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Thermodynamic studies on the hydrogen bonding of cholesterol with proton-acceptor solvents

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Abstract

The standard enthalpies of solution ($\Delta H_s^\ominus$) of cholesterol and cholesteryl methyl ether in carbon tetrachloride and some basic solvents were measured by calorimetery. The obtained $\Delta H_s^\ominus$ values were used for the determination of the enthalpy of the hydrogen-bond complex formation between cholesterol and proton acceptors using the Arnett "pure base" method. The enthalpy of hydrogen-bond complex formation ranges from −10.4 (diethylcarbonate) to $-24.6\ \mathrm{kJ\ mol^{-1}}$ (hexamethylphosphortriamide), being a linear function of the solvent basicity.

INTRODUCTION

Our previous studies [1] have shown that, in the solute–solvent interactions of cholesterol, hydrogen bonds are one of the most important, though not predominant, factors. Owing to its hydroxyl group, a cholesterol molecule behaves as a typical proton donor in relation to proton acceptors [2, 3], and forms complexes with hydrogen bonds. Such bonds are also formed in alcohol systems where the hydroxyl group of the cholesterol is probably both a proton donor and a proton acceptor [4]. Despite its large hydrocarbon radical, in alcohol systems cholesterol behaves as a typical aliphatic alcohol.

The thermodynamics of hydrogen-bond complex formation between cholesterol and proton acceptor compounds has not yet been studied systematically. An exception is the paper of Parker and Bhaskar [5] who have determined by IR spectroscopy that the association enthalpies for cholesterol with triacetin, tributyrin and trilaurin range from −3.5 to $-5.5\ \mathrm{kcal\ mol^{-1}}$. The literature, however, lacks data concerning the interaction between cholesterol and the bases commonly used as solvents.

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The present research was to determine the energetic share of hydrogen bonds in the interaction of cholesterol with solvents of varying basicity.

EXPERIMENTAL

The proton acceptors (reagent grade) were dried using standard procedures and were distilled immediately before the measurements. Cholesterol (Sigma, Standard for Chromatography) was dried for several hours at a temperature of about 80°C under vacuum. Cholesteryl methyl ether (Sigma, anhydrous) was stored before measurements at 0°C in a vacuum over phosphorus pentoxide. The weighing and filling of the ampoules and the calorimeter were carried out in a dry box. The calorimeter used for determining the heats of solution has been described previously [1, 6]. The apparatus error of heat measurements was about ±0.5%.

The enthalpies of solution of cholesterol and cholesteryl methyl ether were measured within the concentration range from 3×10^{-4} to 2×10^{-3} mol kg^{-1}. The enthalpy of solution of both solutes in basic solvents was independent of concentration within the studied concentration range. The values of the standard enthalpies of solution ($\Delta H_s^\ominus$) are, therefore, the averages of 8–12 independent calorimetric measurements.

The enthalpy of the cholesterol–base complex formation was determined by the Arnett et al. [7] "pure base" method, as modified by Spencer et al. [8]. The procedure consists of measurements of the heat of solution of a proton donor and of its model (a compound in which the proton is replaced by a methyl group) in a pure base and in a solvent chosen as an inert reference. The enthalpy of complex formation is calculated from the equation

$$\Delta H_f = (\Delta H_s^A - \Delta H_s^M)_{base} - (\Delta H_s^A - \Delta H_s^M)_{ref} + \Delta H^{corr} \qquad (1)$$

where ΔH_s^A and ΔH_s^M are the enthalpies of solution of the proton donor and the model compound, respectively and ΔH^{corr} is a correction term introduced to the Arnett method by Spencer et al. [8], connected with the difference in the solute–solvent interaction of the acid and its model (ΔH_i^A, ΔH_i^M) and the difference in the cavity enthalpies of the acid and its model (ΔH_c^A, ΔH_c^M) in the reference solvent and the base

$$\begin{aligned}\Delta H^{corr} = {} & (\Delta H_i^A - \Delta H_i^A)_{base} - (\Delta H_i^A - \Delta H_i^M)_{ref} \\ & + (\Delta H_c^A - \Delta H_c^M)_{base} - (\Delta H_c^A - \Delta H_c^M)_{ref} \qquad (2)\end{aligned}$$

The values of the interaction and cavity terms were calculated as described by Spencer et al. [8] using regular solution theory. The values of the solubility parameter δ_H of the basic solvents used in our study, needed for the calculation, were taken from the data of Abraham et al. [9]. Carbon tetrachloride was used as a reference solvent.

