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Theoretical and kinetic analysis of the esterification of undecylenic acid with glycerol

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Abstract

The synthesis of undecylenic acid partial esters can be performed at mild temperature with a classical esterification reaction catalyzed by DBSA. A semi-empirical molecular modeling on the different reaction intermediates indicates that DBSA can strongly decrease their heats of formation through hydrogen bonding. Diester formation seems to be thermodynamically favored with a selectivity for alpha, alpha or alpha, beta forms that depends on the geometry of the catalyst-intermediate configuration. Triesters are not favored but a high selectivity for monoesters requires a kinetic control. Experimental approach, considering different DBSA concentrations and temperature partially confirms the theoretical predictions but surfactant properties of DBSA and monoesters may induce non predicted geometries. Global apparent activation energies are calculated, corresponding to the formation and hydrolysis of mono and diesters. If water trapping allows the decrease of hydrolysis reaction constants, the presence of water and subsequent phase separation may explain differences between theoretical and experimental results and could help increasing monoester selectivity.

Keywords : Semi-empirical, Activation energy, Monoglyceride, Esterification, Kinetic, undecylenic acid

1 Introduction

2 Undecylenic acid is a bio-sourced fatty acid having the peculiarity to possess an easily functionalizable
3 double bond at the extremity of its carbon chain. It can be easily condensed with glycidol to selectively
4 form monoglycerides (Mhanna et al., 2014). Their amphiphilic nature allows interesting surface properties
5 and also bactericidal (Thormar, 2011) and auto-organization (Leser et al., 2006; Nyame Mendendy
6 Boussambe et al., 2017) behaviors. With their terminal double bond, these monoglycerides are also
7 synthons for polymerization (Bigot et al., 2016). However, carcinogenicity of glycidol (Aasa et al., 2019)
8 implies the use of a less toxic and more sustainable reactant as glycerol. The synthesis of monoglycerides
9 is easily obtained with an esterification reaction with glycerol, yielding different glycerol partial esters
10 (Boussambe et al., 2015). It is then important to understand the factors controlling yield and selectivity of
11 these reactions. The kinetic study of the esterification of glycerol with a short chain fatty acid as lauric
12 acids has ever been studied Homogeneous catalysis can be employed, for example potassium or sodium
13 soaps (Szelag and Zwierzykowski, 1998) in which case, the concentration of monoacylglycerol reaches a
14 maximum of 46-49% and can decrease for high reaction rates. Heterogeneous catalysis can also be used,
15 as with mesoporous catalysts SBA-15 (Hermida et al., 2011; Hoo and Abdullah, 2015) which allows high
16 monoglyceride yield (>60%) after 5 hours of reaction. However, high temperatures (130-160°C) are
17 generally used, potentially coupled with low pressure to further water elimination and decrease reaction
18 time. According to the operating conditions, the synthesis of monoesters, diesters and triesters are then
19 reversible or irreversible and are parallel or consecutive reactions respectively. Using surfactant catalysts,
20 it is possible to perform esterification reactions at lower temperatures and without the use of a solvent,
21 the surfactant allowing either a better homogeneity of the medium, either a better withdrawal of water.
22 DBSA (dodecylbenzenesulfonic acid), as a sulfonic acid surfactant, is generally used (Gang et al., 2007;
23 Wallis et al., 2017). To optimize the synthesis of the monoglycerides and understand the role of water on
24 both yield and selectivity, it is important to determine theoretically the different heats of formations of
25 the molecules formed. Besides, in the case of a simple homogeneous acid catalysis, minimum activation

1 energy of the different reactions involved can be estimated in order to get thermodynamic and kinetic
2 estimations of its feasibility. Semi-empirical molecular modeling can allow a fast calculation of these
3 energies. It has gained much precision and has broadened its application field since the first algorithms
4 developed. It can sometimes give comparable accuracies as DFT methods in the prediction of heats of
5 formation (Stewart, 2004). Allied with an experimental kinetic approach, a comprehensive study of the
6 reaction can be undertaken.

7 **Materials and Methods**

8 To determine the geometries and heats of formation of the different molecules involved, they were first
9 drawn with ChemAxon Marvin Sketch 5.11.5 then the most stable conformer was determined with the
10 CONFLEX-MM3 (Goto and Osawa, 1993) molecular mechanics algorithm in SCIGRESS EXPLORER FJ 2.4,
11 allowing variation of the different dihedral angles from -180 to 60 in two steps and of the hydrogen bond
12 length from 1.4 to 3 Å in six steps. The default CONFLEX settings were used (Force field : CAChe MM3
13 Augmented, Electrostatics through MM2/MM3 Bond Dipoles, Energy Minimization with the Conjugate
14 Gradient method, Limit of 5000 stored conformers, Highest Energy Conformer of 100 kcal/mol...) but the
15 van der Waals Cutoff Distance used for electrostatic interactions was increased at 36 Å.

