

Chapter 12

2-Methyltetrahydrofuran: Main Properties, Production Processes, and Application in Extraction of Natural Products

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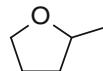
Abstract 2-Methyltetrahydrofuran (MeTHF) is a solvent produced from renewable raw materials by the hydrogenation of products obtained from carbohydrate fractions of hemicellulose from various feedstocks. MeTHF has the advantages to be biodegradable and has a promising environmental footprint, good preliminary toxicology assessments, and an easy recycling. An experimental study was conducted with MeTHF, in comparison to n-hexane, for the extraction of carotenoids and aromas. In parallel to this experimental study, a HSP (Hansen solubility parameters) theoretical study has been realized for the evaluation and the understanding of the interactions between the solvent and different compounds such as triglycerides contained in canola oil, carotenoids, and aromas. The results of these studies show that MeTHF appears to be a potential alternative solvent to n-hexane for the extraction of various products.

12.1 Introduction

Extraction processes appear to take a very large part in industrial processes and produce not only by-products but also waste solvent or wastewater to recycle or eliminate. Extraction solvents generally are organic volatile compounds produced from nonrenewable resources, such as petroleum, and may be harmful for human health and environment. For example, one of the extraction solvents most commonly

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Fig. 12.1 MeTHF structure**Table 12.1** MeTHF major benefits

Biodegradable	Renewable – biomass derived
Noncarcinogenic	Noncorrosive
High solvency power for resins, polymers, and dyes	Stable to acids and bases
Quite low boiling point	Easy to recycle
Low vapor pressure	Not a hazardous air pollutant
Low VOC	Not an ozone-depleting chemical

VOC volatile organic compound

used industrially is n-hexane, a fraction of petroleum. It has the advantage to be quite easy to obtain and to have chemical properties that provide ideal functionalities in terms of solubility for various products such as vegetable oils. Moreover, it is very easy to recycle considering its very low miscibility with water. Nevertheless n-hexane is produced from fossil energies and has recently been classified as CMR 3 which means that it is suspected to be reprotoxic [1].

Biomass-derived chemicals appear to be in accordance with several of the 12 principles of green chemistry described by Anastas and Warner [2] such as the third principle concerning the reduction of hazardous chemical syntheses, the fourth concerning the use of safer chemicals, the tenth concerning the degradation, or the seventh suggesting the use of renewable feedstock. These principles give suggestions for the design of greener products and processes.

In fact, 2-methyltetrahydrofuran (MeTHF) represented in Fig. 12.1 is a solvent produced from renewable raw materials as its reactants can be obtained from biomass by the hydrogenation of products obtained from carbohydrate fractions of hemicellulose from various feedstocks [3–5]. It is biodegradable, has a promising environmental footprint and good preliminary toxicology [6] assessments, and is easy to recycle. Considering all the advantages of this solvent, summarized in Table 12.1, several applications of MeTHF can be found in the literature especially as green solvent in organic chemistry [3, 7], but it can also be considered as an interesting solvent for the extraction of bioactive components from natural sources [8, 9].

12.2 MeTHF Properties

MeTHF represented in Fig. 12.1 (CAS No. 96-47-9, IUPAC name 2-methyltetrahydrofuran), with molecular formula $C_5H_{10}O$, is a clear liquid that is derived from renewable resources as corncobs or sugarcane bagasse. MeTHF is biodegradable,

Table 12.2 Basic properties of MeTHF

Properties	MeTHF
Molecular weight – M (g/mol)	86.1
Melting temperature – T_f (°C)	–136
Normal boiling temperature – T_b (°C)	80.2
Vapor pressure at 20 °C (mm)	102
Density at 20 °C (g/mL)	0.854
Viscosity at 25 °C (cp)	0.46
Flash point (°C)	–11
Enthalpy of vaporization (kJ · kg ^{–1})	375
Dielectric constant at 20 °C	6.97
Solubility in water at 20 °C (g/100 g)	14

