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Elucidation of Structural Isomers from the Homogeneous Rhodium-Catalyzed Isomerization of Vegetable Oils

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The structural isomers formed by the homogeneous rhodium-catalyzed isomerization of several vegetable oils have been elucidated. A detailed study of the isomerization of the model compound methyl linoleate has been performed to correlate the distribution of conjugated isomers, the reaction kinetics, and the mechanism of the reaction. It has been shown that $[RhCl(C_8H_8)_2]_2$ is a highly efficient and selective isomerization catalyst for the production of highly conjugated vegetable oils with a high conjugated linoleic acid (CLA) content, which is highly desirable in the food industry. The combined fraction of the two major CLA isomers [(9*Z*,11*E*)-CLA and (10*E*,12*Z*)-CLA] in the overall CLA mixture is in the range from 76.2% to 93.4%. The high efficiency and selectivity of this isomerization method along with the straightforward purification process render this approach highly promising for the preparation of conjugated oils and CLA. Proposed improvements in catalyst recovery and reusability will only make this method more appealing to the food, paint, coating, and polymer industries in the future.

KEYWORDS: Conjugated linoleic acid; conjugated vegetable oils; homogeneous rhodium-catalyzed isomerization; structural isomers

INTRODUCTION

The isomerization of vegetable oils has been the subject of increasing numbers of scientific studies in recent years. While the initial interest in the conjugation of vegetable oils was driven by the improved drying characteristics of the conjugated oils for coating and paint applications (*1*−*3*), the current focus of the research also involves the synthesis of more reactive comonomers for the preparation of bioplastics via cationic and free radical copolymerizations (*4*, *5*), as well as the synthesis of conjugated linoleic acids (CLAs) (*6*, *7*).

Irrespective of the type of polymerization method used, conjugated oils have proven to be much more reactive monomers than regular oils, resulting in higher vegetable oil incorporation in the resulting copolymers (*4*, *5*). For instance, cationic copolymerization of conjugated vegetable oils with a variety of alkene comonomers has been shown to produce thermosetting materials with improved thermal and mechanical properties when compared to that of their nonconjugated analogues (*4*, *5*). Furthermore, these bioplastics also exhibit excellent damping (*8*) and shape memory (*9*) properties, which are highly desirable in a variety of applications in the aircraft, automobile, and machinery industries.

CLA is a general term which describes a group of positional and geometric isomers of linoleic (*cis*-9,*cis*-12-octadecadienoic) acid. Due to its beneficial properties, which include anticarcinogenesis (*10*), antiatherosclerosis (*11*), enhancement of immune functions (*12*), and body fat reduction (*13*), CLA has been used in a variety of nutritional, therapeutic, and pharmacologic applications (*11*). Thus, it is not surprising that the synthesis of CLA has received considerable attention in recent years (*6*, *7*). For this reason, the conjugation of vegetable oils rich in linoleic fatty acid, such as soybean (51%), cottonseed (53%), corn (57%), walnut (62%), sunflower (64%), grapeseed (70%), and safflower (75%) oils (*6*), represents a promising route to CLA.

There exist numerous reports on the homogeneous isomerization of fatty acid double bonds. Many of those methods are based on transition-metal catalysis utilizing a variety of chromium (*14*), ruthenium (*15*, *16*), and rhodium (*17*−*20*) complexes. In the course of our research in this area, we have recently developed a homogeneous rhodium-catalyzed isomerization procedure for the synthesis of highly conjugated vegetable oils and esters of fatty acids under mild conditions (*21*). For example, the utilization of as little as 0.1 mol % $[RhCl(C_8H_{14})_2]_2$ (C_8H_{14} = cyclooctene), 0.4 mol % (p-$CH_3C_6H_4)_3P$ (TTP), and 0.8 mol % $SnCl_2 \cdot 2H_2O$ (with respect to the amount of vegetable oil) in absolute ethanol at 60 °C for 24 h produces >90% conjugated soybean oil and works well for other natural oils. Herein, we elucidate the structural isomers of the fatty acid methyl esters of CLA obtained from the homogeneous rhodium-catalyzed isomerization of various vegetable oils and subsequent

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transesterification and determine the suitability of this method for the synthesis of CLA.

EXPERIMENTAL PROCEDURES

Materials. The vegetable oils used in this study were Planters peanut (PNT), Mazola corn (COR), Wesson soybean (SOY), low-saturation soybean (LSS), Hain safflower (SAF), and Superb linseed (LIN) oils. All of the oils were purchased in local supermarkets, except the Superb linseed and low-saturation soybean (Select Oil) oils, which were supplied by Archer Daniels Midland Co. (Decatur, IL) and Zeeland Food Service, Inc. (Zeeland, MI), respectively. All of the oils were used without further purification. $RhCl_3 \cdot 3H_2O$ was provided by Kawaken Fine Chemicals Co. Ltd. (Japan) and used as received. (p-$CH_3C_6H_5)_3P$ and absolute ethanol were purchased from Aldrich Chemical Co. and used as received. The CLA gas chromatography (GC) standards methyl *cis*,*cis*-9,12-octadecadienoate [(9*Z*,12*Z*)-CLA], methyl *cis*,*trans*-9,11-octadecadienoate [(9*Z*,11*E*)-CLA], methyl *trans*,*cis*-10,-12-octadecadienoate [(10*E*,12*Z*)-CLA], methyl *cis*,*cis*-9,11-octadecadienoate [(9*Z*,11*Z*)-CLA], methyl *trans*,*trans*-9,11-octadecadienoate [(9*E*,11*E*)-CLA], and *cis*,*trans*-11,13-octadecadienoic acid (>97% purity) were purchased from Matreya Inc. (Pleasant Gap, PA). Prior to GC analysis, *cis*,*trans*-11,13-octadecadienoic acid was converted to its methyl ester by acid-catalyzed esterification in methanol to afford methyl *cis*,*trans*-11,13-octadecadienoate [(11*Z*,13*E*)-CLA]. The methyl esters of palmitoleic (C16:1), oleic (C18:1), and *trans*-vaccenic (*t*-C18-1) acids and all saturated fatty acid standards were obtained from NuChek Prep, Inc. (Elysian, MN). The chlorobis(cyclooctene)rhodium dimer, $[RhCl(C_8H_{14})_2]_2$, was synthesized according to a previously published procedure (*22*). Standard grade silica gel (porosity 60 Å, particle size 32−63 μm, surface area 500−600 m^2/g) was purchased from Sorbent Technologies (Atlanta, GA) and used as received. SPEX certiprep Rh standard ($RhCl_3$ in a matrix of 10% HCl) has been used as a calibration standard for ICP-MS analysis.

