

Article

The Role of Iodine Catalyst in the Synthesis of 22-Carbon Tricarboxylic Acid and Its Ester: A **Case Study**

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Abstract: Here, 22-carbon tricarboxylic acid (C22TA) and its ester (C22TAE) were prepared via the Diels-Alder reaction of polyunsaturated fatty acids (PUFAs) and their esters (PUFAEs) as dienes with fumaric acid (FA) and dimethyl fumarate (DF) as dienophiles, respectively. The role of an iodine catalyst for the synthesis of C22TA and C22TAE in the Diels-Alder type reaction was investigated using a spectroscopic approach. The chemical structures of the products were characterized using proton nuclear magnetic resonance (¹H-NMR) and electrospray ionization mass spectrometry (ESI-MS) analysis. Results showed that nonconjugated dienes can react with dienophiles through a Diels-Alder reaction with an iodine catalyst, and that iodine transformed the nonconjugated double bonds of dienes into conjugated double bonds via a radical process. DF was more favorable for the Diels-Alder reaction than FA. This was mainly because the dienophile DF contained an electron-withdrawing substituent, which reduced the highest and lowest occupied molecular orbital (HOMO–LUMO) energy gap and accelerated the Diels-Alder reaction. By transforming nonconjugated double bonds into conjugated double bonds, iodine as a Lewis acid increased the electron-withdrawing effect of the carbonyl group on the carbon–carbon double bond and reduced the energy difference between the HOMO of diene and the LUMO of dienophile, thus facilitating the Diels-Alder reaction.

Keywords: Diels–Alder reaction; 22-carbon tricarboxylic acid; iodine; ¹H-NMR; ESI-MS

1. Introduction

With the dramatic decrease in global fossil fuels and the increasing environmental problems and concerns, the use of renewable resources received great attention. Promoting sustainable environmental, social, and economic development is now a global consensus [1]. Sustainable bio-based resources are particularly desirable. One approach is the development and utilization of vegetable oil-based lubricants to partially or even comprehensively substitute petrochemical resources. Mineral oil is refined from natural crude oil, and its biodegradability is poor. Mineral oil cannot be used as the base oil of biodegradable lubricating oil because it causes serious pollution when discharged into the environment. It stays in water, soil, forest, and other ecosystems for a long time. It would be highly desirable to develop biodegradable, environmentally benign lubricating oil and its derivatives from plant oil and vegetable oil as raw materials [2].



In 2018, the total output of China's eight major plant oils and vegetable oils, including rapeseed, peanut, soybean, cottonseed, sunflower seed, sesame, flaxseed, and *Camellia oleracea*, was about 60 million tons. With an abundant source of plant oil and vegetable oil, as well as low-cost and well-established refining and processing technology, it could be an excellent renewable resource for preparing biodegradable lubricating oil [3]. Vegetable oil is rich in polyunsaturated fatty acids (PUFAs); PUFAs are hydrocarbon chains with a carboxyl group at one end and a terminal methyl group at the other with two or more double bonds present [4,5]. PUFAs include linoleic acid (LA) with two double bonds, linolenic acid, and eleostearic acid with three double bonds. Polyunsaturated fatty acid esters (PUFAEs) are the products of esterification of PUFAs with alcohols. In particular, 22-carbon tricarboxylic acid (C22TA) and its ester (C22TAE) have excellent lubricating properties which can be prepared via a Diels–Alder reaction of PUFA with PUFAE as diene with dienophile, respectively.

C22TA and C22TAE are new types of bio-based chemicals with superior properties. C22TA and C22TAE have low toxicity, they are environmentally benign with excellent biodegradability, and they are obtained from renewable raw materials, allowing them to be used as substitutes for fossil fuel-based petroleum products [6]. They can be widely used in lubricating oil, resin additive, printing ink, cutting fluid, green surfactant, corrosion inhibitor, and many other chemical industrial products [7–9]. The preparation of C22TA and C22TAE not only reduces the dependence on fossil fuels such as petroleum, but also reduces the pollution to the environment. In addition, preparing value-added products such as C22TA using bio-resources based on vegetable oil constitutes an important field in green chemistry and sustainable engineering. The synthesis of C22TA and C22TAE can be carried out via two main routes. One is a Diels-Alder reaction with vegetable oils, such as linoleic acid, linolenic acid, and their esters which do not contain conjugated double bonds. This reaction is carried out under the catalysis of iodine with a dienophile. Another type of Diels–Alder reaction uses starting materials containing conjugated double bonds such as conjugated linoleic acid (CLA), eleostearic acid, and their esters. In this route, compounds containing conjugated double bonds directly react with a dienophile at high temperature. Both processes are safe and easy to operate, and they have great application potential [10].

