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Structure of Cyclodextrins and Their Complexes. Part 41. Chromatographic and NMR Study of 1,2,3-Tri-t-butylnaphthalene and Its Complex with γ-Cyclodextrin

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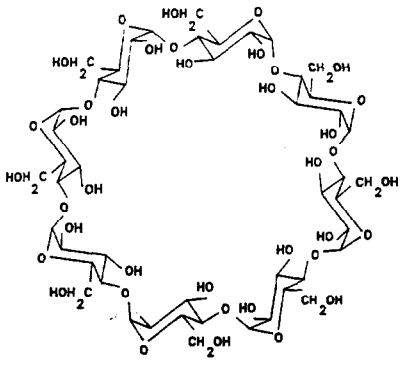
Abstract: The process of complex formation of 1,2,3-tri-t-butylnaphthalene with γ-cyclodextrin was studied by means of gas-liquid chromatography, reversed-phase high performance liquid chromatography and ^{1}H and ^{13}C NMR spectra. In spite of the large volume of the guest molecule, using chromatographic methods, the complex was found to be unusually stable. The stability constant $K_{G,\gamma\text{-CD}}$ was estimated to be ca. 10^{4} M^{-1} in 75 vol% of ethanol in water at 20° C and is greater than 4.4 m^{-1} in glycerin at 90° C. ^{1}H and ^{13}C spectra at room temperature exhibit only minor shifts of the signals upon complexation and the complex formation manifests itself in carbon spectra at low temperatures by significant broadening of the signals. Both reversed-phase high performance liquid chromatography and room temperature ^{1}H NMR spectra suggest a shallow insertion of the guest into the γ-cyclodextrin cavity. There is a surprising inconsistency between the high stability of the complex and the shallow insertion of the guest into the host cavity. Internal rotation of t-butyl groups in the positions 1 and 2 is frozen at 193 K while the remaining group in position 3 rotates almost freely at this temperature. Molecular mechanics calculations using PCMODEL do not reproduce this trend yielding the smallest barrier hindering the rotation for t-butyl group in position 2.

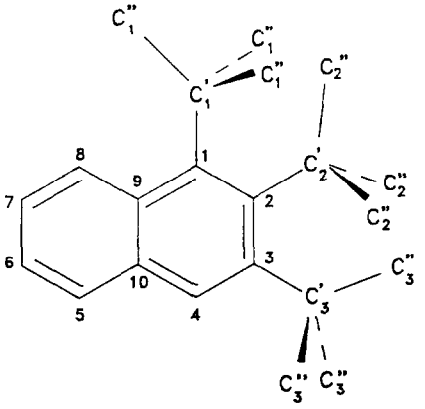
INTRODUCTION

The process of molecular and chiral recognition by cyclodextrins, CDs, is not well understood and their complexes with hydrocarbons serving as hosts seem especially intriguing. An inclusion of a guest into a CD cavity is a complicated phenomenon strongly influenced by experimental conditions such as temperature,

concentration, solvent, etc.[2] Moreover, addition of other compounds can influence the complex formation[3]. Therefore, to obtain reliable experimental data, enabling understanding of the factors determining the complex formation, various independent techniques should be applied. In recent years our group has developed two



