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Model structures for the study of acylated phloroglucinols and computational study of the caespitate molecule ☆

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Abstract

Acylated phloroglucinols are widely spread in nature. Many of them exhibit biological activities, and the natural materials in which they are found have been used in traditional medicine. However, theoretical studies on phloroglucinols are rare, and they have mostly concerned the parent compound, 1,3,5-trihydroxybenzene. In the current work, the influence, on conformational preferences and energy, of the intramolecular hydrogen bond engaging the oxygen atom of the carbonyl group characterising acylated phloroglucinols, and of the geometrical features of the phloroglucinol skeleton, is investigated on four model structures, selected in such a way as to cover all the aspects of interest. All the possible geometrical options for each of these structures were calculated and compared. The results show a preference for the H-bond to form on the same side of a second substituent chain (when present) and the influence of the various aspects of the orientation of the OH groups. These results can constitute a reference for the study of acylated phloroglucinols in general and, more specifically, of acylated phloroglucinols having a second substituent chain besides the acyl chain, as confirmed by the study of the caespitate molecule, an acylated and prenylated phloroglucinol whose prenyl chain ends with an acetic-acid ester group. The presence of the ester function enables the formation of a second intramolecular H-bond with a variety of different geometries for the resulting ring, and conformers with both intramolecular H-bonds account for practically the total population. All the calculations were performed at HF level with the 6-31-G(d,p) basis set. The performance of AM1 and PM3 semiempirical methods was also investigated and found not completely adequate.

Keywords: Acylated phloroglucinols; Caespitate; Intramolecular hydrogen bonding; Resonance-assisted hydrogen bond; Phloroglucinols

1. Introduction

Phloroglucinols are the derivatives of phloroglucinol (1,3,5-trihydroxybenzene), itself a starting compound for the production of several medicines [1]. Phloroglucinols are widely spread in nature. They are found mainly in plants (Guttiferae, Mirtaceae, Cannabinaceae, Rutaceae, Euphorbiaceae and Asteraceae [2]), but also in some marine organisms [3–5], and some are produced by bacteria [5]. Phloroglucinols-containing plants and other natural materials have been utilised in traditional medicine in many areas, from Southern Africa [6–8] to China [9] and to Latin America [10]. Several naturally occurring phloroglucinols exhibit biological activities: antibacterial [4,6–9,11–18], antiviral [14,19–22], antifungal [2,23], antihelmintic [17,24–26], antiallergic [27], antioxidative [1,2,28], antidepressant [29,30], actitivity against plant pathogens [31–35]. Some phloroglucinols exert more than one activity: e.g., 2,4-diacetylphloroglucinol ($C_{10}H_{10}O_5$), produced by many fluorescent *Pseudomonas putrida* bacteria, has antifungal, antibacterial, antihelmintic and phytotoxic activities [36]. Synergistic effects between two phloroglucinols have been observed, like in the case of caespitate and caespitin [8]. Various phloroglucinols are objects of interest for their promising anticancer activity [37–42], their potentialities for HIV treatment [3,43] and for the development of

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drugs against drug-resistant bacteria [44]. Other types of practical applications span from assistance-roles in the clonal propagation of an endangered shrub [45] to the quality control of some food products [46].

Acylated phloroglucinols (frequent among naturally occurring phloroglucinols) are characterised by the presence of a COR group, where R is a branched alkyl [2,14,15,21,47,48] or, in some cases, by two COR groups [27]. Besides their known activities, acylated phloroglucinols are viewed as potential lead structures for the treatment of degenerative diseases [2] and of malaria [2,47].

Caespitate ($C_{17}H_{22}O_6$, acetic acid 2-methyl-4-(2,4,6-trihydroxy-3-isobutyryl-phenyl)-but-2-enyl ester) is an acylated and prenylated phloroglucinol isolated from *Helichrysum caespititium* (Asteraceae), a plant common in the Southern African region and utilised in traditional medicine for the treatment of broncho-pneumonial diseases, sexually transmitted diseases, tuberculosis, ulcerations, and also for wound dressing [6–8]. The isolated compound shows antifungal and antibacterial activities, including antituberculosis activity [6–8], what makes it interesting as a potential drug against the complications of AIDS (low resistance to bacterial and fungal infections, high tuberculosis incidence). The *Z* isomer is the biologically active one [8]. Its structure is shown in Fig. 1, together with the atom numbering utilised in the calculations. The presence of one or more prenyl chains, besides the COR group, is rather frequent in acylated phloroglucinols [23,48–50]. Less frequent is the ester function at the end of a prenyl chain, which characterises the caespitate molecule and is responsible for many of its conformational features.