Huang et al. prepared C22TA via a Diels–Alder reaction using tung oil fatty acids with fumaric acid (FA), and subsequently converted it to the corresponding C22TAE which was then used for epoxy resins [7]. Vijayalakshmi et al. prepared C22TA via a Diels-Alder reaction of dehydrated castor oil fatty acids (containing 48% conjugated and 42% nonconjugated dienes) with FA. The reaction temperature, time, catalyst concentration, and molar ratio of reactants were varied to get maximum yield of the C22TA. The conditions found for maximum yield of C22TA (82.2%) were as follows: temperature of 200 °C, reaction time of 2 h, molar ratio of the reactants of 1:1.1, and catalyst iodine concentration of 0.3% [8]. A Diels–Alder reaction was applied to fatty acids containing both CLA and LA, wherein the nonconjugated portion of LA was also converted to C22TA in the presence of small amounts of iodine in United States (US) Patent. No. 4,081,462. In this invention, the fatty acids were naturally occurring fatty acids high in LA content (above 50%), such as distilled tall oil fatty acid, safflower fatty acid, and sunflower fatty acid. This invention provided a process for making C22TA from available LA in a fatty acid mixture [11]. Previous researchers prepared C22TA and C22TAE with excellent lubricating properties via Diels-Alder reactions. However, no one conducted a systematic and in-depth study on the reaction mechanism. How do PUFAs and their derivatives, dienophiles, and catalysts affect the Diels-Alder reaction? What is the role of the iodine catalyst? Does it only act as a catalyst to convert nonconjugated double bonds to conjugated double bonds? On the other hand, does it also promote and facilitate the Diels–Alder reaction? In this study, C22TA and C22TAE were synthesized and compared using the two routes discussed above. The effects of raw materials and catalysts on the Diels-Alder reaction were compared and studied to further understand the reaction mechanism and to provide theoretical guidance for the industrial production of C22TA and C22TAE.

Photoisomerization of linoleic acid alkyl esters or vegetable oils was suggested as a way of introducing conjugation [12]. Jain et al. used iodine as a catalyst, whereby 22% conjugated linoleic acid

was obtained via irradiation of undiluted oil with ultraviolet (UV) light at 48 °C for 12 h [13]. Andrew et al. used a similar approach, whereby soy oil was converted to 25% total CLA [14]. There were other reports on the preparation of CLA by photoisomerization [15–17], but the reported methods had strict requirements on equipment, with a long reaction time and low conversion rate. Under the catalysis of iodine and without the use of a light source, it remains to be studied whether nonconjugated double bonds can be converted into conjugated double bonds by raising the reaction temperature, so as to promote the preparation efficiency of C22TA and C22TAE. Therefore, in this study, conjugated dienes were also used as raw materials to investigate the yield of C22TA and C22TAE with and without the iodine catalyst, and the role of iodine in the Diels–Alder reaction was discussed based on the data.

Along these lines, in the work reported here, we focused on answering the following questions: What is the role of iodine in the Diels–Alder reaction? What is the effect of substituents of reactants on the reaction efficiency of dienophiles? What is the difference between conjugated double bonds and nonconjugated double bonds when participating in the Diels–Alder reaction? We took a spectroscopy approach by combining the results of ¹H-NMR, ¹³C-NMR, and electrospray ionization mass spectrometry (ESI-MS), and we systematically investigated the reaction processes of different PUFAs, PUFAEs, and dienophiles under different catalytic conditions. To the best of our knowledge, our work is the first attempt at answering these important questions, which have important theoretical and practical significance for the value-added product development of vegetable oil.

2. Results and Discussion

2.1. Synthesis and Characterization

C22TA and C22TAE were prepared via the Diels–Alder reaction of PUFAs and PUFAEs as dienes with fumaric acid (FA) and dimethyl fumarate (DF) as dienophiles, respectively, under various experimental conditions (Table 1). LA and its ester have two double bonds located on carbons 9 and 12, while conjugated double bonds of CLA and its ester were in the 9,11 or 10,12 positions. Each of the two double bonds can be in either *cis* or *trans* configuration [12]. In theory, the products of C22TA and C22TAE have different configurations. However, the purpose of this study was to unveil the mechanism of the Diels–Alder reaction; therefore, no attempt was made to separate the isomers. The ¹H-NMR spectra of dienes, as well as C22TA and C22TAE samples, are shown in Figures 1–4. The isomeric structures are displayed in the figures for dienes, C22TA, and C22TAE, respectively. The attributions of chemical shifts of the protons are labeled in the figure in detail.

