

A Proposed Stereochemical Mechanism for the Improved Preparation of Maleic Anhydride Cycloadduct of CLA

Jieyu He^{1*}, Jiashu Liao², Junyan Qu¹

¹College of Marine Science & Technology, Hainan Tropical Ocean University, Sanya, China

²College of Chemistry & Chemical Engineering, Hunan Institute of Science & Technology, Yueyang, China

Email: *jyhe555@163.com

How to cite this paper: He, J.Y., Liao, J.S. and Qu, J.Y. (2021) A Proposed Stereochemical Mechanism for the Improved Preparation of Maleic Anhydride Cycloadduct of CLA. *Computational Chemistry*, 9, 144-160. <https://doi.org/10.4236/cc.2021.93009>

Received: May 29, 2021

Accepted: July 11, 2021

Published: July 14, 2021

Copyright © 2021 by author(s) and Scientific Research Publishing Inc. This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).

<http://creativecommons.org/licenses/by/4.0/>



Open Access

Abstract

The fatty acid derivatives, prepared from renewable natural oils, can be used as highly promising and potential substitutes for petrochemicals. The study of process improvement and stereochemical mechanism for preparing these derivatives would be beneficial for their industrial production. Conjugated linoleic acid (CLA) containing 9*cis*-11*trans* (9*c*, 11*t*) and 10*trans*-12*cis* (10*t*, 12*c*) isomers was prepared from *Salicornia herbacea* seed oil. Maleic anhydride cycloadduct of CLA (MAC) was prepared by an improved process, and it was characterized by FTIR, ¹H and ¹³C NMR, *etc.* A new method to calculate conformers-ratio of CLA or MAC was also developed. Furthermore, the stereochemical mechanism for the improved preparation of MAC was proposed primarily by the calculation method above. The following observations were made: 1) The yield of MAC could reach as high as 96.7% under mild reaction conditions and with an easy and efficient product separation; 2) The *trans-trans* CLA in the *s-cis* conformation acted as a predominant reactant to *Diels-Alder* [4 + 2] cycloaddition of maleic anhydride, which was the main reaction occurred simultaneously with catalytic configurational isomerizations of CLA in one step; 3) From all studied CLA conformers, the most stable conformation was the *s-trans* conformation of *trans-trans* CLA, while the *s-cis* conformation of *trans-trans* CLA had the most favorable structural parameters for cyclohexenyl ring formation; 4) Four MAC conformers derived from 9*c*, 11*t*- and 10*t*, 12*c*-CLA, were obtained as final main products that were determined to be *cis*-cycloadducts; 5) The *endo/exo* ratios of the *cis*-cycloadducts derived from 9*c*, 11*t*- and 10*t*, 12*c*-CLA, were 2.14:1 and 1.99:1, respectively; and 6) The results obtained from the calculation method above were in excellent accordance with those from our experiments.

Keywords

Maleic Anhydride Cycloadducts, Improved Preparation, Conjugated Linoleic Acid, Stereochemical Mechanism, Conformers-Ratio Calculation, Conformational Isomerization

1. Introduction

As a green and renewable alternative to petroleum-based derivatives, MAC is a promising organic polyacid that can be widely used in the production of resin additives, complexing agents, surfactants, corrosion inhibitors, etc [1] [2] [3]. Traditionally, three independent steps were required to prepare MAC. The first step was the conjugation isomerization of linoleic acid from vegetable oils, by which CLA containing *cis-trans* or/and *trans-cis* isomer(s) was prepared; the configurational isomerization of CLA into *trans-trans* form by a catalyst was carried out during the second step, and the synthesis of MAC by *Diels-Alder* cycloaddition of maleic anhydride with the *trans-trans* CLA was performed during the third step. A one-pot method (*i.e.*, direct reaction of linoleic acid with maleic anhydride) for preparing MAC was reported by *Watanabe et al.* [4], however, a low yield of 58% under high temperature and high pressure was observed. Afterwards, microwave-assisted organic synthesis and continuous-flow techniques to prepare MAC were employed with a relatively higher yield of 86% [5]. To the best of our knowledge, no attempt has been made to prepare MAC by the improved process, as well as to propose the stereochemical mechanism by some calculation methods.

In this work, CLA was prepared by using *Salicornia herbacea* seed oil as a starting material, due to the high content of linoleic acid in this oil. Besides, several improvements for the preparation of MAC were developed. For example, the latter two steps described in the traditional processes (*i.e.*, configurational isomerization and *Diels-Alder* cycloaddition) were merged, and a facile oil-bath approach under mild reaction conditions (e.g., lower temperature and atmospheric pressure) was carried out. Thereby MAC could be prepared in this one-step procedure without any additional solvent or pre-transformation of as-prepared CLA into *trans-trans* form. In addition, the product separation procedures were improved as well; e.g., the rapid and simultaneous separation of the spent catalyst and residual CLA from reaction mixtures could be achieved by using *n*-octane as the selective solvent.

To further study the stereochemical mechanism for the improved preparation of MAC, a new method for calculation of conformers-ratio of CLA or MAC in the stereochemical reactions was developed based on Maxwell–Boltzmann statistics [6] [7]. The influences of structural parameters, electron-donor abilities and stabilities of CLA conformers on the stereochemical reactions were investigated by the developed calculation method, FMO theory [8] and Mopac-AM1

algorithm in Chem3D Ultra 10.0 [9] [10]. The molecular structure of MAC was correctly established firstly. Besides, the two key factors influencing the stereochemical reactions in the preparation of MAC, reaction temperature and catalyst dosage, were also investigated in this work.

2. Materials and Methods

2.1. Materials

All chemicals and solvents used in this work were of analytical grade and purchased from Sinopharm Chemical Reagent CO., Ltd (Shanghai, China). *Salicornia herbacea* seed oil (containing 77.2 wt% of linoleic acid) from Leizhou Peninsula, China, was provided by College of Life Sciences & Ecology at our university. Methyl linoleate was prepared by the transesterification of *Salicornia herbacea* seed oil with methanol for determining the percentage of linoleic acid by gas chromatography (GC).

2.2. Preparation and GC Analysis of CLA

By using *Salicornia herbacea* seed oil as a starting material, CLA was prepared according to the previously reported method [11]. Ethylene glycol (50.0 g) and potassium hydroxide (10.0 g) were added to a 250 mL of round-bottom flask under nitrogen (N_2) atmosphere (N_2 gas was blown at a rate of 30 mL·min⁻¹). The reaction mixture was stirred continuously at 160 °C until all potassium hydroxide was dissolved. Then *Salicornia herbacea* seed oil (25.0 g) was added into the mixture and the reaction was heated up to 180 °C for 4.0 hrs. After the reaction was completed, the mixture was cooled to 80 °C and then acidified with hydrochloric acid (pH < 2), and extracted with 100 mL of hexane. The hexane extract was washed to neutral with double distilled water. Anhydrous sodium sulfate was added to remove residual water. CLA was obtained by vacuum distillation.

