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## Powerful Solvent Effect of Water in Radical Reaction: Triethylborane-Induced Atom-Transfer Radical Cyclization in Water

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**Abstract:** Triethylborane-induced atom-transfer radical cyclization of iodo acetals and iodoacetates in water is described. Radical cyclization of iodo acetal proceeded smoothly both in aqueous methanol and in water. Atom-transfer radical cyclization of allyl iodoacetate (**3a**) is much more efficient in water than in benzene or hexane. For instance, treatment of **3a** with triethylborane in benzene or hexane at room temperature did not yield the desired lactone. In contrast, **3a** cyclized much more smoothly in water and yielded the corresponding  $\gamma$ -lactone in high yield. The remarkable solvent effect of water was observed in this reaction, although the medium effect is believed to be small in radical reactions. Powerful solvent effects also operate in the preparation of medium- and large-ring lactones. Water as a reaction solvent strikingly promoted the cyclization reaction of large-membered rings. Stirring a solution of 3,6-dioxa-8-nonyl iodoacetate in water in the presence of triethylborane at 25 °C for 10 h provided a 12-membered ring product, 4-iodo-6,9-dioxa-11-undecanolide, in 84% yield. On the other hand, reaction in benzene afforded the lactone in only 22% yield. Ab initio calculations were conducted to reveal the origin of the solvent effect of water in the cyclization of allyl iodoacetate. Calculations with the SCRF/CPCM option indicate that the large dielectric constant of water lowers the barrier not only to rotation from the *Z*-rotamer to the *E*-rotamer that can cyclize but also to cyclization constructing the  $\gamma$ -lactone framework. Moreover, the high cohesive energy density of water also effects acceleration of the cyclization because water forces a decrease in the volume of the reactant.

### Introduction

Water is an interesting solvent in organic synthesis because water is cheap, nontoxic, nonflammable, and is expected to show extraordinary solvent effects. It is well-known that water is the solvent of choice for reactions that go through a polar transition state, such as  $S_N1$  reactions, because of the highly polar nature of water that stabilizes a polar substance. Recently, new aspects of the influence of water have been explored, and organic reactions in aqueous media have been rediscovered.<sup>1</sup> Breslow has found that the nonpolar Diels–Alder reaction is strongly

accelerated in water.<sup>2</sup> Claisen rearrangement is another example that illustrates the influence of water on pericyclic reactions.<sup>3</sup> It is established that this rate enhancement is due to the large negative value of the activation volume in the Diels–Alder reaction and that water plays a key role in the acceleration by

(1) (a) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; John Wiley & Sons: New York, 1997. (b) Grieco, P. A. *Organic Synthesis in Water*; Blackie Academic & Professional, London, 1998. (c) Lubineau, A.; Auge, J. In *Modern Solvents in Organic Synthesis*; Knochel, P., Ed.; Springer-Verlag: Berlin Heidelberg, 1999. (d) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023–2035.

(2) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816–7818. For review, see: (a) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159–164. (b) Grieco, P. A. *Aldrichim. Acta* **1991**, *24*, 59–66.

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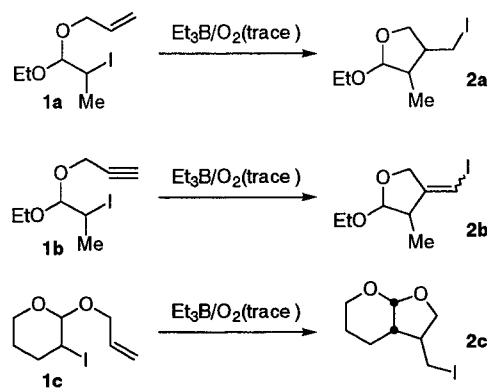
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contracting the volume of a substrate. For ionic reactions, Barbier-type allylation of aldehydes mediated by tin is accelerated in water.<sup>4</sup> In the case of zinc, the yields of the allylated products are improved compared to allylation in organic solvents.<sup>5</sup> Reactions by indium in water have also been developed, and an efficient synthesis of (+)-3-deoxy-D-glycero-D-galacto-nonulosonic acid (KDN) was achieved by applying indium-mediated allylation in water starting with mannose.<sup>6</sup> Lubineau reported that the Mukaiyama aldol reaction was carried out in aqueous solvents without any acid catalyst.<sup>7</sup> The crossed aldol products showed slight syn diastereoselectivity, which was the same as when this reaction was carried out in an organic solvent under high pressure. Lanthanide triflate-catalyzed Mukaiyama aldol reactions in water have also been actively investigated.<sup>8</sup>

On the other hand, radical reactions in water are rare in organic synthesis<sup>9</sup> and remain to be studied. In each case reported, no solvent effects were observed. In general, a medium effect in radical reactions is believed to be almost negligible, and little attention has been paid to the solvent that is employed for radical reactions.<sup>10</sup> We have been exploring the usefulness of water as a solvent in radical reactions.<sup>11</sup> Here we wish to report a triethylborane-induced radical cyclization reaction in water.<sup>12</sup> In the course of our study, a remarkable solvent effect was observed, especially in the cyclization of allyl iodoacetate in water. The cyclization reaction in water gave the desired lactone in higher yield. However, in organic solvents, radical oligomerization or polymerization predominantly occurred, and the desired lactone was poorly obtained. The successful radical lactonization proved unique to an aqueous medium. The results of ab initio calculations disclosing the origin of this solvent effect are also described.