Characterization. All ^{1}H NMR spectroscopic analyses of the conjugated vegetable oils and other compounds were recorded in $CDCl_3$ using a Varian Unity spectrometer at 300 MHz. The methyl esters of CLA were separated and quantified using an HP6890 series gas chromatograph (Hewlett-Packard Co., Wilmington, DE) equipped with an autosampler and flame ionization detector. A SUPELCOWAX-10 capillary column (30 m × 0.25 mm × 0.25 μm film thickness, Supelco, Bellefonte, PA) was used for separation. ICP-MS analysis was performed on a Hewlett-Packard 4500 series ICP-MS spectrometer. The experimental conditions, such as the forward power (1200 W), carrier gas flow (1.2 L/min), sample flow rate (250 μL/min), and sampling depth (7.8 mm), were set for optimal sensitivity.

General Conjugation Procedure. To 10 g (34 mmol) of methyl linoleate in 5 mL of absolute EtOH were added 25 mg (0.034 mmol, 0.1 mol %) of $[RhCl(C_8H_{14})_2]_2$, 41.4 mg (0.136 mmol, 0.4 mol %) of (p-$CH_3C_6H_5)_3P$, and 62 mg (0.272 mmol, 0.8 mol %) of $SnCl_2 \cdot 2H_2O$. The reaction flask was evacuated and refilled with Ar three times and the solution stirred in an oil bath at 60 °C for 24 h. After removal of the ethanol under vacuum, the remaining mixture was dissolved in *n*-pentane and purified by flash chromatography on silica gel. The product obtained in almost quantitative yield was 87.1% conjugated (**Figure 1b**). ^{1}H NMR spectral data of conjugated methyl linoleate ($CDCl_3$): δ 0.88 (t, 3 H, C*H*$_3$CH$_2$), 1.18−1.43 (m, 14 H, C*H*$_2$C*H*$_2$C*H*$_2$-CH$_3$ and OCCH$_2$CH$_2$(C*H*$_2$)$_4$), 1.53−1.68 (m, 2 H, OCCH$_2$C*H*$_2$), 2.00−2.20 (m, 4 H, allylic), 2.23−2.32 (t, 2 H, OCC*H*$_2$), 2.70−2.80 (t, signal for residual bisallylic protons), 3.65 (s, 3 H, OC*H*$_3$), 5.22−6.33 (m, 4 H, C*H*═C*H*−*H*═C*H*).

Conjugation of Methyl Linolenate. The methyl ester of linolenic acid with 92% conjugation was obtained in quantitative yield according to the above-described procedure. ^{1}H NMR spectral data of conjugated methyl linolenate ($CDCl_3$): δ 0.81−1.05 (m, 3 H, C*H*$_3$CH$_2$), 1.20−1.50 (m, 12 H, C*H*$_2$C*H*$_2$CH$_3$ and OCCH$_2$CH$_2$(C*H*$_2$)$_4$), 1.53−1.68 (m, 2 H, OCCH$_2$C*H*$_2$), 1.90−2.23 (m, 6 H, 4 H, allylic, and 2 H, OCC*H*$_2$ overlapped), 2.70−2.80 (t, signal for residual bisallylic protons), 3.65 (s, 3 H, OC*H*$_3$), 5.20−5.50 (m, 2 H, vinylic), 5.55−5.73 (m, 1 H, vinylic), 5.80−6.21 (m, 2 H, vinylic), 6.23−6.54 (m, 1 H, vinylic).

Conjugation of the Vegetable Oils. Conjugated PNT, COR, SOY, SAF, and LIN oils with >95% conjugation were obtained in >99% yield according to the above-described procedure. The ^{1}H NMR spectra of all conjugated vegetable oils correspond closely to the previously reported spectra (*21*).

Kinetic Study. Aliquots were taken at different times during the conjugation reaction and subjected to the same workup as previously described. Samples were analyzed by both ^{1}H NMR spectroscopy and GC−MS to determine the progress of the reaction.

CLA Analysis by GC. Approximately 20 mg of triglyceride, 1 mL of 3 N methanolic HCl (Supelco), and 150 μL of hexane were added to a test tube, which was tightly capped, and incubated in a water bath at 65 °C for 50 min. After the solution was cooled to room temperature, 1 mL of hexane and 8 mL of water were added to the test tube, and the resulting solution was mixed thoroughly and left overnight at room temperature for phase separation. The hexane solution containing the CLA methyl esters was separated and quantified by gas chromatography. To improve the separation and reduce the separation time, the following oven temperature program was used: step 1, temperature ramp from 180 to 200 °C at 5 °C/min; step 2, isothermal hold at 200 °C for 6 min; step 3, temperature ramp from 200 to 220 °C at 10 °C/min; step 4, temperature ramp from 220 to 230 °C at 5 °C/min; step 5, isothermal hold at 230 °C for 6 min. Helium gas was used as a carrier gas, and the column flow rate was 1.0 mL/min. The temperatures of the inlet and detector were 280 and 320 °C, respectively. The flow rates of air, hydrogen gas, and makeup gas (He) at the detector were 350, 35, and 38.3 mL/min, respectively. The area of each peak was integrated by Chemstation software (Hewlett-Packard Co., Wilmington, DE), and the peak areas were used to calculate the fatty acid composition.

Sample Preparation and ICP-MS Analysis. The conjugated vegetable oils were purified by flash chromatography on silica gel using *n*-pentane as a solvent. After removal of the ethanol from the crude reaction mixture under reduced pressure, 150 mL of conjugated oil was diluted with 300 mL of *n*-pentane and passed through a glass frit packed with 60, 90, or 120 g of silica gel to obtain dark red, orange, or yellow solutions, respectively. The solvents were removed under reduced pressure, and the remaining solution was used for ICP-MS analysis to determine the Rh and Sn content. On the basis of the initial concentrations of Rh and Sn, 1 mg/mL samples were prepared by mixing a small amount of conjugated oil with 1% HNO_3 in 50 mL volumetric flasks. The flasks were shaken vigorously to facilitate dissolution of the Rh and Sn salts in water and used for analysis the next day. A blank sample (1 mg/mL) was prepared by mixing regular SOY and DI water in a volumetric flask. After the run, the blank signal was subtracted from all of the subsequent data. The Rh and Sn contents in the samples were calculated using a calibration curve obtained from the analysis of $RhCl_3$ and $SnCl_4$ standard solutions. The original concentration of the standard (1000 ppm) was diluted volumetrically to 100, 10, and 1 ppb with DI water, and the resulting solutions were used for the calibration.