Gamma–cyclodextrin

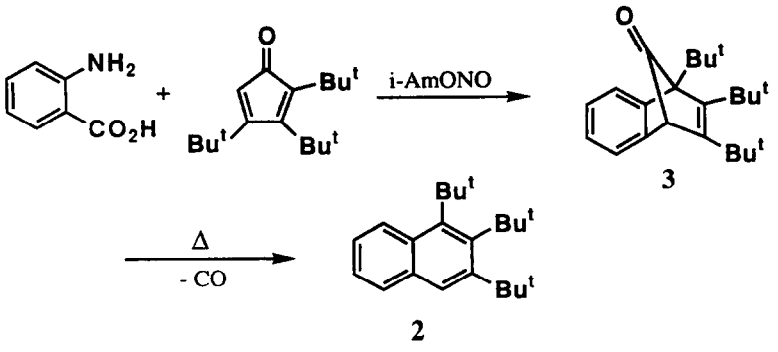


1,2,3–tri–t–Bu–naphthalene

chromatographic methods of application of CDs using them in dissolved state as additives in reversed-phase high performance liquid chromatography, RP-HPLC[4-6], and gas chromatography, GLC[7, 8]. These two methods were initiated and elaborated for analytical purposes but they also seem to be useful as a source of information concerning inclusion processes themselves. Moreover, as these two methods operate under considerably different conditions, i.e., solvent medium, CD concentration and temperature, they cover a relatively large area of research for the study of CD activity. On the other hand, the study of NMR spectra should provide an additional insight into the process of the complex formation. Therefore, in continuation of our works on CDs and their complexes[1, 4-8] a study of a complex of γ-CD **1** with 1,2,3-tri-t-butylnaphthalene **2** (denoted in formulas by the letter G for guest) has been undertaken in spite of the fact that the former molecule seemed too big to fit into the cavity of the latter. The results of the joint chromatographic and NMR studies suggest not only that the complex is formed but they indicate its considerable stability in polar solvents in spite of a shallow insertion of the guest into the γ-CD cavity.

EXPERIMENTAL

Reagents: 1,2,3-Tri-tertbutylnaphthalene **2** was synthesized according to Scheme 1 by using 2,3,4-tri-t-butylcyclopenta-2,4-dienone as starting material. In the Scheme, the Diels-Alder adduct **3** was isolated as a stable compound, and successive thermal decarbonylation afforded **2**[10]. γ-CD was supplied by Chinoin (Budapest, Hungary). All other materials and reagents were commercial products and were used without further purification.



Scheme 1

High Performance Liquid Chromatography, RP-HPLC. Chromatographic runs were carried out at ca. 20°C on a Type 310 HPLC unit (Institute of Physical Chemistry, Polish Academy of Sciences, Warsaw, Poland) equipped with a 0.5 μl injector and UV detector (254nm) containing 1μl flow cell. The column (250 x 1 mm ID) was packed with 5μ LiChrosorb RP 18 (Merck, G). The mobile phase contained 75 vol% ethanol in water and various concentrations of γ-CD not exceeding $2x10^{-3}$ M. The flow rate was 40 μl/min.

Under the assumption that only the complex of 1 : 1 stoichiometry is present in solution, the stability constant $K_{G,\gamma\text{-CD}}$ of the complex under investigation was estimated using the following equation [4-6]

$$k' = \frac{k'_G + k'_{G,\gamma-CD} K_{G,\gamma-CD}[\gamma-CD]}{1 + K_{G,\gamma-CD}[\gamma-CD]}, \quad (1)$$

where k' is the apparent capacity factor observed at given [γ-CD] in the mobile phase, $K_{G,\gamma\text{-CD}}$ is the stability constant of the complex and k_G' and $k'_{G,\gamma\text{-CD}}$ are the capacity factors of the free guest molecule and its γ-CD complex, respectively.

Gas Liquid Chromatography, GLC. A Hewlett Packard 5890 gas chromatograph was used together with a flame-ionization detector and glass columns (2m x 4mm). The packings were prepared in a similar way to the method described earlier (7, 8) by deposition of γ-CD glycerin (Gly) mixtures on Chromosorb W (60-80 mesh) from aqueous solutions; the constant proportion: glycerin/support (20%/80%) was maintained. Columns contained: I) pure glycerin (control) and II) 0.2m[11] solution of γ-CD in glycerin.

The stability of the G,γ-CD complex was estimated using the simplified equation [7, 8].

$$t'_{R(\gamma-CD,Gly)} = t'_{R(Gly)}\left(1 + K_{G,\gamma-CD}[\gamma-CD]\right), \quad (2)$$

where $t'_{R(\gamma\text{-CD, Gly})}$ and $t'_{R(Gly)}$ are the adjusted retention times of the guest on the column containing a given concentration of γ-CD in glycerin and on the column with glycerin alone, respectively. This equation is valid if $G_{\gamma\text{-CD}}$ complex of stoichiometry 1:1 is formed (all other conditions comparable) when the only differing parameter is γ-CD concentration.

^1H and ^{13}C NMR spectra. The ^1H and ^{13}C NMR spectra were measured on a Bruker AM-500 spectrometer operating at 500.13 MHz and 125.76 MHz, respectively, and equipped with a standard variable

temperature unit. The standard conditions for the carbon spectra were : acquisition time 1.18 sec, relaxation delay 2 sec, pulse duration 3 μsec (50° flip angle), number of scans 256 for each spectrum. The spectra were measured in dimethylformamide-d_7 , DMF-d_7 , solutions for 303 - 213 K temperatures, while those at 213 and 193 K were recorded for solutions in the ca. 4 : 1 mixture of DMF-d_7 and $(CD_3)_2CO$, c = 0.1 mol/l.

