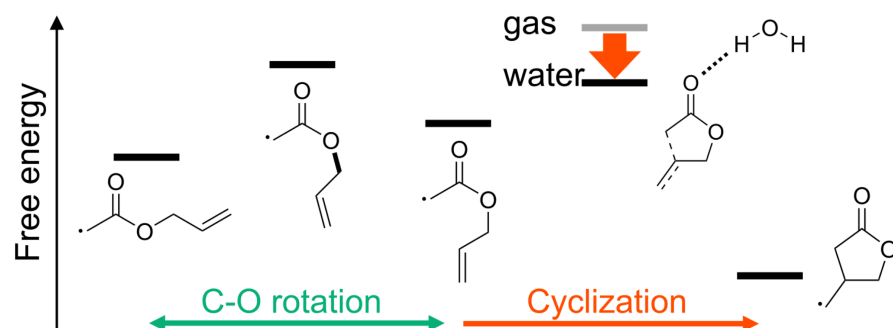


Graphical Abstract

Unique solvent effect of water in radical cyclization reaction

Sara Suzuki, Soni Aman Govind, Kosuke Imamura, Hideki Yorimitsu, Hiroshi Shinokubo, Masahiro Higashi, Hirofumi Sato



Highlights

Unique solvent effect of water in radical cyclization reaction

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- The unique solvent effect of water on the radical cyclization reaction of Z-(allyloxycarbonyl)methyl reaction is analyzed theoretically.
- Aqueous solution promotes the forward cyclization reaction to a greater extent than other polar solvents by lowering its transition state.
- The activation barrier for the cyclization reaction is lowered by formation of hydrogen bonds around the C=O group in aqueous solution.
- The change in solvation structure of water along with the C-C bond formation is also revealed.

Unique solvent effect of water in radical cyclization reaction

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Abstract

The radical cyclization reaction in the aqueous environment by Yorimitsu *et al.* is revisited using the RISM-SCF-cSED method, a hybrid of quantum chemistry and statistical mechanics theory for molecular liquids. The difference between the barrier height of the forward reaction from the intermediate *E*-rot, the cyclization step, and that of the backward reaction is crucial to the reaction yield. Considering the effect of hydrogen bonding through the RISM theory, we found that the barrier height for the forward reaction is lower, especially in water. In other words, considering microscopic solvation effects clearly shows the difference between water and DMSO solvents, explaining the remarkable acceleration of the reaction in the aqueous environment.

Keywords: radical cyclization, RISM-SCF-cSED, hydrogen bonding

1. Introduction

Water often exhibits extraordinary properties because it has a unique hydrogen-bonding network in its liquid state. Such extraordinary properties also appear when water is adopted as a reaction solvent. As a result, some reactions show much higher reaction rates, yields, and selectivity in water rather than in other organic solvents. Especially for the rate enhancement of nonpolar organic reactions, the first observation of the water solvent effect was reported by Breslow; the certain Diels-Alder reactions are a few hundred times faster in water than in other organic solvents[1, 2]. Other examples have been reported afterward, such as Claisen rearrangement and aldol reactions[3, 4]. The advantage of using water as a reaction solvent is not only improved reactivity but also cost and environmental friendliness.

In these perspectives, organic reactions in water solvents have been expanded to various reactions. Yorimitsu *et al.* applied water solvent to simple radical reactions[5, 6]. A simple but interesting result was obtained on the radical cyclization of allyl iodoacetate into γ -lactone, which is usually synthesized by the cyclization of iodo acetal followed by oxidation developed by Stork and Ueno[7, 8]. Although no lactone is obtained by treating allyl iodoacetate with triethylborane/O₂ as a radical initiator in benzene or hexane at room temperature, a high yield is achieved only by changing the solvent to water, 78%. The value is much larger than for other polar solvents: 37% for DMSO and 24% for formamide. The proposed reaction scheme is shown in Figure 1. After radical initiation, the resulting *Z*-rot undergoes C–O rotation to yield the less stable *E*-rotamer (*E*-rot). Radical cyclization and the subsequent iodine atom

