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# Improved hydrotropic extraction of carnosic acid from rosemary and sage with short-chain monoalkyl glycerol ethers

Agathe MAZAUD,<sup>a,b</sup> Raphaël LEBEUF,<sup>a</sup> Mickaël LAGUERRE,<sup>b</sup> Véronique NARDELLO-RATAJ\*<sup>a</sup>

<sup>a</sup> Univ. Lille, CNRS, Centrale Lille, Univ. Artois, UMR 8181 – UCCS – Unité de Catalyse et Chimie du Solide, F-59000 Lille, France

<sup>b</sup> Naturex SA, Flavours Division Givaudan, 250 rue Pierre Bayle, 84140 Avignon, France

E-mail: veronique.rataj-nardello@univ-lille.fr

## Abstract

Hydrotropic extraction in water with biobased amphiphiles is considered as an interesting alternative to conventional extraction with organic solvents. In this study, butyl, isoamyl and pentyl glycerol ethers (C<sub>4</sub>Gly, *i*C<sub>5</sub>Gly and C<sub>5</sub>Gly) are studied for the extraction from rosemary (*Rosmarinus officinalis*) and sage (*Salvia officinalis*) of carnosic acid (CA), a powerful antioxidant used as an alternative to synthetic ones in food and cosmetic industries. First, interactions between pure CA and hydrotropes are studied to set the extraction conditions, resulting in the measurement of the solubility curves and miscibility of CA in these hydrotropic solutions. Then, C<sub>5</sub>Gly is shown to have the highest efficiency to extract CA, that could be rationalised using a molecular model established previously for the C<sub>i</sub>E<sub>j</sub> series of amphiphiles based on their log *P* and molecular volume, with a good agreement. Additionally, the contact angles of the hydrotropic solutions on rosemary leaves indicates that the efficiency of the hydrotrope is also dependent on the interfacial tension.

**Key words**

Rosemary ; Sage ; Carnosic acid ; Extraction ; Hydrotropes ; Alkyl glycerol ethers

## Introduction

Rosemary (*Rosmarinus officinalis*) and sage (*Salvia officinalis*) leaves have been used since Antiquity for culinary purposes as flavouring or food preservatives.<sup>1</sup> Indeed, in the middle of the XX<sup>th</sup> century, they were found to have the highest antioxidant power among 32 different spices such as thyme or paprika.<sup>2</sup> This property was later attributed mostly to carnosic acid (CA)<sup>3,4</sup>, a phenolic diterpenoid which exhibits high radical scavenging capacity thanks to its catechol function.<sup>5</sup> Interestingly, the catechol function can be regenerated after a first oxidation by an isomerisation from the oxidised form of CA into carnosol, allowing CA to participate in two successive antioxidation reactions.<sup>6</sup> Based on consumer requirements and because they are considered to be healthier and more eco-responsible, natural preservatives are increasingly promoted in food and cosmetic industries. In this context, rosemary and sage extracts containing carnosic acid have appeared as excellent alternatives to synthetic antioxidants such as Butylated Hydroxyanisole (BHA) or Butylated Hydroxytoluene (BHT).<sup>7,8</sup>

Conventional methods of extraction using organic solvents such as acetone or ethanol have been used for decades and optimised to isolate carnosic acid from the plant.<sup>9,10</sup> Indeed, the use of such organic solvents is suitable for the solubilisation, and accordingly, the extraction of CA, which is a hydrophobic compound according to its log *P* equal to 5.4 (pH 2, SciFinder<sup>®</sup>, ACD Labs method). However, their use also participates in air pollution by releasing volatile organic compounds in the atmosphere, and presents flammability risks due to their low flash point and explosive limits, leading to the requirement of high-cost equipment for industrials. Therefore, eco-extraction techniques avoiding the use of solvents are currently being explored. For example, supercritical CO<sub>2</sub> (T > 31.06 °C, P > 7.38 MPa)<sup>11-13</sup> and subcritical water (T = 100-374 °C, P = 1.5-22 MPa)<sup>14,15</sup> have been reported for the extraction of CA from rosemary, as well as aqueous solutions containing ionic liquids<sup>16</sup> and deep eutectic solvents.<sup>17</sup>

To avoid the need for specific equipment or expensive compounds, another technique to extract CA consists in resorting to the hydrotropic extraction. Indeed, hydrotropes, which have been first described in the literature in 1916, are water-soluble molecules able to increase the solubilisation of hydrophobic compounds in water.<sup>18</sup> Since then, this definition has been refined and hydrotropes have been distinguished from co-solvents and surfactants by their ability to self-aggregate in unorganised structures and to destabilise liquid crystals.<sup>19,20</sup> Noteworthy, ionic hydrotropes such as sodium xylene sulfonate have been used for a long time for aqueous solubilisation and extraction of hydrophobic compounds.<sup>21,22</sup> However, bio-based hydrotropes such as alkyl polyglycosides (APG) or alkyl glycerol ethers have been considered as highly relevant alternatives to petro-based ionic conventional hydrotropes.

Regarding extractions of CA from rosemary, the use of alkyl polyethylene glycol ethers ( $C_iE_j$ ) and alkyl polyglycosides (APG) have already been reported recently by ourselves.<sup>23,24</sup> The former are petro-based molecules and have been used to establish a relationship between the efficiency of the extractions and the physicochemical descriptors (HLB,  $\log P$ , molecular volume) of the amphiphiles. It was found that  $C_iE_j$  should preferentially have *i*) a small molecular volume ( $< 250 \text{ \AA}^3$ ), *ii*) a  $\log P$  above 1, and *iii*) a linear alkyl chain. As a result,  $C_5E_2$  extracts the highest amount of CA while  $C_4E_1$  is kinetically more efficient. Regarding bio-based and commercially available APGs, similar trends were observed and amyl xyloside ( $iC_5Xyl$ ) was found to be the most effective hydrotrope of the series.

Besides, the interest for alkyl glycerol ethers ( $C_iGly$ , with *i* the number of carbon atoms of the alkyl chain) have grown for their solubilising capacity, recently reported for gallic and syringic acids, and their easy preparation.<sup>25</sup> Indeed, they can be prepared from glycerol and the appropriate aldehyde, carboxylic acid or ester, making them potentially bio-sourced molecules.<sup>26,27</sup> In addition, their eco-toxicity was studied using aquatic bioindicators and alkyl

glycerol ethers were classified as harmless or practically harmless.<sup>28</sup> Interestingly, such hydrotropes have been reported for the extraction of piperine from black pepper.<sup>29</sup>

Herein, we report on a study of butyl, isoamyl and pentyl glycerol ethers, abbreviated as C<sub>4</sub>Gly, *i*C<sub>5</sub>Gly and C<sub>5</sub>Gly respectively, for the extraction of carnosic acid from rosemary and sage. First, the behaviour of the solutions at various concentrations of pure CA and hydrotropes is studied. Then, we report the extraction of CA from ground rosemary and sage and compare the efficacy of the process with that using amyl xyloside (*i*C<sub>5</sub>Xyl) previously reported as an alternative to the alkyl ethylene glycol. Finally, the relationship between the extractions results obtained with whole leaves of rosemary and of the physicochemical descriptors of C<sub>i</sub>Gly is compared to the one established with C<sub>i</sub>E<sub>j</sub>. Surface active properties of the hydrotropic solutions and properties at the interface with rosemary were also investigated.