TABLE 1

Enthalpies of solution (kJ mol^{-1}) of cholesterol (Chol) and cholesteryl methyl ether (ChME) in different solvents and enthalpies of hydrogen-bond complex formation (kJ mol^{-1}) of cholesterol with the proton acceptors

Solvent	DN	$(\delta_H)^2$	$\Delta H_s^{\ominus}$(Chol)	$\Delta H_s^{\ominus}$(ChME)	$\Delta H_f^{\mathrm{Arnett}}$	ΔH^{corr}	$\Delta H_f^{\mathrm{Spencer}}$
Dioxan	14.8	100.0	31.5 ± 0.7	36.0 ± 0.5	−12.2	−0.5	−12.7
Diethylcarbonate	16.0	77.4	26.8 ± 0.3	29.5 ± 0.3	−10.4	−0.1	−10.5
Ethyl acetate	17.1	79.2	28.6 ± 0.4	34.0 ± 0.4	−13.1	−0.1	−13.2
Butanone	17.4	86.0	27.9 ± 0.2	34.1 ± 0.3	−13.9	−0.2	−14.1
Di-[*n*-butyl]-ether	19.0	59.6	18.8 ± 0.4	23.0 ± 0.3	−11.9	+0.2	−11.7
Tetrahydrofuran	20.0	86.4	27.7 ± 0.4	31.3 ± 0.4	−11.3	−0.2	−11.5
Dimethylformamide	26.6	138.9	27.5 ± 0.6	36.3 ± 0.3	−16.5	−1.6	−18.1
Dimethylacetamide	27.8	116.6	23.9 ± 0.6	34.5 ± 0.3	−18.3	−0.9	−19.2
n-Butanol	29.0	129.5	13.9 ± 0.1	26.0 ± 0.4	−19.8	−1.3	−21.1
Tetramethylurea	29.6	118.8	19.7 ± 0.4	31.0 ± 0.4	−19.0	−1.0	−20.0
HMPA	38.8	73.4	12.1 ± 0.1	29.0 ± 0.3	−24.6	0.0	−24.6
Triethylamine		54.8	8.4 ± 0.2	23.3 ± 0.4	−22.6	+0.2	−22.4
Carbon tetrachloride		73.8	31.2 ± 0.2	23.5 ± 0.5			

RESULTS AND DISCUSSION

The values of the standard enthalpies of solution of cholesterol (Chol) and cholesteryl methyl ether (ChME) are given in Table 1, which also includes the values of the enthalpy of complex formation between cholesterol and proton acceptor determined by the Arnett method $\Delta H_f^{\text{Arnett}}$, and those with the Spencer correction term being taken into account, $\Delta H_f^{\text{Spencer}}$. As can be seen, the differences are not very significant. The correction term ΔH^{corr} carries a considerable error because of the rough determination of the dispersion enthalpy (ΔH_i) and of the cavitation enthalpy (ΔH_c). Moreover, for some solvents there are divergent values given in the literature for the solubility parameter δ_H required to calculate ΔH_i and ΔH_c.

The enthalpies of hydrogen-bond complex formation of cholesterol calculated by the "pure base" method (Table 1) are typical for hydrogen bonds formed via the hydroxyl group of alcohols. The ΔH_f values of the cholesterol–proton-acceptor complex can be presented as a linear function of basicity expressed by the Gutmann donor number (DN), Fig. 1.

