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Review

# Characterization of Cyclodextrin/Volatile Inclusion Complexes: A Review

Miriana Kfoury <sup>1</sup>, David Landy <sup>2</sup> and Sophie Fourmentin <sup>2,\*</sup> 

<sup>1</sup> Bioactive Molecules Research Laboratory, Doctoral School of Sciences and Technologies, Faculty of Sciences II, Lebanese University, Fanar, Lebanon; mirianakfoury@hotmail.com

<sup>2</sup> Unité de Chimie Environnementale et Interactions sur le Vivant (UCEIV), EA 4492, SFR Condorcet FR CNRS 3417, Université du Littoral-Côte d'Opale (ULCO), 59140 Dunkerque, France; landy@univ-littoral.fr

\* Correspondence: lamotte@univ-littoral.fr; Tel.: +33-3-28-65-82-54

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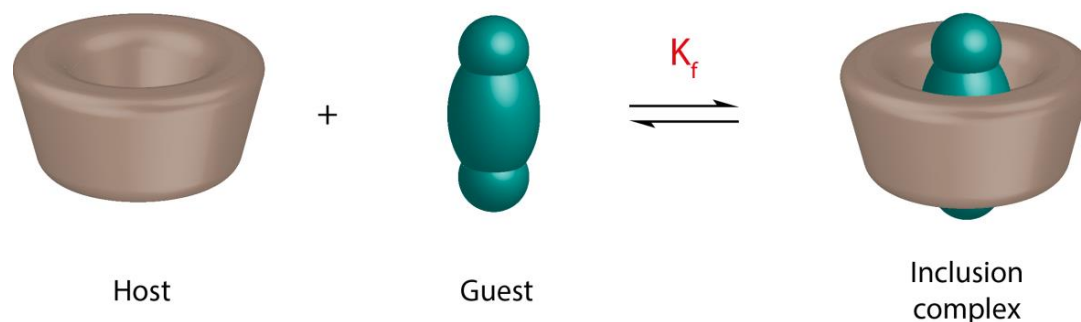
**Abstract:** Cyclodextrins (CDs) are a family of cyclic oligosaccharides that constitute one of the most widely used molecular hosts in supramolecular chemistry. Encapsulation in the hydrophobic cavity of CDs positively affects the physical and chemical characteristics of the guests upon the formation of inclusion complexes. Such a property is interestingly employed to retain volatile guests and reduce their volatility. Within this scope, the starting crucial point for a suitable and careful characterization of an inclusion complex is to assess the value of the formation constant ( $K_f$ ), also called stability or binding constant. This task requires the application of the appropriate analytical method and technique. Thus, the aim of the present paper is to give a general overview of the main analytical tools used for the determination of  $K_f$  values for CD/volatile inclusion complexes. This review emphasizes on the advantages, inconvenients and limits of each applied method. A special attention is also dedicated to the improvement of the current methods and to the development of new techniques. Further, the applicability of each technique is illustrated by a summary of data obtained from the literature.

**Keywords:** cyclodextrin; fluorescence; formation constant; HPLC; ITC; NMR; phase solubility; SH-GC; TOC; UV-Visible; volatiles

## 1. Introduction

The field of supramolecular encapsulation using cyclodextrins (CDs) continues to grow [1]. The use of CD is particularly interesting with volatile compounds [2–6]. Indeed, encapsulation in CDs represents a feasible and efficient tool to retain and modulate the release of the encapsulated volatiles [7–10]. The volatile guests include mainly volatile organic compounds (VOCs), aroma and flavors, anesthetics, etc.

The main feature of CDs is the formation of inclusion complexes with the guests (Figure 1). The most fundamental parameter in the quantitative analysis of the binding strength between the CD and guest is the determination of the formation constant ( $K_f$ ) of each inclusion complex.  $K_f$  values are determined mainly to answer two different types of questions. The first one, which deals with the encapsulation in an absolute mean, is, can a CD encapsulate the guest? The second question is a comparative one, that is, what is the binding strength? Which inclusion complex is more stable?



**Figure 1.** Schematic illustration of the formation of an inclusion complex between a cyclodextrin (host) and a guest.

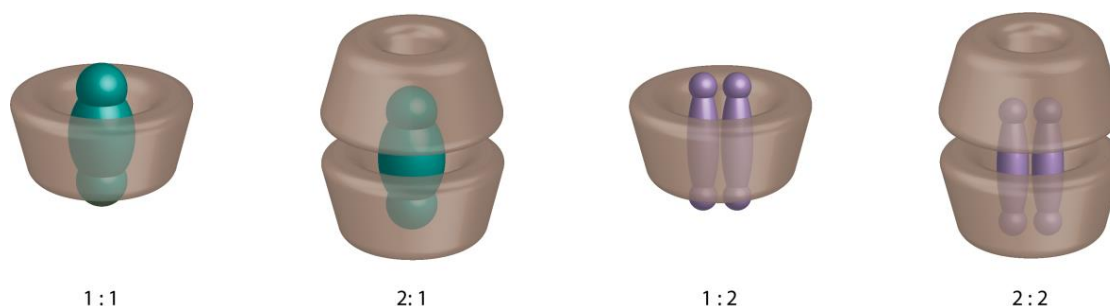
Although a wide number of analytical methods are available for the characterization of inclusion complexes in solution and a large progress in analytical methodologies has been accomplished [3,11], few could be applied to CD/volatile inclusion complexes. This is mainly due to the low aqueous solubility of most of the volatile compounds.

In general, the applied methods can be divided into four main groups: spectroscopic methods: UV-Visible (UV-Vis) spectroscopy [12–14], fluorescence spectroscopy [15,16] and nuclear magnetic resonance spectroscopy (NMR) [2]; chromatographic methods: static headspace coupled to the gas chromatography (SH-GC) [7–9,17–21] and high-performance liquid chromatography (HPLC) [22], calorimetric methods: isothermal titration calorimetry (ITC) [23–25] and solubility studies [10,26–35]. Lately, a new Total Organic Carbon (TOC) method was also developed [36].

The aim of this paper is to provide an overview of the research that has explored the assessment of  $K_f$  values for CD/volatile guest inclusion complexes. The experimental procedures and the obtained data are outlined in more detail. Finally, the advantages and limitations of the applied methods are critically discussed.

## 2. Characterization of Cyclodextrin Inclusion Complexes

The initial step in the characterization of an inclusion complex is the determination of the stoichiometry and formation constant ( $K_f$ ) values. If various stoichiometries could be observed in the literature (Figure 2), most of the inclusion complexes present a 1:1 (CD:guest) stoichiometry [2].



**Figure 2.** Schematic representation of the main stoichiometries of the inclusion complexes.

All the inclusion complexes described in this review possess a 1:1 stoichiometry. In this case, the  $K_f$  could be expressed as:

$$K_f = \frac{[\text{Inclusion complex}]}{[\text{Host}][\text{Guest}]} = \frac{[\text{CD/G}]}{[\text{CD}][\text{G}]} = \frac{[\text{CD/G}]}{([\text{CD}]_T - [\text{CD/G}])([\text{G}]_T - [\text{CD/G}])} = \frac{[\text{CD/G}]}{[\text{CD}]_T[\text{G}]_T - [\text{CD}]_T[\text{CD/G}] - [\text{CD/G}][\text{G}]_T + [\text{CD/G}]^2} \quad (1)$$

with  $[\text{G}]_T$  the initial guest concentration and  $[\text{G}]$  the free guest concentration.  $[\text{CD}]_T$  the initial CD concentration and  $[\text{CD}]$  the free CD concentration.

Various treatments could be used for the resolution of this equation. These treatments will be described in the corresponding sections of the analytical techniques.

Titration experiments using a constant concentration of a species (titrate) and increasing amounts of the other species (titrant) are generally employed. Nevertheless, some alternative approaches suitable for low soluble compounds, such as volatiles, have been also developed, in particular competitive methods and phase solubility studies.

### 2.1. Volatilization Method

The first method used for the determination of  $K_f$  between a CD and a volatile guest was based on the fact that volatile compounds could be driven out from an aqueous solution to gaseous phase by an inert gas bubbling at a constant flow rate in the aqueous solution [37–39]. The volatilization rate of the guest is supposed to be decreased in the presence of the CD. This decrease will depend on the strength of the association with the CD. This method was applied firstly to determine the  $K_f$  for iodine and then of aliphatic, cyclic or aromatic hydrocarbons [38,39]. The obtained results are listed in Table 1.

**Table 1.** Formation constants ( $K_f$ ,  $M^{-1}$ ) for benzene and alkylbenzenes [38].

Guest	$\alpha$ -CD	$\beta$ -CD	$\gamma$ -CD
Benzene	17	120	12
Toluene	33	140	20
Ethylbenzene	110	330	36
<i>o</i> -Xylene	22	300	34
<i>m</i> -Xylene	40	160	27
<i>p</i> -Xylene	72	240	8

This technique, developed by Sanemasa's group, has used home-made device and was no longer used after the 1990s. From this time, Sanemasa's group has worked on the development of static headspace-gas chromatography (SH-GC) methods.