## **Material and methods**

*Plant materials.* Rosemary leaves (*Rosmarinus officinalis*) and sage leaves (*Salvia officinalis*.) were provided by Naturex. They were harvested and dried in Morocco. The dried rosemary leaves contain 2.72 wt.% of CA, whereas the dried sage leaves contain 1.85 wt.% CA according to Soxhlet extractions (24 h, acetone, HPLC quantification).

*Chemicals.* Phosphoric acid was supplied by Sigma-Aldrich. Carnosic acid was purchased from Chengdu Biopurified Phytochemicals. For HPLC analyses, methanol (HPLC grade) was purchased from VWR and trifluoroacetic acid (TFA, 99 %) was from Alfa Aesar. Ultrapure water was obtained from a ThermoFisher apparatus (18.2 MΩ.cm).

*Synthesis of alkyl glycerol ethers (C<sub>i</sub>Gly)* Butyl and pentyl glycerol ether C<sub>4</sub>Gly and C<sub>5</sub>Gly were prepared from their corresponding glycidyl ethers in a one-step-process by condensation with

water at 115 °C over 48 h.<sup>29</sup> *Iso*-amyl glycerol ether *i*-C<sub>5</sub>Gly was prepared from 3-methylbutan-1-ol (98%, Aldrich), epichlorhydrin (99%, Aldrich), ZnCl<sub>2</sub> (98%, Aldrich) and NaOH (VWR) in a two-step process.<sup>29,30</sup> First, 3-methylbutan-1-ol (176 g, 2 mol) and ZnCl<sub>2</sub> (13.7 g, 0.1 mol) were heated to 100 °C under stirring. Epichlorhydrin (200.6 g, 2.17 mol) was added dropwise over 1 h while the solution was kept at 100 °C, then heated to 115 °C for 5 h. Then, the epoxide was formed using a NaOH solution (55 wt.%, 200 mL) at 50 °C and stirred over 65 h. The product was extracted with diethyl ether. The organic phases were washed with water, diluted HCl and water once again, dried over MgSO<sub>4</sub>. The solvent was filtered and evaporated. The epoxide was purified by distillation under vacuum ( $3 \times 10^{-2}$  mbar, 40 – 60 °C, 180 g). Finally, it was heated to 110 °C in excess of water (260 mL) during 48h. Water was evaporated and the product directly distilled under vacuum ( $3 \times 10^{-2}$  mbar, 80 – 90 °C) to give a colorless liquid (110 g, 0.68 mol, 34 %).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 3.86 (m, 1H), 3.76-3.61 (m, 2H), 3.56-3.46 (m, 4H), 2.79 (bs, 1H, OH), 2.41 (bs, 1H, OH), 1.68 (nona,  $J = 6.8$  Hz, 1H), 1.48 (qa,  $J = 6.8$  Hz, 2H), 0.90 (d,  $J = 6.8$  Hz, 6H).

*Solubilisation curve of CA in C<sub>4</sub>Gly.* Hydrotropic solutions of C<sub>4</sub>Gly were prepared at different concentrations and acidified with 1 % (v/v) of phosphoric acid (85%) to avoid CA oxidation in water.<sup>31</sup> Solutions were added with 20-25 g/L of CA and continuously stirred for 24 h at room temperature. If not saturated, more CA was added to reach the saturation. The solution was then filtered using a PTFE syringe filter ( $\Phi = 0.2 \mu\text{m}$ ). The amount of solubilised CA was determined by HPLC quantification.

*Hydrotropic extractions with ground rosemary and sage leaves.* Hydrotropic solutions (10 mL) were prepared a 30 wt.% and acidified at pH 2 with 1% (v/v) phosphoric acid. Extractions were

performed by macerating ground rosemary or sage (1 g) in the hydrotropic solution with a solid:liquid ratio 1:10 w:v under magnetic stirring (250 rpm) at room temperature (25 °C) during 30 min. Then, plants were separated by Büchner filtration (cellulose filter,  $\Phi = 8 \mu\text{m}$ ) and the concentration of CA in the filtrate was quantified by HPLC.

*Hydrotropic extractions with whole rosemary leaves.* All the extractions were performed by macerating 1 g of rosemary leaves in 10 mL of an aqueous solution prepared with 30 wt.% of amphiphile and acidified with 1% (v/v) of phosphoric acid giving pH 2. The solutions were stirred at room temperature for 48 h with an Intelli-Mixer RM-2L rotator. After 24 h, 100  $\mu\text{L}$  of solution were sampled. After 48 h, the solutions were separated from the plant matrix by Büchner filtration under vacuum (cellulose filters,  $\Phi = 8 \mu\text{m}$ ). CA concentration was quantified by HPLC and all experiments were performed twice.

*COSMO-RS calculations of  $\log P$  and  $V_m$  values.* For all  $\text{C}_i\text{E}_j$ , molecular geometries were drawn on COSMO *Quick* (COSMOlogic) which was used to calculate the molecular volumes as well as the octanol-water partition coefficient ( $\log P$ ). This latter is predicted with a COSMO-RS method combined with a non-linear correction term using a Random Forest QSPR, and is valid only at 25 °C.

*Contact angle measurements.* Homogeneous solutions were prepared with 30 wt.% hydrotrope in water. Leaves were chosen as straight as possible and stuck by a double-sided adhesive tape on a microscopic lamella which was locked to the base. Thanks to a syringe, a droplet of 2  $\mu\text{L}$  of hydrotropic solution was deposited on the leaf surface. Contact angles were captured with a Drop Shape Analyser (DSA – 100, Krüss) equipped with a camera. The angle between the drop and the surface of the leaves was measured by the software of the apparatus (Advance).



