ε = 78)	Structure number	Distance (Å)			
		$R_{C_R^{Arg173H^+}-C_R^{Glu277}}$	$R_{C_R^{Arg173H^+}-C_R^{Gln190}}$	$R_{C_R^{Glu277}-C_R^{Gln190}}$	$R_{C_R^{Arg173H^+}-C_R^{Glu282}}$
Acid catalyst (1) (III)	1	10.90	11.81	10.24	7.60
	2	10.86	12.12	11.00	7.94
	3	10.84	12.38	11.67	8.22
	4*	10.81	12.48	11.89	8.33
	5	10.80	12.67	12.39	8.59
	6	10.80	12.87	13.03	8.87
	7	10.78	13.01	13.55	9.08
	8	10.76	13.12	14.01	9.26
	9	10.75	13.22	14.41	9.41
	10	10.74	13.30	14.78	9.56
	11	10.74	13.39	15.17	9.72
	12	10.74	13.48	15.59	9.89
	13	10.75	13.59	16.06	10.06
	14	10.77	13.71	16.58	10.27
Average±SD		10.79±0.05	12.94±0.58	13.60±1.96	9.06±0.83
Cycloelimination (IV)	1	10.77	13.71	16.58	10.27
	2	10.79	13.63	16.56	10.37
	3*	10.79	13.61	16.54	10.32
	4	10.79	13.61	16.54	10.32
	5	10.79	13.59	16.54	10.36
	6	10.79	13.56	16.53	10.46
	7	10.77	13.51	16.51	10.58
	8	10.76	13.46	16.48	10.67
	9	10.75	13.41	16.46	10.76
	10	10.74	13.37	16.43	10.84
	11	10.72	13.32	16.40	10.90
	12	10.70	13.28	16.38	10.96
	13	10.67	13.25	16.37	10.95
	14	10.65	13.20	16.35	10.97
Average±SD		10.75±0.05	13.47±0.16	16.48±0.08	10.62±0.27

Table S3b (Cont.)

Elementary reaction (ε = 78)	Structure number	Distance (Å)			
		$R_{C_R^{Arg173H^+}-C_R^{Glu277}}$	$R_{C_R^{Arg173H^+}-C_R^{Gln190}}$	$R_{C_R^{Glu277}-C_R^{Gln190}}$	$R_{C_R^{Arg173H^+}-C_R^{Glu282}}$
Acid catalyst (2) (V)	1	10.90	11.81	10.24	7.60
	2	10.85	12.03	10.97	8.10
	3*	10.86	12.02	10.81	8.00
	4	10.83	12.18	11.53	8.48
	5	10.82	12.35	12.13	8.8
	6	10.80	12.51	12.79	9.30
	7	10.79	12.63	13.36	9.68
	8	10.76	12.73	13.80	9.92
	9	10.74	12.82	14.22	10.09
	10	10.73	12.89	14.61	10.25
	11	10.72	12.95	14.98	10.40
	12	10.70	13.01	15.34	10.58
	13	10.68	13.10	15.80	10.80
	14	10.65	13.20	16.34	10.97
Average±SD		10.77±0.07	12.59±0.45	13.35±1.98	9.50±1.12

Table S3c

Elementary reaction (ε = 1)	Structure number	Distance (Å)		
		$R_{C_R^{Arg173H^+}-C_R^{Glu277}}$	$R_{C_R^{Arg173H^+}-C_R^{Gln190}}$	$R_{C_R^{Arg173H^+}-C_R^{Glu282}}$
(I)→(II)	1	10.31±0.99	11.29±1.03	–
	2	10.37±0.90	11.30±0.78	–
	3	10.44±0.81	11.30±0.56	–
	4	10.47±0.81	11.19±0.34	–
	5	10.58±0.70	11.04±0.24	–
	6	10.68±0.57	10.99±0.02	–
	7	10.78±0.42	10.97±0.18	–
	8	10.86±0.30	10.99±0.35	–
	9	10.91±0.21	11.01±0.44	–
	10	10.91±0.14	11.08±0.52	–
	11	10.88±0.11	11.16±0.62	–
	12	10.84±0.07	11.26±0.69	–
	13	10.86±0.07	10.79±0.13	–
	14	10.87±0.21	11.28±1.02	–
(III)→(V)	1	10.82±0.07	12.43±1.11	8.48±1.50
	2	10.80±0.05	12.58±0.93	8.79±1.33
	3	10.79±0.04	12.73±0.79	8.98±1.20
	4	10.78±0.04	12.82±0.72	9.02±1.18
	5	10.77±0.03	12.93±0.63	9.23±1.02
	6	10.76±0.03	13.03±0.52	9.51±0.88
	7	10.76±0.03	13.11±0.43	9.74±0.79
	8	10.74±0.03	13.16±0.36	9.90±0.75
	9	10.72±0.04	13.20±0.31	10.03±0.71
	10	10.71±0.04	13.23±0.27	10.14±0.67
	11	10.69±0.04	13.25±0.25	10.25±0.61
	12	10.68±0.05	13.27±0.25	10.49±0.62
	13	10.66±0.06	13.31±0.26	10.52±0.49
	14	10.66±0.07	13.37±0.36	10.70±0.43

Table S3d

Elementary reaction (ε = 78)	Structure number	Distance (Å)		
		$R_{C_R^{Arg173H^+}-C_R^{Glu277}}$	$R_{C_R^{Arg173H^+}-C_R^{Gln190}}$	$R_{C_R^{Arg173H^+}-C_R^{Glu282}}$
(I)→(II)	1	9.84±0.29	11.29±1.04	–
	2	10.38±0.87	11.31±0.76	–
	3	10.42±0.79	11.27±0.50	–
	4	10.53±0.76	11.14±0.42	–
	5	10.60±0.66	11.05±0.29	–
	6	10.69±0.57	10.96±0.18	–
	7	10.78±0.44	10.95±0.04	–
	8	10.87±0.35	10.97±0.23	–
	9	10.94±0.30	10.99±0.33	–
	10	10.93±0.30	11.07±0.41	–
	11	10.91±0.26	11.15±0.52	–
	12	10.88±0.15	10.74±0.04	–
	13	10.89±0.04	10.77±0.15	–
	14	10.39±0.49	11.28±1.03	–
(III)→(V)	1	10.86±0.08	12.44±1.10	8.49±1.54
	2	10.83±0.04	12.59±0.90	8.80±1.36
	3	10.83±0.04	12.67±0.83	8.85±1.28
	4	10.81±0.02	12.76±0.75	9.04±1.11
	5	10.80±0.02	12.87±0.64	9.25±0.97
	6	10.80±0.01	12.98±0.53	9.54±0.82
	7	10.78±0.01	13.05±0.44	9.78±0.75
	8	10.76±0.00	13.10±0.37	9.95±0.71
	9	10.75±0.01	13.15±0.30	10.09±0.68
	10	10.74±0.01	13.19±0.26	10.22±0.64
	11	10.73±0.01	13.22±0.24	10.34±0.59
	12	10.71±0.02	13.26±0.24	10.48±0.54
	13	10.70±0.04	13.31±0.25	10.60±0.48
	14	10.69±0.07	13.37±0.29	10.74±0.40

e) An example for the calculations of the average residue-to-residue distances ($R_{C_R^{Arg173H^+}-C_R^{Glu277}}$ in Tables S3a† and S3c†) and their SD, Eqns. (1) and (2), respectively.