**Preparation of a Methanol Solution of Triethylborane.** To examine radical cyclization in aqueous media, we chose triethylborane as a radical initiator,<sup>13</sup> and a methanol solution<sup>14</sup>

Scheme 1



Entry	Substrate	Solvent	Yield
1	<b>1a</b>	MeOH/H <sub>2</sub> O=3 mL/1 mL	80% (27/29/5/39)
2	<b>1b</b>	MeOH/H <sub>2</sub> O=3 mL/1 mL	80% (45/29/25/1) <sup>a</sup>
3	<b>1c</b>	MeOH/H <sub>2</sub> O=3 mL/1 mL	75% (88/12)
4	<b>1a</b>	H <sub>2</sub> O 10 mL	73% (24/36/7/33)
5	<b>1b</b>	H <sub>2</sub> O 10 mL	83% (43/34/22/2) <sup>a</sup>
6	<b>1c</b>	H <sub>2</sub> O 10 mL	86% (87/13)
7	<b>1a</b>	benzene 3 mL	71% (30/37/4/29)
8	<b>1b</b>	benzene 3 mL	80% (40/39/20/1) <sup>a</sup>
9	<b>1c</b>	benzene 3 mL	80% (88/12)

a) Additional triethylborane (0.20 mmol) was added (2 h after the reaction had started).

of triethylborane was prepared to be handled easily. The stability of triethylborane in methanol was checked by the examination of the <sup>1</sup>H NMR of a CD<sub>3</sub>OD solution of triethylborane. After standing at ambient temperature for one month, no change was observed in the NMR spectrum. Indeed, the solution worked as well for a few months or longer when it was stored under argon atmosphere.

**Radical Cyclization of Iodo Acetals in Aqueous Methanol or in Water.** First, we chose iodine atom-transfer<sup>15</sup> radical cyclization of iodo acetals in aqueous methanol in order to establish tin-free chemistry<sup>16</sup> (Scheme 1). For example, iodo acetal **1a** (1.0 mmol) was dissolved in aqueous methanol (MeOH/H<sub>2</sub>O = 3/1), and triethylborane in methanol (1.0 M, 0.1 mmol, 0.1 mL) was added to the homogeneous solution under argon atmosphere.<sup>17</sup> After being stirred for 2 h, the reaction mixture was extracted and concentrated, followed by silica gel column purification to afford the corresponding tetrahydrofuran derivative **2a** in 80% yield. This success prompted us to perform this reaction in water, in which a heterogeneous reaction medium was formed. Triethylborane in methanol (1.0 M, 0.1 mmol, 0.1 mL) was added to the suspension of **1a** in water (1.0 mmol in 10 mL), and the mixture was stirred vigorously for 2 h. An extractive workup and

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(17) The reaction was performed in a reaction flask equipped with a toy balloon that was filled with argon. Oxygen, which is necessary to produce an ethyl radical from triethylborane, could penetrate the balloon easily, and the concentration of oxygen in the balloon reached 10% after 12 h. Alternatively, air could be introduced with a syringe (2 mL) every 30 min (3 times) after an addition of triethylborane when the flask was kept strictly under argon atmosphere.

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(10) (a) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH Verlagsgesellschaft mbH: Weinheim, 1996. (b) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React.* **1996**, *48*, 301–856.

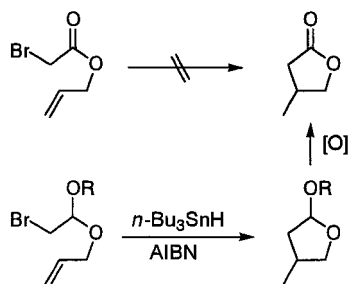
(11) (a) Nakamura, T.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Synlett* **1998**, 1351–1352. (b) Yorimitsu, H.; Wakabayashi, K.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **1999**, *40*, 519–522. (c) Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Chem. Lett.* **2000**, 104–105.

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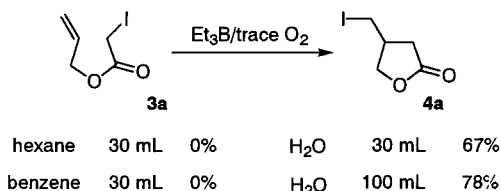
(13) (a) Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547–2548. (b) Nozaki, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1989**, *30*, 923–933.

(14) An attempt to prepare a homogeneous aqueous solution of Et<sub>3</sub>B resulted in failure. Et<sub>3</sub>B floated on the water.

## Scheme 2



## Scheme 3

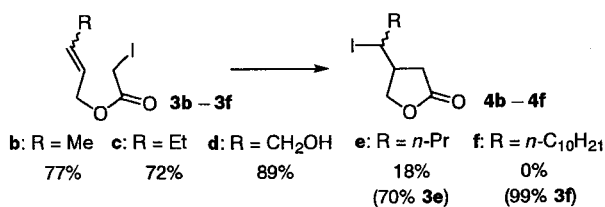


purification provided **2a** in 73% yield. Only a small amount of methanol (0.1 mL) was used in this reaction. We observed a slight difference with respect to stereoselectivity as compared to the reaction performed in benzene, in aqueous methanol, and in water.<sup>18</sup>

