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CONFORMATIONAL ANALYSIS OF E,E-GERMACRANES BY THE METHOD OF MOLECULAR MECHANICS

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Molecular mechanics calculations have been made in order to analyze the reasons for the realization of one of four conformations in sesquiterpene germacranes and to evaluate their relative stabilities in the most probable states. Conformational transitions in unsubstituted 6(7)- and 7(8)-germacrolides and unlactonized germacranes have been modeled.

Germacranes, containing ten-membered rings, are of particular interest from the point of view of the conformational flexibility of molecules, since they permit a large number of hypothetical conformations of the cyclodecane ring. However, the presence in germacranes of endocyclic 1(10)- and 4(5)- double bonds and of methyl and isopropyl groups, or the condensation of the latter to form γ-lactone rings (in the olides) restricts the number of realizable conformations of the cyclodecadiene system to four [1]: a) chair-chair ($_1D^{14}$, $^{15}D_5$), boat-boat ($^1D_{14}$, $^{15}D_5$), c) chair-boat ($^1D_{14}$, $_{15}D^5$), and d) boat-boat ($_1D^{14}$, $_{15}D^5$).

The detection in solution of the four conformers of a *trans*-7(8)-germacrolide — laurenobiolide [2] — and the realization of the nontypical boat-boat (b) conformation of a *trans*-6(7)-germacrolide — montafrusin A [3] — suggested the modeling by molecular mechanics (MM) of the main conformational states and their transitions into one another, and the evaluation of the corresponding energy barriers.

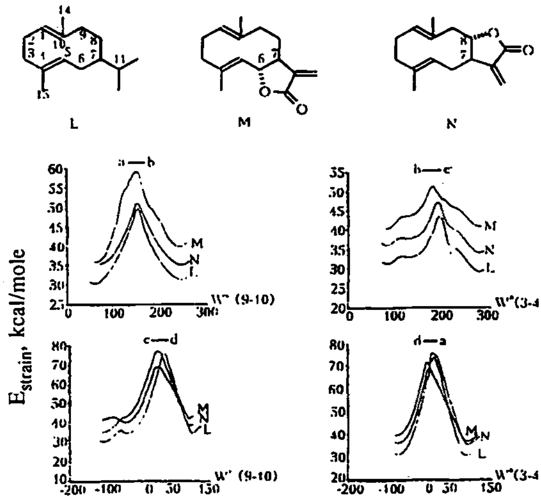

Fig. 1. Conformational transitions in model E,E-germacranes.

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TABLE 1. Torsion Angles (degrees) and Strain Energies (ΔE_{strain}, kcal/mole) Calculated by the MM Method for the Model Compounds L, M, and N

Compound	Type of conformation	Torsion angles												E_{strain}
		1–2	2–3	3–4	4–5	5–6	6–7	7–8	8–9	9–10	10–1	ω_1	ω_2	
	a	–96	49	–84	172	–140	72	–78	77	–119	168	58	92	30.3
L	b	76	26	–94	170	–118	62	–107	71	61	–170	–116	81	31.2
	c	106	–42	93	–170	77	55	–122	58	61	–169	–117	–82	29.5
	d	–76	–26	97	–169	77	64	–107	72	–98	170	79	–79	30.8
	a	–98	48	–84	166	–137	83	–80	70	–115	170	62	90	36.0
M	b	77	27	–94	164	–121	76	–104	59	64	–173	–113	80	40.4
	c	112	–40	92	–164	67	70	–124	46	60	–170	–117	–83	40.9
	d	–114	–26	52	–165	62	81	–91	62	–106	168	71	–122	40.1
	a	–98	46	–86	174	–131	68	–83	81	–116	167	61	92	35.1
N	b	76	26	–95	170	–117	64	–110	70	62	–170	–115	82	36.2
	c	106	–42	93	–170	76	55	–122	56	62	–169	–115	–82	34.6
	d	–76	–28	97	–169	78	64	–110	72	–98	170	79	–78	35.8

As the initial data for the calculation we took the x-ray structural figures for a *trans*-6(7)-germacrolide — eupatolide [4], the macrocycle of which lacks any substituents apart from βOH at C8. On the basis of this structure, using the PC MODEL program, we modeled the molecule of unsubstituted germacrane (L) and of the 6(7)- and 7(8)-lactonized germacrolides (M and N, respectively) — the simplest representatives of germacrolides common in Nature.