Figure 1 shows the ¹H-NMR spectra of LA and the reaction compounds with dienophiles under different catalyst loading. Compound **1** was the reaction product of LA and FA with iodine catalysis. Compound **2** was the reaction product of LA and FA without iodine catalysis. Compound **3** was the reaction product of LA and DF with iodine catalysis. Compound **4** was the reaction product of LA and DF with iodine catalysis.

| Entry | Reaction Conditions | | | Compounds | |
|----------|---------------------|--------------------------|-------------------------------------|--|--------------|
| | Dienes (1 mol) | Dienophiles (1.1 mol) | Catalyst (0.3 wt.%) ¹ | Category | Yield (%) |
| 1 | LA | FA | Iodine | 22-Carbon tricarboxylic acid (C22TA) | 71.9 |
| 2 | LA | FA | / | / | / |
| 3 | LA | DF | Iodine | 22-Carbon tricarboxylic acid dimethyl ester (C22TADME) | 81.3 |
| 4 | LA | DF | / | / | / |
| 5 | ML | FA | Iodine | 22-Carbon tricarboxylic acid monomethyl ester (C22TAMME) | 65.4 |
| 6 | ML | FA | / | / | / |
| 7 | ML | DF | Iodine | 22-Carbon tricarboxylic acid trimethyl ester (C22TATME) | 76.3 |
| 8 | ML | DF | / | / | / |
| 9 10 | CLA CLA | DF DF | Iodine / | 22-Carbon tricarboxylic acid dimethyl ester (C22TADME) | 82.0 79.4 |
| 11 12 | CLAEE CLAEE | FA FA | Iodine / | 22-Carbon tricarboxylic acid monoethyl ester (C22TAMEE) | 74.4 71.4 |
| 13 14 | CLAEE CLAEE | DF DF | Iodine / | 22-Carbon tricarboxylic acid dimethyl monoethyl ester (C22TADMMEE) | 83.3 77.5 |

Table 1. Preparation and yield of 22-carbon tricarboxylic acid (C22TA) and its ester (C22TAE) via Diels–Alder reaction. FA—fumaric acid; DF—dimethyl fumarate; LA—linoleic acid; ML—methyl linoleate; CLA—conjugated linoleic acid; CLAEE—conjugated linoleic acid ethyl ester.

¹ The amount of iodine was the mass percentage of diene.



Figure 1. ¹H-NMR spectra of linoleic acid (LA) and reaction compounds with dienophiles in chloroform-d under different catalyst conditions: compound **1**, reaction product of LA and fumaric acid (FA) with iodine catalysis; compound **2**, reaction product of LA and FA without iodine catalysis; compound **3**, reaction product of LA and dimethyl fumarate (DF) with iodine catalysis; compound **4**, reaction product of LA and DF without iodine catalysis.

Compound 1 was obtained as C22TA. Its molecular formula $C_{22}H_{36}O_6$ was established from ESI-MS, m/z 395.24396 [M – H]⁻. The proton signals at δ H 5.85–5.58 (m) revealed the presence of a double bond of cyclohexene, and δ H 2.95–2.57 (m) revealed the presence of a methine of cyclohexene. The chemical shifts at 129.97, 44.16, and 39.29 ppm were correspondingly attributed to the carbons in the cyclohexene (Figure S21, Supplementary Materials). These results implied that a Diels-Alder reaction occurred between LA and FA in the presence of iodine catalysis. Compound 3 was obtained as 22-carbon tricarboxylic acid dimethyl ester (C22TADME). Its molecular formula $C_{24}H_{40}O_6$ was established from ESI-MS, *m*/z 425.28860 [M + H]⁺, 447.27042 [M + Na]⁺, 463.24426 [M + K]⁺. The proton signals at δ H 5.85–5.50 (m) revealed the presence of a double bond of cyclohexene. Signals at δ H 3.04 (dd) and 2.63–2.46 (m) revealed the presence of a methine of cyclohexene. Signals at δ H 3.82–3.53 (m) revealed the presence of a methoxy of dimethyl ester attached to cyclohexene. The chemical shifts at 129.96, 46.92, and 39.68 ppm were correspondingly attributed to the carbons in the cyclohexene (Figure S22, Supplementary Materials). These results implied that a Diels-Alder reaction occurred between LA and DF with iodine catalysis. However, the ¹H-NMR spectra of compound **2** and compound 4 were similar to that of LA, and no new peak was generated. These results indicated that no Diels-Alder reaction took place between LA and dienophiles (FA or DF) in the absence of iodine catalyst under the same heating conditions. The ¹H-NMR chemical shifts of C22TA and C22TADME in this study were in agreement with the data reported in the literature [18].

