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How Does Aqueous Solubility of Organic Reactant Affect a Water-Promoted Reaction?

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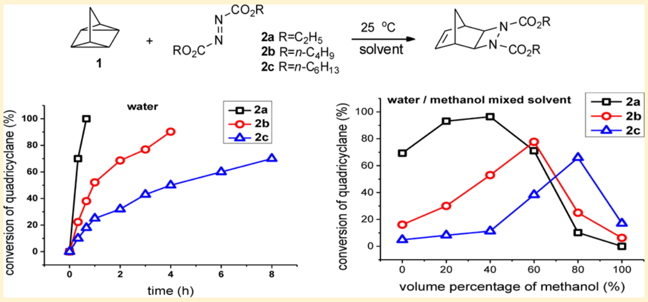
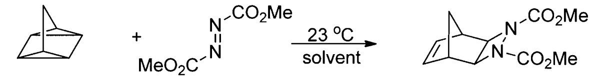
Supporting Information

ABSTRACT: It was widely reported that under the "on water" condition, various water-promoted organic reactions can proceed with very high speed. Thus, it is considered that the aqueous solubility of reactant is not an important issue in these reactions. Three types of water-promoted organic reactions were investigated in the current study to distinguish whether the reaction rate of an aqueous reaction was affected by the aqueous solubilities of the reactants. The results showed that, for a Diels–Alder reaction which was fast under the neat conditions, the aqueous solubilities of reactants had little influence on the reaction. However, for the reactions which proceeded slowly under the neat conditions, such as [2σ+2σ+2π] cycloaddition reactions and epoxide aminolysis reactions, the reactants with good aqueous solubilities proceeded fast in water. Poorly aqueous soluble reactants reacted slowly or did not react under the "on water" condition, and an appropriate amount of organic cosolvent was needed to make the reaction become efficient. This evidence suggested that for these two types of reactions, the dissolution of the reactants in water was required.



INTRODUCTION

In 2005, Sharpless and co-workers reported that several organic reactions, including [2σ+2σ+2π] cycloadditions, ene reactions, Diels–Alder reactions, Claisen rearrangement reactions, and epoxide aminolysis reactions, are much faster in aqueous medium than in organic solvents.[1] The detailed study of the aqueous phase [2σ+2σ+2π] cycloaddition reaction between quadricyclane and dimethyl azodicarboxylate (DMAD) showed that the reaction proceeds fast in heterogeneous suspension (in pure water or in mixed solvents of CH_3OH and H_2O, v:v = 1:3 or 1:1), but slows down considerably in the 3:1 CH_3OH and H_2O mixed solvent in which the reaction system becomes homogeneous (Figure 1). Thus, it is considered that aqueous solubility of organic reactant is not essential to "on water" reactions.



solvent	conc. of the reaction	time to completion
H_2O	4.53 M	10 min
CH_3OH:H_2O = 1:3 (heterogeneous)	4.53 M	10 min
CH_3OH:H_2O = 1:1 (heterogeneous)	4.53 M	10 min
CH_3OH:H_2O = 3:1 (homogeneous)	2 M	4 h

Figure 1. [2σ+2σ+2π] cycloaddition reaction between quadricyclane and dimethyl azodicarboxylate (DMAD) in water and in mixed solvent of water and methanol.

The origin of the great rate-enhancing effect observed under the "on water" condition has drawn great interest in recent years.[2−12] In 2007, Marcus's group applied the model of organic–aqueous interface to explain the "on water" phenomenon.[2] They suggested that there are more free OH groups dangling at the organic–aqueous interface than that in bulk water; thus, the observed highest reaction speed under the "on-water" condition is attributed to the elevated hydrogen-bond activation. In recent years, many reports applied the "on water" catalysis to explain the accelerating effect observed when using water as the reaction medium.[13]

The interfacial catalytic mechanism aroused controversial opinions in 2010. Jørgensen's group reported the quantum and molecular mechanics calculations of the water-promoted Diels–Alder reactions at the vacuum–water interface or in the gas phase.[3] They found the model of two isolated reactants on the water surface leads to a lower degree of catalysis than the fully hydrated reactants, and they concluded that Diels–Alder reactions are accelerated less on the surface of water than in bulk water. Butler and Coyne noticed that reactants with different aqueous solubilities present different reactivities in the aqueous media.[14] Recently, they measured the *endo*/*exo* products ratio for Huisgen cycloadditions to investigate the "in water" and "on water" border.[15] Our previous studies on water-promoted organic reactions also observed strong dependence of reaction rate on the aqueous solubilities of organic reactants.[16]

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Few numbers of organic reactants can totally dissolve in water; thus, for the majority of water-promoted organic reactions, the reactions proceed in a heterogeneous emulsion formed by organic reactants and water. For a heterogeneous aqueous reaction, it might proceed through three possible fashions: (1) "In water" process, that is a small amount of reactants dissolve in water and the reaction occurs; the formed products then dissociate from water. The reaction is a microscopic "in water" process although the reaction appears to be a macroscopic heterogeneous reaction from the beginning to the end. (2) "On water" process, the reaction mainly occurs at the oil−water interface and the heterogeneity of the reaction system is essential to achieving substantial accelerating effect. The heterogeneous emulsion of reactants is gradually transformed to the heterogeneous emulsion of products. (3) "In water" and "on water" reaction pathways present simultaneously, and the contribution of each pathway depends on the reaction type and factors like the aqueous solubilities of the reactants, the concentration of reactants, or the stirring method.

It is very difficult to find a tool to directly study which of the above modes dominates in a certain water-promoted reaction. One possible way to get some information is to detect the relationship between the reaction rates and the aqueous solubilities of the organic reactants. If the reactions proceed as "in water" fashion or the "in water" pathway is predominant, the reaction rates should be exclusively related to the aqueous solubilities of the reactants, i.e. reactants with good aqueous solubilities should react much faster than those having poor aqueous solubilities. If the reaction proceeds as "on water" fashion or the "on water" pathway is predominant, reactants with different aqueous solubilities should have roughly the same reaction rates, or even less aqueous soluble reactants exhibit slightly better reactivity sometimes.