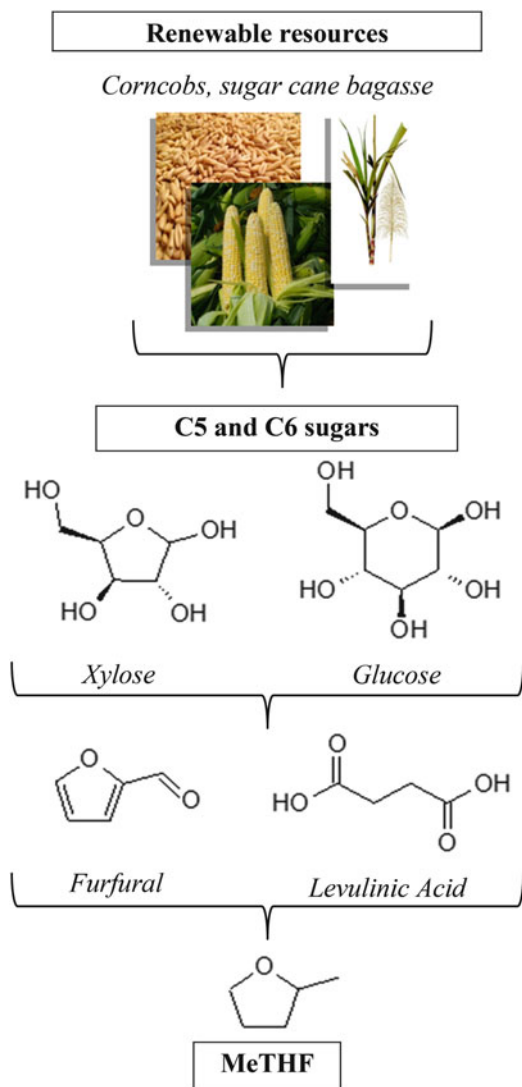
nontoxic, and non-ozone depleting; indeed, it is still not approved yet by the Food and Drug Administration (FDA) to be used for food contact. General properties of MeTHF are presented in Table 12.2. All the presented properties [3, 7, 10] make MeTHF as a suitable compound for several applications especially in the extraction field.

12.3 Production Processes

12.3.1 Raw Materials

Building blocks for the synthesis of MeTHF are issued of carbohydrates derived from lignocelluloses' biomass, which represent the largest terrestrial biomass resources. Although MeTHF can be produced thanks to catalytic processes from furfural or levulinic acid. Both compounds are obtained from the implementation of the concept of biorefinery with the retreatment of by-products such as corncobs or sugarcane bagass generated by agricultural industry. Furfural, a heterocyclic aldehyde with molecular formula $C_5H_4O_2$, is a versatile compound in the fragrance industry. It is a colorless oily liquid with an almond smell. Lignocellulose material can lead to furan molecules by dehydration reactions of carbohydrates from biomass origin. Furfural can be isolated from polysaccharide hemicellulose, polymers of C5 sugars, contained in many plant materials. The pentosan contained in hemicellulose is hydrolyzed in pentose carbohydrates which are dehydrated to furfural in acid conditions using sulfuric or phosphoric acid as catalysts [11]. Levulinic acid is a keto acid with molecular formula $C_5H_8O_3$. It appears as a white crystalline solid, and it is a highly versatile compound with several applications like in resins or plasticizers industry but also as precursor for pharmaceuticals [12]. Levulinic acid can be produced by acid hydrolysis at high temperature of carbohydrates [13], which are C6 sugars such as glucose, galactose, or sucrose, isolated from wood-based feedstock.

Fig. 12.2 Production of MeTHF



12.3.2 Synthesis

MeTHF can be produced from furfural or levulinic acid as shown in Fig. 12.2.

12.3.3 Synthesis from Furfural

MeTHF results from successive hydrogenations, as shown in Fig. 12.3, of furfural (and reactions intermediates) over Ni-Cu, Fe-Cu, Cu-Zn, or Cu-Cr alloy catalysts as

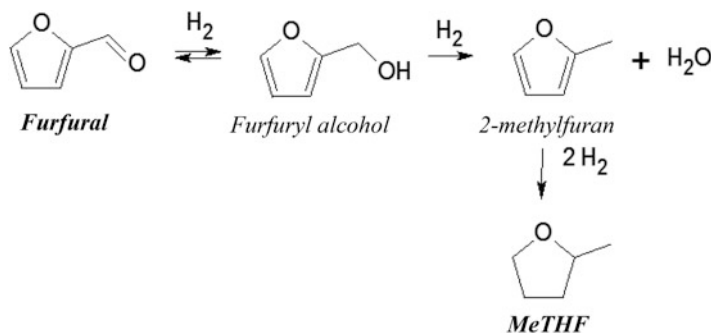


Fig. 12.3 Production of MeTHF from furfural

reported in the literature [14–18]. First, two successive hydrogenations of furfural on the Cu-Zn catalyst allow nearly a complete conversion of the compound to furfuryl alcohol directly converted to 2-methylfuran in a range of temperature of 200–300 °C with a yield higher than 95 % [5].