$$\overline{R}_{C_R^{Arg173H^+}-C_R^{Glu277}} = \frac{\sum_{i=1}^{n} (R_{C_R^{Arg173H^+}-C_R^{Glu277}})_i}{n} \quad (1)$$

$$SD = \sqrt{\frac{\sum_{i=1}^{n} [(R_{C_R^{Arg173H^+}-C_R^{Glu277}})_i - (\overline{R}_{C_R^{Arg173H^+}-C_R^{Glu277}})]^2}{n-1}} \quad (2)$$

For the average residue-to-residue distances made per elementary reaction, n = 14, whereas those made per each model molecular clusters on the NEB potential energy curves, n = 2 for **(I)→(II)** and n = 3 for **(III)→(V)**.

Table S4 Transition structures, total energies in ε = 1 and 78 (E^{Total} and $E^{Total,\varepsilon}$, respectively) and solvation energies (ΔE^{Solv}) on the potential energy curves, obtained from the B3LYP/DZP and NEB methods. Spheres are the CH_3 groups substituting backbone atoms of the **FDC1** enzyme. E^{Total} and $E^{Total,\varepsilon}$ are in au and ΔE^{Solv} in kJ/mol. […] = values obtained in ε = 78.

Table S4

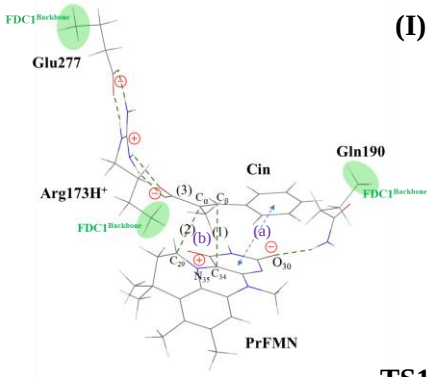
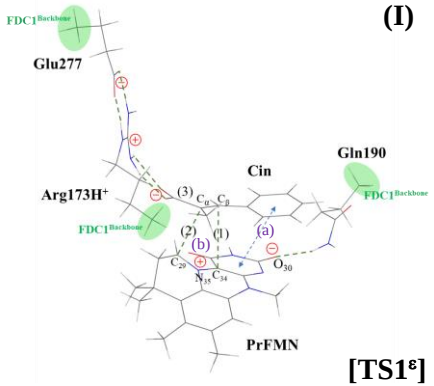
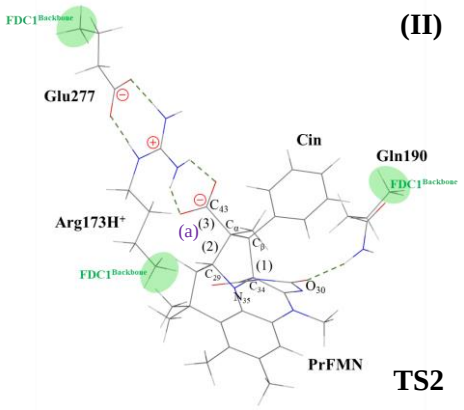
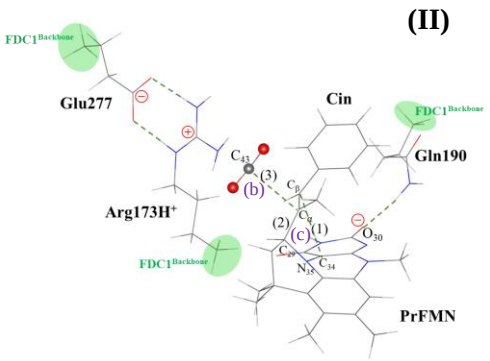
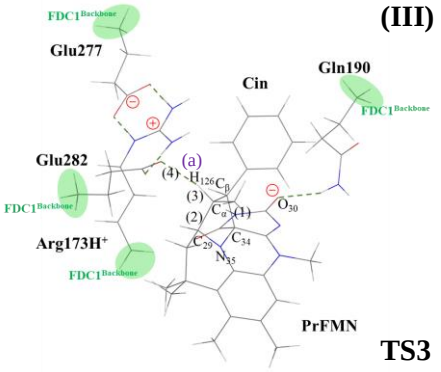
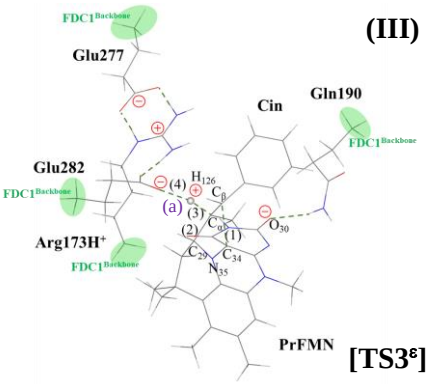
Model molecular cluster ε = 1	E^{Total}	Model molecular cluster ε = 78	E^{Total}	ΔE^{Solv}	R
 **TS1**	-2561. 014226	 **[TS1$^{\varepsilon}$]**	[-2561.107670]	-257.3	(1) $R_{C_\beta^{Cin}-C_{34}^{PrFMN}}$ = 3.30 [3.19] (2) $R_{C_\alpha^{Cin}-C_{29}^{PrFMN}}$ = 2.78 [2.77] (3) $R_{C_\alpha^{Cin}-C_{43}^{Cin}}$ = 1.54 [1.53] (a) formation of π–π stacking intermediate (b) dipolarophile iminium pair formation
 **TS2**	-2561.010601	 **[TS2$^{\varepsilon}$]**	[-2561.108935]	-242.1	(1) $R_{C_\beta^{Cin}-C_{34}^{PrFMN}}$ = 1.74 [3.02] (2) $R_{C_\alpha^{Cin}-C_{29}^{PrFMN}}$ = 1.54 [1.53] (3) $R_{C_\alpha^{Cin}-C_{43}^{Cin}}$ = 1.62 [2.97] (a) C_{43}^{Cin}–C_α^{Cin} extension (b) CO_2 elimination (c) C_β^{Cin}–C_{34}^{PrFMN} dissociation
 **TS3**	-2680.059418	 **[TS3$^{\varepsilon}$]**	[-2680.107193]	-222.2	(1) $R_{C_\beta^{Cin}-C_{34}^{PrFMN}}$ = 1.64 [2.31] (2) $R_{C_\alpha^{Cin}-C_{29}^{PrFMN}}$ = 1.53 [1.55] (3) $R_{C_\alpha^{Cin}-H_{126}^{Glu282}}$ = 1.10 [1.26] (4) $R_{O_{125}^{Glu282}-H_{126}^{Glu282}}$ = 1.99 [1.66] (a) Glu282 protonation to C_α^{Cin}

Table S4 (Cont.)