The linear correlation is somewhat better in the case of $\Delta H_f^{\text{Arnett}}$ (the

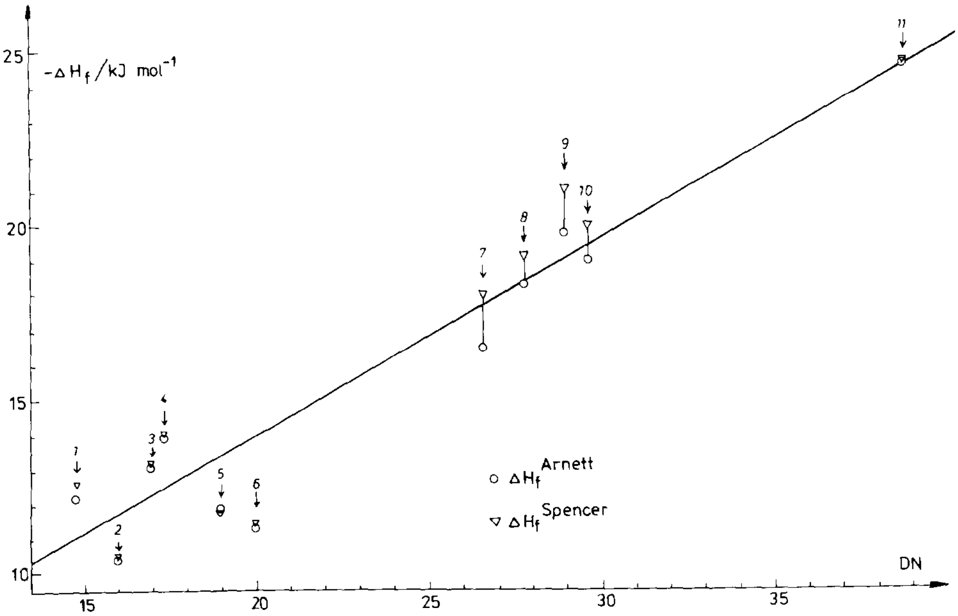

Fig. 1. The enthalpy of complex formation ΔH_f for cholesterol–proton acceptor complexes, plotted against basicity expressed as the Gutmann donor number (DN): O, $\Delta H_f^{\text{Arnett}}$; ▽, $\Delta H_f^{\text{Spencer}}$. 1, Dioxan; 2, diethylcarbonate; 3, ethylacetate; 4, butanone; 5, di-*n*-butyl-ether; 6, tetrahydrofuran; 7, dimethylformamide; 8, dimethylacetamide; 9, *n*-butanol; 10, tetramethylurea; 11, hexamethylphosphortriamide.

TABLE 2

The comparison of the enthalpy of complex formation of cholesterol and *n*-butanol [a]

Hydrogen bond	Literature	ΔH_f (kJ mol^{-1})
TEA–cholesterol	This work	−22.4
TEA–*n*-BuOH	Spencer et al. [13]	−22.5
n-BuOH–cholesterol	This work	−21.1
n-BuOH–*n*-BuOH	Spencer et al. [13]	−21.9
TEA–methanol	Spencer et al. [13]	−24.9

[a] All enthalpies are calculated relative to carbon tetrachloride.

correction term in eqn. (1) is omitted) than in the case of $\Delta H_f^{\text{Spencer}}$. In the presented correlation, we ignored the results of triethylamine (TEA) whose DN has not been precisely determined [10]. In the literature, two DN values are cited for TEA: 30.5 by Taft et al. [11] and 61.0 by Gutmann [12]. The enthalpy of the TEA–cholesterol complex formation obtained here can be compared with literature data obtained by the same method for the *n*-butanol–TEA and *n*-butanol–*n*-butanol systems (Table 2).

As can be seen, the enthalpy of hydrogen-bond complex formation of cholesterol and *n*-butanol with a typical proton acceptor (TEA), as well as with an amphiprotic alcohol (BuOH), is similar. It would appear that cholesterol behaves like a typical alcohol in these specific interactions.

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