MeTHF results in the conversion of 2-methylfuran at lower temperature (100 °C) over Ni-based catalyst with a yield around 86 %. Increasing the temperature would decrease the quantity by conversion in 2-pentanone. The choice of the catalyst also has a great importance in the conversion yield. In fact, MeTHF is the main product of the hydrogenation of furfural depending on the catalyst and on reaction conditions [5].

12.3.4 Synthesis from Levulinic Acid

The synthesis of MeTHF from levulinic acid consists in consecutive catalyzed hydrogenations and dehydrogenations as shown in Fig. 12.4. The catalyzed hydrogenation of the keto group of levulinic acid leads to a hydroxyl acid that results in γ -valerolactone. Further hydrogenation of the keto bond of γ -valerolactone allows the formation of the cyclic hemiacetal in equilibrium with the aliphatic hydroxyl aldehyde. The hydrogenation of the last carbonyl group leads to 1,4-pentanediol that is etherified in MeTHF by dehydration in acid conditions.

The reactions are conducted with a ruthenium catalyst complex with tridentate phosphine ligands and acidic ionic additives in conditions described by Geilen et al. [4].

12.3.5 Recovery of MeTHF

MeTHF can be recovered by conventional distillation, thanks to the solubility behavior of MeTHF/water mixtures and the formation of a favorable azeotrope between the two compounds.

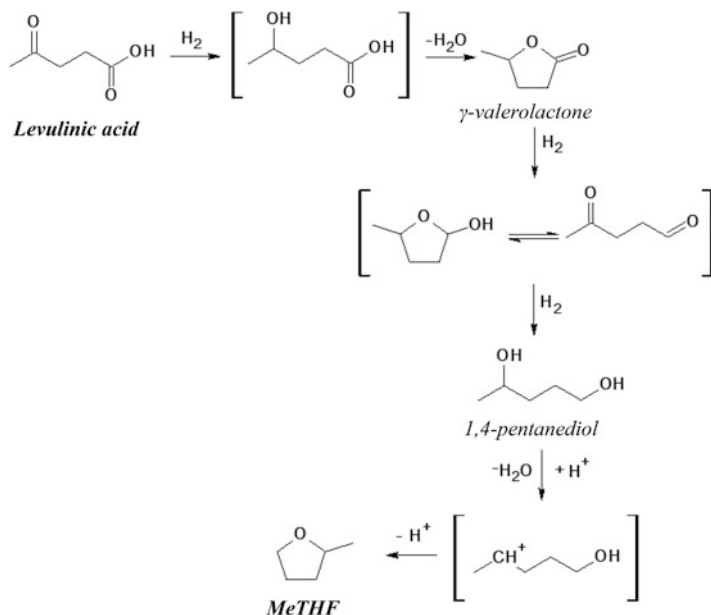


Fig. 12.4 Production of MeTHF from levulinic acid

Table 12.3 Solubility of water in MeTHF and MeTHF in water

Solubility of water in MeTHF		Solubility of MeTHF in water	
Temperature (°C)	wt% water	Temperature (°C)	wt% water
0.0	4.0	0.0	21.0
9.5	4.1	9.5	17.8
19.3	4.1	19.3	14.4
29.5	4.2	29.5	11.4
39.6	4.3	39.6	9.2
50.1	4.4	50.1	7.8
60.7	4.6	60.7	6.6
70.6	5.0	70.6	6.0

As can be seen in Table 12.3, the solubility of water in MeTHF varies very slightly between 0 to 70 °C, whereas the solubility of MeTHF in water decreases a lot as the temperature is increased. Considering these properties, MeTHF/water mixtures need to be separated at least at 60 °C in order to minimize the amount of MeTHF in water [10]. The azeotrope formed between MeTHF and water contains 10.6 % water and so 89.4 % MeTHF. Though MeTHF can be recovered at atmospheric pressure in batch or continuous distillation processes at 60 °C, as shown in Fig. 12.5, considering the recycling of a mixture containing 100 parts MeTHF and 100 parts water [3, 7, 10].