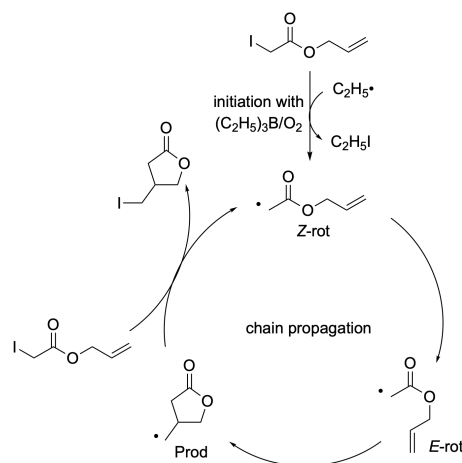


Figure 1: The proposed reaction mechanism.

transfer from the starting allyl iodoacetate complete the radical chain and produce the γ -lactone. To obtain the product, a) *E*-rot should be produced and have a certain lifetime, and b) cyclization can happen in competition with the reverse reaction to *Z*-rot. If these requirements are not fulfilled, intermolecular addition occurs to produce oligomers and polymers. This is the cause of little or no formation of the γ -lactone in less polar solvents. No solvent effect is expected in the process because the iodine atom transfer step is so rapid. The following cyclization step, the rate-determining step, is the key to reaction yield, where the solvent effect plays a certain role. The effect was studied using the polarized-continuum-model (PCM) calculations using the polarizable conductor calculation model

(CPCM)[9, 10] in the previous study[5]. The contribution from the cohesive energy was also discussed based on the geometrical volume utilized in the CPCM computation. However, a specific solute-solvent interaction, such as hydrogen bonding, has never been discussed, which is essential to characterize the fundamental properties of the aqueous solution. Indeed, the effect sometimes plays an essential role in organic chemical reactions, including the Diels-Alder reaction[11, 12].

This paper employed the RISM-SCF-cSED computation[13, 14, 15] to elucidate the role of hydrogen bonding in the radical cyclization of Z-(allyloxy carbonyl)methyl radical. The RISM-SCF-cSED method combines quantum chemical calculation and RISM, which is a statistical mechanics for molecular liquid, providing the electronic structure of the reaction center and the solvation structure around it at a molecular level. The computation with the dimethyl sulfoxide (DMSO) solvent, which shows the second highest yields in the experiment[5], was also compared. The unique solvent effect of water was revealed by visualizing the solvation structure at the transition state (TS).

2. Methods

2.1. The RISM-SCF method

In this method[13, 14, 15], the free energy of the total system $\mathcal{A}$ is defined as the sum of the total (potential) energy of the solute molecule E_{solute} and the solvation free energy $\Delta\mu$.

$$\mathcal{A} = E_{\text{solute}} + \Delta\mu. \quad (1)$$

The electronic structure of the solute molecule and the solvation structure around it are solved self-consistently in this method. The solvation effect on the electronic structure, *i.e.* the polarization, is evaluated by the difference between the energy of the molecule in an isolated state (E_{isolated}) and that in the solution phase (E_{solute})[16, 17].

$$E_{\text{reorg}} = E_{\text{solute}} - E_{\text{isolated}}. \quad (2)$$

The solvation free energy is evaluated by the hyper-netted chain (HNC) approximation

$$\Delta\mu = -\rho k_B T \sum_{\alpha s} \int d\mathbf{r} \left[c_{\alpha s}(r) - \frac{1}{2} h_{\alpha s}^2(r) + \frac{1}{2} h_{\alpha s}(r) c_{\alpha s}(r) \right], \quad (3)$$

or by the gaussian fluctuation (GF) approximation[18]

$$\Delta\mu^{\text{GF}} = -\rho k_B T \sum_{\alpha s} \int d\mathbf{r} \left[c_{\alpha s}(r) + \frac{1}{2} h_{\alpha s}(r) c_{\alpha s}(r) \right], \quad (4)$$

where ρ , k_B , and T are the density of solvent, Boltzmann constant, and temperature, respectively. $h_{\alpha s}$ and $c_{\alpha s}$ are the total and direct correlation functions for the atomic site α in the solute molecule and s in the solvent molecules, respectively.