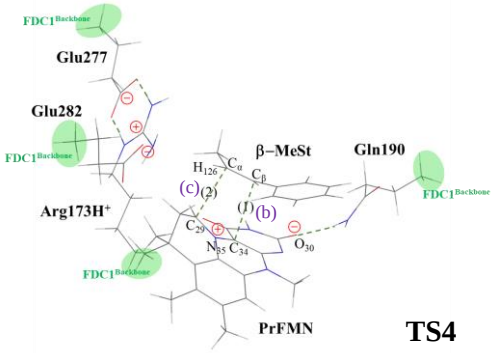
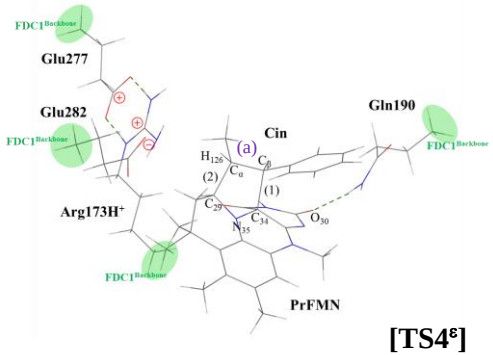
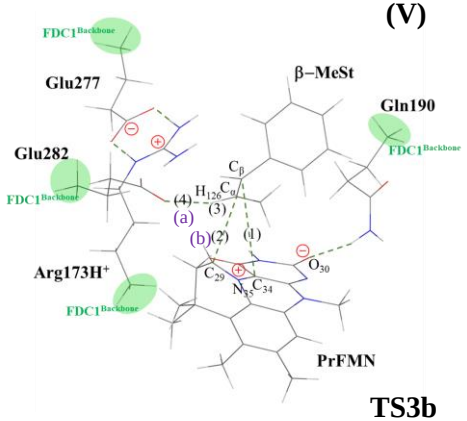
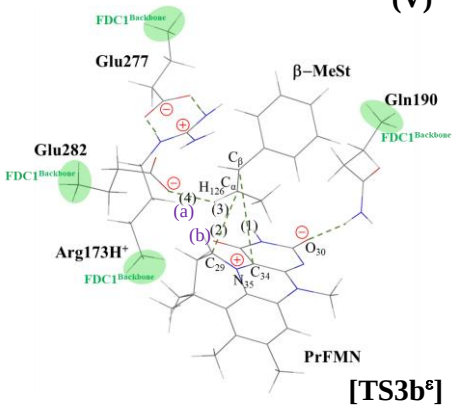
Model cluster ε = 1	E^{Total}	Model cluster ε = 78	E^{Total}	ΔE^{Solv}	R
(IV)  TS4	-2680.049549	(IV)  [TS4$^{\varepsilon}$]	[-2680.139404]	-235.9	(1) $R_{C_\beta^{Cin}-C_{34}^{PrFMN}}$ = 2.93 [1.81] (2) $R_{C_\alpha^{Cin}-C_{29}^{PrFMN}}$ = 2.69 [1.68] (a) C_β^{Cin}–C_{34}^{PrFMN} extension (b) C_β^{Cin}–C_{34}^{PrFMN} dissociation (c) C_α^{Cin}–C_{29}^{PrFMN} dissociation
(V)  TS3b	-2680.047799	(V)  [TS3b$^{\varepsilon}$]	[-2680.141673]	-250.0	(1) $R_{C_\beta^{Cin}-C_{34}^{PrFMN}}$ = 4.18 [4.45] (2) $R_{C_\alpha^{Cin}-C_{29}^{PrFMN}}$ = 2.95 [3.10] (3) $R_{C_\alpha^{Cin}-H_{126}^{Glu282}}$ = 1.12 [1.11] (4) $R_{O_{125}^{Glu282}-H_{126}^{Glu282}}$ = 1.88 [2.05] (a) Glu282 protonation to C_α^{Cin} (b) C_α^{Cin}–C_{29}^{PrFMN} dissociation

Table S5 Thermodynamics and kinetics of the elementary reactions of the enzymatic decarboxylation of α,β-unsaturated acid in ε =1. Rate constants, temperatures and energies are in s^{-1}, K and kJ/mol, respectively; $\Delta E^{\ddagger}$ = energy barrier on the optimized reaction path; $\Delta E^{\ddagger,ZPE}$ = difference between $E^{\ddagger,ZPE}$ of the transition structure and precursor; $\Delta E^{\ddagger,ZPC}$ = zero point energy-corrected energy barrier; $\Delta H^{\ddagger}$ = activation enthalpy; T_c = crossover temperature; T = temperature; $k_{f/r}^{Class}$ = rate constant obtained from classical TST; $k_{f/r}^{Q\text{-}vib}$ = rate constant obtained with quantized vibrations including the zero-point vibrational energy; $k_{f/r}^{S\text{-}Wig}$ = rate constant obtained with quantized vibrations and tunneling correction through the simple Wigner correction; $k_{f/r}^{F\text{-}Wig}$ = full Wigner-corrected rate constant at T above T_c; $k_{f/r}^{Arr}$ = Arrhenius rate constant; f/r = forward or reverse direction; $\Delta G^{\ddagger}$ = activation or relative Gibbs free energy; $\Delta S^{\ddagger}$ = activation entropy; f/r = forward or reverse direction.