16 The semi-empirical model PM7 (Stewart, 2013) was then used with COSMO solvation model (Klamt and
17 Schüürmann, 1993) in MOPAC2016 (Stewart, 2016) to determine the minimum heat of formation of the
18 obtained conformer, considering it is infinitely diluted and embedded in a dielectric continuum. The
19 solvent considered here was glycerol as it is the predominant compound. The solvation radius was yet
20 reduced to 1.3 Å (Klamt, 2011).

21 Kinetic rates of the reactions were obtained by fitting the time evolution of experimental concentrations
22 (mol/kg) of the products and reagents with the least square method within the software GEPASI v3.30
23 (Mendes, 1997, 1993; Mendes and Kell, 1998) considering reversible mass action kinetic types.
24 Convergence was reached with a genetic algorithm and evaluated through the square root sum of the

1 squares (SSQ) and the root mean square error (RMS). Calculated kinetic rates ($\text{kg}\cdot\text{mol}^{-1}\cdot\text{min}^{-1}$) are then
2 expressed as $k = Ae^{(-E_a/RT)}$ where A is a constant ($\text{kg}\cdot\text{mol}^{-1}\cdot\text{min}^{-1}$), E_a is the activation energy (kcal/mol), T is
3 the temperature (K), R is the ideal gas constant ($\text{kcal}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$). Activation energy of the reactions was
4 determined by plotting the logarithm of the kinetic rates versus the inverse of the temperature.

5 The experimental synthesis was carried out in a 4-neck 250mL reactor equipped with a condenser, a dean
6 stark and a mechanical stirrer (500 rpm). Glycerol and undecylenic acid at a molar ratio (2:1) are first
7 poured in the reactor, heated at the desired temperature then the catalyst DBSA (4-
8 Dodecylbenzenesulfonic acid) is added. The samplings done at different times of reaction are
9 immediately frozen prior to analysis. After the reaction, the products are extracted, cooled at ambient
10 temperature and washed 4 times with 100mL of a saturated NaCl solution (Boussambe et al., 2015).
11 Glycerol (98%) was obtained from Sigma-Aldrich, undecylenic acid (99%) was purchased from Acros
12 Organic, and dodecylbenzene sulfonic acid ($\geq 95\%$) was obtained from Sigma-Aldrich.

13 The purity of the molecules was determined by gas chromatography. The sample was injected in a Perkin
14 Elmer Chromatograph coupled with a flame ionization detector. It is equipped with a column Rtx-5
15 (Restek) (length : 15m, internal diameter : 0.32 mm, film thickness : 0.25 μm). The vector gas is helium with
16 a column head pressure of 15 psi. The temperature program is as follows : 55°C for 0.5 min, an increase in
17 temperature of 200°C / min to 340°C, then maintenance at 340°C for 30 min for the injector; 55°C for 0.5
18 min, then an increase of 45°C/min to 80°C and of 10°C/min to 360°C. The detector is fixed at 360°C.

19 The compounds are identified and quantified with an external calibration with purified and isolated
20 molecules.

21 The reaction yield is calculated as:

$$22 \quad Y = \frac{\text{number of moles of monoester formed}}{\text{initial number of moles of undecylenic acid}} \times 100 \quad (\text{E. 1})$$

23 The selectivity is calculated as :

1
$$S = \frac{\text{number of moles of monoester formed}}{\text{total number of moles of mono, di and triesters}} \times 100 \quad (\text{E. 2})$$

2

3 **Results and Discussions**

4 **Thermodynamic approach**

5 The reactional scheme can be approximated with a Fischer mechanism, considering a homogeneous
6 catalysis with DBSA (Dodecyl Benzene Sulfonic Acid).

7 Different products can be obtained through the esterification mechanism:

8 *α monoglyceride : glyceryl 1-monoundecylenate*

9 *β monoglyceride : glyceryl 2-monoundecylenate*

10 *α, β diglyceride : glyceryl 1,2-diundecylenate*

11 *α, α diglyceride : glyceryl 1,3-diundecylenate*

12 *Triglyceride : glyceryl triundecylenate*

13 In the example of α monoglyceride formation, several intermediates (T) are identified (Table 1).

14 Two reactional paths can be hypothesized. One considers the catalyst as a sole proton carrier and the
15 energy is then calculated as the sum of the heats of formation of non-interacting molecules (NIM). This
16 reactional path can be considered for very low concentrations of catalyst. Nine states are then identified
17 (Table 1). The second one considers that interaction can occur between the catalyst and the intermediate
18 so the energy is calculated for the system catalyst-intermediate (IM). In this second case, a higher number
19 of states (around the nine main ones) can be considered according to the different interactions between
20 the catalyst and the intermediate (cf. Supplementary Material) .

21 The minimum energy that must be brought to the system to reach the final state will be considered as
22 equal to the maximum differences between two successive states (Table 2). For the esterification
23 reaction, the energy barrier will be considered both before (*States Initial to Final*) and after activation of
24 undecylenic acid (*States 1 to Final*).

