

Article

Ethyl Linoleate Derivatives from Olefin Metathesis as a Function of the Starting Complex and Reactivity Conditions

Cristina Vidal da S. Neta¹, Yan F. da Silva², Valdemiro P. Carvalho Jr², Benedito dos S. Lima-Neto^{3,*} and José Luiz S. Sá^{1,*}

¹ Centro de Ciências da Natureza, Universidade Estadual do Piauí, 64002-150, Teresina, PI, Brazil.

² Faculdade de Ciências e Tecnologia, Universidade Estadual Paulista, CEP 19060-900, Presidente Prudente, SP, Brazil.

³ Instituto de Química de São Carlos, Universidade de São Paulo, PO Box 780, 13560-970, São Carlos, SP, Brazil.

* Correspondence: zeluizquimica@gmail.com; Tel.: +55-086-99922-1554

* Correspondence: benedito@iqsc.usp.br; Tel.: +55-016-3373-9333

Abstract: Olefin metathesis of ethyl linoleate (EL) was investigated under different conditions of substrate amount, temperature, and catalyst. Second-generation Grubbs catalyst (G2) was used in experiments at 20 and 50 °C for 24 and 48h, whereas first-generation Grubbs catalyst (G1) and [RuCl₂(PPh₃)₂perhydroazepine] (LN) were used in experiments at 50 °C for 24h, with the latter also being investigated in the presence or absence of SnCl₂ as co-catalyst. Catalytic products were analyzed for GC-MS and discussed in terms of relative percent of the metathesis products. With G2 as catalyst, GC-MS chromatograms were similar in all the amounts of EL investigated at 50 °C for 24h, except for ethyl hexadec-9-enoate (compound **K**), which was obtained with different percentage as a function of EL amount (55% for 2 and 5 mL and 65% for 8 mL). An α,ω -dicarboxylic acid with $m/z = 444.00$ (compound **L**) was produced from the experiments at 50 °C for 24h with similar percentage as a function of EL amount. However, the relative percentage of **L** changed with the increase of EL volume in the experiments at 20 °C (ca. 18, 27, and 28%, with 2, 5, and 8 mL of EL, respectively). The olefin metathesis of EL conducted by G1 reached lower selectivity than that conducted by G2 for 24h at 50 °C. Several intense peaks reached with G1 were similar to those obtained with G2, in addition to new peaks of medium intensity. Compound **L** showed higher m/z , similar to that presented with G2, but with lower relative proportion in the mixture. LN was inert for olefin metathesis of EL; however, it was activated in the presence of SnCl₂ at 50 °C for 24h. Different compounds and selectivity as a function of the catalyst type and reaction conditions were obtained.

Keywords: Olefin metathesis; ethyl linoleate; ruthenium.

1. Introduction

Meeting the principles of green chemistry, renewable raw materials significantly contribute to sustainable development and further utilization, such as built-in design for degradation or low toxicity of the resulting products. Vegetable oils are the most widely used renewable resources because of their low toxicity, inherent biodegradability, ready availability, and relatively low price. In the chemical industry, vegetable oils present a wide range of applications, as in soaps, drying agents, coatings, hydraulic fluids, etc. Oils and fats represent a new and well-noted feedstock for the synthesis of lubricants, monomers, and polymers [1-3].

In this context, chemical transformations are conducted across the double bonds of vegetable oil fatty acids via olefin metathesis to prepare new materials. Olefin metathesis is a powerful methodology for the construction of carbon-carbon double bonds in organic synthesis. ROMP (Ring Opening Metathesis Polymerization), RCM (Ring Closing Metathesis) and CM (Cross Metathesis) are examples of olefin metathesis [4-9].

Grubbs catalysts are well-defined Ru-carbene complexes. Their properties are dependent on electronic and steric characteristics, which are modulated for specific applications [4-12]. The olefin metathesis of fatty acids and of their derivatives provides, among other things, the production of different molecules, such as α,ω -dicarboxylic acids. The yields or selectivity are achieved by tuning the choice of the catalyst with the reaction conditions [12]. In this way, the application of catalytic precursors, such as the Lima-Neto Ru-compounds synthesized for ROMP reactions [13-16], can be modulated for other purposes inside of the metathesis type.

In this study, olefin metathesis of ethyl linoleate (EL), mediated by Grubbs first- (G1) and second-(G2) generation metathesis catalysts and $[\text{RuCl}_2(\text{PPh}_3)_2\text{perhydroazepine}]$ (LN) pre-catalyst (Fig. 1), is investigated under different conditions of temperature, reaction time, and concentrations of substrate and additive. It is worth highlighting that the LN complex has never been studied as catalyst in this type of olefin metathesis. These complexes present different ancillary ligands, such as PCy_3 , N-heterocyclic carbene, and perhydroazepine in G1, G2, and LN, respectively, addressing different characteristics to each starting complex. Furthermore, the Werner-type complex LN is considered a first-generation olefin metathesis catalyst owing to the absence of carbene moiety. In this case, the metal-carbene complex is generated in situ via reaction with ethyldiazoacetate (EDA). Thus a study was performed to verify the influence of substrate concentration, time, and temperature in the olefin metathesis of EL mediated by G1, G2, or LN.

