J Mol Model (2005) 11: 135–140
DOI 10.1007/s00894-004-0232-7

ORIGINAL PAPER

Kamlesh Sharma · Carlos Kubli-Garfias

Theoretical mechanism of the formation of cholesteryl chloride from cholesterol and thionyl chloride

Received: 11 May 2004 / Accepted: 11 November 2004 / Published online: 27 January 2005

Abstract This work describes a theoretical approach to the substitution reaction mechanism involving the conversion of cholesterol to cholesteryl chloride. Two chlorosulfite ester molecules were formed as intermediates. An iso-steroid was found as the transition state. The final product was cholesteryl chloride and the side products were HCl and SO_2. Calculations were carried out at high level Hartree–Fock theory, using the 6–31G* basis set. From the electronic structure of the reactants, the most important physicochemical properties involved in the reaction pathway were used. Thus, to determine the participation of each molecule and to explain the mechanism of reaction; the total energy, HOMO and LUMO, atomic orbital contribution to frontier orbitals formation, electrostatic potentials, atomic charges, hardness and dipole moment were used. Characterization of intermediates and transition state was supported by their respective energy minima, fundamental frequencies and equilibrium geometry.

Keywords Cholesterol · Cholesteryl chloride · Reaction Mechanism · ab initio theory

Introduction

Steroidal heterocyclic compounds with pharmacological properties have been synthesized from cholesterol. Likewise, cholesteryl chloride has been used to obtain steroidal epoxide and ketone derivatives. Steroidal epoxide for instance, has been used as starting material to synthesize substituted 1,3-oxathiolane [1] and the steroidal ketone to synthesize substituted spiro-oxazolidine [2].

Cholesteryl chloride has also been used to obtain cholesterol to produce steroid hormones [3]. Interestingly, the method for the synthesis of cholesteryl chloride was reported 100 years ago by Diels and Abderhalden [4].

Although the reaction to form cholesteryl chloride has been established, its electronic mechanism, reaction intermediates, energies and related properties are still unknown. Indeed, to elucidate this mechanism could be useful for the production of steroidal heterocyclic compounds with pharmacological utility. Based on that rationale, it was decided to study cholesteryl chloride formation using ab initio molecular orbital theory.

Method

The molecules of cholesterol (cholest-5-en-3β-ol) and thionyl chloride were used to define the reaction between cholesterol and thionyl chloride to obtain the final product cholesteryl chloride (3β-chloro cholest-5-ene).

The electronic structure, derived properties and lower energy conformation of cholesterol (Ch), thionyl chloride and all the products of the reaction were obtained by high-level ab initio theory. However, molecular calculations started with the semiempirical PM3 method followed by the low-level Hartree–Fock model STO-3G*. The resulting wavefunction, Hessian matrix and the geometry of the molecules obtained were used for a second calculation with the split-valence basis set 3–21G*. The procedure was applied again for a final calculation at the 6–31G* level. The asterisk means that "d" polarization functions were added for carbon, oxygen, sulfur and chlorine atoms.

To assess the reaction mechanism and establish the reaction pathway, the following physicochemical parameters were used: total energy, frontier orbitals (highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO)), the contiguous

K. Sharma · C. Kubli-Garfias (✉)
Laboratorio de Química Hormonal, Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México, Apartado Postal 70-469, México D.F., 04510 Mexico
E-mail: kubli@servidor.unam.mx
Tel.: +52-55-56223815
Fax: +52-55-55500048

orbitals HOMO-1 and LUMO + 1, atomic orbital (AO) contribution, dipole moment (μ), electrostatic charges and electrostatic potential. Likewise the hardness (η) index was used to predict the molecular reactivity. Fundamental frequencies at the semiempirical level (PM3), of intermediates and transition state were calculated to assess the feasibility of intermediates and transition state.

Computer calculations were carried out on a Pentium 4 (3.2 GHz) based computer. The software utilized was Spartan' 04 Windows [5] and ChemDraw Pro 2004.

Results

The reaction pathway consisted of: an initial state (reactants), followed by two intermediates and a transition state. The final products were cholesteryl chloride, hydrochloric acid (HCl) and sulfur dioxide (SO_2).

