doi:10.2533/chimia.2023.70 Chimia 77 (2023) 70–72

Chemical Education

A CHIMIA Column

Topics for Teaching: Fatty Acids

Addition Reactions to Unsaturated Fatty Acids: A Theoretical Study about Mechanisms and Stereochemistry

Carsten A. Vock*

*Correspondence: Dr. C. A. Vock, E-mail: carsten.vock@univie.ac.at
Department of Nutritional Sciences, Faculty of Life Sciences, University of Vienna, Josef-Holaubek-Platz 2 (UZA 2), 1090, Vienna, Austria; Faculty of Chemistry, University of Vienna, Währinger Str. 38-42, 1090, Vienna, Austria

Abstract: After a short introduction about fatty acids, the article refers to an unclear statement by Gibson *et al*. about the kind and number of isomeric products formed by addition of hypochloric acid to palmitoleic acid and linoleic acid. A theoretical approach with detailed mechanistic and stereochemical considerations will lead the reader to the solution of the problem.

Keywords: Chemical Education · Fatty Acids · Reaction Mechanisms · Stereochemistry

Dedicated to Prof. Dr. Reinhard Brückner for his achievements in Organic Chemistry education

Fatty acids and their derivatives (in particular their esters, which form the huge class of lipids) are of enormous importance in living organisms. The expression 'fatty acid' originates from their identification as key constituents of natural glycerol esters, *i.e.* fats and oils. Though saponification of those esters mainly yields unbranched carboxylic acids with 16 to 18 carbon atoms, the definition of fatty acids has been later extended to all chain lengths due to similar pathways in biosynthesis. Therefore, *e.g.*, all members of the homologous series of aliphatic unbranched carboxylic acids are called fatty acids. However, the family of fatty acids also includes highly important unsaturated derivatives containing different numbers of 1,2-disubstituted *Z*-configured double bonds and, occasionally, also branched acids. Some important examples for saturated (**1**, short-chain; **2**, medium-chain; **3**, **4**, long-chain), monounsaturated (**5**, **6**) and polyunsaturated (**7**, **8**) fatty acids are depicted in Fig. 1.

A huge number of beneficial, but also adverse effects on human health have been shown or are supposed to be associated with the uptake of fatty acids as part of nutrition. The supplementation of butyric acid (**1**) resp. its sodium salt is considered (based on experiments with mice) to have beneficial attenuating effects on the development of steatohepatitis.[1–3] Medium-chain fatty acids like caprylic acid (**2**) are energy sources and involved in colon maintenance;[4] their level in feces of people suffering from inflammatory bowel disease is significantly decreased.[5] The role of long-chain saturated fatty acids (SFA) (like palmitic acid (**3**) and stearic acid (**4**)), monounsaturated fatty acids (MUFA) (like palmitoleic acid (**5**) and oleic acid (**6**)), and polyunsaturated fatty acids (PUFA) (like linoleic acid (**7**) and α-linolenic acid (**8**)) in nutrition is controversially discussed. The substitution of SFA against PUFA or MUFA leads to a significant lowering of low

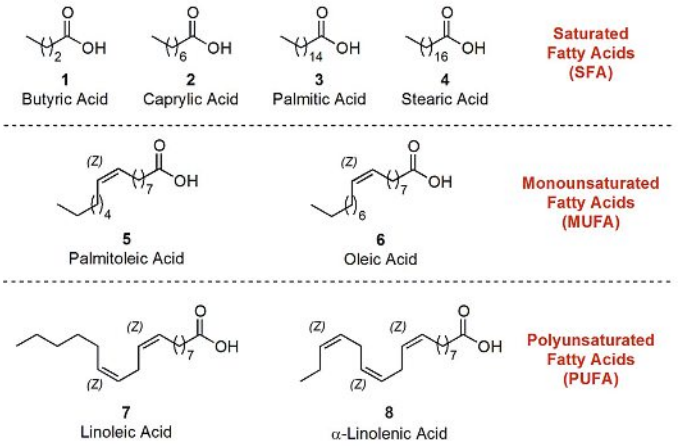


Fig. 1. Some important examples of short-, medium- and long-chain fatty acids with different degrees of unsaturation.

