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Changes in the Solubility of β-Cyclodextrin on Complex Formation: Guest Enforced Solubility of β-Cyclodextrin Inclusion Complexes

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Abstract. The most common native host molecule, β-cyclodextrin (cycloheptaamylose) is able to form inclusion complexes with a large variety of guest molecules (or ions) of different size and shape. The properties of the included guest molecule are highly influenced by the host-guest interaction, and the practical usefulness of β-cyclodextrin is dependent on these effects. These changes are mainly investigated from the point of view of the guest and to a lesser extent from that of the host. In spite of this, the kind of guests and that of the host-guest interactions during the formation of the inclusion complex seem to influence the properties of the hydrophilic domain of β-cyclodextrin (i.e. that of the supramolecule itself), too, and this effect can be well demonstrated by the change of solubility of different β-cyclodextrin inclusion complexes. This change can be best correlated with the solubility of the guest as if the guest enforced its solubility on the supramolecule.

Key words: β-cyclodextrin, solubility enhancement, solubility of the inclusion complexes, guest enforced solubility.

1. Introduction

The formation of a supramolecule produces new properties which can differ essentially from the properties of its building molecules, thus creating the conditions for molecular recognition, transport, catalysis, etc. [1]. In spite of the fact that cyclodextrins (CDs) are mentioned as enzyme mimicing models several times (being really very good and relatively simple model molecules), the changes in the properties of CDs themselves as an effect of inclusion complex formation have been less elucidated or even investigated.

The most important native CD, cyclomaltoheptaose (β-CD) consists of seven glucopyranose units with α(1,4) glycosidic bonds, forming a truncated cone structure [2–6]. The cavity of β-CD has an internal diameter of 0.78 nm and it is rather hydrophobic being lined by hydrogen atoms and glycosidic oxygens. (Their nonbonding electron pairs are directed towards the inside of the cavity, producing there a relatively high electron density.) The hydrophilic domain of β-CD consists of hydroxyl groups: all of the secondary (2,3) ones are located on one (wider)

rim of the cone (forming a complete hydrogen bonded belt) while the primary (6) hydroxyls are collected on the other (narrower) rim, rotating relatively freely (see Figure 1). β-CD forms inclusion complexes with various guests [2–6]. The physical and chemical properties of guests (solubility, volatility, light-sensitivity, etc.) are modified by complex formation, and mainly these changes are investigated and utilized [7]. On the other hand, hardly anything is known about the changes in reactivity of β-CD itself when any guest molecule is included in its cavity. (The finding of the strong inhibitory effect of some guest molecules on acid catalysed ring-opening of β-CD [8] seems to be the single exception, where the host was at the centre of the investigations.)

The solubility of β-CD in water is the lowest among the common CDs. One of the possible explanations of this phenomenon is the assumption that the fit of β-CD (aggregates) to the hydrogen bonded structure of water is rather hindered [9]. Since the alkylated β-CDs with decreased H-bonding abilities have a higher solubility [4] than β-CD, the lower solubility can be better correlated with the rather particular H-bonding system of β-CD itself [10], stabilizing the solid phase.

In contrast to the fact that the increased solubility of the guests in the presence of β-CD is of main practical importance and that precipitation is one of the most commonly used ways for manufacturing the inclusion complexes [4], data on the solubilities of inclusion complexes can be found only when it is at the limit of the solubilizing effect. These data are mostly hidden in figures but they are significantly lower than that of the parent β-CD in all known cases.

The α- and γ-CDs are better dissolved by water, therefore the relatively lower solubilities of their inclusion complexes are less striking. Some specifically substituted CDs, like the hydroxypropylated ones, are able to enhance the solubility of the poorly soluble guests more than a thousand times [5]. No data are published about the solubility of these supramolecular complexes. Nevertheless, they seem to be nearly similar to (but lower than) that of the given CD. In these cases, the groups interacting with the solvent (forming hydrogen bonds to the water molecules) are rather independent and probably less influenced by the complex formation.

The aim of this study is to find a connection between the solubilities of inclusion complexes and their building units, concentrating on the β-CD host itself. Much precise solubility data have been measured and/or collected [13, 14] and the solubility parameters found have been tried to correlate with different constants.

2. Experimental

2.1. CHEMICALS

All chemicals used were of analytical grade and purchased from Sigma-Aldrich Ltd., Hungary, while β-CD (over 99% purity) was a gift of Cyclolab Ltd., Hungary. Distilled water was redistilled from alkaline permanganate solution. The β-CD stock solution of known concentration was nearly saturated. Sodium hydroxide stock solution of 50% (by weight) was prepared to eliminate any carbonate con-