### 2.2. Chromatographic Methods

#### 2.2.1. Static Headspace-Gas Chromatography

Static headspace coupled to gas chromatography (SH-GC) is widely employed to analyze volatile compounds in various fields [40,41]. This technique allows the quantification of a volatile present in a gaseous phase in contact and equilibrium with a condensed phase (liquid or solid) in a closed vial [42]. Although this technique has been used firstly at the end of the 1980s for the determination of  $K_f$  values for volatiles with CD [43], its development really began at the end of the 1990s with the work of Sanemasa and Saito [44,45]. Afterwards, this technique has been widely applied to determine  $K_f$  values for CD/aroma inclusion complexes [8,9,17].

Different treatments were successively developed for the determination of  $K_f$  values. The first SH-GC methods required a calibration curve to evaluate the concentration of the free guest in the presence of CD. The method developed by Saito [45] used a fixed CD concentration and various concentrations of the volatile guest.

$$[G] = \frac{[G]_T}{1 + K_f [CD]} \quad (2)$$

with  $[G]_T$  the initial guest concentration and  $[G]$  the free guest concentration.  $[G]_T$  is known and  $[G]$  could be obtained from the calibration curve.

In the meantime, Sanemasa's group [46] developed a method using a fixed guest concentration and different CD concentrations. The plot of  $A_0/A_{CD}$  versus  $[CD]$  gives a straight line, the slope of which corresponds to the  $K_f$  value:

$$[\text{CD}] = [\text{CD}]_{\text{T}} - \frac{(A_0 - A_{\text{CD}})}{K'} \quad (3)$$

where  $[\text{CD}]_{\text{T}}$  is the initial CD concentration,  $[\text{CD}]$  is the free CD concentration,  $A_0$  is the chromatographic peak area of the volatile guest in water (absence of CD),  $A_{\text{CD}}$  stands for the peak area in the presence of CD and  $K'$  is the slope of the calibration curve.

In 2007, Fourmentin et al. [47] proposed a method that did not require a calibration curve. In this method, a fixed guest concentration and different CD concentrations are used. An algorithmic treatment based on the Equation (4) is used to calculate the  $K_f$  value from the experimental data [48]:

$$[\text{CD}/\text{G}] = -\frac{1}{2} \sqrt{\left[ \left( \frac{1}{K_f} + [\text{CD}]_{\text{T}} + [\text{G}]_{\text{T}} \right)^2 - 4[\text{CD}]_{\text{T}}[\text{G}]_{\text{T}} \right]} + \frac{1}{2} \left( \frac{1}{K_f} + [\text{CD}]_{\text{T}} + [\text{G}]_{\text{T}} \right) \quad (4)$$

The use of gas chromatography allows the quantification but also the separation of volatile compounds. To take benefit from this property, authors have developed methods for the determination of simultaneous  $K_f$  values. Saito reported the simultaneous determination of the  $K_f$  of four aromas [49] and six alkanols [50]. This method is based on Equation (2). The guest's concentration and a calibration curve are required. More recently, Fourmentin et al. [51] have developed a method that precludes the knowledge of the guest's concentration based on the following equation:

$$K_f = \frac{(A_0 - A_{\text{CD}}) - 1}{[\text{CD}]_{\text{T}}} \quad (5)$$

where  $A_0$  and  $A_{\text{CD}}$  are the chromatographic peak areas of each guest in the absence and the presence of CD, respectively and  $[\text{CD}]_{\text{T}}$  is the initial CD concentration.

This method finds particular usefulness in the determination of  $K_f$  values of individual components in a complex mixture where the concentration of each component is not known. This is for example the case of essential oils. Kfoury et al. successfully applied this method for the determination of the  $K_f$  values of aroma compounds with different CD in a wide variety of essential oils [9,52]. Table 2 represents the data collected from the literature on the determination of  $K_f$  values using SH-GC.

**Table 2.** Formation constants ( $K_f$ ,  $\text{M}^{-1}$ ) for CD inclusion complexes with volatile guests obtained by static headspace-gas chromatography (SH-GC).

Guest	$\alpha$ -CD	$\beta$ -CD	$\gamma$ -CD	CRYSMEB	RAMEB	HP- $\beta$ -CD	SBE- $\beta$ -CD
<i>trans</i> -Anethole	710 <sup>a</sup> 1163 <sup>a</sup>	497 <sup>a</sup> 630 <sup>a</sup> 1040 <sup>a</sup>	96 <sup>a</sup>	877 <sup>a</sup> 740 <sup>a</sup>	1110 <sup>a</sup> 1553 <sup>a</sup>	981 <sup>a</sup> 1042 <sup>a</sup>	-
Benzene	19 <sup>b</sup> 20 <sup>c</sup>	128 <sup>d</sup> 111 <sup>c</sup>	9 <sup>c</sup>	-	110 <sup>c</sup>	139 <sup>e</sup> 94 <sup>d</sup> 99 <sup>c</sup>	-
Benzyl acetate	-	-	-	-	-	230 <sup>f</sup>	124 <sup>g</sup>
Benzyl alcohol	52 <sup>h</sup>	64 <sup>h</sup>	-	56 <sup>h</sup>	53 <sup>h</sup>	63 <sup>h</sup>	12 <sup>g</sup>
1-Butanol	73 <sup>i</sup> 74 <sup>j</sup> 81 <sup>k</sup>	14 <sup>k</sup>	2 <sup>k</sup>	-	-	-	-
iso-Butylbenzene	-	-	-	-	-	7665 <sup>l</sup>	-
<i>tert</i> -Butylbenzene	-	9503 <sup>d</sup>	-	-	-	8224 <sup>l</sup> 1863 <sup>d</sup>	-
<i>tert</i> -Butylcyclohexane	-	4092 <sup>d</sup>	-	-	-	2036 <sup>d</sup>	-
Camphene	598 <sup>a</sup>	4825 <sup>a</sup>	360 <sup>a</sup>	6625 <sup>a</sup>	6057 <sup>a</sup>	3033 <sup>a</sup>	-
n-Butylbenzene	-	-	-	-	-	3410 <sup>l</sup>	-

Table 2. Cont.

Camphor	184 <sup>a</sup>	2058 <sup>a</sup>	1048 <sup>a</sup>	1901 <sup>a</sup>	1194 <sup>a</sup>	1280 <sup>a</sup>	
Carbon tetrachloride	40 <sup>m</sup>	164 <sup>m</sup>	-	215 <sup>m</sup>	238 <sup>m</sup>	218 <sup>m</sup>	-
$\beta$ -Caryophyllene	-	28,674 <sup>a</sup>	4004 <sup>a</sup>	11,488 <sup>a</sup>	14,274 <sup>a</sup>	4960 <sup>a</sup>	-
Chloroform	34 <sup>m</sup>	60 <sup>m</sup>	-	55 <sup>m</sup>	93 <sup>m</sup>	61 <sup>m</sup>	-
Cinnamaldehyde	236 <sup>h</sup>	450 <sup>h</sup>	-	595 <sup>h</sup>	1696 <sup>h</sup>	969 <sup>h</sup>	-
Citronellol	223 <sup>h</sup>	3141 <sup>h</sup>	-	3290 <sup>h</sup>	4048 <sup>h</sup>	3290 <sup>f</sup> 2578 <sup>h</sup>	-
Cyclohexane	164 <sup>c</sup>	468 <sup>c</sup> 341 <sup>d</sup>	<10 <sup>c</sup>	-	474 <sup>c</sup>	363 <sup>c</sup> 227 <sup>d</sup>	-
<i>p</i> -Cymene	140 <sup>a</sup>	2505 <sup>a</sup>	88 <sup>a</sup>	2549 <sup>a</sup>	3543 <sup>a</sup>	2213 <sup>a</sup>	-
Dichloromethane	21 <sup>m</sup>	9 <sup>m</sup>	-	9 <sup>m</sup>	12 <sup>m</sup>	10 <sup>m</sup>	-
Ethylbenzene	131 <sup>c</sup>	392 <sup>d</sup> 289 <sup>c</sup>	125 <sup>c</sup>	-	320 <sup>c</sup>	303 <sup>d</sup> 248 <sup>c</sup>	-
Ethylcyclohexane	2017 <sup>c</sup>	646 <sup>c</sup>	8 <sup>c</sup>	-	738 <sup>c</sup>	630 <sup>c</sup>	-
Eucalyptol	13 <sup>a</sup>	615 <sup>a</sup>	742 <sup>a</sup>	688 <sup>a</sup>	673 <sup>a</sup>	334 <sup>a</sup>	-
Eugenol	94 <sup>h</sup>	264 <sup>h</sup>	-	454 <sup>h</sup>	568 <sup>h</sup>	270 <sup>f</sup> 462 <sup>h</sup>	-
Estragole	478 <sup>a</sup>	939 <sup>a</sup>	-	1661 <sup>a</sup>	1761 <sup>a</sup>	1581 <sup>a</sup>	-
Geraniol	90 <sup>h</sup>	528 <sup>h</sup>	-	977 <sup>h</sup>	1100 <sup>h</sup>	1340 <sup>f</sup> 712 <sup>h</sup>	-
1-Heptanol	1493 <sup>j</sup> 1586 <sup>n</sup> 2460 <sup>k</sup>	985 <sup>k</sup>	37 <sup>k</sup>	-	-	-	-
1-Hexanol	935 <sup>j</sup> 509 <sup>n</sup> 860 <sup>k</sup>	260 <sup>k</sup>	13 <sup>k</sup>	-	-	-	-
Isoeugenol	85 <sup>a</sup>	225 <sup>a</sup>	-	263 <sup>a</sup>	514 <sup>a</sup>	441 <sup>a</sup>	-
<i>cis</i> -Jasmone	-	-	-	-	-	1020 <sup>f</sup>	-
Lilial	4387 <sup>a</sup>	56,567 <sup>a</sup>	-	147,617 <sup>a</sup>	166,338 <sup>a</sup>	112,205 <sup>a</sup>	-
Limonene	1289 <sup>o</sup>	3162 <sup>o</sup>	116 <sup>o</sup> 70 <sup>p</sup>	3668 <sup>o</sup>	4386 <sup>o</sup>	4630 <sup>f</sup> 5630 <sup>q</sup> 2787 <sup>o</sup>	4125 <sup>p</sup>
Linalool	32 <sup>o</sup>	366 <sup>o</sup>	138 <sup>o</sup>	816 <sup>o</sup>	833 <sup>o</sup>	940 <sup>f</sup> 596 <sup>o</sup>	-
Linalyl acetate	-	-	-	-	-	1330 <sup>f</sup>	-
Menthol	82 <sup>a</sup>	1731 <sup>a</sup>	105 <sup>a</sup>	2396 <sup>a</sup>	1928 <sup>a</sup>	1079 <sup>a</sup>	-
Menthone	35 <sup>a</sup>	656 <sup>a</sup>	83 <sup>a</sup>	989 <sup>a</sup>	748 <sup>a</sup>	664 <sup>a</sup>	-
Methylcyclohexane	141 <sup>c</sup>	332 <sup>c</sup> 295 <sup>d</sup>	9 <sup>c</sup>	-	374 <sup>c</sup>	253 <sup>c</sup> 202 <sup>d</sup>	-
Methyl heptine carbonate	2905 <sup>a</sup>	226 <sup>a</sup>	-	539 <sup>a</sup>	485 <sup>a</sup>	325 <sup>a</sup>	-
$\alpha$ -iso-Methylionone	71 <sup>h</sup>	9869 <sup>h</sup>	-	15,632 <sup>h</sup>	13,176 <sup>h</sup>	5750 <sup>f</sup> 9789 <sup>h</sup>	-
Myrcene	212 <sup>o</sup>	1431 <sup>o</sup>	138 <sup>o</sup> 126 <sup>p</sup>	959 <sup>o</sup>	1286 <sup>o</sup>	1290 <sup>f</sup> 1360 <sup>q</sup> 575 <sup>o</sup>	1116 <sup>p</sup>
1-Nonanol	13,400 <sup>k</sup>	4900 <sup>k</sup>	141 <sup>k</sup>	-	-	-	-
<i>cis</i> -Ocimene	42 <sup>a</sup>	432 <sup>a</sup>	20 <sup>a</sup>	622 <sup>a</sup>	593 <sup>a</sup>	538 <sup>a</sup>	-
<i>trans</i> -Ocimene	46 <sup>a</sup>	538 <sup>a</sup>	26 <sup>a</sup>	789 <sup>a</sup>	640 <sup>a</sup>	627 <sup>a</sup>	-