The lack of knowledge about the place where the water-promoted reactions occur makes the full understanding of the catalytic function of water impossible and this also hinders the correct application of water-promoted organic reactions. In the current study, we chose three types of organic reactions which exhibit accelerating effect when the reactions are carried out in water. We prepared a series of reactants that have similar reactivities but varying aqueous solubilities. The conversions of the reactants were recorded to distinguish whether the reaction rates are related to the aqueous solubilities of the reactants. For each type of the above reactions, we also detected the changing of reaction rates when varying the ratio of the binary mixed solvent composed of water and water-miscible organic solvent. The results of the experiments showed that for [2σ+2σ+2π] cycloadditions and epoxide aminolysis reactions, the reaction rates were apparently dependent on the aqueous solubilities of the reactants, but the reactants with different aqueous solubilities proceeded equally fast in Diels−Alder reactions.

RESULTS AND DISCUSSION

Kinetic Study of Aqueous Heterogeneous Reactions. We set a series of reactions under the identical reaction conditions (same amount of reactants and solvent, same reaction temperature, flasks of same size, stir bars of same size, same stirring machine, and same stirring rate) and conducted these identical reactions at different time intervals. The conversion of reactants was subsequently analyzed by GC or NMR technique. For [2σ+2σ+2π] cycloaddition reaction, a series of aqueous reactions containing **2a** (0.6 mmol) and quadricyclane (**1**, 0.5 mmol) in water (12 or 100 mL) were run at 25 °C. At different time intervals, we added acetone (50 or 150 mL) to make the reaction system homogeneous and the conversion of quadricyclane of each reaction was analyzed by GC. By using the same method, we conducted the kinetic studies of **2b** and **2c** in water. For the epoxide-aminolysis reactions, 1,2-epoxyalkane (0.5 mmol) and morpholine (1.0 mmol) were reacted at 85 °C in water (12 mL). For the Diels−Alder reactions, cyclopentadiene (0.6 mmol) and fumarates (0.5 mmol) were reacted at 25 °C in water (12 mL).

The above method was applied to carry out the kinetic studies of reactions in water−organic binary solvent systems. For the [2σ+2σ+2π] cycloadditions of **2a** and **1**, six reactions under the same conditions were carried out separately using **2a** (0.6 mmol) and quadricyclane (**1**, 0.5 mmol) in mixed solvent (12 mL) at different ratios at 25 °C. After 10 min, acetone (50 mL) was added to make the reaction system homogeneous, and the conversion of quadricyclane was measured by GC analysis. The cycloaddition reactions of compounds **2b** and **2c** with **1** were carried out under reaction conditions identical to those for **2a**, but the conversions were measured after 1.5 and 3 h, respectively.

For the epoxide-aminolysis reaction of **5a** in water/1,4-dioxane binary system, six reactions under the same conditions were carried out separately using morpholine (**4**, 1 mmol) and **5a** (0.5 mmol) in mixed solvent (12 mL) with different ratios at 85 °C. After 1 h, acetone (50 mL) was added to make the reaction system homogeneous, and the conversion of **5a** was measured by GC analysis. The reactions of **5b**, **5c**, or **5d** with **4** were carried out under reaction conditions identical to those for **5a**, and the conversions were measured after 2.5, 3.5, and 7 h, respectively.

For the Diels−Alder reaction of **8a** and **7** in the water/THF binary system, six reactions under the same conditions were carried out separately using fumarates (0.5 mmol) and cyclopentadiene (**7**, 0.6 mmol) in mixed solvent (12 mL) with different ratios at 25 °C. After 30 min, the reaction was extracted with ethyl acetate (100 mL) and washed with brine, and the solvents were evaporated in vacuo. The conversion of fumarates was measured by ^{1}H NMR spectroscopy. The reactions of **8b**, **8c**, or **8d** with **7** were carried out under reaction conditions identical to those for **8a**, and the conversions were measured after 30 min, 40 min, and 1 h, respectively.

Reaction Rates of Reactants with Different Aqueous Solubilities. The [2σ+2σ+2π] cycloaddition reaction of quadricyclane with azodicarboxylate was first studied in aqueous medium by Sharpless's group.[1] By prolonging the alkyl chain which is far away from the azo functional group (note: DEAD but not DMAD was chosen as the first reactant due to its better stability in water), two DEAD analogues, dibutyl azodicarboxylate (DBAD, **2b**) and dihexyl azodicarboxylate (DHAD, **2c**) having lower aqueous solubilities were synthesized, respectively.[17] The cycloaddition reactions of **2a**, **2b**, **2c** with quadricyclane gave 1,2-diazetidines as the only product. The pseudo-first-order constants of the reactions of **2a**, **2b**, and **2c** with quadricyclane in methanol were $k'_{2a} = 0.68$, $k'_{2b} = 0.46$, $k'_{2c} = 0.42$ respectively, which indicated that these analogues had similar reactivities in homogeneous reaction system. Prolonging the length of the alkyl substitutes has little effect on the compounds' inherent reactivity.

The reaction rates of the [2σ+2σ+2π] cycloadditions of quadricyclane with DEAD (**2a**), DBAD (**2b**), or DHAD (**2c**) in water were then separately monitored (Figure 2). The reaction of DEAD which has the best aqueous solubility was very fast, and the reaction completed in 20 min. Nevertheless, in the reaction of DBAD which has relatively poor aqueous solubility, it took 24 h

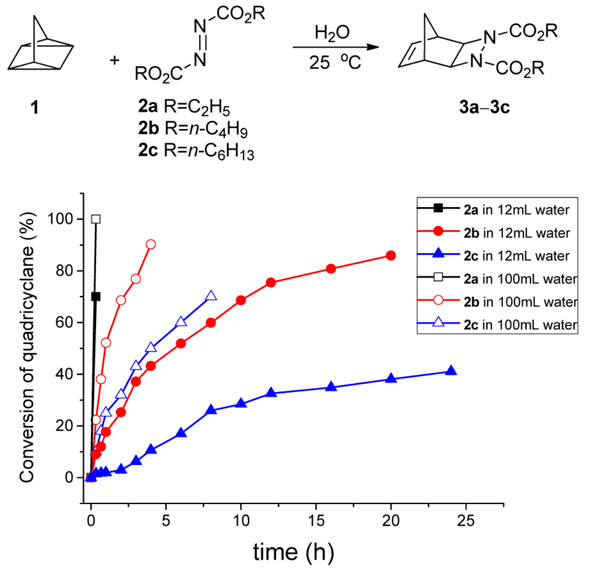

Figure 2. Conversions of quadricyclane (**1**) at different time intervals in the cycloaddition reactions with azodicarboxylates **2a**, **2b**, and **2c** in water (12 or 100 mL) at 25 °C. Concentration of quadricyclane is 0.042 M (in 12 mL water) and 0.005 M (in 100 mL water), concentration of diazocarboxylate is 0.05 M (in 12 mL water) and 0.006 M (in 100 mL water).