RESULTS AND DISCUSSION

Calculation of the Percent Conjugation. The conjugation (*C*, %) for methyl linoleate, methyl linolenate, and all vegetable oils was determined by ^{1}H NMR spectroscopic analysis. **Figure 1** shows the ^{1}H NMR spectra of the methyl esters of regular and conjugated linoleic acids along with their representative structures and peak assignments. The structure on the top right represents (9*Z*,11*E*)-CLA, which is only one of several possible structural isomers of the methyl ester of CLA. The signal at 3.65 ppm (A) in both spectra corresponds to protons in the methoxy group of the methyl ester. The vinylic hydrogens (F) of the nonconjugated ester (**Figure 1a**) are typically detected at 5.2−5.4 ppm, while the methylene protons positioned between the two C═C bonds, also known as the bisallylic protons (G), are observed at 2.7−2.8 ppm. The signal for the bisallylic protons indicates that the C═C bonds in the methyl ester are nonconjugated. Conversely, the vinylic hydrogens (F) of the conjugated ester (**Figure 1b**) are detected in the 5.2−6.4 ppm

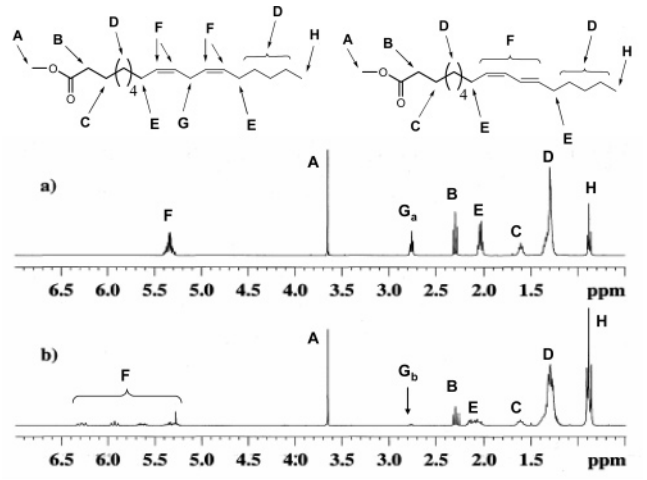


Figure 1. ^{1}H NMR spectra of the methyl esters of (**a**) regular and (**b**) conjugated linoleic acids with their representative structures and corresponding peak assignments.

range as a group of four multiplets, which indicate the existence of conjugation in the diene system. Furthermore, the significantly reduced intensity of the peak due to the bisallylic protons (G) at 2.7−2.8 ppm confirms the existence of conjugation. It is this difference in the intensities of the bisallylic peaks in the spectra of the conjugated and nonconjugated esters that allows us to calculate the conjugation (%) in these esters, as well as in all of the vegetable oils used in this study. The conjugation was calculated according to the following equation:

$$C\,(\%) = 100 - (100G_b/G_a)$$

where G_a and G_b represented the integrated areas of the bisallylic peaks in the regular and conjugated esters, respectively (**Figure 1**). The same method was used for calculation of the *C* of all vegetable oils.

Homogeneous Rhodium-Catalyzed Isomerization of Model Compounds. Linoleic and linolenic acids are the major polyunsaturated fatty acids in most vegetable oils, including the oils used in this study. Because of that, we began our study by elucidating the structural isomers obtained from the rhodium-catalyzed isomerization of two model compounds, the methyl esters of linoleic and linolenic acids. However, due to a lack of GC standards for the conjugated methyl linolenate isomers, we focused on analysis of the isomers of conjugated methyl linoleate. Furthermore, out of the eighteen most likely isomers of methyl linoleate, two of them, (9*Z*,11*E*)-CLA and (10*E*,12*Z*)-CLA, are of particular importance, since they represent derivatives of two CLAs which have been shown to exhibit numerous important biological activities (*7*). Thus, our analysis focused primarily on these isomers.

The isomerization of the methyl esters of linoleic and linolenic acids was performed using as little as 0.1 mol % $[RhCl(C_8H_{14})_2]_2$ catalyst according to the procedure described in the Experimental Procedures. Aliquots were taken at specific times during the reaction and analyzed by ^{1}H NMR spectroscopy and GC, monitoring changes in the bisallylic signal intensities (G, **Figure 1**), which are indicative of the isomerization progress and directly related to disappearance of the starting material. **Figure 2a** shows these changes for the methyl ester of linoleic acid over a period of 24 h. Comparison of the peak intensities before and after the reaction calculates to 87.1% conjugation of the final product. **Figure 2b**, on the other hand, shows changes in both the intensities and appearances of the vinylic signals (F, **Figure 1**). These changes also confirm the progress of the isomerization reaction, but are not appropriate for the straightforward calculation of *C*.

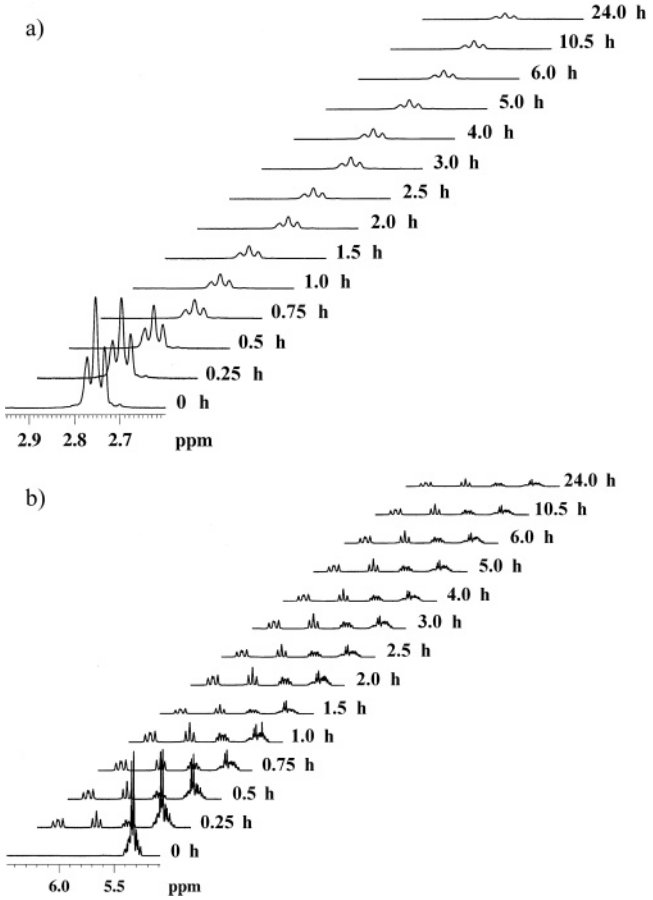


Figure 2. Progress of the isomerization of methyl linoleate monitored by ^{1}H NMR spectroscopic analysis of the (**a**) bisallylic and (**b**) vinylic regions.

