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Molecular Modeling on Garuganin-I

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Summary. The conformation of garuganin-I was analyzed in terms of the mobility of the cyclic structure. Molecular mechanics calculations were applied to show that the interconversion of the optical isomers is not possible at room temperature due to steric interactions. Different possibilities of the distortion of the molecular conformations were calculated and compared with molecular dynamics simulations.

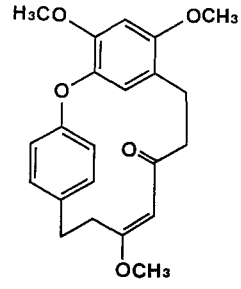
Keywords. Garuganin; Molecular modeling; Macrocyclic biaryl ether; Molecular dynamics.

Molekulares Modelling von Garuganin-I

Zusammenfassung. Die Konformation von Garuganin-I wurde bezüglich der Mobilität der cyclischen Struktur analysiert. Es wurden molekularmechanische Berechnungen herangezogen, die zeigten, daß die Interkonversion der optischen Isomeren bei Raumtemperatur wegen sterischer Wechselwirkungen nicht möglich ist. Es wurden verschiedene Möglichkeiten von Konformationsänderungen berechnet und mit einer Simulation der Molekulardynamik verglichen.

Introduction

Garuganin-I (**1**), a plant product isolated from *Garuga gamblei* King [1–4], shows antibiotic activities [1, 2]. It contains a biaryl ether moiety within a 15-membered macrocyclic ring system as ostentatious structure element. Such biaryl ether substructures can also be observed in other compounds of the same familiy like garuganin-III [5] or garugamblin-I and -III [6]. The biaryl ether is also the characteristic unit of other natural products like acerogenin A [7], a diarylheptanoid,



or galeon and hydroxygaleon [8], tetrandine [9], leprolomin [10], daphnine [11], ricardin A and B [12], and bastadine [13].

Some isodityrosine derived peptides exist in nature and have been synthesized recently [14]. The antibiotics of the vancomycin group contain two or three macrocyclic rings with aryl ether substructures and a diphenyl substructure [15–18]. The glycopeptide antibiotics teicoplanin [19] and ristocetin [20] with three diaryl ether subunits have been studied recently. Bouvardine and deoxybouvardine diaryl are ether groups containing peptides with tumor-inhibiting properties [21]. Especially the small cyclopeptides K-13 and OF4949I-IV [22–24] exhibit similar structural features like the plant product garuganin-I.

In the present work, the conformation of garuganin-I was evaluated and analyzed in terms of the mobility of the macrocyclic ring. Intramolecular distances were calculated and compared with spectroscopic properties of this compound. As the ring structure seems to be rather rigid, distortion motions of the molecules are possible only within certain limits. Some rotational barriers of such motions were calculated using molecular force field methods and the results were compared with molecular dynamics simulations. A comparison of the structure of **1** with a cyclic peptide including the same biaryl ether substructure, OF4949I, was also performed.

Calculations

For the molecular calculations a force field method, based on Allinger's MMP2 parametrization [25], was used, as it is a very fast method and convenient for the determination of geometries of molecules containing aromatic systems and conjugated double bonds. With the program package MOLBMEC [26], used for the calculations described here, it is possible to include various constraints like dihedral angles directly in the minimization procedure. This can be used to calculate the conformational energy of the molecule at any point of the energy surface, and consequently the intramolecular rotation pathway as well as the energy of the rotation barriers can be estimated.

