Indian Journal of Chemistry
Vol. 46B, November 2007, pp. 1855-1859

A comparative crystallographic analysis of the X-ray structure of three cholest-based steroidal molecules

Rajnikant*, Dinesh, Kamni, Bandhan Sharma, Sonam Lotus & Kewal Gupta
Condensed Matter Physics Group, Department of Physics, University of Jammu, Jammu Tawi 180 006, India
E-mail: rkantverma@rediffmail.com

Received 28 November 2006; accepted revised 6 August 2007

The molecular and crystal structures of (+)-4-cholesten-3-one **1** cholesteryl chloroformate **2** and cholesteryl-caprylate **3** have been determined by using X-ray crystallographic and computational techniques. All the three compounds crystallize in the monoclinic space group $P2_1$ with unit cell parameters: a=10.683(5)Å, b=7.861(2), c=14.616(2), β=105.8(2)° for [1], a=12.294(2)Å, b=9.399(8), c=12.787(2), β=113.3(1)° for [2] and a = 12.778(9), b = 9.201(4), c = 14.063(6) Å, β = 93.85(4)° for [3]. The number of molecules per unit cell in case of each structure is 2. The final R-factor for [1] is 0.054, [2] 0.077 and [3] 0.068. Besides some interesting geometrical and structural features, all the three molecules exhibit C-H…O hydrogen bonding. A comparative crystallographic analysis of all the three molecules has been reported in this paper.

Keywords: Steroids, X-ray diffraction, crystal structure, hydrogen bonding

Steroids perform some of the most fundamental biological functions. Cholest-based steroids are known to have multifaceted biological properties[1-3]. Cationic cholesterol is used as source of important strategies in gene transfection namely, use of liposomes made from biosurfactants and harnessing efficient gene transfection by activating the membrane-bound receptor molecules[4]. Cholesterol with oxygen atoms are known as oxysterols and are important intermediates in a number of hepatic and extrahepatic catabolic pathways, most of which generate water-soluble bile acids as final products. Based on largely indirect evidence, oxysterols are generally believed to be important physiological mediators of cholesterol-induced effects [5].

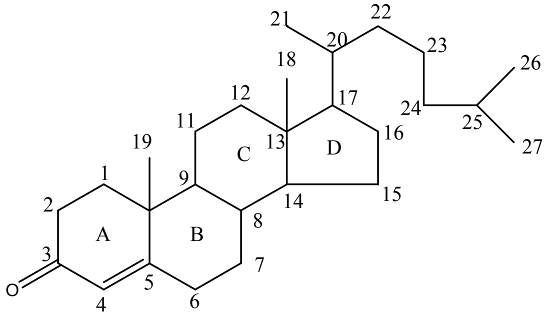
In continuation to our work on the single crystal growth of X-ray diffraction quality crystals and crystallographic analysis of steroidal molecules[6-10], the molecular and crystal structures of (+)-4-cholesten-3-one, cholesteryl chloroformate and cholesteryl-caprylate have been reported in this paper.

All the three compounds were purchased from Aldrich-Sigma, USA and details regarding its chemical synthesis are available in the Aldrich Catalogue {2001}. The chemical structures are presented in **Figure 1**.