to reach 85% conversion of quadricyclane. As for DHAD, the reaction proceeded considerably more slowly in water. The conversion of quadricyclane was 30% after 24 h. It was found that all three reactions were much faster in 100 mL of water than in 12 mL of water. Nevertheless, the reaction rates in 100 mL of water also had strong dependence upon the aqueous solubilities of the azodicarboxylates.

Aqueous phase epoxide aminolysis reactions were also reported many times in the literature.[16a,c,18−21] We carried out a kinetic study of the reactions of morpholine (**4**) with 1,2-epoxyalkane **5a**, **5b**, **5c**, and **5d** with increasing lengths of alkyl chain.[22] The pseudo-first-order constants of **5a**, **5b**, **5c** and **5d** in methanol were $k'_{5a} = 1.37$, $k'_{5b} = 1.22$, $k'_{5c} = 1.14$, $k'_{5d} = 1.02$ respectively, which indicated that they had similar reactivities in homogeneous solution. The rates of epoxide-opening reactions of morpholine with 1,2-epoxyalkanes in water were separately monitored. As illustrated in Figure 3, epoxide **5a** bearing the shortest alkyl chain reacted very fast in water, and reaction of epoxide **5b** exhibited a slightly slower rate. As for epoxide **5c**, in a fixed time of 4 h, we observed that the conversion of **5c** was 13%. The aminolysis of epoxide **5d** bearing the longest alkyl chain barely occurred in pure water within 4 h.

There have been many literatures reporting that Diels−Alder reactions can be remarkably accelerated in aqueous medium and the mechanistic of function of water was also explored.[23−29] We carried out a kinetic study of Diels−Alder reactions of cyclopentadiene with four dialkylfumarates with decreasing aqueous solubilities.[30] The pseudo-first-order constants of the Diels−Alder reactions in THF are $k'_{8a} = 1.26$, $k'_{8b} = 1.21$, $k'_{8c} = 1.12$, $k'_{8d} = 1.09$ respectively, which indicated that they had similar reactivities in homogeneous reaction system. The reactivities of dialkylfumarates **8a**−**8d** in water are shown in Figure 4. The reactions of dialkylfumarate **8a** and **8b** proceeded almost equally fast while **8c** reacted slightly slower. The reaction rate of dialkylfumarate **8d** which has the longest alkyl chain was noticeably lower than **8a**, **8b**, and **8c**. But if taking account the fact that dialkylfumarate **8d** is a solid and therefore have a relatively slower rate when it disperse in water, the reaction rate of dialkylfumarate **8d** should be higher than it appears.

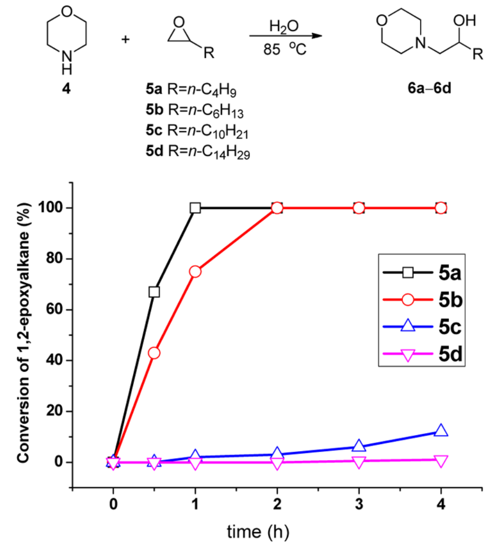

Figure 3. Conversion of 1,2-epoxyalkanes **5a**−**5d** in the reactions with morpholine in water (12 mL) at 85 °C.

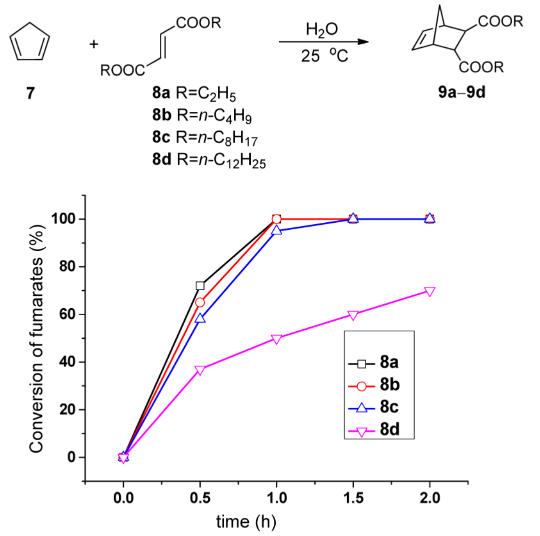

Figure 4. Conversion of dialkylfumarates **8a**−**8d** in the Diels−Alder reactions with cyclopentadiene in water (12 mL) at 25 °C. Measured by ^{1}H NMR in a fixed time.

It appears that the dependence of reaction rate on aqueous solubilities of reactants varied in the above three reaction types. We think this may be related to the catalytic function of water in each reaction. We investigated the relationship between the reaction rate and the amount of water to understand whether the above reactions only proceed in a large volume of water or if these reactions can proceed smoothly in the presence of a very small amount of water. As shown in Figure 5, under the solvent-free conditions, the reaction of thoroughly dried DEAD and quadricyclane was very slow since the conversion of quadricyclane was 6% in 12 min. Adding 1 equiv of water to the reaction system, the conversion of quadricyclane increased to 11%. The reaction rate exhibited substantial increase in 9 mL of water, and the conversion of quadricyclane reached 50%. This experiment indicated that the reaction could take place under the

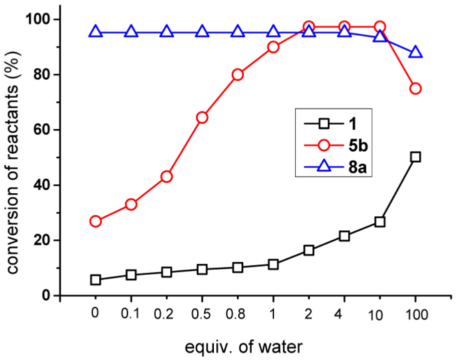

Figure 5. Conversion of reactants in three reactions with increasing amounts of water. The amount of water is relative to the amount of compounds **1**, **5b**, or **8a** respectively.