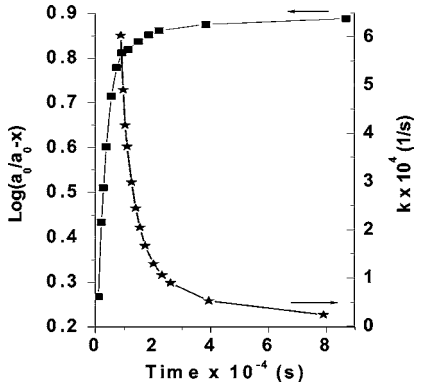
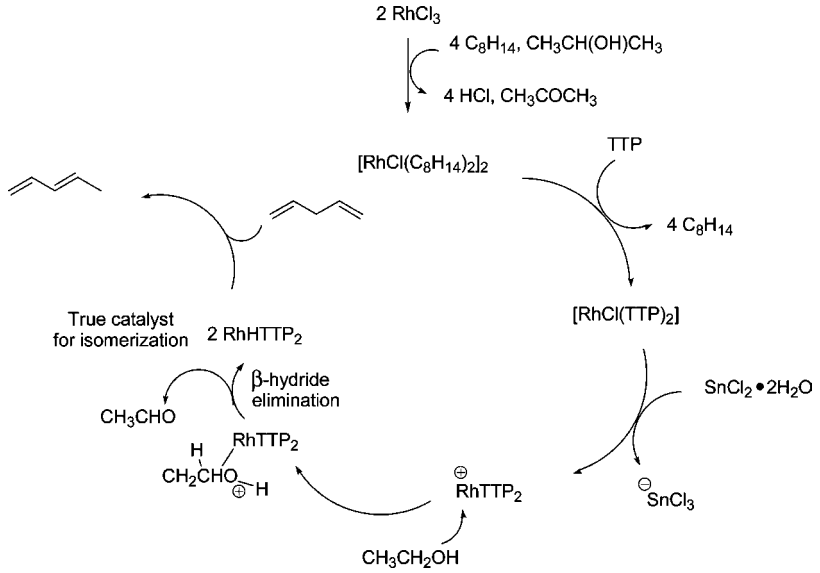


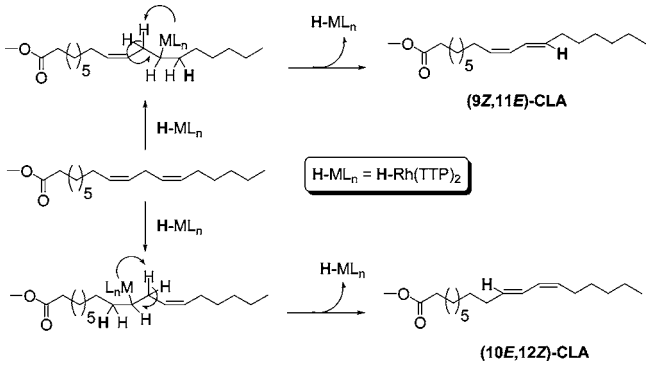
Figure 3. Kinetic study of the isomerization of methyl linoleate.

It has been observed that the intensity of the bisallylic signal rapidly decreases with increasing conversion in the first 2 h of the reaction. At that point, 83.4% of the methyl linoleate has already been conjugated. The initial rate of the reaction exhibits a first-order dependence on the concentration of methyl linoleate (**Figure 3**, black squares). However, in the next 22 h *C* only improves 14.6% with obvious retardation in the reaction rate and deviation from the initial first-order kinetics. A closer analysis of the reaction mechanism reveals several reasons for such behavior. The initial rate constant (*k*) was calculated to be 6×10^{-4} s^{-1}. While fairly constant in the first 2 h of the reaction, the rate constant rapidly decreased through the rest of the isomerization reaction (**Figure 3**, black stars).

Scheme 1. Proposed Mechanism for Homogeneous Rhodium-Catalyzed Isomerization



Scheme 2. Addition–Elimination Mechanism for the Isomerization of Methyl Linoleate



A proposed mechanism for formation of the isomerization catalyst is outlined in **Scheme 1**. The rhodium(I) dimeric catalyst precursor is readily synthesized from $RhCl_3 \cdot 3H_2O$ and cyclooctene in 2-propanol as the solvent (*22*). The labile cyclooctene ligands are susceptible to fast exchange with the tri-*p*-tolylphosphine (TTP) ligands under the reaction conditions to give $RhCl(TTP)_2$. $SnCl_2 \cdot 2H_2O$ then acts as a Lewis acid and generates an electron-deficient $[Rh(TTP)_2]^+$ intermediate, which, upon coordination of the ethanol oxygen, undergoes β-hydride elimination to generate a rhodium hydride, which is the true isomerization catalyst. Isomerization of the model compounds and vegetable oils is then accomplished presumably by an addition−elimination mechanism (*23*) or rearrangement through a transitory π-allyl complex (*24*). While iron- and some palladium-catalyzed isomerizations proceed by a π-allyl complex (*25*−*27*), most other metal-catalyzed isomerizations, including at least one previous rhodium-catalyzed isomerization (*24*), appear to proceed by an addition−elimination mechanism. The presumed mechanism for the rhodium hydride-catalyzed isomerization of methyl linoleate to the corresponding conjugated isomers is shown in **Scheme 2**. It has been shown that an open coordination site in the metal complex and a transition state involving a *syn*-coplanar arrangement of the α- and β-carbons, the β-hydrogen, and the metal center is a prerequisite for the addition−elimination mechanism (*28*). Thus, the mechanism proceeds via three distinct steps: (1) coordination of the rhodium hydride to the olefin, (2) rhodium hydride addition to the double bond, and (3) rhodium hydride elimination by an alternative β-hydrogen to regenerate the rhodium hydride catalyst.

During the initial stages of the reaction, the concentration of the starting, nonconjugated materials is high and the reaction follows approximately first-order kinetics, as shown by the initial linear dependence (**Figure 3**). However, with increasing conversion, the concentration of the conjugated species increases to such an extent that such species start to compete effectively with the starting material for the catalyst in the isomerization reaction. The existence of other positional isomers of CLA suggests that even the conjugated species undergo further isomerization in the presence of the rhodium hydride catalyst (see **Table 1** later in the text). These isomerization reactions account for the formation of the thermodynamically more favorable isomers (9*Z*,11*E*)-CLA and (10*E*,12*Z*)-CLA, as well as other positional isomers, which result from the shift of the conjugated system up or down the fatty acid carbon chain. This is one of the main reasons for the deviation from the first-order kinetics in the later stages of the reaction. Another reason might be slow catalyst decomposition under the reaction conditions. For example, acetaldehyde, which is formed during the initial ethanol rhodium β-hydride elimination step, is known to undergo decarbonylation in the presence of Rh catalysts (*29*−*33*).