The solvation structure is obtained in terms of the radial distribution function (RDF), which represents the probability distribution of the solvent site s as a function of the distance r from the atomic site α in the solute molecule.

$$g_{\alpha s}(r) = h_{\alpha s}(r) + 1. \quad (5)$$

Table 1: Lennard-Jones parameters and atomic charges of DMSO and water solvent and the solute molecule.

	Atom(s)	$\sigma/\text{\AA}$	$\varepsilon/\text{kcal mol}^{-1}$	Charge
DMSO[19]	S	3.560	0.310	0.319
	O	2.630	0.410	-0.459
	CH ₃	3.660	0.225	0.160
Water[20]	O	3.166	0.155	-0.820
	H	1.000	0.056	0.410
Solute[21, 22]	C1	3.500	0.066	—
	C2	3.750	0.105	—
	O3	3.000	0.170	—
	C4	3.500	0.066	—
	C5	3.550	0.076	—
	C6	3.550	0.076	—
	H7	2.420	0.015	—
	H8	2.420	0.015	—
	O9	2.960	0.210	—
	H10	2.420	0.015	—
	H11	2.420	0.015	—
	H12	2.420	0.030	—
	H13	2.420	0.030	—
	H14	2.420	0.030	—

2.2. Computational details

The reaction profile of the radical cyclization of Z-(allyloxy carbonyl)methyl radical was evaluated using the density functional theory (DFT) with the B3LYP functional and 6-31G(d) basis set. As the molecule is open-shell species, spin-unrestricted DFT was adopted. The geometry optimizations were conducted in the gas phase. The effects of DMSO and water solvents were then introduced by the RISM-SCF-cSED method [13, 14, 15]. The hyper-netted chain (HNC) closure was employed to solve the RISM equation. The Lennard-Jones (LJ) parameters and charges of solvent molecules [19] are listed in Table 1. The parameters for the solute were taken from the OPLS all-atom (OPLS-AA) force field [21, 22]. Note that the charge distribution of the solute is self-consistently determined in the RISM-SCF-cSED method.

We used Gaussian 16 program[23] for the geometry optimizations in the gas phase. The PCM method[24, 25, 26], the RISM-SCF-cSED method, or the selected solvent provide different optimized geometries in the solution phase. If individu-

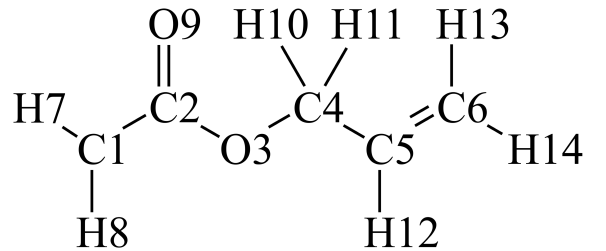


Figure 2: The labeling of the solute molecule.

ally optimized, the solvation effect and the resulting differences in geometry and electronic state changes are mixed up, making analysis difficult. Therefore, we focus only on the solvation effect by fixing the structure in the present study. Note that the optimizations were also performed with the PCM (Table S1), but the difference in the geometry is not significant. The RISM-SCF-cSED method was employed with the GAMESS program [27] modified by us.

3. Results and Discussion

3.1. Free energy profile

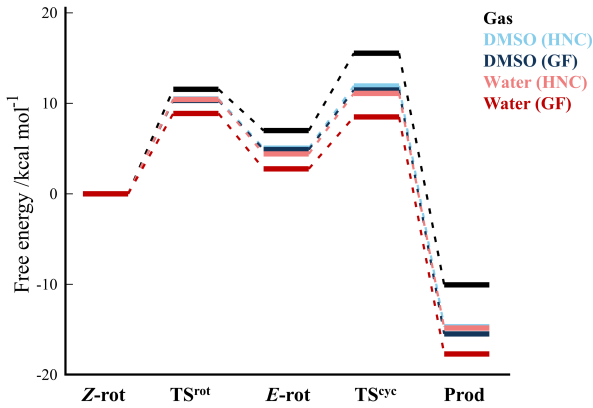


Figure 3: Reaction profile of Z-(allyloxycarbonyl)methyl radical cyclization reaction in the gas phase and in DMSO and water solvent calculated by the RISM-SCF-cSED method.