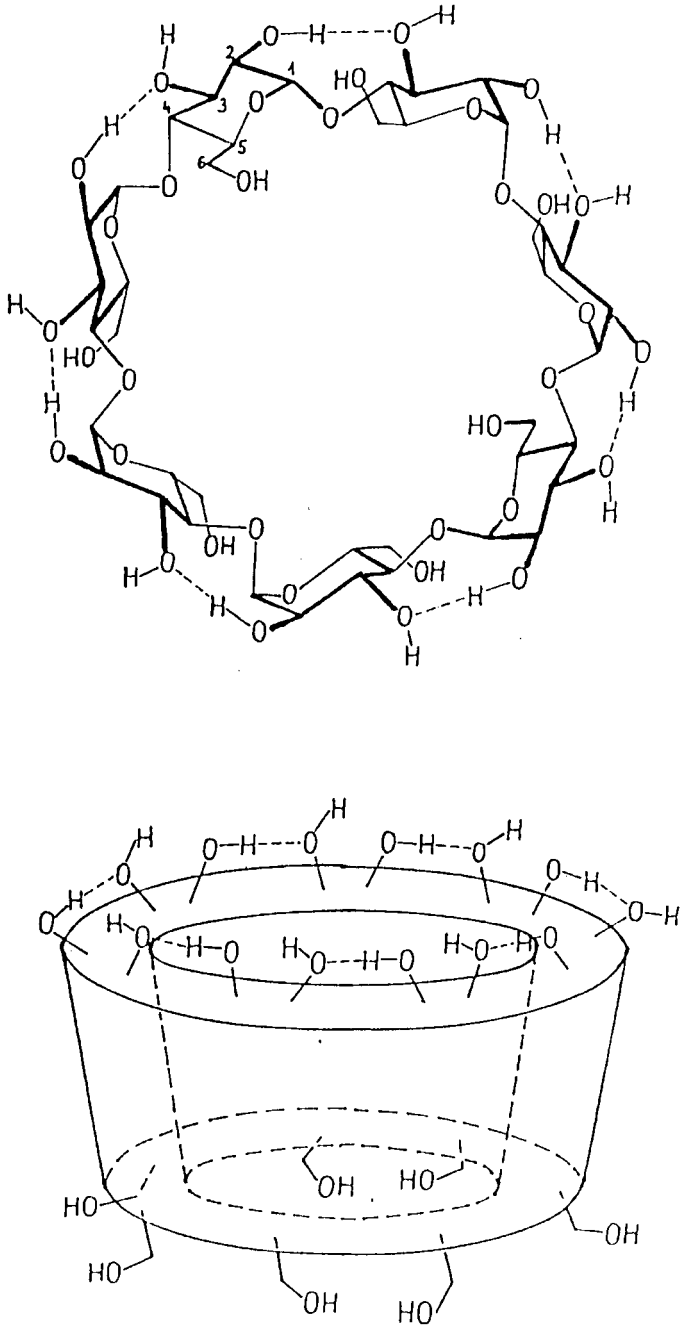

Figure 1. Representation of the β-CD structure.

tamination and stored in a polythene vessel. This concentrated solution was diluted with distilled water (free of carbon dioxide) on preparing its 0.1 M solution freshly, which was standardized against 0.1 M hydrochloric acid of exact concentration. The solutions in solubility measurements contained no salt additive as all of the guests investigated were practically neutral and the investigations could be strongly influenced by the complex formation of CDs with inorganic ions [11, 12].

2.2. SOLUBILITY MEASUREMENTS

During the investigations the temperature was kept strictly constant (generally 25.0 $\pm$ 0.1 °C), using an ultrathermostat (MLW Germany, Type UH). The quantity of the solid sample (guest) needed for saturation of the host (β-CD) solution of given (and known) concentration had been determined in a preliminary test, as real and reproducible data can be best measured with systems containing undissolved guest in an optimum excess. Therefore, about 120% of the amounts measured in preliminary tests were weighed into flasks with polythene stoppers, then β-CD solutions of known, increasing concentrations were pipetted in to them. The whole system was strictly thermostatted and often shaken. When the solid phase contained only one component, the equilibration required about 10–24 hours, but over a whole week was necessary when the solid phase was a mixture of undissolved guest and precipitated inclusion complex(es). Generally, the clear liquid phase could be easily separated from the solid one.

2.3. ANALYSES

To check the amount of the dissolved guest in the separated solutions, precise and appropriate analytical methods (uv-vis spectrophotometry, neutralization titrations, etc.) were used. Since the guests investigated were acids, careful neutralisation titrations with 0.1 M NaOH standard solution were used in the presence of phenolphthalein indicator. The results were also checked by potentiometric titrations, using a Radiometer pHM93 potentiometer with a pHC2406 glass electrode, as well as spectrophotometrically with a Spectromom 195D instrument. Sometimes the β-CD content (weighed by mass) was also checked by optical rotation measurements using a Zeiss Polamat multiwavelength polarimeter. In the last two cases, the results were evaluated using calibration curves with known concentrations.

3. Background to the Computer Calculations

The data – among them the stability constants of the inclusion complexes formed in the equilibria – were evaluated using a computer program.