The progress of the methyl linolenate isomerization was followed in the same manner as that of methyl linoleate. **Figure 4** shows the ^{1}H NMR spectra of regular and conjugated methyl linolenate. Our calculations indicate 98% conjugation of the final product as evidenced by the complete disappearance of the bisallylic signal in the spectrum of the conjugated product.

Elucidation of the Structural Isomers from the Conjugation of Methyl Linoleate. Aliquots taken during the conjugation of methyl linoleate were subjected to GC analysis to determine their CLA compositions and to monitor the progress of the reaction. **Table 1** lists the CLA compositions for 13 samples taken during a 24 h long isomerization reaction. The time intervals at which these samples were acquired are shown in **Figure 2a**. Six commercially available GC standards were used for this analysis: methyl linoleate [(9*Z*,12*Z*)-LA], (9*Z*,11*E*)-CLA, (10*E*,12*Z*)-CLA, (9*Z*,11*Z*)-CLA, (9*E*,11*E*)-CLA, and (11*Z*,13*E*)-CLA. The results indicate that two major CLA isomers are formed during the conjugation reaction, (9*Z*,11*E*)-CLA (33.8%) and (10*E*,12*Z*)-CLA (45.1%). Their retention

Table 1. CLA Compositions of Samples Taken during the Isomerization of Methyl Linoleate As Determined by GC Analysis

fatty acid	0 h	0.25 h	0.5 h	0.75 h	1 h	1.5 h	2 h	2.5 h	3 h	4 h	5 h	6 h	10.5 h	24 h
linoleic acid (C18:0)	100.0	61.5	41.0	37.1	27.5	26.5	24.9	22.8	21.7	20.5	19.1	18.3	17.2	17.2
(9*Z*,11*E*)-CLA		13.9	23.1	25.6	28.0	28.5	29.6	31.2	31.8	32.4	33.3	33.7	34.3	33.8
(10*E*,12*Z*)-CLA		22.7	33.6	34.6	41.5	41.8	42.1	42.6	43.0	43.6	43.9	44.2	44.5	45.1
(9*E*,11*E*)-CLA		1.0	1.2	1.5	1.6	1.6	1.7	1.7	1.8	1.9	1.9	1.9	2.0	2.0
(9*Z*,11*Z*)-CLA		0.9	1.0	1.3	1.5	1.6	1.6	1.6	1.6	1.7	1.8	1.9	1.9	1.9
total	100. 0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

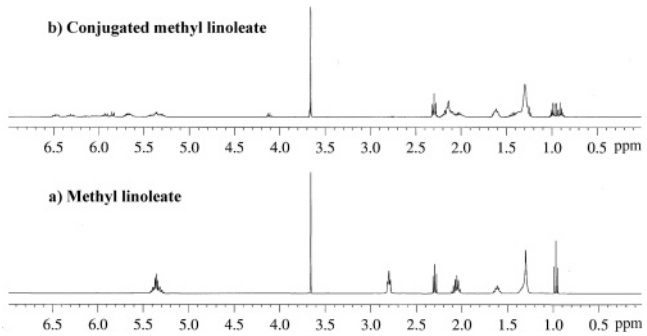


Figure 4. ^{1}H NMR spectra of (**a**) conjugated and (**b**) regular methyl linolenate.

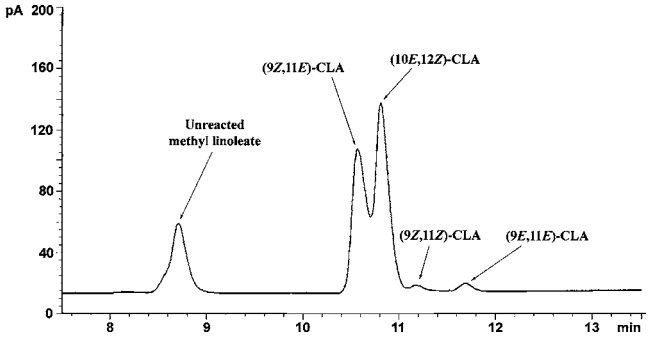


Figure 5. Gas chromatogram of conjugated methyl linoleate (**Table 1**, sample after 24 h).

times (t_r) are 10.58 and 10.81 min, respectively (**Figure 5**). These two isomers account for approximately 79% of all species in the mixture (unreacted methyl linoleate plus all CLA isomers), which translates to 95.2% of all CLA isomers formed during conjugation (**Table 1**). Two other CLA isomers, (9*E*,11*E*)-CLA (t_r = 11.69 min, 2.1%) and (9*Z*,11*Z*)-CLA isomer (t_r = 11.18 min, 1.9%) are also formed, although in much smaller amounts. However, we note that, with a lack of a "state of the art" GC system and authentic samples of (10*E*,12*E*)-CLA and (10*Z*,-12*Z*)-CLA GC standards, we are not able to fully resolve these minor peaks, which most likely consist of mixtures of (9*E*,-11*E*)-CLA and (10*E*,12*E*)-CLA isomers and (9*Z*,11*Z*)-CLA and (10*Z*,12*Z*)-CLA isomers, respectively. The (11*Z*,13*E*)-CLA isomer (t_r = 10.69 min) could not be accounted for, presumably due to overlap with the signals of the two major CLA isomers, (9*Z*,11*E*)-CLA and (10*E*,12*Z*)-CLA. The existence of a peak for methyl linoleate (t_r = 8.71 min) clearly indicates that there is 17.2% unreacted methyl linoleate in the mixture. Thus, on the basis of the GC analysis, *C* is calculated to be 82.9%. When compared to the ^{1}H NMR spectroscopic data, this value is approximately 4−5% lower. We believe this may be caused by the loss of material in the conjugation process due to polymerization. Since CLAs are known to be good drying oils, it is likely that certain small amounts of oligomeric CLAs are formed, as indicated by the dark color of the solution. These oligomers are most likely removed during the flash chromatography process, which accounts for the small loss of material and the observed discrepancy. Also, when compared to the methyl linolenate results (*C* = 98% by ^{1}H NMR), the *C* value for methyl linoleate (87.1% by ^{1}H NMR) is also lower. The reason for this inconsistency is unclear to us at the moment. However, from our experience, we know that a small 10−30% increase in the Rh catalyst load can push *C* to almost quantitative in all cases. It is also important to mention that hydrogenation products are not observed at any time during the isomerization of this model compound.