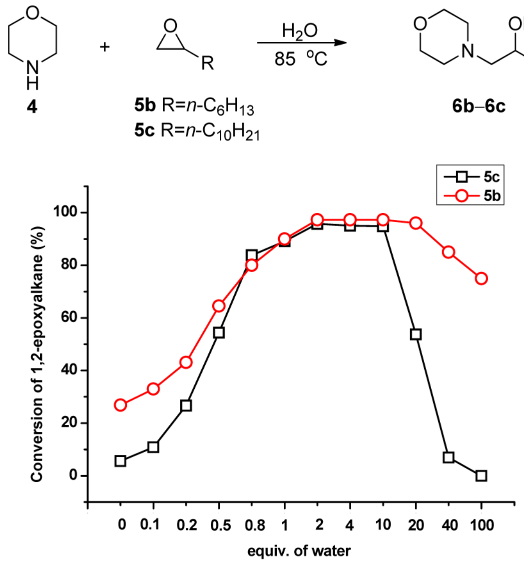

Figure 6. Conversion of epoxides in the aminolysis reaction in different amount of water. The amount of water is relative to the amount of **5b** and **5c**, respectively.

neat conditions or in the presence of a small amount of water. However, only in a large amount of water can the accelerating effect of water be observed. The aminolysis of epoxide **5b** proceeded very slowly under neat conditions. With the addition of a small amount of water (1−10 equiv), the reaction rates increased considerably to 90%. In a large volume of water, the aminolysis of **5b** proceeded at a lower but reasonable rate. The Diels−Alder reaction of diethyl fumarate **8a** and cyclopentadiene under neat conditions is so fast that the conversion of diethyl fumarate reached 92% in 15 min. Adding water to the reaction system has no apparent influence on the reaction rate. The observation that some Diels−Alder reactions can work smoothly under the neat conditions is consistent with previous studies.[1,31]

For the reactions that only proceed fast in large volume of water, like the [$2\sigma+2\sigma+2\pi$] cycloaddition reaction, the aqueous solubilities of the reactants strongly affect the rate of the aqueous reaction. The reactants with short alkyl chains reacted much faster than those having longer alkyl chains. Besides, the concentration of the reactants also has obvious influence on the reaction. Due to the limited solubility of organic compounds, the aqueous system is always saturated, increasing the amount of water can help the reactants disperse and then dissolve in water thus the reaction was much faster. For the reactions which already proceed with a high speeds under the neat condition, like the Diels−Alder reaction, the reaction proceeded almost equally fast under neat condition, with small amount of water, or with large amount of water. Only carefully planned kinetic studies choosing short reaction time can distinguish the rate differences of the above three conditions. Thus, in this type of aqueous reaction, the aqueous solubilities of the reactants did not affect the rate of the aqueous reaction.

But it still puzzled us why the aminolysis reaction of **5c** and **5d** are much slower than that of **5a** and **5b** when evidence showed that 1 equiv of water could make the reaction of **5b** work efficiently. We than compared the reactivities of **5b** and **5c** in increasing amount of water (Figure 6). Under the neat condition, both reactions of **5b** and **5c** proceeded slowly. With the addition of 1 equiv of water, both reactions achieved the highest rates. However, when increasing the amount of water continuously, the aminolysis of **5b** still proceeded at a reasonable rate, but the rate of the reaction of **5c** decreased significantly and the reaction did not occur in 40 mL of water (100 equiv). This experiment showed when the epoxide dissolved in morpholine containing 1 equiv of water (water is miscible with morpholine), the intermolecular reaction proceed very fast due to the high concentration of each reactant. When an increasing amount of water was added to the reaction system, epoxide dissociated from the aqueous solution of morpholine, and thus, the bimolecular reaction slowed down. If the aqueous solubility of the epoxide is very poor, the reaction could not proceed further in the diluted aqueous solution.

Change of the Reaction Rates in Water/Organic Binary Solvent Systems at Different Ratios. Water/organic binary solvent systems have been employed as a mechanistic tool to investigate water-promoted reactions.[1,4,9,29,31−37] The cycloadditions of quadricyclane (**1**) and DMAD have been studied in the water/methanol binary system by Sharpless's group before;[1] four ratios were studied (water/methanol = 1:0; 3:1; 1:1; and 1:3) therein, and they found that the heterogeneity of the reaction system is essential to achieving a great accelerating effect. We systematically measured the conversion of quadricyclane in the [$2\sigma+2\sigma+2\pi$] cycloaddition reaction with azodicarboxylates **2a**, **2b**, and **2c** at six different ratios of mixture solvent (Figure 7). The data determined were reproducible to within 6%.

For the reaction of DEAD (87 mg, 94 uL, 0.6 mmol) and quadricyclane (47 uL, 0.5 mmol) in 12 mL of pure water, the conversion of quadricyclane was 69% at 10 min, and this value increased to 93% in an aqueous solution containing 20 vol % of methanol. When 40 vol % of methanol was present in the aqueous solution, DEAD became totally soluble. The reaction mixture finished as a clear solution, and the conversion of quadricyclane at 10 min was 96%, representing the highest reaction rate. When the vol % of methanol was increased to 60, quadricyclane dissolved in the mixed solvent, but the conversion of quadricyclane dropped sharply. The reaction rate decreased further in the mixed solvent containing 80 vol % of methanol and barely took place in pure methanol in 10 min.

