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COMPARISON OF QSPR PROPERTIES FOR CHOLESTEROL AND CHOLESTANOL OLIGOMERIC ASSOCIATION FORMS

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This paper represents a continuation of our recent works and has as objective the comparison of the QSPR properties ($S_{solv\ acc}$, molecular volume, log P, refractivity, polarizability), the energy of interaction and the lengths of the hydrogen bonds for two sterols oligomers. These species have a crucial role in the fatty acids metabolism. Some of the cholesterol and cholestanol oligomer forms were evidenced experimentally in previous studies. Using the values of the interaction energy, the stability of different oligomers was judged. For the cyclic dimer and the cyclic hexamer of cholestanol positive values for the interaction energy were obtained. These values indicate the impossibility of their formation.

INTRODUCTION

Cholesterol and cholestanol represent two related sterols with a special role in metabolism. Cholesterol is the most abundant steroid in the human body and in food and, as a consequence, its *beneficial* or *malefic* role is very debated in literature.[1] Cholestanol (5,6-dihydrocholesterol) is a minor component of the human body and of food, but an increase in its serum concentration induces a pathological condition named *cerebrotendinous xanthomatosis* (CTX).[2]

Thus, their auto-association in different solutions is analysed with multiple experimental methods, especially with thermodynamic and spectral methods.[3-7] Their behaviour has been considered typical for monohydroxy alcohols, where hydrogen bonding is of central importance from the theoretical and practical standpoints. We studied the auto-association by IR spectroscopy at constant and variable temperature in different solutions of cholesterol[8] and cholestanol.[9] We obtained data which confirm those of Senegacnik and Klofutar concerning the cholesterol oligomeric species in analysed protic and non-protic solvents.[6,10,11] For cholestanol our data are the first appearing in the literature and show the differences in the character of oligomeric species. To describe some microscopic and macroscopic properties of these oligomeric species it was opportune to use molecular modelling.

In this paper, using two methods of molecular modelling (MM+ and AM1), we comparatively analysed QSPR properties for cholesterol and cholestanol dimers, trimers, tetramers and hexamers *i.e.*, oligomeric association forms, experimentally emphasised in solution.

RESULTS AND DISCUSSION

In order to calculate the QSPR properties ($S_{solv\ acc}$–solvent accessible surface, molecular volume, log P, refractivity, polarizability) of the oligomeric association forms of cholesterol and cholestanol we started from the general schema of the oligomeric forms of alcohols[8]. The comparative evaluation of these properties for monomers and linear/cyclic dimers is given in Tables 1 and 2.

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Table 1

Calculated properties by the MM+/AM1 methods for cholesterol and cholestanol

Properties	Cholesterol		Cholestanol	
	MM+	AM1	MM+	AM1
$S_{solv\ acc}$ (Å^2)	679.00	668.43	680.74	667.27
Volume (Å^3)	1236.56	1214.49	1241.66	1220.82
Log P	7.17	7.17	7.61	7.61
Refractivity (Å^3)	120.63	120.62	119.77	119.77
Polarizability (Å^3)	47.67	47.67	47.86	47.86
H_{form} (kcal/mol)		-132.64		-158.15
$d_{\alpha\text{-}OH}$* (Å)	0.94	0.96	0.94	0.96
$\nu_{O\text{-}H}$ (cm^{-1}) in IR calculated spectra		3502.22		3502.41

* α – free OH group[6,8]

Table 2

Calculated properties by the MM+/AM1 methods for linear/cyclic dimer of cholesterol and cholestanol

Properties	Cholesterol dimers			Cholestanol dimers	
	MM+		AM1	MM+	AM1
	linear	cyclic	linear	linear	linear
$S_{solv\ acc}$ (Å^2)	1239.41	1298.11	1214.65	1257.57	1233.59
Volume (Å^3)	2386.78	2442.76	2335.63	2412.89	2364.36
Log P	14.35	14.07	14.21	15.08	15.08
Refractivity (Å^3)	241.23	237.70	239.47	237.77	237.77
Polarizability (Å^3)	95.34	94.06	94.70	95.08	95.08
E_{int} (kcal/mol)	-5.27	-0.15		-7.00	
ΔH_{form} (kcal/mol)			-4.94		-3.11
$d_{O\ldots H}$ (Å)	2.27	3.02; 3.06	2.14	2.32	2.17
$d_{\beta\text{-}OH}$ (Å)*	0.94		0.94	0.94	0.97
$d_{\gamma\text{-}OH}$ (Å)*	0.94		0.96	0.94	0.96
$d_{\delta\text{-}OH}$*		0.94			

*β – proton acceptor OH group, γ – proton donor OH group; δ – internal OH group which acts as proton donor and proton acceptor [6,8]

Considering the equilibrium:

$$n\,A \leftrightarrow A_n$$

where n is the number of monomer units, the *energy of interaction* (E_{int}), respectively the *enthalpy of formation* (ΔH_{form}) result from the following relations:

$$E_{\text{int}} = E_{A_n} - nE_A$$

$$\Delta H_{form} = H_{A_n} - nH_A$$

The structure optimisation by molecular mechanics with the MM+ force field and semi-empirical AM1, RHF method, *in vacuo*, for monomers shows insignificant differences of the QSPR properties and frequences of vibration. The lengths of the OH bonds ($d_{\alpha\text{-}OH}$) are equal for both sterols, H_{form} is more negative for cholestanol.