The torsion angles were obtained from the results of the calculation of the four conformations of the cyclodecadiene ring possible according to Z. Samek (a-d) for the three model molecules, with complete optimization of the geometries of structures L, M, and N (Table 1). A comparison of the calculated (for M) torsion angles of the germacrane ring and those found by an x-ray structural investigation (for eupatolide) showed good agreement and confirmed the correctness of the calculations.

The strain energy E_{strain}, the main determinant of conformational stability (see Table 1), shows that the chair-chair conformation (a) is the most stable in a 6(7)-lactonized germacranolide. In M, this conformation is 4-5 kcal/mol more favorable ($E_{\text{strain}} = 36.0$ kcal/mole) than the other three forms. In the L (and also the N) molecule the difference in the strain energy of the four conformational states does not exceed 1-2 kcal/mole. Consequently, the probabilities of finding the L and N molecules in any of the four conformational states are close.

Thus, the values of the energy states of the three model germacranes in conformations a, b, c, and d confirm the great lability of the linearly lactonized germacranolides as compared with the nonlinearly lactonized compounds [1].

In Nature, conformational transitions in the germacrane cyclodecadiene ring take place in complex fashion. However, to a first approximation, all mutual transitions can be modeled by successive changes in the torsion angles around the C3–C4 and C9–C10 bonds. This means that it is possible to achieve a transition from one conformational state into another by rotation of the plane fragments containing the endocyclic double bonds.

To perform a conformational transition we took the torsion angles C8–C9–C10–C14 (ω_1) and C2–C3–C4–C15 (ω_2), the original (initial and final) values of which are given in Table 1. It can be seen that in the four energetically favorable conformers the torsion angles ω_1 and ω_2 have values of 60 to 80° or −80° to −120°. Variation of these torsion angles with a step of 5° was carried out from 50° to −130° or, conversely, from −130° to 50°, depending on just how the conformational change was effected. For each step the residual geometry of the molecule was fully optimized. Rotation was carried out alternately, beginning with one angle and then the other. For example, beginning with conformation *a*, by changing the angle ω_1 we passed to conformation b and then, by changing torsion angle ω_2, from conformation b to c, and so on. Each transition was subjected to the reverse change of the torsion angle — with a return to the initial conformation. These transitions can be denoted as $a \Leftrightarrow b \Leftrightarrow c \Leftrightarrow d \Leftrightarrow a$. Energy diagrams of the conformational transitions for the three types of model compounds are given in Fig. 1.

On modeling a transition in the reverse direction, a displacement of the barrier (similar to phenomenon of linear "hysteresis") with a small change in its height was observed. This phenomenon fits well into the logic of the mechanical model, with a jump in the conformation only after a certain strain has been reached. As a result of this, there are somewhat different points of conformational transitions close to the maxima, although the curves do not differ in the region of the minima. In the graphs, the conformational transitions have been averaged for the opposite directions of rotation.

The height of the barrier (ΔE_{strain}) of the $a \Leftrightarrow b$ transition for the model 6(7)-germacrolide proved to be the maximum (of the order of 25 kcal/mole), while for the nonlactonized germacrane it was 20 kcal/mole, and the minimum (15 kcal/mole) was found for the 7(8)-germacrolide. This means that at room temperature the $a \Leftrightarrow b$ transition is unlikely for the 6(7)-germacrolides, while for the 7(8)-germacrolides the probability of this transition is substantially higher. The value of ΔE_{strain} for the $b \Leftrightarrow c$ transition of the 6(7)- and 7(8)-germacrolides is of the order of 10 kcal/mole, and for the nonlactonized germacrane it amounts to 15 kcal/mole, which indicates freer conformational transitions. However, in all three model compounds the $c \Leftrightarrow d$ and $d \Leftrightarrow a$ transitions are unlikely, since ΔE_{strain} for them is considerably higher — of the order of 30-45 kcal/mole.

EXPERIMENTAL

The conformational calculations for the hypothetical model molecules were conducted on a PC of the IBM PC AT-386/387 type using the MMX86 program [5] with full optimization of the geometries of the molecules and the standard parameters of the potentials. To construct the model and hypothetical molecules, we used the PC MODEL program. Some of the calculations by the MM method were conducted with this program.

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