It is obvious that the solubility of the guest (G) can be increased by the CD (host, H) when they interact with each other. This interaction can be represented in a general form as

$$pH+qG \Leftrightarrow H_pG_q \tag{1}$$

(where p and q indicate the stoichiometric factors) and the equilibrium constant (β) can be defined in the usual way:

$$\beta_{pq} = [H_pG_q]/([H]^p \times [G]^q). \tag{2}$$

The computer program is based on the rule of mass balance, using the total concentrations of the reactants (again in general form) as

$$c_H = \Sigma p\beta_{pq}[H]^p[G]^q, \tag{3}$$

$$c_G = \Sigma q\beta_{pq}[H]^p[G]^q, \tag{4}$$

where β_{10} and β_{01} are obviously equal to 1.

Knowing the total concentrations (c_H and c_G) and assuming different (but realistic) β_{pq} values, [H] and [G] can be calculated in an iterative procedure. Recalculating the values of the total concentrations (c), the best fit characterized by the minimum in the next summary is sought:

$$U = \Sigma(c_{\text{calculated}} - c_{\text{measured}})^2, \tag{5}$$

assuming different sets of β_{pq} values (trying possibly the lowest number of constants).

As it will be seen, the systems under discussion can be characterized by three simple combinations: (a) only a single 1:1 inclusion complex is formed; (b) 1:1 and 1:2, or (c) 1:1 and 2:1 complexes are both formed. Therefore, Equations (3) and (4) can be simplified as follows:

$$c_{H(a)} = [H] + \beta_{11}[H][G], \tag{3a}$$

$$c_{G(a)} = [G] + \beta_{11}[H][G], \tag{4a}$$

$$c_{H(b)} = [H] + \beta_{11}[H][G] + \beta_{12}[H][G]^2, \tag{3b}$$

$$c_{G(b)} = [G] + \beta_{11}[H][G] + 2\beta_{12}[H][G]^2, \tag{4b}$$

$$c_{H(c)} = [H] + \beta_{11}[H][G] + 2\beta_{21}[H]^2[G], \tag{3c}$$

$$c_{G(c)} = [G] + \beta_{11}[H][G] + \beta_{21}[H]^2[G]. \tag{4c}$$

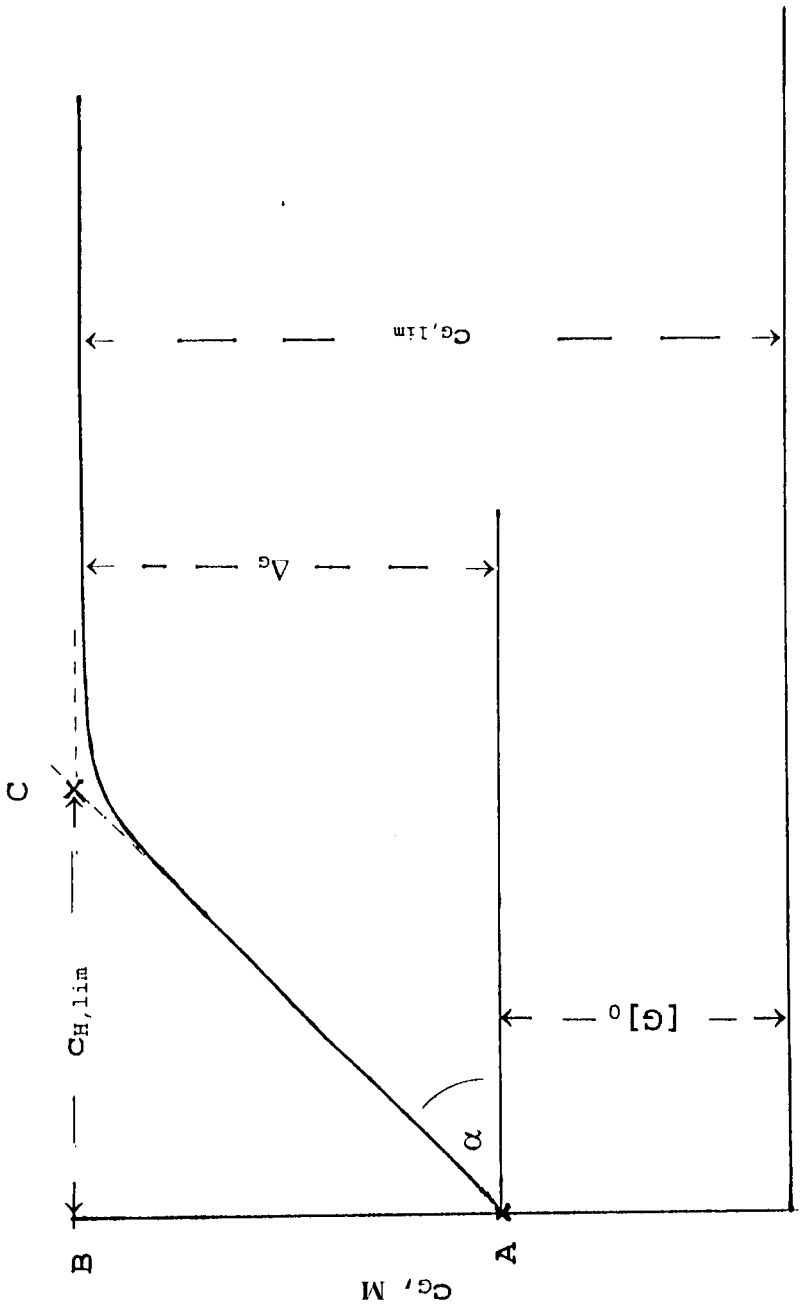

Figure 2. Representation of the equilibria between the solid and solution phases in guest (G) and β-cyclodextrin (H) interactions.