RESULTS AND DISCUSSION

Reversed-phase High Performance Liquid Chromatography. The results of the studies on G, γ-CD complexation carried out by RP-HPLC method are presented in Fig. 1 and Fig. 2. It is clear from equation 1 that without significant difference between the values of k'_G and $k'_{G,\ \gamma\text{-CD}}$ the complexation equilibria cannot be analyzed by the RP-HPLC method. The variation of k'_G with γ-CD concentration is shown in Fig. 1 and exemplified by chromatograms in Fig. 2. It indicates that this difference must be considerable under the conditions of experiment. In effect the method may be applied for estimation of the degree of complexation and in consequence for estimation of the stability constant of the complex $K_{G,\ \gamma\text{-CD}}$. At the same time a relatively large and constant value of k' (51% of k'_G) has been observed for concentrations of γ-CD greater than $5x10^{-4}$M. Such a behaviour seems to indicate that it is the value of capacity factor of the complex itself $k'_{G,\ \gamma\text{-CD}}$. In this work the stability constant has been estimated on the basis of this assumption. As written above, this assumption is valid only if the complex of 1:1 stoichiometry is formed. Unfortunately, by such a crude procedure only the order of magnitude of the stability constant could be estimated at present. It was found to be unusually high : $K_{G,\ \gamma\text{-CD}}$ is of the order 10^4M^{-1} at 20°C in 75 vol% ethanol in water. It is quite astonishing that the complex is so stable although the significant value of its adsorption on ODS phase $k'_{G,\ \gamma\text{-CD}}$ suggests a shallow insertion of G into the γ-CD cavity on the basis of the following mechanism. Hydrophobic guest molecules are known to be strongly adsorbed on hydrophobic ODS stationary phase from polar solutions of mobile phases where they exist in the free, uncomplexed form. On the contrary, in complexed state with a complete insertion in the CD cavities they are not adsorbed as are not CDs themselves. Such a behaviour has been observed in [4, 5, 6 and references quoted in the last one]. To confirm our finding in an independent way a separate set of experiments have been carried out using Knauer's Chiral Detector. It yielded a very close to zero value of capacity factor of pure γ-CD on ODS phase under conditions of experiments. These facts seem to indicate that the considerable adsorption of the complex under investigation is mainly due to the part of the guest molecule situated outside the γ-CD cavity.

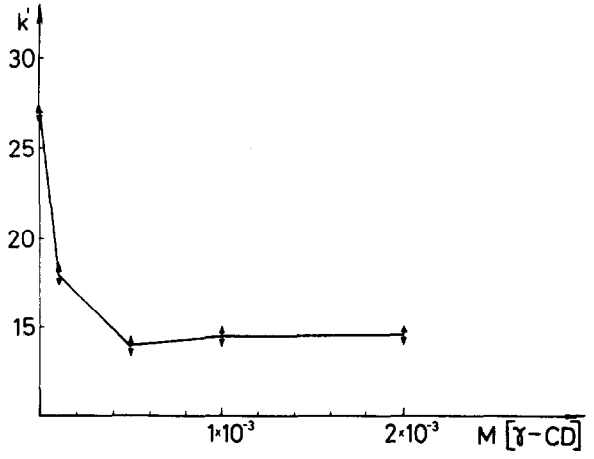


Fig. 1. k' values vs γ-CD concentrations (M) in mobile phase solutions (75 vol% ethanol in water) determined at 20°C on LiChrosorb RP18 column.

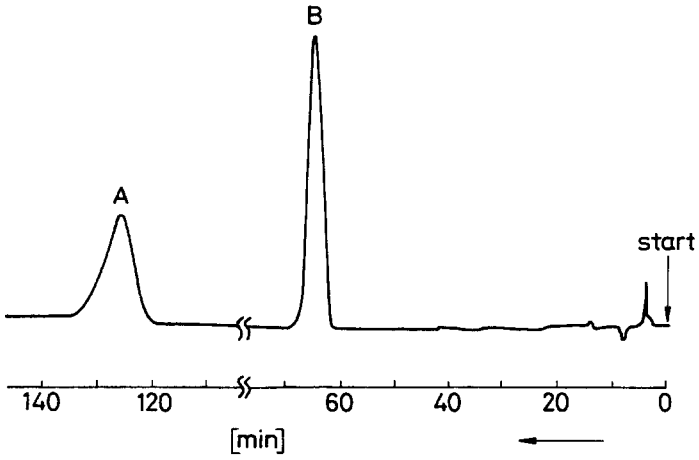


Fig. 2. Two chromatograms of the guest eluted A) by 75 vol% ethanol in water and B) by $1x10^{-3}$M solution of γ-CD in 75% ethanol in water. All other conditions were the same.