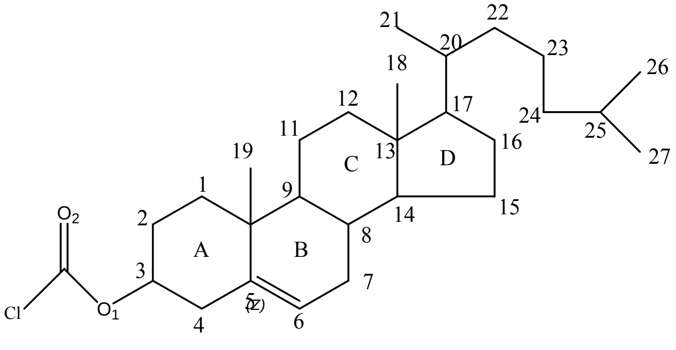
Experimental Section

The single crystals of compounds **1**, **2** and **3** were obtained by slow evaporation technique using acetone, ethyl acetate and toluene as solvents. Three-dimensional intensity data for transparent rectangular plate-like single crystals of **1**, **2** and **3** were collected on an Enraf-Nonius CAD-4 diffractometer using MoKα radiation (λ= 0.71073Å) scan mode was employed for data collection with θ-range of 2.13-24.99° (1), 2.91-32.53° (2) and 2.08-24.97° (3), respectively. A total of 2381 reflections were recorded in case of **1** out of which 2250 were found unique ($0 \le h \le 12$, $-2 \le k \le 9$, $-17 \le l \le 16$) and 1697 as observed [$F_o > 4\sigma (F_o)$]. In case of **2**, 7239 reflections were recorded of which 7233 were found unique ($-18 \le h \le 18$, $11 \le k \le -11$, $-19 \le l \le 19$) and 3256 were treated as observed [$F_o > 4\sigma (F_o)$]. In case of **3**, 3236 reflections were recorded of which 3093 were found unique ($0 \le h \le 15$, $0 \le k \le 10$, $-16 \le l \le 16$) and 1652 were treated as observed [$F_o > 4\sigma (F_o)$]. Two standard reflections *i.e.* ($\bar{3}\ 0\ \bar{4}$) and ($0\ \bar{3}\ \bar{4}$) for **1**, ($1\ 2\ 3$) & ($1\ 2\ \bar{3}$) for **2** and ($1\ 2\ 3$ & $1\ \bar{2}\ 3$) for **3** were measured every 100 reflections and no significant variation in the intensity data was observed. Reflection data for all the three compounds were corrected for Lorentz and polarization effects.

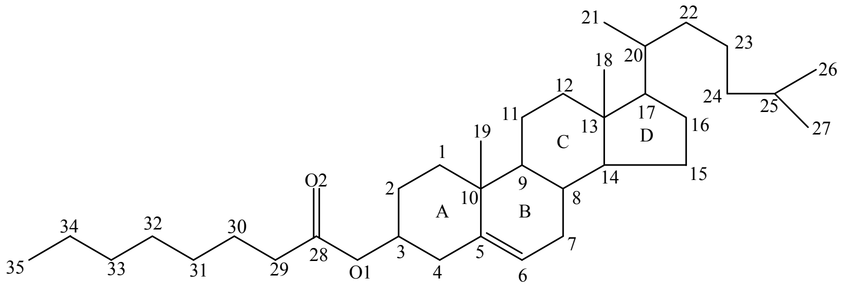
Note: Supplementary data including bond angles, torsion angles and details of hydrogen atoms for all the three steroidal molecules is available with the corresponding author and it can be provided on request.



1



2



3

Figure 1 — Chemical structure of (+)-4-cholesten-3-one **1**, cholesteryl chloroformate **2** and cholesteryl-caprylate **3**

The structure of all the three compounds has been determined by employing Direct methods using SHELXS software[11]. All non-hydrogen atoms of the molecules were located from the E-map. Full-matrix least–squares refinement of the three structures has been carried out by using SHELXL program[12]. The positional and thermal parameters for non-hydrogen atoms were refined anisotropically. All hydrogen atoms in **1**, **2** and **3** were fixed stereochemically. Refinement of **1**, **2** and **3** has yielded a final R-factor of 0.055, 0.077 and 0.068, respectively. The maximum and minimum value for the residual electron density is 0.38 and –0.18eÅ^{-3} (1), 0.22 and –0.27eÅ^{-3} (2) and 0.20 to-0.17 eÅ^{-3} (3), respectively. Atomic scattering factors were obtained from International Tables for Crystallography (1992, Vol. C Tables 4.2.6.8 and 6.1.1.4). The crystallographic data for the compounds **1**, **2** and **3** are listed in **Table I**. A general view of the molecule indicating atom numbering scheme for **1, 2** and **3** (thermal ellipsoid drawn at 50% probability) is shown in **Figure 2** (ref. 13**)**. The geometrical calculations were performed using PARST program[14].