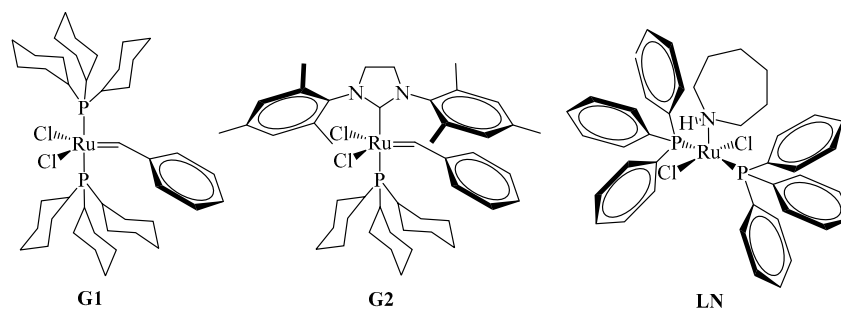


Figure 1. Grubbs first-(G1) and second-(G2) generation metathesis catalysts and $[\text{RuCl}_2(\text{PPh}_3)_2\text{perhydroazepine}]$ (LN) pre-catalyst.

2. Results and Discussion

2.1. Olefin metathesis with G2

Figure 2 presents the GC-MS sample chromatograms of the substrate and of the different volumes of substrate with G2 (2mL; 5 mL; 8 mL) after 24h at 50 °C.

The retention times in the chromatogram of the sample without G2 after 24h at 50 °C are identical to those of the chromatogram of a fresh sample of substrate (Figure 2-a; Figure S1), confirming no occurrence of reaction in the absence of catalyst. Four main peaks are observed in the chromatogram (Figure 2-a). They are attributed to ethyl palmitate at 12 min ($m/z = 284.00$; compound **A**; 10.3%), ethyl linoleate at 15 min ($m/z = 308.00$, compound **B**), ethyl oleate at 15.2 min

($m/z = 310.00$; compound **C**), and ethyl stearate at 15.5 min ($m/z = 312.00$; compound **D**, 2.9%). The peaks at 15 and 15.2 min coalesced and represented 87.1% of the sample, but the main percentage regards ethyl linoleate (compound **B**). Figure 3 illustrates the chemical structures of the identified compounds.

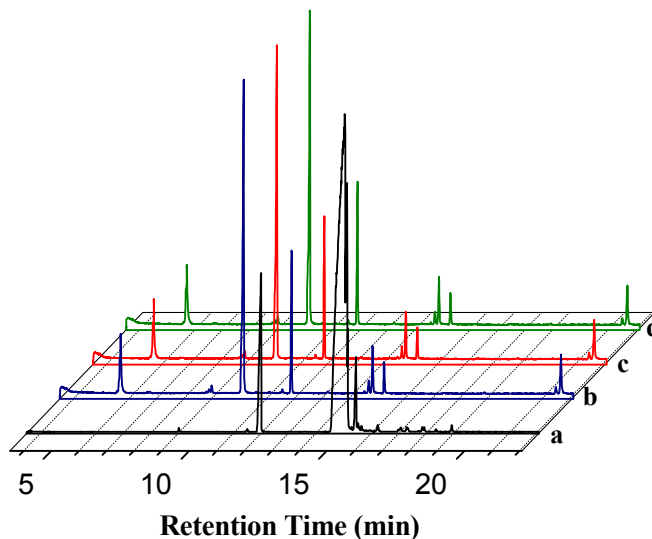


Figure 2. GC-MS chromatograms from experiments with different amounts of substrate after 24h at 50 °C without G2 (a, 2 mL) and with G2 (b, 2 mL; c, 5 mL; d, 8 mL).

When 2 mL of sample was left 24h in the presence of G2 at 50 °C, new peaks in the chromatogram were observed (Figure 2-b), suggesting the occurrence of reaction. The same new peaks were observed in the chromatograms from reactions with different volumes of substrate, and they presented similar intensities; perhaps a saturation conversion was obtained (Figure 2-c;d). The peaks of the **A** (12 min) and **D** (15.5 min) compounds remain, considering that they are saturated molecules. The peaks at 15 min (compound **B**) and 15.2 min (compound **C**) significantly decreased in intensity, suggesting that olefin metathesis occurred. Metathesis with the esters **B** (linoleate; with two olefins) and **C** (oleate; with one olefin) can result in various new olefin compounds, which can undergo further metathesis over the run.