Elucidation of the Structural Isomers from the Isomerization of Various Vegetable Oils. The conjugation of SOY and other oils was monitored in a manner similar to that described above. In this case, the CLA isomer analysis was more difficult to perform due to the existence of a large number of saturated and other unsaturated fatty acid esters. **Table 2** lists the CLA and other fatty acid compositions for 11 samples taken during the 24 h long isomerization of SOY. **Figure 6** shows the progress of the isomerization of SOY monitored by ^{1}H NMR spectroscopic analysis along with the time intervals at which these samples were acquired. **Figure 7** shows a GC chromatogram of the conjugated SOY (CSOY) at the end of the isomerization reaction (see **Table 2**, sample after 24 h) with complete peak assignments. On the basis of the ^{1}H NMR spectroscopic analysis of its bisallylic peaks, the conjugated SOY sample was 99% conjugated. During the conjugation reaction, the 53.8% linoleic acid present in the regular SOY was almost quantitatively converted into its conjugated isomers. Again, the two major CLA isomers were (9*Z*,11*E*)-CLA (19.7%) and (10*E*,12*Z*)-CLA (20.9%), which account for approximately 81.3% of all CLA isomers in the mixture. The rest of the CLA mixture was composed primarily of (9*E*,11*E*)-CLA (8.7%) and a small amount of (9*Z*,11*Z*)-CLA (0.6%). When compared with the data obtained from the analysis of methyl linolenate (95.2%), the overall fraction of the two major CLA isomers, (9*Z*,11*E*)-CLA and (10*E*,12*Z*)-CLA, was much lower (81.3%). On the other hand, the fraction of the (9*E*,11*E*)-CLA isomer was dramatically increased, while the fraction of the thermodynamically less favorable (9*Z*,11*Z*)-CLA isomer remained low. The observed differences might be a consequence of the lower effective concentration of the linoleic fatty acid in the SOY triglyceride system when compared to the pure methyl linolenate model system. According to the GC data (see **Tables 1** and **2**), the isomerization of the linoleic fatty acid in the SOY triglyceride system proceeds much faster than that of the pure methyl linolenate model system. It is possible that, once produced, the CLA isomers in the SOY system have more time to isomerize further and yield higher amount(s) of other thermodynamically more favorable CLA isomers, such as (9*E*,11*E*)-CLA (**Table 2**). The GC results further confirm that the initial 8.5% linolenic fatty acid present in the pure SOY was quantitatively converted into a mixture of conjugated isomers (CLN entry in **Table 2**). The retention times of these peaks have been confirmed by comparison with the retention times of the peaks observed in the GC chromatogram of the 98% conjugated methyl linolenate. On the basis of these results, the overall *C* of the conjugated

Table 2. CLA Compositions of Samples Taken during the Isomerization of SOY As Determined by GC Analysis

fatty acid	0 h	0.5 h	1 h	1.5 h	2 h	2.5 h	3 h	3.5 h	4.5 h	5.5 h	10 h	24 h
myristic (C14:0)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.1
palmitic (C16:0)	11.4	12.5	12.9	12.9	12.7	13.1	13.2	13.3	13.4	13.3	13.3	12.9
palmitoleic (C16:1)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.1	0.2	0.1
stearic (C18:0)	3.8	4.1	4.2	4.3	4.3	4.3	4.3	4.3	4.3	4.3	4.3	4.4
oleic (C18:1)	20.8	20.9	21.3	21.4	21.4	21.5	21.7	21.6	21.6	21.5	21.5	21.7
trans-vaccenic (*t*-C18:1)[a]	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
linoleic (C18:2)	53.8	23.4	13.9	9.7	6.9	5.5	4.5	3.9	2.9	2.5	1.3	0.7
linolenic (C18:3)	8.5	0.8	0.3	0.2	0.1							
(9*Z*,11*E*)-CLA		11.0	13.9	16.0	17.3	17.7	18.0	18.3	18.6	18.7	19.3	19.7
(10*E*,12*Z*)-CLA		11.8	16.0	17.4	18.7	19.3	19.5	19.6	20.1	20.4	20.5	20.8
(9*Z*,11*Z*)-CLA		0.3	0.4	0.5	0.5	0.5	0.6	0.6	0.5	0.5	0.5	0.6
(9*E*,11*E*)-CLA		5.6	6.7	7.1	7.6	7.6	7.7	7.9	8.0	8.1	8.6	8.7
CLN[b]		7.8	8.5	8.8	8.7	8.7	8.7	8.8	8.7	8.8	8.8	8.8
total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

[a] *trans*-Vaccenic acid is usually found in small amounts in milk fat due to rumen biohydrogenation, and it is not common in vegetable oils. However, *cis*-vaccenic acid is found in some plant oils in small amounts (see *J. Pharm. Pharm. Sci.* **2002**, *5*, 231–233 and references therein). It is possible that *trans*-vaccenic acid occurs in vegetable oils either due to the oil manufacturing process or due to isomerization of *cis*-vaccenic acid at the high temperatures employed in the GC analysis. [b] Isomers of the conjugated methyl linolenate (based on the GC analysis of 92% conjugated methyl linolenate and subsequent retention time comparisons).

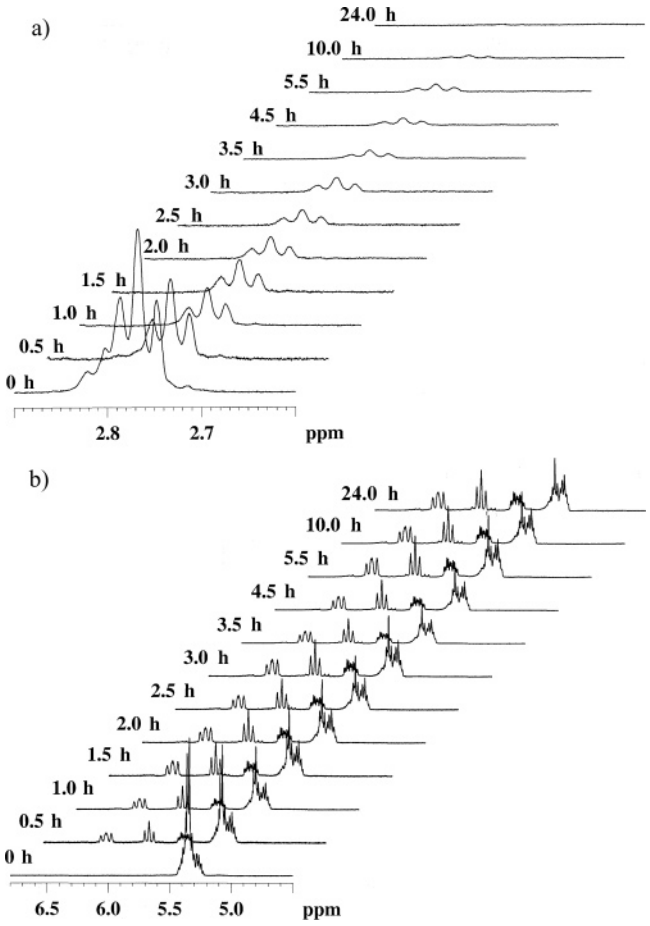


Figure 6. Progress of the isomerization of SOY monitored by ^{1}H NMR spectroscopic analysis of the (**a**) bisallylic and (**b**) vinylic regions.