density lipoprotein-cholesterol (LDL-C) – considered as risk factor for the development of coronary heart disease (CHD) – in blood and is therefore recommended.[6,7] However, there is no evidence for beneficial effects of generally lowering SFA with persons already suffering from CHD.[8] Olive oil, which consists mainly of MUFA **6**, has positive effects on CHD and associated diseases[9] as well as Type 2 diabetes;[10] however, those effects seem to be associated with the food olive oil and are not necessarily observed with other MUFA-rich oils.[9,10] In guinea pigs, a PUFA-rich diet has a significant influence on saliva cortisol levels.[11]

The topic of this article, however, shall not be a full overview of the nature of fatty acids and their beneficial or harmful effects on humans' health, but the discussion of an interesting mechanistic and stereochemical problem, more or less accidently discovered when reading an article about water disinfection. In 1986, Gibson, Haley, Righton and Watts reported the formation of chlorohydrin adducts of mono- and diunsaturated fatty acids when treated with HOCl at pH 7 under typical water disinfection conditions.[12] Within the publication, the authors expect the formation of two isomeric products during treatment of monounsaturated **5** and four isomeric products during treatment of diunsaturated **7**. After intensive discussion of mechanistic and stereochemical aspects in a basic Organic Chemistry course for Nutritional Scientists, these numbers seemed a little underestimated; therefore, the following theoretical experiment was set up and introduced into the course as an exercise.

General Remarks/Restrictions

- Although not stated by Gibson *et al.*,[12] the double bonds in the fatty acids are assumed to have the natural *Z*-configuration!
- For the theoretical experiment, only addition reactions to the double bonds are considered! Possible further products (isomerization products, elimination products, cyclization products *etc*.) shall be neglected!

- The addition of Br_2 to double bonds exclusively forms the *anti*-addition product, which means: the intermediate bromonium ion is opened in a S_N2 reaction by backside attack of the formed bromide ion Br^-!
- The addition of HOCl to double bonds proceeds (like the addition of Cl_2) *via* an intermediate chloronium ion, which is in equilibrium with ring-opened carbenium ions. The nucleophilic attack of the chloride ion Cl^- occurs (at least in part) as S_N1 reaction, so *anti*- as well as *syn*-addition product are formed!

Task/Exercise

How many isomeric compounds do you expect theoretically (using all your mechanistic and stereochemical knowledge and in particular the fact that for addition reactions *via* chloronium ion intermediates also *syn*-addition products are observed) for (i) the addition of Br_2, (ii) the addition of Cl_2 and (iii) the addition of HOCl to the double bonds of **5** and **7**? Draw the structures of all the compounds.

Partial Solution

We start with monounsaturated fatty acid **5**. The detailed mechanism for the addition of Br_2 to the double bond is shown in Scheme 1. In the first step, two enantiomeric bromonium ions **9a** and **9b** are formed, which will be opened by backside S_N2 attack of the bromide ion. For each bromonium ion **9a/b**, there are two possibilities for attack of Br^- at C9 or C10, so altogether four attacks can be counted; however, comparison of the formed compounds reveals only two (enantiomeric) products **10a** and **10b**.

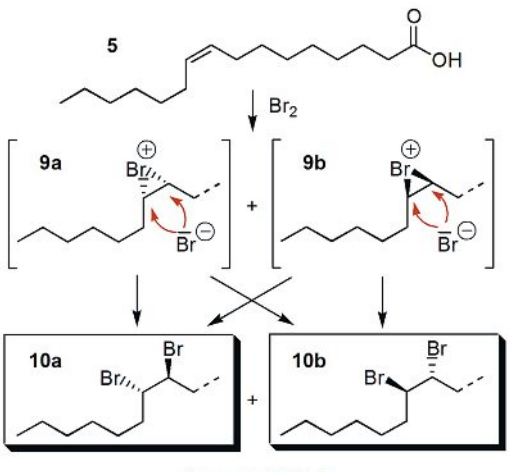
The chlorination of the double bond of **5** is more complicated; the detailed mechanism is shown in Scheme 2. In analogy to the bromination, two enantiomeric chloronium ions **11a** and **11b** are formed in the first step. Those are, however, more strained than the bromonium ions and therefore in equilibrium with ring-opened carbocations **12aa/12ab** and **12ba/12bb**, respectively. Although the ratio will not be perfectly 1:1, the chloride ion is able to attack the carbocations from both sides, so not only *anti*-, but also *syn*-addition compounds are formed, presumably as minor products, following a S_N1 mechanism. For each carbocation **12aa/12ab/12ba/12bb**, two products are possible, so altogether eight attacks can be counted; however, comparison of the formed compounds reveals only four products **13a–d**, which are *syn*- and *anti*-addition product (diastereoisomers), each as pair of enantiomers.