The reactants showed the following facts: The lone pairs of the O atom in Ch form a electrostatic potential and its $2p_x$ AO contributes to the HOMO. The $3p_x$ AO of the S atom contributes to the LUMO of $SOCl_2$. This sulfur atom also produces a positive electron-deficient zone. These conditions are sufficient to initiate the reaction. Thus, the positively charged sulfur atom binds easily with the electronegative oxygen of the Ch OH-group. This complementarity is clearly observed in the encoded electrostatic potential map on the electron density surface.

The reaction occurs because the $3p_x$ AO (LUMO) of the electrophilic S atom is capable of accepting one electron, and the $2p_x$ AO (HOMO) of the nucleophilic Ch oxygen is capable of giving away one electron forming a covalent bond. As a consequence, Cl2 is eliminated as a chloride ion. Figure 1, shows the electronic and molecular properties of the reactants at the initial state of the reaction.

After the release of a chloride ion, the first intermediate is formed, a chlorosulfite ester · HCl (cholesteryl chlorosulfonate · HCl). In this case, the electrostatic potential map, the atomic charge values and the $3p_z$ AO of the Cl2 atom (HOMO) were electronically adequate and close enough for reacting with the H atom of the O1–H moiety of Ch. The oxygen (O1) as part of the LUMO also participates through its $2p_x$ AO.

The reaction continues when the H atom donates its $1s$ electron to O1 and is released as a proton. The proton attracts an electron from Cl2 (charge −0.295) forming hydrochloric acid (HCl). Figure 2 shows some electronic and molecular properties associated with the formation of the first intermediate, chlorosulfite ester · HCl.

The release of HCl marks the formation of the second intermediate, also a chlorosulfite ester, HCl (cholesteryl chlorosulfonate, HCl). According with the computed data, the following occurs: the $1s$ AO (LUMO) of the electrophilic proton from HCl attacks the lone pair of electrons of Cl1, which is more negative than Cl2. Next, the Cl1-$3p_z$ AO (LUMO) attracts one electron from the contiguous S-$3p_x$ AO (HOMO). This forces to Cl1 and its recently joined H atom to leave, restoring the molecule of HCl.

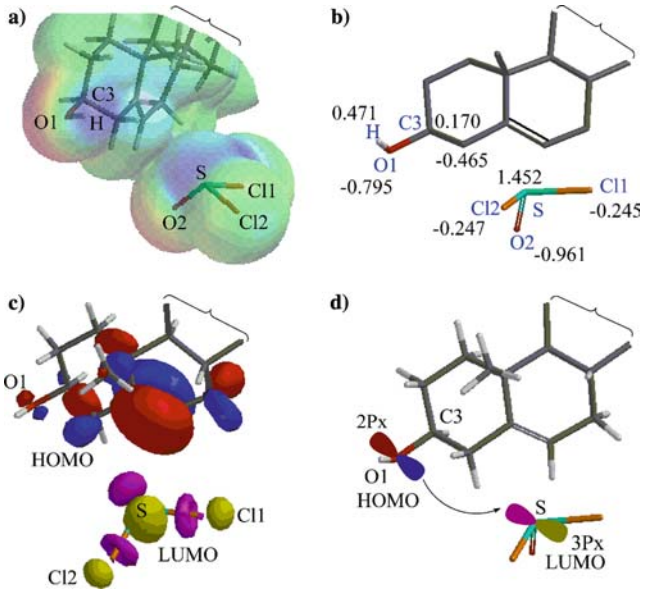


Fig. 1 Electronic properties at the initial state of the reaction. Only the A, B-ring system of Ch and $SOCl_2$ are shown. **a** Encoded electrostatic potential, blue regions are positively charged and red regions are negatively charged, **b** atomic charges, **c** HOMO and LUMO locations, **d** Atomic orbitals O1-$2p_x$ (HOMO) and S-$3p_x$ (LUMO), *arrow* shows electron transfer from O1 to S