Table 2. Cont.

1-Octanol	2532 <sup>j</sup> 4820 <sup>k</sup>	1910 <sup>k</sup>	67 <sup>k</sup>	-	-	-	-
1-Pentanol	302 <sup>i</sup> 286 <sup>k</sup> 188 <sup>n</sup> 291 <sup>k</sup>	61 <sup>k</sup>	3 <sup>k</sup>	-	-	-	-
2-Pentanol	115 <sup>k</sup>	25 <sup>k</sup>	3 <sup>k</sup>	-	-	-	-
$\alpha$ -Pinene	1778 <sup>o</sup>	2588 <sup>o</sup>	214 <sup>o</sup> 217 <sup>p</sup>	2999 <sup>o</sup>	2395 <sup>o</sup>	5400 <sup>f</sup> 4750 <sup>q</sup> 1637 <sup>o</sup>	1892 <sup>p</sup>
$\beta$ -Pinene	1018 <sup>o</sup>	4587 <sup>o</sup>	633 <sup>o</sup> 404 <sup>p</sup>	5141 <sup>o</sup>	4450 <sup>o</sup>	6650 <sup>f</sup> 7070 <sup>q</sup> 3151 <sup>o</sup>	4904 <sup>p</sup>
Pulegone	30 <sup>a</sup>	332 <sup>a</sup>	82 <sup>a</sup>	1025 <sup>a</sup>	796 <sup>a</sup>	676 <sup>a</sup>	-
Sabinene hydrate	108 <sup>a</sup>	2108 <sup>a</sup>	708 <sup>a</sup>	1308 <sup>a</sup>	1882 <sup>a</sup>	772 <sup>a</sup>	-
Sevoflurane	18 <sup>r</sup>	150 <sup>r</sup>	9 <sup>r</sup>	-	-	163 <sup>r</sup>	-
$\gamma$ -Terpinene	37 <sup>a</sup>	1309 <sup>a</sup>	40 <sup>a</sup>	1950 <sup>a</sup>	2066 <sup>a</sup>	1488 <sup>a</sup>	-
$\alpha$ -Terpineol	126 <sup>a</sup>	1143 <sup>a</sup>	89 <sup>a</sup>	1223 <sup>a</sup>	1287 <sup>a</sup>	761 <sup>a</sup>	-
Thymol	-	-	-	-	-	806 <sup>a</sup>	-
Toluene	36 <sup>b</sup> 38 <sup>s</sup> 29 <sup>c</sup>	142 <sup>s</sup> 158 <sup>d</sup> 172 <sup>c</sup>	33 <sup>c</sup>	-	171 <sup>s</sup> 144 <sup>c</sup>	182 <sup>e</sup> 163 <sup>s</sup> 131 <sup>d</sup> 170 <sup>c</sup>	-
<i>o</i> -Xylene	18 <sup>b</sup> 10 <sup>c</sup>	184 <sup>c</sup>	57 <sup>c</sup>	-	225 <sup>c</sup>	263 <sup>e</sup> 187 <sup>c</sup>	-
<i>m</i> -Xylene	60 <sup>b</sup> 36 <sup>c</sup>	100 <sup>c</sup>	18 <sup>c</sup>	-	216 <sup>c</sup>	222 <sup>e</sup> 167 <sup>c</sup>	-
<i>p</i> -Xylene	124 <sup>b</sup> 132 <sup>c</sup>	218 <sup>c</sup>	32 <sup>c</sup>	-	300 <sup>c</sup>	323 <sup>e</sup> 236 <sup>c</sup>	-

CD: cyclodextrin; CRYSMEB: low methylated- $\beta$ -cyclodextrin; RAMEB: randomly methylated- $\beta$ -cyclodextrin; HP- $\beta$ -CD: 2-hydroxypropyl- $\beta$ -cyclodextrin; SBE- $\beta$ -CD: sulfobutylether- $\beta$ -cyclodextrin. <sup>a</sup> [2], <sup>b</sup> [45], <sup>c</sup> [53], <sup>d</sup> [51], <sup>e</sup> [54], <sup>f</sup> [55], <sup>g</sup> [43], <sup>h</sup> [49], <sup>i</sup> [56], <sup>j</sup> [57], <sup>k</sup> [44], <sup>l</sup> [58], <sup>m</sup> [47], <sup>n</sup> [50], <sup>o</sup> [17], <sup>p</sup> [52], <sup>q</sup> [49], <sup>r</sup> [59], <sup>s</sup> [60].

### 2.2.2. High-Performance Liquid Chromatography

The stability of inclusion complexes is also studied by high-performance liquid chromatography (HPLC). The application of HPLC to evaluate  $K_f$  values requires the modification of the system. Generally the mobile phase is modified with CD [61]. This implies that the adsorption of CD on the stationary phase is very weak and, thus, it does not influence its properties. The guest molecule is injected in the system. It is adsorbed at the surface of the stationary phase and encapsulated by CD in the mobile phase. The obtained inclusion complexes are not adsorbed on the stationary phase. The guest that forms the most stable inclusion complex with CD is firstly eluted from the HPLC column [61,62]. The retention factor (R) of the guest is determined as a function of the CD concentration. Then, the  $K_f$  value is obtained as follows:

$$R = \frac{R_0}{1 + K_f[CD]} \quad (6)$$

where R and  $R_0$  are the retention factor observed in the system with and without the CD, respectively.  $K_f$  is the formation constant of the inclusion complex and [CD] is the concentration of CD in the mobile phase.

The  $K_f$  value of the  $\beta$ -CD/camphor inclusion complex was successfully determined using HPLC and was equal to  $350 \text{ M}^{-1}$  [61].  $K_f$  values for  $\beta$ -CD inclusion complexes with geraniol, (+)-terpineol and (–)-terpineol were also assessed. They were equal to 334, 413 and  $399 \text{ M}^{-1}$ , respectively [62].