The percentages of CLA isomers were determined by GC, which was performed on a Shimadzu GC-2010/AOC-20i. The chromatographic conditions were selected as follows: FID detector; chromatographic column, DB-WAX (20 m × 0.25 mm × 0.25 μm); temperature programmed: column temperature was kept constant at 140 °C for 4 min, then increased to 230 °C at a rate of 30 °C/min and kept constant for 20 min; carrier gas (N_2) flow-rate 1.28 mL/min; pressure 128 kPa; sample size 2 μL; and split ratio 1:30. The two major isomers, 9*c*, 11*t* and 10*t*, 12*c*, in as-prepared CLA, were quantitatively determined by GC. And 9*c*, 11*t* isomer accounted for 63.82 wt%.

2.3. Improved Preparation of MAC

An improved process for preparing MAC was carried out. CLA (14.85 g, about 0.05 mol of carboxyl group), maleic anhydride (5.88 g, 0.06 mol) and iodine (0.04 g, 0.31 mmol) were added to a 100 mL of round-bottom flask under nitrogen (N_2) atmosphere (N_2 gas was blown into the reaction at a rate of 15 mL·min⁻¹).

The mixture was evenly dispersed under stirring and heated up to 60°C for 4.0 hrs in an oil-bath. After the reaction was completed, 50 mL of *n*-octane was added into the reaction; and the mixture was stirred to obtain a homogeneous dispersion. After being cooled to the room temperature, the mixture was filtrated to remove the solvent. The residual solid on the filter paper was collected and dissolved in 50 mL of diethyl ether, which was washed using deionized water until the filtrate became neutral. A white solid of MAC (approx. 18.3 g) could be obtained by removing ether *via* distillation. The crude product was purified by recrystallization from petroleum ether/diethyl ether (volume ratio of 4:1). Melting point: 56.5°C; Elemental analysis (C₂₂H₃₄O₅): measured value (calculated value, %): C, 69.90 (69.81); H, 9.08 (9.06).

2.4. FTIR and NMR Characterization of MAC

FTIR spectrum was recorded on a Shimadzu FTIR-8400S spectrophotometer in the range of 400 to 4000 cm⁻¹ by the KBr pellet pressed technique. ¹H and ¹³C NMR spectra were recorded on a Bruker AV 400 NMR spectrometer in CDCl₃; and chemical shifts were referenced to an internal standard tetramethylsilane (TMS).

3. Results and Discussions

3.1. Effects of Reaction Temperature on Yield of MAC

The reaction temperature played a decisive role in the preparation of MAC by CLA. The yields of MAC under different reaction temperatures were shown (Figure 1). The conditions for the improved preparation of MAC were optimized as follows: molar ratio of CLA to maleic anhydride: 1:1.2, reaction time: 4.0 hrs, and catalyst dosage: 0.2 wt%.

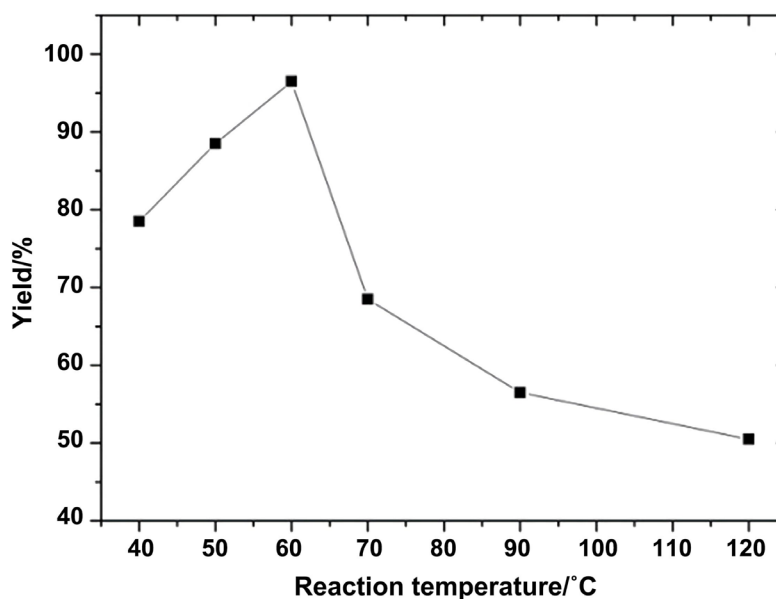


Figure 1. Effects of different reaction temperatures on yield of MAC.

It can be seen from **Figure 1** that the yield of MAC increased with an increase in the reaction temperature range 40°C to 60°C, and the highest yield of 96.7 wt% was obtained at 60°C. Then the yield decreased as the reaction temperature increased from 60°C to 120°C, indicating that the cycloaddition reaction was thermally reversible, and high reaction temperature was beneficial to the reverse reaction. Therefore, the cycloaddition reaction was carried out at 333.15 K (*i.e.*, 60°C); and a high yield of 96.7 wt% could be obtained for MAC, which was much higher than the results previously reported.

3.2 Effects of Catalyst Dosage on Yield of MAC

The cycloaddition of maleic anhydride could form a normal *Diels-Alder* adduct, which could be greatly facilitated if CLA has a *trans-trans* form [12]. Many methods available for the isomerization of CLA into *trans-trans* form from the *cis-trans* and *trans-cis* form were reported (e.g., *p*-toluene sulfonic acid-catalyzed, sulfur powder-catalyzed), while iodine was chosen as a catalyst in this work because side reactions and undesired double-bond migration could be minimized [13]. The yields of MAC under different dosages of iodine catalyst were shown (**Figure 2**). The conditions were set as follows: molar ratio of CLA to maleic anhydride: 1:1.2, reaction time: 4.0 hrs; and reaction temperature: 60°C.

It can be seen from **Figure 2** that the yield of MAC could reach as high as 96.7% at the catalyst dosage of 0.2 wt% (*versus* the total mass of the reactants). No desired product would be obtained in the absence of the catalyst, iodine, while a solid gel would be formed. This may be attributed to the fact that polymerization reaction, rather than *Diels-Alder* cycloaddition, would occur in the absence of iodine. That is to say, the [4 + 2] cycloaddition reaction between *trans-trans* CLA and maleic anhydride occurred due to the catalytic properties of configurational isomerization of CLA [14]. In addition, fewer yields would be obtained when

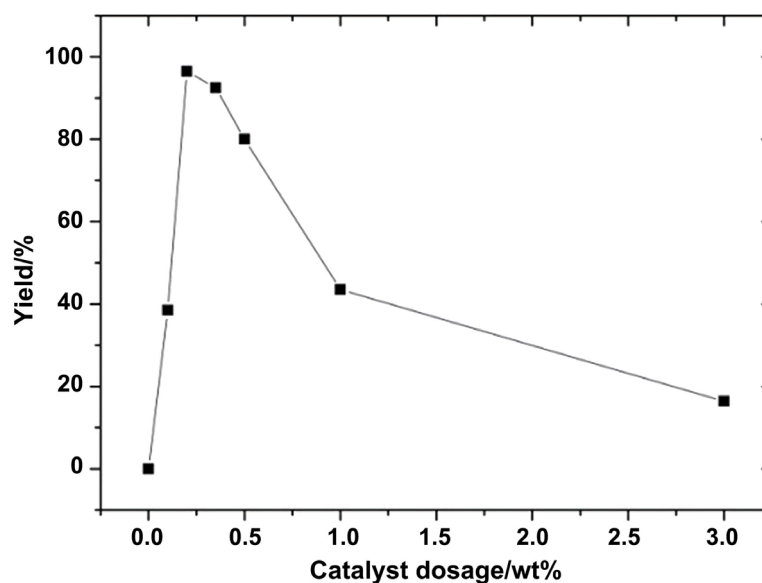


Figure 2. Effects of different catalyst dosages on yield of MAC.