Products from self-metathesis of **B** in the inner olefin would be the compounds **G** ($m/z = 448.00$) and **H** ($m/z = 168.00$), as illustrated in Figure 4, but these compounds were not identified in the chromatograms, as occurred in olefin metathesis of methyl linoleate. In addition, the compounds **E** ($m/z = 368.00$) and **F** ($m/z = 248.00$) should be products of the self-metathesis of **B** in the external olefin (double bond furthest from the carboxylic function), but these compounds were also not identified in the chromatograms, as it occurred in the olefin metathesis of methyl linoleate [5,17]. The production of **E** was also expected from the self-metathesis of **C** (Figure 5), in addition to compound **I** ($m/z = 252.00$), which was identified by the peak at 5.7 min. Compound **E** would also be produced in the cross-metathesis of the external olefin of **B** with **C**, also producing **K** ($m/z = 250.00$), which did not appear. Thus the absence of **E** suggests a facility to undergo cross-metathesis with other olefin molecules to produce new olefins. This produced the ethyl hexadec-9-enoate ($m/z = 282.00$; compound **J**) identified at 10.2 min (Figure 2) from the metathesis of **E** with other olefin molecules

formed in the process. Compound **J** was the major product obtained, with its amount increasing with the substrate amount (55% from 2 or 5 mL; 65% from 8 mL), the self-metathesis in the external olefin of **B** (considering the amount of **B**), and the self-metathesis of **C** (considering presence of **I**) as the main source. The peak observed at 22 min is attributed to compound **L** ($m/z = 444.00$), which can be produced by successive olefin metatheses [18].

The conversion of **B** reached 85%, and no significant variation was observed when different amounts of the initial substrate were used. The conversion was measured using the fragment at 12 min relative to the saturated compound **A** as internal standard. The **A**:**B** ratio is constant in the three chromatograms. However, a progress in the reaction as a function of time influenced the relative percent of the product mixture from the metathesis. When increasing the time from 24 to 48h, the percentage of **J** appeared with lower relative value (38-42%), whereas the relative percentage of **L** increased to 21-27% (Figure 6). Probably, **J** was consumed to form **L** by successive metathesis reactions. This shows a tendency for formation of compound of the type α,ω -dicarboxylic acids with molecular weight of $m/z = 444.00$. The conversion of compound **B** was c.a. 94% for 48h.