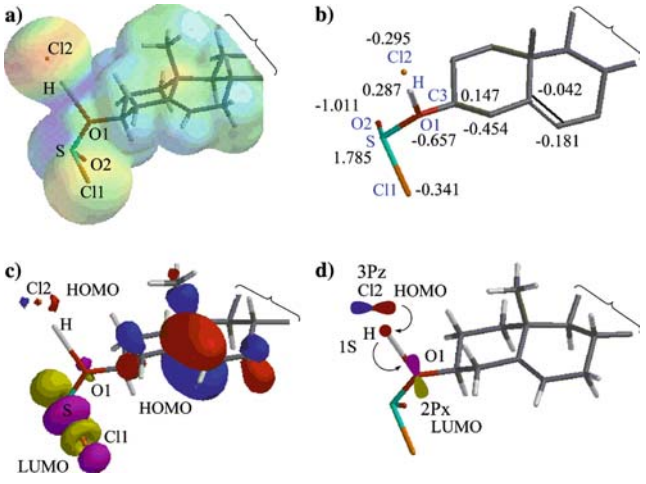


Fig. 2 Main electronic and molecular properties of the first intermediate: **a** encoded electrostatic potential, **b** participating atomic charges, **c** HOMO and LUMO location, **d** HOMO Cl2-$3p_z$, H-1S AOs and LUMO O1-$2p_x$, H-1S AOs, *arrows* show electrons transfer

The S, O1, C3, C5 and C6 atoms participate in a simultaneous rearrangement (Fig. 3). Thus, the S-$3p_y$ AO (now as part of the LUMO) attracts one electron from the O1-$2p_z$ AO (HOMO) forming a π-bond between the S and O1 atoms. The formation of the π-bond