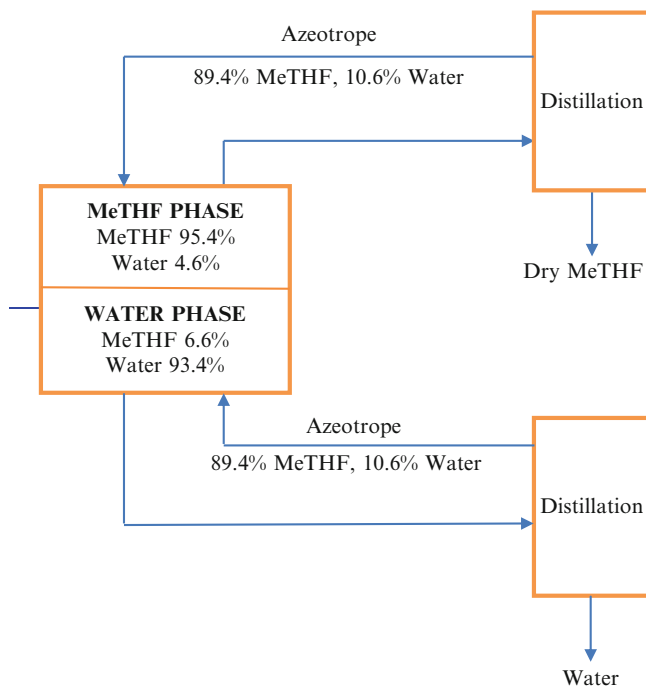


Fig. 12.5 Recovery of MeTHF at 60 °C

12.4 Applications

MeTHF has many applications as solvent for organic synthesis [3, 7, 10], but considering its various properties it looks very promising as alternative to commonly used petroleum solvent for extraction of natural products [8, 9]. A literature search did not yield any reference to earlier reports on using MeTHF as solvent for the extraction of natural products, although using MeTHF for the extraction of carotenoids or aromas that usually imply solvents as n-hexane can be considered.

12.4.1 Extraction of Carotenoids

Solvents issued from petroleum are the one currently used for the extraction of carotenoids. A study was conducted to evaluate the potential of MeTHF compared to n-hexane, the solvent currently used by industrials.

A kinetic study was conducted during 3 h with n-hexane and MeTHF. Figure 12.6 gives the yield of total carotenoids extracted for 1 g of dry carrots.

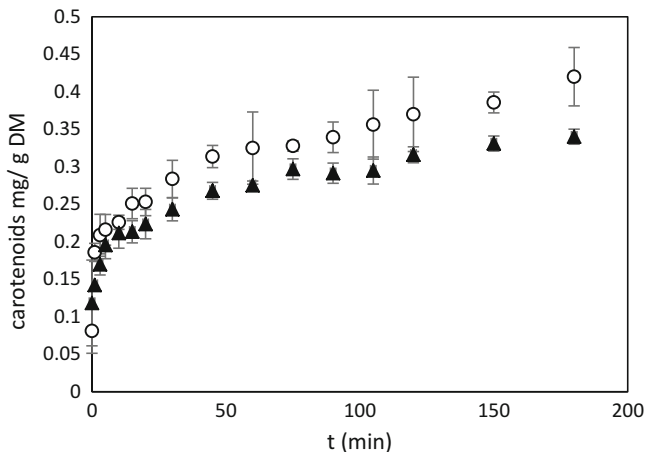


Fig. 12.6 Kinetic of total carotenoids extracted from carrots (○ MeTHF, ▲ n-hexane)

As can be seen from Fig. 12.6, the extraction is realized in two steps. A first solvent-exchange surface interaction takes place for a short time frame. Thus, starting accessibility δX_s (in mg carotenoids/g dry material) corresponding to a “washing” step reveals the amount of carotenoids obtained in a very short time frame (t near 0) through the convection of solvent interacting with the exchange surface. Afterward, the main part of the extraction is controlled through various penetration processes of the solvent within the carrot particles (capillarity, molecular diffusivity, etc.). The driving force of the global operation is the gradient of concentration and the model can be similar to Fick’s law with an effective diffusivity D_{eff} ($\text{m}^2 \cdot \text{s}^{-1}$) as the process coefficient [19].