1 The documentation on PM7 accuracy (Stewart, 2016) does not take into account fatty molecules but
2 indicates that the average unsigned error for the heats of formation calculated with the PM7 for
3 molecules containing hydrogen, carbon, oxygen and sulphur is 3.5 kcal/mol (180 molecules). Considering
4 this value, two energies would be significantly different if $\Delta E > 7 \text{ kcal/mol}$ and two energy differences
5 significantly different if $\Delta(\Delta E) > 14 \text{ kcal/mol}$. Hence, even if the structural proximity of the molecules may
6 decrease the additivity of the calculation errors, the comparison of the barrier heights calculated for the
7 different reactions must be taken with caution.

8 Intermediates can be largely stabilized with hydrogen or electronic interactions coming from the catalyst
9 (DBSA, DBSA⁻, H₃O⁺, H₂O). If DBSA is considered, the sulfonate group can stabilize the protonated
10 carbonyl, reducing the energy required for the formation of this intermediate (Fig. 1). Energy differences
11 between successive states can then be largely decreased. With the presence of DBSA in the vicinity of the
12 intermediates, in the example of the formation of *α monoglyceride*, energy differences lie around 7 and
13 11 kcal/mol for direct and reverse reactions, respectively (Table 2).

14 *α monoglyceride through α mono-esterification*

15 An example of representation of the different energies calculated during the reactional path is given for
16 the case of the *α mono-esterification* of glycerol with undecylenic acid (Fig. 2).

17 The difference between the initial and final state semi-empirical (SE) energies is only 4.5 kcal/mol (Fig. 2),
18 which is not significant. E(a₁) and E(a₂) corresponding to a charge rearrangement have not a high
19 difference in energies. The same remark can be applied to the difference between E(4) and E(5).

20 Considering the non-interacting system, in the direct sense, the critical step is acid activation which
21 directly depends on the catalyst used. The high difference between E(I) and E(a₁) (34 kcal/mol with DBSA)
22 is high due to the unstable protonated undecylenic acid. This corresponds to the minimum energy that
23 has to be overcome in order to reach the final state (Fig. 2). This step is the critical step for all the
24 reactions considered (Table 2) so it is important to also consider the steps beyond acid activation. It is

1 then the protonation of the alcohol function (2->3) which requires the highest energy in the direct sense
2 (24 kcal/mol) while it is the protonation of the ether oxygen (2-1) in the reverse sense (38 kcal/mol).
3 Considering the entire reaction path, it seems clear that the rate constants of the direct and reverse
4 reactions should be quite similar, which is relevant to the athermicity observed for esterification
5 reactions. Consequently, for this unique reaction, temperature could only have a kinetic effect and should
6 not modify the yield at equilibrium.

7 Considering the interacting system, maximal energy difference in the direct sense (7 kcal/mol) is largely
8 and significantly lower. In the reverse sense, it is a bit superior (11 kcal/mol) but not significantly
9 different. Hence, the presence of the catalyst at a higher concentration will largely reduce activation
10 energies.

11 *β monoglyceride through β mono-esterification*

12 In the non-interacting system, the energy profile is similar to the α -esterification. This indicates that both
13 forms should be formed with a low concentration of DBSA. With the interacting system, the maximum
14 energy differences between successive states are nearly identical in direct and reverse senses (13 and 12
15 kcal/mol, respectively). The values seem to be a bit superior to those found for α monoglyceride,
16 particularly for the direct sense. Even if the difference is not significant, α monoglyceride may then be
17 preferentially formed.

18 *α, α diglyceride through esterification of the α monoester*

19 The approximation of consecutive reactions will be made, diester being then synthesized from a
20 monoester and undecylenic acid. Indeed, considering the very low probability of a simultaneous contact
21 of two undecylenic acid with glycerol, parallel reactions could only occur if the contact between
22 undecylenic acid and glycerol anchored with an acid induce a latent time inferior to the time needed to
23 accomplish the steps of the mono-esterification. Considering the energy differences between the

1 different intermediates, the anchoring of another acid could mainly take place between the step number
2 2 and the final one.

3 In the non-interacting mode, the minimum energy to overcome for the direct sense is 34 kcal/mole, quite
4 superior to the value of the reverse sense at 26 kcal/mole (Fig. 3). However, after acid activation, just 12
5 kcal/mol are required between states 2 and 3, a value inferior to those obtained for mono-esterification.
6 Hence, activated acid would rather react with a monoester than with glycerol. In interacting mode, the
7 energies are 13 kcal/mole and 12 kcal/mol for the direct and the reverse sense, respectfully. In this mode,
8 the values are within the range of those obtained for monoesterification. For both modes, it will be
9 difficult to avoid the formation of the diester, even by playing with temperature or by trapping water. So,
10 an excess of glycerol seems to be the only way to favor the formation of the monoester.