### 2.3. Spectroscopic Methods

#### 2.3.1. UV-Visible Spectroscopy

The common approach to determine  $K_f$ , using UV-Visible spectroscopy, is the direct titration method. One component of the complex (generally the CD) is gradually added to a fixed concentration of the other component of the system (the guest). Meanwhile, the variation in the absorbance peak of the guest is monitored. The CD are silent (they do not absorb). This reduces the complexity of the analysis. The obtained experimental results (absorbance values) are then compared and fitted to binding models to calculate the  $K_f$  value. Many researchers still make assumptions based on outdated linear regression methods to determine  $K_f$ . These include Benesi-Hildebrand, Scott and Scatchard plots (Table 3). The assessment of a  $K_f$  value is based on the examination of the slope and intercept of these plots.

**Table 3.** Summary of the equations of linear regression methods.

Method	Equation
Benesi-Hildebrand <sup>a</sup>	$\frac{1}{\Delta_i} = \frac{1}{K_f \times \Delta_{\max} \times [\text{CD}]_i} + \frac{1}{\Delta_{\max}}$
Scott <sup>b</sup>	$\frac{[\text{CD}]_i}{\Delta_i} = \frac{1}{K_f} + [\text{CD}]_i$
Scatchard <sup>c</sup>	$\frac{\Delta_i}{[\text{CD}]_i} = -K_f \times \Delta_i + K_f \times \Delta_{\max}$

<sup>a</sup> [63], <sup>b</sup> [64], <sup>c</sup> [65].  $\Delta_i$  stands for the experimental variation of the guest absorbance upon CD addition.  $\Delta_{\max}$  is the experimental variation of the guest absorbance when it is totally encapsulated.  $[G]$  is the concentration of the guest.  $[\text{CD}]_i$  is the concentration of CD at each titration point.

The Benesi-Hildebrand plot was also used in the literature to calculate  $K_f$  values for several inclusion complexes with volatile guests (Table 4). However, these linear regression approaches frequently involve assumptions. They mainly presume the concentration of CD at equilibrium to be equal to its initial concentration. It is also assumed that the variations in the absorbance are proportional to the complex concentration and that the complex is fully formed (all guest is encapsulated) at the end of titration (high CD concentrations). Thus, typically when performing a direct titration experiment a starting molar ratio of  $[\text{CD}]/[\text{guest}]$  equal to 100 is required to perform accurate evaluation of  $K_f$  [66].

Some  $K_f$  values are much higher or lower than the range of most  $K_f$ . This could be related to the wrong application of linear equations [67], the use of low CD concentrations and thus not respecting the experimental conditions of linear regression approaches [68] or the incautious choice of the correct wavelength leading to diffraction phenomena [69]. Also, the inclusion of the guest in the CD cavity might be associated with a bathochromic or a hypsochromic shift of its maximum absorbance wavelength. Thus, the measurements should occur at a precise and unique wavelength for all the spectra.

These linear transformations are now being less exploited in the profit of the non-linear regression. This approach is readily achieved by the power of computer software equipped with an algorithm. The algorithm postulates a  $K_f$  value and an intrinsic response for the fully complexed species, e.g., absorbance values, and compares them to the experimental results.  $K_f$  and intrinsic response are varied until the best fit is obtained.



**Table 4.** Formation constant ( $K_f$ ,  $M^{-1}$ ) values of CD/volatile guest inclusion complexes determined by UV-Visible spectroscopy.

Guest	Method	$\alpha$ -CD	$\beta$ -CD	$\gamma$ -CD	CRYSMEB	RAMEB	HP- $\beta$ -CD
Acetophenone	BH	140 <sup>a</sup>	188 <sup>a</sup>	-	-	-	-
Allyl isothiocyanate	SD	-	36 <sup>b</sup>	-	-	-	-
<i>trans</i> -Anethole	SD	927 <sup>c</sup>	542 <sup>d</sup>	-	1039 <sup>c</sup>	1815 <sup>c</sup>	845 <sup>d</sup>
Anisole	BH	-	209 <sup>a</sup>	-	-	-	-
Anisyl alcohol	SD	-	107 <sup>e</sup>	-	130 <sup>e</sup>	125 <sup>e</sup>	156 <sup>e</sup>
Benzaldehyde	BH	102 <sup>a</sup>	150 <sup>a</sup>	-	-	-	-
Benzene	BH	29 <sup>a</sup>	194 <sup>a</sup>	-	-	-	-
Benzoic acid	BH	-	120 <sup>f</sup>	-	-	-	-
Benzonitrile	BH	78 <sup>a</sup>	170 <sup>a</sup>	-	-	-	-
Benzyl alcohol	BH	96 <sup>a</sup>	143 <sup>a</sup>	-	-	-	-
	SD	-	63 <sup>e</sup>	-	57 <sup>e</sup>	55 <sup>e</sup>	54 <sup>e</sup>
Benzyl chloride	BH	204 <sup>a</sup>	280 <sup>a</sup>	-	-	-	-
Bromobenzene	BH	540 <sup>a</sup>	322 <sup>a</sup>	-	-	-	-
Camphor	-	3 <sup>g</sup>	19 <sup>g</sup>	-	-	-	-
Carvacrol	SD	454 <sup>h</sup>	2620 <sup>h</sup>	999 <sup>h</sup>	2421 <sup>h</sup>	3564 <sup>h</sup>	2154 <sup>h</sup>
Chlorobenzene	BH	112 <sup>a</sup>	196 <sup>a</sup>	-	-	-	-
Cineole	-	6 <sup>g</sup>	29 <sup>g</sup>	-	-	-	-
Citral	-	8 <sup>g</sup>	31 <sup>g</sup>	-	-	-	-
3,4-Dimethoxy benzaldehyde	BH	98 <sup>i</sup>	157 <sup>i</sup>	-	-	-	-
<i>N,N</i> -Dimethylaniline	BH	172 <sup>a</sup>	252 <sup>a</sup>	-	-	-	-
Estragole	SD	335 <sup>j</sup>	987 <sup>j</sup>	52 <sup>j</sup>	1584 <sup>j</sup>	1916 <sup>j</sup>	1508 <sup>j</sup>
Ethyl benzoate	BH	361 <sup>a</sup>	539 <sup>a</sup>	-	-	-	-
Ethyl phenyl ether	BH	171 <sup>a</sup>	308 <sup>a</sup>	-	-	-	-
<i>N</i> -Ethyl aniline	BH	128 <sup>a</sup>	217 <sup>a</sup>	-	-	-	-
Ethylbenzene	BH	104 <sup>a</sup>	389 <sup>a</sup>	-	-	-	-
Eugenol	BH	$4.95 \times 10^4$ <sup>k</sup>	$3.96 \times 10^5$ <sup>k</sup>	$1.47 \times 10^5$ <sup>k</sup>	-	-	4555 <sup>l</sup>
	-	10,633 <sup>l</sup>	23 <sup>g</sup>	-	-	-	-
	SD	350 <sup>c</sup>	322 <sup>e</sup>	-	401 <sup>e</sup>	521 <sup>e</sup>	445 <sup>e</sup>
Fluorobenzene	BH	39 <sup>a</sup>	91 <sup>a</sup>	-	-	-	-
Furaneol	-	1.1 <sup>g</sup>	7 <sup>g</sup>	-	-	-	-
Geraniol	BH	-	51 <sup>m</sup>	-	-	-	-
	-	9 <sup>g</sup>	44 <sup>g</sup>	-	-	-	-
4-Hydroxy-3,5-dimethoxy benzaldehyde	BH	269 <sup>i</sup>	372 <sup>i</sup>	-	-	-	-
<i>p</i> -Hydroxybenzaldehyde	BH	-	72 <sup>n</sup>	-	-	-	-
Iodobenzene	BH	1200 <sup>a</sup>	846 <sup>a</sup>	-	-	-	-
Isoeugenol	SD	178 <sup>c</sup>	304 <sup>e</sup>	-	240 <sup>e</sup>	547 <sup>e</sup>	452 <sup>e</sup>
Limonene	-	14 <sup>g</sup>	55 <sup>g</sup>	-	-	-	-
Menthol	-	10 <sup>g</sup>	35 <sup>g</sup>	-	-	-	-
<i>N</i> -Methylaniline	BH	83 <sup>a</sup>	131 <sup>a</sup>	-	-	-	-
Methyl benzoate	BH	213 <sup>a</sup>	317 <sup>a</sup>	-	-	-	-
Methyl cinnamate	-	4 <sup>g</sup>	20 <sup>g</sup>	-	-	-	-
Nerol	BH	-	26 <sup>m</sup>	-	-	-	-
Nerolidol	SD	-	-	-	-	-	8168 <sup>o</sup>

Table 4. Cont.