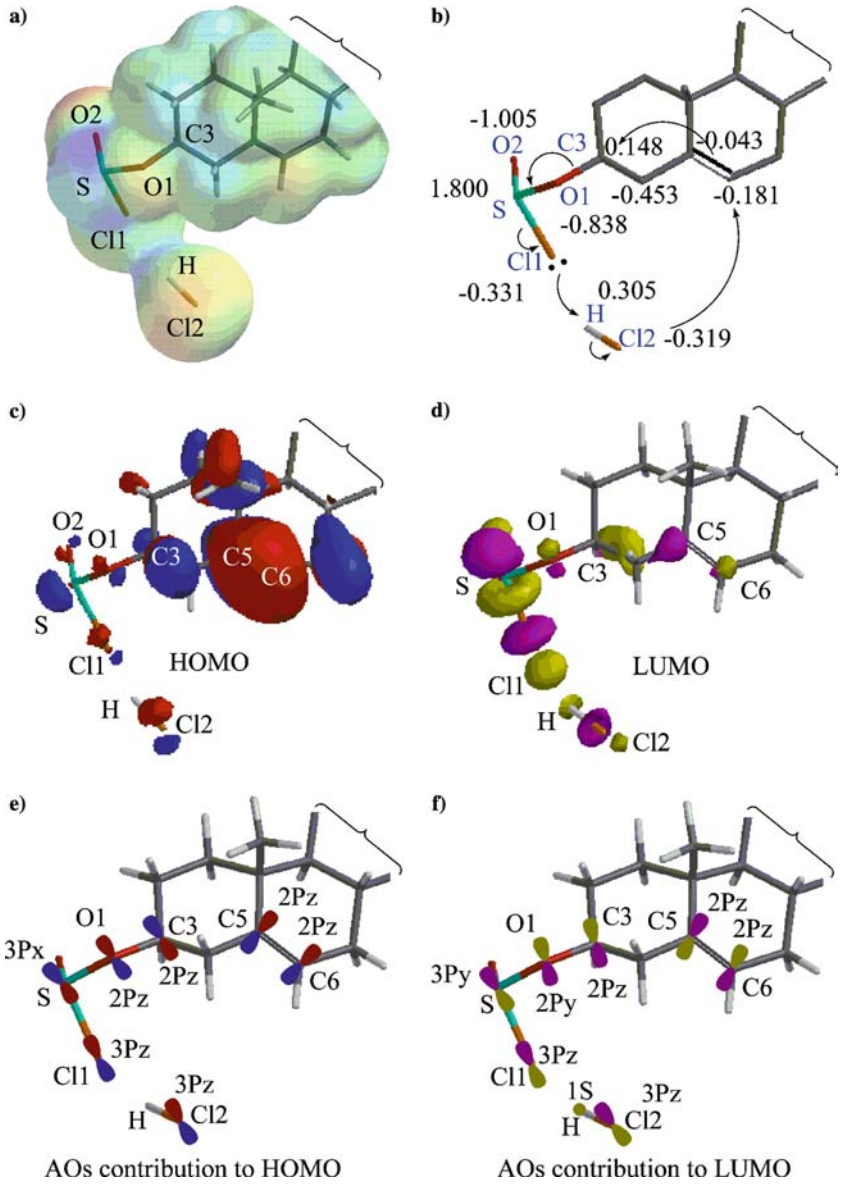


Fig. 3 Main electronic and molecular properties of the second intermediate: **a** encoded electrostatic potential, **b** atomic charges and electron transfer, **c** HOMO location, **d** LUMO location, **e** contribution of atomic orbitals to HOMO, **f** contribution of atomic orbitals to LUMO.

causes the transfer of an electron from the C3-2p_z AO (HOMO) to the O1-2p_y AO (LUMO), breaking the C3-O1 bond and leaving the C3 atom electron-deficient. Thus the C3-2p_z AO (LUMO) attracts an electron from the 2p_z AO of the π-bonded C5 (HOMO), forming a partial bond between the C3 and C5 atoms. This partial bond produces the attraction of an electron from the C6 2p_z AO (HOMO), breaking the C5–C6 π-bond. This makes the C6 atom electrophilic. It then attracts an electron from the 3p_z AO of Cl2, forming a bond between C6 and Cl2. Figure 3 shows the relevant electronic and molecular properties of the second intermediate chlorosulfite ester, HCl.

The transition state is an iso-steroid (*i*-steroid). This state of the reaction resulted after the formation of the C6–Cl2 single bond and the C3–C5 partial bond, as well as the breaking of the C5–C6 double bond and the C3–O1 single bond in the second intermediate.

In this case, the reaction proceed as follows: the H-1*s* AO (LUMO) from HCl attacks the Cl2 lone pair of electrons. Besides, the Cl2-3p_z (LUMO) attracts one electron from the contiguous C6-2p_z AO (HOMO) forcing to Cl2 and its recently joined H atom to leave forming again HCl (Fig. 4).

Concurrently, the C5–C6 π-bond is restored since the C6-2p_z AO (LUMO) attracts an electron from its neighbor the C5-2p_z AO (HOMO). The breaking of the C3–C5 partial bond occurs because the C5-2p_z AO (LUMO) attracts an electron from the C3-2p_z AO (HOMO). Finally, the C3-2p_z AO (LUMO) attracts an electron from the Cl1-3p_z AO (HOMO), forming a bond between C3 and Cl1 atoms yielding the final product cholesteryl chloride. Additionally, the side products HCl and SO_2 are formed. Figure 4 shows the properties and electronic rearrangement involved in the formation of the transition state. The final products are also shown.