Table S5

Elementary reaction (ε = 1)	$\Delta E^{\ddagger}$	$\Delta E^{\ddagger,ZPE}$	$\Delta E^{\ddagger,ZPC}$	$\Delta H^{\ddagger}$	T_c	T	$k_{f/r}^{Class}$	$k_{f/r}^{Q\text{-}vib}$	$k_{f/r}^{S\text{-}Wig}$	$k_{f/r}^{F\text{-}Wig}$	$k_{f/r}^{Arr}$	$\Delta G^{\ddagger}$	$\Delta S^{\ddagger}$
1,3-dipolar cycloaddition (React → TS1)	50.0	6.1	56.1	58.2	3	200	4.55×10^{-1}	1.88×10^{-1}	1.89×10^{-1}	1.89×10^{-1}	2.16×10^{-2}	51.1	3.6×10^{-2}
						277	5.47×10^{3}	3.43×10^{3}	3.44×10^{3}	3.44×10^{3}	2.75×10^{2}	49.0	3.3×10^{-2}
						300	3.43×10^{4}	2.32×10^{4}	2.32×10^{4}	2.32×10^{4}	1.79×10^{3}	48.4	3.3×10^{-2}
						371	2.50×10^{6}	1.96×10^{6}	1.96×10^{6}	1.96×10^{6}	1.23×10^{5}	46.8	3.1×10^{-2}
1,3-dipolar cycloaddition (TS1 ← Int1)	51.0	-9.3	41.7	58.0	3	200	2.40×10^{2}	2.41×10^{3}	2.41×10^{3}	2.41×10^{3}	2.72×10^{2}	35.4	1.1×10^{-1}
						277	1.24×10^{6}	4.54×10^{6}	4.54×10^{6}	4.54×10^{6}	3.72×10^{5}	32.4	9.2×10^{-2}
						300	5.08×10^{7}	1.28×10^{8}	1.28×10^{8}	1.28×10^{8}	2.64×10^{6}	30.2	9.3×10^{-2}
						371	3.25×10^{8}	6.96×10^{8}	6.96×10^{8}	6.96×10^{8}	4.36×10^{7}	28.7	7.9×10^{-2}
Decarboxylation (Int1 → TS2)	60.2	-5.0	55.2	56.1	4	200	1.58×10^{-7}	1.09×10^{-6}	1.09×10^{-6}	1.09×10^{-6}	1.29×10^{-7}	71.1	-7.5×10^{-2}
						277	3.82×10^{-3}	1.26×10^{-2}	1.26×10^{-2}	1.26×10^{-2}	1.02×10^{-3}	77.8	-7.8×10^{-2}
						300	2.76×10^{-2}	7.92×10^{-2}	7.92×10^{-2}	7.92×10^{-2}	6.10×10^{-3}	79.8	-7.9×10^{-2}
						371	2.77×10^{0}	5.85×10^{0}	5.85×10^{0}	5.85×10^{0}	3.73×10^{-1}	86.0	-8.1×10^{-2}
Decarboxylation (TS2 ← Int2)	118.3	7.9	126.2	119.8	4	200	6.53×10^{-27}	4.11×10^{-27}	4.11×10^{-27}	4.11×10^{-27}	4.85×10^{-28}	149.3	-1.5×10^{-1}
						277	2.69×10^{-18}	2.49×10^{-18}	2.49×10^{-18}	2.49×10^{-18}	1.91×10^{-19}	161.2	-1.5×10^{-1}
						300	1.30×10^{-16}	1.27×10^{-16}	1.27×10^{-16}	1.27×10^{-16}	9.66×10^{-18}	164.8	-1.5×10^{-1}
						371	1.12×10^{-12}	1.17×10^{-12}	1.17×10^{-12}	1.17×10^{-12}	7.44×10^{-14}	176.2	-1.5×10^{-1}
Acid catalyst (1) (Int2b → TS3)	42.4	7.2	49.6	46.9	15	200	3.30×10^{5}	5.81×10^{4}	5.86×10^{4}	5.86×10^{4}	6.59×10^{3}	30.1	8.4×10^{-2}
						277	4.04×10^{8}	1.70×10^{8}	1.71×10^{8}	1.71×10^{8}	1.37×10^{7}	24.1	8.2×10^{-2}
						300	1.63×10^{9}	7.94×10^{8}	7.97×10^{8}	7.97×10^{8}	6.03×10^{7}	22.4	8.2×10^{-2}
						371	4.18×10^{10}	2.78×10^{10}	2.78×10^{10}	2.78×10^{10}	1.70×10^{9}	17.4	8.0×10^{-2}
Acid catalyst (1) (TS3 ← Int3)	55.2	-2.9	52.3	53.9	15	200	8.39×10^{6}	1.55×10^{7}	1.56×10^{7}	1.56×10^{7}	1.77×10^{6}	20.8	1.7×10^{-1}
						277	8.78×10^{10}	1.28×10^{11}	1.29×10^{11}	1.29×10^{11}	1.05×10^{10}	8.8	1.6×10^{-1}
						300	5.37×10^{11}	7.53×10^{11}	7.56×10^{11}	7.56×10^{11}	5.72×10^{10}	5.3	1.6×10^{-1}
						371	3.68×10^{13}	4.70×10^{13}	4.72×10^{13}	4.72×10^{13}	2.94×10^{12}	(-5.6)	1.6×10^{-1}

Table S5 (Cont.)

Elementary reaction (ε = 1)	$\Delta E^{\ddagger}$	$\Delta E^{\ddagger,ZPE}$	$\Delta E^{\ddagger,ZPC}$	$\Delta H^{\ddagger}$	T_c	T	$k_{f/r}^{Class}$	$k_{f/r}^{Q\text{-}vib}$	$k_{f/r}^{S\text{-}Wig}$	$k_{f/r}^{F\text{-}Wig}$	$k_{f/r}^{Arr}$	$\Delta G^{\ddagger}$	$\Delta S^{\ddagger}$
Cycloelimination (Int3 → TS4)	81.0	-11.5	69.5	75.2	7	200	5.19×10^{-5}	5.24×10^{-4}	5.25×10^{-4}	5.25×10^{-4}	5.95×10^{-5}	60.9	7.2×10^{-2}
						277	4.08×10^{1}	1.31×10^{2}	1.31×10^{2}	1.31×10^{2}	1.06×10^{1}	56.5	6.8×10^{-2}
						300	5.82×10^{2}	1.54×10^{3}	1.54×10^{3}	1.54×10^{3}	1.17×10^{2}	55.2	6.7×10^{-2}
						371	2.86×10^{5}	5.07×10^{5}	5.07×10^{5}	5.07×10^{5}	3.16×10^{4}	51.0	6.5×10^{-2}
Cycloelimination (TS4 ← Prod)	50.2	3.5	53.7	52.8	7	200	8.20×10^{-3}	2.04×10^{-3}	2.04×10^{-3}	2.04×10^{-3}	2.37×10^{-4}	58.6	-2.9×10^{-2}
						277	3.71×10^{1}	1.46×10^{1}	1.46×10^{1}	1.46×10^{1}	1.16×10^{0}	61.6	-3.2×10^{-2}
						300	1.93×10^{2}	8.24×10^{1}	8.25×10^{1}	8.25×10^{1}	6.28×10^{0}	62.5	-3.2×10^{-2}
						371	8.99×10^{3}	4.68×10^{3}	4.68×10^{3}	4.68×10^{3}	2.97×10^{2}	65.4	-3.4×10^{-2}
Acid catalyst (2) (Int2b → TS3b)	72.9	-7.5	65.4	71.0	31	200	2.63×10^{5}	5.02×10^{5}	5.21×10^{5}	5.22×10^{5}	5.74×10^{4}	26.5	2.2×10^{-1}
						277	5.37×10^{10}	6.72×10^{10}	6.86×10^{10}	6.86×10^{10}	5.47×10^{9}	10.3	2.2×10^{-1}
						300	5.87×10^{11}	6.90×10^{11}	7.02×10^{11}	7.02×10^{11}	5.28×10^{10}	5.5	2.2×10^{-1}
						371	1.56×10^{14}	1.62×10^{14}	1.64×10^{14}	1.64×10^{14}	1.01×10^{13}	(-9.4)	2.2×10^{-1}
Acid catalyst (2) (TS3b ← Prod)	54.7	-2.3	52.4	55.8	31	200	1.10×10^{7}	4.73×10^{6}	4.91×10^{6}	4.92×10^{6}	5.31×10^{5}	22.8	1.7×10^{-1}
						277	1.07×10^{11}	5.17×10^{10}	5.27×10^{10}	5.27×10^{10}	4.22×10^{9}	10.9	1.6×10^{-1}
						300	6.41×10^{11}	3.22×10^{11}	3.28×10^{11}	3.28×10^{11}	2.47×10^{10}	7.4	1.6×10^{-1}
						371	4.23×10^{13}	2.34×10^{13}	2.37×10^{13}	2.37×10^{13}	1.44×10^{12}	(-3.4)	1.6×10^{-1}