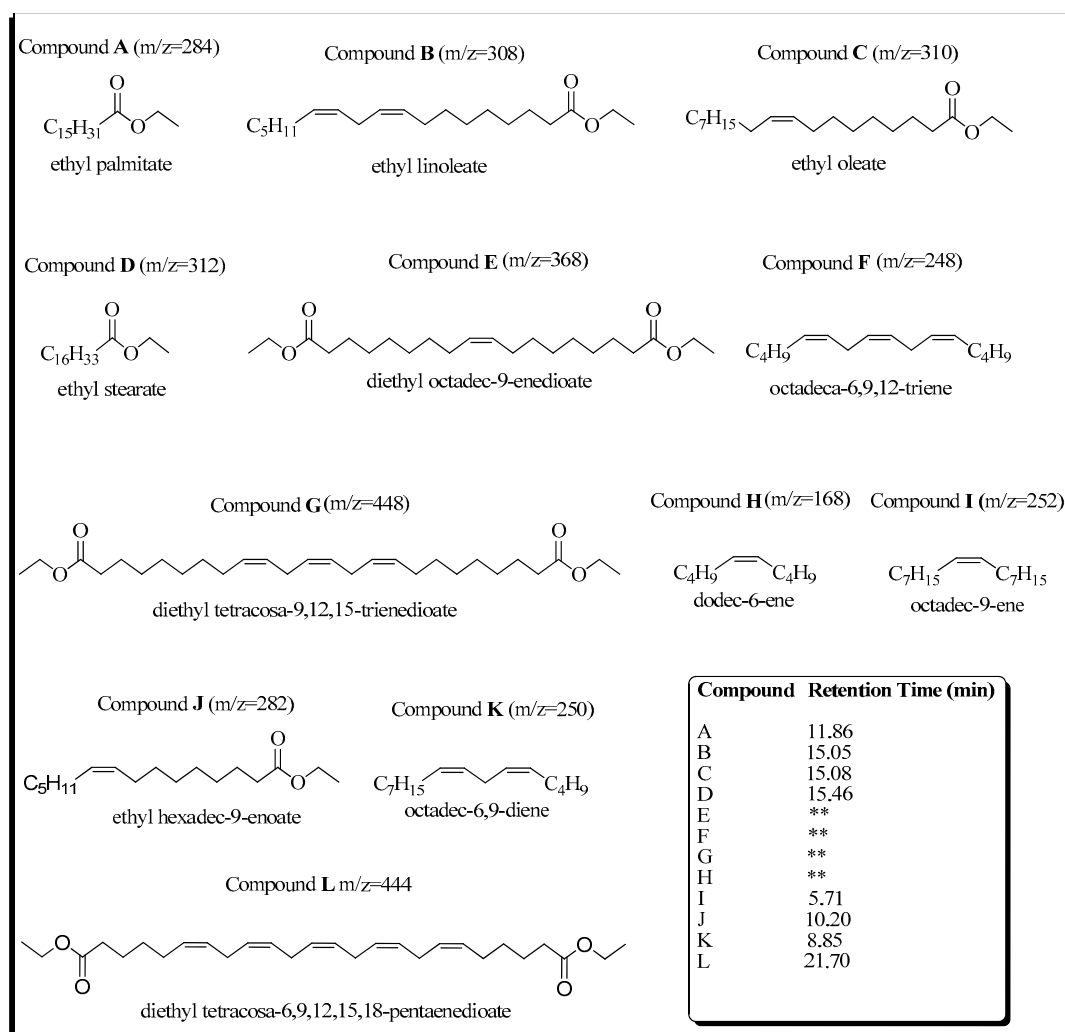


Figure 3. Illustration of the compounds identified in the GC-MS chromatograms.

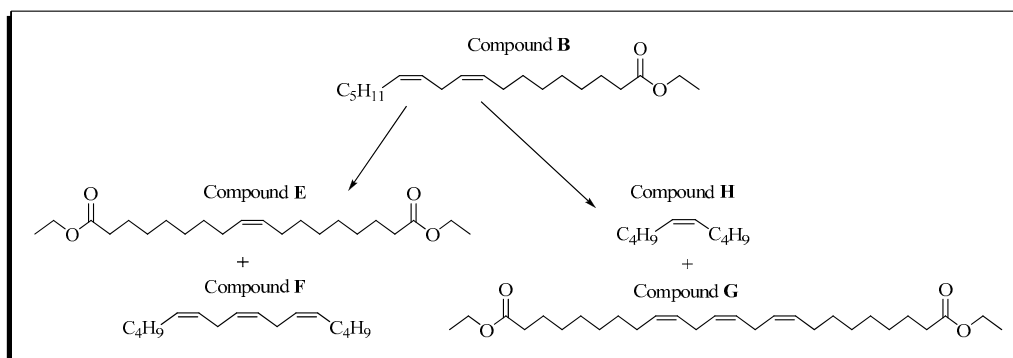


Figure 4. Illustration of the products from self-metathesis of B in the external an dinner double bonds with G2 at 50 °C for 24h.

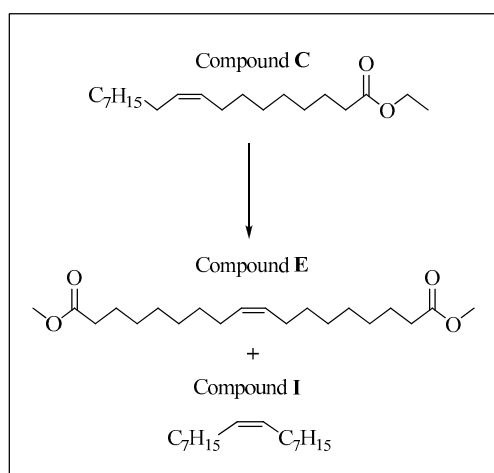


Figure 5. Illustration of the products from self-metathesis of C with G2 at 50 °C for 24h.