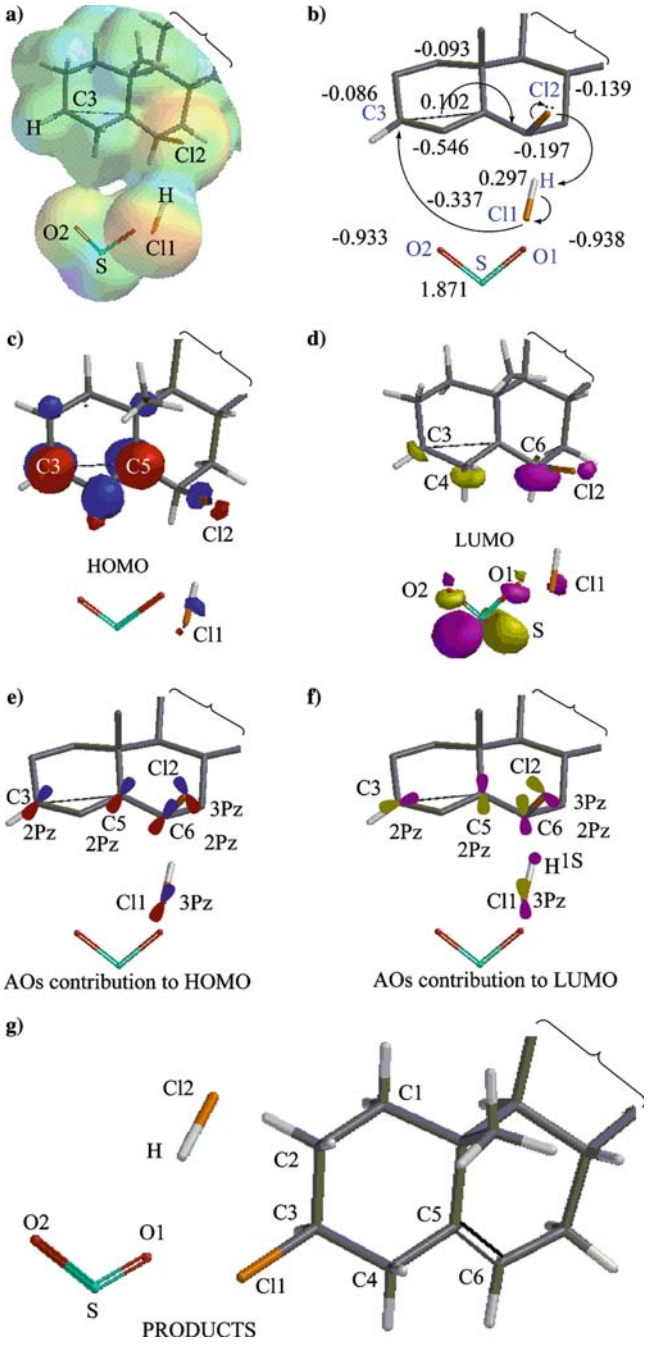


Fig. 4 Electronic and molecular properties of the transition state (iso-steroid): **a** encoded electrostatic potential, **b** atomic charges and electron transfer, **c** HOMO, **d** LUMO, (**e**) contribution of atomic orbitals to HOMO, **f** contribution of atomic orbitals to LUMO **g** final products

The fundamental frequencies calculated in the first and second intermediates were all positive. Although in the transition state the values were also positive, in this case the tendency to zero was marked. Besides, along the reaction pathway, the total energy, hardness and common parameters of all molecules changed importantly. The values of total energy, frontier orbitals energies, hardness and dipole moment, are presented in Table 1. Figure 5 depicts the total energy differences along the reaction pathway.

A summary of the proposed mechanistic reaction pathway in cholesteryl chloride formation is showed in Fig. 6.

Discussion

The synthesis of cholesteryl chloride has been used to obtain substances with pharmacological potentiality in the fields of virology and bacteriology [1, 2]. The present paper deals with the theoretical synthesis pathway of cholesteryl chloride using cholesterol and thionyl chloride as reactants. The electronic properties of cholesterol were similar to those reported elsewhere [6].

Along the reaction two intermediates are formed followed by an *i*-steroid as transition state. The final products were cholesteryl chloride, HCl and SO_2.

The reaction of Ch with the thionyl chloride moiety originates a substitution of the cholesterol C3–OH group by Cl with retention of configuration. The formation of an *i*-steroid as transition state results when the nucleophilic chloride ion is bonded to the electrophilic C6. Interestingly, the participation of the Δ^5-ene bond in this kind of reaction and the formation of an *i*-steroid has been shown experimentally [7]. Thus, in substitution reactions with 3β-hydroxy-Δ^5-ene steroid molecules such as cholesterol, the C5–C6 π-bond is broken under the right conditions, forming a partial bond between C3 and C5, allowing an additional atom bonded at C6 forming the *i*-steroid. This permits the C3 configuration to be maintained and the 6β-substituted 3:5-*cyclo*steroid to form.