Figure 3 shows the free energy profile of the reaction along with the profile illustrated in Fig. 1. Table 2 summarizes the relative free energies to the reactant, including the intermediate (*E*-rot), two transition states (TSs), *i.e.* TS^{rot} and TS^{cyc}. The activation barriers from the intermediate (E_a^{rot} and E_a^{cyc}), and the difference between them, $\Delta E_a = E_a^{\text{cyc}} - E_a^{\text{rot}}$, are also listed. ΔE_a is the key to controlling the reaction: A positive ΔE_a means that even if an intermediate is produced, the cyclization step is inhibited, and the reverse reaction to the reactant is promoted. The negative value corresponds to the second step subsequently occurring more readily. The CPCM results from Ref. [5] are also included for comparison.

As reported in the previous study, ΔE_a in the gas phase is positive at about 4 kcal/mol, making it difficult to reach the product under kinetic control. By introducing the solvation effect, both barriers become lowered, especially the height of the cyclization step received more stabilization. In the present computations, TS^{cyc} is significantly stabilized by several kcal/mol, while *E*-rot and TS^{rot} stabilized by a few kcal/mol. These overall trends are generally consistent with both the CPCM method [5] and the present RISM-SCF-cSED method. Still, determining ΔE_a is very sensitive, and careful consideration of solvent effects is essential. With the CPCM method, ΔE_a is decreased to 0.70 kcal/mol in DMSO and 0.34 kcal/mol in water, indicating the cyclization step more readily occurs in solution. The

aqueous environment promotes the reaction, although the difference between the solvents is only 0.36 kcal/mol. Note that, for both cases, the reverse reaction is still slightly preferable. When employing the RISM-SCF-cSED method, ΔE_a is 1.43 kcal/mol in DMSO and 0.67 kcal/mol in water (HNC formula), and 1.15 kcal/mol in DMSO and -0.38 kcal/mol in water (GF formula). The difference between the two solvents is 0.76 kcal/mol (HNC) and 1.53 kcal/mol (GF), and the difference is remarkable in the latter formula. It is well established that the results from the GF are generally closer to the experimental measurements [28], whereas those from the HNC overestimate the values, especially in water [29], as a results of the term, $h_{\alpha s}^2(r)$, in the Eq. (3) [30]. In particular, the negative ΔE_a indicates that the second step is much more enhanced in the aqueous environment, which supports the experimentally observed results. The other difference between the formula appears in the overall reaction profile. The free energies in water solvent calculated by the GF formula are more stable than the DMSO by about 2 kcal/mol. This is consistent with the experimental difference in the yield. On the contrary, the HNC formula gave similar values in both solvents, implying the overestimation in the solvation-free energy for the water environment. The difference between the two solvents is clearly shown by considering the microscopic explicit solute-solvent interaction using the RISM-SCF-cSED method. As expected, the specific solvation plays a key role, as discussed later.

3.2. Difference in solvent effects on the TSs

The difference in ΔE_a between solvents is interpreted by the contributions from the electronic structure of the solute and the solvation structure[16]. Based on eq(1) and eq(2), the free energy of TS^{rot} or TS^{cyc} is represented by

$$\mathcal{G}^{\text{cyc/rot}} = E_{\text{isolate}}^{\text{cyc/rot}} + E_{\text{reorg}}^{\text{cyc/rot}} + \Delta\mu^{\text{cyc/rot}}, \quad (6)$$

and therefore ΔE_a is given by the corresponding three terms. Notice that the contribution from *E*-rot is common and does not appear.

$$\Delta E_a = \Delta E_{\text{isolated}}^{\text{cyc-rot}} + \Delta E_{\text{reorg}}^{\text{cyc-rot}} + \Delta\Delta\mu^{\text{cyc-rot}}. \quad (7)$$

Each term on the right-hand side corresponds to the energy difference in the isolated system, the energy difference in the reorganization, and the difference in the solvation-free energy, respectively. The first term, $\Delta E_{\text{isolated}}^{\text{cyc-rot}}$, comes only from the difference between TS^{rot} and TS^{cyc} in an isolated state, and is common for all the methods and solvents (3.99 kcal/mol). We also conducted the computations with more sophisticated levels and found slight $\Delta E_{\text{isolated}}^{\text{cyc-rot}}$ increase (Table S2). It should be noted, however, that this does not affect the notable difference between the solvents.