*Quantification of carnosic acid concentration by HPLC.* Samples to be analysed were previously diluted by 10 in methanol (HPLC grade) containing 0.1 % (v/v) of TFA and filtered with 0.2 µm PTFE syringe filters. Analyses were performed using an HPLC apparatus LC 20AD from Shimadzu equipped with an autosampler (injection = 10 µL), a C<sub>18</sub> column (Interchim, 5 µm particle, 3.0 x 150 mm) maintained at 30 °C, and a UV detector (SPD 20A) set at 210 and 230 nm. The mobile phase was a mixture of methanol (0.1% TFA)/water in a 80:20 v/v ratio, in isocratic mode, with a flow rate at 0.5 mL/min, releasing CA after 12 min of retention time.

## Results and Discussion

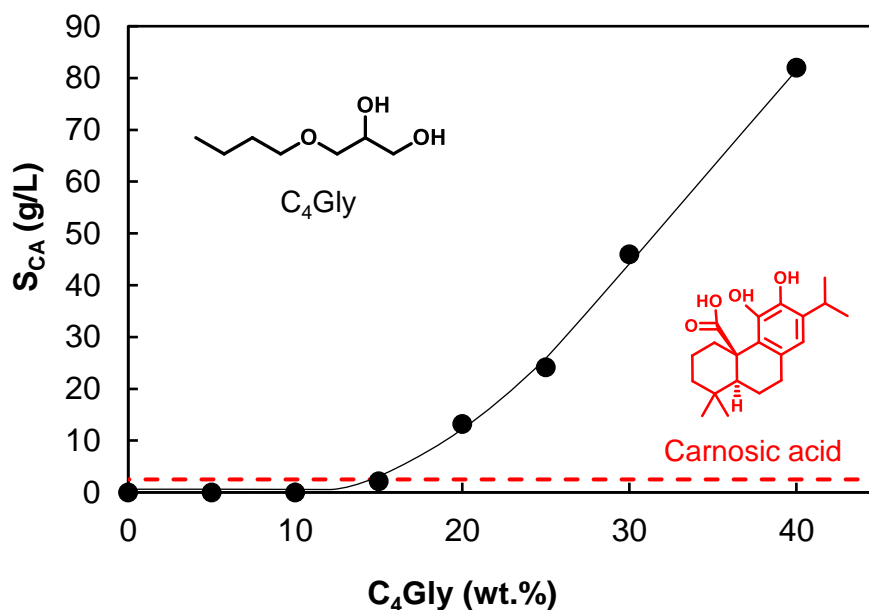
### 1. Solubilisation of carnosic acid in hydrotropic solutions of monoalkyl glycerol ethers

Ethylene glycol monobutyl ether C<sub>4</sub>E<sub>1</sub> has been reported as giving the best performances in terms of carnosic acid solubilisation and extraction from rosemary.<sup>23</sup> However, C<sub>4</sub>E<sub>1</sub>, which is most of the time petro-based, is classified as a VOC.<sup>32</sup> Short chain glycerol 1-monoethers, abbreviated C<sub>i</sub>Gly with *i* the number of carbons of the alkyl chain, are well-known for their hydrotropic properties since 2006.<sup>33,34</sup> Interestingly, glycerol monobutyl ether C<sub>4</sub>Gly has been reported as one of the two possible alternatives (beside isosorbide monobutylether C<sub>4</sub>Iso-endo) to C<sub>4</sub>E<sub>1</sub> over 138 molecules according to a COSMO-RS (COnductor-like Screening MOdel for Real Solvents) approach.<sup>35</sup> In addition, regarding its ability to solubilise the hydrophobic Disperse Red 13, C<sub>4</sub>E<sub>1</sub> is less efficient compared to C<sub>4</sub>Gly and C<sub>5</sub>Gly at a hydrotropic concentration of 1 M, whereas at 2M of hydrotropes, it is as efficient as C<sub>5</sub>Gly, and 3 times more efficient than C<sub>4</sub>Gly.<sup>29,36</sup> Furthermore, it has also been reported that C<sub>5</sub>Gly is able to extract similar amount of piperine from black pepper than C<sub>4</sub>E<sub>1</sub> (3.0 vs. 2.8 g/L respectively).<sup>29</sup> Due to their boiling point in the range of that of solvents (but out of the VOC domain, > 250 °C), butyl, pentyl, isoamyl and hexyl ethers of glycerol (abbreviated resp. C<sub>4</sub>Gly, C<sub>5</sub>Gly, *i*C<sub>5</sub>Gly and C<sub>6</sub>Gly) are also called “solvo-surfactants”. Since C<sub>6</sub>Gly is not miscible with water below 38 wt.%, it was not studied herein.<sup>25</sup>

Contrary to APGs, no large scale commercial source of C<sub>i</sub>Gly exists so far. Therefore, C<sub>4</sub>, C<sub>5</sub>, and *i*C<sub>5</sub>Gly were synthesised in pure form at the laboratory scale. They are potentially bio-sourced molecules which can be synthesised by a “green” approach in a one-step catalytic reductive alkylation of glycerol with an appropriate aldehyde, carboxylic acid or ester.<sup>26,27</sup> Herein, for the sake of convenience, alkyl glycerol ethers were synthesised by opening their corresponding epoxide with water under heating. Indeed, butyl glycidyl ether is commercially


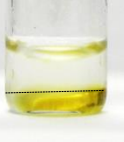

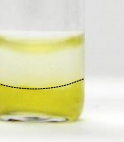

available, making the synthesis of C<sub>4</sub>Gly very easy. For the other alkyl glycerol ether, their corresponding epoxide were synthesised in two steps from their corresponding alcohol and epichlorhydrin, as previously reported.<sup>29</sup>

In view of using aqueous C<sub>i</sub>Gly solutions to extract CA from rosemary, the solubility of CA in the hydrotropic solutions was first studied. Indeed, CA is a phenolic diterpenoid which is naturally insoluble in water, as proven by a positive log *P* of 5.4 (SciFinder, ACD Laboratories method). However, its water-solubility has already been increased by other hydrotropes such as C<sub>4</sub>E<sub>2</sub> or *i*C<sub>5</sub>Xyl (resp. 25 and 14 g/L of CA above 30 wt.% hydrotrope).<sup>23,24</sup> **Figure 1** shows the solubility of CA in aqueous solutions of C<sub>4</sub>Gly at various concentrations at pH 2 to avoid the deprotonation of CA, which would increase its degradation into carnosol.<sup>37</sup> Noteworthy, if all available CA is extracted from rosemary with a plant:solution ratio of 1:10 (g:mL), only 2.7 g/L will be present in the solution, as indicated by the red dotted line.<sup>24</sup> According to **Figure 1**, only 15 wt.% C<sub>4</sub>Gly are required to solubilise such amount of CA. Similarly, a concentration of CA of 1.85 g/L will be reached after an extraction from sage. More interestingly, a 30 wt.% solution of C<sub>4</sub>Gly seems to be more efficient than C<sub>4</sub>E<sub>2</sub> and *i*C<sub>5</sub>Xyl to solubilise CA, with up to 46 g/L quantified in the solution.