According to Fick’s first law [19]

$$\frac{\rho_s}{\rho_d} (\vec{v}_s - \vec{v}_d) = -D_{\text{eff}} \vec{\nabla} \left(\frac{\rho_s}{\rho_d} \right)$$

It can be assumed the absence of expansion or shrinkage of the solid particles which are not moving, i.e., $\vec{v}_d = 0$ and $\rho_d = \text{constant}$.

$$\rho_s \vec{v}_s = -D_{\text{eff}} \vec{\nabla} \rho_s$$

Crank’s solution for a sphere

$$\frac{X_\infty - X}{X_\infty - X_{t_0}} = \sum_{i=1}^{\infty} \frac{6}{i^2 \pi^2} \exp \left(-\frac{i^2 \pi^2 D_{\text{eff}}}{r_d^2} (t - t_0) \right)$$

$$\frac{X_\infty - X}{X_\infty - X_{t_0}} = A \exp(-k(t - t_0))$$

Table 12.4 Starting accessibility and effective diffusivity for the extraction of carotenoids from carrots with n-hexane and MeTHF

Solvent	δX_s (mg/g DM)	D_{eff} ($\cdot 10^{10}$ m ² /s)
n-Hexane	0.220	0.009
MeTHF	0.269	0.013

$$\text{Ln} \left(\frac{X_{\infty} - X}{X_{\infty} - X_{t_0}} \right) = -k (t - t_0)$$

$$D_{\text{eff}} = k \frac{r_d^2}{\pi^2}$$

Starting accessibility: value obtained by extrapolating diffusion model to $t = 0$:
 $X_0 \neq (X_i = 0)$

$$X_0 - X_i = X_0 = \delta X_s$$

with

δX_s : starting accessibility (g of extract/g of dry material)

D_{eff} : effective diffusivity (m² s⁻¹)

ρ_s : apparent density of the solute within the solid matrix (kg m⁻³)

ρ_d : apparent density of the solid dry material (kg m⁻³)

v_s : velocity of the solute (m s⁻¹)

v_d : velocity of the solid dry material (m s⁻¹)

X_{∞} : amount of solute within the matrix (mg · g⁻¹ dry material)

d_p : radius

X : amount of solute extracted at time t (mg · g⁻¹ dry material)

k : transfer coefficient (m · s⁻¹)

Starting accessibility and diffusivity were calculated using previous equations. Starting accessibility is determined by extrapolating the value for $t = 30$ min at $t = 0$. Calculated values are listed in Table 12.4. Starting accessibility appears to be higher for MeTHF than for n-hexane, and D_{eff} is 1.5 times higher with MeTHF than with n-hexane. This means that the washing step with MeTHF permits to solvate a higher amount of carotenoids at the surface of the matter than n-hexane does which suggests that there is a part of the solute extracted almost instantly that comes from the layers of cells the most exposed to the solvent. The same trend is observed for the effective diffusivity D_{eff} where the value for n-hexane is $0.009 \times 10 - 10$ m²/s and $0.013 \times 10 - 10$ m²/s for MeTHF. This means that the extraction is faster with MeTHF than with n-hexane. This is probably due to the difference of boiling point (69 °C vs 80 °C); a higher temperature increases the extraction, even if a higher temperature can increase the risk of a degradation of the extract. The carotenoid content in dry carrots was determined by HPLC analysis. After 6 h extraction

MeTHF permits to extract 419 $\mu\text{g/g}$ dry matter, whereas n-hexane permits to extract 338 $\mu\text{g/g}$ dry matter which represents 23 % more carotenes extracted with MeTHF compared to n-hexane.

12.4.2 Extraction of Aromas

n-Hexane has been used as an extraction solvent for aromas of buds black currant. Recent regulation have banned numerous common organic solvents, as n-hexane, that have been recognized as hazardous to human health and environment. It is urgently to replace n-hexane by alternative solvents that minimize health and environmental risk. MeTHF can be considered as a good solvent from a (HSE) Health Safety Environment point of view which makes it a good candidate for the replacement of organic solvents. Performance trials using MeTHF and n-hexane were conducted in bud black currant.

The quality of oils extracted by these solvents was evaluated. Compounds were identified using GC-MS, while the content of separated components was measured by GC-FID (Table 12.5). A total of 30 major compounds (in agreement with the literature [20, 21]) were identified in n-hexane extract. The results reported in Table 12.5 show that the relative proportions of these compounds are similar for both solvents.