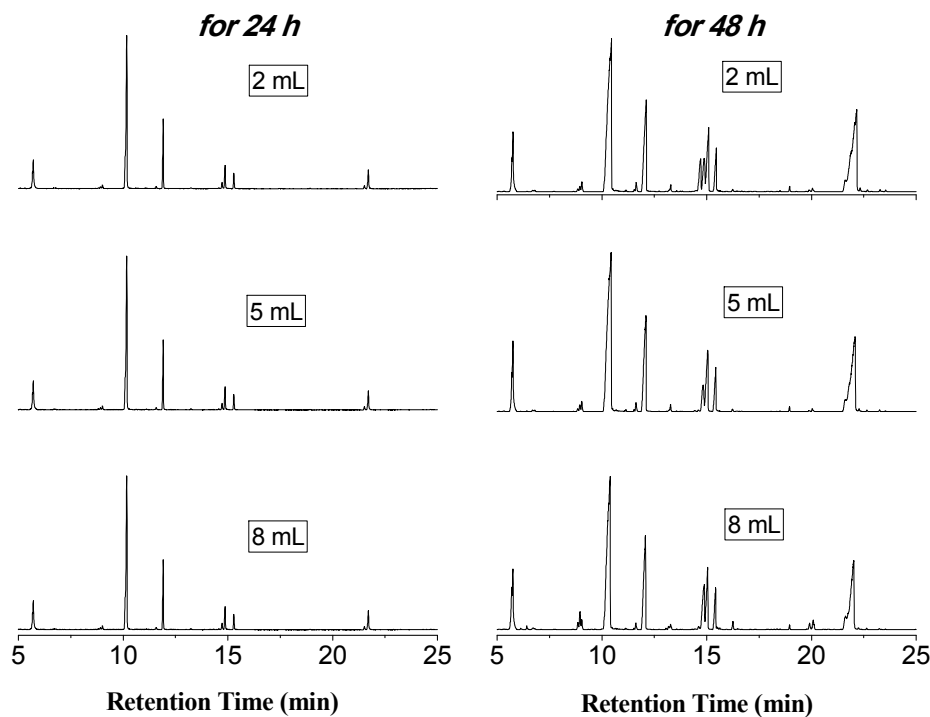


Figure 6. GC-MS chromatograms from experiments with different amounts of substrate (2 mL; 5 mL; 8 mL) after 24 and 48h at 50 °C with G2.

The GC-MS chromatograms from experiments performed at 20 °C for 24h presented a composition dependent on the starting substrate amount. The two major products, compounds **J** and **L**, obtained at 50 °C, showed greater production, and increased with substrate volume. The obtained relative percentages of **J** were 18, 27, and 28%, for 2, 5, and 8 mL of substrate, respectively. For **L**, the obtained relative percentages were 7, 18, and 22%, for 2, 5, and 8 mL, respectively. This is associated with the disappearance of the peak at 15.2 min, relative to compound **C**, which results in c.a. 22, 10, and 8%, for 2, 5, and 8 mL of the starting volume, respectively. This feature did not occur with similar molecules such as methyl linoleate, in which the selectivity of the products obtained was not influenced by the substrate:catalyst ratio [6]. The conversion values of compound **B** at 20 °C were c.a. 98, 92, and 92% with 2, 5, and 8 mL, respectively. High conversion values were obtained, but selectivity was lower.

2.2. Olefin metathesis with G1

Studies were performed with 2 and 5 mL of substrate for 24h at 50 °C, which were the best conditions observed with G2 in terms of selectivity.

With 2 mL and G1, the GC-MS chromatogram (Figure 7) showed the following products: **I** (5.7 min; c.a.7.0%), **K** (8.9 min; 4.6%), and **L** (21.9 min; 16.0%), in addition to **A** (11.9 min; 12.2%), **B** (15.0 min), and **C** (15.2 min; 38.0% is referent to the **B** plus **C** peak integration). Other non-identified compounds were produced with peaks between 16.5 and 20 min.

The percentage of **I** was similar to that observed when G2 was used, suggesting the occurrence of metathesis of **C**. The appearance of **K** indicates that G1 is able to provide the cross-metathesis of the external olefin of **B** with **C**, and that **K** was not consumed for further metathesis. Compound

L was produced in lower proportion in the mixture with G1 as catalyst; 16% compared with c.a. 21% with G2. The rich chromatogram obtained with G1 as catalyst is indicative of lower selectivity than with G2, but with occurrence of considerable activity.

The GC-MS chromatogram obtained from reaction with 5 mL also presented unknown compounds with peaks from 16.5 up to 19.5 min, corresponding to 10% of the total area (Figure 7). The peaks observed at 5.7, 8.9, 11.9, 15.5, and 22.0 min are attributed to compounds **I** (3.4%), **K** (3.4%), **A** (10.3%), **B** (74%), and **L** (2%), respectively.

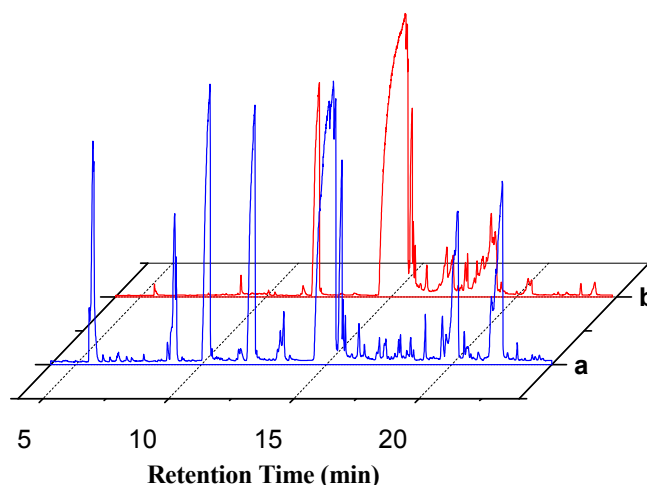


Figure 7. GC-MS chromatograms from experiments with different amounts of substrate after 24h at 50 °C with G1 (a; 2 mL; b, 5 mL).

