

CONFORMATIONAL ANALYSIS OF DODEC-3Z-ENOLIDE — A COMPONENT OF THE AGGREGATION PHEROMONE OF *Cryptolestes pusillus*

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*A conformational analysis has been made of one of the components of the aggregation pheromone of *Cryptolestes pusillus* — a pest of grain stores. The 12 most probable states of dodec-3Z-enolide have been studied by the method of molecular mechanics, and the geometric parameters and the localization of the electric charges have been determined for the most stable conformation.*

The flat grain beetle *Cryptolestes pusillus* severely damages grain and the products of its processing. The aggregation pheromone of this beetle includes three cyclic macrolides. One of them — dodec-3Z-enolide — has been synthesized by the Wittig reaction. For this purpose, 3-bromopropan-1-ol was oxidized with the Jones reagent and the resulting acid was boiled with triphenylphosphine in acetonitrile to give the phosphonium salt. On reaction with *tert*-butyl chromate, nonane-1,9-diol gave 9-hydroxynonanal. The Wittig reaction was the key stage in the synthesis. Potassium *tert*-butanolate in DMFA was used as the base. The cyclization of 12-hydroxydodec-3Z-enoic acid was achieved by the use of 2,2'-dipyridyl disulfide [1]. In the present paper we give the results of a study of the 12 most probable states of dodec-3Z-enolide using the method of molecular mechanics (ALCHEMY 2 TRIPOS ASSOCIATES).

We have investigated one of the conformations of this macrolide previously [2]. As the initial structure for conformational analysis we took a set of the most favorable structures of cyclotetradecane, a complete study of which has been made by T. H. Keller et al. [3]. These authors found the six most favorable conformations of cyclotetradecane, four of which were based on the diamond lattice, while two had nondiamond structures but possessed a fairly low strain energy.

In order to pass to the 13-membered ring, four ordinary bonds in *trans-trans* linkage are replaced by a *cis*-olefinic fragment with three bonds: atoms 13, 1, 2, and 3. To pass to the lactone, appropriate substitutions are made in the β - and γ -positions to the double bond. A single conformer is obtained for the symmetric structures (3) and (6), while two structures with different positions of the lactone fragment are possible for the asymmetric conformations. For compound (5) (Table 1) an additional variant of the position of the olefinic fragment is possible, since in the 14-membered ring a plane fragment is forced by five ordinary bonds. In this way, the 12 most probable conformations of dodec-3Z-enolide are obtained (see Table 1).

Table 1 gives the relative energies of steric strain, three-dimensional structures, and polar maps [4] of these states of dodec-3Z-enolide. The energy of the most stable state (1a) was taken as zero. The polar maps permit the best comparison of the conformations with one another. Along the radii of a polar map are plotted the values of the dihedral angles in the interval of $-\pi$ to $+\pi$, while the numbers of the sectors correspond to the numbering of the atom of the ring. As a result, we obtain a simple plane graphical pattern unambiguously linked with the three-dimensional structure of the molecule. Such graphical patterns (graphs) permit the revelation of structures having spatial similarity, elements of symmetry in a ring structure, and structures that are conformationally close. It can also be seen from Table 1 that the range of energies reaches 13.5 kcal/mole. If we limit ourselves to a range of energies of up to 10 kcal/mole, only six conformations fall into it: (1a), (1b), (2a), (3a), (4a) and (5d).

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TABLE 1. Energy and Conformational States of Dodec-*cis*-3-enolide

Number of the structure		Energy of steric strain, kcal/mole	Three-dimensional structure	Polar maps
1	a	0		
	b	9.0		
2	a	6.7		
	b	10.1		
3	a	7.3		
4	a	8.5		
	b	12.2		
5	a	11.1		
	b	13.5		
	c	13.1		
	d	9.6		
6	a	13.6		

Apparently, the construction of the ring of the lactone from the most sterically favorable conformations of cyclotetradecane should lead to a more energetically favorable lactone. On passing from the 14-membered ring to a 13-membered olefinic ring this was actually the case, and the most favorable proved to be a diamond-like structure. However, the introduction of the lactone fragment entailed a redistribution of the structures under consideration with respect to the magnitude of steric strain. The symmetric diamond structure that was most favorable before this [2] passed into the third position with respect to steric strain [Table 1, structure (3a)].

