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CONFORMATIONAL STUDY OF THE CEMBRANOLIDE DITERPENE DENTICULATOLIDE BY MOLECULAR MECHANICS METHOD

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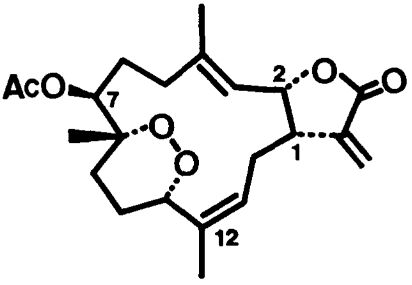
Abstract: The most stable conformation of denticulatolide (**1**), an ichthyotoxic cembranolide, obtained as a major metabolite of the soft coral, *Lobophytum denticulatum*, was given by molecular mechanics calculations and it was confirmed by ^{1}H NMR measurement. The geometry of 14-membered carbocycle of **1** was found to be different from that of derivative (**2**) especially around the juncture part of γ-lactone. The molecular mechanics calculation successfully reproduced the conformational changes between **1** and **2**.

In the previous paper[1)] we have reported the structure of denticulatolide (**1**), a peroxide-containing cembranolide diterpene, isolated as a major metabolite of the soft coral, *Lobophytum denticulatum*. The compound **1** is an ichthyotoxic material and its structure and relative configuration was determined on the basis of chemical and spectral data and by X-ray analysis of a derivative (**2**). We are interested in the conformation of **1** since the structure of this molecule is rather unusual because of the cis geometry of one of the double bonds and its unprecedented location (Δ^{12} not usual Δ^{11}) among natural cembranoids.

Cembranoid diterpenes possessing the flexible macrocyclic skeleton are interesting class of natural compounds. However, only few studies on the conformation of the macrocyclic cembrane type molecules have been made so far, by ^{13}C NMR and X-ray crystallographic method.[2)] We use the molecular mechanic method to study the most stable conformations of the 14-membered macrocycles, **1** and **2**. Here we report the successful results.



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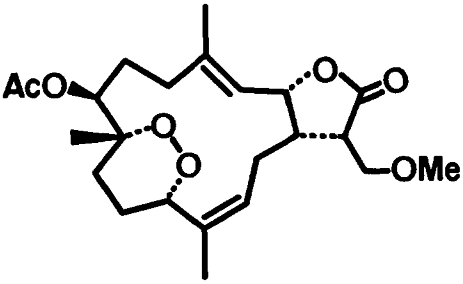

2

The molecular mechanics calculations were performed using a slightly modified version of Allinger's MM2 program.[3] Initial geometries of the molecule for energy minimization are usually given by measuring Dreiding molecular model. However it seems difficult to apply the method for a molecule having large membered cyclic system because the molecule is so flexible[4] and a very large number of structures are possible for input geometries. Furthermore, manual model building cannot cover all the possible input geometries systematically. Hence a systematic and complete method for generating all the plausible initial geometries is necessary. For this purpose, we have developed a computer program to generate all the possible starting geometries for macrocycles.[5,6] Since MM2 program cannot be applicable for the molecule having the conjugated π-system because of the lack of the appropriate torsional parameters, a VESCF-MO method of MMPI[7] program was combined to obtain the torsional parameters of enone system[8] of **1**.

Conformation of 2. In order to test the practical validity of the program, we have first applied our program to compound **2**, the geometry of which is known from X-ray analysis. To simplify the calculation, the methoxymethyl group of **2** was replaced by a methyl group. The calculated global energy minimum structure **3a** is nearly superimposable to the X-ray structure of **2**, in which γ-lactone ring have nearly perpendicular arrangement to a mean plane of 14-membered carbocycle. The calculated torsional angles of 14-membered carbocycle are almost identical to observed ones as shown in Fig. 1. The geometry of 14-membered carbocycle of the second best conformer (**3b**) is similar to that of **3a** except around the juncture part of γ-lactone ring. In **3b** the lactone ring serves to make it flatter than **3a** as shown in Fig. 2. The observed ^{1}H NMR vicinal coupling constants of **2** are in good agreement with the calculated values[9] of **3a**, suggesting that the conformation of **2** in the solution phase is the same with **3a** obtained by the MM2 calculations.