Finally, the addition of HOCl to the double bond of **5** is the most demanding example of the theoretical exercise; the detailed mechanism is shown in Scheme 3. Though the formation of chloronium ions **14a–b** and the ring-opened carbocations **15aa/ab/ba/bb** is – with exception of the counterion OH^- – identical to the mechanism of the chlorine addition (see Scheme 2), the non-symmetric nature of HOCl leads to the formation of two different regioisomers. For each of them, the full set of four stereoisomers in analogy to the chlorine addition can be generated. Altogether, a set of eight products **16a–h** can be expected: two regioisomers, each consisting of a *syn*- and *anti*-addition product (diastereoisomers), with again each as pair of enantiomers.

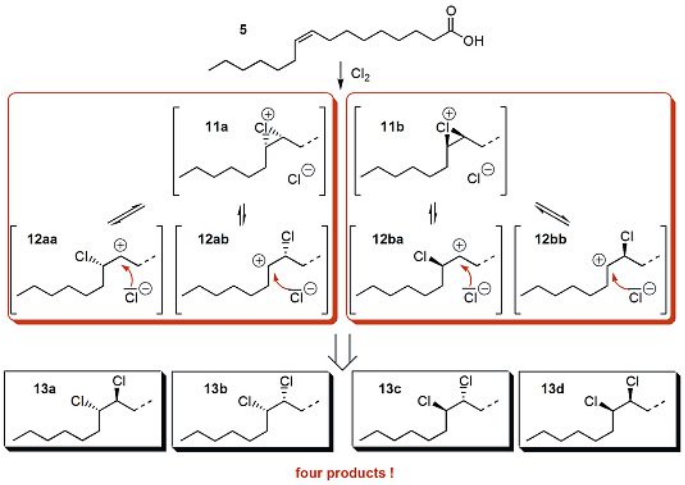
In summary, the addition of Br_2 to the double bond of **5** leads to two, the addition of Cl_2 to four and the addition of HOCl to eight possible isomeric products.

There is also a possibility to calculate the number of isomers for those types of fatty acids mathematically. If there is no further restriction, the number of possible isomers z can be derived from the number of stereocenters n formed after addition reaction by the equation:

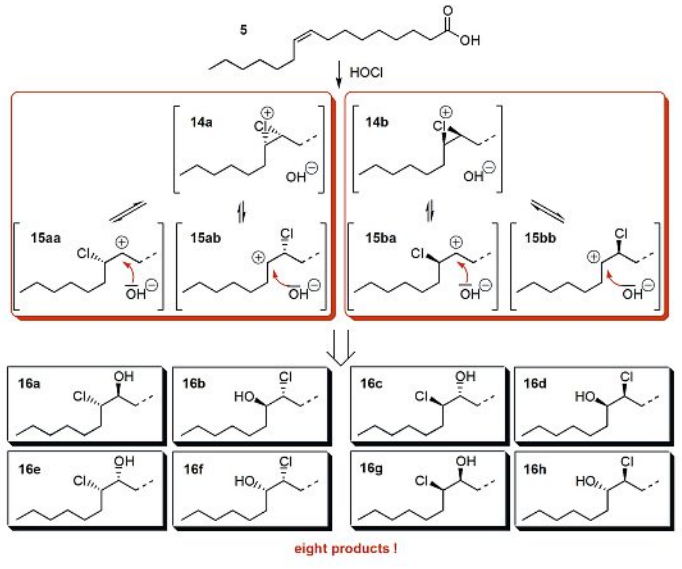
$$z = \mathbf{2}^n$$



Scheme 1. Detailed mechanism for the formation of enantiomeric products **10a** and **10b** from **5** by addition of Br_2 to the double bond. For clarity, free electron pairs are only drawn where necessary.



Scheme 2. Detailed mechanism for the formation of diastereoisomeric products **13a–d** (two pairs of enantiomers) from **5** by addition of Cl_2 to the double bond. For clarity, free electron pairs are only drawn where necessary, and detailed arrows for the reactions **11**/**12** → **13** like in Scheme 1 have been omitted



Scheme 3. Detailed mechanism for the formation of regio- and stereoisomeric products **16a–h** from **5** by addition of HOCl to the double bond. For clarity, free electron pairs are only drawn where necessary, and detailed arrows for the reactions **14**/**15** → **16** like in Scheme 1 have been omitted.