Nitrobenzene	BH	89 <sup>a</sup>	279 <sup>a</sup>	-	-	-	-
Nootkatone	-	7 <sup>g</sup>	32 <sup>g</sup>	-	-	-	-
N-Phenylacetamide	BH	103 <sup>a</sup>	157 <sup>a</sup>	-	-	-	-
Phenol	BH	40 <sup>a</sup>	95 <sup>a</sup>	-	-	-	-
Phenylacetylene	BH	86 <sup>a</sup>	230 <sup>a</sup>	-	-	-	-
Phenylamine	BH	15 <sup>a</sup>	86 <sup>a</sup>	-	-	-	-
Sabinene hydrate	SD	108 <sup>P</sup>	2108 <sup>P</sup>	708 <sup>P</sup>	1308 <sup>P</sup>	1882 <sup>P</sup>	772 <sup>P</sup>
$\alpha$ -Terpineol	SD	126 <sup>P</sup>	1143 <sup>P</sup>	89 <sup>P</sup>	1223 <sup>P</sup>	1287 <sup>P</sup>	761 <sup>P</sup>
Thymol	SD	107 <sup>h</sup>	1467 <sup>h</sup>	233 <sup>h</sup>	2386 <sup>h</sup>	3337 <sup>h</sup>	488 <sup>h</sup>
Toluene	BH	36 <sup>a</sup>	214 <sup>a</sup>	-	-	-	-
<i>o</i> -Vanillin	BH	105 <sup>i</sup>	250 <sup>i</sup>	-	-	-	-
Vanillin	BH	163 <sup>i</sup>	100 <sup>n</sup>	-	-	-	-
	-	1.6 <sup>g</sup>	296 <sup>i</sup>	-	-	-	-
<i>p</i> -Vinyl guaiacol	-	2 <sup>g</sup>	17 <sup>g</sup>	-	-	-	-

CD: cyclodextrin; CRYSMEB: low methylated- $\beta$ -cyclodextrin; RAMEB: randomly methylated- $\beta$ -cyclodextrin; HP- $\beta$ -CD: 2-hydroxypropyl- $\beta$ -cyclodextrin; SBE- $\beta$ -CD: sulfobutylether- $\beta$ -cyclodextrin; BH: Benesi-Hildebrand; SD; spectral displacement. <sup>a</sup> [73], <sup>b</sup> [74], <sup>c</sup> [75], <sup>d</sup> [20], <sup>e</sup> [13], <sup>f</sup> [76], <sup>g</sup> [67], <sup>h</sup> [77], <sup>i</sup> [78], <sup>j</sup> [52], <sup>k</sup> [69], <sup>l</sup> [68], <sup>m</sup> [79], <sup>n</sup> [14], <sup>o</sup> [80], <sup>p</sup> [81].

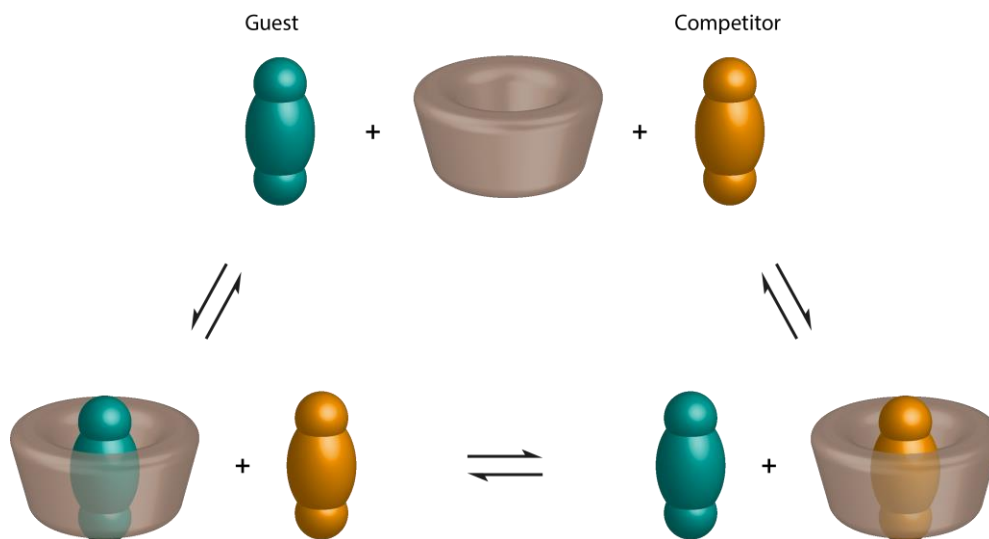
Moreover, a distinguished analytical improvement of the determination of  $K_f$  values was established by Landy et al. [48]. Authors have used the derivatives of the spectra instead of the absorption curves to calculate the  $K_f$  value. This avoids the difficulties related to experimental errors, to small spectral variations and to the optical presence of CD. CD could, occasionally, result in very weak values of absorbance.

The development of these algorithmic treatments solved the problems related to making assumptions. However, it cannot beat the experimental pitfalls for the application of titration experiments for CD/volatile guest inclusion complexes; (a) the loss of the volatile compound by evaporation while collecting a large number of experimental points; the constancy of the guest concentration is an essential point when measuring the variations in the absorbance, (b) the potential influences of impurities, (c) the very poor chromophore of volatile compounds and (d) the very poor solubility of the volatile guests, though the concentration chosen must lie within the region where the absorption peak is within the limits of the Beer–Lambert Law.

Thus, alternative methodologies that can yield more reliable results were developed. Many studies focused on the determination of  $K_f$  values for CD/guest inclusion complexes by competition with dyes [70]. The competition is monitored by UV-Visible spectroscopy. This method is also called the spectral displacement method. It is not restricted to be applied with a precise dye or CD. Though, the competitive system should be optimized before application. Mainly, the stability ( $K_f$  value) of the CD/competitor (via a direct titration) should be evaluated. Moreover, to obtain accurate measurements, the selected indicator dye should possess an equal, or higher,  $K_f$  with CD than that the competing guest [71,72]. The most used dyes, employed as competitors, are the phenolphthalein and the methyl orange. CD reduce the purple phenolphthalein and orange methyl orange solutions upon encapsulation. The addition of the colorless competing guest leads to the restoration of the color by expelling the dye from the CD cavity (Figure 3).

The data collected from the differences between the absorbance values allow the evaluation of  $K_f$ , using an algorithmic treatment. The spectral displacement approach seems to be the method of choice for volatile hydrophobic guests that could not be studied by direct method; (a) the concentration of the guest may be lower than with the titration method, (b) it may be applied to chromophore-less guests, and (c) it reduces the loss by volatilization, since the guest is directly added to the competition

system containing the CD, which allows its solubilization and its retention in solution due to its inclusion in the cavity. Therefore, this method has been further applied for CD/volatile guest inclusion complexes. Table 4 summarizes the  $K_f$  values determined by UV-Visible spectroscopy and collected from the literature.



**Figure 3.** Schematic representation of the spectral displacement method.

### 2.3.2. Fluorescence Spectroscopy

Fluorescence spectroscopy is a useful technique for studying the formation of CD inclusion complexes with fluorescent guests in solution. Due to its high sensitivity, fluorescence spectroscopy allows working with very low guest concentrations [11,82,83]. The CD-induced fluorescence variation allows monitoring encapsulation and quantification of binding strength ( $K_f$  value) with the fluorescent guest [82].

Generally, titration experiments are carried out. The object is to follow the variation (commonly enhancement) in the fluorescence intensity of the guest as a function of the CD concentration. As in the case of the UV-Visible spectroscopy, the next point is to set an equation that relates the measured fluorescence signal to the total concentration of the CD and the guest. Also, the equations are mostly simplified or transformed to linear equations: Benesi-Hildebrand, Scott or Scatchard.

In addition, any treatment should be only applied at very low absorbance values where the values of the fluorescence intensity vary linearly with the binding magnitude.

The first observation of fluorescence enhancement of volatile guests upon inclusion in CD was reported by Hoshino et al. 1981 [84]. Authors have calculated  $K_f$  values for  $\beta$ -CD inclusion complexes with benzene, phenol, ethoxybenzene, aniline, *N*-methylaniline, *N,N*-dimethyl-aniline, and *N,N*-diethylaniline (Table 5). Application of fluorimetric studies has been extended to a wide variety of CD/volatile inclusion complexes. The results are listed in Table 5.

Fluorescence spectroscopy could be considered as a suitable alternative to UV-Visible spectroscopy due to its lower detection limit. Moreover, the fluorescence intensity enhancement upon CD encapsulation results in lowering the limits of detection of poorly fluorescent guests [86,87].

Although fluorescence spectroscopy is fast and very sensitive, the preparation of samples is tricky because a strict cautious is required to avoid any interferences [11,83].

Still, most technologically interesting CD/guest inclusion complexes are themselves non-fluorescent. Thus, competitive methods are being developed to enlarge the application of fluorescence spectroscopy, mainly for fluorophore-free guests. CD are able to enhance the fluorescence of 8-anilino-naphthalene-1-sulfonic acid (ANS) and 2-p-toluidinylnaphthalene-6-sulfonate (TNS) upon encapsulation due to the variation of the polarity of the environment of these dyes [88,89]. The addition

of a competitive guest to CD/ANS or CD/TNS solutions results in a decrease in the fluorescence as the fluorophore is moved out of the cavity [90]. This variation in the fluorescence intensity allows the determination of the  $K_f$  value of CD/fluorophore-free guest inclusion complex.

**Table 5.** Formation constant ( $K_f$ ,  $M^{-1}$ ) values for cyclodextrin/volatile guest inclusion complexes determined by fluorescence spectroscopy.