The *i*-steroids are sensitive to acids, thus the electrophilic proton from HCl attacks on the lone pair of Cl attached at C6, breaking the Cl–C6 bond, and the C5–C6 π-bond is recovered. Finally, cholesteryl chloride is formed. Thus, a complete retention of configuration at C3 from cholesterol to cholesteryl chloride is the result of two successive inversions, that is: Δ^5-steroid to 3:5-*cyclo*steroid and 3:5-*cyclo*steroid to Δ^5-steroid.

As expected through the reaction, some molecular properties changed importantly. The changes in hardness, dipole moment, total energy and frontier orbitals correlated quite well with the reaction pathway. Thus, the total energy from the reactants increases through the intermediates, reaching a peak in the transition state and decreasing at the end products. The transition state is the least stable, as indicated by its frequency analysis and highest energy. However, it readily acquires a low energy state forming finally the highly stable products. Since the energy of the products is lower than the energy of reactants, the reaction is exothermic. This negative enthalpy agrees with the experimental reaction, since the temperature increases

Table 1 Values of the electronic properties of the different states involved in the synthesis of cholesteryl chloride

Compounds	Energy[a]	SHOMO[b]	HOMO[b]	LUMO[b]	SLUMO[b]	$\eta^{b,c}$	μ^{d}
Reactants	−2515.33866	−10.54714	−9.19524	1.24577	1.78537	3.97473	3.70
1st intermediate	−2515.32668	−10.62426	−9.42870	1.39141	4.12280	4.01864	3.75
2nd intermediate	−2515.31183	−10.78436	−9.47954	1.41012	4.22983	4.03471	4.40
Transition state	−2515.30470	−10.84725	−9.58725	1.43255	4.93901	4.07735	4.42
Final products[e]	−2515.36918	−10.51181	−9.99693	1.54998	4.95777	4.22347	2.82

[a]Hartrees
[b]electron Volts (eV)
[c]Hardness. Calculated by the formula $\eta = -(\epsilon_{HOMO}-\epsilon_{LUMO})/2$
[d]Dipole moment in Debyes
[e]The properties and values are considering the three products altogether

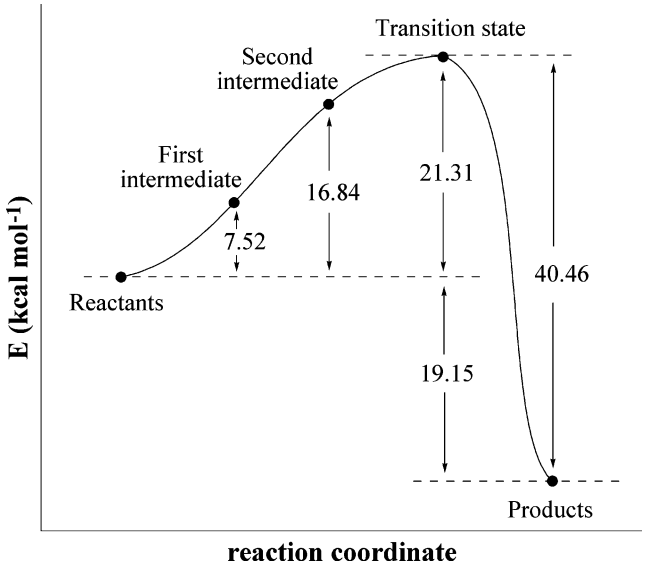


Fig. 5 Curve of the total energy differences (kcal mol^{-1}) along the reaction pathway. Thermodynamically the reaction is exothermic as observed by the final energy value