11 *α , β diglyceride through esterification of the α monoester.*

12 The formation of α , β diglyceride is considered here through esterification of the α mono-ester as α and
13 β mono-esters have nearly identical calculated heats of formation (-223 and -222 kcal/mol, respectively)
14 and it is hypothesized that steric hindrance between two adjacent chains is comparable between the two
15 esterification modes. In the non non-interacting mode, if acid activation remains the higher global barrier
16 (34 kcal/mol), α_2 form may react more easily in alpha position (12 kcal/mole) than in beta position (25
17 kcal/mol). In the reverse sense, the energy barrier (39 kcal/mole) is higher. In this mode, alpha, alpha
18 form may be preferentially formed.

19 In interacting mode, however, the barrier is equivalent for direct and reverse reactions (19 kcal/mole and
20 20 kcal/mole) but it is superior to those encountered for the alpha, alpha form and we can suppose a
21 preference, at least at low temperatures, of the alpha, alpha form compared to the alpha, beta form.

22 *Triglyceride formation through esterification of the α , α or α , β diester.*

23 Here, whatever the esterification considered, no stabilization is observed between the initial and final
24 states (Fig. 4). Considering the non-interacting mode, in the case of the esterification of a α , α ester, the

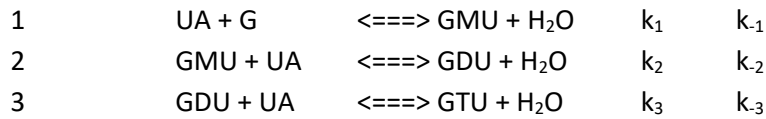
1 minimum energy to overcome in the direct sense, after acid activation, is higher than for the other
2 esterification reactions (26 kcal/mol) but similar to the monoesterification. Esterification of the α , β
3 diester requires less energy (19 kcal/mol) but the formation of this triester is limited by the energy
4 needed to form the α , β diester. In interacting mode, for both esterifications in alpha or beta position, it is
5 noteworthy that hydrolysis reaction will require less energy than esterification and α , α diester may be
6 preferentially formed in this reverse reaction (7 kcal/mol compared to 14 kcal/mol for α , β diester). It will
7 then be difficult to stabilize the triester. Triester will be formed if temperature is elevated and water
8 largely trapped.

9 According to this theoretical approach, in non-interacting mode, considering DBSA as a sole proton
10 carrier, it would be possible to play with temperature in order to favor α , α DG but it may be difficult to
11 avoid the formation of triesters. In interacting mode, it would be possible to kinetically favor mono and
12 diglycerides and to limit the formation of triesters.

13 **Experimental kinetic approach**

14 Considering this first theoretical approach, esterification reactions will be made with an excess of glycerol
15 but the effect of water will be evaluated and experimental apparent activation energies will be evaluated.
16 At ambient temperature, undecylenic acid is liquid but is not miscible with glycerol and a biphasic system
17 is encountered. With the presence of a certain amount of DBSA, acting as both surfactant and catalyst,
18 the system becomes quickly monophasic after a few minutes at 25°C. The system can then be considered
19 as homogeneous at the beginning of the reaction then the presence of water can induce a phase
20 separation. Two compartments are considered, the first one with glycerol and water, the second one with
21 the fatty acid and the glycerol esters.

22 The hypothesis of following consecutive reactions will be made, considering that the diester can only be
23 formed from the monoester, undecylenic acid being less concentrated.



4 UA : Undecylenic acid

5 GMU : Glycerol Monoundecylenate

6 GDU : Glycerol Diundecylenate

7 GTU : Glycerol Triundecylenate

8 G : Glycerol

9 k_i : rate constant of the direct reaction i.

10 k_{-i} : rate constant of the reverse reaction -i

11 GMU represents the sum of α and β forms and GDU represents the sum of α , α and α , β forms.

12 The system can be approximated with first order simultaneous differential equations, with activity
 13 coefficients equal to unity:

$$14 \quad \frac{d[\text{UA}]}{dt} = -k_1[\text{UA}][\text{G}] + k_{-1}[\text{GMU}][\text{H}_2\text{O}] - k_2[\text{GMU}][\text{UA}] + k_2[\text{GDU}][\text{H}_2\text{O}] - k_3[\text{GDU}][\text{UA}] + k_3[\text{GTU}][\text{H}_2\text{O}] \quad (\text{E. 3})$$

$$15 \quad \frac{d[\text{G}]}{dt} = -k_1[\text{UA}][\text{G}] + k_{-1}[\text{GMU}][\text{H}_2\text{O}] \quad (\text{E. 4})$$

$$16 \quad \frac{d[\text{GMU}]}{dt} = +k_1[\text{UA}][\text{G}] - k_{-1}[\text{GMU}][\text{H}_2\text{O}] - k_2[\text{GMU}][\text{UA}] + k_2[\text{GDU}][\text{H}_2\text{O}] \quad (\text{E. 5})$$