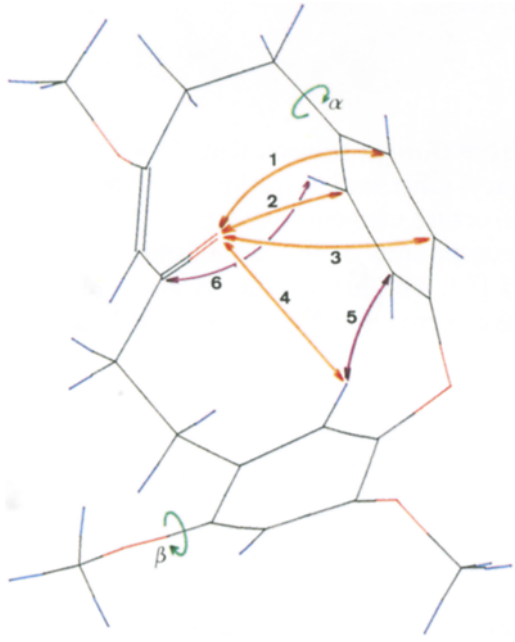
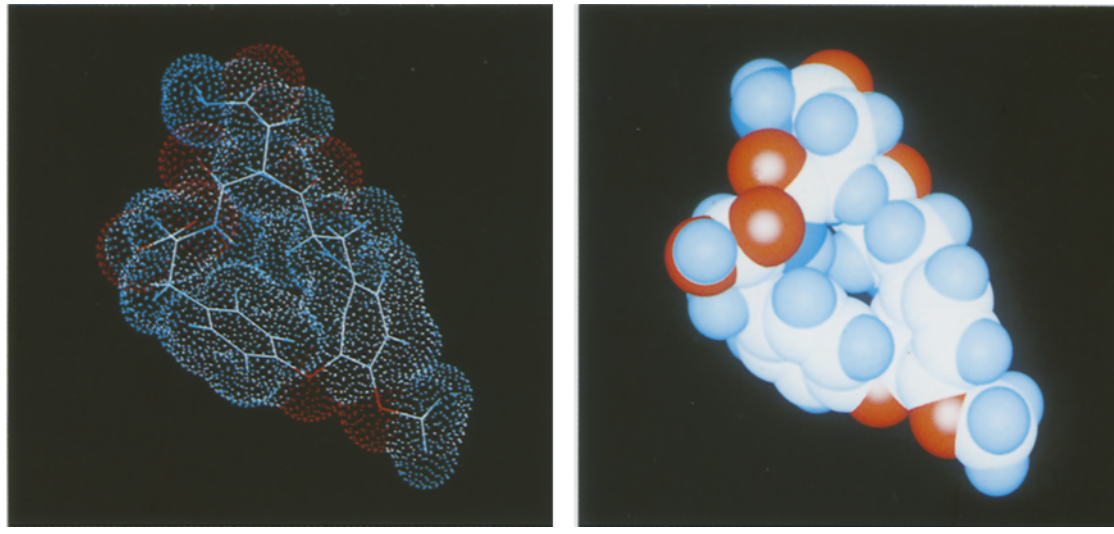


Fig. 1. Lowest energy conformation of garuganin-I (**1**) with some intramolecular distances: *1*: 4.08; *2*: 3.18; *3*: 4.31; *4*: 2.77; *5*: 2.88; *6*: 4.18 Å. The definition of the angles α and β is included



a b

Fig. 2. Space-filling model (a) and Van der Waals surface (b) of **1**

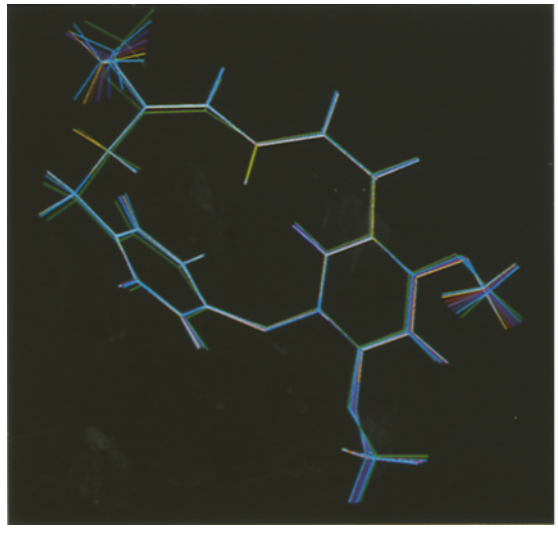


Fig. 4

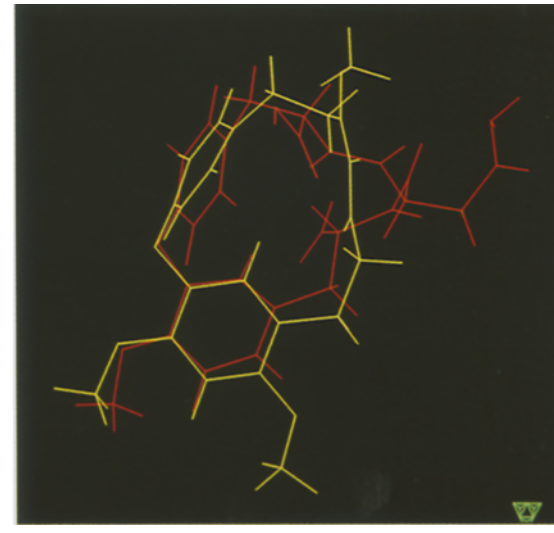


Fig. 6

Fig. 4. Superposition of some different conformations of **1** obtained by a molecular dynamics simulation

Fig. 6. Comparison of the structures of **1** (yellow) and OF4949I (red)

The molecular mechanics calculations were done on an IBM 3090 mainframe.