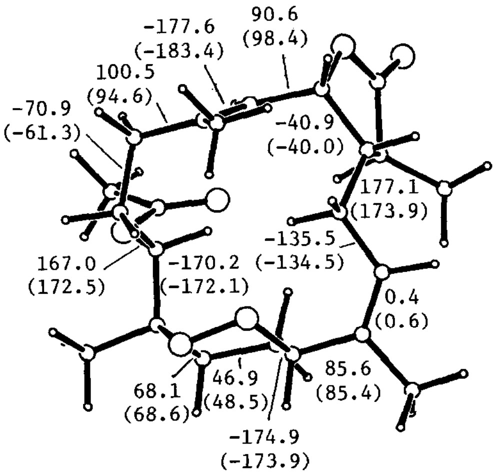

Fig. 1. Geometry of **3a** with torsion angles (°) of the 14-membered carbocycle and the observed values of **2** in parenthesis.

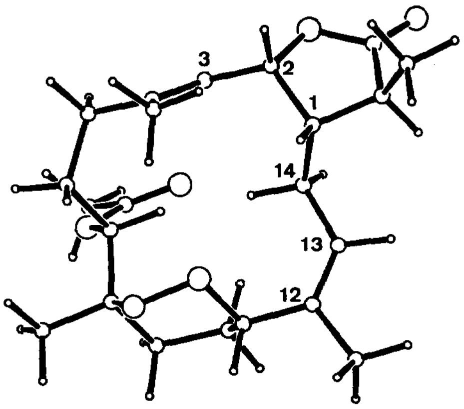

Fig. 2. Geometry of **3b**.

Conformation of 1. Successful prediction of the most stable conformation of 2 encouraged us to apply the method to denticulatolide (**1**). A total of 67 possible initial structures obtained by our program was submitted to the energy minimization process. The most stable conformation (**1a**, Fig.3) was obtained seven times from different input conformations. The structure **1a** is quite similar to that of the second most stable geometry of **2**. The ^{1}H NMR vicinal coupling constants observed in **1** were compatible (Table 1) with the calculated[9)] on the structure **1a**. These results suggest that the most stable conformation obtained by the calculation corresponds to the one observed in the solution phase. Conformational stability of this form is suggested by the large energy gap between **1a** and **1b**, and this premise was supported by the temperature independent ^{1}H NMR spectra.

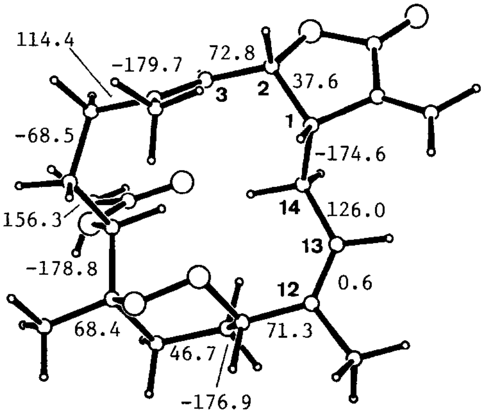

Fig. 3. Geometry of **1a** and torsion angles (°).

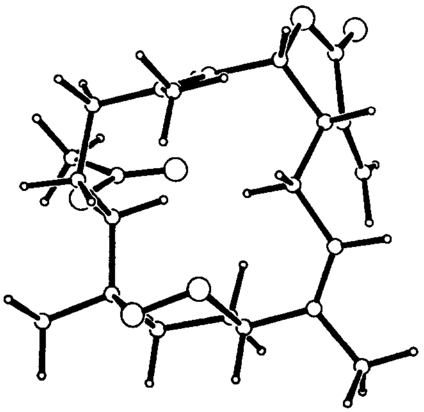

Fig. 4. Geometry of **1b**.