In spite of their chemical and pharmacological properties, theoretical studies of phloroglucinols are still scarce and have focused mostly on the parent compound [51]. A study of the keto-enol equilibrium of 1,3,5-trihydroxybenzene [52] showed that the enol form is by large the preferred one, also in relation to the stability of the aromatic ring. A comparison of the two conformers corresponding to the two different mutual orientations of the OH groups [53] showed that their energies are close (the energy of the non-uniform orientation being 1.00 kcal/mol higher) and that the rest of the molecular geometry is not affected by this orientation, as long as planarity is maintained.

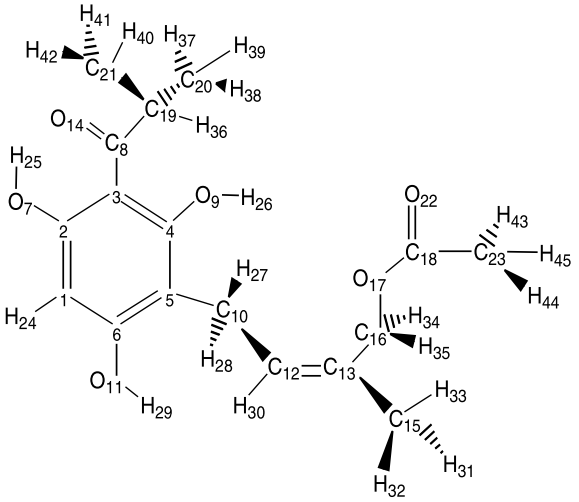

Fig. 1. Structure formula of the *Z* isomer of the caespitate molecule.

The initial part of the current study investigates the influence, on conformational preferences, of the COR group and of the geometric features of the phloroglucinol skeleton. The dominant feature of the COR group is the ability of the carbonyl oxygen atom to form an intramolecular hydrogen bond with one of the neighbouring OH groups of the phloroglucinol skeleton. Intramolecular H-bonds are the objects of increasing interest because of their influence on molecular activity and reactivity [54–56], including major features of biological activity, from molecular recognition [57,58] to antitumor activity [59], what makes the investigation of intramolecular H-bonds a key issue in the study of biologically active molecules. Their ability to form intramolecular H-bonds is actually at the basis of the utilisation of some phloroglucinols as templates to direct reactivity in the solid state [60].

In acylated phloroglucinols, because of the position of the C=O group with respect to the benzene ring, the donor and the acceptor atoms are connected by a system of π-conjugated double bonds and, therefore, the H-bond can be considered a resonance-assisted H-bond [61–63]. The H-bond closes a six-member ring with a basically uniform shape. The investigation of the characteristics of this H-bond, and of the influence, on the energy of the molecule, of the H-bond and of the geometrical features of the phloroglucinol skeleton and the COR group, is more effectively carried out on conveniently simplified model structures, minimising interferences from the specific details of more complex substituent chains. Four simplified structures were selected and all their possible conformers calculated, to cover all the information obtainable from the study of model structures. Consistent patterns were obtained both for the characteristics of the H-bond and for the influence of geometry-related factors, thus contributing all the obtainable information that can be relevant for the investigation of biological activity (the knowledge of the finest details of molecular conformations being fundamental for the understanding of the biological activity of molecules [64]). The results can serve as references for the study of acylated phloroglucinols in general and, more specifically, of acylated phloroglucinols with another substituent chain besides the COR group, like caespitate [6–8], and the compounds presented in [8,14,15,21,22,27,48–50].

The study of the caespitate molecule was aimed at identifying the main conformational preferences and the main factors influencing conformational preferences and energy (a complete systematic *ab initio* conformational investigation of a molecule of this size, and with the high degree of flexibility conferred by the ester chain, would not be affordable, because of the enormous number of possible conformations). The lowest energy conformers have two intramolecular H-bonds and account for practically the