**Figure 1.** CA solubility curves in C<sub>4</sub>Gly aqueous solution at pH 2, 25 °C after equilibration for 24 h. Dotted line shows the maximum concentration of CA which can be extracted from rosemary for an extraction at a plant:solution ratio = 1:10 (g:mL).

As far as C<sub>5</sub>Gly and *i*C<sub>5</sub>Gly are concerned, solubility curves could not be determined because a phase separation occurred before any saturation could be reached when CA was added, as shown for C<sub>5</sub>Gly in **Figure 2**. A residual solid was observed only below 5 wt.% of C<sub>5</sub>Gly, however, no CA was detected in the supernatant by HPLC analysis. Therefore, this solution was certainly below or just at the Minimal Hydrotropic Concentration (MHC), in agreement to the one reported at 4.8 wt.% from DR-13 solubility curves. Above the MHC, no saturation was reached since the 10, 15 and 20 wt.% C<sub>5</sub>Gly formed two phases: (*i*) an amphiphile-rich lower phase, which contain CA and (*ii*) a amphiphile-poor phase, which is enriched in water. Noteworthy, the amphiphile-rich phase is found at the bottom of the tube, contrary to C<sub>*i*</sub>E<sub>*j*</sub> aqueous solutions because of their densities (C<sub>5</sub>Gly: 1.06<sup>38</sup> vs C<sub>4</sub>E<sub>1</sub>: 0.90<sup>39</sup>). By increasing the hydrotrope concentration to 30 wt.%, the system becomes homogeneous.

<b>C<sub>5</sub>Gly (wt.%)</b>	<b>5</b>	<b>10</b>	<b>15</b>	<b>20</b>	<b>30</b>
<b>Aspect</b>					

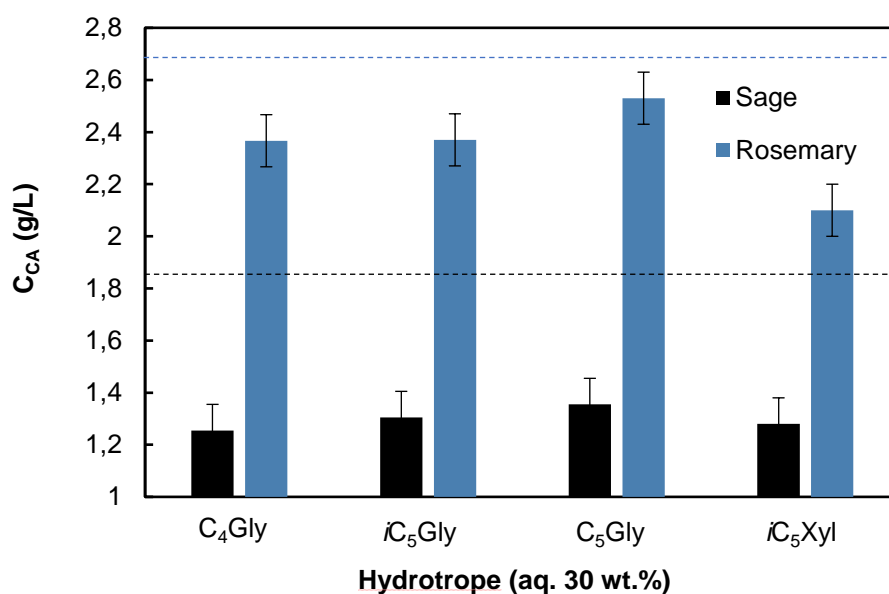
**Figure 2.** Pictures of C<sub>5</sub>Gly solution after addition of 20 g/L CA, at pH 2, 25 °C. No residual solid is observed except in the 5 wt.% C<sub>5</sub>Gly solution, below the MHC. CA is solubilised in the yellow amphiphile-rich lower phase.

Interestingly, C<sub>5</sub>Gly and *i*C<sub>5</sub>Gly in aqueous solution do not reach a Cloud Point (CP) below 100 °C, but a CP-phase separation has already been observed for both amphiphiles using the salting out property of Na<sub>2</sub>SO<sub>4</sub> and NaCl.<sup>33,36</sup> Besides, an extrapolated CP was determined at 158 °C for C<sub>5</sub>Gly using the Na<sub>2</sub>SO<sub>4</sub>, NaCl, and NaBr salting out effects.<sup>33</sup> The same phenomenon has already been observed for C<sub>*i*</sub>E<sub>*j*</sub> interacting with CA, and the decrease of the CP induced by the addition of CA was studied for solutions of C<sub>4</sub>E<sub>1</sub>.<sup>23</sup> Therefore, it is likely that the CP of C<sub>5</sub>Gly and *i*C<sub>5</sub>Gly is decreased below room temperature due to the presence of CA. Nevertheless, despite this phase separation phenomenon prevents the measurement of the CA solubility in hydrotropic solutions, it did not seem to reduce the efficiency of the extraction considering extractions of rosemary with C<sub>*i*</sub>E<sub>*j*</sub>, which seems to be mainly governed by the polarity ( $\log P$ ), amphiphilicity (HLB) and molecular volume of the hydrotrope.

## **2. Extractions of CA from ground rosemary and sage.**

One particularity of CA is to be a rare secondary metabolite as it has only been found in nine species of plants (CA or its derivatives), all from the Lamiaceae family, which includes most aromatic herbs (*e.g.* mint, thyme, sage, oregano). Among these plants, rosemary has the highest concentrations, between 0.3 to 5 wt.% in dried leaves, followed by sage, which can reach up to

2-3 wt.% in dried leaves.<sup>4</sup> In the other species such as thyme, CA has already been detected but its concentration would not be suitable at an industrial scale. Although the extraction of CA is generally investigated with rosemary, extractions have also been reported with sage, using maceration in acetone or methanol or supercritical CO<sub>2</sub>.<sup>40,41</sup> In **Figure 3**, hydrotropic extractions of CA in solutions from rosemary and sage are compared using solutions of 30 wt.% C<sub>i</sub>Gly. The experimental conditions (30 min of stirring, 30 wt.% hydrotrope) were chosen as they were found to be optimal according to a 2<sup>4</sup> experimental design for the extraction of CA from rosemary with a solution of *i*C<sub>5</sub>Xyl.<sup>24</sup> The results obtained with *i*C<sub>5</sub>Xyl for rosemary and sage were added for comparison to **Figure 3**, as *i*C<sub>5</sub>Xyl was the most efficient hydrotrope of the APG series.



