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Differences between ΔH and ΔS Values of the 1:2 Complexes of Camphor Enantiomers with α-Cyclodextrin Determined by NMR Titrations and by Other Techniques

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ΔH_{12} and ΔS_{12} values for the 1:2 complexes of camphor enantiomers with α-cyclodextrin by NMR titrations, carried out from 25 to 48°C, yielded -16.0 ± 0.2 kcal/mol and 28.3 ± 0.3 e.u. for **1a**@**2** and -9.8 ± 0.2 kcal/mol and 9.1 ± 0.2 e.u. for **1b**@**2**. A comparison of the values obtained by other groups, using isothermal titration calorimetry and reversed-phase liquid chromatography, showed considerable differences except the ΔH_{12} and ΔS_{12} for **1a**@**2**, obtained by NMR and ITC methods. The reason of the differences, involving RPLC, are not discussed in view of internal inconsistencies of this method. On the other hand, the disagreement between the ITC and NMR results seems to be due to the difference in solvents (H_2O and D_2O, respectively) used in both methods, which causes deuteration of all 36 OH groups of the host cyclodextrins. Interestingly, the deuteration causes a lowering of the absolute values of ΔH_{12} and ΔS_{12} for **1b**@**2**, while the corresponding values of the complex with the second enantiomer are either unchanged or undergo only small changes upon the complexation.

Key words: chiral recognition, cyclodextrin, NMR, thermodynamic parameters, isotope effect

Thermodynamic parameters of the complexation of enantiomeric species is indispensable for characterization of both the complexation process itself and chiral recognition [1]. However, a search of ISI databasis has revealed that few determinations of ΔH and ΔS for the cyclodextrin complexes with enantiomers have been published [2–7]. In our recent ^{1}H NMR study we have shown that camphor enantiomers **1a** and **1b** form complexes of 1:2 stoichiometry with α-cyclodextrin **2**, α-CyD [8]. Benesi-Hildebrand [9] analysis of titration curves yielded the overall stability constant $\beta_2 = K_1 \cdot K_2$ equal to $(3.30 \pm 0.8) \cdot 10^5\ M^{-2}$ and $(1.95 \pm 0.5) \cdot 10^5\ M^{-2}$ for (1*R*,4*R*)- **1a** and (*1S*,4*S*)- **1b** enantiomers, respectively. The analysis of the same curves, using the program developed by the Hunter group [10], yielded the β_2 values of $(6.66 \pm 0.1) \cdot 10^5\ M^{-2}$ and $(3.65 \pm 0.3) \cdot 10^5\ M^{-2}$. The values determined by the two methods differ much

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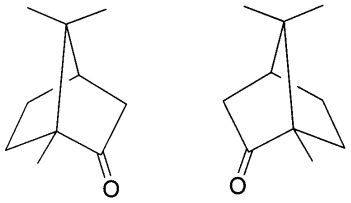
Scheme

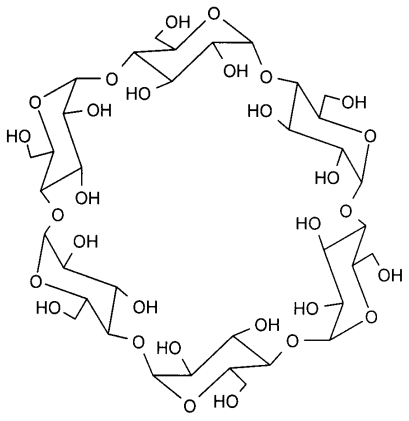


(+)*1R,4R*

1a

(-)*1S,4S*

1b



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larger than arising from the errors of their determination. However, these β_2 values exhibit a similar trend and the difference in free energies of the complexes with two enantiomers $\Delta\Delta G$ values (0.31 ± 0.21 and 0.34 ± 0.11 kcal/mol) determined by these two methods are practically identical. In addition, stepwise stability constants K_1 (for the 1:1 complexation) and K_2 (for the addition of one host molecule to the 1:1 complex of the respective camphor enantiomer with α-CyD) were determined using the Hunter program, yielding very small and practically the same values of K_1 (of *ca.* 9 M^{-1}) for the first complexation step, while the K_2 values evidenced a considerable chiral recognition since they were equal to $(7.14 \pm 0.9) \cdot 10^5$ M^{-1} and $(4.53 \pm 1) \cdot 10^5$ M^{-1} for the complexes with **1a** and **1b**, respectively. As will be described elsewhere [11], we believe that the character of experimental dependence of chemical shifts on the concentration does not allow one to separate the overall stability constant into the stepwise K_1 and K_2 ones. Therefore, in this work only overall values of enthalpy ΔH and entropy ΔS for the complexes will be reported.

Enthalpy and entropy of complexation for the complexes of (+)- and (–)-enantiomers of camphor **1** with α-CD were also measured by reversed-phase liquid chromatography, RPLC, using as solvent H_2O with either methanol or ethanol admixture [6]. The authors reported the ΔH and ΔS values adjusted to zero alcohol content. Thus, the quantities they measured should be the same for two series. However, as will be discussed in detail below, both enthalpy and entropy values differed considerably. They were also completely different from the values determined using isothermal titration calorimetry [12]. Cyclodextrin complexes are extremely labile, dynamic species sensible to experimental conditions. In particular, the complexation is known to depend on the solvent used and the timescale of the applied experimental technique [13]. Therefore, it seemed of interest to determine ΔH and ΔS for the complexes formation for both camphor enantiomers using NMR titrations [14].