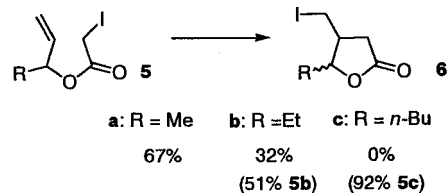
**Radical Cyclization of Allyl Iodoacetate and Its Derivatives.** Next, we focused on atom-transfer radical cyclization of allyl iodoacetate. The indirect halo acetal method was developed by Stork<sup>19</sup> and Ueno<sup>20</sup> because direct cyclization of  $\alpha$ -halo esters into  $\gamma$ -butyrolactones is an inefficient process.<sup>21</sup> Lactones are usually produced from this strategy by oxidation of the products prepared from radical cyclization of bromo acetal, as shown in Scheme 2. Indeed, treatment of allyl iodoacetate **3a** with triethylborane in benzene or hexane at room temperature yielded no lactone **4a** (Scheme 3). The iodide was consumed, and many products of high molecular weight were formed. In contrast, in water, **3a** cyclized much more smoothly and yielded lactone **4a** in high yield. Treatment of allyl iodoacetate **3a** (1.0 mmol) in water (30 mL) with triethylborane (1.0 M methanol solution, 0.1 mL, 0.1 mmol) at 25 °C for 3 h provided **4a** in 67% yield. Furthermore, the yield of **4a** increased to 78% at lower concentration [0.01 M, **3a** (1.0 mmol)/H<sub>2</sub>O (100 mL)].

This powerful solvent effect also operates in a related system (Scheme 4). Crotyl iodoacetate **3b** and 2-pentenyl iodoacetate

## Scheme 4



## Scheme 5



**3c** provided the corresponding lactones **4b** and **4c** in 77% and 72% yield, respectively. 4-Hydroxy-2-butenyl iodoacetate **3d** also yielded  $\gamma$ -butyrolactone **4d** in good yield (89%). In contrast, iodoacetate **3e**, which has a longer alkyl substituent (propyl group) on the terminal olefinic carbon, afforded the corresponding lactone **4e** in only 18% yield after stirring for 12 h upon treatment with triethylborane. More than one-half of the iodide **3e** (70%) remained unchanged at the end of the reaction. Moreover, 2-tridecenyl iodoacetate **3f** provided no cyclized  $\gamma$ -lactone **4f**, and **3f** was recovered completely. Similar results were obtained when **5a**, **5b**, and **5c** were employed as substrates (Scheme 5). Whereas **5a** provided the corresponding lactone **6a** in 67% yield, **5c** did not afford any lactone **6c**, and **5c** was recovered unchanged.<sup>22</sup> This favorable solvent effect of water was revealed by using ab initio calculation (vide infra).

3-Butenyl iodoacetate **7** (1.0 mmol) yielded  $\delta$ -lactone **8**, which is generated through 6-exo cyclization, in 42% yield upon treatment with triethylborane in water (30 mL). Again, the yield of **8** increased to 70% at lower concentration [0.01 M, **7** (1.0 mmol)/H<sub>2</sub>O (100 mL)].

Water was superior to hexane or benzene in the case of the reaction of  $\alpha$ -iodo ketone **9**, 1-iodo-5-hexen-2-one, which underwent 6-endo cyclization to afford 4-iodocyclohexanone (**10**), as previously reported by Curran and Chang.<sup>23</sup>

**Radical Cyclization to Give Medium- and Large-Ring Lactone in Water.** Construction of medium and large rings via a radical process is challenging work.<sup>24,25</sup> We examined the preparation of medium-ring lactones (Scheme 8). Treatment of  $\alpha$ -iodo ester **11** (1.0 mmol) with triethylborane (0.1 mmol) in

(18) We could not elucidate what the differences were because separation of diastereomers by silica gel column chromatography was difficult.

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(21) Direct approaches to lactones with variation of substituents, which brings about the Thorpe–Ingold effect, and reaction conditions have been reported. (a) Surzur, J.-M.; Bertrand, M. P. *Pure Appl. Chem.* **1988**, *60*, 1659–1668. (b) Curran, D. P.; Chang C.-T. *Tetrahedron Lett.* **1987**, *28*, 2477–2480. (c) Oumar-Mahamat, H.; Moustrou, C.; Surzur, J.-M.; Bertrand, M. P. *J. Org. Chem.* **1989**, *54*, 5684–5688. (d) Belletire, J. L.; Mahmoodi, N. O. *Tetrahedron Lett.* **1989**, *30*, 4363–4366. (e) Lee, E.; Ko, S. B.; Jung, K. W. *Tetrahedron Lett.* **1989**, *30*, 827–828. (f) Barth, F.; O–Yang, C. *Tetrahedron Lett.* **1990**, *31*, 1121–1124. (g) Hanessian, S.; Di Fabo, R.; Marcoux, J.-F.; Prud'homme, M. *J. Org. Chem.* **1990**, *55*, 3436–3438. (h) Curran, D. P.; Tamine, J. *J. Org. Chem.* **1991**, *56*, 2746–2750. (i) Clough, J. M.; Pattenden, G.; Wight, P. G. *Tetrahedron Lett.* **1989**, *30*, 7469–7472. (j) Pirrung, F. O. H.; Steaman, W. J. M.; Hiemstra, H.; Speckamp, W. N.; Kaptein, B.; Boesten, W. H. J.; Schoemaker, H. E.; Kamphuis, J. *Tetrahedron Lett.* **1992**, *33*, 5141–5144. (k) Lee, E.; Yoon, C. H.; Lee, T. H. *J. Am. Chem. Soc.* **1992**, *114*, 10981–10982.