4. Results

Measuring the solubility enhancement (total concentration) of a given guest (G) as a function of the increasing concentration of host (H, in this discussion β-CD), the correlation starts with a linear part [13] (see Figure 2, the line of **A**–**C**).

As the solution is in equilibrium with the solid phase containing undissolved guest (and the temperature is kept constant), the equilibrium concentration of the uncomplexed guest must be also constant, $[G]_0$. (The intersection at point **A** gives this very important value.) The concentration of dissolved guest (free and complexed) can be characterized in this range (in general form, as discussed above) as follows:

$$c_G = \Sigma q \beta_{pq} [H]^p [G]_0^q. \tag{6}$$

The linearity of the **A**–**C** part is obvious when $p = 1$ (in this case q can be 1, 2 or both, higher values exist only theoretically), but often an almost linear relationship could be found also when $p = 2$ (first of all because of the accidental errors of measurements or the minor value of β_{21}) [13].

As the slope ($\tan \alpha$) can be directly read and the correlation between this value and the formation constants is (again in general form):

$$\tan \alpha = (c_G - [G]_0)/c_H = (\Sigma q \beta_{pq} [H]^p [G]_0^q - [G]_0)/(\Sigma p \beta_{pq} [H]^p [G]_0^q), \tag{7}$$

it can be used for the calculation of the stability constant when only one complexed species exists (which is mainly the 1:1 one). [Based on the data of the **A**–**C** part and Equations (3)–(4), the "two species problem" can also be solved, using a personal computer [13].]

Increasing the concentration of β-CD (in the presence of solid G) to a higher extent, the solubility increasing effect can be stopped (Figure 2, point **C**). This indicates that the solution is saturated with the inclusion complex, and the solid phase starts to contain both undissolved guest and precipitated inclusion complex. As the temperature is constant and the components of this solid phase are also in equilibrium with the solution phase, it follows that both [G] (=$[G]_0$) and c_G (=$c_{G,lim}$) must be constant. This limited value is characterized as

$$c_{G,lim} = \text{const.} = \Sigma q \beta_{pq} [H]^p [G]_0^q. \tag{8}$$

Since β_{pq} and $[G]_0$ are also constants in Equation (8), the whole expression could be constant if [H] is also constant. This special and important value will be indicated further as $[H]_{lim}$.

It is obvious, that the limit of c_G ($c_{G,lim}$, Figure 2 point **B**) is equal to the sum of the highest concentrations of the free and complexed guest (i.e., to the sum of their solubilities at the given temperature):

$$c_{G,lim} = \Sigma q \beta_{pq} [H]_{lim}^p [G]_0^q. \tag{9}$$

It follows that all of the added β-CD will be precipitated as insoluble inclusion complex when the concentration of inclusion complex formed exceeds the limit defined by the solubilities of the inclusion complexes. The limited total concentration of the host can be characterized similarly to that of the guest:

$$c_{\mathrm{H,lim}} = \Sigma p\beta_{pq}[\mathrm{H}]_{\mathrm{lim}}^{p}[\mathrm{G}]_{0}^{q}, \tag{10}$$

and it remains constant (generally, only with few very interesing exception [13]) as long as the solid phase also contains solid guest.

The value of $c_{\mathrm{H,lim}}$ (which was not used earlier) is also a quantity which can be measured directly and can be characterized by the total host concentration (c_{H}) existing at point **C** (see Figure 2). Since $[\mathrm{G}]_0$ is known and the β_{pq} values have been calculated [as discussed with Equation (7)], Equation (10) becomes a first-degree equation for $[\mathrm{H}]_{\mathrm{lim}}$ when $p = 1$, and a (similarly simple) quadratic one, when $p = 2$.

The solubility of the guest in the form of inclusion complex(es) can be calculated as follows:

$$\Delta_{\mathrm{G}} = c_{\mathrm{G,lim}} - [\mathrm{G}]_0, \tag{11}$$

while the concentration of complexed host is

$$\Delta_{\mathrm{H}} = c_{\mathrm{H,lim}} - [\mathrm{H}]_{\mathrm{lim}}. \tag{12}$$

It follows that several very characteristic quantities can be obtained and computed: Table 1 presents the primary data, Table 2 surveys the β_{pq} values, while other constants and characteristic ratios can be found in Tables 3 and 4.