**Figure 3.** Concentration in the filtrate of CA extracted from ground rosemary and sage leaves after 30 min of stirring by 30 wt.% C<sub>i</sub>Gly and *i*C<sub>5</sub>Xyl solutions, at 1:10 plant:solution ratio. Dotted lines show the maximum concentration of CA which can be extracted from rosemary and sage leaves.

Regarding extractions of rosemary, C<sub>5</sub>Gly is the most efficient hydrotrope with a concentration of CA in the filtrate of 2.53 g/L. *i*C<sub>5</sub>Gly and C<sub>4</sub>Gly show a similar efficiency (2.37 g/L CA recovered in the filtrate) and *i*C<sub>5</sub>Xyl is less efficient than all C<sub>*i*</sub>Gly with a CA concentration of 2.1 g/L. Regarding extractions of sage, those three latter hydrotropes extract  $\approx 1.3 \text{ g/L} \pm 0.04$ , whereas C<sub>5</sub>Gly is once again the best hydrotrope with 1.36 g/L CA. The recovery rate, i.e. the amount of available CA in the plant which has been extracted, can be estimated to 59 % for sage and 75 % for rosemary when the extraction is performed with 30 wt.% C<sub>5</sub>Gly. Therefore, the extraction of sage is less efficient than that with rosemary.

### 3. Rationalisation of the hydrotrope efficiency

In a previous paper, a mathematical relationship has been established between the physicochemical descriptors of the hydrotropes and their efficiency.<sup>23</sup> As shown in eqs. 1 and 2 the model involves the polarity of the hydrotrope ( $\log P$ ), its molecular volume ( $V_m$ ) and the concentration of CA extracted and recovered in the filtrate.

$$r^2 = \left(\frac{V_m - 240}{100}\right)^2 + (\log P - 1.37)^2 \quad (1)$$

$$C_{CA} = 1.2 \times \exp(-0.3r^2) \quad (2)$$

To apply this model to the C<sub>*i*</sub>Gly, their  $V_m$  and  $\log P$  have been calculated with Cosmo Quick<sup>®</sup> using the Cosmo-RS method.<sup>42</sup> All these data are compiled in **Table 1**. Moreover, the Critical Aggregation Concentration (CAC) is also an important physicochemical property of amphiphiles, which can be experimentally measured by tensiometry for example. CAC and surface tension at the CAC ( $\sigma_{CAC}$ ) have already been reported for C<sub>4</sub>Gly, C<sub>5</sub>Gly, *i*C<sub>5</sub>Gly and are also given in **Table 1**.<sup>33</sup>

**Table 1.** Physicochemical descriptors of alkyl glycerol ethers C<sub>i</sub>Gly.

Abbreviation	CAC <sup>a</sup>		$\sigma_{\text{CAC}}^{\text{a}}$ (mN/m)	V <sub>m</sub> <sup>b</sup> (Å <sup>3</sup> )	log P <sup>b</sup>	HLB <sup>c</sup>
	wt. %	mol/L				
C <sub>4</sub> Gly	8.9	0.6 <sup>33</sup>	28.6 <sup>33</sup>	196	1.23	12.3
C <sub>5</sub> Gly	2.4	0.15 <sup>33</sup>	23.9 <sup>33</sup>	217	1.77	11.4
<i>i</i> C <sub>5</sub> Gly	5.8	0.36 <sup>33</sup>	25.3 <sup>33</sup>	218	1.67	11.4

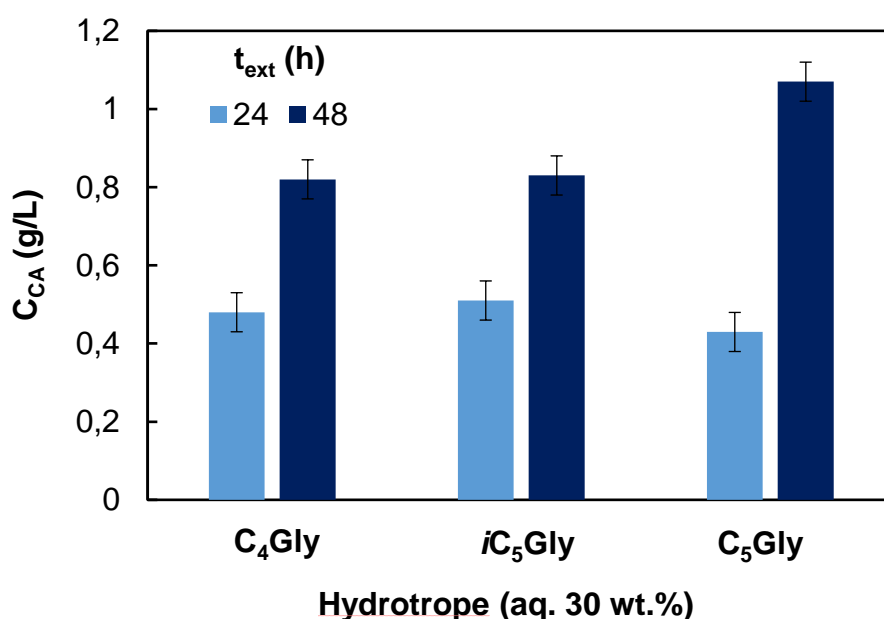
<sup>a</sup> Measured by tensiometry at 25 °C. <sup>b</sup> From Cosmo-Quick®, with a calculation based on the COSMO-RS method and refined with real values of similar molecules; <sup>c</sup> Calculated according to Griffin's relation.

The CAC are ranged in the following order: C<sub>5</sub>Gly < *i*C<sub>5</sub>Gly < C<sub>4</sub>Gly. Indeed, log(CAC) or log(CMC) linearly decreases with increasing *i* as already reported for linear ethoxylates with alkyl chains from 4 to 16 carbons,<sup>44</sup> alkyl erythritol and pentaerythritol with linear alkyl chains from 5 to 12 and 10 respectively.<sup>36</sup> Furthermore and as expected, the minimal surface tensions decrease while increasing *i*. Finally, for a given alkyl chain (C<sub>4</sub> and *i*C<sub>5</sub>), the alkyl glycerol ethers seem more surface active than alkyl glycosides<sup>24</sup> despite the fact that their polar head seem to have almost no effect on the CAC. Among the predicted descriptors (V<sub>m</sub>, log P and HLB), only log P differentiates the C<sub>5</sub>Gly isomers, and as expected, V<sub>m</sub> is lower and HLB is higher for C<sub>4</sub>Gly. As far as C<sub>i</sub>E<sub>j</sub> are concerned, the most efficient hydrotropes have a small molecular volume (< 250 Å<sup>3</sup>), a linear alkyl chain and a log P > 1, and C<sub>5</sub>E<sub>2</sub> was found as the best one. All the studied alkyl glycerol ethers meet these requirements. C<sub>5</sub>Gly and *i*C<sub>5</sub>Gly show a CAC similar to the one of C<sub>5</sub>E<sub>2</sub> (0.29 mol/L) and smaller  $\sigma_{\text{CAC}}$  (29.2 mN/m for C<sub>5</sub>E<sub>2</sub>).