(22) The yields of lactone might be parallel to the solubility of  $\alpha$ -iodo ester in water. The solubility of **1a–1f**, **3a**, and **3b** is: **1a**,  $1.0 \times 10^{-2}$  M; **1b**,  $4.4 \times 10^{-3}$  M; **1c**,  $1.4 \times 10^{-3}$  M; **1d**,  $1.7 \times 10^{-1}$  M; **1e**,  $4.0 \times 10^{-4}$  M; **1f**,  $<1.0 \times 10^{-4}$  M; **3a**,  $5.1 \times 10^{-3}$  M; and **3b**,  $4.0 \times 10^{-4}$  M. The solubility of  $\alpha$ -iodo ester in water was roughly determined as follows: water (100 mL) was added to a 200-mL Erlenmeyer flask containing  $\alpha$ -iodo ester (2.0 mmol) and the mixture was stirred vigorously for 30 min. The resulting mixture stood undisturbed for 30 min. During that time, the  $\alpha$ -iodo ester that did not dissolve in water sank to the bottom of the flask. Half of the volume of the water (50 mL) was taken out from the water layer with a syringe and the  $\alpha$ -iodo ester which dissolved in the water was extracted using ethyl acetate ( $3 \times 20$  mL). The remaining  $\alpha$ -iodo ester, after evaporation of the combined organic layer, was weighed.

(23) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140–3157. They obtained 4-iodocyclohexanone in 56% yield under irradiation with a sunlamp in the presence of hexamethylditin.

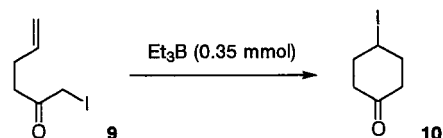
(24) (a) Lee, E.; Yoon, C. H.; Lee, T. H. *J. Am. Chem. Soc.* **1992**, *114*, 10981–10982. (b) Lee, E.; Yoon, C. H.; Lee, T. H.; Kim, S. Y.; Ha, T. J.; Sung, Y.-S.; Park, S.-H.; Lee, S. *J. Am. Chem. Soc.* **1998**, *120*, 7469–7478.

(25) For a recent review for medium size ring: Rousseau, G. *Tetrahedron* **1995**, *51*, 2777–2849.

## Scheme 6

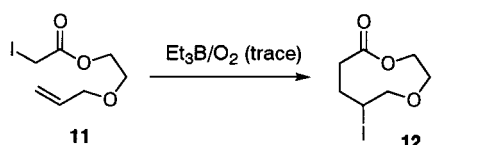


## Scheme 7

hexane 20 mL 6% (70% **9**)benzene 20 mL 9% (66% **9**)

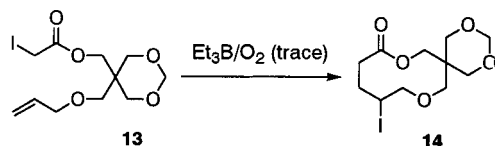
water 20 mL 59%

## Scheme 8

MeOH 20 mL 0% MeOH / H<sub>2</sub>O 18/2 mL 12%

hexane 20 mL 10% 10/10 mL 36%

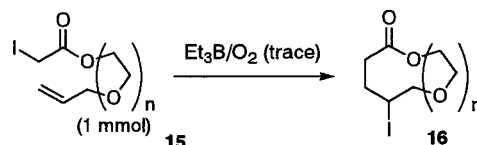
benzene 100 mL 23% 7/13 mL 46%

H<sub>2</sub>O 20 mL 33% 5/15 mL 42%H<sub>2</sub>O 100 mL 69% 2/18 mL 26%benzene 20 mL 80% H<sub>2</sub>O 20 mL 75%

water (100 mL) provided nine-membered lactone **12** in 69% yield. Conversely, the atom-transfer cyclization reaction of **11** in benzene (100 mL) afforded the corresponding lactone in only 27% yield. Interestingly, using the ratio methanol/water = 7/13 as a solvent yielded the lactone in the highest yield among the varying ratios of water in aqueous methanol. The endo cyclization product was obtained as a single isomer in each solvent without contamination by an exo product. In the case of cyclization of **13**, **14** was obtained in good yield both in benzene and in water.

Scheme 9 shows that water as a reaction solvent strikingly promoted the cyclization of a large-membered ring. Stirring a solution of **15a** (1.0 mmol) in water (30 mL) in the presence of  $\text{Et}_3\text{B}$  (1.0 M MeOH solution, 0.1 mL, 0.1 mmol) at 25 °C for 10 h provided a 12-membered ring **16a** in 56% yield. In contrast, the reaction of **15a** in benzene in the presence of a hexane solution of triethylborane (1.0 M, 0.1 mL, 0.1 mmol) afforded the lactone in only 22% yield, along with the recovered starting material **15a** (78%). Similar results were obtained in the reaction of **15b** ( $n = 3$ ) and **15c** ( $n = 4$ ). The exact role of water in promoting these radical reactions is not clear at this stage. We assume that a hydrogen bond to oxygen in the carbonyl group

## Scheme 9

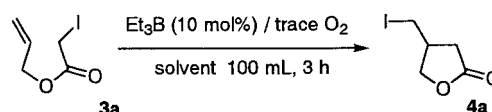


	benzene 20 mL	water 20 mL	water 100 mL
<b>15a</b> $n = 2$	10 h, 22% (78%) <sup>a</sup>	10 h, 56%	8 h, 84%
<b>15b</b> $n = 3$	3 h, 41% (43%) <sup>a</sup>	3 h, 75%	10 h, 86% <sup>b</sup>
<b>15c</b> $n = 4$	6 h, 14% (83%) <sup>a</sup>	6 h, 70%	4 h, 98%

a) Starting material was recovered.

b)  $\text{Et}_3\text{B}$  was added twice (0.05 mmol x 2).