5. Discussion

As can be seen in Table 1, the solubility of benzoic acid (HBz) is higher than that of β-CD. Nevertheless, it is increased by 50% in the presence of excess host (as represented in Table 3 by $\mathrm{Q} = c_{\mathrm{G,lim}}/[\mathrm{G}]_0$ value). The solubility of the HBz-β-CD inclusion complex (Table 4, Δ_H) is lower than those of the parents (or nearly equal to that of β-CD). The characteristics of other derivatives of benzoic acid (salicylic, *o*- and *m*-toluic acids in Tables 1–4) can be regarded as general ones and they are rather similar, in spite of the fact that the stability constants of their inclusion complexes (Table 2) are different. [The stability of the β-CD complex with *m*-toluic acid is, e.g., nearly five times higher than that of *o*-toluic acid, but the relative solubility enhancements (Table 3, Q) are the same because of the limited lower solubility of the complex.]

The solubility series of ω-phenyl carboxylic acids is more complicated. The first member, phenylacetic acid is rather soluble in water (better than β-CD itself, as its solubility is 1.44×10^{-1} M [13, 14]), and no solubility limit can be reached within

Table I. Primary (measured) values characterizing the solubility of the β-CD inclusion complexes

Guest	$[G]_0$[a]	$c_{H,lim}$[b]	$c_{G,lim}$[c]
Benzoic acid[d]	$(2.75 \pm 0.02) \times 10^{-2}$	$(1.40 \pm 0.02) \times 10^{-2}$	$(4.22 \pm 0.07) \times 10^{-2}$
Salicylic acid[d]	$(1.61 \pm 0.02)310^{-2}$	$(4.71 \pm 0.06) \times 10^{-3}$	$(2.04 \pm 0.04) \times 10^{-2}$
o-Toluic acid[d]	$(9.36 \pm 0.11) \times 10^{-3}$	$(4.94 \pm 0.05) \times 10^{-3}$	$(1.29 \pm 0.03) \times 10^{-2}$
m-Toluic acid[d]	$(7.77 \pm 0.09) \times 10^{-3}$	$(3.22 \pm 0.03) \times 10^{-3}$	$(1.07 \pm 0.02) \times 10^{-2}$
Phenylpropionic acid[e]	$(6.24 \pm 0.04) \times 10^{-2}$	$(4.12 \pm 0.07) \times 10^{-3}$	$(6.63 \pm 0.07) \times 10^{-2}$
Phenylbutyric acid[e]	$(1.40 \pm 0.02) \times 10^{-2}$	$(1.90 \pm 0.05) \times 10^{-3}$	$(1.61 \pm 0.03) \times 10^{-2}$
Phenylvaleric acid[e]	$(4.14 \pm 0.06) \times 10^{-3}$	$(1.92 \pm 0.05) \times 10^{-3}$	$(6.71 \pm 0.11) \times 10^{-3}$
Cinnamic acid[e]	$(3.63 \pm 0.06) \times 10^{-3}$	$(1.50 \pm 0.06) \times 10^{-3}$	$(4.74 \pm 0.09) \times 10^{-3}$
5-Phenyl-2,4-pentadienoic acid[e]	$(2.3 \pm 0.1) \times 10^{-4}$	$(4.2 \pm 0.2) \times 10^{-3}$	$(1.00 \pm 0.05) \times 10^{-3}$
Phenylundecanoic acid[e]	$(5.0 \pm 1.0) \times 10^{-4}$	$(4.8 \pm 0.2) \times 10^{-3}$	$(1.5 \pm 0.1) \times 10^{-3}$

[a] Solubility of the guest, in the absence of β-CD, M [13, 14].
[b] The limited concentration of the host (β-CD, see text) at saturation, M. {The solubility of β-CD itself is $(1.52 \pm 0.01) \times 10^{-2}$ M [at 25 °C] and $(1.84 \pm 0.03) \times 10^{-2}$ M [at 30 °C], respectively.}
[c] The final concentration of the guest (free + complexed) at saturation, M.
[d] T = 25 °C.
[e] T = 30 °C.

Table II. Stability (formation) constants characterizing the inclusion complexes

Guest	β_{11}[a]	β_{12}[b] or β_{21}[c]	T (°C)
Benzoic acid	$(7.94 \pm 0.12) \times 10^2$	$\beta_{12} = (3.18 \pm 0.33) \times 10^3$	25
Salicylic acid	$(6.6 \pm 0.6) \times 10^2$	–	25
o-Toluic acid	$(2.7 \pm 0.3) \times 10^2$	–	25
m-Toluic acid	$(1.30 \pm 0.15)310^3$	–	25
Phenylpropionic acid	$(2.8 \pm 0.3) \times 10^2$	–	30
Phenylbutyric acid	$(6.5 \pm 0.9) \times 10^2$	$\beta_{12} = (1.10 \pm 0.23) \times 10^4$	30
Phenylvaleric acid	$(9.7 \pm 1.5) \times 10^2$	$\beta_{12} = (2.50 \pm 0.50) \times 10^5$	30
Cinnamic acid	$(4.8 \pm 0.9) \times 10^2$	$\beta_{12} = (1.70 \pm 0.33) \times 10^4$	30
5-Phenyl-2,4-pentadienoic acid	$(7.3 \pm 1.1) \times 10^2$	$\beta_{21} = (1.0 \pm 0.2) \times 10^5$	30
Phenylundecanoic acid	$(4 \pm 1) \times 10^2$	$\beta_{21} = (5 \pm 1) \times 10^4$	30