catalyst dosage increased from 0.2 to 3.0 wt%, which may be due to the possible addition reaction between CLA and excessive iodine. Therefore, a small quantity of iodine was employed to induce the isomerization of *cis-trans* and *trans-cis* into *trans-trans* form during simultaneous cycloaddition of maleic anhydride. Nevertheless, there were too many different conformers for the same *trans-trans* CLA, and which conformations (-ratios) of desired product molecules would be generated from their cycloaddition reactions should be clearly demonstrated. Therefore, it is important to deeply investigate the possible stereochemical mechanism for the cycloaddition reaction abovementioned.

3.3. FTIR Analysis of MAC

FTIR spectrum of MAC purified by recrystallization was shown as **Figure 3**.

It can be seen from **Figure 3** that main absorption peaks were found as follows. The peaks at 3027.8, 1637.0 and 726.9 cm^{-1} could be attributed to $\nu(\text{C-H})$, $\nu(\text{C=C})$ and $\omega(\text{C-H})$ of cyclohexenyl group, respectively. The peaks at 1848.0, 1783.1 and 1192.3 cm^{-1} corresponded to $\nu_s(\text{C=O})$, $\nu_{as}(\text{C=O})$ and $\nu(\text{C-O})$ of pentacyclic dianhydride group, respectively. And the peaks at 2500.0 - 3550.0, 1703.5, and 939.8 cm^{-1} could be assigned to $\nu(\text{O-H})$, $\nu(\text{C=O})$ and $\delta(\text{C-OH})$ of carboxyl group, respectively. The presence of cyclohexenyl group confirmed that *Diels-Alder* [4 + 2] cycloaddition was carried out.

3.4. ^1H NMR Analysis of MAC

^1H NMR spectrum of the purified MAC was shown as **Figure 4**.

The specific analysis of **Figure 4** was as follows. ^1H NMR (CDCl_3 , 400 MHz) ppm: 5.82 (s, 2H), 3.36 - 3.35 (dd, $J = 4.5$ Hz, 2H), 2.37 - 2.34 (t, $J = 7.5$ Hz, 2H), 2.24 - 2.23 (m, 2H), 1.92 - 1.81(m, 2H), 1.80 - 1.74 (m, 2H), 1.66 - 1.63 (q, $J = 7$

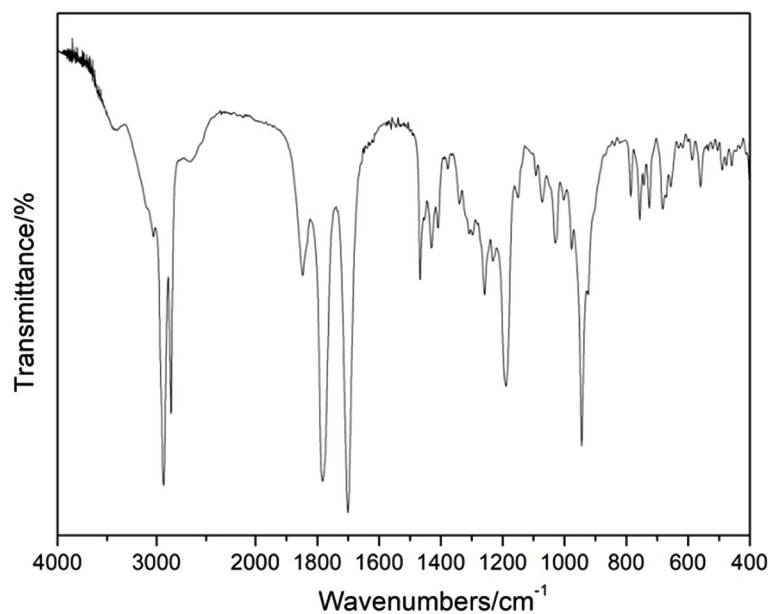


Figure 3. FTIR spectrum of MAC.

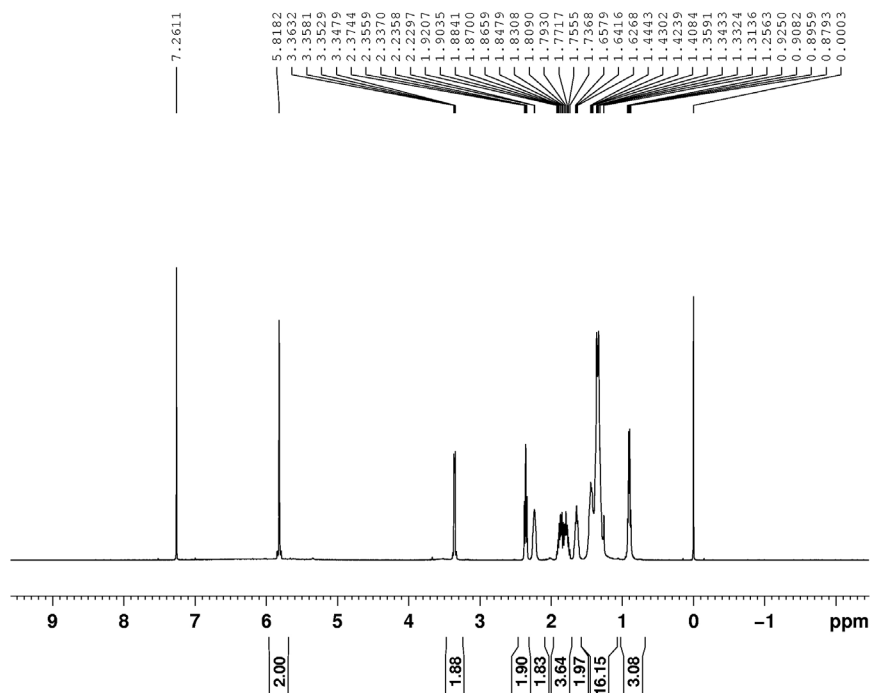


Figure 4. ^1H NMR spectrum of MAC.

Hz, 2H), 1.44 - 1.41 (m, 4H), 1.36 - 1.33 (m, 8H), 1.31 - 1.26 (m, 4H), and 0.93 - 0.88 (t, $J = 7$ Hz, 3H). The result of ^1H NMR analysis was consistent with that of FTIR.

3.5. ^{13}C NMR Analysis of MAC

^{13}C NMR spectrum of the purified MAC was given as **Figure 5**.