**Table 1.** Radical Cyclization of Allyl Iodoacetate in Various Solvents



solvent	yield (%)	dielectric constant <sup>a</sup>	$E_T^b$ (kcal/mol)	cohesive energy density <sup>c</sup> (cal/mol <sup>3</sup> )
water	78	78.39	63.1	550.2
DMSO	37	46.45	45.1	168.6
formamide	24	111.0	55.8	376.4
DMF	13	36.71	43.2	139.2
acetonitrile	13	35.94	45.6	139.2
methanol	6	32.66	55.4	208.8
2,2,2-trifluoroethanol	18	26.67	59.8	
ethanol	3	24.55	51.9	161.3
THF	<1	7.58	37.4	86.9
dichloromethane	<1	8.93	40.7	
benzene	<1	2.27	34.3	83.7
hexane	<1	1.88	31.0	52.4

<sup>a</sup> Reproduced from ref 27. <sup>b</sup> Reproduced from ref 28. <sup>c</sup> Reproduced from ref 29.

could be formed to activate the  $\alpha$ -carbonylmethyl radical<sup>26</sup> and that hydrophobic interaction could also accelerate the cyclization.

**Ab Initio Calculation and Discussion.** As described above, radical cyclization of allyl iodoacetate is much easier in water than it is in benzene or hexane. To investigate the solvent effect in detail, the cyclization was examined in various solvents. Table 1 summarizes the results in addition to the dielectric constant<sup>27</sup>,  $E_T(30)$  polarity parameter,<sup>28</sup> and cohesive energy density<sup>29</sup> for various solvents. In each case, the byproduct was an oligomer or polymer of allyl iodoacetate. It is obvious that polar solvents such as DMSO, DMF, or  $\text{CH}_3\text{CN}$  yielded the lactone in better yield than nonpolar solvents, that is, benzene, hexane, and dichloromethane. More interestingly, water was found to be an outstanding solvent among these solvents, even taking the polar nature of water into account.

It is established that the rate-determining step is the cyclization step in the iodine atom-transfer radical reaction, and iodine transfer is so rapid that we need not consider the solvent effect in the atom-transfer step.<sup>30</sup> To clarify the origin of the solvent effect, we carried out ab initio calculations on the cyclization of the (allyloxycarbonyl)methyl radical using the Gaussian 98

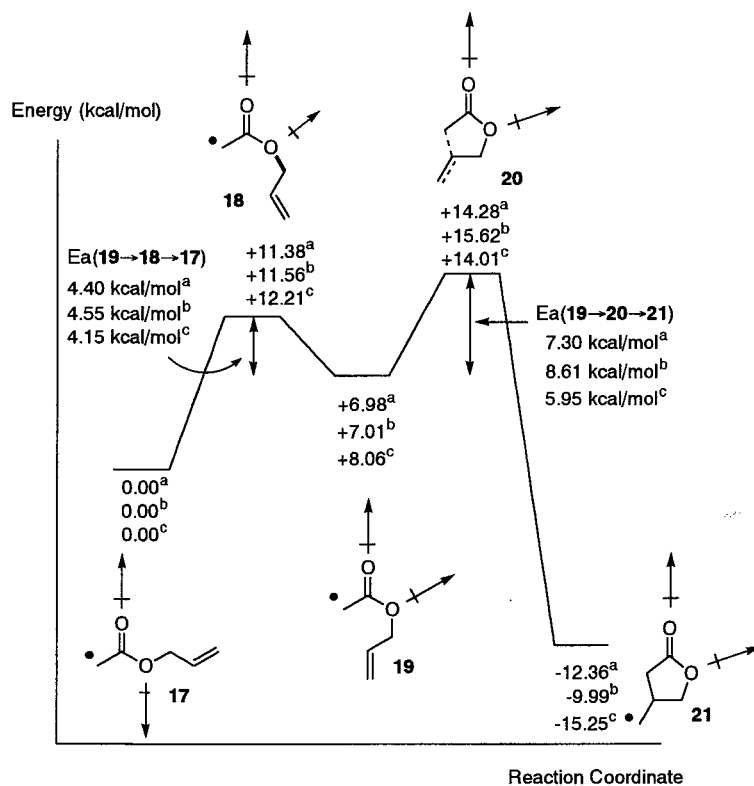
(26) For a recent review for use of a Lewis acid in radical reaction, see: Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2562–2579.

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**Scheme 10.** Calculated Energy Profile for the Transformation of the Z-(allyloxycarbonyl)methyl Radical into Its Cyclized Form in a Vacuum<sup>d</sup>

	17	18	19	20	21
total energy (au)	-345.11641 <sup>a</sup>	-345.09828 <sup>a</sup>	-345.10529 <sup>a</sup>	-345.09365 <sup>a</sup>	-345.13611 <sup>a</sup>
	-345.03972 <sup>b</sup>	-345.02129 <sup>b</sup>	-345.02854 <sup>b</sup>	-345.01483 <sup>b</sup>	-345.05563 <sup>b</sup>
	-344.12488 <sup>c</sup>	-344.10543 <sup>c</sup>	-344.11204 <sup>c</sup>	-344.10257 <sup>c</sup>	-344.14919 <sup>c</sup>
relative energy (kcal/mol)	0.00 <sup>a</sup>	11.38 <sup>a</sup>	6.98 <sup>a</sup>	14.28 <sup>a</sup>	-12.36 <sup>a</sup>
	0.00 <sup>b</sup>	11.56 <sup>b</sup>	7.01 <sup>b</sup>	15.62 <sup>b</sup>	-9.99 <sup>b</sup>
	0.00 <sup>c</sup>	12.21 <sup>c</sup>	8.06 <sup>c</sup>	14.01 <sup>c</sup>	-15.25 <sup>c</sup>
dipole moment (Debye)	1.6433 <sup>a</sup>	3.6482 <sup>a</sup>	4.4132 <sup>a</sup>	4.5977 <sup>a</sup>	4.2826 <sup>a</sup>
	1.8288 <sup>c</sup>	3.9707 <sup>c</sup>	4.9190 <sup>c</sup>	5.2192 <sup>c</sup>	5.1930 <sup>c</sup>

a) B3LYP/6-31G\* without zero-point energy and thermal energy corrections.