In the case of linear dimers it can be observed that the $S_{solv\ acc}$, volume, log P (partition coefficient defined as the ratio of the concentration of the compound in octanol and in water) and ΔH_{form} are higher for cholestanol than for cholesterol. The refractivity, polarizability and E_{int} are higher for the linear dimers of cholesterol than those of the linear dimers of cholestanol. The OH bond lengths are close for the linear dimers and for the monomers of the both sterols. The hydrogen bond lengths are comparable with the literature values,[12] but are higher for the linear dimer of cholestanol than for the linear dimer of cholesterol by approximately 0.022 Å by MM+ and 0.029 Å by AM1.

Fig. 1 shows the structure of the cyclic dimer of cholesterol optimised by the MM+ method with RMS gradient 0.015 kcal/(Å·mol).

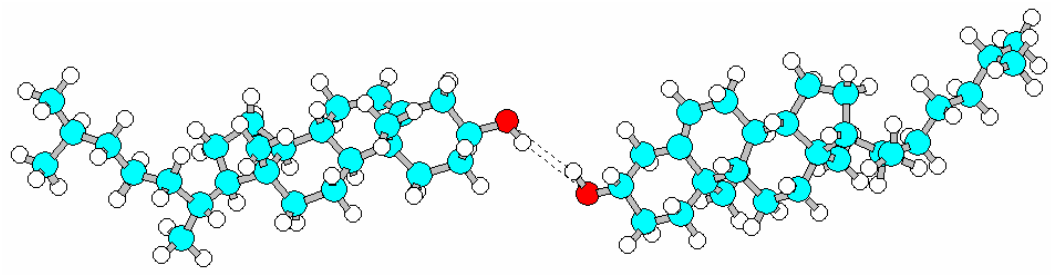

Fig. 1 – The structure of the cyclic dimer of cholesterol optimised by the MM+ method.

The calculated E_{int} for the cyclic dimer of cholesterol is –0.15 kcal/mol. This value indicates the possibility of cyclic dimer formation, in concordance with the experimental data.[11] The value of E_{int} for the cyclic dimer of cholestanol is 29.15 kcal/mol and indicates that this oligomer does not exist.

Comparing these properties for cholesterol dimers we found that the energy of interaction for the linear dimer is more negative than for the cyclic dimer and this shows that the linear dimer is more stable than the cyclic one.

The structure of linear trimers was optimised by the MM+ method. Table 3 shows the calculated properties for these trimers.

Table 3

Calculated properties by the MM+ method for linear trimers/tetramers of cholesterol and cholestanol

Properties	Trimer		Tetramer	
	Cholesterol	Cholestanol	Cholesterol	Cholestanol
$S_{solv\ acc}$ (Å^2)	1523.4	1545.69	1823.67	1860.93
Volume (Å^3)	3280.47	3330.07	4209.12	4293.23
Log P	21.24	22.55	28.28	30.03
Refractivity (Å^3)	358.23	355.77	477.17	473.77
Polarizability (Å^3)	141.73	142.31	188.76	189.53
E_{int} (kcal/mol)	-23.16	-26.13	-152.24	-40.23
$d_{O...H}$(Å)	2.21; 2.21	2.29; 2.30	2.24; 2.14; 2.26	2.24; 2.41; 2.27
$d_{\beta\text{-}OH}$ (Å), $d\ \gamma_{\text{-}OH}$ (Å), $d\ \delta_{\text{-}OH}$ (Å)	0.94	0.94	0.94	0.94

It can be observed that: *(i)* $S_{solv\ acc}$, the volume, the polarizability, log P and the hydrogen bond length have higher values for the linear trimers of cholestanol than for the linear trimers of cholesterol; *(ii)* the refractivity, the energy of interaction are higher for the linear trimers of cholesterol than for cholestanol; *(iii)* the OH bond length is close to those of monomers.