Table 3 shows these terms in the DMSO and water results. The dominant is the solvation-free energy $\Delta\Delta\mu^{\text{cyc-rot}}$. They all are negative values, denoting that the TS^{cyc} is stabilized than TS^{rot}. Comparing the two solvents, the change is larger in water, -3.3 kcal/mol (HNC) or -4.2 kcal/mol (GF), indicating that TS^{cyc} is greatly solvated in the aqueous solution. On the other

Table 2: Relative free energy of Z-(allyloxycarbonyl)methyl radical cyclization reaction and the activation barriers in the gas phase and in DMSO and water (in kcal/mol). CPCM results are taken from [5].

		solvent	Z-rot	TS ^{rot}	E-rot	TS ^{cyc}	Prod	E_a^{rot}	E_a^{cyc}	ΔE_a
Gas			0.00	11.55	6.99	15.54	-10.06	4.56	8.55	3.99
RISM-SCF-cSED	HNC	DMSO	0.00	10.49	5.05	11.92	-14.69	5.44	6.87	1.43
	GF	DMSO	0.00	10.32	4.89	11.48	-15.48	5.44	6.59	1.15
	HNC	water	0.00	10.43	4.41	11.10	-14.83	6.02	6.69	0.67
	GF	water	0.00	8.88	2.76	8.50	-17.70	6.12	5.74	-0.38
CPCM [5]		DMSO	0.00	9.17	3.86	9.87	-18.71	5.31	6.01	0.70
		water	0.00	8.81	3.04	9.13	-19.77	5.77	6.09	0.34

hand, $\Delta E_{\text{reorg}}^{\text{cyc-rot}}$ is smaller at about 1 kcal/mol. In fact, the spin density distribution in both solvents is not so different from that of the isolated molecule. Because E_{reorg} is generally positive, the negative values indicate that the electronic structure of TS^{rot} is slightly more distorted by the solvation than that of TS^{cyc}.

In general, greater distortion of the electronic structure of the solute molecules is expected in a more polar solvent, causing larger polarization. Actually, due to hydrogen bonding effects, the molecular orbitals are more deformed than those in the gas phase or the DMSO solvent. The change in dipole moment with the reaction follows this trend as shown in Table 4. The dipole moment of each reaction step is largest in water and smallest in the gas phase, as expected from the theoretical calculation with the CPCM model[5]. In the reaction process, the maximum dipole moment is observed at TS^{cyc}, where the values are 4.58, 5.53, and 6.57 D, respectively, in the gas, DMSO, and water. Such kind of solvent dependence is correlated to the dielectric constant of solvents, which could also be considered in the CPCM model[9, 10].

3.3. Solvation structures

The difference in solvation structure also plays an important role in stabilizing the TS^{cyc}. Figure 4 shows the RDFs of (a) H atoms in water solvent and (b) CH₃ groups in DMSO solvent around the carbonyl O atom of TS^{cyc}. H atoms in water solvent distributed sharply around the carbonyl O atom ca. 1.8 Å. Since the peak position between the two oxygens is about 3 Å, O...H-O interacted linearly, indicating the strong hydrogen-bonding interaction. In contrast, the distribution of CH₃ groups in DMSO solvent shifts outward around 3.3 Å. Using the RDF of S...O, S-CH₃...O angle is estimated as 141°, a relatively weaker interaction. Although these trends are observed at each

Table 3: The difference in solvation effects between TS^{rot} and TS^{cyc} (in kcal/mol).

		$\Delta E_{\text{reorg}}^{\text{cyc-rot}}$	$\Delta \Delta \mu^{\text{cyc-rot}}$	ΔE_a
DMSO	HNC	-0.83	-1.73	1.43
	GF	-0.83	-2.01	1.15
Water	HNC	-0.16	-3.32	0.67
	GF	-0.16	-4.20	-0.38

Table 4: Dipole moment (in Debye) along the reaction.

	Z-rot	TS ^{rot}	E-rot	TS ^{cyc}	Prod
Gas	1.65	3.65	4.41	4.58	4.35
DMSO	2.00	4.27	5.23	5.53	5.03
Water	2.54	5.02	6.19	6.57	5.80

step of the reaction process, the effect is the most prominent at the TS^{cyc} (Figure S1).