Table S6 Thermodynamics and kinetics of the elementary reactions of the enzymatic decarboxylation of α,β-unsaturated acid in ε = 78. Rate constants, temperatures and energies are in s^{-1}, K and kJ/mol, respectively; $\Delta E^{\ddagger,\varepsilon}$ = energy barrier on the optimized reaction path; $\Delta E^{\ddagger,ZPE,\varepsilon}$ = difference between $E^{\ddagger,ZPE,\varepsilon}$ of the transition structure and precursor; $\Delta E^{\ddagger,ZPC,\varepsilon}$ = energy barrier with the zero-point vibrational energy; $\Delta H^{\ddagger,\varepsilon}$ = activation enthalpy; T_c = crossover temperature; T = temperature; $k_{f/r}^{Class,\varepsilon}$ = rate constant obtained from classical TST; $k_{f/r}^{Q\text{-}vib,\varepsilon}$ = rate constant obtained with quantized vibrations including the zero-point vibrational energy; $k_{f/r}^{S\text{-}Wig,\varepsilon}$ = rate constant obtained with quantized vibrations and tunneling correction through the simple Wigner correction; $k_{f/r}^{F\text{-}Wig,\varepsilon}$ = full Wigner-corrected rate constant at T above T_c; $k_{f/r}^{Arr,\varepsilon}$ = Arrhenius rate constant f/r = forward or reverse direction; $\Delta G^{\ddagger,\varepsilon}$ = activation or relative Gibbs free energy; $\Delta S^{\ddagger,\varepsilon}$ = activation entropy; f/r = forward or reverse direction.

Table S6

Elementary reaction (ε = 78)	$\Delta E^{\ddagger,\varepsilon}$	$\Delta E^{\ddagger,ZPE,\varepsilon}$	$\Delta E^{\ddagger,ZPC,\varepsilon}$	$\Delta H^{\ddagger,\varepsilon}$	T_c	T	$k_{f/r}^{Class,\varepsilon}$	$k_{f/r}^{Q\text{-}vib,\varepsilon}$	$k_{f/r}^{S\text{-}Wig,\varepsilon}$	$k_{f/r}^{F\text{-}Wig,\varepsilon}$	$k_{f/r}^{Arr,\varepsilon}$	$\Delta G^{\ddagger,\varepsilon}$	$\Delta S^{\ddagger,\varepsilon}$
1,3-dipolar cycloaddition (React$^{\varepsilon}$ → TS1$^{\varepsilon}$)	48.0	-0.4	47.6	48.0	123	200	5.86×10^{-1}	5.92×10^{-1}	9.62×10^{-1}	1.23×10^{0}	6.76×10^{-2}	49.2	-6.0×10^{-3}
						277	1.83×10^{3}	1.84×10^{3}	2.44×10^{3}	2.61×10^{3}	1.50×10^{2}	50.4	-8.7×10^{-3}
						300	8.85×10^{3}	8.89×10^{3}	1.14×10^{4}	1.19×10^{4}	6.84×10^{2}	50.8	-9.3×10^{-3}
						371	3.49×10^{5}	3.50×10^{5}	4.14×10^{5}	4.23×10^{5}	2.21×10^{4}	52.1	-1.1×10^{-2}
1,3-dipolar cycloaddition (TS1$^{\varepsilon}$ ← Int1$^{\varepsilon}$)	43.8	-0.3	43.5	43.8	43	200	5.07×10^{0}	5.09×10^{0}	5.48×10^{0}	5.50×10^{0}	5.89×10^{-1}	45.6	-9.0×10^{-3}
						277	7.81×10^{3}	7.83×10^{3}	8.14×10^{3}	8.16×10^{3}	6.28×10^{2}	47.1	-1.2×10^{-2}
						300	3.28×10^{4}	3.29×10^{4}	3.40×10^{4}	3.40×10^{4}	2.57×10^{3}	47.5	-1.2×10^{-2}
						371	9.37×10^{5}	9.38×10^{5}	9.59×10^{5}	9.59×10^{5}	5.85×10^{4}	49.1	-1.4×10^{-2}
Decarboxylation (Int1$^{\varepsilon}$ → TS2$^{\varepsilon}$)	38.8	-14.7	24.1	31.7	44	200	3.86×10^{6}	7.25×10^{7}	7.83×10^{7}	7.86×10^{7}	8.45×10^{6}	18.2	6.8×10^{-2}
						277	2.56×10^{9}	1.16×10^{10}	1.21×10^{10}	1.21×10^{10}	9.63×10^{8}	14.3	6.3×10^{-2}
						300	9.14×10^{9}	3.27×10^{10}	3.39×10^{10}	3.39×10^{10}	2.51×10^{9}	13.1	6.2×10^{-2}
						371	1.78×10^{11}	3.92×10^{11}	4.01×10^{11}	4.01×10^{11}	2.43×10^{10}	9.2	6.1×10^{-2}
Decarboxylation (TS2$^{\varepsilon}$ ← Int2$^{\varepsilon}$)	69.3	5.9	75.2	75.0	44	200	4.71×10^{-9}	1.74×10^{-10}	1.88×10^{-10}	1.89×10^{-10}	1.98×10^{-11}	85.7	-5.4×10^{-2}
						277	5.25×10^{-4}	4.92×10^{-5}	5.12×10^{-5}	5.13×10^{-5}	3.94×10^{-6}	90.6	-5.6×10^{-2}
						300	5.10×10^{-3}	5.75×10^{-4}	5.96×10^{-4}	5.96×10^{-4}	4.40×10^{-5}	92.1	-5.7×10^{-2}
						371	1.03×10^{0}	1.80×10^{-1}	1.85×10^{-1}	1.85×10^{-1}	1.12×10^{-6}	96.8	-5.9×10^{-2}
Acid catalyst (1) (Int2b$^{\varepsilon}$ → TS3$^{\varepsilon}$)	136.6	-7.4	129.2	127.9	61	200	3.40×10^{-25}	4.11×10^{-23}	4.73×10^{-23}	4.80×10^{-23}	4.81×10^{-24}	134.0	-3.1×10^{-2}
						277	2.98×10^{-15}	8.90×10^{-14}	9.60×10^{-14}	9.64×10^{-14}	7.00×10^{-15}	137.0	-3.3×10^{-2}
						300	2.63×10^{-13}	5.91×10^{-12}	6.31×10^{-12}	6.33×10^{-12}	4.48×10^{-13}	138.0	-3.4×10^{-2}
						371	9.11×10^{-9}	1.04×10^{-7}	1.09×10^{-7}	1.09×10^{-7}	6.51×10^{-9}	141.1	-3.6×10^{-2}
Acid catalyst (1) (TS3$^{\varepsilon}$ ← Int3$^{\varepsilon}$)	161.7	-22.1	139.6	142.5	61	200	5.88×10^{-30}	9.89×10^{-26}	1.14×10^{-25}	1.16×10^{-25}	1.11×10^{-26}	144.1	-8.0×10^{-3}
						277	3.48×10^{-18}	2.12×10^{-15}	2.29×10^{-15}	2.30×10^{-15}	1.60×10^{-16}	145.7	-1.2×10^{-2}
						300	7.00×10^{-16}	2.26×10^{-13}	2.41×10^{-13}	2.42×10^{-13}	1.74×10^{-14}	146.1	-1.2×10^{-2}
						371	1.66×10^{-10}	1.26×10^{-8}	1.32×10^{-8}	1.32×10^{-8}	7.91×10^{-10}	147.6	-1.4×10^{-2}