Taking the same experimental procedure, the reaction of quadricyclane with compounds **2b** and **2c** were carried out. For reactions of both compounds, the conversion of quadricyclane increased initially, reaching a maximum before decreasing with further addition of methanol. These curves look similar to the curve of DEAD, but it is worth noting that the vertexes of the curves shifted to the right. The reaction rate of dibutyl

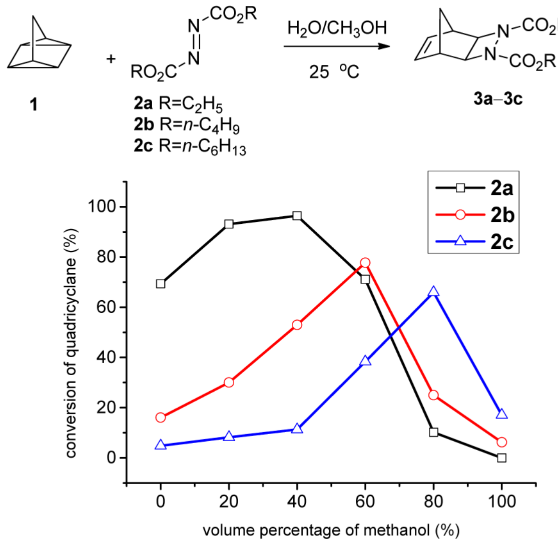

Figure 7. Conversion of quadricyclane (**1**) in the cycloaddition reaction with DEAD (**2a**), DBAD (**2b**), and DHAD (**2c**).

azodicarboxylate **2b** reached the highest point in the binary solvent composed of 60 vol % of methanol (DBAD became soluble in this mixed solvent). For dihexyl azodicarboxylate (DHAD) with the longest alkyl chain, the reaction rate reached the highest point in the binary solvent composed of 80 vol % of methanol (DHAD became soluble in this mixed solvent).

As shown in Figure 7, compared with Sharpless's experiment which employed DMAD as the reactant, we also found the reaction of DEAD bearing the short alkyl chain was fast in pure water or mixed solvent containing a low vol % of methanol. However, our study showed that pure water was not the optimal medium for DEAD and also its two analogues. Besides, contrary to their conclusion that a heterogeneous emulsion is essential to achieving a great accelerating effect, we found that the reaction rate reached the highest point in the binary solvent with 40 vol % of methanol when DEAD became soluble at this point. The reaction of **2b** or **2c** also reached the highest point where **2b** and **2c** became soluble in the mixed solvent. Thus, the great rate-enhancing effect did not depend on the heterogeneity of the reaction system. Even when the reaction system is heterogeneous, the increase of organic cosolvent also has influence on the reaction rate.

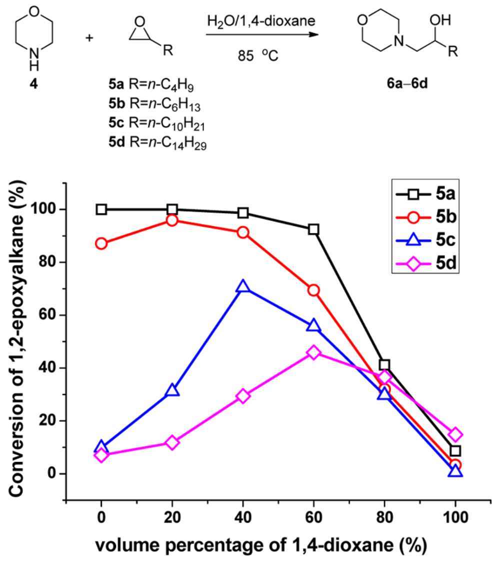

Figure 8. Conversion of epoxides **5a**−**5d** in the aminolysis reactions with morpholine in water/1,4-dioxane mixed solvent system.

We endeavored to provide further insight into the other water-promoted reactions in order to check if the phenomenon present above is limited to the $[2\sigma+2\sigma+2\pi]$ cycloaddition reactions. The binary mixtures of water/1,4-dioxane were used to study the change of the reaction rate of epoxide aminolysis reaction from a heterogeneous emulsion to a homogeneous solution. Since the boiling point of water/1,4-dioxane system at different ratios ranges from 87 to 101 °C,[38] we controlled the reaction temperature at 85 °C in order to prevent the experimental results from being disturbed by the different refluxing temperatures. As illustrated in Figure 8, the curves can be divided into two different types. Epoxide **5a**, which has the shortest alkyl chain among the four selected epoxides, reacted fast when the volume percentage of 1,4-dioxane was between 0%−60%. Then the reaction rates decreased sharply with further decrease of the ratio of water. Nevertheless, the reaction rates of **5b**, **5c**, and **5d** first increased with the addition of 1,4-dioxane, reaching a maximum before decreasing with further addition of 1,4-dioxane. The solvent compositions in which the reaction reached the maximum reaction rate were right-shifted with the elongation of the alkyl substituents.

The studies of the Diels−Alder reactions of cyclopentadiene with dialkylfumarates **8a**−**8d** in water/THF mixtures at 293 K (Figure 9) showed that reactions of **8a**, **8b**, and **8c** proceeded optimally in pure water. Upon the increase of the volume percentage of THF, the conversion of dialkylfumarates decreased gradually. When it came to didodecylfumarate **8d**, in pure water, the conversion of **8d** was 69% in the fixed time of 1.5 h, and the conversion slightly increased to 83% in the mixed solvent of 20% THF. However, further addition of THF decreased the reaction rate like the trend for dialkylfumarates **8a**−**8c**.

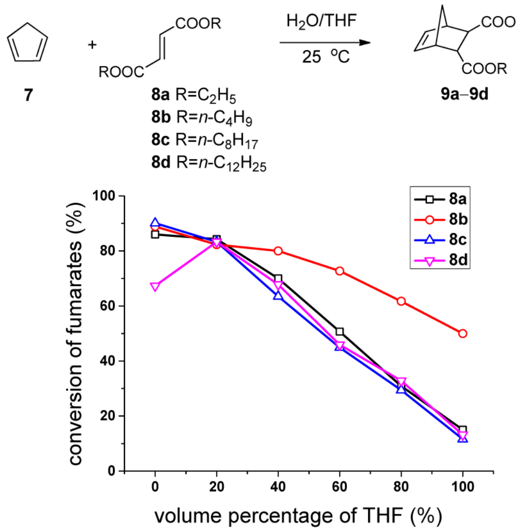

Figure 9. Conversion of dialkylfumarates **8a**−**8d** in the Diels−Alder reactions with cyclopentadiene in mixed water/THF solvent system.