The attribution of the ^{13}C NMR chemical shifts in **Figure 5** was as follows. ^{13}C NMR (CDCl_3 , 100 MHz) ppm: 178.9 (COOH), 171.8 and 171.7 (C-1' and C-3'), 132.9 and 132.8 (C-5' and C-6'), 44.3 (C-3'a), 44.2 (C-7'a), 37.5 (C-4'), 37.4 (C-7'), 34.0 (C-2), 32.2 (C-4''), 31.7 (C-8), 30.1 (C-1''), 29.7 (C-3''), 29.3 (C-5), 29.1 (C-6), 29.0 (C-4), 27.6 (C-7), 27.4 (C-2''), 24.7 (C-3), 22.7 (C-5''), and 14.1 (C-6''). Accordingly, MAC molecular structure illustrated in **Figure 5** was obtained.

3.6. Stereochemical Mechanism for the Preparation of MAC

3.6.1. Proposed Stereochemical Reactions

Based on the experimental results, the possible stereochemical reactions in the preparation of MAC are proposed (**Scheme 1**).

As can be seen from **Scheme 1**, four stereochemical reactions are involved in the preparation of MAC: 1) constitutional isomerization of linoleic acid, *i.e.*, conjugated isomerization Equation (1); 2) configurational isomerization of CLA, *i.e.*, *cis/trans* isomerization Equation (4) and Equation (5); 3) conformational isomerization of conjugated dienes of CLA, *i.e.*, isomerization of conformer **1**, **2**, **6** and **7** into conformer **3**, **4**, **9** and **10**, respectively; and 4) cycloaddition reaction, *e.g.*, *Diels-Alder* reaction Equation (8) and Equation (9).

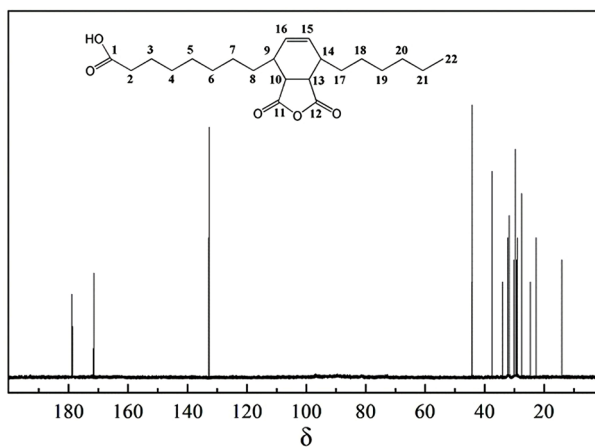
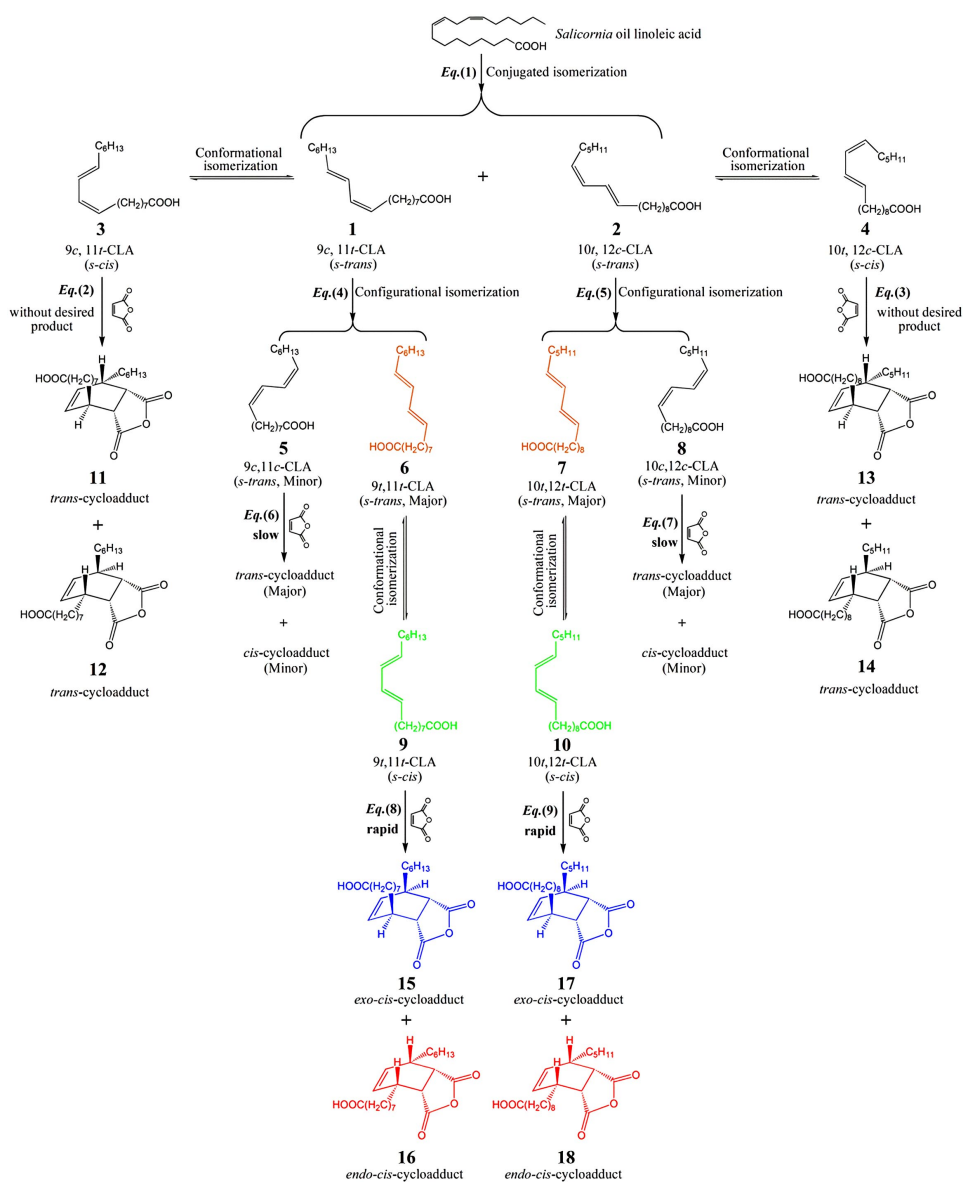


Figure 5. ^{13}C NMR spectrum of MAC.



Researches on the *Diels-Alder* reactions of simple conjugated dienes with maleic anhydride have been intensively concerned, allowing us to predict the reactions involving more complex conjugated dienes, such as CLA. Conjugated dienes can exist in two different planar conformations: an *s-trans* conformation and an *s-cis* conformation. *S-trans* means that the conjugated double bonds are *trans* about the single bond (*s* = single); while *s-cis* means that the conjugated double bonds are *cis* about the single bond. As far as we know, even in the same configuration, CLA can exist in many different conformations due to the free rotation of the single C-C bond. Hence, it is very critical for CLA conformer to display a more favorable geometric structure to react with maleic anhydride more appropriately. To further confirm this hypothesis, the influence of structural parameters of CLA conformers on the stereochemical reactions was firstly investigated by Mopac-AM₁ algorithm in Chem3D Ultra 10.0.