Figure 2 shows the ¹H-NMR spectra of methyl linoleate (ML) and the reaction compounds with dienophiles under different catalyst conditions. Compound **5** was the reaction product of ML and FA with iodine catalysis; compound **6** was the reaction product of ML and FA without iodine catalysis; compound **7** was the reaction product of ML and DF with iodine catalysis; compound **8** was the reaction product of ML and DF with iodine catalysis; compound **8** was the reaction product of ML and DF without iodine catalysis.

Compound 5 was obtained as 22-carbon tricarboxylic acid monomethyl ester (C22TAMME). Its molecular formula $C_{23}H_{38}O_6$ was established from ESI-MS, m/z 409.25961 [M – H]⁻. The proton signal at δ H 5.85–5.50 (m) revealed the presence of a double bond of cyclohexene, and that at δ H 3.08–2.48 (m) revealed the presence of a methine of cyclohexene. The chemical shifts at 129.94, 44.15, and 39.20 ppm were correspondingly attributed to the carbons in the cyclohexene (Figure S23, Supplementary Materials). These results implied that a Diels–Alder reaction occurred between ML and FA with iodine catalysis. Compound 7 was obtained as 22-carbon tricarboxylic acid trimethyl ester (C22TATME). Its molecular formula $C_{25}H_{42}O_6$ was established from ESI-MS, m/z 439.30475 [M + H]⁺, 461.28638 [M + Na]⁺, 477.26047 [M + K]⁺. The proton signal at δ H 5.99–5.50 (m) revealed the presence of a double bond of cyclohexene, and that at δ H 3.04(dd), 2.67–2.43 (m) revealed the presence of a methine of cyclohexene. The chemical shifts at 129.97, 46.91, and 39.67 ppm were correspondingly attributed to the carbons in the cyclohexene (Figure S24, Supplementary Materials). These results implied that a Diels-Alder reaction occurred between ML and DF with iodine catalysis. However, the ¹H-NMR spectra of compound 6 and compound 8 were similar to that of starting material ML, and no new peak was observed. These results indicated that no Diels-Alder reaction took place between ML and dienophiles (FA or DF) in the absence of iodine catalyst and under the same heating conditions.



Figure 2. ¹H-NMR spectra of methyl linoleate (ML) and the reaction compounds with dienophiles in chloroform-d under different catalyst conditions: compound **5**, reaction products of ML and FA with iodine catalysis; compound **6**, reaction products of ML and FA without iodine catalysis; compound **7**, reaction products of ML and DF with iodine catalysis; compound **8**, reaction products of ML and DF without iodine catalysis.

The results in Figures 1 and 2 showed that dienes without conjugated double bonds must have iodine as a catalyst to facilitate the Diels–Alder reaction. Under heating conditions, without a catalyst, the nonconjugated double bonds of dienes cannot be converted efficiently to conjugated double bonds. In order to further investigate the role of iodine in the Diels–Alder reaction, more studies were carried out by investigating the reaction of PUFAs containing conjugated double bonds as dienes with dienophiles under different conditions.

Figure 3 shows the ¹H-NMR spectra of CLA (conjugated linoleic acid) with conjugated double bonds and the reaction compounds with dienophiles under different catalyst conditions. Compound **9** was the reaction product of CLA and DF with iodine catalysis; compound **10** was the reaction product of CLA and FA without iodine catalysis.

Both compound **9** and compound **10** were obtained as C22TADME, the same as Compound **3**. Its molecular formula $C_{24}H_{40}O_6$ was established from ESI-MS: compound **9**, *m*/*z* 425.28876 [M + H]⁺, 447.27066 [M + Na]⁺, 463.24426 [M + K]⁺; compound **10**, *m*/*z* 425.28879 [M + H]⁺, 447.27072 [M + Na]⁺, 463.24438 [M + K]⁺. The proton signal of compound **9** at δ H 3.13–2.98 (m) and the proton signal of compound **10** at δ H 2.63–2.42 (m) revealed the presence of a methine of cyclohexene, while the proton signals of compound **9** and compound **10** at δ H 3.72–3.61 (m) revealed the presence of a methoxy of dimethyl ester attached to cyclohexene. The chemical shifts of compound **9** and compound **10** at 129.95, 46.91, and 39.67 ppm were correspondingly attributed to the carbons in the cyclohexene (Figures S25 and S26, Supplementary Materials). These results implied that a Diels–Alder reaction occurred between CLA and DF with and without iodine catalysis. Dienes containing conjugated double bonds such as CLA can react with dienes under heating conditions.