$$17 \quad \frac{d[\text{H}_2\text{O}]}{dt} = +k_1[\text{UA}][\text{G}] - k_{-1}[\text{GMU}][\text{H}_2\text{O}] + k_2[\text{GMU}][\text{UA}] - k_2[\text{GDU}][\text{H}_2\text{O}] + k_3[\text{GDU}][\text{UA}] - k_3[\text{GTU}][\text{H}_2\text{O}] \quad (\text{E. 6})$$

$$18 \quad \frac{d[\text{GDU}]}{dt} = +k_2[\text{GMU}][\text{UA}] - k_2[\text{GDU}][\text{H}_2\text{O}] - k_3[\text{GDU}][\text{UA}] + k_3[\text{GTU}][\text{H}_2\text{O}] \quad (\text{E. 7})$$

$$19 \quad \frac{d[\text{GTU}]}{dt} = +k_3[\text{GDU}][\text{UA}] - k_3[\text{GTU}][\text{H}_2\text{O}] \quad (\text{E. 8})$$

20 Gas chromatography analysis gives the concentration of undecylenic acid, diglyceride and
 21 monoglycerides. Glycerol concentration is deduced from these.

$$22 \quad [\text{G}] = [\text{G}]_i - ([\text{GMU}] + [\text{GDU}]) \quad (\text{E. 9})$$

$$23 \quad [\text{H}_2\text{O}] = 3[\text{UA}]_i - ([\text{G}] + [\text{GMU}] + [\text{GDU}] + [\text{UA}]) \quad (\text{E. 10})$$

24 Besides, an excess of glycerol is used to decrease the amount of diesters.

1 $[G]_i = 2[UA]_i$ (E. 11)

2 At equilibrium:

3 $k_1[UA][G] = k_{-1}[GMU][H_2O]$ (E. 12)

4 and the equilibrium constants can be expressed as :

5 $K_{GMU} = k_1/k_{-1} = ([GMU][H_2O])/([UA][G])$ (E. 13)

6 $K_{GDU} = k_2/k_{-2} = ([GDU][H_2O])/([GMU][UA])$ (E. 14)

7 The advancement of the reaction is related to the consumption rate of undecylenic acid.

8 $v = -d[UA]/dt = k_1[UA][G] - k_{-1}[GMU][H_2O] + k_2[GMU][UA] - k_{-2}[GDU][H_2O]$ (E. 15)

9 Posing x as the concentration of GMU and y as the concentration of GDU, a_0 and $2a_0$ the initial
10 concentrations of acid and glycerol.

11 $[UA] = a_0 - x - 2y$; $[G] = 2a_0 - x - y$ et $[H_2O] = x + 2y$ (E. 16)

12 $v = ax^2 + by^2 + cxy + dx + ey$ (E. 17)

13 The reaction rate should then follow a complex polynomial law of the 2nd order.

14 **Determination of the influence of water.**

15 At 80°C, 0.125 eq. DBSA, the reaction is first conducted without molecular sieves. The low values of SSQ
16 and RMS indicate a good superposition of experimental and regressed data (Table 3). The constant rates
17 corresponding to the monoester and diester formation and hydrolysis are similar. This is conform to the
18 molecular modelling with similar activation energies for direct and reverse reactions. Equilibrium
19 constants are close to unity, as the ratio K_{GMU}/K_{GDU}

20

1 The evolution of the yield (Y) and selectivity (S) in monoester shows that yield reaches a maximum value
2 of 60% around 15 minutes of reaction while selectivity continuously decreases. After 90 min of reaction
3 (Fig. 5), Y=51% and S=70%.

4 With the use of molecular sieves (3Å), the rate constants are different and water trapping favor direct
5 reactions with higher rate constants than for the hydrolysis ones. Indeed, the direct sense of the first
6 reaction is twice faster than the reverse sense. The second reaction, corresponding to diester formation
7 has higher rate constants than the first one.

8 Monoester selectivity remains at high values during the reaction while the yield gradually increases until
9 the steady state. The equilibrium constant K_{GMU} is twice the value obtained without molecular sieves
10 while K_{GDU} is slightly higher. K_{GMU}/K_{GDU} is then higher than without molecular sieves so both yield and
11 selectivity are increased (Y= 65 % ; S = 77%).

12 Extended water trapping would increase the rate constant of the diester and triester formation. Hence,
13 the simple molecular sieves will be used for the following reactions.

14 **Apparent activation energies**

15 With partial water trapping and a non-continuum system, only apparent activation energies of the
16 different reactions will be calculated. Three catalysts concentrations will be considered : 0, 0.08 eq. and
17 0.125 eq. using 3 or 4 temperatures.

18 *Reaction without catalyst*

19 In the absence of catalyst, only the reaction above 80°C allows the measurable formation of glycerol
20 esters. Even at 100°C, the equilibrium is not reached due to the very low rate constant of the first
21 reaction. Hence, only the activation energy of the direct formation of the monoglyceride can be
22 calculated (Fig. 6) : $E_a = 26$ kcal/mole. A Fisher Mechanism can't be considered but this value is in the
23 range of the minimum energies calculated in the non-interacting mode with DBSA.

