



Investigation of oxidation attack sites in sterols: Thermodynamics of hydrogen atom transfer



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ABSTRACT

B3LYP study of 7 naturally occurring sterols was carried out in terms of O–H and C–H bond dissociation enthalpies (BDE) to identify thermodynamically favored oxidation attack site. In all compounds, O–H BDEs are significantly higher than C–H BDEs. Found results showed that sterol nuclei are more susceptible to the oxidation than side chains. Lowest BDE values were found for the C14–H bond in the majority of molecules with C14 atom in the α -position to a C=C double bond. C5=C6–C7=C8 alternating double bonds cause further drop in C14–H BDE. Because the nuclei are responsible for the reported oxidation instability of sterols, 15 various steroid nuclei were also investigated.

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1. Introduction

Sterols, a member of steroid compounds, are essential for the organization and functions of the plasma membrane in eukaryotic cells [1,2]. Cholesterol represents the predominant sterol in vertebrates, ergosterol in yeast and fungi, and phytosterols (sitosterol, stigmasterol, campesterol, vernosterol) in plants [1–3]. Sterols, Fig. 1, consist of triterpenoid nucleus and the side chain [2], usually with one or more C=C double bonds in the molecule. If they possess double bond between C5 and C6 carbons in the nucleus, they are denoted as Δ^5 -sterols; in Δ^7 -sterols, C7=C8 double bond is present.

Up to the present time, several hundreds of natural sterols were identified [2]. In the last two decades, phytosterols received much attention because of their cholesterol-lowering properties [2]. On the other hand, susceptibility of sterols to oxidation during food processing and storage can be a serious problem especially in sterol-enriched functional foods [4]. The oxidation of sterols, as a free radical chain reaction, starts with the formation of hydroperoxides. C=C double bonds easily undergo radical attack followed by hydrogen atom abstraction at the carbon atoms in the α -positions to the double bonds. Such allylic type of hydrogen atoms can be easily abstracted due to the relatively low C–H bond dissociation

enthalpy (BDE) [5]. The final oxidation products of sterols are hydroxy, keto and epoxy compounds [4,6,7].

Oxidation products of sterols (oxysterols) may have negative health effects [4,6,8]. On the other hand, certain oxysterols, as sterols metabolites, play an important role in biological systems [9]. Because the physiological activity of all steroid compounds depends also on the oxidation state of the nuclei, their oxidation (especially enzymatic transformations) represents an important field of current research [10–12]. One of the most important reactions of the steroid functionalization is the introduction of the OH groups into the nucleus [10].

In the previous work [13], for experimentally identified oxidation attack sites, we have studied C–H and O–H bond dissociation enthalpies in several Δ^5 - and Δ^7 -phytosterols and Δ^5 -cholesterol using DFT/B3LYP/6-31G* method. We have confirmed that C–H bonds exhibiting lowest BDE values actually correspond to the experimentally identified oxidation attack sites. Despite of very intensive experimental study of sterols and their oxidation under various conditions, theoretical studies of this process are not available. Therefore, in this work we decided to study mainly sterols containing more than one C=C double bond in the nucleus: ergosterol, dehydroergosterol, $\Delta^{5,7}$ -cholesterol, ergosta-4,7,22E-trien-3 β -ol and vernosterol (Fig. 2 a–e). Lanosterol and zymosterol (Fig. 2f and g) possess only one double bond in the nucleus and belong to the Δ^8 -sterols, which were not previously studied.

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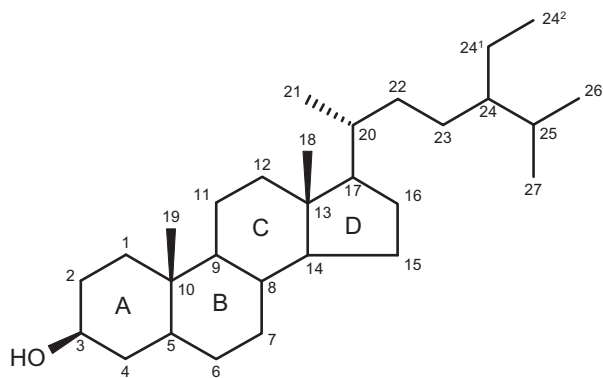


Fig. 1. Atom numbering in sterols.

Together with $\Delta^{5,7}$ -cholesterol, they represent intermediates in the metabolism of squalene to Δ^5 -cholesterol [3,5].