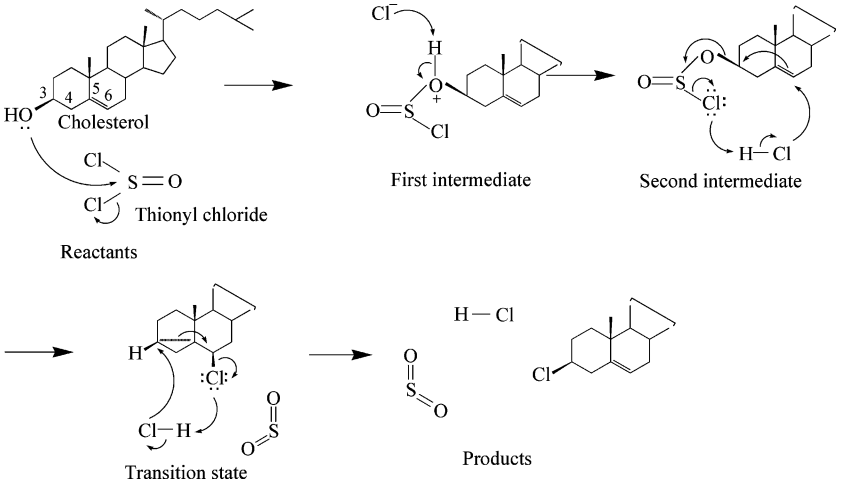
when cholesterol and thionyl chloride are mixed at room temperature.

The reaction showed that energies of LUMO and SLUMO increased linearly along the way. While HOMO and SHOMO showed an inverse tendency. This data support the feasibility of the reaction. It is clear that the Fukui postulate [8] is fulfilled since electrons in orbitals with high energy are more susceptible to receive the nucleophilic species, whereas the electrons in orbitals with low energy are more susceptible to receive the electrophilic species.

The hardness values increased linearly through the reaction. This property supports the correctness of the reaction pathway, since according to Pearson [9] soft molecules are more reactive than hard molecules.

The dipole moment increased along the route of intermediates because the polar thionyl chloride molecule modified the charge distribution of the

Fig. 6 Synopsis of the reaction pathway. The reaction starts when the lone pair of electrons of the Ch oxygen interact with the sulfur atom releasing a chloride ion. As a result the first intermediate is formed. Next, in the first intermediate the nucleophilic chloride ion bonds the electrophilic hydrogen atom releasing HCl yielding the second intermediate. In the second intermediate the electrophilic H-atom from HCl bonds with the lone pair of electrons of the Cl atom adjacent to the sulfur atom restoring HCl. Concurrently, SO_2 is liberated and causes the formation of C3–C5 partial bond and breaking of the C5–C6 π-bond originating the transition state. In the transition state, the electrophilic H from HCl bonds with the Cl lone pair of electrons at C6–Cl, forming again HCl and leaving the C6 atom electron-deficient, which restores the C5–C6 π-bond and breaks the C3–C5 partial bond. Finally the electrophilic C3 atom and the nucleophilic Cl atom form a bond yielding cholesteryl chloride. Besides HCl and SO_2 are formed as side products. *Arrows* show the rearrangement of electrons



system. Hardness and dipole moment parameters were helpful to provide a logical explanation of the nature in which the reactions occur and show that the hydrosolubility from cholesterol to cholesteryl chloride increases.

It is concluded that the mechanism of reaction of the cholesteryl chloride synthesis has been demonstrated using ab initio molecular orbital theory. This reaction is the result of two successive inversions and is clearly exothermic.

Acknowledgements Dr. K. Sharma thanks to the "Instituto de Investigaciones Biomédicas", for the postdoctoral fellowship. The technical assistance of Mr. Ricardo Vázquez-Ramirez is highly appreciated.

References

1. Sharma K, Saleem K, Salim A (2002) Indian J Chem 41B:2676–2678
2. Sharma K, Saleem K, Salim A (2003) Indian J Chem 42B:2866–2868
3. Marker RE, Kamm O, Oakwood TS, Laucius JF (1936) J Am Chem Soc 58:1948–1950
4. Diels O, Abderhalden E (1904) Ber 37:3092–3103
5. Spartan Version 1.0.0 (2003) Wavefunction Inc., 18401 Von Karman Avenue, Suite 370, Irvine, CA 92612, USA
6. Cabrera-Vivas BM, Ramírez JC, Martínez-Aguilera LMR, Kubli-Garfias C (2002) J Mol Struct, (Theochem) 584:5–14
7. Shoppee CW, Summers GHR (1952) J Chem Soc:3361–3374
8. Fukui K (1982) Science 218:747–754
9. Pearson RG (1987) J Chem Educ 64:561–567