Guest	Method	$\alpha$ -CD	$\beta$ -CD	HP- $\beta$ -CD
Aniline	SC	-	50 <sup>a</sup>	-
Benzene	SC	-	196 <sup>a</sup>	-
Cinnamaldehyde	BH	-	-	928 <sup>b</sup>
3,4-Dimethoxybenzaldehyde	BH	124 <sup>c</sup>	343 <sup>c</sup>	-
<i>N,N</i> -Diethylaniline	SC	-	862 <sup>a</sup>	-
<i>N,N</i> -Dimethylaniline	SC	-	217 <sup>a</sup>	-
Ethoxybenzene	SC	-	286 <sup>a</sup>	-
Eucalyptol	BH	-	-	1200 <sup>d</sup>
	SC	-	-	1112 <sup>d</sup>
Eugenol	BH	-	357 <sup>e</sup>	420 <sup>e</sup>
	SC	-	-	-
Geraniol	BH	-	-	1320 <sup>d</sup>
	SC	-	-	1064 <sup>d</sup>
4-Hydroxy-3,5-dimethoxy benzaldehyde	BH	373 <sup>c</sup>	493 <sup>c</sup>	-
Limonene	BH	-	-	1667 <sup>d</sup>
	SC	-	-	1700 <sup>d</sup>
Linalool	BH	-	-	1500 <sup>d</sup>
	SC	-	-	1260 <sup>d</sup>
<i>N</i> -Methylaniline	SC	-	53 <sup>a</sup>	-
Phenol	SC	-	40 <sup>a</sup>	-
	BH	-	-	2000 <sup>d</sup>
$\alpha$ -Pinene	SC	-	-	1842 <sup>d</sup>
	BH	-	-	1667 <sup>d</sup>
$\beta$ -Pinene	SC	-	-	1671 <sup>d</sup>
	BH	-	-	867 <sup>d</sup>
Pulegone	SC	-	-	798 <sup>d</sup>
	BH	-	-	1400 <sup>d</sup>
Thymol	SC	-	-	1313 <sup>d</sup>
	BH	295 <sup>c</sup>	384 <sup>c</sup>	-
<i>o</i> -Vanillin	BH	183 <sup>c</sup>	320 <sup>c</sup>	-

CD: cyclodextrin; HP- $\beta$ -CD: 2-hydroxypropyl- $\beta$ -cyclodextrin; BH: Benesi-Hildebrand; SC: Scatchard.  
<sup>a</sup> [84], <sup>b</sup> [15], <sup>c</sup> [77], <sup>d</sup> [19], <sup>e</sup> [85].

Finally, one must be careful in interpreting and comparing  $K_f$  values determined using various techniques, especially those evaluated by fluorescence spectroscopy. When applying fluorescence technique, new species, excited state guest, are involved. The latter can bind to CD in a different strength due to the modification of the electrostatic interactions in the complex. This could result in incoherent  $K_f$  values as compared to other techniques [91].

### 2.3.3. Nuclear Magnetic Resonance

Nuclear magnetic resonance (NMR) spectroscopy is a powerful tool and is becoming a routine method for the characterisation of CD inclusion complexes. It is mainly employed for the elucidation of the geometric accommodation of the guest inside the CD cavity but also for the determination of the  $K_f$  value [92]. NMR provides a direct evidence on the inclusion of the guest in the CD. This is based on the fact that, if the guest is encapsulated, then the physical or chemical environment of the guest and cavity hydrogens (H3 and H5 of the CD) will be affected leading to a modification of the NMR spectra [93].

The NMR shift titrations are one of the most used methods to evaluate the  $K_f$  value. They are based on the measurements of the chemical shift ( $\delta$ ) changes upon varying concentrations of the CD and/or the guest. Interestingly, the concentration of the species responsible for the signal has to remain strictly constant [48]. Landy et al. have calculated the  $K_f$  values for the inclusion complexes of  $\beta$ -CD and four phenol derivatives, using an algorithmic treatment applied to the chemical shifts variations of the inner hydrogens of  $\beta$ -CD [48]. The  $K_f$  values of the inclusion complexes of benzoic acid [94] and fenchone [95] with native CD or derivatives were studied using  $^1\text{H}$  NMR. The dependences of chemical shift variation of the guests' protons versus CD concentration were used for the  $K_f$  calculation. Also, DOSY titrations were performed and resulted in a  $K_f$  value equal to  $9.8 \text{ M}^{-1}$  for  $\beta$ -CD/vanillin inclusion complex [96]. The DOSY titrations relies on the observation of the variation in the diffusion coefficients (D) of the guest's protons. The obtained  $K_f$  values for inclusion complexes studied with NMR spectroscopy are listed in Table 6.

**Table 6.** Formation constant ( $K_f$ ,  $\text{M}^{-1}$ ) values of cyclodextrin/volatile guest inclusion complexes determined by NMR spectroscopy.

Guest	Observed Signal	$\alpha$ -CD	$\beta$ -CD	$\gamma$ -CD	HP- $\alpha$ -CD	HP- $\beta$ -CD	HP- $\gamma$ -CD
Benzoic acid	$\delta$	842 <sup>a</sup>	306 <sup>a</sup>	-	731 <sup>a</sup>	447 <sup>a</sup>	551 <sup>a</sup>
Carvacrol	$\delta + D$	-	1736 <sup>b</sup>	-	-	-	-
<i>m</i> -Cresol	$\delta$	48 <sup>c</sup>	125 <sup>c</sup>	97 <sup>c</sup>	-	130 <sup>c</sup>	-
(+)-Fenchone	$\delta$	-	550 <sup>d</sup>	-	-	-	-
(-)-Fenchone	$\delta$	-	523 <sup>d</sup>	-	-	-	-
Nootkatone	$\delta + D$	-	5750 <sup>e</sup>	-	-	-	-
Phenol	$\delta$	19 <sup>c</sup>	60 <sup>c</sup>	3 <sup>c</sup>	-	-	-
Thymol	$\delta + D$	-	1344 <sup>b</sup>	-	-	-	-
Vanillin	D	-	9.8 <sup>f</sup>	-	-	-	-

CD: cyclodextrin; HP- $\alpha$ -CD: 2-hydroxypropyl- $\alpha$ -cyclodextrin; HP- $\beta$ -CD: 2-hydroxypropyl- $\beta$ -cyclodextrin; HP- $\gamma$ -CD: 2-hydroxypropyl- $\gamma$ -cyclodextrin;  $\delta$ : chemical shift; D: diffusion coefficient. <sup>a</sup> [94], <sup>b</sup> [77], <sup>c</sup> [97], <sup>d</sup> [95], <sup>e</sup> [14], <sup>f</sup> [96].

Lately, a new NMR method has been developed and validated. It consists on an algorithmic treatment and a global analysis to determine the  $K_f$  value [77]. This analysis explores, at the same time, the variation of several signals of the guest's protons e.g., the chemical shifts ( $\delta$ ) and the diffusion coefficients (D) [14,77]. Furthermore, it combines simultaneously the responses of numerous protons of the guest. Authors, have applied this method successfully for the inclusion complexes with different aromas: carvacrol, thymol and nootkatone (Table 6).

One of the most important advantages of the NMR titrations is that the detected variations reveal at the same time the conformation of the obtained inclusion complex, which is impossible to extract from other spectroscopic, chromatographic or calorimetric methods [92]. However, the NMR spectroscopy experiences also some drawbacks. The  $K_f$  values obtained in the deuterated solvents e.g.,  $\text{D}_2\text{O}$  are slightly different than in water. Also, deuterated solvents are generally provided in small amount, leading to errors in the concentration calculations when compared to water [48].

#### 2.4. Isothermal Titration Calorimetry

Isothermal Titration Calorimetry (ITC) is the only technique which gives access to both  $K_f$  values and additional thermodynamic data, in a simultaneous way [98]. Indeed, the injection of one of the CD/guest partners on the other induces a heat release (or more rarely, a heat consumption) which is directly proportional to both inclusion stability and enthalpy ( $\Delta H$ ). As a result, recording the time dependence of the differential power applied to the measuring cell leads to a thermogram, from which a binding isotherm can be extracted. This isotherm corresponds to the heat as a function of species concentrations, generally expressed as a molar ratio. A full algorithmic treatment can then be employed to minimize the difference between experimental and theoretical isotherms, affording the most probable values of  $K_f$  and  $\Delta H$ , according to the postulated binding model. It is then straightforward to derive binding free enthalpy ( $\Delta G$ ) and entropy ( $\Delta S$ ). Within this scope, it is noteworthy to mention that thermodynamic data derived from linear van't Hoff plots ( $\ln K_f$  versus  $1/T$ ) are generally biased [99], since heat capacity variations of CD complexes are usually different from zero, thus leading to a temperature dependence of both inclusion enthalpy and entropy. In this respect, calorimetric approaches should be considered as the only tool able to afford a reliable thermodynamic picture of inclusion complexes. Finally, non-conventional ITC experiments might be used when classical titrations failed to afford accurate results [100].

$K_f$  values, inclusion enthalpy and entropy obtained for the complexes formed between volatile guests and native  $\alpha$ -CD or  $\beta$ -CD are summarized in Table 7. If most complexes correspond to 1:1 stoichiometry, linear chains with more than 7 carbons or bulky molecules like camphor can also involve 2:1 inclusion complexes, especially with  $\alpha$ -CD [101,102].