Figure 3. ¹H-NMR spectra of conjugated linoleic acid (CLA) and the reaction compounds with dienophiles in chloroform-d under different catalyst conditions: compound **9**, reaction products of CLA and DF with iodine catalysis; compound **10**, reaction products of CLA and DF without iodine catalysis.

Figure 4 shows the ¹H-NMR spectra of conjugated linoleic acid ethyl ester (CLAEE) with conjugated double bonds and the reaction compounds with dienophiles under different catalyst conditions. Compound **11** was the reaction product of CLAEE and FA with iodine catalysis; compound **12** was the reaction product of CLAEE and FA without iodine catalysis; compound **13** was the reaction product of CLAEE and DF with iodine catalysis; compound **14** was the reaction product of CLAEE and DF without iodine catalysis.

Both compound **11** and compound **12** were obtained as 22-carbon tricarboxylic acid monoethyl ester (C22TAMEE). Its molecular formula $C_{24}H_{40}O_6$ was established from ESI-MS: compound **11**, *m/z* 423.27524 [M – H]⁻; compound **12**, *m/z* 423.27551 [M – H]⁻. The proton signals of compound **11** at δ H 5.74 (s) and compound **12** at δ H 5.76 (m) revealed the presence of a double bond of cyclohexene; those of compound **11** at δ H 2.87 (d) and δ H 2.19–1.94 (m) and compound **12** at δ H 2.87 (d) and δ H 2.04–1.89 (m) revealed the presence of a methine of cyclohexene. The chemical shifts of compound **11** at 129.92, 44.14, and 39.53 ppm were correspondingly attributed to the carbons in the cyclohexene (Figure S27, Supplementary Materials). The chemical shifts of compound **12** at 129.85 and 44.15 ppm were correspondingly attributed to the carbons in the cyclohexene (Figure S28, Supplementary Materials). These results implied that a Diels–Alder reaction occurred between CLAEE and FA with and without iodine catalysis. Dienes containing conjugated double bonds such as CLAEE can react with dienes under heating conditions.

Both compound **13** and compound **14** were obtained as 22-carbon tricarboxylic acid dimethyl monoethyl ester (C22TADMMEE). Its molecular formula $C_{26}H_{44}O_6$ was established from ESI-MS: compound **13**, *m*/*z* 453.31989 [M + H]⁺, 475.30170 [M + Na]⁺, 491.27563 [M + K]⁺; compound **14**, *m*/*z* 453.32010 [M + H]⁺, 475.30191 [M + Na]⁺, 491.27591 [M + K]⁺. The proton signals of compound **13** at δ H 5.84–5.72 (m) and compound **14** at δ H 5.90 (m) revealed the presence of a double bond of cyclohexene. Those of compound **13** at δ H 3.03 (m) and δ H 2.64–2.39 (m) and compound **14** at δ H 3.72–3.61 (m) revealed the presence of a methoxy of dimethyl ester attached to cyclohexene. The chemical shifts of compound **13** at 129.10, 46.91, and 39.67 ppm were

correspondingly attributed to the carbons in the cyclohexene (Figure S29, Supplementary Materials). The chemical shifts of compound **14** at 130.05, 46.91, and 39.67 ppm were correspondingly attributed to the carbons in the cyclohexene (Figure S30, Supplementary Materials). These results implied that a Diels–Alder reaction occurred between CLAEE and DF with and without iodine catalysis. Dienes containing conjugated double bonds such as CLAEE can react with dienes under heating conditions.



Figure 4. ¹H-NMR spectrum of conjugated linoleic acid ethyl ester (CLAEE) and the reaction compounds with dienophiles in chloroform-d under different catalyst conditions: compound **11**, reaction products of CLAEE and FA with iodine catalysis; compound **12**, reaction products of CLAEE and FA without iodine catalysis; compound **13**, reaction products of CLAEE and DF with iodine catalysis; compound **14**, reaction products of CLAEE and DF with iodine catalysis; compound **14**, reaction products of CLAEE and DF without iodine catalysis.

The results of ¹H-NMR, ¹³C-NMR, and ESI-MS supported the successful synthesis of C22TA and C22TAE. All C22TAs and their esters, C22TADME, C22TAMME, C22TATME, C22TAMEE, and C22TADMMEE, were liquid at room temperature, which would be desirable for many applications.

2.2. The Role of Iodine in Diels-Alder Reaction

The reaction yields of C22TA and C22TAE prepared via Diels–Alder reaction under different experimental conditions, calculated according to the ¹H-NMR spectra, are shown in Table 1.