1 *Reaction with catalyst at a concentration of [DBSA]=0.08 equ.*

2 With 0.08 equ., all the activation energies can be calculated but at low temperatures, hydrolysis reaction
3 of the diester may be not equilibrated enough to get a precise value (Fig. 7). Triester concentrations are
4 too low to determine the activation energies of triester formation and hydrolysis.

5 Activation energies are closer to the minimum energies obtained by molecular modeling in the interacting
6 mode than those calculated for the non-interacting one. This may mean that even at a low concentration,
7 DBSA can interact closely with reactants, perhaps due to its amphipathic properties. Contrary to what
8 was expected, activation energies of the reversed (hydrolysis) reactions are inferior to the direct ones
9 (Table 4), indicating that these reactions can't be avoided. The pKa of DBSA was predicted at -1.84 with
10 methods based on partial charge distribution (Marvin Sketch calculator) and measured at 2.55 (Massoumi
11 et al., 2009). Consequently, with the presence of water, it may dissociate enough to consider the
12 presence of free hydronium ions, which would modify the mechanisms considered in molecular modeling.
13 Besides, partial esters being amphipathic as DBSA, they may place in its vicinity, within interfacial zones,
14 being more easily hydrolyzed. Diester formation requires here approximately the same activation energy
15 as monoester formation. Increasing the temperature will decrease the equilibrium time but should not
16 bring any improvement of the selectivity in monoesters.

17 *Reaction with catalyst at a concentration of [DBSA]=0.125 equ.*

18 Even if some reaction constants remain imprecise, activation energies can be approximated (Fig. 8). If the
19 activation energies were comparable for mono and di-esterification at a concentration of 0.08eq DBSA,
20 they now seem to be lower for the mono-esterification, which is closer to what was expected with
21 molecular modeling. In this case, it may be possible to get a variation of the selectivity in monoester with
22 temperature.

23 Using a catalyst as DBSA allows a strong decrease of activation energies for monoester formation.
24 Increasing its concentration seems to slightly decrease activation energy for monoester formation but its

1 effect on diester formation and hydrolysis is still uncertain. It is then interesting to compare yields and
2 selectivities obtained in the different experiments performed.

3 **Yield and Selectivity**

4 Considering the theoretical high activation energy for the formation of triesters, it is difficult to reach
5 equilibrium state at moderate temperatures and moderate water trapping. At 30°C or at [DBSA]=0eq,
6 monoester formation can be very slow and no maximum of monoester concentration ($d[GMU]/dt=0$) is
7 reached at a reasonable time. It is yet possible to determine the maximum monoester yield and
8 associated selectivity with time for temperatures of 50, 80 and 100°C and DBSA concentrations of 0.08
9 and 0.125eq (Table 5).

10 Maximum yields and selectivity are not significantly different even if selectivity at [DBSA]=0.08eq seems
11 to be a bit superior for a reaction time not always superior. The slower accumulation of monoester at
12 100°C and [DBSA]=0.125eq could come from a lower activation energy for hydrolysis reaction. For this
13 catalysis concentration, higher selectivity at lower temperatures could be explained by higher activation
14 energies for diester formation.

15 The good monoester selectivity could be correlated to important equilibrium constants ratio K_{GMU}/K_{GDU} . It
16 seems advantageous to remain at a DBSA concentration of 0.08eq. Increasing temperature accelerate
17 monoester formation but may slightly decrease selectivity.

18 **Discussion**

19 To increase the precision of the results, the research of the most stable conformer could explicitly include
20 the solvent and the reactional medium in molecular dynamics. However, using DFT to calculate
21 theoretical activation energies would be very time consuming due to the high number of atoms and
22 intermediates. The presence of DBSA, even at a low concentration allows its effective interaction with
23 the intermediates to stabilize them and decrease the energy barriers placed in the pathway of the
24 production of glyceryl esters. This interaction may be fostered by the amphipathic properties of DBSA and

1 glyceryl partial esters expressed when water is released. If triester formation can be largely slowed down
2 with low temperatures, diester formation can't be avoided. However, allied with a moderate catalyst
3 concentration and glycerol excess, compartmentation is a critical parameter to get high yield and
4 selectivity of glyceryl monoester. After just one hour of reaction at a low temperature of 80°C, with DBSA
5 at a concentration of 0.08 eq. and a simple molecular sieves, a yield and selectivity in monoesters of 64%
6 and 85% are obtained, respectfully. Obtaining or preparing standards of all the isomer forms of mono-
7 and diesters and correctly separating them by gas chromatography to get the evolution of the
8 concentrations of each isomer was beyond the scope of this study. Besides, it would have certainly made
9 kinetic regression very complex even if some reactions as acyl migration from the β -monoglyceride to the
10 α form may have an impact on the kinetic analysis of hydrolysis reactions (Boswinkel et al., 1996). Hence,
11 the distinction between α or β monoglycerides and enantiomeric diglycerides, as observed for enzymatic
12 acylation (Coleman et al., 1986; Lehner et al., 1993) could not be experimentally achieved but was
13 theoretically approached here with DBSA. This indicated slightly lower but not significantly different
14 barrier energy for the reaction path leading to α monoglyceride compared to β monoglyceride and a
15 lower energy barrier for the formation of α, α diglycerides than for the formation of α, β diglyceride,
16 starting from α monoglyceride. The comparison between the simple theoretical and experimental
17 approaches indicates that semi-empirical modeling allows a good perception of the barriers to overcome
18 in order to get a good selectivity and yield for the esterification of glycerol with fatty acids.