Also, Table 3 gives the calculated properties of the linear tetramers of both sterols. On analysing these values it can be observed that: *(i)* the $S_{solv\ acc}$, volume, log P and energy of interaction are higher for cholestanol tetramers than for cholesterol. The interaction energy for cholesterol tetramers is –152.24 kcal/mol and for cholestanol tetramers it is –40.23 kcal/mol, indicating the higher stability of cholesterol tetramers; *(ii)* the refractivity is higher for the cholesterol tetramer (as expected) than for cholestanol; *(iii)* the OH bond length is close to that of unassociated molecules; *(iv)* the value differences between these properties increase with the association order.

Figs. 2 and 3 represent the structures of the cyclic tetramer of cholestanol and hexamer of cholesterol, optimised by MM+ with RMS gradient 0.05 kcal/(Å·mol). Table 4 gives the calculated properties for these oligomers. On analysing these values for tetramers it can be observed that: *(i)* $S_{solv\ acc}$., log P, the polarizability and the hydrogen bond length are higher for the cyclic tetramers of cholestanol than for cholesterol; *(ii)* the volume and the refractivity are higher for the cyclic tetramers of cholesterol than for cholestanol; *(iii)* the OH bond lengths are close in the cyclic tetramer and in the linear ones.

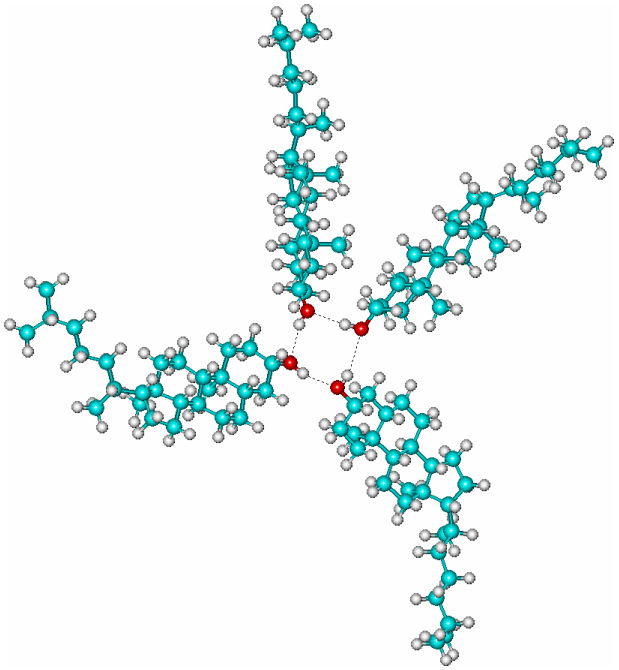

Fig. 2 – The structure of the cyclic tetramer of cholestanol optimised by the MM+ method.

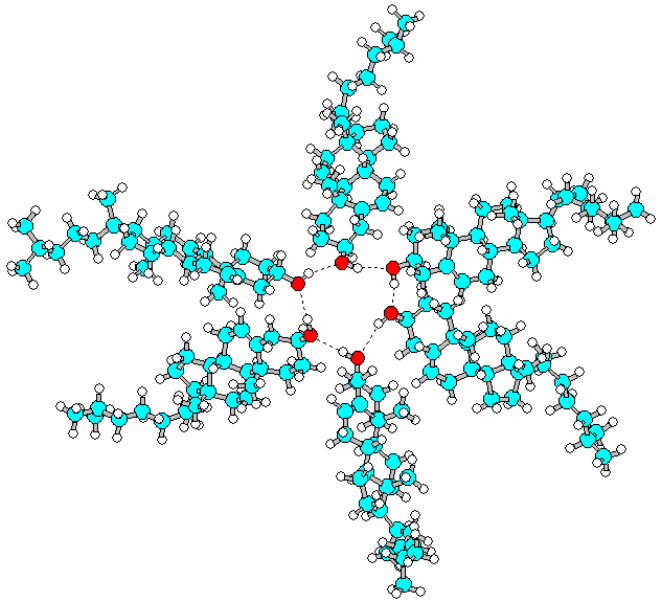

Fig. 3 – The structure of the cyclic hexamer of cholesterol optimised by the MM+ method.

Table 4

Calculated properties by the MM+ method for cyclic tetramers/hexamer of cholesterol and cholestanol

Properties	Tetramers		Cholesterol hexamer
	Cholesterol	Cholestanol	
$S_{solv\ acc}$ (Å^2)	2377.21	2342.09	3429.70
Volume (Å^3)	4737.54	4717.49	6984.87
Log P	28.14	29.89	42.21
Refractivity (Å^3)	475.41	472.01	713.11
Polarizability (Å^3)	118.12	188.89	282.19
E_{int} (kcal/mol)	-8.75	-19.44	-19.28
$d_{O...H}$(Å)	2.11; 2.43; 2.84; 2.16	2.42; 2.25; 2.70; 2.26	2.23; 2.28; 2.19, 2.42; 2.11; 2.41
$d_{\delta\text{-}OH}$ (Å)	0.94	0.94	0.94

The cyclic hexamer of cholesterol is likely to be present in CCl_4 solutions of cholesterol, as described in papers.[6, 8] Unfortunately, the solubility of cholestanol in this solvent does not permit a spectral analysis.[9] But, the calculated E_{int} for the cyclic hexamer of cholestanol is 68.48 kcal/mol and shows that the oligomer does not exists.