3.6.2. Structural Parameters of CLA and MAC Conformers

The Mopac-AM₁ algorithm in Chem3D Ultra 10.0 was employed to optimize the geometric structures of CLA and MAC conformers. This method was operated as follows: 1) draw 3D molecular structural models of different conformers by Chem3D Ultra 10.0; 2) start two “Minimize Energy” procedures successively in “MM2” and “Mopac interface” module on “Calculations” menu to alternatively optimize the geometric structure of these conformers till the standard formation enthalpy ($\Delta_f H_m^\theta$) remained almost unchanged (the gap between two $\Delta_f H_m^\theta$ s from adjacent optimizations was less than 0.1 Kcal·mol⁻¹); and 3) calculate quantum-chemical parameters of the optimized conformers by Mopac-AM₁ algorithm. The optimized geometric structures of CLA and MAC conformers derived from conformer **1** (*i.e.*, 9*c*, 11*t*-CLA) could be obtained (**Figure 6**). And the theoretical structural parameters of the conjugated dienes of CLA before and after cycloaddition reaction are also shown (**Table 1**).

It is obvious that no significant difference in both bond angles and bond lengths could be observed for CLA conformers or MAC conformers (**Table 1**). However,

Table 1. A comparison of theoretical structural parameters of the conjugated dienes before (in CLA) and after (in MAC) cycloaddition reaction.

Conformer		Bond angle/°		Bond length/Å			Dihedral angle/°	C ₉ →C ₁₂ distance/Å	
		C ₉ -C ₁₀ -C ₁₁	C ₁₀ -C ₁₁ -C ₁₂	C ₉ -C ₁₀	C ₁₀ -C ₁₁	C ₁₁ -C ₁₂	C ₉ -C ₁₀ -C ₁₁ -C ₁₂		
CLA	1	<i>s-trans</i>	124.8	123.0	1.341	1.448	1.341	-179.7	3.689
	3	<i>s-cis</i>	124.7	122.8	1.341	1.448	1.340	179.7	3.687
	5	<i>s-trans</i>	124.8	124.7	1.341	1.447	1.341	-179.0	3.703
	6	<i>s-trans</i>	123.1	123.0	1.340	1.448	1.341	179.9	3.677
	9	<i>s-cis</i>	125.1	125.4	1.340	1.447	1.341	-15.0	3.010
MAC	15	<i>exo-cis</i>	120.7	121.7	1.490	1.336	1.491	1.5	2.880
	16	<i>endo-cis</i>	119.6	119.5	1.491	1.338	1.491	0.0	2.809

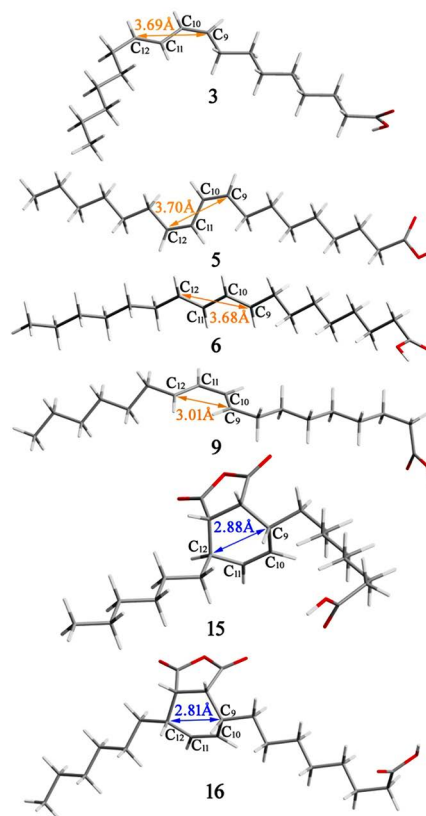


Figure 6. Optimized geometric structures of CLA and corresponding MAC conformers.

bond angles of CLA conformers were larger than those of MAC conformers. In addition, C_9-C_{10} and $C_{11}-C_{12}$ bond lengths of CLA conformers were shorter than those of MAC conformers, whereas $C_{10}-C_{11}$ bond of CLA conformers were relatively longer. We can speculate that the cyclohexenyl ring formation between maleic anhydride and conjugated dienes of CLA was responsible for the decrease in bond angles of MAC conformers. The stronger electron-withdrawing effect of dienophile (*i.e.*, maleic anhydride) would result in the increase in C_9-C_{10} and $C_{11}-C_{12}$ bond lengths of MAC conformers, and the transformation of $C_{10}-C_{11}$ bond geometry from sp^3-sp^3 hybridization (in CLA) into sp^2-sp^2 hybridization (in MAC) could lead to the decrease in $C_{10}-C_{11}$ bond lengths of MAC conformers. Normally, short bond will be formed if the s -character of a hybridized orbital increases. Obviously, greater proportion of s -character could be observed in the sp^2 hybridization than in the sp^3 hybridization.

Noticing that $C_9-C_{10}-C_{11}-C_{12}$ dihedral angle and $C_9 \leftrightarrow C_{12}$ distance of conformer **9** were distinctly different from those of other four CLA conformers (*i.e.*, conformer **1**, **3**, **5** and **6**), while the values of conformer **9** were close to those of MAC conformers (*i.e.*, conformer **15** and **16**). Although conformer **3** had the same *s-cis* conformation as conformer **9**, the values of $C_9-C_{10}-C_{11}-C_{12}$ dihedral angle and $C_9 \leftrightarrow C_{12}$ distance of the latter were much closer to those of MAC conformers than the former. Therefore, among all the CLA conformers derived from conformer **1** (*i.e.*, 9*c*, 11*t*-CLA), only conformer **9** displayed the most favorable

structural parameters for ring formation.

Similarly, through the comparison of structural parameters of other five CLA conformers (*i.e.*, conformer **2**, **4**, **7**, **8** and **10**) with those of corresponding MAC conformers (data not shown), we could find that among all the CLA conformers derived from conformer **2** (*i.e.*, 10*t*, 12*c*-CLA), conformer **10** exhibited more favorable structural parameters for ring formation, which was similar to conformer **9**.

3.6.3. Establishment of Conformers-Ratio Calculation Method

To deeply study the stereochemical mechanism for the preparation of MAC, we also developed a new method for calculating conformers-ratio (*i.e.*, N_i/N_j) of CLA or MAC. The calculation method can be defined as Expression (1).

$$\frac{N_i}{N_j} = \exp\left[\frac{(\Delta_f H_{m,j}^\theta - \Delta_f H_{m,i}^\theta)}{RT}\right] \quad (1)$$

where N_i and N_j are the numbers of conformer i and j , respectively; $\Delta_f H_{m,j}^\theta$ and $\Delta_f H_{m,i}^\theta$ ($\text{J}\cdot\text{mol}^{-1}$) are the standard formation enthalpies of conformer i and j , respectively; T (K) is the equilibrium temperature of reaction system (*i.e.*, 333.15 K, see 3.1); and R ($\text{J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$) is the Boltzmann constant.