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21

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- 15

1 **Fig. 1** Activation of undecylenic acid with DBSA. Hydrogen bonds (blue lines) between undecylenic acid
2 and DBSA allow a stabilization of this intermediate

3 **Fig. 2** Energy of the different molecular systems at the different steps of the reactional pathway of the
4 formation of glyceryl α -monoundecylenate. Interacting Molecules IM (lower plot), Non Interacting
5 Molecules NIM (upper plot).

6 **Fig. 3** Energy of the different molecular systems at the different steps of the reactional pathway of the
7 formation of glyceryl α,α -diundecylenate. IM (lower plot), NIM (upper plot).

8 **Fig. 4** Energy of the different molecular systems at the different steps of the reactional pathway of the
9 formation of glyceryl tri-undecylenate from α, α diester. IM (lower plot), NIM (upper plot).

10 **Fig. 5** Evolution of monoester yield and selectivity with a reaction at 80°C, 0.125 eq. DBSA. A) Without
11 molecular sieves ; B) With molecular sieves

12 **Fig. 6** Variation of the logarithm of the rate constant of the direct reaction of the formation of
13 monoglyceride with the inverse of temperature ([DBSA]=0 eq.)

14 **Fig. 7** Variation of the logarithm of the rate constants of the direct and reverse reactions of the formation
15 of monoglyceride (a and b) and the direct and reverse reactions of the formation of diglyceride (c et d)
16 with the inverse of temperature ([DBSA]=0.08 eq.)

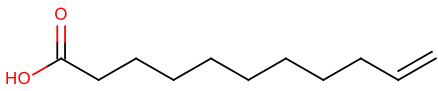
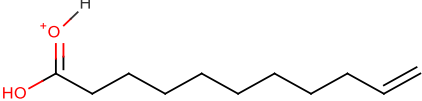
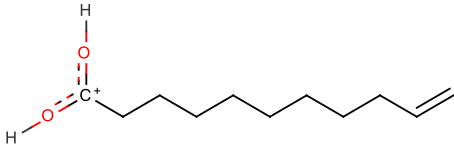
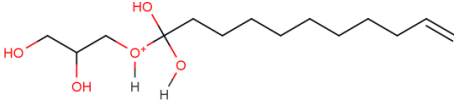
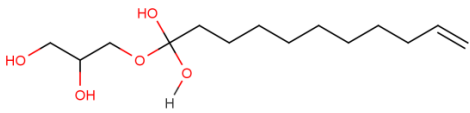
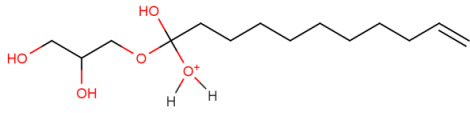
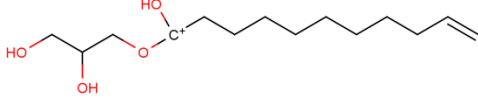
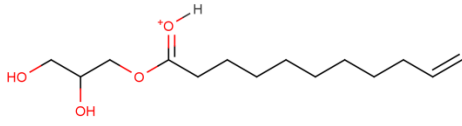
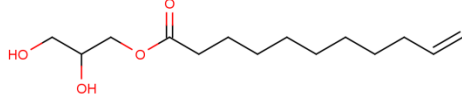
17 **Fig. 8** Variation of the logarithm of the rate constants of the direct and reverse reactions of the formation
18 of monoglyceride (a and b) and the direct and reverse reactions of the formation of diglyceride (c et d)
19 with the inverse of temperature ([DBSA]=0.125 eq.)

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Table 1. Main steps of the reactional pathway with the molecules involved – NIM (Non Interacting Molecules), IM (Interacting Molecules)