This is valid for the chlorine addition, for which – due to the lack of mechanistic restrictions – the full set of possible isomers is accessible. For the bromination, the mechanistic restriction of the *anti*-addition rules out half of the possible isomers; the equation for the bromination would be:

$$z = \mathbf{2}^{n-1}$$

For the addition of HOCl, the problem of regioisomers has to be included; however, there is no full permutation possible, since OH and Cl substituents have to be attached to one double bond (OH/OH or Cl/Cl at the same double bond is not possible). The easiest way for mathematic display is the introduction of *m* as number of double bonds. Each double bond forms two regioisomers during the addition of HOCl, and each regioisomer gives the full set of 2^n stereoisomers. So, the following equation results:

$$z = \mathbf{2}^{m} \cdot \mathbf{2}^{n} = \mathbf{2}^{(m+n)}$$

However, *m* and *n* are connected *via*: $\boldsymbol{n = 2 \cdot m}$ (one double bond leads to two stereocenters). So, the final equation for the number of isomers can be expressed as

$$z = \mathbf{2}^{3m}$$ (for the number of double bonds)

or as

$$z = \mathbf{2}^{1.5n}$$ (for the number of stereocentres formed).

The demanding task to verify the former considerations by repeating Schemes 1–3 for diunsaturated fatty acid **7** shall be left to the reader. As conclusion, the statement of Gibson *et al.* about the number of resulting isomers during the HOCl addition[12] can be interpreted as consideration of the possible regioisomers, but definitely not as full determination of all stereoisomers.

Acknowledgements

Logistic support from the Environmental Research Network (ERN) at the University of Vienna, Vienna, Austria is gratefully acknowledged. The author would like to thank Prof. Dr. Reinhard Brückner for the inspiration to set up demanding theoretical experiments for Basic Organic Chemistry courses.

Received: November 28, 2022

[1] C. J. Jin, C. Sellmann, A. J. Engstler, D. Ziegenhardt, I. Bergheim, *Br. J. Nutr.* **2015**, *114*, 1745, https://doi.org/10.1017/S0007114515003621.
[2] D. Zhou, Q. Pan, F. Z. Xin, R. N. Zhang, C. X. He, G. Y. Chen, C. Liu, Y. W. Chen, J. G. Fan, *World J. Gastroenterol.* **2017**, *23*, 60, https://doi.org/10.3748/wjg.v23.i1.60.
[3] A. Baumann, C. J. Jin, A. Brandt, C. Sellmann, A. Nier, M. Burkard, S. Venturelli, I. Bergheim, *Nutrients* **2020**, *12*, 951, https://doi.org/10.3390/nu12040951.
[4] A. Gregor, S. Auernigg-Haselmaier, S.Trajanoski, J. König, K. Duszka, *Nutrients* **2021**, *13*, 3807, https://doi.org/10.3390/nu13113807.
[5] M V. De Preter, K. Machiels, M. Joossens, I. Arijs, C. Matthys, S. Vermeire, P. Rutgeerts, K. Verbeke, *Gut* **2015**, 64, 447, https://doi.org/10.1136/gutjnl-2013-306423.
[6] L. Schwingshackl, B. Bogensberger, A. Benčič, S. Knüppel, H. Boeing, G. Hoffmann, *J. Lipid Res.* **2018**, *59*, 1771, https://doi.org/10.1194/jlr.P085522.
[7] R. P. Mensink, 'Effects of Saturated Fatty Acids on Serum Lipids and Lipoproteins: A Systematic Review and Regression Analysis', World Health Organization, Geneva, Switzerland, **2016**.
[8] L. Schwingshackl, G. Hoffmann, *BMJ Open* **2014**, 4, e004487, https://doi.org/10.1136/bmjopen-2013-004487.
[9] L. Schwingshackl, G. Hoffmann, *Lipids in Health and Disease* **2014**, *13*, 154, https://doi.org/10.1186/1476-511X-13-154.
[10] L. Schwingshackl, A.-M. Lampousi, M. P. Portillo, D. Romaguera, G. Hoffmann, H. Boeing, *Nutrition & Diabetes* **2017**, *7*, e262, https://doi.org/10.1038/nutd.2017.12.
[11] M. Nemeth, E. Millesi, K.-H. Wagner, B. Wallner, *Br. J. Nutr.* **2018**, *120*, 1240, https://doi.org/10.1017/S0007114518002660.
[12] T. M. Gibson, J. Haley, M. Righton, C. D. Watts, *Environ. Technol.* **1986**, *7*, 365, https://doi.org/10.1080/09593338609384423.