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Hydrogen bonds between cholesterol and nitrogen bases — a thermodynamic study

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Abstract

Values of the equilibrium constant and of the enthalpy of hydrogen bond complex formation (ΔH_f) between cholesterol and some nitrogen bases (1-butylamine, di-1-butylamine, tri-1-butylamine, triethylamine, pyridine, acetonitrile, and benzonitrile) have been determined by calorimetry and IR spectroscopy. The enthalpies found for nitriles satisfy the linear correlation of ΔH_f and Gutmann's donor number, determined previously for oxygen bases. Values of ΔH_f for amines do not satisfy this relationship. The effect of steric hindrance in the amines on the thermodynamic data of the cholesterol–amine complex formation is discussed.

INTRODUCTION

Cholesterol, 5(6)-cholesten-3-ol, containing one hydroxyl group in addition to a large hydrocarbon group, behaves as a typical proton donor in relation to basic compounds [1]. Studies on the energetics of specific interactions of cholesterol are rather rare. The existing data obtained by calorimetry [1–4] and spectroscopy [5–7] concern interactions with compounds whose basic properties are due to a free pair of electrons on the oxygen atom. The characteristics of the hydrogen bonds, such as –O–H···O=X (where X is C, P, S) and –O–H···O< (ethers, alcohols), have been mainly studied, so far. The properties of cholesterol as a proton donor are similar to those of alcohols. The enthalpy of hydrogen bond complex formation (ΔH_f) reported hitherto is in the range from -10.5 to -14.0 kJ mol^{-1} for weak proton-acceptors (ethers, ketones), from -17.5 to -19.5 kJ mol^{-1} for amides, and from -20.5 to 23.5 kJ mol^{-1} for strongly basic P=O bases (HMPA, phosphine oxide) [1]. The enthalpies of hydrogen bond complex formation for cholesterol with oxygen bases correlate linearly with the Gutmann donor number ($-\Delta H_f = 0.54(\mathrm{DN}) + 2.89$, $n = 21$, $r = 0.974$, s.d. $= 0.9$). The Badger–Bauer correlation is less well satisfied ($-\Delta H_f = 0.055\Delta\nu + 7.45$, $n = 14$, $r = 0.890$, s.d. $= 1.4$).

The present study examines the energetics of hydrogen bonding between cholesterol and proton acceptors whose basic properties are due to the free

pair of electrons on nitrogen (–O–H···N≡). The study includes nitriles, such as acetonitrile and benzonitrile, and several amines, such as pyridine, 1-butylamine (BA), di-1-butylamine (DBA), tri-1-butylamine (TBA) and triethylamine (TEA).

EXPERIMENTAL

Materials

Nitriles (reagent grade) were dried by standard methods [8] and distilled under reduced pressure immediately before the measurements were made. Amines were distilled over metallic sodium, also under reduced pressure. Carbon tetrachloride (POCh Gliwice p.a.) was distilled and then dried with 4A sieves. Cholesterol (Sigma, Standard for Chromatography) was dried for more than 10 h at about 80°C over P_2O_5 in a vacuum. Cholesteryl methyl ether (Sigma, anhydrous) was stored before measurements under a vacuum over P_2O_5 for about one week. The weighing of calorimeter ampoules, the preparation of solutions and the filling of IR cells were all carried out in a dry box. IR measurements were recorded on a Brucker JFS 85 spectrophotometer within the range 4000–3000 cm^{-1}. Infrasil 4-cm quartz cells were used, which made possible measurements in the concentration range 5×10^{-4}–1.5×10^{-3} mol dm^{-3}, where cholesterol in CCl_4 is present exclusively as a monomer. A resolution of 1 cm^{-1} was used and 128 scans were accumulated. Calorimetric measurements were carried out with a calorimeter, as described previously [9]. The accuracy of the temperature measurement was about $\pm 0.8\%$.

Method

In most of the systems under study, the enthalpy of hydrogen bond complex formation was determined using the 'pure base' method of Arnett et al. [10]. This method, as compared with the other procedure used (the 'high dilution' method), avoids the use of carbon tetrachloride as a solvent. This is very important with aliphatic amines because some amines undergo slow chemical reactions in CCl_4 [11]. This rules out the use of this solvent in the calorimetric method. Carbon tetrachloride could be used in the "fast" spectroscopic method, but the error of the determined equilibrium constants was evaluated as about 20%.

