Molecular mechanics and dynamics study of DNA–furocoumarins complexes: Effect of methylation of the angular derivatives on the intercalation geometry

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SUMMARY

Results of molecular mechanics calculations on intercalation complexes between DNA and angelicin derivatives: angelicin, 4'-methylangelicin, 5'-methylangelicin, 4,4'-dimethylangelicin, 4,5'-dimethylangelicin, 4,6,4'-trimethylangelicin and 4,6,5'-trimethylangelicin, are presented. The correlation between the presence of methyl groups and an increase in DNA photobinding affinity is discussed on the basis of the molecular structures. The influence of the orientation of the angelicins within the intercalation cavity is also discussed. Finally, the consequences of the dynamical behaviour of angelicin in the intercalation site are studied.

INTRODUCTION

Furocoumarins are heterocyclic compounds resulting from the fusion of a furan ring to a coumarin molecule. They are widely studied for their use in the photochemotherapy of skin diseases [1] and as molecular probes in molecular biology [2]. Figure 1 represents the general skeleton of the linear furocoumarin or psoralen. The biological activity of furocoumarins relies upon their capacity to bind covalently to DNA pyrimidine bases under influence of UV-A irradiation, in a three-step reaction [3]. The first step consists of a noncovalent intercalation of the drug between two base pairs. Upon UV-A irradiation, monophotoadducts are formed by C4 photoaddition between the 5,6 bond of a pyrimidine and either the 4',5' ethylenic bond (furan-side

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Abbreviations. CNDO: complete neglect of differential overlap; NMR: nuclear magnetic resonance; rms: root mean square; UV-A: ultraviolet light of class A (320 < λ < 400 nm).

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Fig. 1. Chemical structure of the psoralen.

adduct) or the 3,4 double bond (pyrone-side adduct) of the furocoumarin. In the last step, the furocoumarins linked by the furan side can absorb a second photon and, if the geometrical configuration is favourable, can form an interstrand cross-link by reacting with a pyrimidine belonging to the opposite strand of the DNA.

The most important application of furocoumarins, and of psoralen in particular, is their use in PUVA therapy (i.e. psoralen plus UV-A). In such treatments, psoralen derivatives are given orally or per os and the skin region to be treated is irradiated by UV light of class A (320 < \( \lambda \) < 400 nm). This treatment generally induces an efficient regression of skin cell proliferation, which has been largely connected to the above-quoted DNA photomodifications (monoadducts and/or interstrand cross-links), although the involvement of other macromolecular photomodifications is also suspected [4]. An undesired side-effect of PUVA therapy is the potential mutagenic and carcinogenic character of the treatment and several attempts have been made this last decade to look for new psoralen derivatives that would show less pronounced mutagenic and carcinogenic side-effects. The general guideline which has been proposed to search for new derivatives was to modify the chemical structure of the psoralen skeleton in order to avoid the formation of interstrand cross-links which are thought to be responsible for the mutagenicity and carcinogenicity of psoralens.

Among the ways to hinder the formation of cross-links is the use of angular furocoumarins, or angelicins, which have been proposed and largely studied by a group in Padova [5–7]. Figure 2a gives the chemical structure of angelicin. Although angelicins can photoreact through their 4',5' and 3,4 double bonds in solution [8–10], they are supposed to be unable to induce interstrand cross-links within DNA, for geometrical reasons. Indeed, the chemical structure of the various photoadducts formed within DNA by angelicins is progressively elucidated [8,11–14], and no biphotoadduct formed within DNA has been isolated to date. It is now clear that the geometrical arrangements allowed in the first step of the noncovalent angelicin–DNA intercalation determine the subsequent photoreactions. Therefore, a structural survey of the various intercalation complexes may be of help in the understanding of the angelicin photoreaction mechanism and especially in the explanation of the specific behaviour of the molecules, induced by the variations in design from the original angelicin.

Since no crystallographic or NMR data concerning these intercalation complexes are available, a theoretical approach can be of help. Indeed, model building and molecular mechanics (energy minimization) techniques are suitable to study intercalation complexes [15–18]. It has already been shown that these techniques yield molecular models which, although not as accurate as X-ray or NMR structures, are nevertheless precise enough to study intercalation complexes [15–21]. In particular, a good account of the experimental data has been obtained with molecular models of linear furocoumarins [19,20].

We have therefore built, energy-minimized and studied the intercalation complexes formed by