The diffusion of CA is highly facilitated by the grinding, which helps the release of the phytochemicals in the hydrotropic solution by breaking the cell barriers. Indeed, in the case of the extraction of CA by solutions of *i*C<sub>5</sub>Xyl, the extraction yield could be increased by a factor 5 while the time of extraction was reduced from 48 h to 30 min.<sup>24</sup> Nevertheless, the slow extraction of rosemary constituents is interesting to compare the ability of hydrotropes to diffuse through cell barriers because more important differences can be observed between them.



Therefore, extractions of CA from whole leaves of rosemary instead of ground ones were performed and the results after 24 and 48 h are shown in **Figure 4**. As a result, after 24 h of extraction, C<sub>5</sub>Gly extracts only 0.4 g/L of CA, whereas C<sub>4</sub>Gly and *i*C<sub>5</sub>Gly have the same efficiency with 0.5 g/L CA recovered. However, the order of efficiency after 48 h is reversed, finding the same one obtained with ground leaves over 30 minutes. Noteworthy, with 1.07 g/L CA extracted after 48 h, C<sub>5</sub>Gly is competitive with the best C<sub>i</sub>E<sub>j</sub> (C<sub>5</sub>E<sub>2</sub>: 1.21, C<sub>4</sub>E<sub>1</sub>: 1.02 g/L CA).<sup>23</sup>

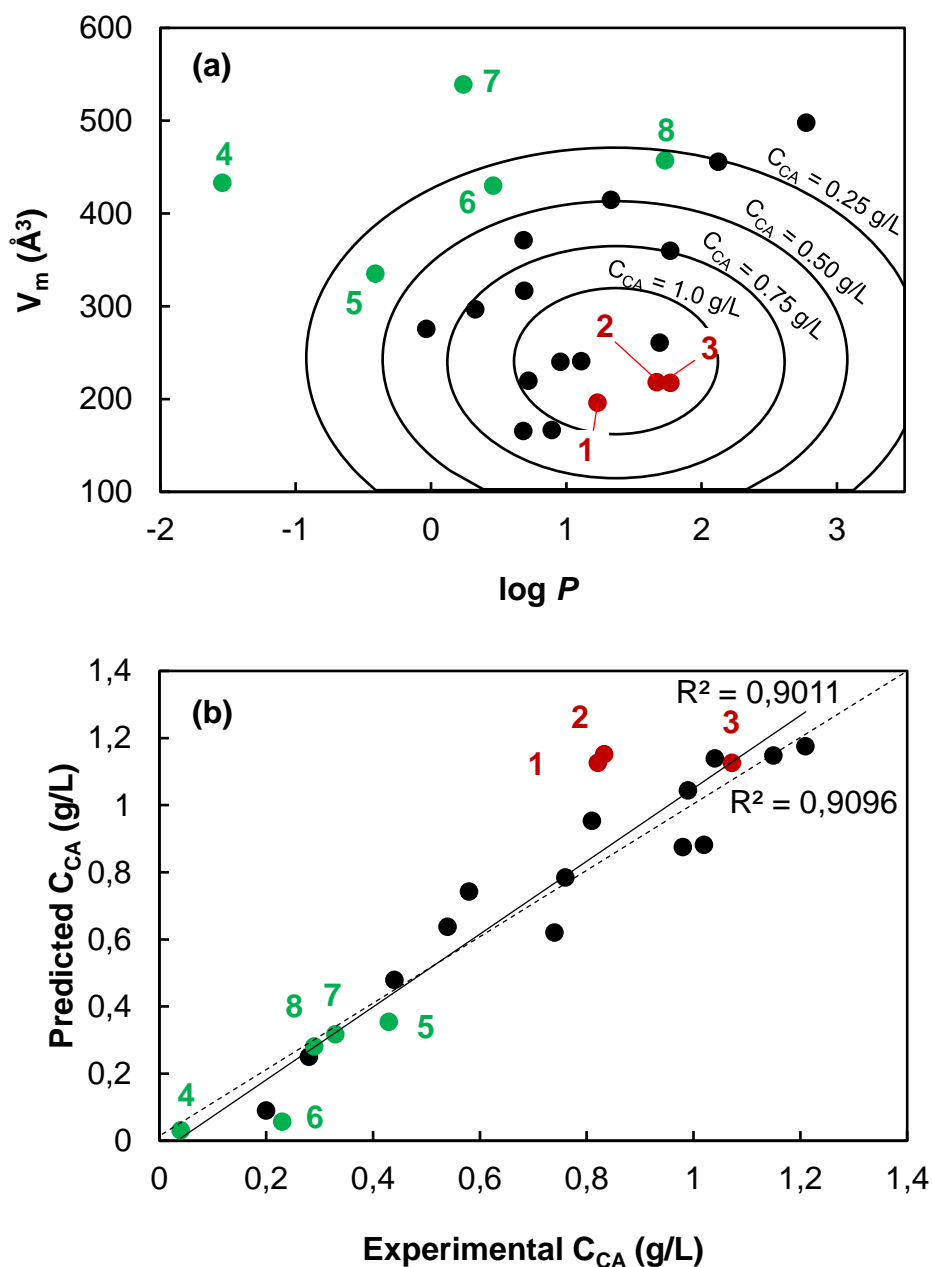


**Figure 4.** Concentration in the filtrate of CA extracted from whole rosemary leaves with 30 wt.% C<sub>i</sub>Gly solutions after 24 and 48 h of stirring.

These results can be compared to those obtained with C<sub>i</sub>E<sub>j</sub> and APG, in regards to their physicochemical descriptors log P and molecular volume  $V_m$ , for which a relationship with the extracted CA was obtained using C<sub>i</sub>E<sub>j</sub>.<sup>23</sup> For visual illustration, they are positioned in the corresponding contour-line graph (**Figure 5a**) and those descriptors are used to predict the CA concentration recovered in the filtrate after extraction, which can be correlated to the experimental values (**Figure 5b**). Alkyl glycerols are located at the center of the circles,

meaning that they are close to the maximum efficiency, and more than 1 g/L CA should be recovered in the filtrate after extraction. This is the case for C<sub>5</sub>Gly, which extracts 1.07 g/L CA, but not for C<sub>4</sub>Gly and *i*C<sub>5</sub>Gly which extract respectively 0.82 and 0.83 g/L CA. Concerning APG, C<sub>4</sub>Glu and C<sub>6,-2</sub>Glu are further from the center than the contour line representing a concentration of CA of 0.25 g/L, meaning that their extraction should result in filtrates less concentrated than 0.25 g/L. As well, *i*C<sub>5</sub>Xyl, C<sub>7</sub>Glu and C<sub>8/10</sub>Glyco should extract between 0.25 and 0.5 g/L of CA. All these predictions are in a rather good agreement with the experimental values of 0.01 g/L (C<sub>4</sub>Glu), 0.23 g/L (C<sub>6,-2</sub>Glu), 0.43 g/L (*i*C<sub>5</sub>Xyl), 0.33 g/L (C<sub>7</sub>Glu) and 0.29 g/L (C<sub>8/10</sub>Glyco).