The 'pure base' method consists of determining the enthalpy of solution of a proton donor $\Delta H_s^{\wedge}$ and its model ΔH_s^{M} (a compound in which the proton is substituted by a $-CH_3$ group) in pure base and in a solvent chosen as an inert reference. The enthalpy of complex formation ΔH_f is calculated from the relation

$$\Delta H_f = (\Delta H_s^A - \Delta H_s^M)_{base} - (\Delta H_s^A - \Delta H_s^M)_{ref,solv}$$

Cholesteryl methyl ether was used as the cholesterol model compound and carbon tetrachloride as the reference solvent. We have found no concentration dependence of the enthalpy of solution for cholesterol and cholesteryl methyl ether in the solvent under study. The values of ΔH_s used in the calculation are the averages of 8–12 direct measurements of the enthalpy of solution in the concentration range from 3×10^{-4} to 2×10^{-3} mol dm^{-3}.

A modified version of Arnett's 'high dilution' method [12], was used for the determination of the enthalpy of complex formation of cholesterol with pyridine and acetonitrile. An excess of proton acceptor B (base) (concentration from 0.20 to 0.25 mol dm^{-3}), in relation to cholesterol A (acid) (concentration from 0.05 to 0.06 mol dm^{-3}) in CCl_4, was used. The following system of equilibria was considered.

$$A + B = AB \quad K_f = \frac{[AB]}{[A][B]} \quad \Delta H_f \tag{1}$$

$$iA = A_i \quad K_i = \frac{[A_i]}{[A]^i} \quad \Delta H_i \tag{2}$$

For the description of equilibria in the investigated systems, it was assumed that the self-association of cholesterol in the concentration range used consists mainly of the formation of even self-associates [13, 14], i.e. dimers and tetramers. The values of equilibrium constants (K_2 = 1.1 dm^3 mol^{-1}, K_4 = 102 dm^9 mol^{-3}) and the enthalpy of tetramerization, $\Delta H_4 = -59$ kJ mol^{-1} (per tetramer mol) were taken from ref. 14 and the enthalpy of cholesterol dimerization, $\Delta H_2 = -14.5$ kJ mol^{-1}, was taken from our previous paper [1]. Equilibrium constants of the hydrogen bond complex formation K_f at 298 K were determined from the absorption of the free hydroxyl group ν(OH) (3622 cm^{-1}) of cholesterol.

The thermal effect on mixing cholesterol solution (A) with base solution (B) is a result of the enthalpy change connected with the formation of the associates under investigation (eqn. (1)), the enthalpy change due to the equilibrium shift of cholesterol self-association (eqn. (2)), and the enthalpy of dilution of both components. The enthalpy of dilution was determined in separate calorimetric measurements.

The enthalpy of hydrogen bond complex formation of cholesterol is expressed as

$$\Delta H_f = (\Delta H_{exp} - \Delta H_{dil} - \Delta H_{mon})/n_k \tag{3}$$

where ΔH_{exp} is the experimentally measured enthalpy of mixing in the tricomponent system, ΔH_{dil} is the enthalpy of mutual dilution of cholesterol solution and base solution, ΔH_{mon} the enthalpy change associated with equilibrium shift (eqn. (2)) due to the complex formation, and n_k the amount of the complex being formed.

The amounts of the complex and the respective forms of cholesterol n-mers before and after the calorimetric measurement were calculated by solving eqns. (1) and (2).

RESULTS AND DISCUSSION

The enthalpies of solution ΔH_s of cholesterol and cholesteryl methyl ether and the enthalpies of hydrogen bond complex formation of cholesterol with the examined proton acceptors are given in Table 1. The table also contains values of the equilibrium constants of cholesterol–base complexes in CCl_4, as well as shifts in the ν(OH) band. The different behaviour of nitriles and amines as proton acceptors necessitates separate discussions of the results obtained for each group of examined compounds.

Nitriles

Nitriles are weak proton-acceptors, but because of their relatively high dielectric permittivity, they are often used as solvents, especially in physicochemical investigations of electrolytes. The poor solubility of cholesterol in acetonitrile makes it impossible to measure the enthalpy of solution in this solvent. This is probably due to weak solute–solvent specific interactions (low DN = 14.1) and a low contribution of dipolar interaction in the cholesterol–acetonitrile system. The high Hildebrand parameter[16] of acetonitrile ($\delta_H = 11.9\ cal^{1/2}\ cm^{-3/2}$) is probably connected with a high contribution of cavitation forces, impeding the solubility of the large cholesterol molecule. Benzonitrile, however, with a lower basicity (DN = 11.9), is characterized by a considerably lower δ_H value ($8.4\ cal^{1/2}\ cm^{-3/2}$) which makes cholesterol sufficiently soluble in this solvent.