Extracts obtained with n-hexane and MeTHF, respectively, contain 47.73 and 42.88 % of non-oxygenated compounds, while the amounts of oxygenated compounds, respectively, were 25.26 and 17.06 %. The principal volatile compounds were δ -3-carene (21.45 % with n-hexane and 17.55 % with MeTHF) and terpinolene (11.34 % with n-hexane and 8.16 % with MeTHF), followed by other important compounds as sabinene, β -caryophyllene, caryophyllene oxide, p-cymen-8-ol, trans β -ocimene, β -phellandrene, β -myrcene, α -humulene, cis β -ocimene, spathulenol, humulene epoxide, limonene, terpinolene epoxide, and 3-carene-5-one. Some of these main compounds are represented in Fig. 12.7. Besides, the higher extraction yield (7.10 %) obtained with MeTHF compared to n-hexane (3.87 %) is probably due to the fact that MeTHF allows the extraction of other compounds as amino acids, flavonoids, and phospholipids.

12.4.3 Comprehension of Solubility of Primary and Secondary Metabolites of Various Natural Products by Using Hansen Theoretical Prediction

Hansen solubility parameters (HSP) of solvents and solutes have been studied using HSP theoretical prediction [22]. HSP provides a convenient and efficient way to characterize solute/solvent interactions according to the general “like

Table 12.5 Major compounds extracted with n-hexane and MeTHF

Compounds	RI	n-hexane (%)	MeTHF (%)
α -Thujene ^a	929	0.25	0.28
α -Pinene ^a	938	0.93	0.79
Camphene ^a	945	–	–
Sabinene^a	968	4.93	3.88
β -Pinene ^a	973	0.85	0.75
β-Myrcene^a	983	1.86	1.46
2-Carene ^a	1,001	0.31	0.27
Alpha phellandrene ^a	998	0.17	0.15
δ-3-Carene^a	1,002	21.45	17.55
α -Terpinene ^a	1,009	0.81	0.69
p-Cymene ^a	1,013	0.82	0.56
β-Phellandrene^a	1,022	2.06	1.57
Limonene^a	1,025	1.41	1.07
transβ-ocimene^a	1,026	2.79	2.24
cisβ-ocimene^a	1,037	1.69	1.35
γ -Terpinene ^a	1,040	0.25	0.29
4-Terpinyl acetate	1,030	–	–
cis sabinene hydrate ^a	1,068	0.35	0.22
α -p-Dimethylstyrene ^a	1,071	–	–
Terpinolene^a	1,080	11.34	8.16
trans sabinene hydrate ^a	1,097	0.33	0.23
Terpinolene epoxide		1.22	0.46
cis verbenol	1,110	–	–
Dehydrolinalool ^a	1,124	–	–
trans sabinol ^a	1,130	–	–
Pinocarvone	1,135	–	–
p-Cymen-8-ol^a	1,163	2.85	1.73
Terpin-4-ol ^a	1,173	–	–
α -Terpineol ^a (p-menth-1-en-8-ol)	1,180	–	–
Eucarvone	1,240	–	–
Bornyl acetate ^a	1,270	0.36	0.35
3-Caren-5-one		1.13	0.69
α -Terpinyl acetate ^a	1,340	0.32	0.35
Sesquiterpenes			
β -Elemene ^a	1,380	0.22	–
α-Humulene^a	1,452	1.82	2.32
α -Muurolene ^a	1,477	–	–
Germacrene D ^a	1,480	0.82	1.29
γ -Cadinene ^a	1,513	–	–
δ -Cadinene ^a	1,524	–	–
Spathulenol^a	1,576	1.61	1.14
Caryophyllene oxide^a	1,562	4.16	2.69
Aromadendrene oxide (1)	1,595	–	–
Humulene epoxide II^a	1,600	1.59	1.04
Hardwickic acid		5.1	11.06

(continued)

