Aneta Baj
Zakład Chemii Produktów Naturalnych
Instytut Chemii

05.10.2018 r.

Promotor: dr hab. Stanisław Witkowski, prof. UwB
Promotor pomocniczy: dr Piotr Wałejko

# SYNTHESIS AND STRUCTURAL INVESTIGATION OF NOVEL VITAMIN E ANALOGUES

The subject of doctoral dissertation concerns investigations in the field of vitamin E chemistry (α-tocopherol). The aim of this work was to gain more information about stereoelectronic, dynamic and conformational preferences present in tocopherols, mainly in the dihydropranyl ring.

Vitamin E was discovered over 90 years ago and still enjoys unflagging interest by the specialists in various fields. Unlike other vitamins, it is involved in the regulation a wide variety of physiological processes, including regulation of gene expression and intercellular communication. In addition, it reveals antioxidant, anti-inflammatory, neuroprotective, proapototic and cholesterol-lowering effects. Many studies have shown that vitamin E supplementation may reduce the risk of a number of diseases such as cardiovascular diseases, cataracts, Alzheimer's disease, Parkinson's or type 2 diabetes etc. Despite extensive research, the actual role and mechanism of action is under discussion. Researchers postulated that they are associated with antioxidant activity and effect of stabilizing membranes. Vitamin E, incorporated into double layers of phospholipid biological membranes, protects the cells from the damaging attacks of free radicals, especially reactive oxygen species (ROS). Vitamin E provides an adequate fluidity, durability and permeability to cell membranes, and in this way regulate their structural and functional properties. The high effectiveness of vitamin E as a phenolic antioxidant is correlated with substituent effects and stereoelectronic influences. Specific electronic and conformational effects have also a significant influence on the

mechanism of the incorporation and functioning of the vitamin in the membrane environment. Due to this reason, structural studies of 6-chromanolic systems are of great importance.

α-Tocopherol (α-T) is the most important member of vitamin E family. Tocopherols are the subject of many structural studies due to the presence of a conformationally labile dihydropyranyl ring. In this field research are focused on the influence of the substituent in the C-6 position on the geometry of the heterocyclic ring in α-tocopherol and its model compounds (Trolox and PMHC). There is a little research on the influence of substituents in the C-2 position on the conformational preferences of the chroman-6-ol system, as so far no influence of O1 on the dynamics and conformational preferences of the chroman system has been undertaken.

For spectroscopic and structural studies, a group of vitamin E analog modified in the O-1 and / or C-2 position were designed and synthesized. The main goal of the synthetic work was to obtain not described earlier in the literature analogues of vitamin E containing the 1,2,3,4-tetrahydronaphthalene skeleton in the place of the chromane system. As a result of the work carried out, a simple and efficient procedure of synthesis novel 1-carbaanalogs: 1-carba-2-nor-Trolox and 1-carba-Trolox, 1-carba-2-nor-α-tocopherol and 1-carba-α-tocopherol has been developed. The newly obtained 6-hydroxy-1,2,3,4-tetrahydronaphthalenes are interesting candidates for quantitative determination of influence of the oxygen atom O1 on antioxidant activity of 6-hydroxychromanol system. In the second part of the synthetic work, a series of α-T analogues with shorter carbon fragment ($C_1$, $C_2$, $C_6$) in place of the long phytyl chain were obtained. In the last part of the synthetic work was new 2-desmethylanalogs: 2-or-Trolox and 2-nor-α-model were synthetized.

The subject of the second part of the research were spectroscopic and structural studies. The obtained model compounds were studied to structural investigations by means of NMR spectroscopy (in solution and solid state). The influence of the O1 oxygen atom and the substituent at the C-2 position on dynamics and conformational preferences was investigated. The values of $\Delta G^{\ddagger}$ have been taken as a measure of the energetic barrier. $^{13}C$ NMR IG (250 K) spectra were estimated for the content of the two main conformers present in the equilibrium. The results of the experiments were compared with theoretical calculations (DFT) and available XRD data.

In order to quantify the stabilizing effect of oxygen atom O1 on the tocopheroxyl radicals formed, studies on the antioxidant activity of selected model compounds were carried

out. Removal of the heterocyclic oxygen atom should change chemical and structural properties of the system (e.g., conformational preferences, antioxidant activity), which are important for the vitamin E activity. A new of carbocyclic analogues of vitamin E were screened for their in vitro antioxidant activity by inhibition of the controlled initiation of styrene oxidation and by 2,2-diphenyl-1-picrylhydrazyl free radical quenching assay. The effect of 1-carba-α-tocopherol on the stability of phospholipid model membranes and thermotropic properties was also investigated.

Aneta Baj