[a] $\beta_{11} = [H \cdot G]/([H] \times [G])$.
[b] $\beta_{12} = [H \cdot 2G]/([H] \times [G]^2)$.
[c] $\beta_{21} = [2H \cdot G]/([H]^2 \times [G])$.

the solubility range of β-CD. The characteristics of the next three acids (Tables 1–4) change monotonously and those of *trans*-cinnamic acid (3-phenyl-propenoic acid) are also similar. The data of 5-phenyl-2,4-pentadienoic and phenylundecanoic acids differ most since the solubilities of both the free guests and the complexes are extremely low. The relative increases in the total concentration of the guest (Q, Table 3) are the highest in these two last cases. The explanation of this phenomenon is rather simple, as these species also form 2:1 (β-CD to acid) complexes.

As the Tables (first of all the variety and magnitude of the stability constants) show, the composition of the solutions are very different. Similarly, the insoluble inclusion complex(es) in the solid phase can be of very different stoichiometry. It seems that the phase rule, which is essential in the explanation of most solubility investigations [15, 16] is less useful in these cases. The explanation of this rather strange phenomenon can be traced back to the special structure of solid CD inclusion complexes [2–7]: β-CD and its differently complexed species can form (in appearance unstoichiometric) "solid solutions". It follows, that a rather wide range of stoichiometries can be realized, very often highly different from that experienced in the solution. (The discrepancy between the stoichiometries found in solid and solution phases led some authors to assume the existence of "complexes of infinite stability" [14].)

To analyse the amount of the complexed guest in the solid phase is very complicated in the presence of its free form, it follows that indirect investigations [17] have to contain some suppositions. In contrast to this, it is very interesting and important, that – at a strictly constant temperature – the stoichiometries in both phases are well reproducible. Accepting this fact, the stoichiometry of the com-

Table III. Constants, solubility differences and ratios characterizing the guests and their inclusion complexes

Guest	$[H]_{lim}$[a]	pK_A[b]	Δ_G[c]	Q[d]	T (°C)
Benzoic acid	5.52×10^{-4}	4.20	1.47×10^{-2}	1.52	25
Salicylic acid	4.05×10^{-4}	2.99	4.30×10^{-3}	1.27	25
o-Toluic acid	1.40×10^{-4}	3.91	3.54×10^{-3}	1.38	25
m-Toluic acid	2.90×10^{-4}	4.27	2.93×10^{-3}	1.38	25
Phenylpropionic acid	2.23×10^{-4}	4.66	3.90×10^{-3}	1.06	30
Phenylbutyric acid	1.57×10^{-4}	4.76	2.10×10^{-3}	1.15	30
Phenylvaleric acid	2.04×10^{-4}	4.8	2.57×10^{-3}	1.62	30
Cinnamic acid	5.07×10^{-4}	4.44	1.11×10^{-3}	1.31	30
5-Phenyl-2,4-pentadienoic acid	3.2×10^{-3}	4.5[e]	7.7×10^{-4}	4.3_5	30
Phenylundecanoic acid	3.5×10^{-3}	4.9[e]	1.0×10^{-3}	3.0	30

[a] Equilibrium concentration of the host at saturation, see text.
[b] Ref. [18].
[c] $\Delta_G = c_{G,lim} - [G]_0$ {solubility of the guest in form of inclusion complex(es) at the given temperature, M}.
[d] $Q = c_{G,lim}/[G]_0$.
[e] Extrapolated.

Table IV. Data in solutions equlibrated with the solid phase containing both solid guest and inclusion complex(es)

Guest	Δ_H[a]	r[b]	K_s[c]	T (°C)
Benzoic acid	1.34×10^{-2}	1.097	1.07×10^{-5}	25
Salicylic acid	4.30×10^{-3}	1.0	6.52×10^{-6}	25
o-Toluic acid	3.54×10^{-3}	1.0	1.31×10^{-6}	25
m-Toluic acid	2.93×10^{-3}	1.0	2.25×10^{-6}	25
Phenylpropionic acid	3.90×10^{-3}	1.0	1.39×10^{-5}	30
Phenylbutyric acid	1.74×10^{-3}	1.207	9.08×10^{-7}	30
Phenylvaleric acid	1.72×10^{-3}	1.494	4.47×10^{-8}	30
Cinnamic acid	9.93×10^{-4}	1.118	9.49×10^{-7}	30
5-Phenyl-2,4-pentadienoic acid	1.0×10^{-3}	0.77	5.1×10^{-6}	30
Phenylundecanoic acid	1.3×10^{-3}	0.77	1.0×10^{-5}	30

[a] $\Delta_H = c_{H,lim} - [H]_{lim}$, concentration of the complexed host, M.
[b] $r = \Delta_G/\Delta_H$.
[c] Solubility product, $[H]_{lim} \times [G]_0^{\mathbf{r}}$, see text.

plex(es) present in the solid phase can be assumed to correspond exactly with the ratio of the complexed guest and host concentrations (at saturation) as follows:

$$r = \Delta_G/\Delta_H = (\Sigma q\beta_{pq}[H]^p_{lim}[G]^q_0 - [G]_0)/(\Sigma p\beta_{pq}[H]^p_{lim}[G]^q_0 - [H]_{lim}), \quad (13)$$

where Δ_G and Δ_H symbolize the guest and host concentrations in the complex(es). It follows that the r constant [Equation (13)] is practically a weighted ratio of the p and q stoichiometric factors, without concrete chemical meaning. (The values calculated using the data of the measurements are collected in Tables 3 and 4.)