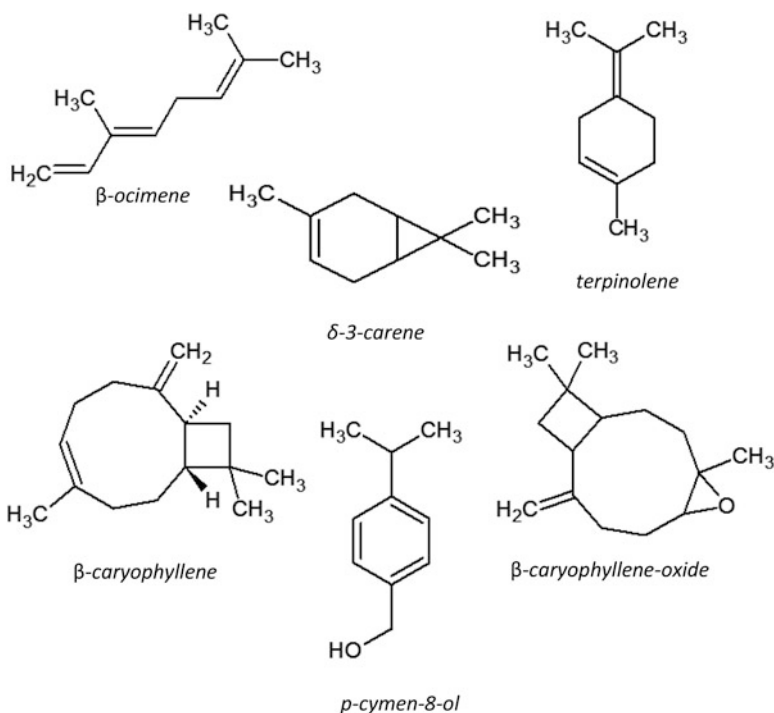
Table 12.5 (continued)

Compounds	RI	n-hexane (%)	MeTHF (%)
Yields		3.87 %	7.10 %
Total non-oxygenated		47.95 %	42.88 %
Total oxygenated		25.26 %	17.06 %
Global identification		73.21 %	59.94 %

RI retention indices

The percentage correspond to percent of total peak area (%)

^aAromas already known in this matrix

**Fig. 12.7** Principal volatile compounds in bud black currant

dissolves like” rule. HSP has been found to be superior for more applications to acknowledged Hildebrand parameter, which the fundamental total cohesive energy density is partitioned by atomic dispersion forces (δ_d^2), molecular polar forces arising from dipole moments (δ_p^2), and hydrogen bonds (exchange of electrons, proton donor/acceptor) between moleculars (δ_h^2), as given in Eq. (12.1):

$$\delta_{\text{total}}^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \quad (12.1)$$

Table 12.6 Hansen solubility parameters of various solvents and extracts

	Compounds	δ_d (MPa ^{1/2})	δ_p (MPa ^{1/2})	δ_h (MPa ^{1/2})	δ_{total} (MPa ^{1/2})
Solvent	n-Hexane	15	0	0	15
	MeTHF	16.8	4.8	4.6	17.7
Carotenoids in carrots	β -Carotene	17.4	0.8	1.7	17.5
	Lutein	17.8	1.3	4.5	18.4
	Zeaxanthin	17.8	1.4	4.8	18.5
Main aroma compounds in black currant	Terpinolene	17.2	1.9	4.3	17.8
	δ -3-Carene	16.4	1.1	2.2	16.6
	β -Caryophyllene	16.8	0.7	2.2	16.6
	Sabinene	16.5	1.6	2.1	16.7
	trans β -ocimene	16.4	1.5	2.6	16.7
Possible triglycerides in rapeseed oil	Rapeseed oil ¹	16.4	4.7	4.2	17.6
	Rapeseed oil ²	16.6	4	4.1	17.5
	Rapeseed oil ³	16.6	4.1	3.6	17.5
	Rapeseed oil ⁴	16.5	4.2	4.6	17.6
	Rapeseed oil ⁵	16.4	4	4.5	17.5

¹Triglyceride (R₁ C18:1n9, R₂ C18:2n6, R₃ C18:3n3)

²Triglyceride (R₁ C18:1n9, R₂ C18:1n9, R₃ C18:2n6)

³Triglyceride (R₁ C18:1n9, R₂ C18:2n6, R₃ C18:2n6)

⁴Triglyceride (R₁ C18:1n9, R₂ C18:1n9, R₃ C18:3n3)

⁵Triglyceride (R₁ C18:2n6, R₂ C18:2n6, R₃ C18:3n3)

where δ_{total} is the Hansen total solubility parameter, which now consists of its three partitioned HSP in terms of dispersion (δ_d), polar (δ_p), and hydrogen-bonding (δ_h) force, respectively.