EXPERIMENTAL

Two series of 1 mM solutions of (1*R*,4*R*)-(+)-camphor (Fluka, purity > 97.0%) or (1*S*,4*S*)-(–)-camphor (Merck, purity > 99 %) in D_2O with α-CD (Wacker) were prepared in such a way that the concentration of α-CD was 1–12 times higher than that of the corresponding camphor enantiomer. All ^{1}H NMR spectra were measured on the Varian Unity Plus 500 spectrometer, using the ID_PFG probehead with actively shielded z-gradient coil. The samples were inserted in the magnet and leaved for at least 15 minutes for the equilibration. The temperature was controlled by the standard VT unit. In all cases 7.2 ms high power $\pi/2$ ^{1}H pulse was used and 32 scans were acquired with the relaxation delay of 2s and FID acquisition time of 1.4s. Benesi-Hildebrand method [9] was used to determine the overall stability constants β_2 then free energy for complex formation ΔG and ΔH and ΔS values were calculated using standard formulae.

RESULTS AND DISCUSSION

The values of overall stability constants β_2 and free energy for complex formation ΔG at different temperatures determined in this work for the complexes of **2** with both camphor enantiomers **1a** and **1b** are collected in Table 1, while the differences between the values pertaining to both enantiomers $\Delta\Delta H$ and $\Delta\Delta S$ are shown in Table 2 together with the values from [6] and [12]. An inspection of the data in Table 1 reveals that both β_2 and $-\Delta G$ decrease with temperature increase. $\Delta\Delta G$ for the complexes of (+)- and (–) camphor, **1a**, **1b**, respectively, equals to 0.4 kcal/mol at 25°C. However, this value is practically zero at 48°C, although the decrease in free energies of the complexes stabilization $-\Delta G$ is not very pronounced (they equal to *ca.* 10% for the **1a@2** complex and are less than 5% for the complex with the second enantiomer of camphor).

Table 1. Stability constants β_2 and free Gibbs energies ΔG for the complexes of camphor enantiomers **1a** and **1b** with α-CD **2** at different temperatures calculated from the NMR titration data.

t, °C	**1a@2**		**1b@2**	
	β_2, $l^2 \cdot mol^{-2}$	$-\Delta G$, kcal/mol	β_2, $l^2 \cdot mol^{-2}$	$-\Delta G$, kcal/mol
25	$(4.0\pm1.2)\cdot10^5$	7.6±0.2	$(1.7\pm0.8)\cdot10^5$	7.2±0.3
30	$(2.2\pm0.1)\cdot10^5$	7.41±0.03	$(1.2\pm0.1)\cdot10^5$	7.06±0.05
25	$(1.5\pm0.2)\cdot10^5$	7.29±0.06	$(9.8\pm0.7)\cdot10^4$	7.03±0.04
40	$(9.5\pm1.7)\cdot10^4$	7.2±0.1	$(7.5\pm0.8)\cdot10^4$	6.98±0.04
44	$(7.1\pm1.5)\cdot10^4$	7.0±0.1	$(6.4\pm1.1).10^4$	7.0±0.1
48	$(5.0\pm0.7)\cdot10^4$	6.9±0.1	$(5.2\pm0.5)\cdot10^4$	6.92±0.06

Table 2. Comparison of the enthalpy and entropy of complex formation between camphor enantiomers **1a**/**1b** and α-CD **2** determined by ITC, NMR and chromatography.

		NMR[b]		
	ITC [12][a]	(this work)	Chromatography [6]	
ΔH_{12}(**1a@2**), kcal/mol	–15.98	–(16.0±0.2)	–6.30[c]	–14.32[d]
ΔH_{12}(**1b@2**), kcal/mol	–16.01	–(9.8±0.2)	–4.26[c]	–12.90[d]
$-\Delta S_{12}$(**1a@2**), e.u.	26.9	28.3±0.6	2.08[c]	9.12[d]
$-\Delta S_{12}$(**1b@2**), e.u.	28.7	9.1±0.8	0.43[c]	7.84[d]

[a]in water, [b]in D_2O, [c]in water-ethanol solution, [d]in water-methanol solution.

The data collected in Table 2 reveal how much an apparently the same value, describing CD complexes, measured by various experimental techniques in different conditions (solvent, temperature) can vary. As mentioned in the introduction, chromatographic measurements were carried out in H_2O with the admixture of either methanol or ethanol. Then, the data were analysed with the alcohol content going to zero. If the alcohols were not involved in the complexation process, the values obtained should be the same for both alcohols. An inspection of the data reported in [6] clearly shows that ethanol plays an active role in the complexation of both camphor enantiomers by α-CD. The absolute values of ΔH and ΔS, determined by RPLC for the complexes with both enantiomers, are considerably smaller than those measured by ITC and NMR methods, except ΔH_{12} for the **1a@2** complex, that is bigger than the corresponding value determined by NMR. The differences are especially big for the entropy of formation ΔS_{12} for **1a@2**. It should be reminded that the NMR spectra were measured in D_2O solutions, in which all 36 hydroxylic OH groups of the 1:2 complexes were instantly exchanged to OD. This could influence the dynamic properties of the complexes under study, resulting in changes in thermodynamic quantities describing the **1@2** complexes. Keeping this in mind, it is of interest to compare the NMR results obtained in our group with the ITC measurements. Somewhat surprisingly, the enthalpy term ΔH_{12} for **1a@2** is practically identical when measured by both the latter methods, while the values of ΔS_{12}(**1a@2**), determined by the same methods, seem to be in a reasonable agreement. On the other hand, the ΔH_{12} and ΔS_{12} values for the complex with **1b**, measured by ITC, are considerably bigger than those obtained using NMR, with enthalpy term differing almost by a factor of 2 and the entropy term even by a factor of 3. Therefore, it seems that deuteration of all 36 OH groups only slightly influences the more stable 1: 2 complex involving **1a** enantiomer. On the other hand, it seems to influence considerably the values of ΔH_{12} and ΔS_{12} of the complex with the less stable enantiomer of the guest.

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