As our aim is to find a correlation between the solubility and other constants of the given inclusion complex(es), the problem is which value is best suited for characterizing the solubility itself? From a practical point of view, the relative increase of the solubility of the guest (Q, Table 3) is a clear representation for this purpose and often used in the literature (e.g., Ref. [5]). Similarly, the highest possible concentration of the guest [$c_{G,lim}$, see Equation (9) and Table I] could also be used, or the complexed guest or host concentrations (Δ_G or Δ_H, Tables 3–4).

Considering the circumstances, the expression of the solubility product (mostly used in physical chemistry) becomes a rather strange form because of the mixed stoichiometry:

$$K_s = [H]_{lim} \times [G]^r_0, \quad (14)$$

where r is not a real stoichiometric number as discussed [Equation (13)]. (The calculated r and K_s values are also collected in Table 3.) To check the validity of the K_s values in the cases of inclusion complexes, solid β-CD-HBz has been prepared and its solubility measured as a function of additional HBz concentration (c'_G). After Equation (14), the decrease of solubility (expressed as c_H) is to be expected, which was experimentally proved, as shown in Figure 3.

Among the constants characterizing the guest and/or its inclusion complex(es), first of all the stability constant(s) (given in Table 2) could be thought important, then the K_A value (as the guests discussed are acids) and finally, the solubility of the guest itself (being also a rather characteristic constant of the guest). Some correlations are shown graphically in Figure 4, and an attempt was made to calculate them using the least squares method, but neither the β_{pq} nor the K_A values fit well to any of the solubility constants mentioned. It is rather surprising that a very poor correlation can be found between the solubility and stability constant of the inclusion complex, since the chemical background seems to be identical. In contrast to this, no correlations were assumed (and found) with acid dissociation constants.

The best fit can be found between $c_{G,lim}$ and $[G]_0$ (confidence level is 98.39%) as supported also by Figure 4. The correlation is also relatively good between K_s and $[G]_0$, or Δ_G and $[G]_0$. Practically it means that generally the less soluble guest produces less soluble inclusion complex(es) than the better soluble one, and the solubility of the inclusion complex is always lower than that of β-CD. It looks

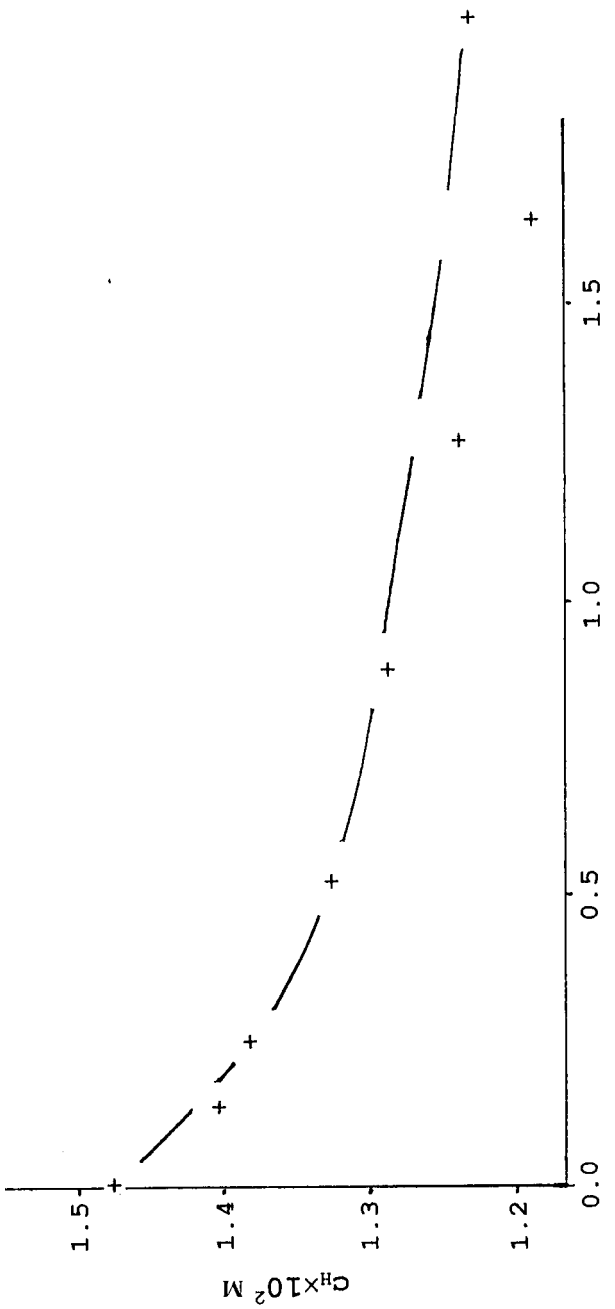

Figure 3. Solubility change of the β-CD–HBz inclusion complex as a function of the excess HBz, where c'_G indicates the concentration of excess HBz and the continuous line represents the calculated values.