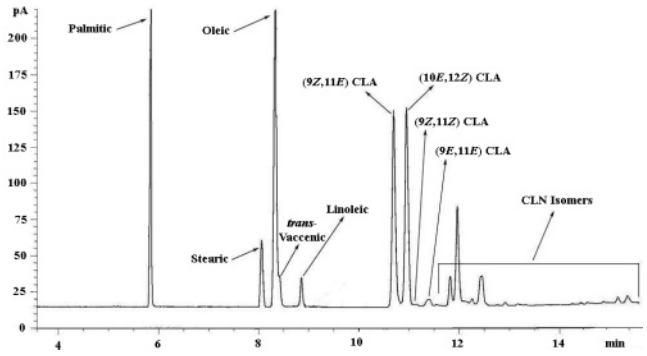


Figure 7. Gas chromatogram of conjugated SOY (**Table 2**, sample after 24 h).

SOY has been calculated to be 99.9%. This is in excellent agreement with the value obtained from the ^{1}H NMR spectroscopic analysis.

The results summarized in **Table 3** also show that the amount of all CLA isomers formed during the reaction (49.8%) is approximately 4% lower than the initial amount of linoleic fatty acid in the pure SOY. This is distributed among the more saturated fatty acid components (stearic and oleic acids) as shown by the small increase in their content. Although minor, this suggests that hydrogenation is a possible concomitant side reaction. However, contrary to these facts, a small increase (~1.5%) in the palmitic acid (C16:0) content is also observed. Since chain scission is fairly unlikely to occur during the isomerization process, this suggests that experimental error may be responsible for the observed discrepancies and that hydrogenation may not occur at all. At this moment we are uncertain as to the extent of hydrogenation. Anyhow, if present at all, its contribution is fairly small, and it does not drastically change the overall efficiency of the isomerization process.

Table 3 lists fatty acid compositions for several commercially available vegetable oils and their conjugated analogues prepared by our homogeneous rhodium-catalyzed isomerization process over the course of 24 h. The vegetable oils shown in the table are arranged according to their initial linoleic fatty acid content. The isomerization results indicate that all oils are essentially quantitatively converted into their corresponding conjugated isomers. Again, the major CLA isomers formed are the (9*Z*,-11*E*)-CLA and (10*E*,12*Z*)-CLA isomers. Their total content in the overall CLA mixture varies from 80.8% in CLIN to 93.3% in CCOR. It appears that the highest fraction of these two isomers is found in vegetable oils which have intermediate amounts of both linoleic and linolenic fatty acids. For instance, the intermediate cases, CCOR (93.4%) and CLS (91.7%), have the highest content of the two major CLA isomers. This suggests that the presence of a certain amount of linolenic acid in the pure oil favors the formation of the two major CLA isomers. On the other hand, its excess (LIN, 80.8%, has 53.0% linolenic acid) or scarcity (SAF, 76.2%, has 0.2% linolenic acid) shows the opposite effect. At the same time, the fraction of the thermodynamically more stable (9*E*,11*E*)-CLA isomer follows

Table 3. Fatty Acid Composition Comparisons for Several Regular Vegetable Oils and Their Conjugated Analogues As Determined by GC Analysis

Fatty acid	LIN	CLIN	PNT	CPNT	SOY	CSOY	COR	CCOR	LSS	CLS	SAF	CSAF
myristic (C14:0)					0.1	0.2				0.1	0.1	0.2
palmitic (C16:0)	5.5	6.5	12.4	12.7	11.5	12.9	11.6	11.6	4.38	4.6	7.7	8.2
palmitoleic (C16:1)	0.1	0.2	0.2	0.3	0.1	0.2	0.1	0.2	0.10	0.1	0.1	0.1
stearic (C18:0)	3.5	4.2	2.5	2.7	3.8	4.8	1.8	2.0	3.25	3.5	2.1	2.2
oleic (C18:1)	20.0	23.4	52.0	52.1	19.9	24.0	26.9	28.1	19.16	20.6	13.7	14.5
trans-vaccenic (C18:1)[a]	0.9	0.8	0.8	1.0	1.4	2.1	0.8	0.8	1.11	1.2	0.8	0.8
linoleic (C18:2)	17.0		32.0	0.7	55.6	3.2	57.5	0.8	63.50	0.6	75.3	2.1
linolenic (C18:3)	53.0				7.6		1.3		8.50		0.2	
(9*Z*,11*E*)-CLA		8.1		13.3		20.7		24.6		27.5		26.8
(10*E*,12*Z*)-CLA		8.5		14.2		21.9		26.5		29.5		27.5
(9*Z*,11*Z*)-CLA		1.0				1.1		0.8		1.0		0.8
(9*E*,11*E*)-CLA		3.0		3.0		4.1		2.8		4.1		16.2
CLN[b]		44.4				4.9		1.8		7.2		0.5
total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
C (%)		100.0		100.0		99.9		100.0		100.0		100.0
major CLA fraction[c] (%)		80.8		90.3		89.1		93.4		91.7		76.2
(9*E*,11*E*)-CLA fraction[d] (%)		14.6		9.7		8.6		5.1		6.6		22.7
(9*Z*,11*Z*)-CLA fraction[e] (%)		4.6		0		2.3		1.5		1.7		1.1

[a] See footnote *a* in **Table 2**. [b] Isomers of the conjugated methyl linolenate (based on the GC analysis of 92% conjugated methyl linolenate and subsequent retention time comparisons). [c] Fraction (%) of both major CLA isomers [(9*Z*,11*E*) and (10*E*,12*Z*)] in the overall CLA mixture. [d] Fraction (%) of the (9*E*,11*E*)-CLA isomer in the overall CLA mixture. [e] Fraction (%) of the (9*Z*,11*Z*)-CLA isomer in the overall CLA mixture.

the opposite trend. While relatively low for CSOY, CCOR, and CLS (8.6%, 5.1%, and 6.7% respectively), the (9*E*,11*E*)-CLA content in CLIN and CSAF increases substantially (14.6% and 22.7%, respectively). Conversely, the fraction of the thermodynamically less stable (9*Z*,11*Z*)-CLA isomer remains low in all samples.