A derivation of Expression (1) could be obtained. According to Maxwell-Boltzmann statistics, the conformers-ratio (N_i/N_j) under thermodynamic equilibrium can be derived as Expression (2).

$$\frac{N_i}{N_j} = \frac{\exp(-E_i/RT)}{\exp(-E_j/RT)} = \exp\left[\frac{(E_j - E_i)}{RT}\right] \quad (2)$$

where E_i and E_j ($\text{J}\cdot\text{mol}^{-1}$) are the energies of conformer i and j , respectively; T (K) is the equilibrium temperature of the system; and R ($\text{J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$) is the Boltzmann constant. We also tried to find the relations between E_i and $\Delta_f H_{m,i}^\theta$, as well as the relations between E_j and $\Delta_f H_{m,j}^\theta$. According to the thermodynamic definition of standard formation enthalpy, E_i and E_j in Expression (2) can be calculated by Expression (3) and (4), respectively.

$$\Delta_f H_{m,i}^\theta = E_i - (E_C + E_{\text{O}_2} + E_{\text{H}_2}) \quad (3)$$

$$\Delta_f H_{m,j}^\theta = E_j - (E_C + E_{\text{O}_2} + E_{\text{H}_2}) \quad (4)$$

where E_C , E_{O_2} and E_{H_2} ($\text{J}\cdot\text{mol}^{-1}$) are the energies of carbon, oxygen gas and hydrogen gas, respectively. When both i and j are CLA or MAC isomers, i has the same value of $(E_C + E_{\text{O}_2} + E_{\text{H}_2})$ as j . Thereby, we can derive Expression (5) from Expression (3) and (4). Finally, Expression (2) can be rewritten into Expression (1) in terms of Expression (5).

$$E_j - E_i = \Delta_f H_{m,j}^\theta - \Delta_f H_{m,i}^\theta \quad (5)$$

3.6.4. Conformers-Ratios, FMO Energy Levels and $\Delta_f H_m^\theta$ s of CLA and MAC

Based on the determined geometric structures of CLA and MAC conformers

(see 3.6.2), we could investigate the influences of electron-donor abilities and stabilities of CLA conformers on the stereochemical reactions of **Scheme 1**. FMO theory assumes that chemical reactivity correlates with E_{HOMO} (energy of the highest occupied molecule orbital) and E_{LUMO} (energy of the lowest unoccupied molecule orbital). The conformer with higher E_{HOMO} should be a better electron-donor, while the conformer with lower E_{LUMO} should be a better electron-acceptor; and a higher electron-donor ability of CLA conformer will greatly facilitate the cycloaddition reaction of maleic anhydride. The energy gap ΔE (*i.e.*, $E_{\text{LUMO}} - E_{\text{HOMO}}$) reflects the chemical stability of a molecule; and the lower the ΔE value is, the more easily the electron transition occurs, and the higher the chemical reactivity is. In addition, as a measure for the stability of molecular structure, the more negative the $\Delta_f H_m^\theta$ value is, the more stable the conformer would be, and consequently the more favorable the formation reaction is.

In order to investigate the influences of electron-donor abilities and stabilities of CLA conformers on the stereochemical reactions, three parameters (*i.e.*, E_{HOMO} , E_{LUMO} and $\Delta_f H_m^\theta$) of all CLA conformers and MAC conformers were exported from Chem3D Ultra 10.0 (**Table 2**). Based on the data of $\Delta_f H_m^\theta$ s, the conformers-ratios of CLA and MAC were calculated by Expression (1). The calculated results, together with their ΔE s, are also shown in **Table 2**.

Table 2. Conformers-ratios, FMO energy levels and $\Delta_f H_m^\theta$ s of CLA and MAC conformers.

	Conformer	$E_{\text{HOMO}}/\text{eV}$	$E_{\text{LUMO}}/\text{eV}$	$\Delta E/\text{eV}$	$\Delta_f H_m^\theta/\text{kJ}\cdot\text{mol}^{-1}$	Conformers-ratio	Reaction equation		
CLA	<i>s-trans</i> 1	-8.848	0.361	9.209	-652.06	$N_2 : N_1 = 0.52 : 1$	Equation (1)		
	2	-8.821	0.390	9.211	-649.59	($N_1\% = 65.79\%$)			
	<i>s-cis</i> 3	3	-8.886	0.315	9.201	-625.42	$N_3 : N_1 = 6.7 \times 10^{-5} : 1$	<i>Conformational isomerization</i>	
		4	-8.797	0.403	9.200	-646.37	$N_4 : N_2 = 0.31 : 1$		
	<i>s-trans</i> 5	5	-8.848	0.352	9.200	-648.57	$N_6 : N_5 = 8.06 : 1$	Equation (4)	
		6	-8.854	0.362	9.216	-654.35	$N_7 : N_8 = 19.45 : 1$		
	7	7	-8.844	0.372	9.216	-654.37		Equation (5)	
		8	-8.819	0.379	9.198	-646.15			
MAC	<i>s-cis</i> 9	9	-8.852	0.454	9.306	$N_9 : N_3 = 1941 : 1$	<i>Conformational isomerization</i>		
		10	-8.883	0.435	9.318	-647.80		$N_9 : N_5 = 0.46 : 1$	
	<i>trans-cycloadducts</i>	11	-10.303	0.272	10.575	-1163.94	$N_{10} : N_4 = 1.68 : 1$ $N_{10} : N_8 = 1.81 : 1$	(predominant reactants)	
		12	-10.282	0.275	10.557	-1164.48	without desired product		
		13	-10.289	0.278	10.567	-1163.76	without desired product	Equation (3)	
		14	-10.296	0.264	10.560	-1166.49			
		<i>cis-cycloadducts</i>	15	-10.228	0.294	10.522	-1162.10	$N_{16} : N_{15} = 2.14 : 1$	Equation (8) (main reaction)
			16	-10.303	0.271	10.574	-1164.21		
			17	-10.270	0.269	10.539	-1164.30	$N_{18} : N_{17} = 1.99 : 1$	Equation (9) (main reaction)
			18	-10.316	0.261	10.577	-1166.20		

It can be seen from **Table 2** that by Expression (1), the calculated value of the weight percentage of conformer **1** in as-prepared CLA (*i.e.*, 65.79 wt%) was excellently consistent with the experimental value in this work (*i.e.*, 63.82 wt%, as shown in 2.2), which was also in accordance with the results previously reported [15], indicating that Expression (1) possessed acceptability and accuracy for estimating conformers-ratio under thermodynamic equilibrium.

It was almost impossible for *Diels-Alder* reaction Equation (2) to be carried out because the percentage of conformer **3** was really low (trace level, $N_3 : N_1 = 6.7 \times 10^{-5} : 1$); and the very low percentage of conformer **4** originating from the less $N_2 : N_1$, and especially $N_4 : N_2$, was very unfavorable for *Diels-Alder* reaction Equation (3). In comparison with conformer **9** and **10**, conformer **3** and **4** had less negative $\Delta_f H_m^\circ$ s, indicating that the former two were more stable than the latter two ($N_9 : N_3 = 1941 : 1$; $N_{10} : N_4 = 1.68 : 1$). Obviously, it would become much more difficult for Equation (2) and Equation (3) to be carried out, particularly in the presence of iodine catalyst which was more preferential for the formation of conformer **9** and **10** rather than conformer **3** and **4**. More importantly, conformer **3** and **4** displayed more unfavorable geometric structures for ring formation in comparison with conformer **9** and **10** (see **Table 1**). Therefore, *Diels-Alder* reaction Equation (2) and Equation (3) could hardly occur; and the results obtained from the calculated conformers-ratios and the $\Delta_f H_m^\circ$ s, were in excellent agreement with those from the experiments in this work, *e.g.*, no desired product could be obtained in the absence of iodine catalyst (see 3.2).