The changes in the distribution of O atoms in water solvent around the carbon atoms forming the bonds are shown in (c) and (d). One is the terminal carbon atom (C1), which initially forms the radical center; the other is the fifth carbon (C5), which bonds with C1 to form a new bond. As the new bond is formed, the directly solvating water molecules are kicked out, and the height of the RDF becomes lower and lower as the reaction proceeds. C1, which is still exposed to the solvent after bond formation, virtually retains its peak. Conversely, C5 is embedded in the surrounding carbon by cyclization, and the solvent is accessible only from above and below the ring, leading to the disappearance of the first peak.

4. Conclusions

In the present study, the radical cyclization reaction in the aqueous environment by Yorimitsu *et al.* is revisited using the RISM-SCF-cSED method, a hybrid quantum chemistry and statistical mechanics theory for molecular liquids. Considering the microscopic solvation effect, the barrier height from the intermediate E-rot was examined. We found that the barrier height of the forward reaction, *i.e.*, the cyclization step is lowered by the solvation effect, especially in water. While solvation sensitively affects the energy level, the difference between water and DMSO solvents is clearly shown. Namely, the reaction in the aqueous environment is more stabilized. At the same time, the electronic structure is not significantly affected by the environment, meaning that the solvation effect is primarily important. From the analysis of RDFs, typical hydrogen bonding is formed between the oxygen atoms of the radical and hydrogen in water.

Although the oligomerization of radical species is suggested in the original report, the present work focuses on the solvation effect of a unimolecular reaction corresponding to the di-

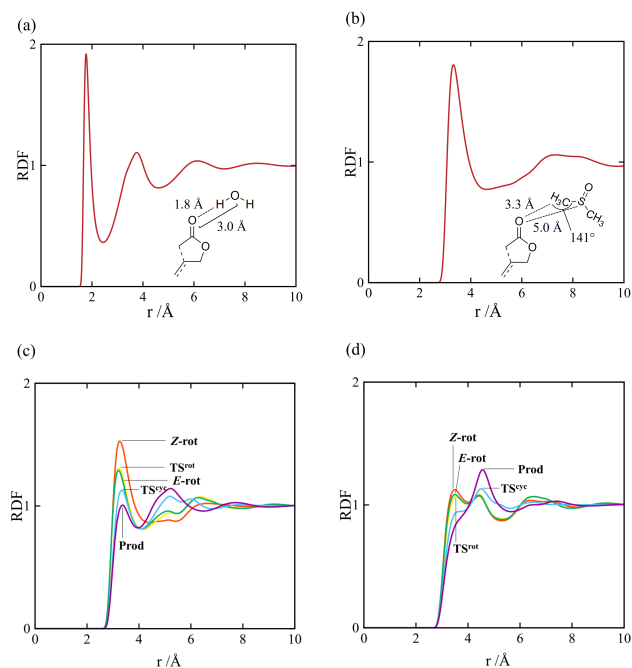


Figure 4: The RDFs of (a) H atoms in water solvent and (b) CH₃ groups in DMSO solvent around the carbonyl O atom (O9) of the solute molecule in TS^{sc} and the change in RDF of O atoms in water around (c) C1 atom and (d) C5 atom during the C1-C5 bond formation.

lute limit condition. Further investigation might be desirable to grasp the overall picture of the phenomenon more accurately.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials to "Unique solvent effect of water in radical cyclization reaction"

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Table S1: The selected bond lengths (Å) of optimised structures in the isolated state and in aqueous phase calculated by the PCM.