The modeling of **1** was done on an Evans and Sutherland PS 390 graphic system connected to a VAX 8530 using SYBYL [27] software.

A least square atom matching algorithm was used as fitting procedure for the comparison of **1** with the cyclic peptide OF4949I.

The molecular dynamics calculations were done on a Personal Iris 4 D 25 workstation using INSIGHT II/DISCOVER [28]. A simulation temperature of 600 K was used to facilitate the sampling

of the conformational space. The simulation was performed with time steps of 10^{-15} s over a range of 1 200 ps, using the DISCOVER force field [29]. The first 200 ps were taken for the equilibration of the system. The geometries of each picosecond were stored and used for the graphical representation. Every 10 ps the geometry was minimized by a steepest descent and a Newton-Raphson algorithm in order to find different energy minima.

Results and Discussion

The lowest energy conformation of garuganin-I (**1**) calculated by the molecular mechanics program MOLBMEC is given in Fig. 1. The diameter of the ring system

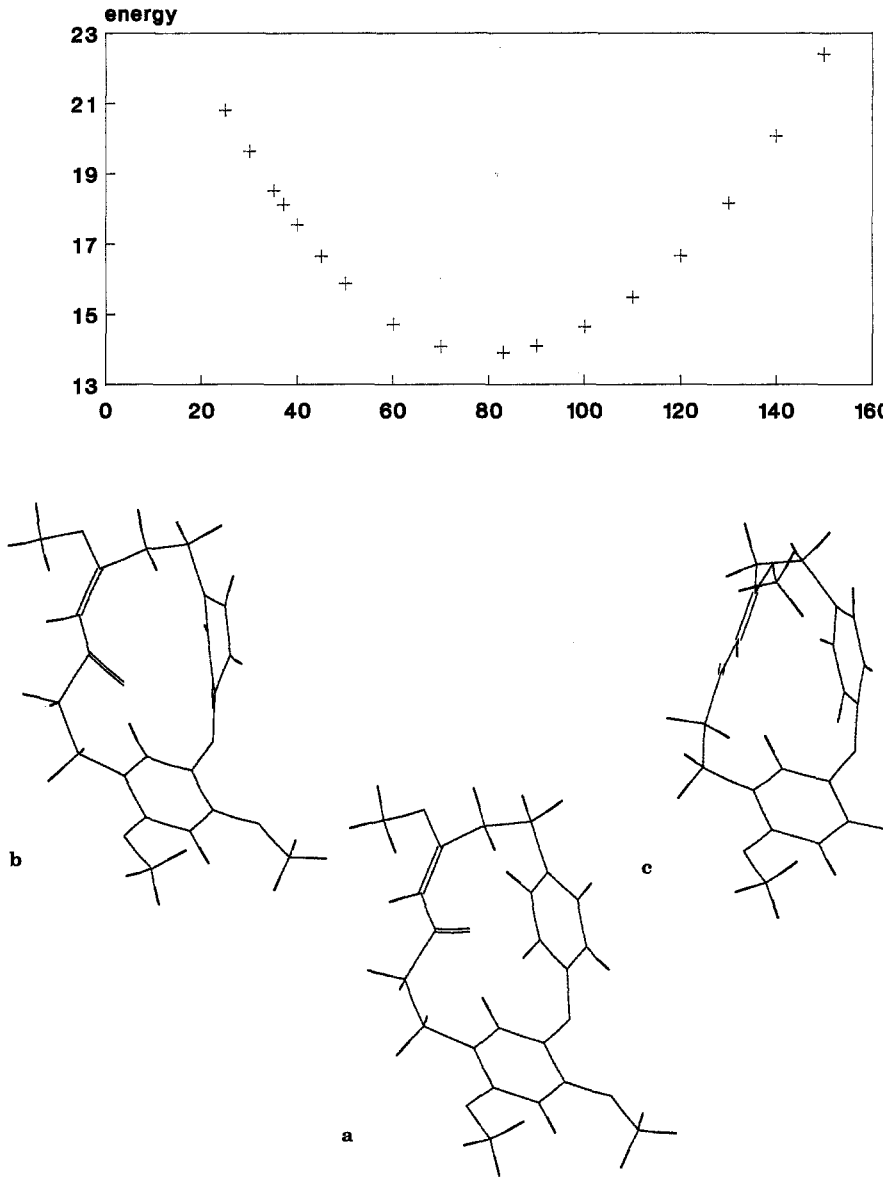


Fig. 3. Dependence of the total energy on the dihedral angle α (energy in kcal/mol, angle values in degrees). The drawings show the minimum conformation (a), the non equilibrium conformation for an angle $\alpha = 30°$ (b), and the conformation for an angle $\alpha = 140°$ (c)

seems to be rather small. Some selected intramolecular distances are included in Fig. 1.