If a wide range of enthalpy and entropy variation is observed, the mean values of  $\Delta H$  and  $-\Delta S$  are respectively equal to  $-19.1$  and  $4.4$  kJ/mol for  $\alpha$ -CD, and to  $-9.1$  and  $-8.3$  kJ/mol for  $\beta$ -CD. Accordingly, on an averaged point of view, while enthalpy and entropy positively and equally contribute to  $\beta$ -CD complexation, inclusion within  $\alpha$ -CD is essentially enthalpy driven, entropy being weakly disfavorable. Such results could be anticipated from the respective size of  $\alpha$ -CD and  $\beta$ -CD: the narrower  $\alpha$ -CD should lead to more constrained inclusion structures, which imply stronger interactions between CD and guest but also less freedom between the two partners. Within this scope, if no enthalpy/entropy compensation can be established for all guests included in Table 7, such trend clearly appears for guests with homogeneous structures, as pointed out by [103,104]. For instance, the complexation occurring between  $\alpha$ -CD and linear alkanols is characterized by a strong correlation between the  $\Delta H$  and  $-\Delta S$  components ( $R^2$  equal to 0.84, if the values of Fujisawa, which are unusually high, are excluded), thus reasserting the opposite character of interaction and freedom upon inclusion.

**Table 7.** Formation constants ( $K_f$ ,  $M^{-1}$ ), inclusion enthalpy ( $\Delta H$ , kJ/mol) and entropy ( $-\Delta S$ , kJ/mol). obtained for the complexes formed between volatiles and native  $\alpha$ -CD or  $\beta$ -CD determined by calorimetry.

Guest	$\alpha$ -CD			$\beta$ -CD		
	$K_f$	$\Delta H$	$-\Delta S$	$K_f$	$\Delta H$	$-\Delta S$
Benzene	-	-	-	107 <sup>a</sup>	-3.5	-8.1
(-)-Borneol	-	-	-	19,750 <sup>b</sup>	-23.2	-1.3
(+)-Borneol	-	-	-	18,640 <sup>b</sup>	-20.9	-3.5
4-Bromophenol	708 <sup>c</sup>	-25.6	9.2	851 <sup>c</sup>	-12.2	-4.5
1-Butanol	83 <sup>d</sup>	-10.7	-0.2	-	-	-
	100 <sup>e</sup>	-9.9	-1.5	-	-	-
	80 <sup>f</sup>	-10.9	0.1	-	-	-
	9153 <sup>g</sup>	-7.9	-14.7	1430 <sup>g</sup>	3.0	-21.0

Table 7. Cont.

4-Chlorophenol	295 <sup>c</sup>	−20.1	6	407 <sup>c</sup>	−11.9	−3.0
Cyclobutanol	63 <sup>e</sup>	−5.5	−4.8	-	-	-
	30 <sup>i</sup>	−11.5	3	14 <sup>i</sup>	3.7	−10.2
	-	-	-	2344 <sup>b</sup>	−11.6	−7.6
Cycloheptanol	25 <sup>e</sup>	−32	24	-	-	-
	-	-	-	2200 <sup>f</sup>	−12.4	−6.7
	68 <sup>i</sup>	−12.5	2	2197 <sup>i</sup>	−12.4	−6.7
Cyclohexanol	-	-	-	707 <sup>b</sup>	−6.1	−10.2
	-	-	-	701 <sup>f</sup>	−6.3	−9.9
	62 <sup>j</sup>	−12.8	2.7	776 <sup>j</sup>	−6.6	−9.8
Cyclooctanol	-	-	-	4425 <sup>b</sup>	−15.7	−5.1
	28 <sup>e</sup>	−40	32	-	-	-
	235 <sup>i</sup>	−3.9	−9.5	4405 <sup>i</sup>	−16.4	−4.4
Cyclopentanol	-	-	-	168 <sup>b</sup>	−3.9	−8.8
	-	-	-	175 <sup>f</sup>	−4.6	−8.2
	83 <sup>e</sup>	−8.8	−2.1	-	-	-
	36 <sup>i</sup>	−11.5	2.6	172 <sup>i</sup>	−4.6	−8.2
Ethanol	7 <sup>e</sup>	−2.5	−2.2	-	-	-
	7184 <sup>g</sup>	−0.9	−21.0	1319 <sup>g</sup>	1.1	−18.9
1-Heptanol	1168 <sup>d</sup>	−22.8	5.3	-	-	-
	377 <sup>e</sup>	−20.6	5.9	-	-	-
	24,113 <sup>g</sup>	−34.6	9.6	17,459 <sup>g</sup>	−7.9	−16.3
	1503 <sup>k</sup>	−28.6	10.4	-	-	-
1-Hexanol	705 <sup>d</sup>	−18.2	1.9	-	-	-
	523 <sup>e</sup>	−13.9	−1.6	-	-	-
	840 <sup>f</sup>	−17.5	0.8	-	-	-
	7788 <sup>g</sup>	−29.1	6.9	5871 <sup>g</sup>	0.6	−22.1
	906 <sup>k</sup>	−21.3	4.5	-	-	-
4-Iodophenol	881 <sup>l</sup>	−26.3	9.5	955 <sup>l</sup>	−16.1	−0.9
Methanol	0 <sup>g</sup>	-	-	0 <sup>g</sup>	-	-
4-Methylphenol	37 <sup>c</sup>	−17.7	8.6	251 <sup>c</sup>	−12.5	−1.2
4-Nitrophenol	104 <sup>l</sup>	−23	11.5	296 <sup>l</sup>	−10.2	−3.9
	219 <sup>c</sup>	−25.8	12.5	347 <sup>c</sup>	−12.0	−2.4
1-Nonanol	480 <sup>e</sup>	−36.2	20.9	-	-	-
Nootkatone	-	-	-	5801 <sup>m</sup>	−14.4	−7.1
1-Octanol	220 <sup>e</sup>	−22.0	9.0	-	-	-
	246 <sup>d</sup>	−14.9	1.3	-	-	-
	287 <sup>f</sup>	−14.7	0.7	-	-	-
	275 <sup>e</sup>	−11.8	−2.1	-	-	-
	18,927 <sup>g</sup>	−13.9	−10.4	9153 <sup>g</sup>	2.2	−24.8
1-Pentanol	428 <sup>k</sup>	−13.8	−1.2	-	-	-
	37 <sup>c</sup>	−10.2	0.6	93 <sup>c</sup>	−12.2	1.2
	23 <sup>d</sup>	−6.8	−1.0	-	-	-
	27 <sup>e</sup>	−6.1	−2.1	-	-	-
	1319 <sup>g</sup>	−6.6	−11.2	1168 <sup>g</sup>	1.9	−19.4

<sup>a</sup> [105], <sup>b</sup> [106], <sup>c</sup> [107], <sup>d</sup> [101], <sup>e</sup> [108], <sup>f</sup> [109], <sup>g</sup> [110], <sup>h</sup> [102], <sup>i</sup> [103], <sup>j</sup> [111], <sup>k</sup> [112], <sup>l</sup> [113], <sup>m</sup> [14].

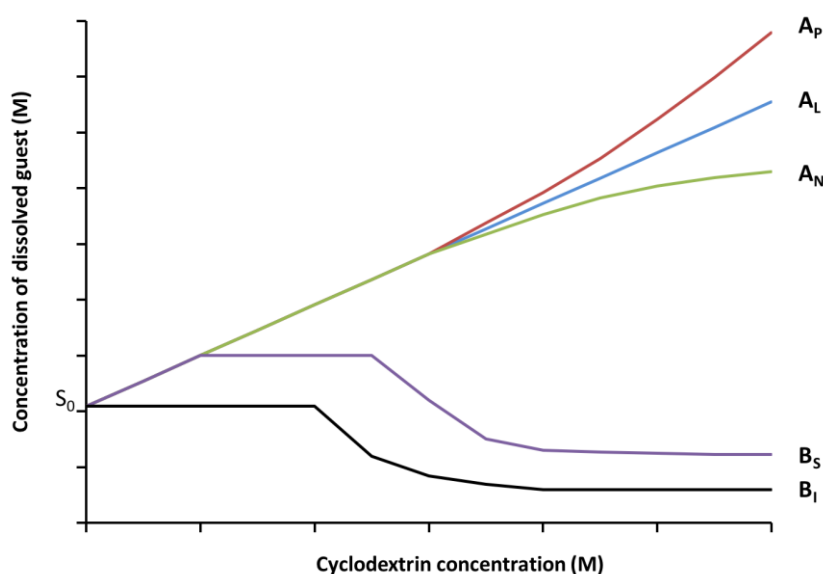
In addition, the negative  $\Delta H$  values recorded for most complexes may constitute a valuable proof of the prominent influence of direct interactions (van der Waals, hydrogen bonds) on the complex

stability. The fact that entropy may also favor the inclusion process demonstrates that hydrophobic forces also represent a part of the inclusion stabilization.

Many articles [101,102,105] demonstrated that inclusion complexes are characterized by significant negative heat capacity variations ( $\Delta C_p$ ), which substantiates the strong influence of solvophobic effects. The observed increase in affinity and in favorable entropy when moving from H<sub>2</sub>O to D<sub>2</sub>O also pleads in favor of the solvent organization as a driving force for inclusion [102,104]. Finally, analogous conclusions can be drawn from the salt effect [108,114].

### 2.5. Phase Solubility Studies

Solubility measurements are performed according to the method developed by Higuchi and Connors, 1965 [115]. Excess amounts of guest are added to aqueous solutions containing various concentrations of CD and agitated until equilibrium. Thereafter, the solutions are filtered and the amount of the solubilized guest could be determined using various analytical methods (HPLC, UV-Visible, SH-GC, etc.). Phase solubility diagrams (Figure 4) are obtained by plotting the solubility of the guest as a function of the CD concentration.