In [13], we have also found that different side chains negligibly affect BDEs in the nucleus as well as that the nuclei are more susceptible to the oxidation attack than side chains. Thus, one of the aims of this work is to perform O–H and C–H BDE calculations for 15 various types of the steroid nuclei in order to shed light on the effect of the nucleus structure on preferred oxidation sites.

2. Computational details

All calculations were performed using Gaussian 09 program package [14]. The geometries of all compounds and radical structures were optimized using DFT method with Becke's three parameter hybrid functional with Lee–Yang–Parr correlation potential (B3LYP) [15] functional without any constraints (energy cut-off of 10^{-5} kJ mol $^{-1}$, final RMS energy gradient under 0.01 kJ mol $^{-1}$ Å $^{-1}$).

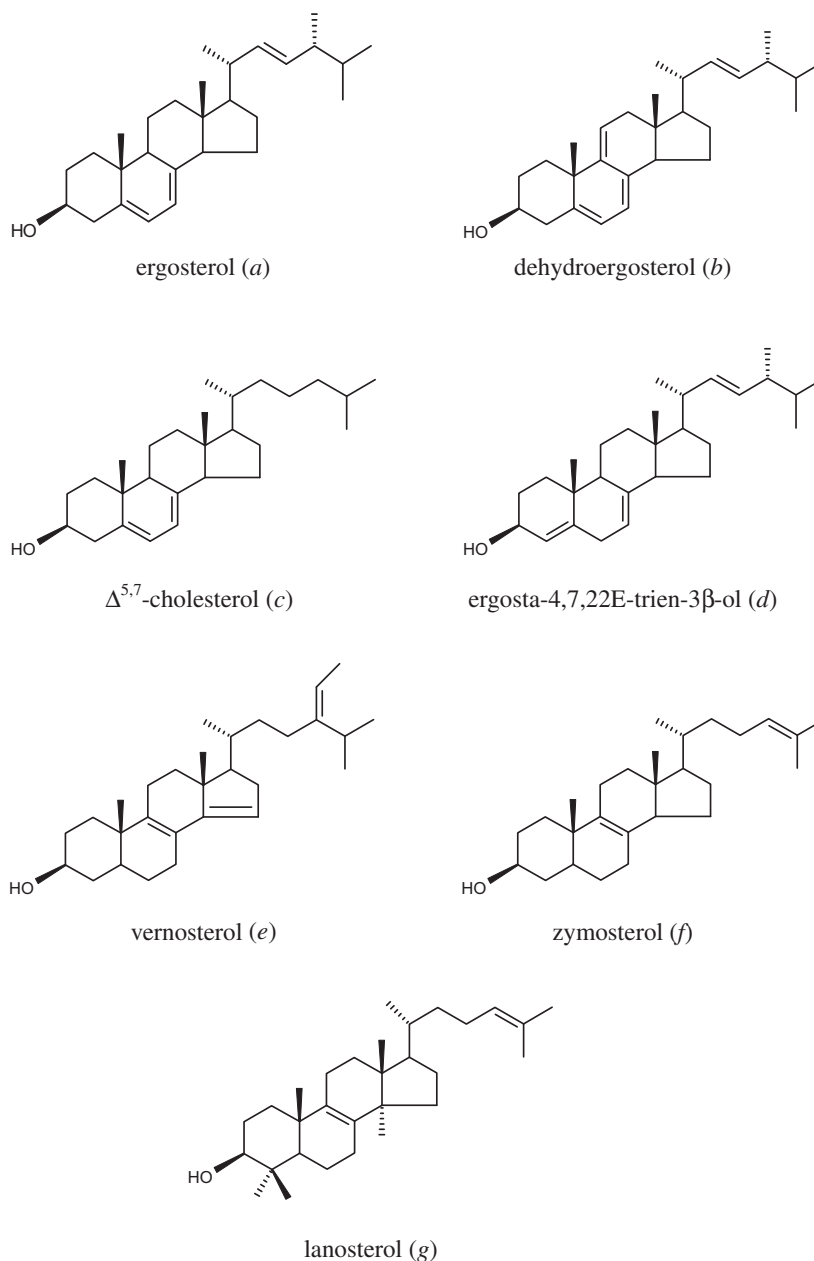


Fig. 2. Studied naturally occurring sterols.

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