The molecular structure of **1** is mainly determined by the steric interaction of the aromatic ring atoms with the opposite part of the aliphatic chain. The small distances within the macrocyclic ring do not allow a free rotation of the *para*-substituted aromatic ring. Fig. 2 shows a space-filling model as well as a Van der Waals surface of the molecule, demonstrating the rather compact conformation.

1 appears therefore to be a flat and rigid molecule without a pronounced flexibility. For the investigation of minor possibilities of movements the barriers of some dihedral angles were calculated using constraints. As a typical example, the energy barrier of the angle α (shown in Fig. 1) is given in Fig. 3.

As demonstrated in the figure, the potential curve is rather flat in the neighbourhood of the energetic minimum, but the potential barriers increase drastically when the aromatic ring interfers sterically with the opposite chain. Larger changes of the dihedral angle α lead to a twist distortion of the molecule, which can be seen from the drawings in Fig. 3. Of course, as force field methods are mainly parametrized for minimum conformations, the geometries of such transition states can be calculated only with lower accuracy. Nevertheless, it seems to be clear from Figs. 2 and 3 that neither the transition between the two optically different conformations of **1** is possible due to the strong steric hindrance of the molecule nor the *para*-substituted aryl ring is allowed to rotate freely. This is in agreement with the experimental results that a change of the optical state or a coalescence of the protons of the *para*-substituted aryl ring in the NMR spectrum cannot be observed at room temperature [4].

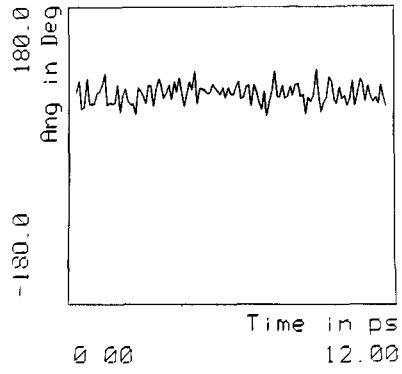


Fig. 5. Molecular dynamics simulation of the time dependence of the dihedral angles α (a) and β (b). Data points at every picosecond are shown in the presentation. The definition of α and β is given in Fig. 1

A systematic analysis of the various conformations of a ring system of this size is a difficult task, because the cyclic structure leads to additional steric constraints. For the investigation of the different conformations of **1** molecular dynamics calculations were applied, in order to find the structures with highest probabilities – or lowest energies – and to gain some insight about the intramolecular motions of the compound. As a result of the analysis the lowest energy conformation was found together with some conformational minima of higher energy. In Fig. 4 some of these conformational minima of **1**, with comparable energy, are superimposed.

From Fig. 4 it can be seen that the possibilities of a distortion of the macrocyclic ring system are rather limited. Deviations of the dihedral angles of a few degrees are possible, but the whole macrocyclic ring system shows no large structural changes or inversion processes. Of course there exists some free rotation and motion of the side chains, which leads also to various local minima with more or less the same conformation of the cyclic structure.

In addition to the relevant conformations of **1**, estimated by the molecular dynamics simulation described above, some information on the mobility of different parts of the molecule can be obtained. Fig. 5 a shows the time dependence of the angle α, which reflects the motion within the macrocycle. Even at the high temperature of 600 K no large changes of the angle can be detected. In contrary, the time dependence of the angle β (β is shown in Fig. 1), which is located in a side chain of the molecule, indicates a nearly free rotation (Fig. 5 b).

The lowest energy conformation of **1** was used for a comparison of **1** with the small cyclic peptide OF4949I which also contains a diarylether subunit. These common structural elements were superimposed and the peptide chain was fitted to the chain of **1** by a least squares algorithm [27]. The result of the optimized superposition of both molecules is given in Fig. 6.

Such a modeling leads to a rather energetically favorable geometry of the peptide, from which up to now no detailed structural information is known.

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