Under heating conditions, a Diels–Alder reaction did not take place between dienes and dienophiles in the absence of iodine catalyst, while Diels–Alder reactions occurred with iodine catalysis. These results indicated that the isomerization catalyst was necessary to transform the dienes of nonconjugated double bonds into a suitable configuration for the reaction [19]. The iodine catalyst was important for conjugated double bond formation. There are many methods of making conjugated double bonds; however, iodine was selected in this study, because iodine can minimize side reactions and unnecessary double-bond migrations [20].

In general, the Diels–Alder reactions occur with dienophiles containing conjugated double bonds [7,20–22]. Therefore, the participation of LA and its esters in the Diels–Alder reaction was due to the conversion of the nonconjugated double bonds into conjugated double bonds. The Diels–Alder

reaction could occur on the conjugated double bonds at C9 and C11 for 9t,11t CLA and its ester or at C10 and C12 for 10t,12t CLA and its ester [23,24]. Herein, the reactions of PUFAs and dienophiles without catalysts were used as the reference reaction for the discussion of subsequent mechanisms with iodine catalysts and PUFA. No attempt was made to separate the isomers in this study.

Diels–Alder reactions can occur between LA and its ester with dienophiles under the catalysis of iodine [11,25]. The possible mechanism of iodine converting nonconjugated double bonds into conjugated double bonds of LA and its ester, along with the traditional alkali isomerization mechanism, is shown in Scheme 1. It was proposed that iodine turned nonconjugated double bonds into conjugated double bonds via radical processes. The mechanism of iodine isomerization of LA was possibly the same as that of photoisomerization in the presence of iodine [23]. However, the process was initiated via heat source. As shown in Scheme 1, under heating, iodine formed two I[•] radicals, which in turn reacted with the unsaturated molecule. When I[•] abstracted an allylic hydrogen, positional isomerization process, the main bases used include inorganic bases NaOH and KOH, and organic bases sodium ethoxide, sodium methoxide, tetraethyl ammonium hydroxide, etc. [28–30]. The essence of alkali isomerization involves the process of a carbon anion, and its reaction mechanism features the base grabbing the protons of the allylic hydrogen of LA and its ester to generate a carbon anion, followed by the carbon anion rearranging to form a stable conjugated structure, thereby achieving a conjugated product [31,32].



Scheme 1. Mechanism of iodine and alkali isomerization of LA.

As can be seen from the results of entries 1–8 in Table 1, it was difficult for nonconjugated dienes and dienophiles to react without a catalyst. In addition, with iodine catalysis, the substituent on dienes and dienophiles had an effect on the efficiency of the Diels–Alder reaction. The yields of C22TA (C22TAE) in the reaction of LA with FA and DA were 71.9% and 81.3%, respectively. The yield of the latter was 13.1% higher than that of the former. The yields of C22TA (C22TAE) from ML in the reaction with FA and DF were 65.4% and 76.3%, respectively. The yield of the latter was 16.7% higher than that of the former. The yield of C22TA (C22TAE) prepared via the reaction of dienes with FA was lower than that with DF. The same trend was observed for entries 11–14 in Table 1. The yield of C22TA (C22TAE) prepared via reaction with FA was lower than that with DF with and without catalyst. With catalyst, the yields of CLAEE reacting with FA and DF were 74.4% and 83.3% respectively, while the yields were 71.4% and 77.5%, respectively, without the catalyst.

This was mainly because DF, the dienophile with an electron-withdrawing group, was more favorable for the Diels–Alder reaction than FA [33]. According to frontier molecular orbital theory

(FMO), the Diels–Alder reaction is controlled by the suprafacial in-phase interaction of the highest occupied molecular orbital (HOMO) of one component and the lowest unoccupied molecular orbital (LUMO) of the other [34,35]. The reactivity of a Diels–Alder reaction depends upon the HOMO–LUMO energy gap of the components: a lower energy difference results in a lower transition state energy of the reaction. Electron-withdrawing substituents lower the energies of both HOMO and LUMO, while electron-donating groups increase their energies [36]. In general, a normal Diels–Alder reaction is accelerated by electron-donating substituents in the diene and by electron-withdrawing substituents in the diene phile [37].

As can be seen from the results of entries 9–14 in Table 1, Diels–Alder reactions between dienes and dienophiles containing conjugated double bonds could occur without a catalyst. However, the iodine catalyst had a certain positive effect on the efficiency of the Diels–Alder reaction. The yields of C22TAE were 82.0%, 79.4%, 74.4%, 71.4%, 83.3%, and 77.5%, respectively, under the conditions of CLA and DF, CLAEE and FA, and CLAEE and DF with and without catalyst. The results showed that the yields of C22TAE with iodine catalyst were higher than those without catalyst.