Table S6 (Cont.)

Elementary reaction (ε = 78)	$\Delta E^{\ddagger,\varepsilon}$	$\Delta E^{\ddagger,ZPE,\varepsilon}$	$\Delta E^{\ddagger,ZPC,\varepsilon}$	$\Delta H^{\ddagger,\varepsilon}$	T_c	T	$k_{f/r}^{Class,\varepsilon}$	$k_{f/r}^{Q\text{-}vib,\varepsilon}$	$k_{f/r}^{S\text{-}Wig,\varepsilon}$	$k_{f/r}^{F\text{-}Wig,\varepsilon}$	$k_{f/r}^{Arr,\varepsilon}$	$\Delta G^{\ddagger,\varepsilon}$	$\Delta S^{\ddagger,\varepsilon}$
Cycloelimination (Int3$^{\varepsilon}$ → TS4$^{\varepsilon}$)	77.4	-10.0	67.4	69.8	51	200	1.36×10^{-7}	4.66×10^{-6}	5.15×10^{-6}	5.19×10^{-6}	5.46×10^{-7}	68.7	5.5×10^{-3}
						277	5.89×10^{-2}	5.06×10^{-1}	5.34×10^{-1}	5.35×10^{-1}	4.09×10^{-2}	69.3	1.8×10^{-3}
						300	7.46×10^{-1}	4.97×10^{0}	5.21×10^{0}	5.22×10^{0}	3.79×10^{-1}	69.5	1.0×10^{-3}
						371	2.79×10^{2}	1.06×10^{3}	1.10×10^{3}	1.10×10^{3}	6.67×10^{1}	70.0	-5.4×10^{-4}
Cycloelimination (TS3$^{\varepsilon}$ ← Prod$^{\varepsilon}$)	44.3	6.9	51.2	47.3	51	200	2.59×10^{-4}	6.57×10^{-5}	7.27×10^{-5}	7.32×10^{-5}	7.70×10^{-6}	64.3	-8.5×10^{-2}
						277	4.33×10^{-1}	1.98×10^{-1}	2.09×10^{-1}	2.09×10^{-1}	1.57×10^{-2}	71.5	-8.7×10^{-2}
						300	1.85×10^{0}	9.35×10^{-1}	9.79×10^{-1}	9.80×10^{-1}	7.04×10^{-2}	73.7	-8.8×10^{-2}
						371	5.48×10^{1}	3.41×10^{1}	3.52×10^{1}	3.52×10^{1}	2.15×10^{0}	80.6	-9.0×10^{-2}
Acid catalyst (2) (Int2b$^{\varepsilon}$ → TS3b$^{\varepsilon}$)	46.6	-5.2	41.4	44.5	55	200	9.60×10^{2}	2.61×10^{3}	2.93×10^{3}	2.96×10^{3}	3.07×10^{2}	35.2	4.7×10^{-2}
						277	2.37×10^{6}	4.26×10^{6}	4.53×10^{6}	4.54×10^{6}	3.41×10^{5}	32.6	4.3×10^{-2}
						300	1.09×10^{7}	1.83×10^{7}	1.93×10^{7}	1.93×10^{7}	1.39×10^{6}	31.8	4.2×10^{-2}
						371	3.87×10^{8}	5.59×10^{8}	5.78×10^{8}	5.79×10^{8}	3.47×10^{7}	29.4	4.1×10^{-2}
Acid catalyst (2) (TS3b$^{\varepsilon}$ ← Prod$^{\varepsilon}$)	38.1	-1.7	36.4	37.3	55	200	9.43×10^{2}	1.33×10^{3}	1.50×10^{3}	1.52×10^{3}	1.49×10^{6}	36.4	4.5×10^{-3}
						277	5.59×10^{5}	6.85×10^{5}	7.31×10^{5}	7.33×10^{5}	5.50×10^{4}	36.8	1.8×10^{-3}
						300	1.95×10^{6}	2.33×10^{6}	2.46×10^{6}	2.47×10^{6}	1.80×10^{5}	36.9	1.3×10^{-3}
						371	3.60×10^{7}	4.08×10^{7}	4.23×10^{7}	4.24×10^{7}	2.51×10^{6}	37.5	-5.4×10^{-4}

Table S7 Equilibrium constants ($K^{S\text{-}Wig} = k_f^{S\text{-}Wig}/k_r^{S\text{-}Wig}$) for the enzymatic decarboxylation of α,β-unsaturated acid in ε = 1 and 78, respectively. Temperatures are in kJ/mol. $k_{f/r}^{S\text{-}Wig}$ = rate constant obtained with quantized vibrations and tunneling correction through the simplified Wigner correction; f/r = forward or reverse direction.