Table 1. Coupling constants (Hz).

Protons	J(calcd)	J(obsd)
H- 1, H- 2	6.7	6.1
H- 2, H- 3	6.3	7.1
H- 1, H-14a	11.9	12.1
H- 1, H-14b	0.8	2.5
H-13, H-14a	11.5	11.4
H-13, H-14b	3.1	4.0

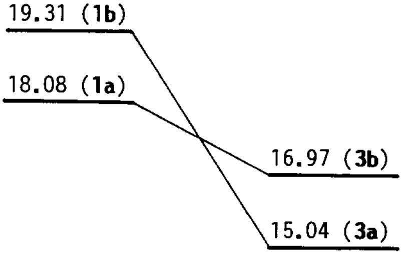

Fig. 5. Steric energy diagram (kcal/mol).

The second most stable conformation of **1** (**1b**) lies 1.23 kcal/mol above **1a**. The lactone unit of **1b** is fused almost perpendicular to the mean plane of the 14-membered carbocycle, as was found in the structure of **3a** (Fig. 4). While the nearly perpendicular arrangement of γ-butyrolactone in compound **1** should destabilize the system more than flat disposition, the situation is reversed in the methyl derivative (**3**). These relationships are summarized in Fig. 5.

The approach we used for the prediction of the stable conformations of macrocyclic system thus proved to be powerful as witnessed by the successful reproduction of conformational changes caused by the substituent on the γ-lactone ring in **1** and **3**.

References and notes

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5) Our program is outlined as follows: Starting from the first known three atoms (defined by two bond distances $r^{1,2}$ and $r^{2,3}$ and angle of the two bonds $\theta^{1,2,3}$), the fourth atom can be obtained knowing the next bond distance ($r^{3,4}$), angle ($\theta^{2,3,4}$), and a torsion angle ($\phi^{1,2,3,4}$). Changing the torsional angle from 0°to 360° by a certain degree of increment (resolution) generate some sets (=12 if resolution angle equal 30°) of the coordinates of the first four atoms of a macrocycle. Remaining atoms can be generated by repeating the process until to reach the terminal atom. A total of 12^{n-3}(if resolution = 30°) coordinate sets must be calculated when a saturated n-membered carbocyclic system is being treated, and this is the time consuming part of the calculation. To shorten the computation time, a half chain length criterion was applied. Since the end-to-end distance in a fully extended form of a half chain length should be a maximum transannular contact in the macrocycle, any chain having longer distance than this was omitted before calculating the coordinates of the terminal atom. Any chain which has a reasonable bonding distance (ring closure criterion: 1.0 - 2.0Å) between the both ends was assumed to be a possible cyclic starting geometry. Application of other criteria for ring closure which are bond angle of the two ends of the chain (90° - 130°) and transannular closest contact can further reduce the number of the geometries to be optimized. All the remaining geometries thus obtained were subjected to geometry optimization.

6) Similar approach is used in the program RINGMAKER; W. C. Still and I. Galynker, Tetrahedron, **37**, 3981 (1981); W. C. Still in "Current Trends in Organic Synthesis" pp 223 - 246, H. Nozaki ed., Pergamon Press (1983).

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8) Following parameters for enone systems were used.

streching: $(C=)C^{sp2}-C^{sp2}(=O)$ 6.37(k_s), 1.4767Å(L_0)

torsion:	V_1	V_2	V_3
$C^{sp2}=C^{sp2}-C^{sp2}=O$	0.910	2.091	0.0
$C^{sp2}=C^{sp2}-C^{sp2}-OR$	0.0	2.091	0.0
$C^{sp3}-C^{sp2}-C^{sp2}=O$	0.150	2.091	0.0
$C^{sp3}-C^{sp2}-C^{sp2}-OR$	-1.140	2.091	0.0

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