2.2.1. Olefin metathesis with LN

No compounds were produced from metathesis in experiments with LN for 24h at 50 °C with 5 mL of substrate. Similar reactions in the presence of SnCl₂ as additive, with [Ru]:[Sn] ratios of 1:1 or 1:2 mol, resulted in productive metathesis reaction. The chromatograms were similar to those obtained with 5 mL of substrate and G1 (Figure 8), with peaks relative to compounds **I** (5.71 min), **J** (10.2 min), and **L** (22.0 min). In addition, peaks at 8.9 min (2.5%) and a set of peaks from 16.5 to 19.5 min also appeared. This shows the similarity between LN in the presence of additive and G1 with respect to activity and selectivity. Similar studies conducted with Rh complexes in the presence of SnCl₂ for olefin isomerization provided high conversion of methyl linoleate, showing the necessity of activation of the starting complex [19].

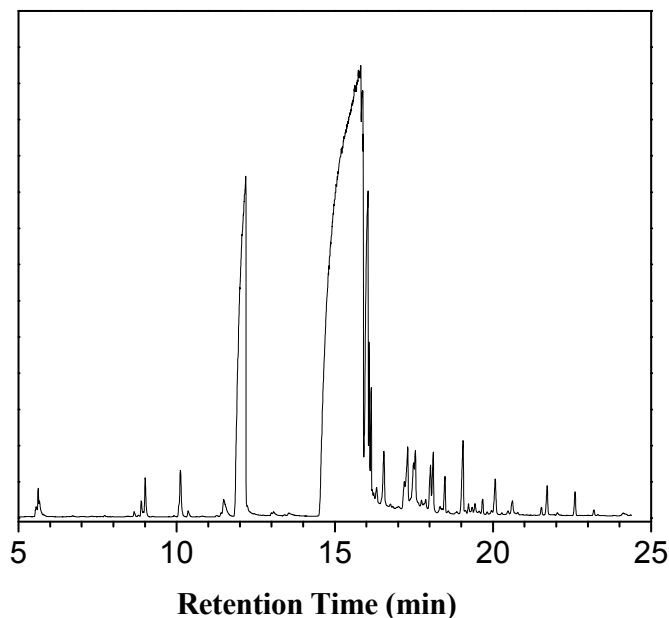


Figure 8. GC-MS chromatogram from reaction of 5 mL of substrate with LN in the presence of SnCl₂ at 50 °C for 24h.

In an attempt to understand the role of SnCl₂ in the reaction, cyclic voltammograms of LN in the absence and presence of SnCl₂ were performed (Figure S2). In the absence of SnCl₂, an anodic potential (E_{anod}) at 0.76 V and a cathodic process at 0.58 V (E_{cath}), vs. Ag/AgCl, corresponding to the Ru^{II/III} redox process were obtained. In the presence of SnCl₂, the voltammogram presented $E_{\text{anod}} = 1.05$ V and $E_{\text{cath}} = 0.54$ V. This shift in the potentials suggests that a new species resulted from the interaction of LN with SnCl₂. As the anodic potential is higher than that in the pure complex, the interaction occurred with SnCl₂ decreased the electronic density in the metal center. A possible interaction can occur with the phosphine phenyl rings, increasing the electronic π -acceptor nature of the phosphine, then increasing the oxidation potential of the Ru(II) species. The metathesis reaction occurs when phosphines are displaced from the metal coordination sphere to permit the coordination of olefin [13,14]. Thus the presence of SnCl₂ interaction provides a more effective phosphine displacement to the occurrence of the metathesis reaction. The olefin is very large and a decrease in steric hindrance provides better coordination of the olefin. Nevertheless, activation of the olefin does not occur appropriately, as demonstrated by the low conversion.

3. Materials and Methods

3.1. General remarks

All reactions and manipulations were performed under nitrogen atmosphere following standard Schlenk techniques. Ethyl linoleate (EL), ethyl diazoacetate (EDA), Grubbs first-(G1) and second-(G2) generation catalysts, $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$, $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$, tetrabutylammoniumhexafluorophosphate ($n\text{-Bu}_4\text{NPF}_6$), perhydroazepine, and PPh_3 were purchased from Aldrich and used as received. $[\text{RuCl}_2(\text{PPh}_3)_2(\text{perhydroazepine})]$ (LN) was obtained according to previously described synthetic procedures and its purity was verified by satisfactory elemental analysis and spectroscopic examination ($^{31}\text{P}\{^1\text{H}\}$ - and ^1H -NMR; FTIR) [13].