Table S7

Elementary reaction (ε = 1)	T	K^{Class}	$K^{Q\text{-}vib}$	$K^{S\text{-}Wig}$	$K^{F\text{-}Wig}$	K^{Arr}
1,3-dipolar cycloaddition (React ⇌ Int1)	200	1.90×10^{-3}	7.81×10^{-5}	7.81×10^{-5}	7.81×10^{-5}	7.93×10^{-5}
	277	4.43×10^{-3}	7.57×10^{-4}	7.58×10^{-4}	7.58×10^{-4}	7.41×10^{-4}
	300	5.22×10^{-3}	1.14×10^{-3}	1.14×10^{-3}	1.14×10^{-3}	6.78×10^{-4}
	371	7.69×10^{-3}	2.82×10^{-3}	2.82×10^{-3}	2.82×10^{-3}	2.83×10^{-3}
Decarboxylation (Int1 ⇌ Int2)	200	2.41×10^{19}	2.66×10^{20}	2.66×10^{20}	2.66×10^{20}	2.66×10^{20}
	277	1.42×10^{15}	5.07×10^{15}	5.07×10^{15}	5.07×10^{15}	5.34×10^{15}
	300	2.11×10^{14}	6.25×10^{14}	6.25×10^{14}	6.25×10^{14}	6.31×10^{14}
	371	2.48×10^{12}	5.00×10^{12}	5.00×10^{12}	5.00×10^{12}	5.01×10^{12}
Acid catalyst (1) (Int2b ⇌ Int3)	200	3.93×10^{-2}	3.75×10^{-3}	3.75×10^{-3}	3.75×10^{-3}	3.72×10^{-3}
	277	4.60×10^{-3}	1.33×10^{-3}	1.33×10^{-3}	1.33×10^{-3}	1.30×10^{-3}
	300	3.03×10^{-3}	1.05×10^{-3}	1.05×10^{-3}	1.05×10^{-3}	1.05×10^{-3}
	371	1.14×10^{-3}	5.90×10^{-4}	5.90×10^{-4}	5.90×10^{-4}	5.78×10^{-4}
Cycloelimination (Int3 ⇌ Prod)	200	6.33×10^{-3}	2.58×10^{-1}	2.58×10^{-1}	2.58×10^{-1}	2.51×10^{-1}
	277	1.10×10^{0}	9.01×10^{0}	9.01×10^{0}	9.01×10^{0}	9.16×10^{0}
	300	3.02×10^{0}	1.87×10^{1}	1.87×10^{1}	1.87×10^{1}	1.87×10^{1}
	371	3.18×10^{1}	1.08×10^{2}	1.08×10^{2}	1.08×10^{2}	1.07×10^{2}
Acid catalyst (2) (Int2b ⇌ Prod)	200	2.38×10^{-2}	1.06×10^{-1}	1.06×10^{-1}	1.06×10^{-1}	1.08×10^{-1}
	277	5.04×10^{-1}	1.30×10^{0}	1.30×10^{0}	1.30×10^{0}	1.30×10^{0}
	300	9.15×10^{-1}	2.14×10^{0}	2.14×10^{0}	2.14×10^{0}	2.14×10^{0}
	371	3.68×10^{0}	6.93×10^{0}	6.93×10^{0}	6.93×10^{0}	7.00×10^{0}

Table S7 (Cont.)

Elementary reaction (ε = 78)	T	$K^{Class,\varepsilon}$	$K^{Q\text{-}vib,\varepsilon}$	$K^{S\text{-}Wig,\varepsilon}$	$K^{F\text{-}Wig,\varepsilon}$	$K^{Arr,\varepsilon}$
1,3-dipolar cycloaddition (React$^{\varepsilon}$ ⇌ Int1$^{\varepsilon}$)	200	1.16×10^{-1}	1.16×10^{-1}	1.76×10^{-1}	2.23×10^{-1}	1.15×10^{-1}
	277	2.35×10^{-1}	2.35×10^{-1}	3.00×10^{-1}	3.21×10^{-1}	2.39×10^{-1}
	300	2.70×10^{-1}	2.70×10^{-1}	3.34×10^{-1}	3.51×10^{-1}	2.66×10^{-1}
	371	3.72×10^{-1}	3.73×10^{-1}	4.31×10^{-1}	4.41×10^{-1}	3.78×10^{-1}
Decarboxylation (Int1$^{\varepsilon}$ ⇌ Int2$^{\varepsilon}$)	200	8.19×10^{14}	4.15×10^{17}	4.15×10^{17}	4.15×10^{17}	4.26×10^{17}
	277	4.88×10^{12}	2.36×10^{14}	2.36×10^{14}	2.36×10^{14}	2.45×10^{14}
	300	1.79×10^{12}	5.68×10^{13}	5.68×10^{13}	5.68×10^{13}	5.70×10^{13}
	371	1.73×10^{11}	2.17×10^{12}	2.17×10^{12}	2.17×10^{12}	2.16×10^{12}
Acid catalyst (1) (Int2b$^{\varepsilon}$ ⇌ Int3$^{\varepsilon}$)	200	5.78×10^{4}	4.15×10^{2}	4.14×10^{2}	4.14×10^{2}	4.34×10^{2}
	277	8.57×10^{2}	4.21×10^{1}	4.20×10^{1}	4.20×10^{1}	4.37×10^{1}
	300	3.76×10^{2}	2.62×10^{1}	2.61×10^{1}	2.61×10^{1}	2.57×10^{1}
	371	5.50×10^{0}	8.24×10^{0}	8.23×10^{0}	8.23×10^{0}	8.23×10^{0}
Cycloelimination (Int3$^{\varepsilon}$ ⇌ Prod$^{\varepsilon}$)	200	5.27×10^{-4}	7.08×10^{-2}	7.09×10^{-2}	7.09×10^{-2}	7.09×10^{-2}
	277	1.36×10^{-1}	2.55×10^{0}	2.55×10^{0}	2.55×10^{0}	2.60×10^{0}
	300	4.03×10^{-1}	5.32×10^{0}	5.32×10^{0}	5.32×10^{0}	5.39×10^{0}
	371	5.09×10^{0}	3.12×10^{1}	3.12×10^{1}	3.12×10^{1}	3.11×10^{1}
Acid catalyst (2) (Int2b$^{\varepsilon}$ ⇌ Prod$^{\varepsilon}$)	200	1.02×10^{0}	1.96×10^{0}	1.95×10^{0}	1.95×10^{0}	2.06×10^{0}
	277	4.24×10^{0}	6.22×10^{0}	6.20×10^{0}	6.20×10^{0}	6.19×10^{0}
	300	5.61×10^{0}	7.85×10^{0}	7.83×10^{0}	7.83×10^{0}	7.73×10^{0}
	371	1.08×10^{1}	1.37×10^{1}	1.37×10^{1}	1.37×10^{1}	1.38×10^{1}

Table S8 Coordinates (Å) of equilibrium and transition structures of the model molecular clusters (Tables S2[†] and S4[†], respectively) obtained from B3LYP/DZP geometry optimizations and the NEB method in $\varepsilon = 1$ and 78.