Gas Liquid Chromatography. The great stability of the G,γ-CD complex found by RP-HPLC method encouraged us to undertake investigations by independent GLC technique since the complexation effects, if not considerable, were expected to be at least perceptible at much higher temperatures also.

Simple examination of the equation (2) indicates that if 1,2,3-tri- t-butylnaphthalene does form a complex with γ-CD under conditions of experiment then as a rule

$$t'_{R(\gamma\text{-}CD,Gly)} > t'_{R(Gly)}, \tag{3}$$

i. e., $t'_{R(\gamma\text{-}CD,\ Gly)}$ observed for CD column must be greater than $t'_{R(Gly)}$ for the pure matrix solvent. In the present studies we have found that at the temperature of 90°C, G is eluted from glycerin column at $t'_{R(Gly)}$ equal 170 min, while from the column containing 0.2 m solution of γ-CD it is not eluted at all up to 320 min. Thus, by applying the values mentioned above in equation (2) as a first approximation one may conclude that at 90°C the stability constant $K_{G,\ \gamma\text{-}CD}$ in glycerin must be greater than 4.4 m^{-1}. The determination of a more accurate value of $K_{G,\ \gamma\text{-}CD}$ requires further studies using columns containing lower concentration of γ-CD. Anyhow, taking into consideration the very high temperature of the measurements, 90°C, the estimated value indicates that the complex must be very stable in agreement with the results obtained by RP-HPLC method.

NMR spectra. ^1H and ^{13}C room temperature NMR spectra of the mixture of **1** and **2** dissolved in DMF-d_7, are superpositions of the spectra of the pure components. The assignment of the guest signals could not be taken from the corresponding literature data on methylated naphthalene[8] since the latter studies were carried out long ago and the skeleton of the molecule analyzed in this work is distorted from planarity due to strong nonbonded repulsions of the neighboring t-butyl groups[10]. The assignment of the proton and carbon signals based on fully coupled ^{13}C spectrum and selective homonuclear and heteronuclear decoupling techniques as well as heteronuclear correlation experiments is given below.

The signal assignment seems to indicate that, surprisingly, the barrier to internal rotation of t-butyl group at 3-position is the smallest. The barriers calculated on the basis of molecular mechanics[13] using the program PCMODEL[14] do not reproduce the experimental trend yielding the smallest barrier for the t-butyl group in 2-position. It is not surprising that the MMX model combining molecular mechanics calculations with semiempirical quantum calculations do not describe properly barriers to internal rotations of the methyl groups in highly congested 1,2,3-tri-t-butylnaphthalene.

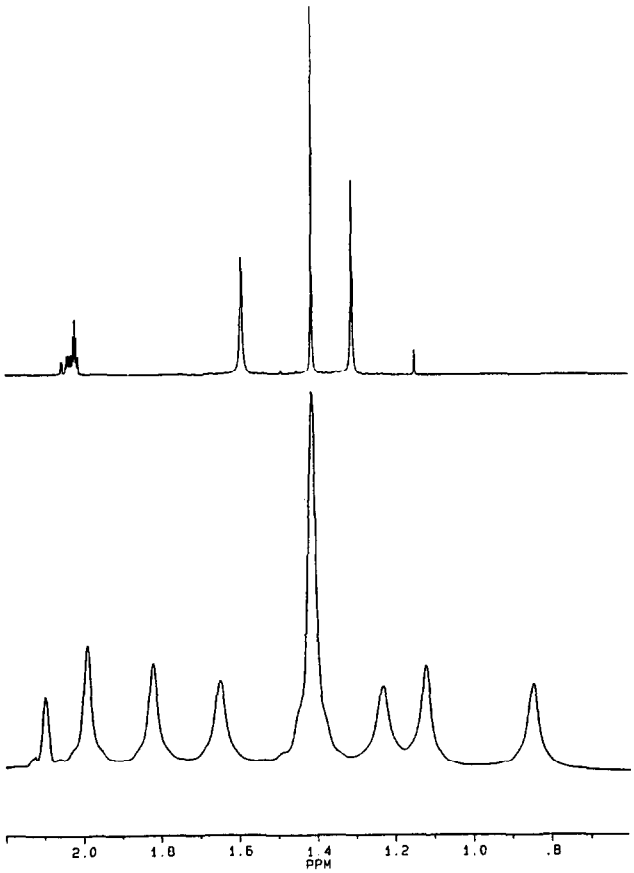


Fig. 3. ^{1}H NMR spectra of aliphatic region of the guest at (top) room temperature and (bottom) 193 K.