The model predicts well the efficiency of C<sub>5</sub>Gly but overestimate the one of *i*C<sub>5</sub>Gly and C<sub>4</sub>Gly, nevertheless, they are effectively efficient hydrotropes, more than most of the C<sub>*i*</sub>E<sub>*j*</sub>. The regression coefficient decreases only from 0.91 to 0.90 taking all of the compounds compared to only C<sub>*i*</sub>E<sub>*j*</sub>, therefore, the model established to predict the concentration of CA extracted by aqueous solutions at 30 wt.% C<sub>*i*</sub>E<sub>*j*</sub> can be considered also valid for C<sub>*i*</sub>Glyco and C<sub>*i*</sub>Gly.



**Figure 5.** (a) Prediction of the concentration of extracted CA from whole rosemary leaves after 48 h by  $C_i$ Gly (red) and  $C_i$ Glyco (green) according to the contour plot versus molecular volume ( $V_m$ ) and  $\log P$  obtained with  $C_iE_j$  (black). Each contour line is calculated by Eq.1 and 2 and corresponds to a concentration of CA extracted of 0.25, 0.5, 0.75 and 1 g/L as indicated. (b) Correlation between experimental and predicted concentration of CA extracted from whole rosemary leaves after 48 h.  $C_i$ Gly are indicated in red (1:  $C_4$ Gly, 2:  $iC_5$ Gly, 3:  $C_5$ Gly), APG in

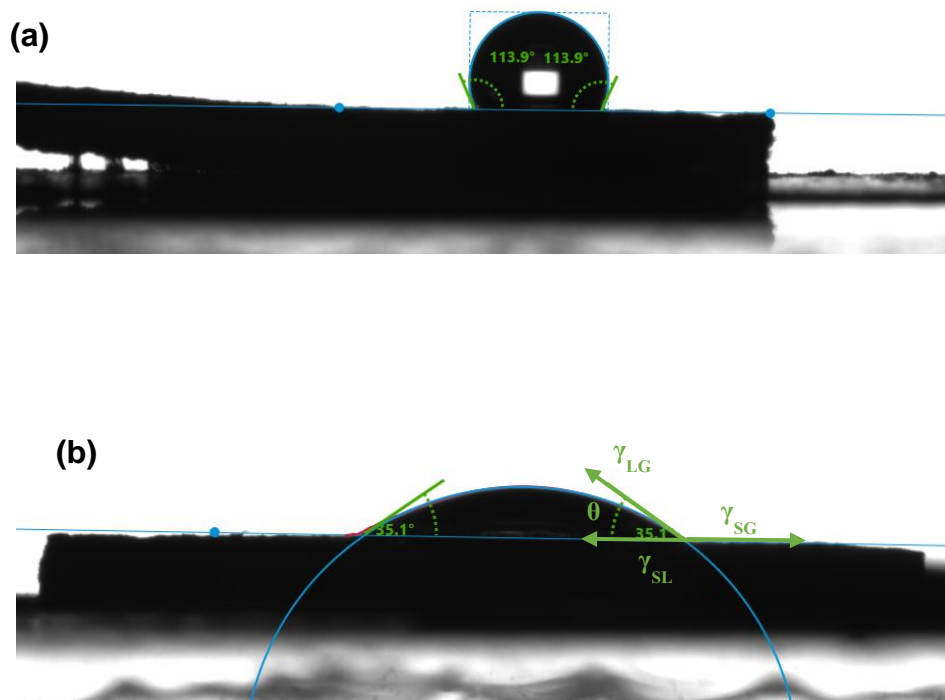
green (4: C<sub>4</sub>Glu, 5: *i*C<sub>5</sub>Xyl, 6: C<sub>6,-2</sub>Glu, 7: C<sub>7</sub>Glu, 8: C<sub>8/10</sub>Glyco), and C<sub>i</sub>E<sub>j</sub> in black. The dotted line shows the regression for C<sub>i</sub>E<sub>j</sub> only and the solid one is the regression line with all points.

#### 4. Interfacial tension between rosemary leaf and hydrotropic solutions.

In the previous relationship, it is difficult to differentiate two isomers, such as C<sub>5</sub>E<sub>2</sub> and *i*C<sub>5</sub>E<sub>2</sub> or C<sub>5</sub>Gly and *i*C<sub>5</sub>Gly. However, the branching of the alkyl chain has clearly a negative effect on the efficiency of the hydrotrope. This has been previously attributed to a bigger volume, but was not reflected by the estimation of the CA concentration in the filtrate. Indeed, all the models estimate almost the same efficiency for *i*C<sub>5</sub>Gly and its isomer C<sub>5</sub>Gly while *i*C<sub>5</sub>Gly is about 20 % less efficient. We thus looked at the difference of their surface tension and the influence it could have on the leaves to explain the effect of the branching on the extraction efficiency. At that aim, contact angles of 2 μL droplets of water and hydrotropic solutions were measured on the upper side of rosemary leaves, as shown in **Figure 6**. To limit the impact of the variability of the plant surface, which is inherent to the material, each contact angle was calculated from the mean value of ten measurements, resulting in standard deviation of about 5°, a common value for contact angle measurements on plant materials.<sup>45</sup>

Contact angle ( $\theta$ ) reflects the wettability of the surface by the hydrotropic solution, and is connected with  $\gamma_{SG}$ , the surface free energy of rosemary,  $\gamma_{LG}$ , the interfacial tension between rosemary and the hydrotropic solution and  $\gamma_{SL}$ , the surface tension of the hydrotropic solution, also noted  $\sigma$ , by the Young equation (**Eq.3**):

$$\gamma_{SG} = \gamma_{SL} + \gamma_{LG} \cos \theta \quad (3)$$



**Figure 6.** Contact angle of water (a) and an aqueous solution of C<sub>5</sub>Gly at 30 wt.% (b) on the upper side of rosemary leaves.