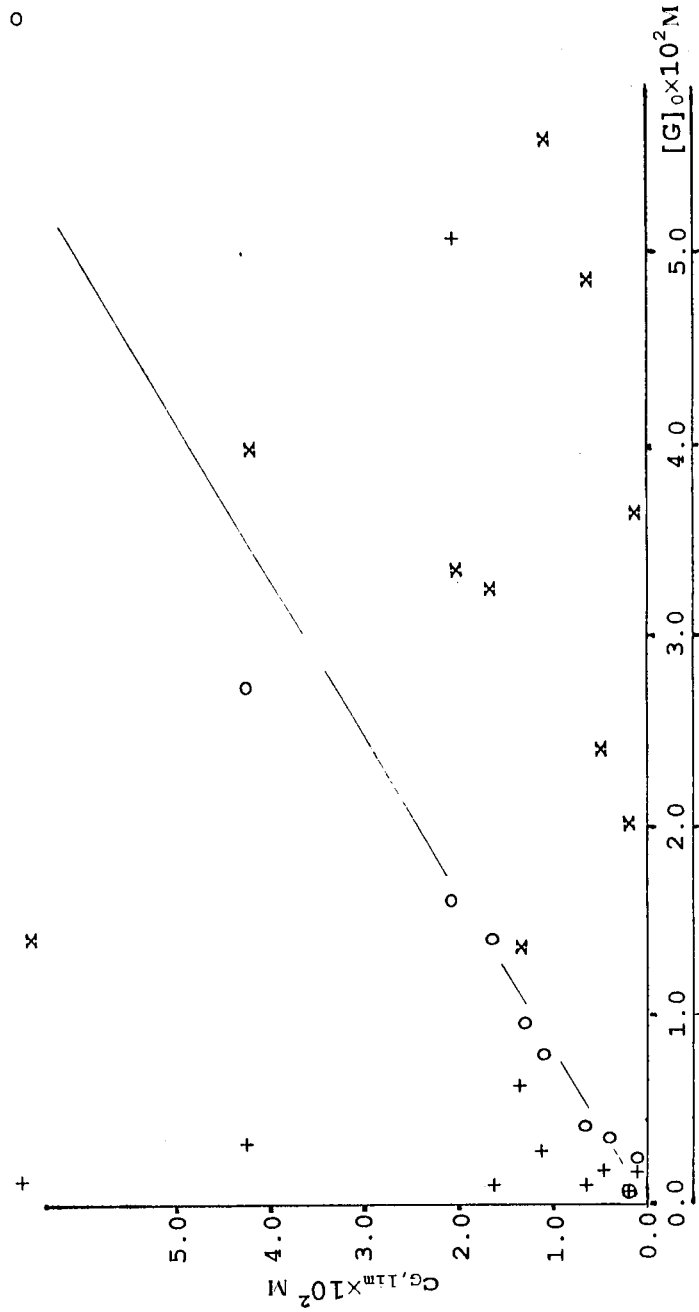

Figure 4. Correlations between the enhanced solubility of the guest ($c_{G,lim}$) and its solubility ($[G]_0$, **o**), its acid dissociation constant (K_A, +), or the stability constant of its β-CD complex (β_{11}, ×), respectively.

as if the guest forced its solubility upon the β-CD during the inclusion complex formation. The phenomenon experienced in this special field of supramolecular chemistry can be named as guest enforced solubility (GES).

It seems (as the solubilities of both β-CD and its inclusion complexes must be connected to and dependent on the same hydrophilic domain) that the H-bonding abilities of hydroxyl groups (i.e., the components of the hydrophilic domain mentioned) must be highly influenced by the inclusion of the guest and consequently the supramolecular species formed has new and different properties.

Much data (among them those measured by NMR) are known also in solution on the properties of CD inclusion complexes [2–7], but the discussions concentrate first of all on the results proving the host–guest interaction. The changes in the hydrophilic area are also detected, but no further conclusions have been drawn. It can be assumed that the interactions between CD and the included guest hinder the hydration, the main factor in water solubility (or promote the CD – CD hydrogen bonded interaction, leading to the same result).

Since the molecules of the model compounds investigated are relatively simple and small, a perfect fit into the cavity of the host can be assumed, therefore the direct interaction between the guest and solvent molecules can be neglected.

To understand and explain the phenomena completely, some further experimental and theoretical investigations are needed, but it can be assumed that the practice gets some initatives in solving their problems and some more exact data will be published.

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