b) B3LYP/6-31G\* with zero-point energy and thermal energy corrections.

c) PMP2/6-31+G\*\*//UHF/6-31G\* without zero-point energy and thermal energy corrections.

<sup>d</sup> An arrow with a crossed end symbolizes a dipole moment that makes a large contribution to the net dipole moment of a molecule.

program.<sup>31</sup> All structures were optimized with Becke's three-parameter hybrid exchange functional and the Lee–Yang–Parr correlation functional (B3LYP)<sup>32</sup> and the 6-31G\* basis set. Zero-

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point energy and thermal energy corrections were made for all of the calculated energies, and the sums of electronic and thermal free energies were obtained. The zero-point energies were not scaled, and the enthalpic corrections were made at 298.150 K. To confirm whether the calculations at the B3LYP level are proper or not, additional calculations were made at the PMP2 level using the 6-31+G\*\* basis set at the optimized UHF/6-31G\* geometry. The results of these calculations in a vacuum are shown in Scheme 10. Three calculations show similar results, although some numeric differences are observed. Therefore, we choose to discuss the result obtained from the B3LYP calculations with zero-point energy and thermal energy corrections. It is known that the Z-rotamer **17** is much more stable than the E-rotamer **19** and that most of the ester molecules are present

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**Table 2.** Calculated Relative Energy (kcal/mol) for the Transformation of the Z-(allyloxycarbonyl)methyl Radical into Its Cyclized Form in Various Solvents Using the SCRf/CPCM Option

solvent	17	18	19	20	21	$E_a$		$\Delta E_a^c$
						(19→18→17)	(19→20→21)	
water	0.00 <sup>a</sup>	8.81 <sup>a</sup>	3.04 <sup>a</sup>	9.13 <sup>a</sup>	-19.77 <sup>a</sup>	5.77 <sup>a</sup>	6.09 <sup>a</sup>	0.34 <sup>a</sup>
	0.00 <sup>b</sup>	9.82 <sup>b</sup>	7.35 <sup>b</sup>	9.59 <sup>b</sup>	-20.29 <sup>b</sup>	2.47 <sup>b</sup>	2.24 <sup>b</sup>	-0.23 <sup>b</sup>
DMSO	0.00 <sup>a</sup>	9.17 <sup>a</sup>	3.86 <sup>a</sup>	9.87 <sup>a</sup>	-18.71 <sup>a</sup>	5.31 <sup>a</sup>	6.01 <sup>a</sup>	0.70 <sup>a</sup>
	0.00 <sup>b</sup>	10.54 <sup>b</sup>	5.36 <sup>b</sup>	10.37 <sup>b</sup>	-20.13 <sup>b</sup>	5.18 <sup>b</sup>	5.01 <sup>b</sup>	-0.17 <sup>b</sup>
methanol	0.00 <sup>a</sup>	9.19 <sup>a</sup>	3.48 <sup>a</sup>	9.83 <sup>a</sup>	-18.75 <sup>a</sup>	5.71 <sup>a</sup>	6.35 <sup>a</sup>	0.64 <sup>a</sup>
	0.00 <sup>b</sup>	9.87 <sup>b</sup>	4.57 <sup>b</sup>	9.99 <sup>b</sup>	-20.56 <sup>b</sup>	5.30 <sup>b</sup>	5.42 <sup>b</sup>	0.12 <sup>b</sup>
dichloroethane	0.00 <sup>a</sup>	9.54 <sup>a</sup>	4.36 <sup>a</sup>	10.77 <sup>a</sup>	-17.89 <sup>a</sup>	5.18 <sup>a</sup>	6.41 <sup>a</sup>	1.23 <sup>a</sup>
	0.00 <sup>b</sup>	10.72 <sup>b</sup>	5.69 <sup>b</sup>	10.87 <sup>b</sup>	-19.78 <sup>b</sup>	5.03 <sup>b</sup>	5.18 <sup>b</sup>	0.15 <sup>b</sup>
benzene	0.00 <sup>a</sup>	9.87 <sup>a</sup>	4.91 <sup>a</sup>	11.34 <sup>a</sup>	-16.86	4.96 <sup>a</sup>	6.43 <sup>a</sup>	1.47 <sup>a</sup>
	0.00 <sup>b</sup>	11.33 <sup>b</sup>	6.56 <sup>b</sup>	11.81 <sup>b</sup>	-18.22 <sup>b</sup>	4.77 <sup>b</sup>	5.25 <sup>b</sup>	0.48 <sup>b</sup>