Results and Discussion

The bond distances for non-hydrogen atoms are presented in **Table II**. Geometrical details of intra-

Table I — Crystal data and structure refinement details

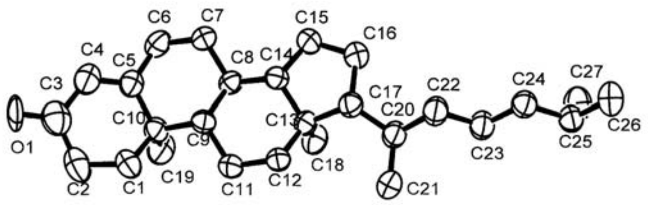
	Compd **1**	Compd **2**	Compd **3**
Empirical Formula	$C_{27}H_{44}O$	$C_{28}H_{45}O_2Cl$	$C_{35}H_{60}O_2$
Formula weight	769.24	449.12	512.83
Temperature	293(2)K	293(2)K	293(2)K
Radiation	MoKα	MoKα	MoKα
Wavelength	0.71073Å	0.71073Å	0.71073Å
Unit cell dimensions	a = 10.683(5),	a = 12.294(2),	a = 12.778(9)
	b = 7.861(2),	b=9.399(8)	b = 9.201(4)
	c=14.616(2)Å,	c=12.787(2)Å,	c = 14.063(6) Å
	β=105.8(2)°	β = 113.3(1)°	β = 93.85(4)°
Volume	1181.13(7) Å^3	1356.7(1) Å^3	1649.6(2) Å^3
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1$	$P2_1$	$P2_1$
Z	2	2	2
ρ_{calcd}, Mg/m^3	1.081	1.099	1.032
F(000)	428	492	572
No. of standard reflections	2 ($\bar{3}$ 0 $\bar{4}$; 0 $\bar{3}$ $\bar{4}$)	2 (1 2 3 ; 1 2 $\bar{3}$)	2 (1 2 3 ; 1 $\bar{2}$ 3)
Limiting indices	0 ≤ h ≤ 12	-18 ≤ h ≤ 18	0 ≤ h ≤ 15
	-2 ≤ k ≤ 9	11 ≤ k ≤ -11	0 ≤ k ≤ 10
	-17≤ l ≤ 16	-19 ≤ l ≤ 19	-16 ≤ l ≤ 16
No. of reflections collected	2381	7239	3236
Reflections unique	2250	7233	3093
Observed reflections	1697	3256	1652
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Goodness-of –fit on F^2	1.067	1.057	1.243
Final R factor	0.055	0.077	0.068
Largest diff. Peak & hole	0.38 & -0.18eÅ^{-3}	0.22 & -0.27eÅ^{-3}	0.22 & -0.27eÅ^{-3}

and intermolecular interactions are presented in **Table III**.

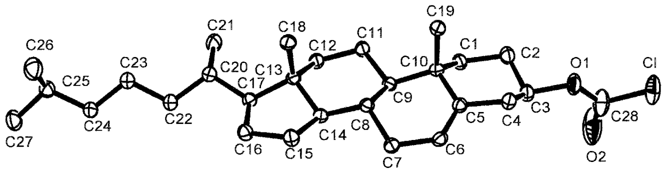
The bond lengths and bond angles in structures (**1**, **2** and **3**), by and large, agree well with the values as reported in the literature for some analogous structures[6-10]. In case of **1**, there is significant deviation in bond length between C3=O1 [1.30(8)Å]. The bond angles C2-C3-O1 and C4-C3-O1 indicate that ketone group is inclined at an angle of 122° with respect to ring A. This inclination of O1 could be due to strong intermolecular C26-H26c…O11 hydrogen interaction. In case of **2**, the length of bond O1-C28 [1.259(2) Å] is smaller than its theoretical value [1.32 Å] and shortening of this bond could be due to the ketone group (O2) which act as a bifurcated acceptor and is responsible for intra- and intermolecular hydrogen bonding. In case of **3** the double bond character of C5 = C6 is confirmed by its distance of 1.320(1)Å. The length of bond C28=O2 [1.169(2) Å] is much shorter than its standard value [1.20Å]. The shortening of this bond in the present structure may be due to some thermal disorder present in the ketone group atoms. There is a slight deviation of bond lengths for side chain atoms (C29 - C35) and this deviation could be attributed due to the presence of thermal disorder.