For $[2\sigma+2\sigma+2\pi]$ cycloaddition reactions and epoxide aminolysis reactions, the reaction rates in water strongly depend on the aqueous solubilities of reactants, the conversion of the reactants in the binary solvent system recorded after a fixed time showed two types of curves, the first one is the "ever-decreasing" type represented by the reaction of **5a**. This is because epoxide **5a** with the shortest alkyl chain can partially dissolve in water and react smoothly (the aqueous solubility of **5a** at room temperature is 3.1 g/L).The second type of curve is the "up and down" type represented by the reactions of **2a**−**2c** and **5b**−**5d**. Apparently, the reactions of these reactants do not proceed optimally in pure water. Actually, organic cosolvent was needed to dissolve the reactants, and the reaction rate increased with the addition of organic cosolvents. The best volume percent of organic cosolvent for getting the highest reaction rate was related to the aqueous solubilities of reactants; reactant with poor aqueous solubility needed an increasing amount of organic cosolvent.

When it comes to the reason why the reaction rate of **5a** decreased upon the addition of organic cosolvent, and also the reaction rates of **2a**−**2c** and **5b**−**5d** decreased after excess amount of organic cosolvent was added, the rate-enhancing effect in water mainly derives from hydrogen-bonding activation, beneficial hydrophobic effect, high polarity of water, or a mix of the three effects.[2−11] The decrease of the reaction rate upon the addition of organic cosolvent is likely due to the diminution of hydrogen-bonding activation, the reduction of hydrophobic effect, or a lower polarity of the resulted reaction medium. In order to verify our assumption, three organic cosolvents, 1,4-dioxane, acetone, and methanol which have different hydrogen bond formation ability and apparent dielectric constants (2.21, 20.56, 32.66 respectively),[39] were used in further investigation of the [2σ+2σ+2π] cycloaddition reaction between quadricyclane and DEAD. As shown in Figure 10, in the reaction using 1,4-dioxane as the organic cosolvent, the maximum of the reaction rate was at 20 vol % of 1,4-dioxane. When using acetone as the organic cosolvent, the reaction rate reached the maximum at 30 vol % of acetone. The best ratio for using methanol as the cosolvent was 40 vol %. The reason for the right shift of the vertex of the curve from 1,4-dioxane to methanol might be related to the different solubility of quadricyclane in these three solvents. The nonpolar 1,4-dioxane can dissolve hydrophobic quadricyclane better; thus, with the addition of relatively small amount of 1,4-dioxane, the reaction could reach the highest reaction speed. However, a larger amount of methanol was required for the optimal reaction rate, but the reaction was less affected in an excessive amount of methanol compared with 1,4-dioxane and acetone. This may due to the hydrogen bond formation ability and high dielectric constant of methanol.

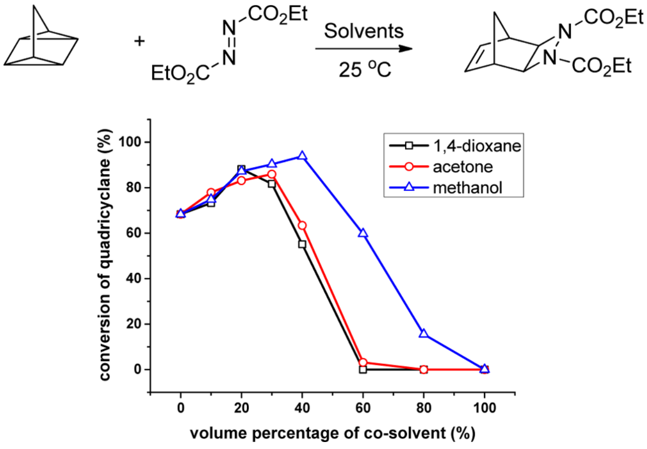

Figure 10. Conversion of quadricyclane in different organic cosolvents.

The experimental results of the Diels−Alder reaction are far different from that of [2σ+2σ+2π] cycloaddition reactions and the epoxide-aminolysis reactions. The reactions of cyclopentadiene with **8a**, **8b**, and **8c** all proceeded optimally in pure water. Because all the reactants have poor solubilities in water, tiny oil droplets are formed when stirring the two reactants in water. The reaction might actually proceed in the tiny oil droplets containing both of the reactants since the reaction exhibited a high reaction rate under neat conditions. Adding organic solvent results in a low concentration of each reactant and thereby decreased the reaction rate. The reason for a slightly higher reaction rate of **8d** in the mixed solvent containing 20% of THF might be due to the solid **8d** mixing better with cyclopentadiene in the presence of a small amount of organic solvent.

■ CONCLUSION

In summary, we prepared a series of reactants with different aqueous solubilities and compared their reaction rates in pure water and in mixed aqueous−organic binary solvents at various ratios. It was found that for reactions which could proceed very fast under the neat conditions, like the Diels−Alder reactions between cyclopentadiene and fumarates, the aqueous solubilities of reactants had very little influence on the rate of the aqueous reaction. However, for reactions which proceeded very slowly under the neat reaction conditions, the addition of water could remarkably promote the reaction, such as [2σ+2σ+2π] cycloaddition reactions and the epoxide aminolysis reactions; reactants with different aqueous solubilities reacted at apparently different rates. The reactants with good aqueous solubilities reacted fast in water and reactants with poor aqueous solubilities reacted slowly or not at all. In addition, appropriate dilution of the aqueous system could sometimes make the reaction proceed more efficiently. This evidence suggested that, when conducting these two types of reactions in aqueous solution, the dissolution of the reactants in water was crucial for the efficient progress of the reactions. Reactants with poor aqueous solubilities always needed organic cosolvents to help them dissolve or disperse in water. The required amount of organic cosolvent depended on the aqueous solubility of the reactant. However, an excess amount of organic cosolvent would diminish the accelerating effect of water.