3.2. Analyses

GC-MS analyses were performed in a Shimadzu QP2010-SE, with the capillary column Rtx®-5MS (30 m x 0.25 mm x 0.25 μm) and He as carrier gas. The oven initial temperature was 100 °C, increasing to 180 °C with heating rate of 10 °C/min; it was then held for 1 min, followed by new heating rate of 4 °C/min for 10 min until 250 °C. The injector and detector transfer line temperatures were 270 and 350 °C, respectively. Elemental analyses were conducted using an EA1110CHNS-O Carlo Erba Instrument. ^1H and $^{31}\text{P}\{^1\text{H}\}$ NMR spectra were obtained in CDCl_3 at 298 K on a BrukerDRX-400 spectrometer operating at 400.13 and 161.98 MHz, respectively. The chemical shifts obtained were reported in ppm relative to TMS or 85% H_3PO_4 . Electrochemical measurements were performed using an AutolabPGSTAT204 potentiostat with a stationary platinum disk and a wire as working and auxiliary electrodes, respectively. The reference electrode was Ag/AgCl. The measurements were performed at 25 °C \pm 0.1 in CH_2Cl_2 with 0.1 mol L^{-1} of $n\text{-Bu}_4\text{NPF}_6$.

3.4. Self-metathesis of EL

A Schlenk flask containing a magnetic stirring bar was charged with a catalyst (G1, G2, or LN; 1.0 mmol). The reactor was purged of air by applying three vacuum/nitrogen cycles before ethyl linoleate (2, 5 or 8 mL) and ethyl diazoacetate (only for LN) were added with a dried syringe under argon atmosphere. The solution was stirred for specific times (24 or 48h) at 25 or 50 °C in thermostatic oil bath. The products were analyzed by GC-MS spectrometry.

5. Conclusions

First-(G1) and second-(G2) generation Grubbs complexes and the non-carbene $[\text{RuCl}_2(\text{PPh}_3)_2\text{perhydroazepine}]$ (LN) complex were successfully used for olefin metathesis of ethyl linoleate (EL). Their ability as metathesis catalysts under different conditions were evaluated.

In general, the catalytic activity was very different in function of the catalyst, and three products were observed. When comparing the results between G1 and G2, it could be clearly observed that the consumption of EL was higher with G2, where the presence of a NHC ligand in the coordination sphere provides high α -donor character [1-11]. The LN complex was inert; however, it was activated in the presence of SnCl_2 .

The results show the influence of simple variables in the cross- and self-metathesis of fatty acid ester derivatives even in low-purity substrates. In addition, studies with LN introduce this

compound as an active pre-catalyst in this type of metathesis, considering that our research group has already reported the mathatetical activity of LN for ROMP reactions [13, 14].The steric hindrance and electronic proprieties of LN allowed reactivity in the presence of SnCl₂, promoting the olefin metathesis of EL.

We understand that this investigation on the selectivity of olefin metathesis for simple compounds, as a function of reaction conditions, provides an important guide to obtain high selectivity in more complex molecules.

Acknowledgments: The authors are indebted to GERATEC research lab, CAPES and CNPq for financial supports.