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C	25.1231456	18.1598693	23.9034867
C	23.6745526	17.6897992	23.7788405
C	22.7114283	18.4816620	24.6651309
C	21.2757744	17.9643690	24.5846639
N	20.3825644	18.8085196	25.3535730
C	19.1514795	18.4458635	25.7293068
N	18.6388474	17.2472354	25.3997800
N	18.4068671	19.3292765	26.4035441
C	26.2109967	9.1279857	31.7602379
C	27.0823665	9.1414136	30.5046187
C	26.2911766	9.2766129	29.2047990
C	25.4710485	8.0322411	28.8518332
O	25.6202901	6.9598756	29.4279785
N	24.5763765	8.2218472	27.8494357
C	18.9573207	24.8856238	26.9253591
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C	21.0800090	23.4614072	26.8080287
C	20.4863461	22.0748751	26.4899206
O	19.4119237	21.7513520	27.0654296
O	21.1452889	21.3663868	25.6825153
C	19.3015657	9.1783462	22.2692572
C	18.5321422	9.5197648	21.1626339
C	18.4149911	10.8699678	20.7563191
C	21.8354197	10.6748374	24.4675484
C	19.0086366	11.8809158	21.5462826
C	23.8134433	11.0160271	25.6215263
C	19.9295535	13.9060392	20.3434025
C	18.8316874	13.4011313	21.3051879
C	20.1479484	13.7032315	23.4469560
O	24.7389535	10.6665901	26.3588296
N	22.8149868	10.1834945	25.2127245
C	22.7759696	12.9401128	24.4184502
O	22.8375059	14.1363748	24.1219084
C	21.7240011	12.0172260	24.0733377
N	20.5610125	12.4691738	23.3914582
C	17.4383650	13.8214576	20.7861193
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C	17.6831022	11.1531442	19.4611733
C	20.0124601	10.1418835	22.9937269
N	20.8539253	9.7808016	24.0409770
C	20.8642102	8.4094424	24.5326616
O	18.8977136	14.4261964	25.6279427
C	18.0104924	14.4243960	26.5329392
O	17.2332043	15.3764100	26.8045883
C	17.8665804	13.1635114	27.4007375
C	18.8055041	12.2030501	27.2668436
C	18.9818327	10.9198886	27.9583720
C	17.9479679	10.1813331	28.5711877
C	18.2093390	8.9623161	29.1978630
C	19.5046403	8.4413584	29.2339747
C	20.5424765	9.1487559	28.6205709
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H	17.4926161	19.0339665	26.7167615
H	18.7877269	20.2782529	26.6798539
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H	25.2248248	19.2258571	23.6405292
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H	16.7699028	8.6070380	20.2662227
H	18.2769889	8.2592781	19.4054842
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O	19.740993	21.743181	28.318914
O	21.678550	21.565481	27.185315
C	18.867206	8.472891	22.375565
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C	21.352216	10.174995	24.457514
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C	19.745521	13.105334	23.069944
O	24.278242	10.327558	26.301500
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C	20.406081	7.924853	24.722178
O	19.823855	15.519299	24.868823
C	18.712221	14.961298	25.131570
O	17.575405	15.468983	25.046107
C	18.769408	13.505488	25.645119
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C    18.533446 13.409664 22.277467
H    17.640338 13.200636 22.893871
H    18.500231 14.487184 22.071898
C    17.586228 7.507113 20.485568
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H    18.108743 7.324840 19.531950
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N    23.337652 11.866396 24.938465
H    24.117828 12.482452 25.156049
C    17.520658 12.672465 25.509263
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C      25.2826432     16.6702261     23.9525516
C      24.4689996     17.9638778     23.9603435
C      23.5985878     18.1340824     25.2079888
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N	21.9018900	19.6426467	26.3039937
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N	20.1893904	18.1883447	25.6759979
N	19.9654772	19.5759722	27.5376131
C	26.8188829	10.2918003	32.2312703
C	26.8291670	10.3949821	30.7061015
C	25.5097112	10.9037009	30.0945303
C	24.3697314	9.8990808	30.2380070
O	23.8502984	9.6446095	31.3209155
N	24.0195774	9.2725332	29.0853267
C	20.3635839	24.9003358	29.3543727
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C	22.4032538	23.3677283	29.5185732
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O	20.7313949	21.7566023	28.9092877
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C	19.7677542	8.7473753	22.2098468
C	19.1240638	8.9756795	20.9940917
C	19.0411623	10.2916482	20.4802978
C	21.9531303	10.4538529	24.6254894
C	19.5591960	11.3763739	21.2248647
C	23.9402877	10.8886736	25.7342346
C	20.7285486	13.3660469	20.1788474
C	19.4369341	12.8822874	20.8745449
C	20.3529776	13.4627645	23.2058296
O	24.7588976	10.6696853	26.6167604
N	22.8719758	10.0671170	25.4663710
C	23.2609976	12.3810332	23.8866031
O	23.5580778	13.1253931	22.9795416
C	21.8238046	11.8924808	24.1978548
N	20.9269127	12.1159875	23.0952822
C	18.2176750	13.2713939	20.0109925
C	20.2793617	11.1008360	22.4206089
C	18.4474519	10.4592744	19.0959136
C	20.3593038	9.7871244	22.9215195
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C	21.1188976	8.1802868	24.6571493
O	21.1237658	15.7499471	24.8286218
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C	21.3155520	12.9530994	25.3422171
C	21.2593135	12.4869510	26.7777576
C	20.5153556	11.3786053	27.2188958
C	20.5068551	11.0057355	28.5618063
C	21.2351956	11.7348343	29.5044198
C	21.9617672	12.8494416	29.0876067
C	21.9728709	13.2174159	27.7414547
H	23.8226073	17.9848139	23.0644842
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H	22.9728429	17.2361908	25.3365578
H	24.2370741	18.2168475	26.1049063
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126

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