<sup>a</sup> B3LYP/6-31G\* <sup>b</sup>PMP2/6-31+G\*\*//UHF/6-31G\* <sup>c</sup> $\Delta E_a = E_a(19 \rightarrow 20 \rightarrow 21) - E_a(19 \rightarrow 18 \rightarrow 17)$

as the Z-rotamer.<sup>33</sup> The more stable Z-rotamer is topologically prohibited from cyclizing, and conversion into the E-rotamer is essential for the cyclization. At the B3LYP/6-31G\* level with the zero-point energy and thermal energy corrections, the Z-rotamer is more stable than the E-rotamer by 7.01 kcal/mol. The activation barrier to rotation from **17** to **19** [ $E_a(17 \rightarrow 18 \rightarrow 19)$ ,<sup>34</sup> 11.56 kcal/mol] is higher than that to 5-exo cyclization from **19** to **21** [ $E_a(19 \rightarrow 20 \rightarrow 21)$ , 8.61 kcal/mol]. Moreover, the activation barrier to rotation from **19** to **17** [ $E_a(19 \rightarrow 18 \rightarrow 17)$ ] is calculated to be 4.55 kcal/mol, which is much smaller than  $E_a(19 \rightarrow 20 \rightarrow 21)$ . Therefore, even when **19** manages to be formed through the high activation barrier, the reverse path, **19**→**18**→**17**, proceeds predominantly, the cyclization fails, and intermolecular addition, providing oligomers, takes place. These results show that the cyclization of allyl iodoacetate is difficult because (1)  $E_a(17 \rightarrow 18 \rightarrow 19)$  is large for the short-lived **17** to surmount the barrier to rotation smoothly; (2)  $E_a(19 \rightarrow 20 \rightarrow 21)$  is larger than  $E_a(19 \rightarrow 18 \rightarrow 17)$ ; (3) the lifetime of radical species **17** and **19** is too short to allow cyclization, because competitive intermolecular radical addition occurs. The results shown in Table 1 imply that the use of water as a solvent could overcome these difficulties.

The dipole moment is an important factor in considering the solvent effect, because a molecule with a larger dipole moment is more stabilized in a polar solvent. Scheme 10 shows that the net dipole moment of the radical species increases, in particular, as the rotation of the ester bond proceeds. Therefore, it is assumed that polar solvents probably promote the overall cyclization reaction.<sup>35</sup>

To confirm this assumption, polarized-continuum-model calculations using the polarizable conductor calculation model based on the self-consistent reaction field theory (SCRf/CPCM)<sup>36</sup> were performed at the B3LYP/6-31G\* and PMP2/6-31+G\*\*//UHF/6-31G\* levels on the cyclization of the (allyloxycarbonyl)methyl radical to estimate how **17**→**21** are stabilized in continuum with the dielectric constant as a modeled solvent. The results, performed in water, DMSO, methanol, dichloromethane, and benzene are summarized in Table 2. The results are as expected; that is, a more polar solvent favors the

reaction path leading to the cyclized form **21**. We take the results in benzene and in water at the B3LYP/6-31G\* level into account and get an easy explanation for the calculated solvent effect on the radical cyclization of (allyloxycarbonyl)methyl radical. The barriers to rotation from the Z-rotamer to the E-rotamer,  $E_a(17 \rightarrow 18 \rightarrow 19)$ , decrease to 9.87 and 8.81 kcal/mol in benzene and in water, respectively. This means that water stabilizes **18** and **19** more efficiently than it does **17** and that water promotes the rotation from **17** to **19**. Furthermore, in water,  $E_a(19 \rightarrow 18 \rightarrow 17)$  and  $E_a(19 \rightarrow 20 \rightarrow 21)$  are calculated to be 5.77 and 6.09 kcal/mol, respectively. The difference between  $E_a(19 \rightarrow 18 \rightarrow 17)$  and  $E_a(19 \rightarrow 20 \rightarrow 21)$  in water is much smaller (0.32 kcal/mol) than in a gas phase. On the other hand, calculation at the B3LYP/6-31G\* level reveals that  $E_a(19 \rightarrow 20 \rightarrow 21)$  is larger than  $E_a(19 \rightarrow 18 \rightarrow 17)$  by 1.47 kcal/mol in benzene. Therefore, cyclization from **19** to **21** is almost as fast as the undesirable rotation from **19** to **17** is in water, whereas the former is slower than the latter in benzene. The PMP2/6-31+G\*\*//UHF/6-31G\* calculations with the SCRf/CPCM option also lead to the same explanation.  $E_a(17 \rightarrow 18 \rightarrow 19)$  in water is smaller than that in benzene by 1.5 kcal/mol, which supports the same suggestion that interconversion from **17** to **19** is easier in water than it is in benzene, as calculated at the B3LYP/6-31G\* level. Additionally, the PMP2/6-31+G\*\*//UHF/6-31G\* calculations indicate that  $E_a(19 \rightarrow 20 \rightarrow 21)$  is smaller than  $E_a(19 \rightarrow 18 \rightarrow 17)$  by 0.23 kcal/mol and that cyclization from **19** to **21** is preferable to rotation from **19** to **17** in water. Thus, it becomes clear that the large dielectric constant of water promotes both rotation from **17** to **19** and cyclization from **19** to **21**.

Conducting the CPCM method reveals that a larger dielectric constant is favorable in the cyclization of the (allyloxycarbonyl)-methyl radical. However, it is difficult to explain the results of this powerful solvent effect of water that is shown in Table 1 by only the effect of a large dielectric constant. This effect seems too small to account for the dramatic differences between water and other solvents. In the CPCM method, each solvent is modeled as a homogeneous and isotropic continuous medium with a dielectric constant. Hydrogen bonds, which give water some extraordinary characteristics, are not taken into account. To discuss the reaction in water, it is necessary to pay attention to its cohesive energy density. Water, which is known for the

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(34)  $E_a(A \rightarrow B \rightarrow C)$  is defined as an activation energy in starting from A to reach C via a transition state B.