For the optimised oligomer species of cholesterol and cholestanol the solvent accessible surface ($S_{solv\ acc}$) and the volume vary linearly with the number of monomer units. Thus, *(i)* by linear regression for open oligomers of cholesterol the correlation coefficient is 0.9851 for the solvent accessible surface and 0.9983 for the volume and for those of cholestanol 0.9853, respectively 0.9985; (*ii)* for the cyclic oligomers of cholesterol the correlation coefficient is 0.9996 concerning the solvent accessible surface and 0.9999 for the volume. The higher values of the calculated log P for cholestanol and its associated species toward cholesterol species are obvious from all the tables. This is in accord with the greater toxicity of cholestanol in the human body, emphasised by Seyama.[2]

CALCULATION METODS

The molecular modelling of auto-association of cholesterol and cholestanol *in vacuo* was performed using HyperChem Release 6.01 Program for Windows 2000, Hypercube Inc., installed on a PC Intel Pentium 4, CPU 2.8 GHz, 512 MB of RAM, using the following methods:

– the molecular mechanics, force field MM+, the calculation of the electronic term by bond dipoles approximation, geometry optimisation with Polack-Ribiere algorithm. The used RMS gradient was 0.001 kcal/Å mol for the monomer and linear dimer; for the cyclic dimer, linear trimer and tetramer – 0.015 kcal/Å mol; for the cyclic tetramer and hexamer – 0.05 kcal/Å mol;

– the quantum mechanics, semi-empirical method AM1, RHF, Polack-Ribiere algorithm, gradient RMS = 0.01 kcal/Å mol.

These various gradients had to be used because of the increased oligomers complexity and the limited character of our computing resources.

CONCLUSIONS

The results of the modelling studies indicate differences between the values corresponding to some properties ($S_{solv\ acc}$, volume, log P, refractivity, polarizability and energy of interaction) and insignificant differences concerning the bond length of the type $d_{O....H}$, $d_{\beta\text{-}OH}$, $d_{\gamma\text{-}OH}$, $d_{\delta\text{-}OH}$ between the oligomers of the two studied sterols.

The energy of interaction allows comparison of the stability of different oligomers of the two compounds and shows the impossibility of formation for the cholestanol cyclic dimer and hexamer.

$S_{solv\ acc}$ is a significant property concerning the oligomers reactivity/stability. A linear increase for $S_{solv\ acc}$ and volume with the number of monomer units for the oligomers of cholesterol and cholestanol was obtained.

Log P values reflect the difference between the hydrophilic and the hydrophobic character of the examined oligomers and shows the higher toxicity of cholestanol and its auto-association species towards those of cholesterol.

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REFERENCES

1. F. Bettellheim & J. Mark, "Introduction to general organic & biochemistry", 5th Ed. Saunders College Publ., Forth Worth, 1998.
2. Y. Seyama, *J. Mat. Food*, **2003**, *6*, 217.
3. P. Goralski, *Thermochim. Acta*, **1994**, *235*, 31.
4. P. Goralski, *J. Chem. Thermod*., **1993**, *25*, 367.
5. M. Costas and D. Paterson, *J. Chem. Soc. Faraday Trans*., **1985**, *81*, 655.
6. M. Senegacnik, jr. and C. Klofutar, *Spectrochimica Acta Part A*, **1997**, *53*, 1495.

7. B.W. Foster, J. Robeson, N.Tagata, J.M.Beckerdite, R.L.Huggins and E.T.Adams, *Journal of Physical Chemistry*, **1981**, *24*, 3715.
8. C. Mandravel, V. Chiosa, C. Teodoreanu and I. Stanculescu, *Rev. Roum. Chim.*, **2005**, 50, 683-688.
9. V. Chiosa, C. Teodoreanu, I. Stanculescu and C. Mandravel, *Anal. Univ. Buc*., **2005**, Ser. Chem., *XIV*, 247-252.
10. M. Senegacnik and C. Klofutar, *10th Int. Symp. Spectroscopy Theory Practice, Bled, Slovenia, 14-17 April 1997, Book of abstracts (Ljubljana), Slovenian Chemical Society, Spectroscopic Section,* 1997, *L-11*, 77.
11. M. Senegacnik, jr. and C. Klofutar, *Spectrochimica Acta Part A*, **1998**, *54*, 709.
12. C. Mandravel and I. Stănculescu, "Interactions moléculaires", Ed. Univ. Buc., 2004, p. 90.