CONCLUSIONS

To summarize, as shown by RP-HPLC and GLC study as well as by NMR spectra, 1,2,3-tri-t-Bu-naphthalene forms a stable complex with γ-CD although there is only shallow insertion of the guest into the host cavity. The stability of the complex is unusually high. It is equal to ca. 10^4 M^{-1} at 20°C as estimated by RP-HPLC and the complex is present even at 90°C (the value of the constant bigger than 4.4 m^{-1} was found by GLC method). In NMR spectra the complex formation manifests itself only by the signals broadening especially pronounced in carbon spectra at low temperatures. At 193 K internal rotations of the methyl groups in 1- and 2-positions are frozen, while the third methyl group exhibits relatively free rotation at this temperature. Model molecular mechanics calculations do not reproduce this trend.

Tri-t-Bu naphthalene
^{1}H NMR [DMF-d_7] δ (ppm):
8.21 (1H, dddd, J = 8.6 Hz, 1.1 Hz, 0.8 Hz, 0.6 Hz; H8), 7.67 (1H, dddd, J = 7.9 Hz, 1.6 Hz, 0.6 Hz, 0.6 Hz; H5), 7.52 (1H, dd, J = 0.8 Hz, 0.6 Hz; H4), 7.29 (1H, ddd, J = 8.6 Hz, 6.8 Hz, 1.6 Hz; H7), 7.24 (1H, ddd, J = 7.9 Hz, 6.8 Hz, 1.1 Hz; H6), 1.65 (1H, s; H1"), 1.47 (1H, s; H3"), 1.37 (1H, s; H2").
^{13}C NMR [DMF-d_7] δ (ppm):
150.4 (C1), 149.9 (C3), 148.4 (C2), 133.2 (C9), 132.0 (C10), 128.0 (C5), 125.7 (C8), 123.8 (C6), 123.6 (C7), 123.4 (C4), 42.8 (C2'), 41.4 (C1'), 39.8 (C3'), 36.3 (C2"), 35.6 (C1"), 34.9 (C3").

By lowering of the temperature all signals in proton and carbon spectra are broadened and at low temperatures half-line widths in the latter are significantly bigger in the spectra of the complex than those observed for the free host. The corresponding values measured for ^{13}C spectra are collected in Table 1. We believe that this effect is due to a hindering of the host mobility by the guest. Due to ring currents aromatic guests are known to induce chemical shift differences in the absorption region of the host[9, 12]. This effect is not observed in the complex under investigation although voluminous substituents force entering of the guest into the host cavity from the aromatic ring side. Thus, in agreement with both consideration of molecular models and the results of chromatographic studies presented above, the entrance of 1 into the γ-CD cavity must be very shallow and the complex formation manifests itself in the NMR spectra only by the signals broadening at low temperatures.

Table 1. Half-line widths of cyclodextrin signals (in Hz) in ^{13}C spectra in free γ-CD and complexed with 1,2,3-tri-t-Bu-naphthalene in (DMF-d_7) and DMF-d_7 plus acetone-d_6 solutions

	Signals							
	103 ppm	81 ppm	73 ppm			60 ppm	solvent	T
Complex	110	90	nm*	nm*	nm*	160	DMF+Acet	193K
Free γ-CD	63	56	nm*	nm*	nm*	>75	"	"
Complex	14.0	13.5	13.5	11.9	12.3	22.2	"	223K
Free γ-CD	10.5	12.0	9.9	9.7	10.1	18.2	"	"
Complex	24.0	26.3	nm*	nm*	25.4	35.7	DMF	223K
Free γ-CD	18.4	18.4	17.2	15.2	15.7	28.7	"	"
Complex	2.7	2.7	2.9	2.4	2.5	4.2	"	297K
Free γ-CD	2.1	2.2	1.8	1.9	2.1	3.1	"	"

*-not measured

By lowering the temperature, the signals of t-butyl groups in ^{1}H spectra at 1.65, 1.47 and 1.36 ppm exhibit interesting behaviour. In addition to the broadening at low temperatures, the rotations of t-butyl groups in the positions 1 and 2 are considerably hindered and their signals are close to coalescence in the spectra measured at 213 K. At 193 K both rotations are frozen yielding six signals of methyl protons at 1.99, 1.82, 1.65 and 1.23, 1.12, 0.84 ppm, respectively. The ^{1}H spectrum revealing the splitting is presented in Fig. 3.

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