(35) Intramolecular Diels–Alder reaction of 2-furfurylmethyl fumarate was reported, and the strong solvent effect was rationalized with a similar explanation. Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1989**, *111*, 5469–5470.

(36) Barone, V.; Cossi, M. *J. Phys. Chem. A* **1998**, *102*, 1995–2001. They have reported that the calculated solvation energies for neutral molecules in water by a conductor solvent model at both HF and DF levels are in very good agreement with experimental data. Although SCRf calculations using a cavity determined self-consistently from an isodensity surface (SCRf/SCIPCm) were conducted, the calculations failed to converge.

**Table 3.** Calculated Volumes ( $\text{\AA}^3$ ) of **17–21** in Water

V(17)	V(18)	V(19)	V(20)	V(21)
156.67019 <sup>a</sup>	156.54624 <sup>a</sup>	155.32790 <sup>a</sup>	148.28529 <sup>a</sup>	131.65214 <sup>a</sup>
155.95854 <sup>b</sup>	155.88738 <sup>b</sup>	154.61012 <sup>b</sup>	147.73254 <sup>b</sup>	130.69289 <sup>b</sup>

<sup>a</sup> B3LYP/6-31G\*:  $\Delta V^\ddagger = V(\mathbf{20}) - V(\mathbf{19}) = -7.04 \text{ \AA}^3/\text{molecule} = -4.24 \text{ cm}^3/\text{mol}$  <sup>b</sup> PMP2/6-31+G\*\*//UHF6-31G\*:  $\Delta V^\ddagger = V(\mathbf{20}) - V(\mathbf{19}) = -6.88 \text{ \AA}^3/\text{molecule} = -4.14 \text{ cm}^3/\text{mol}$ .

highest cohesive energy density (550.2 cal/cm<sup>3</sup>) among the solvents, due to its hydrogen-bond network, requires the highest energy necessary to form a cavity for a reactant in water. Therefore, a reaction in which the volume of a reactant decreases is strongly accelerated in water in order to occupy the smallest possible volume of a cavity. Rate enhancement in the Diels–Alder reaction in water is suggested to be due to this effect.<sup>1,2</sup> We assumed that this acceleration effect would work in the case of the cyclization of the (allyloxycarbonyl)methyl radical and focused on the volume of each radical **17–21** that appeared in each output file of the SCRFF/CPCM calculation (Table 3). Whereas the rotation step appears to be unrelated to acceleration, ring closure would be strongly enhanced, due to decreasing the volume of the radical. Compound **20** is smaller than **19**; therefore, transition state **20** is more stabilized than **19**, and the activation barrier to cyclization becomes smaller in water than it is in a vacuum. Thus, the cyclization step is accelerated by high cohesive energy, in addition to the electrostatic effect.<sup>37</sup>

Curran and Tamine<sup>21h</sup> reported successful iodine atom-transfer radical cyclization of allyl iodoacetate in the presence of hexabutyliditin under irradiation with a sunlamp in benzene at reflux, although the same reaction failed at room temperature.

(37) Quantitative discussion seems difficult regarding the relationship between the activation volume and rate enhancement. In the case of the Diels–Alder reaction, the value of the decrease in the volume of activation ( $\Delta V^\ddagger$ ) in forming the transition state is between  $-20$  and  $-45 \text{ cm}^3/\text{mol}$ . The value of  $\Delta V^\ddagger$  typically is  $-10 \text{ cm}^3/\text{mol}$  for Cope and Claisen rearrangement. In the present cyclization step,  $\Delta V^\ddagger$  is calculated as  $-4.24 \text{ cm}^3/\text{mol}$  and  $-4.14 \text{ cm}^3/\text{mol}$  at the B3LYP/6-31G\* and PMP2/6-31+G\*\*//UHF/6-31G\* levels of theory, respectively. For the value of  $\Delta V^\ddagger$ , see: van Eldik, R.; Asano, T.; Le Nobel, W. J. *Chem. Rev.* **1989**, *89*, 549–688.

They attributed the success to the higher temperature that induces rapid rotation of the ester bond. Scheme 10 indicates that their speculation is correct. At a higher temperature, (allyloxycarbonyl)methyl radical **17** possesses sufficient energy to surmount the barrier to rotation. *E*-rotamer **19**, some of which have sufficient energy to pass the second barrier to cyclization, can cyclize. The intramolecular cyclization to yield the lactone would predominate the intermolecular radical addition to afford oligomeric products. On the other hand, in our case, a similar reaction was performed in water, even at room temperature, to furnish the lactone in high yield. The solvent effect of water is rationalized from the results of the calculation and is summarized as follows. The large dielectric constant of water reduces the barrier to rotation to make rotation easier than in benzene. Once **17** isomerizes to **19**, the cyclization becomes easier, not only because water has a large dielectric constant, but also because water strongly forces a decrease in the volume of the reactant.

In conclusion, organic chemists can control the reactivity of a carbanion by changing its counterion, solvent, and reaction temperature. In contrast, shifting a reaction path in a radical reaction is more difficult because *free* radicals are active species.<sup>26</sup> The medium effect had been regarded as being negligible. The present study has demonstrated that the solvent is an important variable in free radical chemistry. Water offers control of radical reactions.

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**Supporting Information Available:** Experimental details, characterization data, and the Cartesian coordinates for **17–21** optimized at the B3LYP/6-31G\* and UHF/6-31G\* levels. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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