| States | Molecules and intermediates (T) | Expression of the heats of formation (E_f) |
|---------|---|---|
| Initial |  | NIM : $E_f(T_{\text{Initial}}) + E_f(\text{Glycerol}) + E_f(\text{DBSA})$ IM : |
| a1 |  | NIM : $E_f(T_{a1}) + E_f(\text{Glycerol}) + E_f(\text{DBSA-})$ IM : $E_f(T_{a1} \text{ \& \; DBSA-}) + E_f(\text{Glycerol})$ |
| a2 |  | NIM : $E_f(T_{a2}) + E_f(\text{Glycerol}) + E_f(\text{DBSA-})$ IM : $E_f(T_{a2} \text{ \& \; DBSA-}) + E_f(\text{Glycerol})$ |
| 1 |  | NIM : $E_f(T_1) + E_f(\text{DBSA-})$ IM : $E_f(T_1 \text{ \& \; DBSA-})$ |
| 2 |  | NIM : $E_f(T_2) + E_f(\text{DBSA})$ IM : $E_f(T_2 \text{ \& \; DBSA})$ |
| 3 |  | NIM : $E_f(T_3) + E_f(\text{DBSA-})$ IM : $E_f(T_3 \text{ \& \; DBSA})$ |
| 4 |  | NIM : $E_f(T_4) + E_f(\text{H}_2\text{O}) + E_f(\text{DBSA-})$ IM : $E_f(T_4 \text{ \& \; DBSA-}) + E_f(\text{H}_2\text{O})$ |
| 5 |  | NIM : $E_f(T_5) + E_f(\text{H}_2\text{O}) + E_f(\text{DBSA-})$ IM : $E_f(T_5 \text{ \& \; DBSA-}) + E_f(\text{H}_2\text{O})$ |
| Final |  | NIM : $E_f(T_{\text{Final}}) + E_f(\text{H}_2\text{O}) + E_f(\text{DBSA})$ IM : |

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4

1 **Table 2. Maximum energy differences calculated between successive states for different esterification reactions**

| <i>Product obtained</i> | Non interacting molecules | | | Interacting molecules | |
|--|---|---|---|--|--|
| | <i>Esterification</i> | | <i>Hydrolysis</i> | <i>Esterification</i> | <i>Hydrolysis</i> |
| | ΔE_{max} (I ->F) (kcal/mol) | ΔE_{max} (1-> F) (kcal/mol) | ΔE_{max} (F ->I) (kcal/mol) | ΔE_{max} (I->F) (kcal/mol) | ΔE_{max} (F->I) (kcal/mol) |
| <i>α MG</i> | 34 | 24 | 38 | 7 | 11 |
| <i>β MG</i> | 34 | 23 | 40 | 13 | 12 |
| <i>α, α DG from α MG</i> | 34 | 12 | 26 | 13 | 12 |
| <i>α, β DG from α MG</i> | 34 | 25 | 38 | 19 | 20 |
| <i>TG from α, β DG</i> | 34 | 19 | 21 | 27 | 14 |
| <i>TG from α, α DG</i> | 34 | 26 | 27 | 16 | 7 |

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1 **Table 3. Comparison of the kinetic parameters obtained with or without molecular sieves**

| Reaction rate | k_1 | k_{-1} | k_2 | k_{-2} | K_{GMU} | K_{GDU} | SSQ | RMS |
|---|-----------------|------------------|-----------------|------------------|-----------|-----------|-------|-------|
| 80°C, 0.125 eq. DBSA | 0.049± 0.001 | 0.041 ± 0.001 | 0.057± 0.002 | 0.046 ± 0.002 | 1.19 | 1.22 | 0.003 | 0.016 |
| 80°C, 0.125 eq. DBSA, molecular sieves | 0,034± 0,001 | 0,014 ± 0,001 | 0,081± 0,01 | 0,055 ± 0,01 | 2.51 | 1.47 | 0.003 | 0.019 |

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1 **Table 4. Measured apparent activation energies of direct and reverse esterification reactions**

| | Without catalyst | [DBSA]=0.08 eq | [DBSA]=0.125eq | Semi-Empirical (IM) | Semi-Empirical (NIM) |
|------------------|------------------|----------------|----------------|---------------------|----------------------|
| Ea ₁ | 26 | 15-16 | 13-14 | 7-13 | 34 |
| Ea ₋₁ | - | 11 | 7-10 | 11-12 | 38-40 |
| Ea ₂ | - | 15-18 | 16-20 | 13-19 | 34 |
| Ea ₋₂ | - | 8-14 | 15-19 | 12-20 | 26-39 |

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1 **Table 5. Yield (Y) and selectivity (S) of glycerol monoundecylenate at maximum concentration**

| | | [DBSA]=0,08eq | [DBSA]=0,125eq |
|-------|-------------------|---------------|----------------|
| 50°C | Time to [GMU]max | 110' | 85' |
| | K_{GMU}/K_{GDU} | 2.0 | 1.4 |
| | Y_{max} (GMU) | 64% | 63% |
| | S_{max} (GMU) | 87% | 84% |
| 80°C | Time to [GMU]max | 60' | 20' |
| | K_{GMU}/K_{GDU} | 2.4 | 1.7 |
| | Y_{max} (GMU) | 64% | 66% |
| | S_{max} (GMU) | 85% | 80% |
| 100°C | Time to [GMU]max | 7' | 48' |
| | K_{GMU}/K_{GDU} | 1.7 | 1.9 |
| | Y_{max} (GMU) | 67% | 68% |
| | S_{max} (GMU) | 81% | 78% |

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