In general, the more similar the two δ_{total} are, the greater the affinity between solutes and solvents. The chemical structures of the solvents and solutes discussed in this article could be mutually transformed by JChemPaint ver. 3.3 to their Simplified Molecular Input Line Entry Syntax (SMILES) notations, which were subsequently used to calculate the solubility parameters of extracts and extractants. These solubility parameters were further modeled to a frequently used two-dimensional HSP graph for better visualization of the solute/solvent interaction due to insignificant differences between δ_{dS} (HSPiP Version 4.1.03, Denmark).

Since MeTHF was firstly used as extractant for natural products, it is interesting to introduce methods for predicting its physicochemical properties and the solubility parameters of its extracts, most of which do not exist in HSP database. The useful prediction method proposed by Yamamoto was applied to calculate HSP of solutes and solvents only through their chemical structures due to its stability and high accuracy comparing to other HSP estimation methods. Yamamoto-Molecular Break (Y-MB) method breaks SMILES into corresponding functional groups and thus estimates various physicochemical properties. The theoretical physicochemical properties of extractants and the HSP of their main extracts were obtained by Y-MB calculation through their chemical structures, which were represented in Table 12.6.

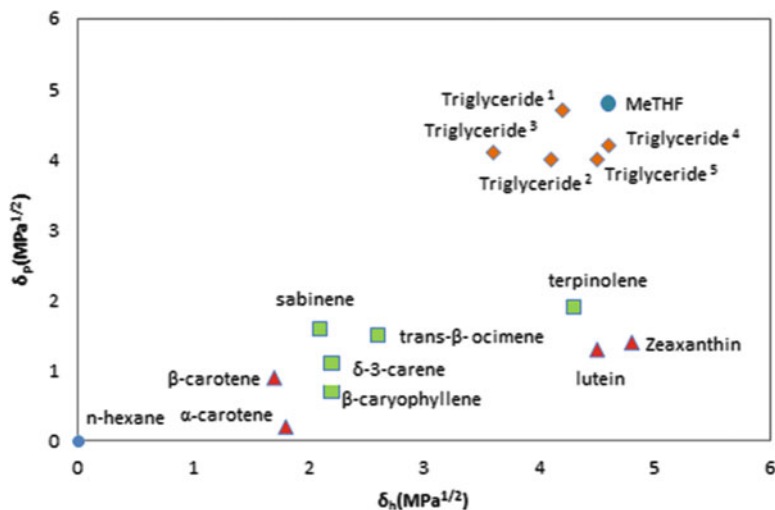


Fig. 12.8 General two-dimensional diagram of Hansen solubility parameters for all solutes (♦ possible triglycerides in rapeseed oils, ■ aroma compounds in black currant, and ▲ carotenoids in carrot) in solvents (• n-hexane and MeTHF)

MeTHF has nearly the same molecular weights (≈ 86.1 g/mol) as that of n-hexane. Moreover, it has higher boiling (82.4 °C) and flash point (-1.9 °C) in comparison to n-hexane (69 °C and -23.3 °C, respectively), which signifies MeTHF is a less flammable and less hazardous azeotrope with water. MeTHF with higher HSP values is considered higher polarity than n-hexane. The major drawback of using MeTHF is its higher viscosity and density than n-hexane, which can induce lower global identification in the component analysis, as well as its relatively high boiling point which may lead to higher energy consumption in its recovery. In addition, MeTHF with higher dielectric constant (6.97) has also found to be stable in acids and base, which allows the extraction more efficient and stable. Besides, this agro-solvent from renewable resources also has low volatility, which improves safety and reduces solvent consumption and CO_2 emissions. Considering all these aspects, MeTHF could be theoretically considered a better alternative solvent to n-hexane in various extractions.

The two-dimensional (2-D) graph of δ_p versus δ_h has usually been used as references for easy understanding of solubility in solvent extraction as the result of the insignificant δ_d . Figure 12.8 illustrated that all combination possibilities of triglycerides in rapeseed oils were distinguished by small variations depending on their constituent fatty acids. According to the “like extracts like” principle, the triglycerides of rapeseed oil may be the most possible solutes in MeTHF, while the main aroma compounds in black currant seemed more likely to dissolve in n-hexane. Regarding carotenoids in carrots, lutein and zeaxanthin were more soluble in MeTHF, whereas α - and β -carotene were closed to n-hexane. These predicted results were generally in accordance with experimental results even though MeTHF gave

higher total extraction yield than n-hexane in all independent extraction of rapeseed oil, aroma compounds, and carotenoids, which have further proved MeTHF as the alternative solvent to n-hexane for the extraction of natural compounds from plants.

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