This was mainly because iodine is a mild Lewis acid. Lewis acids can greatly accelerate cycloaddition [38]. The catalytic effect is explained by FMO theory, considering that the coordination of the carbonyl oxygen by a Lewis acid increases the electron-withdrawing effect of the carbonyl group on the carbon–carbon double bond and lowers the LUMO dienophile energy [39]. It reduces the energy difference between the HOMO of dienes and the LUMO of dienophiles, thus facilitating the Diels–Alder reaction [37].

3. Materials and Methods

3.1. Materials

Linoleic acid (LA, 60%, Acros Organics) was purchased from Beijing Innochem Co., Ltd., Beijing, China. Fumaric acid (FA, 99%) was purchased from Shanghai Shanpu Chemical Co., Ltd., Shanghai, China. Dimethyl fumarate (DF, 97%, Accela) was purchased from Shanghai Shaoyuan Co., Ltd., Shanghai, China. Methyl alcohol (99.5%), sulfuric acid (98%), potassium hydroxide (95%), and iodine (99.5%) were purchased from Tianjin Chemical Reagent Co., Ltd., Tianjin, China. Conjugated linoleic acid (CLA, 85%) and conjugated linoleic acid ethyl ester (CLAEE, 70%) were obtained from Xinjiang Technical Institute of Physics and Chemistry (Xinjiang, China.). All chemicals were used without further purification unless notified. Deionized water was used throughout the experiments.

3.2. Synthesis of Methyl Linoleate (ML)

A typical procedure for the synthesis of ML was as follows: firstly, 100 g of LA, 70 g of methyl alcohol, and 1.4 g of sulfuric acid as catalyst were mixed in a 250-mL three-neck round-bottom flask and refluxed at 80 °C for 6 h. The flask was equipped with a mechanical stirrer, a thermometer, and a condenser. The reaction products were separated with by-product glycerol using a separating funnel for standing stratification. The supernatant was crude ML. Then, the crude ML was washed with deionized water (50 °C) to a neutral pH. The crude product was transferred into a 250-mL three-neck round-bottom flask for vacuum distillation at 60 °C to remove the residual water and methyl alcohol. Finally, the product ML was obtained.

3.3. Synthesis of 22-Carbon Tricarboxylic Acid (C22TA) and 22-Carbon Tricarboxylic Ester (C22TAE)

C22TA and C22TAE were synthesized using the method of Vijayalakshmi et al. [8]. Firstly, 1 mol of PUFA or PUFAE and 1.1 mol of dienophiles were mixed in a 250-mL three-neck round-bottom flask. To this one-step process, catalytic amounts of iodine were 0 wt.% or 0.3 wt.% based on the amounts of PUFA or PUFAE. The flask was equipped with a mechanical stirrer, a thermometer, and a condenser. The reaction mixture was heated up within 30 min to 200 °C and maintained at 2 h. The unreacted dienophile was removed by vacuum distillation in steam (<15 MPa, 200 °C). PUFAs used in this study

were LA and CLA. PUFAEs used in this study were ML and CLAEE. Dienophiles used in this study were FA and DF. The typical synthesis routes of C22TA and C22TAE are shown in Scheme 2.



Scheme 2. The typical synthesis routes of 22-carbon tricarboxylic acid (C22TA) and its ester (C22TAE).

3.4. Characterization

NMR spectra were recorded on an NMR spectrometer (Varian, Palo Alto, CA, USA) at 400 (¹H) or 100 (¹³C) MHz in deuterated chloroform (CDCl₃) or deuterated dimethyl sulfoxide (DMSO-d₆). Chemical shifts relative to that of chloroform (7.24) or DMSO (2.47) were reported. ESI-MS spectra were determined on a Waters UPLC-Quattro Premier XE UPLC–MS/MS (Ultimate 3000/Q-Exactive, Thermo Fisher Scientific., Waltham, MA, USA). The ESI flow rate of the electrospray ion source was 1–2000 μ L·min⁻¹.

4. Conclusions

¹H-NMR, ¹³C-NMR, and ESI-MS spectrometry were used to investigate the efficiency of Diels–Alder reactions under different reaction conditions. PUFAs (PUFAEs) such as LA, ML, CLA, and CLAEE were used as dienes, fumaric acid and dimethyl fumarate were used as dienophiles, and iodine was used as a catalyst to investigate the yield of C22TA (C22TAE) with or without catalyst. Results showed that, for dienes without conjugated double bonds to participate in a Diels–Alder reaction, iodine was necessary as the catalyst. Under heating conditions, without iodine catalyst, the nonconjugated double bonds of dienes cannot be converted effectively to conjugated double bonds. For dienes with conjugated double bonds, Diels–Alder reactions can occur with dienes under heating conditions without catalyst. However, the yield of C22TAE with iodine catalyst was higher than that without iodine catalyst. The yield of C22TA (C22TAE) prepared via the reaction of diene with DF was higher than that with FA. The mechanism of the Diels–Alder reaction for the synthesis of C22TA (C22TAE) is proposed below.