In case of **1**, ring A adopts *sofa* conformation[15] with asymmetry parameter ΔC_s (C1) = 5.95, ring B exists in chair conformation with asymmetry parameters ΔC_2 (C5-C10) = 4.56 and ΔC_s (C5) = 1.19, ring C occurs in chair conformation with asymmetry parameters ΔC_2 (C9-C11) = 2.50 and ΔC_s (C9) = 5.39 and ring D shows the half-chair conformation with asymmetry parameter ΔC_2 (C13-C14) = 7.33.

In case of **2**, ring A adopts *chair* conformation with asymmetry parameters ΔC_2 (C2-C3) = 1.95 and ΔC_s (C2) = 2.97, ring B exists in half-chair conformation with asymmetry parameter ΔC_2 (C5-C6)=1.80, ring C occurs in chair conformation with asymmetry parameters ΔC_2 (C9-C11) = 4.80 and ΔC_s (C9) = 2.52 and ring D shows the half-chair conformation with asymmetry parameter ΔC_2 (C13-C14) = 5.73. The ring conformations have been calculated with the values of torsion angles which show that rings A and B have different conformations while the rings C and D in case of compounds **1** and **2** have same conformations.



Compd 1



Compd 2

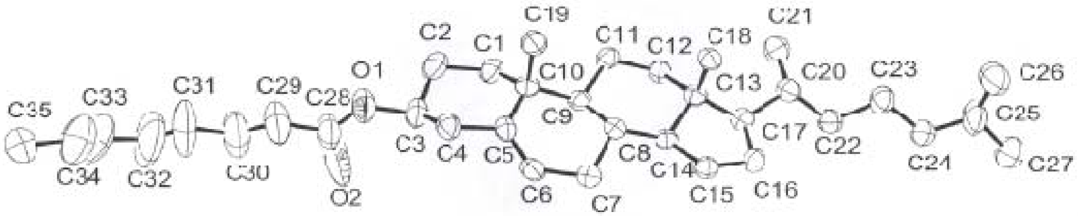


Figure 2—General view of comounds **1 2** and **3** (thermal ellipsoids dram at 50% probability level)

Table II — Bond distances (Å) for the non-hydrogen atoms (e.s.d.'s are given in the parentheses)

	Compd **1**		
O1-C3	1.300(8)	C2-C3	1.478(9)
C3-C4	1.481(9)	C17-C20	1.541(7)
C20-C21	1.524(7)	C20-C22	1.540(7)
C22-C23	1.517(7)	C23-C24	1.530(6)
C24-C25	1.509(7)	C25-C26	1.523(6)
C25-C27	1.505(6)		
	Compd **2**		
O1-C3	1.494(5)	O1-C28	1.193(9)
O2-C28	1.203(2)	Cl-C28	1.697(7)
C5-C6	1.325(6)	C17- C20	1.514(6)
C20-C21	1.531(7)	C20-C22	1.519(5)
C22-C23	1.514(6)	C23-C24	1.502(5)
C24-C25	1.506(7)	C25-C26	1.474(9)
C25-C27	1.524(7)		
	Compd **3**		
C22-C23	1.500(1)	C3-O1	1.468(1)
C23-C24	1.528(1)	C24-C25	1.455(2)
C5-C6	1.320(1)	C25-C26	1.308(3)
C25-C27	1.513(2)	C28-O1	1.259(2)
C28-O2	1.169(2)	C28-C29	1.519(2)
C29-C30	1.335(3)	C30-C31	1.526(3)
C31-C32	1.533(4)	C32-C33	1.645(4)
C33-C34	1.310(4)	C34-C35	1.550(3)

Table III — Hydrogen bonding and short contact geometry (Å, º)

D-H…AH	…A(Å)	D…A(Å)	D-H…A(°)
	Compd **1**		
C26-H26c…O1$^{(i)}$	2.71(1)	3.521(1)	142.7(6)
Symmetry Code : (i) x-1, y, z + 1			
	Compd **2**		
C8-H8…O2	1.51(1)	1.970(2)	102.5(6)
C19-H19c…O2$^{(i)}$	2.72(1)	3.154(1)	108.1(4)
Symmetry Code : (i) -x + ½, -y, -z + ½ + 1			
	Comd **3**		
C3–H3…O2	2.21(1)	2.59(2)	101.9(1)
C30-H30b…O2	2.67(1)	2.88(3)	92.3(2)

In case of **3**, ring A adopts *chair* conformation with asymmetry parameters ΔC_2 (C2 - C3) = 2.19 and ΔCs(C3) = 3.38. The average value of torsion angles in this ring is 111.8(6)°. Ring B exists in half-chair conformation with asymmetry parameters ΔC_2 (C5-C6) = 3.80. Ring C also occurs in chair conformation with asymmetry parameters ΔC_2(C9-C11) = 5.38 and ΔCs(C9) = 2.23. The five membered ring D occurs in half-chair conformation with asymmetry parameters $\Delta C_2(C13\text{-}C14) = 2.68$.