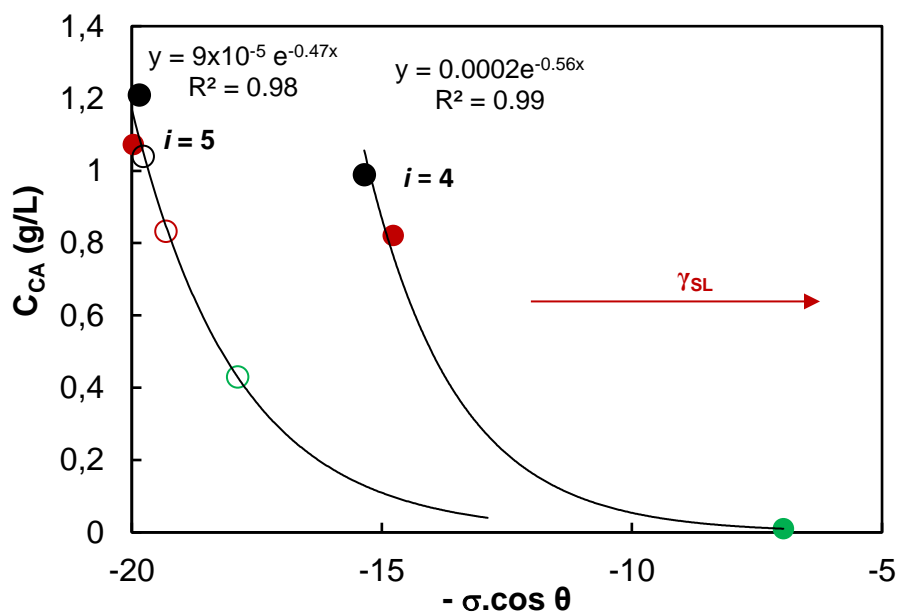
**Table 2** summarises the contact angles with rosemary and the surface tensions ( $\sigma$ ) of water and the aqueous solutions containing 30 wt.% of hydrotropes, which have been measured at this concentration specifically for more precision. As expected, the presence of a hydrotrope decreases both  $\theta$  and  $\sigma$  compared to neat water. Moreover,  $\theta$  evolves with the alkyl chain length in the following order: C<sub>4</sub> > C<sub>5</sub> > *i*C<sub>5</sub> for both C<sub>i</sub>E<sub>2</sub> and C<sub>i</sub>Gly series. Excluding the difference of glycoside nature, the same phenomenon occurs with C<sub>4</sub>Glu > *i*C<sub>5</sub>Xyl. The polar head also influences both  $\theta$  and  $\sigma$  in the following order: for the C<sub>4</sub> series, E<sub>2</sub> < Gly < sugar (Glu) and for the C<sub>5</sub> and *i*C<sub>5</sub> series, Gly < E<sub>2</sub> < sugar (Xyl).

**Table 2.** Contact angles observed between 2  $\mu\text{L}$  droplets of aqueous hydrotropic solutions at 30 wt.% (or water) and the upper sides of rosemary leaves and surface tension of these solutions.

	$\theta$ ( $^\circ$ )	$\sigma$ (mN/m)
<b>Water</b>	106.4 $\pm$ 5.9	72.8
<b>C<sub>4</sub>Gly</b>	58.9 $\pm$ 5.9	28.6
<b>C<sub>5</sub>Gly</b>	41.9 $\pm$ 7.1	26.8
<b><i>i</i>C<sub>5</sub>Gly</b>	40.2 $\pm$ 5.3	25.3
<b>C<sub>4</sub>E<sub>2</sub></b>	56.8 $\pm$ 5.9	28.0
<b>C<sub>5</sub>E<sub>2</sub></b>	48.6 $\pm$ 6.2	30.0
<b><i>i</i>C<sub>5</sub>E<sub>2</sub></b>	46.1 $\pm$ 4.3	28.5
<b>C<sub>4</sub>Glu</b>	79.1 $\pm$ 3.7	37.0
<b><i>i</i>C<sub>5</sub>Xyl</b>	51.9 $\pm$ 6.2	29.0

Since  $\gamma_{\text{SG}}$  only depends on the plant surface, the value of  $-\sigma \cdot \cos \theta$  depends only on the interfacial tension  $\gamma_{\text{SL}}$  as shown by **Eq.4**. Those values were plotted against the concentration of CA extracted by the hydrotropic solutions in **Figure 7**. Interestingly, for a similar alkyl chain length, the concentration of extracted CA seems to increase exponentially when  $\gamma_{\text{SL}}$  decreases, meaning that the concentration of extracted CA also depends on the interfacial tension in addition to the alkyl chain length  $i$ . Indeed, when the interfacial tension decreases, interactions between the hydrotrope and the plant increases, which probably results in a higher adsorption of the hydrotropes on the plant, hence an easier diffusion inside. However, this assumption should be verified for more amphiphiles.

$$\sigma \cos \theta = \gamma_{\text{SL}} - \gamma_{\text{SG}} \quad (4)$$



**Figure 7.** Evolution of the concentration of CA extracted from whole rosemary leaves after 24 and 48 h of stirring by 30 wt.%  $C_iGlyco$  (green),  $C_iGly$  (red) and  $C_iE_2$  (black) with  $-\sigma \cos \theta$ , *i.e.* with the interfacial tension  $\gamma_{SL}$ . Empty points represent branched alkyl chains.

## Conclusion

In the ether family, monoalkyl glycerols lay between alkyl ethylene glycols and alkyl glycosides in terms of polarity by possessing two hydroxyl groups. Their efficiency regarding rosemary extraction is however closer to that of  $C_iE_j$  than that of alkyl glycosides. Therefore, monoalkyl glycerols turn out to be another potential biosourced alternative to  $C_iE_j$  to extract carnosic acid with a higher extraction efficiency than alkyl glycosides due to their smaller molecular volume. The extraction efficiency is not fully related to the solubilisation capacity because the solubility of pure carnosic acid was higher at 2M of  $C_4Gly$  compared to  $C_4E_2$  (46 g/L vs 25 g/L) whereas the extraction yield was slightly lower. Indeed, the ability of the hydrotrope to diffuse inside the plant also seems to play a crucial role on extraction yields, as showed by the relation between  $\log P$ , the molecular volume and the efficiency of the hydrotrope in a model developed with  $C_iE_j$ , which rather fits for alkyl glycosides and alkyl glycerols. In addition, we showed that

the extraction efficiency is also related to the interfacial tension of the hydrotropic solution for a given alkyl chain length, rationalising the deleterious effect of the branching of the alkyl chain.

Overall, this work highlights the use of pentyl glycerol ether as an efficient extractant for carnosic acid from two different matrixes (rosemary and sage) in aqueous media, at room temperature, and without special equipment. This may potentially be transposed to many others plant materials.

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