With regard to our previous discussion of hydrogenation, we noticed that the isomerization of LIN resulted in a 9% decrease in conjugated linolenic acid content (initial 53.0% content vs 44.4% CLN content, **Table 3**). Closer inspection revealed that this amount was redistributed among the CLA isomers, as well as stearic and oleic acids, in CLIN upon conjugation. The magnitude of the discrepancy in this case strongly suggests the existence of hydrogenation as a side reaction, which accounts for the conversion of linolenic fatty acid into more saturated C18 fatty acids in the CLIN sample and, therefore, leads to their fractional increase. However, on the basis of the results with other oils, we noticed that the contribution of hydrogenation in other oils was either drastically lower or did not exist at all. This suggests that the high content of linolenic fatty acid in LIN enhances the hydrogenation side reaction.

Product Purification and ICP-MS Analysis. To be useful for any food applications, conjugated oils and CLAs need to be devoid of any toxic metals or other organics. Therefore, the ease and efficiency of their purification are important issues. During the course of our investigation, we observed that simple flash chromatography of the conjugated model compounds and vegetable oils on silica gel with *n*-pentane as the solvent was an efficient and straightforward purification method. The amount of silica gel needed for complete removal of the toxic metals (Rh and Sn) and organics (TTP) was optimized by performing flash chromatography using silica gel beads made with varying amounts of silica gel (see the Experimental Procedures). The untreated solution of conjugated oils and catalyst mixture had a dark red color, which was indicative of a high content of transition metal. With an increase in the amount of silica gel used in the purification, the color of the resulting solution changed from red to orange to yellow. The final yellow color, of course, closely resembled the natural color of most of the vegetable oils. To determine the content of both Rh and Sn in each of these colored solutions, we subjected them to ICP-MS analysis. For that purpose, an ICP-MS calibration curve (**Figure 8**) was generated using standard solutions of $RhCl_3$ and $SnCl_4$. For example, the results obtained from the analysis of the CSOY solutions are shown in **Table 4**. The data indicate that the red solution of CSOY contained 13.4 ppb Rh and 1.4 ppb Sn (**Table 4**, entry 3), while the orange solution contained 8.51 and 0.86 ppb Rh and Sn, respectively (**Table 4**, entry 2). The yellow solution obtained after purification on the largest silica gel bed (**Table 4**, entry 1) had 0.78 and 0.57 ppb Rh and Sn, respectively. The concentrations of these two metals are therefore at the threshold level set by the Food and Drug Administration (FDA) in July 1995 (*34*) and should not raise any toxicological issues.

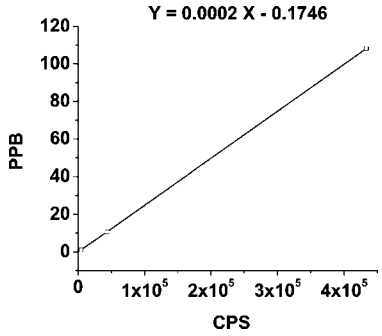


Figure 8. ICP-MS calibration curve for Rh.

Table 4. Concentrations of Rh and Sn in Three Separate CSOY Samples

entry	CPS[a] (Rh)	C_{Rh} (ppb)[b]	CPS[a] (Sn)	C_{Sn} (ppb)[b]
1	4700	0.78	3745	0.57
2	43432	8.51	5170	0.86
3	68048	13.43	7658	1.36

[a] CPS = counts per second. [b] ppb = parts per billion.

On the basis of these findings, we conclude that homogeneous rhodium-catalyzed isomerization represents an extremely efficient and selective method for the conjugation of both model compounds and vegetable oils. This method preserves the original structure of the substrates and only causes rearrangement of the carbon−carbon double bonds in the system. It offers certain advantages over the alkali-metal-based methods (*7*), because it does not cause hydrolysis of the final product. In

fact, it yields highly conjugated products, which are of considerable interest in the paint, coating, and polymer industries (*1*−*5*). Also, straightforward flash chromatographic purification affords an easy way to obtain very pure conjugated products devoid of any major amounts of residual catalyst and thus eliminates numerous issues raised by contamination. This approach is also very interesting from the food industry standpoint, because it mainly produces (9*Z*,11*E*)-CLA and (10*E*,12*Z*)-CLA isomers. The fraction of these two important isomers in the overall CLA mixture of conjugated oils is in the range from 76.2% to 93.4%.

Due to this high conversion and selectivity, this approach offers tremendous potential for CLA preparation. However, to determine the suitability of this method for the industrial production of food-grade CLA, one must consider the overall economics of the process. The main concern is, of course, the high cost of the Rh catalyst, which, aside from its high efficiency and selectivity, renders this process more expensive than the existing alkali-metal-based processes. Recycling of the catalyst is known to reduce the overall cost significantly, and it still represents one of the main considerations in the design of highly efficient processes (*35*−*39*). One approach toward fast and efficient catalyst recovery would be immobilization on a solid support (*40*). The main disadvantage of this method lies in the fact that catalyst efficiency usually decreases significantly after a couple of cycles due to leakage from the solid support. Another approach, first developed by Horvath (*41*), takes advantage of the limited miscibility of partially or fully fluorinated compounds with nonfluorinated ones in fluorous biphasic systems (FBSs). For instance, a typical FBS consists of a fluorous phase containing a dissolved catalyst and some other nonfluorous phase, which can be any organic or inorganic solvent with limited or no solubility in the fluorous phase. Usually, the fluorous phase consists of a perfluorinated hydrocarbon and a fluorous-phase-compatible catalyst. For that purpose the catalyst often contains fluorinated ligands to enhance its solubility in the fluorous media. The chemical transformations in these systems then occur either in the fluorous phase or at the interface of the two phases. In their original work (*41*), Horvath and coworkers demonstrated efficient extraction of a rhodium catalyst from toluene after catalytic hydroformylation of olefins. The successful catalyst recovery under the mild conditions coupled with retention of the catalyst's efficacy offers huge potential for industrial application of homogeneous catalysis in the future. This approach has been reviewed extensively and proven useful in numerous catalytic processes (*42*−*48*).

In the near future, we intend to utilize this approach and optimize the overall isomerization process. We believe that these improvements may render this homogeneous rhodium-catalyzed isomerization industrially applicable for the production of CLA.

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