(a) Z-rot			(b) TS ^{rot}		
	isolated state	aqueous phase		isolated state	aqueous phase
C1–C2	1.448	1.447	C1–C2	1.440	1.437
C2–O3	1.364	1.359	C2–O3	1.384	1.381
O3–C4	1.449	1.452	O3–C4	1.443	1.452
C4–C5	1.502	1.501	C4–C5	1.503	1.501
C5–C6	1.332	1.333	C5–C6	1.333	1.334
C2–O9	1.223	1.227	C2–O9	1.222	1.227

(c) E-rot			(d) TS ^{cyc}		
	isolated state	aqueous phase		isolated state	aqueous phase
C1–C2	1.448	1.447	C1–C2	1.471	1.465
C2–O3	1.367	1.360	C2–O3	1.368	1.361
O3–C4	1.438	1.449	O3–C4	1.435	1.445
C4–C5	1.503	1.501	C4–C5	1.513	1.512
C5–C6	1.333	1.334	C5–C6	1.362	1.363
C2–O9	1.222	1.229	C2–O9	1.211	1.220
			C5...C1	2.262	2.260

(e) Prod		
	isolated state	aqueous phase
C1–C2	1.525	1.519
C2–O3	1.367	1.358
O3–C4	1.439	1.450
C4–C5	1.550	1.548
C5–C6	1.486	1.486
C2–O9	1.202	1.210
C5–C1	1.548	1.519

Table S2: Relative energy of Z-(allyloxycarbonyl)methyl radical cyclization reaction and the activation barriers in the gas phase calculated by B3LYP, CCSD, and CCSD(T) with 6-31G(d) basis sets and MP2 with 6-311G(d,p) basis sets using optimized geometries with B3LYP/6-31G(d) (in kcal/mol).

	Z-rot	TS ^{rot}	E-rot	TS ^{cyc}	Prod	E_a^{rot}	E_a^{cyc}	ΔE_a
B3LYP/6-31G(d)	0.00	11.38	6.98	14.29	-12.36	4.41	7.31	2.91
CCSD/6-31G(d)	0.00	11.80	7.93	17.57	-14.25	3.87	9.64	5.77
CCSD(T)/6-31G(d)	0.00	12.10	7.93	16.53	-14.05	4.17	8.60	4.43
B3LYP/6-311G(d,p)	0.00	11.65	7.41	15.20	-10.17	4.24	7.79	3.55
MP2/6-311G(d,p)	0.00	15.92	10.56	20.67	-19.24	5.37	10.12	4.75

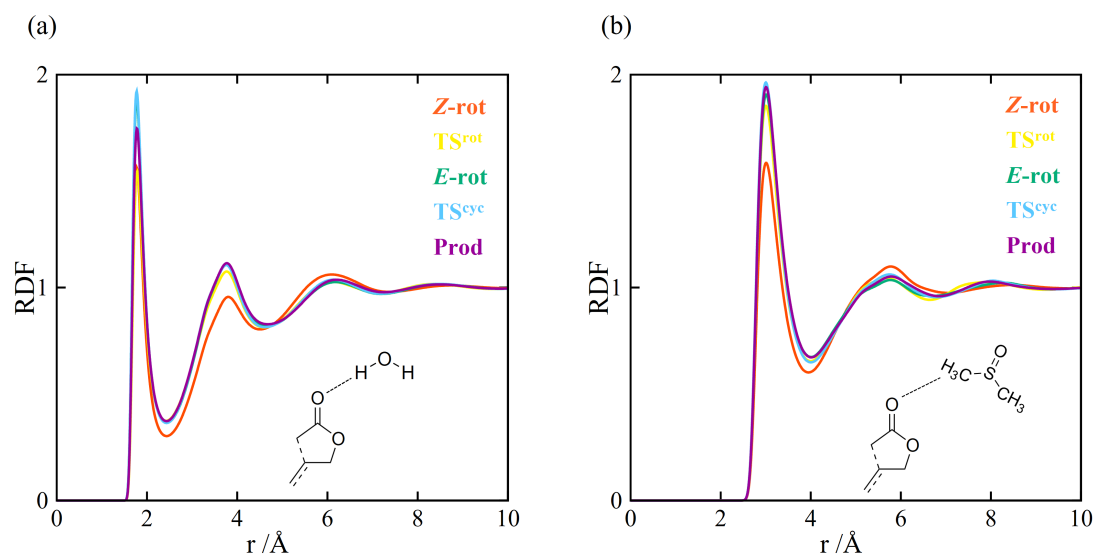


Figure S1: The change in RDFs of (a) H atoms in water solvent and (b) CH₃ groups in DMSO solvent around the carbonyl O atom (O9) of the solute molecule in the reaction process.