**Figure 4.** Phase solubility profiles and classification of inclusion complexes according to Higuchi and Connors [115].

The  $K_f$  values could be obtained from the linear part of the phase solubility diagram.

$$K_f = \frac{\text{slope}}{S_0(1 - \text{slope})} \quad (7)$$

where  $S_0$  is the solubility of the guest in the absence of CD, slope is the slope of the phase solubility diagram.

This method is widely used for the determination of the  $K_f$  of CD/guest inclusion complexes. In the case of volatile guests, it was mainly applied to fragrance materials and in a lesser extend to anesthetics and organic volatile compounds. Table 8 gathers some  $K_f$  values obtained with HP- $\beta$ -CD for different guests and using different analytical methods.



**Table 8.** Formation constant ( $K_f$ ,  $M^{-1}$ ) values of HP- $\beta$ -CD/volatile guest inclusion complexes determined by phase solubility studies using various techniques.

Guest	HPLC	SH-GC	UV-Visible	Sodium Thiosulfate Titration
<i>trans</i> -Anethole	-	-	1510 <sup>a</sup>	-
Benzene	-	-	121 <sup>b</sup>	-
Benzyl acetate	306 <sup>c</sup> 275 <sup>d</sup>	-	-	-
Carvacrol	-	-	2123 <sup>e</sup>	-
Citral	1560 <sup>c</sup>	-	-	-
Citronellol	3740 <sup>c</sup>	-	-	-
Estragole	-	-	1412 <sup>a</sup>	-
Ethylbenzene	-	-	435 <sup>b</sup>	-
Eugenol	-	-	445 <sup>a</sup>	-
Iodine	-	-	-	38 <sup>f</sup>
Isoeugenol	-	-	449 <sup>a</sup>	-
(+)-Limonene	3350 <sup>c</sup>	4730 <sup>g</sup>	-	-
Linalool	1610 <sup>c</sup> 720 <sup>d</sup>	940 <sup>g</sup>	-	-
Linalyl acetate	137 <sup>c</sup>	-	-	-
$\alpha$ -iso-Methylionone	29,500 <sup>c</sup>	-	-	-
Myrcene	-	1240 <sup>g</sup>	-	-
Nootkatone	-	-	3700 <sup>h</sup>	-
(-)- $\alpha$ -Pinene	-	5780 <sup>g</sup>	-	-
(-)- $\beta$ -Pinene	-	7360 <sup>g</sup>	-	-
Propofol	-	-	3972 <sup>i</sup>	-
Thymol	-	-	1282 <sup>e</sup>	-
Toluene	-	-	287 <sup>b</sup>	-
<i>o</i> -Xylene	-	-	305 <sup>b</sup>	-
<i>m</i> -Xylene	-	-	210 <sup>b</sup>	-
<i>p</i> -Xylene	-	-	353 <sup>b</sup>	-

<sup>a</sup> [75], <sup>b</sup> [116], <sup>c</sup> [117], <sup>d</sup> [118], <sup>e</sup> [77], <sup>f</sup> [119], <sup>g</sup> [21], <sup>h</sup> [14], <sup>i</sup> [120].

The fact that the presence of CD has an impact on the physicochemical properties of the guest (e.g., absorption, volatility) results in the necessity to dilute the solutions obtained after filtration to cancel this effect and determine the accurate guest concentration. This dilution is often omitted in the phase solubility studies or conducted using an inappropriate solvent leading to wrong  $K_f$  determination.

## 2.6. Total Organic Carbon

Total organic carbon (TOC) is mainly used in monitoring water quality or cleanliness of pharmaceutical manufacturing equipment [121]. Recently, a new TOC method was developed and applied for studying CD inclusion complexes [36]. Authors have performed TOC measurements to determine the amount of solubilized guest in the filtrates of phase solubility studies. No significant differences were observed for  $K_f$  values obtained for HP- $\beta$ -CD/eugenol inclusion complex using UV-Visible spectroscopy ( $416 M^{-1}$ ) [75] and TOC measurements ( $481 M^{-1}$ ) [36]. Authors have also conducted successfully phase solubility studies for eleven essential oils.

The TOC method is interesting for volatiles that generally do not possess a chromophore or a fluorophore moiety because it is non-specific. This technique can be also applied to any molecule that cannot be studied by conventional techniques, making it a universal method for any compound or mixture of compounds. However, this cannot lead to the determination of  $K_f$  values in the case of mixtures.

## 2.7. Comparison of Formation Constants Obtained with Different Methods

Some of the volatile guests were studied with various methods. Table 9 gathered some of the  $K_f$  values obtained for their inclusion complexes using various techniques. As can be seen, for some of the guests (e.g., benzene and toluene) there is a good correlation between the data even though values were obtained with a gap of 20 years. However, for eugenol, we can notice a  $10^4$  factor between

values obtained with UV-Visible spectroscopy. If we compare values obtained with different methods we can conclude that the  $K_f$  value for  $\beta$ -CD/eugenol inclusion complex is in the order of  $10^2 \text{ M}^{-1}$ . This order of magnitude is in good agreement with values for other aromatic derivatives. Therefore, there is a need to determine  $K_f$  values with accurate analytical protocols in order to obtain reliable results. Moreover, the order of magnitude of some well-known structure (aromatic ring, adamantane derivatives, cyclic compounds) should be a reference for authors.

**Table 9.** Example of formation constant ( $K_f$ ,  $\text{M}^{-1}$ ) values obtained with different methods for some selected guest.

Guest	SH-GC	UV-Visible	Fluorescence	HPLC	ITC	NMR	Phase Solubility
<i>trans</i> -Anethole	630 <sup>a</sup>	542 <sup>b</sup>	-	-	-	-	537 <sup>c</sup>
	1040 <sup>a</sup>						
	497 <sup>a</sup>						
Benzene	128 <sup>d</sup>	194 <sup>f</sup>	196 <sup>g</sup>	-	107 <sup>h</sup>	-	-
	111 <sup>e</sup>						
Camphor	2058 <sup>a</sup>	19 <sup>i</sup>	-	350 <sup>j</sup>	-	-	-
Eugenol	264 <sup>k</sup>	$3.96 \times 10^{51}$	357 <sup>n</sup>	-	-	-	513 <sup>c</sup>
		23 <sup>l</sup>					
		322 <sup>m</sup>					
Limonene	3162 <sup>a</sup>	55 <sup>i</sup>	-	-	-	-	-
	2230 <sup>a</sup>						
Phenol	-	95 <sup>f</sup>	40 <sup>g</sup>	-	93 <sup>o</sup>	120 <sup>p</sup>	-
Thymol	-	1467 <sup>q</sup>	1400 <sup>r</sup>	-	-	1344 <sup>q</sup>	1150 <sup>q</sup>
Toluene	142 <sup>s</sup>	214 <sup>f</sup>	-	-	-	-	-
	158 <sup>d</sup>						
	172 <sup>e</sup>						
Vanillin	-	100 <sup>t</sup>	384 <sup>u</sup>	-	-	9.8 <sup>v</sup>	-
		296 <sup>u</sup>					
		17 <sup>i</sup>					

<sup>a</sup> [2], <sup>b</sup> [20], <sup>c</sup> [75], <sup>d</sup> [51], <sup>e</sup> [53], <sup>f</sup> [73], <sup>g</sup> [84], <sup>h</sup> [105], <sup>i</sup> [67], <sup>j</sup> [61], <sup>k</sup> [49], <sup>l</sup> [69], <sup>m</sup> [13], <sup>n</sup> [85], <sup>o</sup> [107], <sup>p</sup> [48], <sup>q</sup> [77], <sup>r</sup> [19], <sup>s</sup> [60], <sup>t</sup> [14], <sup>u</sup> [78], <sup>v</sup> [96].

Concerning the various analytical methods used for the determination of  $K_f$  values of volatile guests, SH-GC seems to be the method of choice, because it analyses directly the signal of the guest without any interference of the CD signal.

### 3. Conclusions

CD are one of the most appropriate encapsulation materials for volatile guests. The great interest and the advantages of the use of CD inclusion complexes have been widely discussed and documented in the literature. The analytical characterization of the inclusion complex is crucial to best exploit the potential offered by CDs to the encapsulated volatile guests. A careful determination of the  $K_f$  value of a CD inclusion complex represents the basic fundamental step. This allows the extraction of valuable information concerning CD/guest interactions and strength of binding. However, for some compounds the literature data show very different results. These errors are mainly related to the misuse of the analytical methods and the non-respect of analytical conditions. Therefore, the determination of  $K_f$  values with different methods or the comparison of the literature data could give a good estimation of the order of magnitude of these  $K_f$  values.

Spectroscopic, chromatographic and calorimetric techniques have played and still play an important role for this purpose. Titration experiments are usually carried out using linear methods and this apparently simple method seems to be the main source of error. Therefore, one has to be careful when determining  $K_f$  value because this step is more complex than it seems to be.

This review presented an overview of the analytical techniques and methods applied for the determination of  $K_f$  values for CD/volatile guest inclusion complexes. It has focused on the advantages, pitfalls and obtained results of each. It also emphasized the search for improving these available methods and developing new techniques in order to have a panel fitting quite all the experimental cases.

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