References

1. Verhé, R. Industrial Products from Lipids and Proteins, in: C. V. Stevens, R. Verhé (Eds.), *Renew. Bioresources Scope Modif. Non-Food Appl.*, John Wiley & Sons, Ltd, 2004: pp. 208–250. M.R. Islam., DOI: <http://doi/10.1002/ejlt.200900138/pdf>
2. M.D.H. Beg, S.S. Jamari, Development of Vegetable-Oil-Based Polymers, *J. Appl. Polym. Sci.* 2014, v.131, p.13. DOI:10.1002/app.40787
3. U. Biermann, U. Bornscheuer, M.A 338 .R. Meier, J.O. Metzger, H.J. Schäfer, Oils and Fats as Renewable Raw Materials in Chemistry, *Angew. Chemie Int.* 2011, v. 50, p.3854–3871. DOI:<http://doi/10.1002/anie.201002767>
4. Alev Tüzün, Gerard Lligadas, Juan C. Ronda †, Marina Galià, Virginia Cádiz. Castor oil-derived benzoxazines: Synthesis, self-metathesis and properties of the resulting thermosets. *European Polymer Journal*.2016, v.75, p. 56–66. DOI:<http://dx.doi.org/10.1016/j.eurpolymj.2015.12.004>.
5. Bengi Özgün Öztürk, Beyza Topo_glu and Solmaz Karabulut Şehitoglu., Metathesis reactions of rapeseed oil derived fatty acid methyl esters induced by monometallic and homobimetallic ruthenium complexes. *Eur. J. Lipid Sci. Technol.* 2015, v. 117, p. 200-208. DOI:<http://doi/10.1002/ejlt.201400342>
6. Hatice Mutlu, Robert Hofsaß, Rowena E. Montenegro and Michael A. R. Meier. Self-metathesis of fatty acid methyl esters: full conversion by choosing the appropriate plant oil. *RSC Adv.*, 2013, v. 3, p. 4927–4934. DOI: 10.1039/C3RA40330K
7. Georgios C. Vougioukalakis. Recent Advances in Olefin Metathesis. *Molecules* 2016, v. 21, p.1751. DOI: <http://dx.doi.org/10.3390/molecules21121751>
8. Araceli Martínez, Selena Gutiérrez and Mikhail A. Tlenkopatchev. Metathesis Transformations of Natural Products: Cross-Metathesis of Natural Rubber and Mandarin Oil by Ru-Alkylidene Catalysts. *Molecules* 2012, p. 176001-6010. DOI: 10.3390/molecules17056001.
9. Pierre H. Dixneuf*, Christian Bruneau and Cédric Fischmeister. Alkene Metathesis Catalysis: A Key for Transformations of Unsaturated Plant Oils and Renewable Derivatives. *Oil & Gas Science and Technology – Rev. IFP Energies nouvelles*.2016, v. 71, p.19. DOI: <http://dx.doi.org/10.2516/ogst/2015033>
10. IVIN, K. J.; MOL, J. C. Olefin metathesis and metathesis polymerization New York: Academic Press, 1997.
11. GRUBBS, R. H., Olefin Metathesis. *Tetrahedron*, v. 60, p. 7117-7140, 2004.
12. Helen L. Ngo; Kerby Jones; Thomas A. Foglia., Metathesis of unsaturated fatty acids: Synthesis of long-chain unsaturated- α,ω -dicarboxylic acids *Journal of the American Oil Chemists' Society*, 2006, v. 83, p. 629–634. DOI: 10.1007/s11746-006-1249-0

13. SÁ, J. L. S.; VIEIRA, L. H. ; NASCIMENTO, E. S. P.; LIMA NETO, B. S., The influence of perhydroazepine and piperidine as further ancillary ligands on Ru-PPh₃-based catalysts for ROMP of norbornene and norbornadiene. *Applied Catalysis. A, General*, 2010, v. 374, p. 194-200. DOI: <http://dx.doi.org/10.1016/j.apcata.2009.12.013>.
14. SILVA SÁ, J. L.; NASCIMENTO, E. S. P.; FONSECA, L. R.; LIMA-NETO, B. S., Ring opening metathesis copolymerization of norbornene with norbornadiene from solutions with different mole fractions of the comonomers catalyzed by Ru-amine complexes. *Journal of Applied Polymer Science*. 2013, v. 127, p. 3578-3585, 2013. DOI: 10.1002/app.37741.
15. CARVALHO JUNIOR, V. P.; FERRAZ, C. P.; SÁ, J. L. S.; LIMA NETO, B. S., ROMP COMO UM MÉTODO VERSÁTIL PARA A OBTENÇÃO DE MATERIAIS POLIMÉRICOS DIFERENCIADOS. *Química Nova*, 2012, v. 35, p. 791-801.
16. FONSECA, L. R.; NASCIMENTO, E. S. P.; SILVA SÁ, J. L.; LIMA-NETO, B. S., The ring size of cyclic amines as a relevant feature in the activity of Ru-based complexes for ROMP. *New Journal of Chemistry*, 1987, v. 39, p. 4063-4069, 2015. DOI: 10.1039/C5NJ00321K
17. Kathryn A. Alexander, Emily A. Paulhus, Gillian M.L. Lazarus, Nicholas E. Leadbeater. Exploring the reactivity of a ruthenium complex in the metathesis of biorenewable feedstocks. *Journal of Organometallic Chemistry*. 2016, v. 812, p. 74-80. DOI: 10.1016/j.jorganchem.2015.09.018
18. Helen L. Ngo, Kerby Jones, and Thomas A. Foglia*. Metathesis of Unsaturated Fatty Acids: Synthesis of Long-Chain Unsaturated- ω,ω -Dicarboxylic Acids. *JAACS*, 2006, v. 83, p. 229-634. DOI: 10.1007/s11746-006-1249-0
19. Arno Behr, Henning Witte and Zeynep Bayrak. Homogeneous metal complex catalyzed conjugation of methyl linoleate. *Eur. J. Lipid Sci. Technol.* 2013, v. 115, p. 721-728. DOI: 10.1002/ejlt.201200429



© 2017 by the authors. Licensee *Preprints*, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons by Attribution (CC-BY) license (<http://creativecommons.org/licenses/by/4.0/>).