It is remarkable that $\Delta_f H_m^\circ$ s of conformer **6** and **7** were the most negative among all the studied CLA conformers, indicating that these two conformers were the most stable structures. That is to say, Equation (4) and Equation (5) could be successfully carried out in the presence of the catalyst, iodine. Therefore, conformer **6** and **7** were determined as the predominant products of Equation (4) and Equation (5), respectively. According to the corresponding conformers-ratios, it is obvious that conformer **5** and **8** were the by-products of Equation (4) and Equation (5), respectively (**Table 2**).

No remarkable differences among six E_{HOMO} s of conformers **5** to **10** could be observed. In comparison with that of conformer **6**, E_{HOMO} of conformer **9** was a little less negative, indicating that the latter possessed slightly higher electron-donor ability than that of the former. Simultaneously, conformer **9** had higher E_{LUMO} in comparison with conformer **6**, which indicated that the electron-accepting ability of the former was inferior to that of the latter. In terms of Lewis acid-base theory, this also means that conformer **9** might possess superior electron-donor ability than conformer **6**, which could facilitate the cycloaddition reaction between conformer **9** and maleic anhydride.

Although the ratio of conformer **9** to conformer **5** was a little low ($N_9 : N_5 = 0.46 : 1$), the former did act as a predominant reactant for Equation (8), which could be ascribed to the following factors. Firstly, conformer **6**, instead of conformer **5**, was determined as the predominant product of Equation (4) ($N_6 : N_5 = 8.06 : 1$). Secondly, the conformational transformation of confor-

mer **6** into conformer **9** could be easily carried out because Equation (8) was a synergistic and rapid reaction that could occur in one-step without appearance of any active intermediate. More importantly, among all studied CLA conformers derived from conformer **1**, conformer **9** rather than conformer **6** had the most favorable structural parameters for ring formation. Therefore, conformer **9** was the predominant reactant for *Diels-Alder* reaction Equation (8), which was the main reaction in the preparation of MAC; while Equation (6) was a side reaction since conformer **5** with low percentage ($N_5 : N_6 = 1 : 8.06$) acted as the reactant for Equation (6), and in comparison with conformer **9**, conformer **5** was also significantly inferior for ring formation due to its geometric structure.

Similarly, we could deduce that conformer **10** was the predominant reactant for *Diels-Alder* reaction Equation (9) that was another main reaction in the preparation of MAC. Due to the existence of two different isomers (*i.e.*, *9c*, *11t* and *10t*, *12c*) in as-prepared CLA, the two main reactions were therefore involved in the preparation of MAC. In comparison with conformer **9**, conformer **10** showed another advantage for acting as the predominant reactant, such as the value of $N_{10} : N_8 (=1.81)$ was much greater than that of $N_9 : N_5 (=0.46)$. In addition, it is obvious that Equation (7) was another side reaction in the preparation of MAC, which was similar to Equation (6).

According to FMO theory, the cycloaddition reaction of Equation (8) occurred between HOMO of conformer **9** and LUMO of maleic anhydride, where the bonding electrons excited from the HOMO level into the LUMO level. The products of Equation (8) (*i.e.*, conformer **15** and **16**) were determined to be *cis*-cycloadducts that displayed *exo* and *endo* conformations, respectively, which might be due to the fact that conformer **9** was in a relatively stable *s-cis* conformation, and Equation (8) was a stereospecific *cis*-addition reaction. Similarly, other two *cis*-cycloadduct products with respectively *exo* and *endo* conformations (*i.e.*, conformer **17** and **18**) could be obtained from Equation (9). As shown in **Table 2**, *cis*-cycloadducts were determined as main products in the preparation of MAC; and the *endo/exo* ratios of the *cis*-cycloadducts derived from *9c*, *11t* and *10t*, *12c*-CLA, were calculated to be 2.14:1 and 1.99:1, respectively, by Expression (1). Obviously, higher percentage of *endo* conformation rather than *exo* conformation could be formed, even though the former was more sterically congested and less thermodynamically stable. This could be attributed to the fact that the *endo* conformation was stabilized by π orbital overlap of the C=O groups in maleic anhydride with the HOMO of conformer **9** or conformer **10**, *i.e.*, so-called “secondary orbital overlap” [12].

Although $\Delta_f H_m^\theta$ s of *trans*-cycloadducts (e.g., conformer **11**, **12** and **14**) were a little more negative than those of *cis*-cycloadducts (e.g., conformer **15**, **16** and **18**), no desired products would be obtained via Equation (2) and Equation (3) as explained previously. Even if *trans*-cycloadduct was probably formed from Equation (6) or Equation (7), its percentage was much lower than that of *cis*-cycloadduct since Equation (6) and Equation (7) were merely side reactions. Therefore,

Table 3. Conformational nomenclatures for the prepared MAC.

MAC	Nomenclature
Conformer 15	<i>Exo-cis</i> -8-[(3a <i>S</i> ,4 <i>S</i> ,7 <i>R</i> ,7a <i>R</i>)-7-hexyl-1,3-dioxo-3a,4,7,7a-tetrahydro-2-benzofuran-4-yl]-octanoic acid
Conformer 16	<i>Endo-cis</i> -8-[(3a <i>S</i> ,4 <i>S</i> ,7 <i>R</i> ,7a <i>R</i>)-7-hexyl-1,3-dioxo-3a,4,7,7a-tetrahydro-2-benzofuran-4-yl]-octanoic acid
Conformer 17	<i>Exo-cis</i> -9-[(3a <i>S</i> ,4 <i>S</i> ,7 <i>R</i> ,7a <i>R</i>)-7-pentyl-1,3-dioxo-3a,4,7,7a-tetrahydro-2-benzofuran-4-yl]-pelargonic acid
Conformer 18	<i>Endo-cis</i> -9-[(3a <i>S</i> ,4 <i>S</i> ,7 <i>R</i> ,7a <i>R</i>)-7-pentyl-1,3-dioxo-3a,4,7,7a-tetrahydro-2-benzofuran-4-yl]-pelargonic acid

trans-cycloadduct was obtained only as by-product in the preparation of MAC.

Based on the description and discussion of the above, the stereochemical mechanism for the improved preparation of MAC could be proposed as **Scheme 1**.

3.6.5. Conformational Nomenclatures of MAC

According to the systematic nomenclature, the four conformers of prepared MAC were named (**Table 3**).