From the experimental results observed in this study, the fact that some reactants react faster in heterogeneous aqueous solution (with no or a small amount of organic cosolvent) than in homogeneous mixed aqueous−organic binary solvent do not exclusively point to an interfacial catalysis mechanism. The "on water" phenomenon could also be attributed to the following: (1) The reactions can proceed efficiently under neat condition, adding an increasing amount of organic solvent decreases the concentration of reactants, and thus the reaction becomes slower. (2) The reactants have reasonable aqueous solubilities, and the reaction rate is the fastest in pure water. Adding water-miscible organic solvent decreases the degree of hydrogen-bond activation, the hydrophobic effect, or the polarity of the reaction medium, and thus, the reaction is slower in the homogeneously aqueous−organic binary solvents. However, for other reactants with poor aqueous solubilities, the pure water reaction medium no longer delivers the fastest reaction rate; adding an appropriate amount of organic cosolvent can make the reaction more efficient, and sometimes the highest reaction rates are achieved in a homogeneous aqueous−organic solvent system.

In this respect, a newly reported water-promoted reaction should not be classified into the "on water" catalysis simply because the reaction is faster in water than in organic solvent. More research should be done to distinguish the role that water plays in those aqueous reactions. Also, the aqueous solubilities of the reactants should be placed with high value while conducting a water-promoted reaction. The mechanistic function of water in promoting organic reactions might be complicated and deserve more research efforts.

■ EXPERIMENTAL SECTION

General Methods. Water was purchased from Watson's or from Milli-Q Ultrapure Water Purification System. Flash column chromatography was performed using the indicated solvent system on Qingdao-Haiyang silica gel (200−300 mesh). All of the compounds were characterized by ^{1}H NMR and ^{13}C NMR. Peaks recorded are relative to the internal standards: TMS (δ = 0.00) for ^{1}H NMR and $CDCl_3$ (δ = 77.00) for ^{13}C NMR spectra. High-resolution mass spectral analyses (HRMS) were performed on a high-resolution MALDI-FT-ICR mass spectrometer.

Compound **1** was prepared according to the literature reports.[40] Compound **4** was freshly distilled prior to its use. Cyclopentadiene was freshly cracked from its dimer. Morpholine was purified according to the standard method to ensure its purity. All reactions were carried out in aerial atmosphere. Reaction temperatures reported in the schemes were the temperatures of the oil bath or the water bath.

*Preparation of Dialkyl Azodicarboxylate **2b**−**2c**. Dibutyl Azodicarboxylate (**2b**).* To the solution of hydrazine hydrate (1.25 g, 25 mmol), water (10 mL) and methanol (10 mL) was added *n*-butyl chloroformate (6.83 g, 50 mmol) under ice bath and stirring, the reaction mixture was stirred for 1.5 h, and then, the reaction was extracted with EtOAc, washed with brine, and dried over anhydrous Mg_2SO_4, and the solvent was evaporated in vacuo to give dibutyl hydrazine-1,2-dicarboxylate. The crude product was used without further purification. To a solution of dibutyl hydrazine-1,2-dicarboxylate was added NBS (4.45 g, 25 mmol); the reaction was monitored by TLC. After reacting for 30 min, the solution was diluted by CH_2Cl_2 (100 mL). The resulting mixture was washed by pure water and brine and dried over anhydrous Mg_2SO_4; the solvent was evaporated in vacuo to give the crude product; the residue was purified by silica gel chromatography (0−2% EtOAc/P.E. as an eluent); and the desired product **2b** was obtained as a yellow liquid (4.14 g, 72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.45 (t, J = 6.8 Hz, 4H), 1.82−1.75 (m, 4H), 1.48−1.41 (m, 4H), 0.97 (t, J = 7.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.4, 69.2, 30.4, 18.8, 13.5.

*Dihexyl Azodicarboxylate (**2c**).* Prepared according to the general procedure; 4.93 g, yield: 69%; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.44 (t, J = 6.4 Hz, 4H), 1.83−1.76 (m, 4H), 1.45−1.38 (m, 4H), 1.34−1.32 (m, 8H), 0.90 (t, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.4, 69.5, 31.2, 28.4, 25.2, 22.4, 13.9.

*Diethyl-3,4-diazatricyclo[4.2.1.02,5]non-7-ene-3,4-dicarboxylate (**3a**).*[1] Prepared according to the kinetic study procedure; 122 mg, yield: 92%; colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.99 (s, 2H), 4.18 (q, J = 6.8 Hz, 4H), 4.12 (s, 2H), 3.24 (s, 2H), 1.83 and 1.64 (AB system, J_{AB} = 10.0 Hz, 2H), 1.24 (t, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.3, 135.5, 64.8, 62.4, 43.8, 40.5, 14.5.

*Dibutyl-3,4-diazatricyclo[4.2.1.2,5]non-7-ene-3,4-dicarboxylate (**3b**).* Prepared according to the kinetic study procedure; 143 mg, yield: 89%; colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.06 (s, 2H), 4.23−4.14 (m, 4H), 4.19 (s, 2H), 3.30 (s, 2H), 1.89 and 1.70 (AB system, J_{AB} = 10.0 Hz, 2H), 1.67−1.62 (m, 4H), 1.45−1.35 (m, 4H), 0.94 (t, J = 7.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.3, 135.4, 66.1, 64.7, 43.7, 40.4, 30.8, 18.8, 13.6; HRMS (MALDI-FT-ICR) exact mass calcd for $C_{17}H_{26}N_2O_4$: m/z 345.1790 ([M + Na]$^+$), found: m/z 345.1788 ([M + Na]$^+$).

*Dihexyl-3,4-diazatricyclo[4.2.1.2,5]non-7-ene-3,4-dicarboxylate (**3c**).* Prepared according to the kinetic study procedure; 166 mg, yield: 88%; colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.06 (s, 2H), 4.22−4.12 (m, 4H), 4.19 (s, 2H), 3.30 (s, 2H), 1.89 (d, J = 10 Hz, 1H), 1.71−1.63 (m, 5H), 1.40−1.26 (m, 12H), 0.89 (t, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 159.5, 135.6, 66.6, 64.8, 43.8, 40.6, 31.4, 28.8, 25.4, 22.5, 14.0; HRMS (MALDI-FT-ICR) exact mass calcd for $C_{21}H_{34}N_2O_4$: m/z 401.2416 ([M + Na]$^+$), found: m/z 401.2408 ([M + Na]$^+$).