The cholesterol–nitrile complexes are characterized by low values of ΔH_f and K_f (Table 1). The enthalpies of complex formation of nitriles well satisfy the correlation $\Delta H_f = f(DN)$, found previously for oxygen bases (Fig. 1).

The ΔH_f values calculated on this basis are similar in magnitude to those found experimentally: acetonitrile, $\Delta H_f^{(exp)} = 10.7\ kJ\ mol^{-1}$, $\Delta H_f^{(calc)} = 10.9\ kJ\ mol^{-1}$; benzonitrile, $\Delta H_f^{(exp)} = 9.1\ kJ\ mol^{-1}$, $\Delta H_f^{(calc)} = 9.7\ kJ\ mol^{-1}$.

Amines

Amines are strongly basic compounds. They possess high Gutmann donor numbers which, however, have not yet been precisely determined [17]. With strong proton donors (substituted phenols, carboxylic acids, 1,1-dinitroethane), amines also form, in addition to the hydrogen bond complexes, complexes arising from proton transfer [18–20].

TABLE 1

Enthalpies of solution of cholesterol ΔH_s°(chol), cholesteryl methyl ether ΔH_s°(ChME), enthalpies of complex formation ΔH_f of cholesterol with different proton acceptors, equilibrium constants K_f of cholesterol, and shifts of the ν(OH) band. Units: ΔH in kJ mol^{-1}

No.	Proton acceptor	DN	ΔH_s°(chol) in kJ mol^{-1}	ΔH_s°(ChME) in kJ mol^{-1}	ΔH_f in kJ mol^{-1}	K_f in dm^3 mol^{-1}	$\Delta\nu$(OH) in cm^{-1}
1	Benzonitrile	11.9	26.3 ± 0.5	27.7 ± 0.4	-9.1 [a]	1.0 ± 0.1	75
2	Acetonitrile	14.1	–	–	-10.7 ± 0.8 [b]	1.0 ± 0.2	76
3	Pyridine	33.1	–	–	-16.0 ± 1.0 [b]	2.4 ± 0.3	280
4	1-Butylamine	42	8.8 ± 0.1	30.7 ± 0.6	-29.6 [a]	4.0 ± 0.8	350
5	Di-1-butylamine	–	5.5 ± 0.1	20.6 ± 0.3	-22.8 [a]	2.4 ± 0.2	370
6	Tri-1-butylamine	50	14.0 ± 0.2	22.2 ± 0.4	-15.9 [a]	0.8 ± 0.1	300
7	Triethylamine	61	8.4 ± 0.2 [c]	23.3 ± 0.4 [c]	-22.6 [a,c]	1.6 ± 0.3	410
8	Carbon tetrachloride		31.2 ± 0.3 [d]	23.5 ± 0.5 [c]			

[a] 'Pure base' method. [b] 'High dilution' method. [c] Ref. 3. [d] Ref. 15.

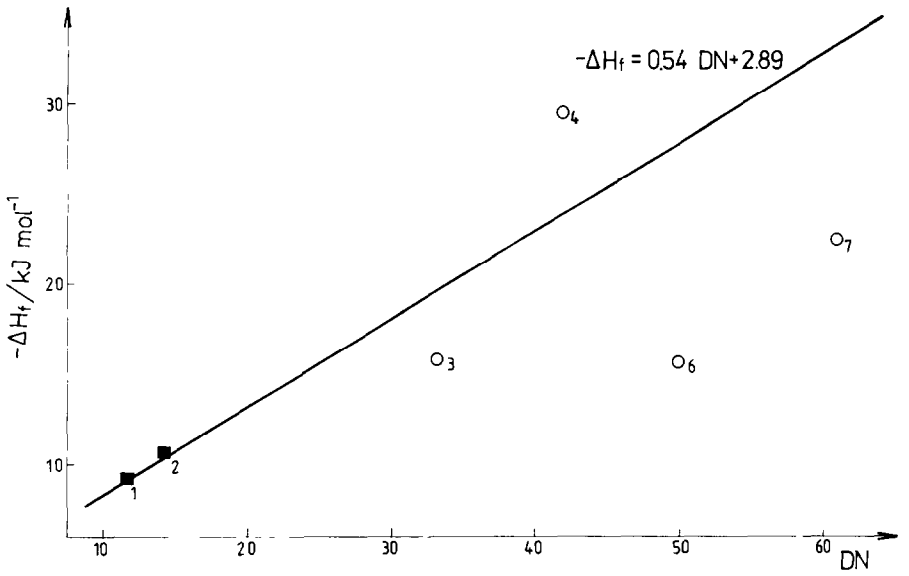

Fig. 1. Enthalpy of hydrogen bond complex formation of cholesterol as a function of Gutmann's donor number: —, oxygen bases [1]; ○, amines; ■, nitriles. Numbering as in Table 1.