(1) The catalyst iodine plays two roles in the synthesis of C22TA (C22TAE). On the one hand, it transforms the nonconjugated double bonds of diene into conjugated double bonds via radical processes. Then, the conjugated diene participates in a Diels–Alder reaction to form C22TA (C22TAE). On the other hand, iodine can indeed improve the yield of C22TA (C22TAE), which is beneficial to the reaction. Compared with the Diels–Alder reaction system without the catalyst, iodine as a Lewis acid increases the electron-withdrawing effect of the carbonyl group on the carbon–carbon double bond and lowers the LUMO dienophile energy. It reduces the energy difference between the HOMO of diene and the LUMO of dienophile, thus facilitating the Diels–Alder reaction.

(2) The type of diene determines whether an iodine catalyst needs to be added for the synthesis of C22TA (C22TAE). For dienes without conjugated double bonds, iodine must be added as a catalyst to prepare C22TA (C22TAE). However, for dienes with conjugated double bonds, C22TA (C22TAE) can be obtained without iodine, but the product yield can be improved by adding iodine to the reaction system. However, one should keep in mind that, with the addition of iodine, the prepared product usually has a deep brown color and an extra decolorization procedure is usually needed.

(3) The type of substituent in the dienophile directly affects the yield of C22TA (C22TAE). When the dienophile has electron-withdrawing substituents, the efficiency of the Diels–Alder reaction is higher, and the yield of C22TA (C22TAE) is higher. The electron-withdrawing substituents in the dienophile reduce the HOMO–LUMO energy and accelerate the normal Diels–Alder reactions. C22TA (C22TAE) synthesized in this study has excellent biodegradability, superior properties, and great

market potential. The spectroscopic data and proposed mechanism of the Diels–Alder reaction could be useful for the design and preparation of C22TA (C22TAE) and cyclohexene derivatives.

Supplementary Materials: The following are available online at http://www.mdpi.com/2073-4344/9/12/972/s1: Figure S1: ESI-MS spectrum of compound 1 C22TA; Figure S2: ESI-MS spectrum of compound 3 C22TADME; Figure S3: ESI-MS spectrum of compound 5 C22TAMME; Figure S4: ESI-MS spectrum of compound 7 C22TATME; Figure S5: ESI-MS spectrum of compound 9 C22TADME; Figure S6: ESI-MS spectrum of compound 10 C22TADME; Figure S7: ESI-MS spectrum of compound 11 C22TAMEE; Figure S8: ESI-MS spectrum of compound 12 C22TAMEE; Figure S9: ESI-MS spectrum of compound 13 C22TADMMEE; Figure S10: ESI-MS spectrum of compound 14 C22TADMMEE; Figure S11: ¹H-NMR spectrum of compound 1 C22TA; Figure S12: ¹H-NMR spectrum of compound 3 C22TADME; Figure S13: ¹H-NMR spectrum of compound 5 C22TAMME; Figure S14: ¹H-NMR spectrum of compound 7 C22TATME; Figure S15: ¹H-NMR spectrum of compound 9 C22TADME; Figure S16: ¹H-NMR spectrum of compound 10 C22TADME; Figure S17: ¹H-NMR spectrum of compound 11 C22TAMEE; Figure S18: ¹H-NMR spectrum of compound 12 C22TAMEE; Figure S19: ¹H-NMR spectrum of compound 13 C22TADMMEE; Figure S20: ¹H-NMR spectrum of compound 14 C22TADMMEE; Figure S21: ¹³C-NMR spectrum of compound 1 C22TA; Figure S22: ¹³C-NMR spectrum of compound 3 C22TADME; Figure S23: ¹³C-NMR spectrum of compound 5 C22TAMME; Figure S24: ¹³C-NMR spectrum of compound 7 C22TATME; Figure S25: ¹³C-NMR spectrum of compound 9 C22TADME; Figure S26: ¹³C-NMR spectrum of compound 10 C22TADME; Figure S27: ¹³C-NMR spectrum of compound 11 C22TAMEE; Figure S28: ¹³C-NMR spectrum of compound 12 C22TAMEE; Figure S29: ¹³C-NMR spectrum of compound 13 C22TADMMEE; Figure S30: ¹³C-NMR spectrum of compound 14 C22TADMMEE.

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Table of Contents: The Role of Iodine Catalyst in the Synthesis of 22-Carbon Tricarboxylic Acid and Its Ester: A Case Study.



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