In the monoclinic space group $P2_1$, the molecules of all the three compounds are linked by C-H…O hydrogen interactions. In compounds, the structure is stabilized by an intermolecular C-H…O interaction where the hydrogen donor atom is C26 and O1 is the acceptor atom. The C(methyl)-H bond in the molecule at (x,y,z) form a hydrogen bond (**Table III**) with the O(ketone) atom of the molecule at (x-1, y, z+1) position. The molecular structure of compound **2** is stabilized by one C8(sp^3)-H…O2 intramolecular interaction and one C19(sp^3)-H…O2 intermolecular interaction. In both the interactions, O2 acts as bifurcated acceptor. Compd **3** exhibits two C-H…O intramolecular interactions. In both the interactions, O2 is the only acceptor atom while C3 and C30 are the donor atoms. The geometrical details of these interactions are presented in **Table IV**. Based on the pioneering work of Desiraju and Steiner[16] on the weak hydrogen bond, the distinction between the strength of hydrogen bonds has been made on the basis of distance D(X…A)Å, d(H…A) Å and angle θ(X-H…A)^o cut-off criteria and in the present case all the hydrogen bonds are weak and results are in consonance with the finding of Desiraju and Steiner[16].

Acknowledgement

One of the authors (Rajnikant) is thankful to the Department of Science and Technology, New Delhi for the financial support under Project No.SR/S2/CMP-47.

References

1 Williams-ashman H G & Reddi A H, *Annun Rev Physiol*, 33, **1971**, 31.

2 Jensen E V & Desombre E R, *Annun Rev Biochem,* 41, **1972**, 203.

3 Duax W L, Weeks C M & Roherer D C, *Topics of stereochemistry,* edited by N L Allinger and E L Eliel (Wiley, New York), 9, **1976**, 271.

4 Nakanishi M, *Current Medicinal Chemistry,* 10(14), **2003**, 1289.

5 Bjorkhem I, *J Clin Invest,* 110, **2002**, 725.

6 Rajnikant, Gupta V K, Khan E H, Shafi S, Hashmi S, Shafiullah, Varghese B & Dinesh, *Crystallography Reports,* 46 (6), **2001**, 963.

7 Rajnikant, Gupta V K, Shafi S, Khan E H, Firoz J, Shafiullah & Gupta R, *Cryst Res Tech,* 36 (2), **2001**, 215.

8 Rajnikant, Gupta V K, Shafi S, Khan E H, Firoz J, Shafiullah & Gupta R, *Cryst Res Tech,* 36 (4-5), **2001**, 471.

9 Rajnikant, Gupta V K, Shafi S, Khan *E H,* Hashmi S, Shafiullah, Varghese B & Dinesh, *Cryst Res Tech,* 36 (11), **2001**, 1281.

10 Rajnikant, Gupta V K, Shafi S, Khan E H, Hashmi S, Shafiullah, Varghese B & Dinesh, *Crystallography Reports,* 47 (1), **2002**, 75.

11 Sheldrick G M, *SHELXS97:Program for the solution of crystal structures,* University of Gottingen, Germany, **1997**a.

12 Sheldrick G M, *SHELXL97:Program for the refinement of crystal structures.* University of Gottingen, Germany, **1997**b.

13 Farrugia L J, *J Appl Cryst,* 30, **1997**, 565.

14 Nardelli M, ***Comput Chem,*** 7, **1993**, 95.

15 Duax W L & Norton D A, *Atlas of Steroid Structure*, (New York, Plenum), 1, **1975**.

16 Desiraju G R & Steiner T *The weak hydrogen bond in structural chemistry and biology,* (IUCr Oxford Press, New York), 48, **1999**.