*l-(4-Morpholino)-2-hexanol (**6a**).*[41] Prepared according to the kinetic study procedure; 89 mg, yield:95%; colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76−3.64 (m, 5H), 3.39 (br s, 1H), 2.68−2.63 (m, 2H), 2.40−2.23 (m, 2H), 2.35 (dd, J = 3.2, 12.4 Hz, 1H), 2.28−2.22 (m, 1H), 1.47−1.41 (m, 2H), 1.40−1.32 (m, 4H), 0.91 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 67.0, 65.9, 64.8, 53.6, 34.5, 27.7, 22.8, 14.0.

*l-(4-Morpholino)-2-octanol (**6b**).*[42] Prepared according to the kinetic study procedure; 100 mg, yield: 93%; colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75−3.68 (m, 5H), 3.39 (br s 1H), 2.69−2.63 (m, 2H), 2.39−2.36 (m, 2H), 2.35 (dd, J = 2.8, 12.4 Hz, 1H), 2.28−2.22 (m, 1H), 1.52−1.45 (m, 2H), 1.45−1.20 (m, 8H), 0.88 (t, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 67.0, 65.9, 64.7, 53.6, 34.8, 31.8, 29.4, 25.5, 22.6, 14.0.

*l-(4-Morpholino)-2-dodecanol (**6c**).*[16c] Prepared according to the kinetic study procedure; 129 mg, yield: 95%; colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76−3.65 (m, 5H), 3.41 (br s, 1H), 2.68−2.63 (m, 2H), 2.39−2.22 (m, 4H), 1.47−1.26 (m, 18H), 0.88 (t, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 66.9, 65.8, 64.7, 53.5, 34.7, 31.8, 29.6, 29.5, 29.2, 25.5, 22.5, 14.0.

*l-(4-Morpholino)-2-hexadecanol (**6d**).*[43] Prepared according to the kinetic study procedure; 155 mg, yield: 95%; white solid, mp: 36−38 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76−3.65 (m, 5H), 2.69−2.64 (m, 2H), 2.39−2.22 (m, 4H), 1.47−1.25 (m, 26H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 67.0, 65.9, 64.7, 53.6, 34.8, 31.9, 29.7, 29.6, 29.6, 29.6, 29.6, 29.3, 25.6, 22.7, 14.1.

*Diethyl Bicyclo[2.2.1]hept-5-ene-(2-endo,3-exo)-dicarboxylate (**9a**).*[44] Prepared according to the kinetic study procedure; 117 mg, yield: 98%; colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.28 (dd, 1H, J = 3.2, 5.6 Hz), 6.07 (dd, 1H, J = 2.8, 5.6 Hz), 4.17 (q, 2H, J = 7.2 Hz), 4.12−4.07 (m, 2H), 3.38 (t, 1H, J = 4.0 Hz), 3.27 (br s, 1H), 3.12 (br s, 1H), 2.68 (dd, 1H, J = 1.6, 4.8 Hz), 1.61 (d, 1H, J = 8.8 Hz), 1.47−1.44 (m, 1H), 1.30−1.22 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 173.2, 137.5, 135.0, 60.8, 60.5, 47.8, 47.7, 47.2, 47.1, 45.7, 14.2, 14.2.

*Dibutyl Bicyclo[2.2.1]hept-5-ene-(2-endo,3-exo)-dicarboxylate (**9b**).*[45] Prepared according to the kinetic study procedure; 138 mg, yield: 94%; colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.28 (dd, J = 3.2, 5.6 Hz, 1H), 6.07 (dd, J = 2.8, 5.6 Hz, 1H), 4.11 (t, J = 6.4 Hz, 2H), 4.07−4.02 (m, 2H), 3.38 (t, J = 4.0 Hz, 1H), 3.26 (br s, 1H), 3.11 (br s, 1H), 2.68 (dd, J = 1.2, 4.4 Hz, 1H), 1.67−1.56 (m, 5H), 1.47−1.35 (m, 5H), 0.96−0.91 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.5, 173.3, 137.5, 135.1, 64.7, 64.4, 47.9, 47.7, 47.2, 47.2, 45.6, 30.6, 30.6, 19.1, 13.7, 13.7.

*Dioctyl Bicyclo[2.2.1]hept-5-ene-(2-endo,3-exo)-dicarboxylate (**9c**).*[46] Prepared according to the kinetic study procedure; 191 mg, yield: 94%; colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29 (dd, J = 3.2, 5.2 Hz, 1H), 6.07 (dd, J = 2.8, 5.6 Hz, 1H), 4.10 (t, J = 6.4 Hz, 2H), 4.01−4.00 (m, 2H), 3.38 (t, J = 4.0 Hz, 1H), 3.26 (br s, 1H), 3.11 (br s, 1H), 2.68 (dd, J = 1.2, 4.0 Hz, 1H), 1.67−1.56 (m, 5H), 1.45 (dd, J = 1.6, 8.8 Hz, 1H), 1.37−1.23 (m, 20H), 0.88 (t, J = 6.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.4, 173.2, 137.5, 135.0, 64.9, 64.6, 47.8, 47.6, 47.2, 47.1, 45.6, 31.7, 29.1, 28.5, 25.8, 22.6, 14.0.

*Didodecyl Bicyclo[2.2.1]hept-5-ene-(2-endo,3-exo)-dicarboxylate (**9d**).* Prepared according to the kinetic study procedure; 238 mg, yield: 92%; colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.28 (dd, J = 3.2, 5.6 Hz, 1H), 6.06 (dd, J = 2.8, 5.6 Hz, 1H), 3.37 (t, J = 4.0 Hz, 1H), 3.26 (br s, 1H), 3.11 (br s, 1H), 2.68 (dd, J = 1.2, 4.4 Hz, 1H), 1.67−1.56 (m, 5H), 1.45 (dd, J = 1.6, 8.8 Hz, 1H), 1.19−1.40 (m, 40H), 0.88 (t, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.3, 173.1, 137.4, 135.0, 64.8, 64.5, 47.8, 47.6, 47.1, 47.1, 45.6, 31.8, 29.5, 29.5, 29.3, 25.8, 22.6, 14.0.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Typical GC and NMR analysis, ^{1}H NMR, ^{13}C NMR spectra of substrates and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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