4. Conclusions

By the improved process described in this article, MAC was prepared in a high yield of 96.7%, which can provide important references for industrial production of MAC. The new calculation method that possessed acceptability and accuracy for estimating conformers-ratio of CLA or MAC was established, and mainly by this calculation method, the stereochemical mechanism for the improved preparation of MAC was proposed, which can function as a theoretical basis for the determination and separation of related conformers. And the following conclusions were also obtained:

- 1) The catalytic configurational isomerization of CLA, as well as *Diels-Alder* [4 + 2] cycloaddition of the isomerized CLA with maleic anhydride, were mainly involved and occurred simultaneously in one step for the preparation of MAC.
- 2) It was confirmed that the cycloaddition occurred mainly between maleic anhydride and *trans-trans* CLA, rather than between maleic anhydride and *cis-trans* or *trans-cis* CLA. From all studied CLA conformers, the most stable one was the *s-trans* conformation of *trans-trans* CLA, while its *s-cis* conformation had the most favorable structural parameters for cyclohexenyl ring formation.
- 3) The *trans-trans* CLA in the *s-cis* conformation acted as a predominant reactant for the cycloaddition of maleic anhydride, which was confirmed as the main reaction in the improved process.
- 4) Four MAC conformers derived from 9*c*, 11*t*- and 10*t*, 12*c*-CLA, were obtained as final main products and determined to be *cis*-cycloadducts, which were also named according to the systematic nomenclature. And the *endo/exo* ratios of the *cis*-cycloadducts derived from 9*c*, 11*t*- and 10*t*, 12*c*-CLA, were calculated to be 2.14:1 and 1.99:1, respectively.
- 5) The results obtained by the calculation method were in good consistent with those of our experiments.

Acknowledgements

The authors are grateful for financial supports from the National Natural Science Foundation of China (No. 21762016) and the Innovation & Entrepreneurship Training Project for College Students in Hainan Province (No. S201911100030).

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

- [1] Sullivan, M.J., Binette, M.L. and Aoyama, S. (2019) Two-Piece Golf Ball Comprising Highly Neutralized Polymer Layer. Acushnet Company, New Bedford.
- [2] Huang, K., Zhang, P., Zhang, J.W., Li, S.H., Li, M., Xia, J.L. and Zhou, Y.H. (2013) Preparation of Biobased Epoxies Using Tung Oil Fatty Acid-Derived C₂₁ Diacid and C₂₂ Triacid and Study of Epoxy Properties. *Green Chemistry*, **15**, 2466-2475. <https://doi.org/10.1039/c3gc40622a>
- [3] Ursula, B., Anton, J. and Juergen, O.M. (2012) Esters of Maleinized Fatty Compounds as Plasticizers. *European Journal of Lipid Science and Technology*, **114**, 49-54. <https://doi.org/10.1002/ejlt.201100136>
- [4] Watanabe, S., Fujita, T., Fukuda, S., Hirano, K. and Sakamoto, M. (1986) Characteristic Properties as Cutting Fluid Additives of the Products from the Reaction of Unsaturated Fatty Acids with Maleic Anhydride. *Materials Chemistry and Physics*, **15**, 89-96. [https://doi.org/10.1016/0254-0584\(86\)90091-X](https://doi.org/10.1016/0254-0584(86)90091-X)
- [5] Moreno, M., Victoria Gomez, M., Cebrian, C., Prieto, P., Hoza, A. and Moreno, A. (2012) Sustainable and Efficient Methodology for CLA Synthesis and Identification. *Green Chemistry*, **14**, 2584-2594. <https://doi.org/10.1039/c2gc35792e>
- [6] Ojha, D.P. (2005) Ordering of a Thermotropic Mesogen at Phase Transition Temperature-A Statistical Approach Based on Quantum Mechanics. *Journal of Theoretical & Computational Chemistry*, **4**, 803-810. <https://doi.org/10.1142/S0219633605001805>
- [7] Hartung, J., Daniel, K., Rummey, C. and Bringmann, G. (2006) On the Stereoselectivity of 4-penten-1-oxyl Radical 5-exo-trig Cyclizations. *Organic & Biomolecular Chemistry*, **4**, 4089-4100. <https://doi.org/10.1039/b611473c>
- [8] Jin, P., Yang, L., Liu, C., Chen, M. Q., Hou, Q. H., Li, L. L. and Zhao, Y. J. (2017) A Comparative Study on the N-Heterocyclic Carbene Adducts of I_h-C₆₀, D_{5h}-C₇₀ and Sc₃N@I_h-C₈₀. *Physical Chemistry Chemical Physics*, **19**, 17598-17606. <https://doi.org/10.1039/C7CP02696J>
- [9] Liu, Q., Chen, C.J., Zhang, L. and Gao, K. (2016) Two New Indole Alkaloids from *Hunteria Zeylanica*. *Journal of Asian Natural Products Research*, **18**, 349-353. <https://doi.org/10.1080/10286020.2015.1092961>
- [10] El Merbouh, B., Bourjila, M., Tijar, R., El Bouzaidi, R.D., El Gridani, A. and El Mouhtadi, M. (2014) Conformational Space Analysis of Neutral and Protonated Glycine Using a Genetic Algorithm for Multi-Modal Search. *Journal of Theoretical & Computational chemistry*, **13**, Article No. 1450067. <https://doi.org/10.1142/S0219633614500679>
- [11] Chin, S.F., Liu, W., Storkson, J.M., Ha, Y.L. and Pariza, M.W. (1992) Dietary Sources of Conjugated Dienoic Isomers of Linoleic Acid, a Newly Recognized Class

- of Anticarcinogens. *Journal of Food Composition and Analysis*, **5**, 185-197.
[https://doi.org/10.1016/0889-1575\(92\)90037-K](https://doi.org/10.1016/0889-1575(92)90037-K)
- [12] Arrieta, A., Cossio, F.P. and Lecea, B. (2001) Direct Evaluation of Secondary Orbital Interactions in the Diels-Alder Reaction between Cyclopentadiene and Maleic Anhydride. *Journal of Organic Chemistry*, **66**, 6178-6180.
<https://doi.org/10.1021/jo0158478>
- [13] Eulitz, K., Yurawecz, M.P., Sehat, N., Fritsche, J., Roach, J.A.G., Mossoba, M.M., Kramer, J.K.G., Adlof, R.O. and Ku, Y. (1999) Preparation, Separation and Confirmation of the Eight Geometrical *cis/trans* Conjugated Linoleic Acid Isomers 8,10-through 11,13-18:2. *Lipids*, **34**, 873-877.
<https://doi.org/10.1007/s11745-999-0435-z>
- [14] Arca, M., Sharma, B.K., Price, N.P.J., Perez, J.M. and Doll, K.M. (2012) Evidence Contrary to the Accepted Diels-Alder Mechanism in the Thermal Modification of Vegetable Oil. *Journal of the American Oil Chemists Society*, **89**, 987-994.
<https://doi.org/10.1007/s11746-011-2002-x>
- [15] Wu, Y., Yang, R.Q., Chen, M.Z. and Liao, X.B. (2012) Antitumor Activity of Conjugated Linoleic Acid Converted from Linoleic Acid in *Salicornia herbacea* Seed Oil. *Food Science*, **33**, 318-322. (In Chinese)