It is often assumed that the basicity of the electron pair of nitrogen in tertiary amines increases with the number of carbon atoms. There are, however, many data in the literature showing that the proton-acceptor ability of amines does not follow "inductive order". It can even be different in different solvents. Comparing such basicity parameters as DN, β, β_2^H and proton affinity for TEA and TBA, one can assume that the basicity of TEA is higher than that of TBA. The data given in Table 1 also suggest that TEA is a stronger proton-acceptor than TBA in relation to cholesterol. The value of the ν(OH) band shift, a relative measure of hydrogen bond strength, is also higher for TEA (410 cm^{-1}) than for TBA (300 cm^{-1}). The formation of stronger hydrogen bonds by TEA than by TBA cannot be attributed to the difference in dipole interactions or the mechanism of complex stabilization by forming a more polarizable structure [21]. Indeed, such structures would stabilize the formation of TBA complexes more than TEA complexes.

The anomalous behaviour of tertiary amines in the formation of hydrogen bond complexes has been explained by Scott and coworkers [22, 23] in terms of the steric hindrance due to the alkyl groups. Taking into consideration the fact that the hydrocarbon group of cholesterol is very large, this phenomenon would seem to be of great importance. The effect of the steric factor is apparent in the analysis of the 1-butylamine series. The increase in basicity, BA < DBA < TBA, is accompanied by a distinct decrease in the values of ΔH_f and K_f for the complex formation with cholesterol. Similar changes in ΔH_f have been observed by Spencer et al. in the study on 1-butanol–amine complexes [24].

TABLE 2

Comparison of enthalpies of complex formation for cholesterol–amine and 1-butanol–amine systems

	$(C_4H_9)NH_2$	$(C_4H_9)_2NH$	$(C_4H_9)_3N$	$(C_2H_5)_3N$	Pyridine
ΔH_f(cholesterol)/kJ mol^{-1}	−29.6	−22.8	−15.9	−22.6	−16.0 [b]
ΔH_f(1-butanol)/kJ mol^{-1}	−28.6 [a]	−23.1 [a]	−17.8 [a]	−22.5 [a]	−16.4 [b,c]

[a] Ref. 24. [b] In CCl_4. [c] Ref. 25.

The data given in Table 2 show that cholesterol generally forms complexes of strengths similar to those of 1-butanol. The differences in the ΔH_f values for each proton donor depend, however, on the steric hindrance of the amine. For BA, with the lowest steric hindrance, the ΔH_f of cholesterol complexes is higher than for 1-butanol. In the case of DBA, TEA and pyridine, similar values of ΔH_f are observed for both donors, but for TBA the cholesterol complexes are characterized by a clearly lower enthalpy change than for the complexes with 1-butanol. This is to be expected because TBA possesses the highest steric hindrance and because the alkyl group of cholesterol is considerably larger than 1-butanol. Spencer et al. [24], in an analysis of amine–alcohol hydrogen bond interactions, have suggested the formation of additional >N–H···O bonds in the case of primary and secondary amines. The enthalpy of formation of such bonds is about 3–5 kJ mol^{-1} in systems where alcohol is used as the solvent and amine as the solute. Although, from our examinations, such interactions cannot be excluded, they are not likely to affect the values of ΔH_f given in Table 1. The use of an amine as a solvent and cholesteryl methyl ether as a model compound in the 'pure base' calculations means that the effect of >N–H···O interactions is cancelled.

The values ΔH_f obtained for amines, unlike those of oxygen bases and nitriles, do not correlate with Gutmann's donor number (Fig. 1). Except for BA, the ΔH_f values for all the secondary and tertiary amines fall below the straight line $\Delta H_f = f(DN)$. The tetrahedrite structure of amines promotes the steric hindrance and can lead to the different behaviour of amines and nitriles as proton donors.

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