Figure 1 shows the three-dimensional structure of the most favorable form of the (1a) molecule. The mutual screening of protons characteristic for the 14-membered carbon ring [3] is not observed in this case. The electric charges of the atoms are localized mainly on the carbonyl group: -0.40 electron units on the oxygen and $+0.41$ on the carbon. The π -electronic system of the olefinic bond well compensates the redistribution of electron density close to it: the charges on C12-C2 are not more than 0.04 of the electronic charge. The charges on O4 and the only charged carbon, C5, are, respectively, -0.17 and 0.13 of a unit. According to this, the highest activity for chemical interactions must be expected for carbon C5.

In an analysis of dipole-dipole interaction, only an electrostatic interaction of the carbonyl group with two bonds is distinguished: repulsion from the C1-C2 bond -0.72 kcal·DC and attraction to the O4-C5 bond -1.66 kcal·DC. The other

TABLE 2. Geometric Parameters of the Main Conformation of Dodec-3Z-enolide

1 the atoms i j k l	Bond lengths i-j (Å)	Valence angles i-j-k (deg.)	Dihedral angles i-j-k-l (deg.)	Dihedral angles before the introduction of the lactone group
1 2 3 4	1.51	111	102	60
2 3 4 5	1.52	110	-174	-180
3 4 5 6	1.34	119	75	60
4 5 6 7	1.41	111	34	60
5 6 7 8	1.54	115	59	60
6 7 8 9	1.54	114	-173	-180
7 8 9 10	1.54	114	54	60
8 9 10 11	1.54	116	55	60
9 10 11 12	1.54	114	-169	-180
10 11 12 13	1.54	113	54	60
11 12 13 1	1.54	112	76	60
12 13 1 2	1.51	127	1	0
13 1 2 3	1.34	127	-113	-60

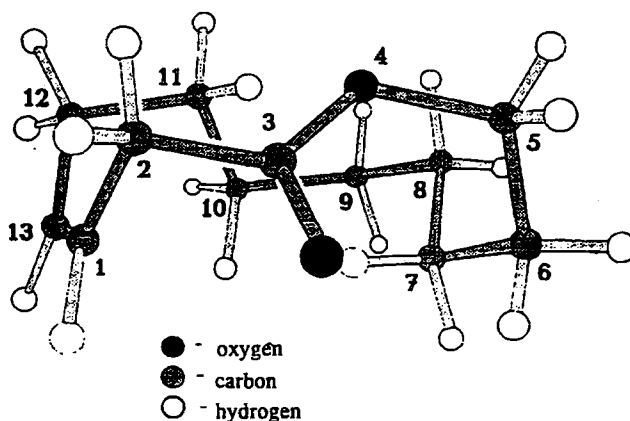


Fig. 1. Spatial structure of dodec-3Z-enolide in conformation (1a).

electrostatic interactions are insignificant. It is obvious that the methylene protons of the C6–C11 chain form a neutral hydrophobic surface of the lactone passive to the chemical manifestation of this compound.

Analysis of the components of the steric strain has shown that approximately 60% of the contribution to the energy of the molecule must be ascribed to van der Waals interaction, while approximately 30% of the energy contribution corresponds to the strain caused by the distortion of valence angles. The largest of the contributions of interaction through space is exhibited by the olefinic protons H1–H13, the carbonyl carbon C3 with the methylene carbon C-5, the carboxylic carbon C-3 with the equatorial hydrogen H5, the equatorial H7 and axial H10 hydrogens, and the axial H8 and equatorial H11 hydrogens.

The bond lengths are close to the unstrained values. The valence angles in our case are somewhat large. The dihedral angles deviate substantially from the noneclipsed conformation, although qualitatively they remain close to the initial form of the lactone constructed on a diamond lattice by the geometry optimization procedure (last column of Table 2 or dotted line in the graph of structure (1), Table 1). Particularly large changes took place in the angles C1–C2–C3–C4 and C13–C1–C2–C3. Nevertheless, after optimization the structure of dodec-3Z-enolide retained its basic features.

Thus, it has been shown that the conformations of the lactone must be more monotonic than the conformations of cyclotetradecane. For the 14-membered cyclic structures the energy gap between the most favorable conformation and the following one was 1.1 kcal/mole, while in the lactones under consideration it is 6.7 kcal/mole; i.e., the population of the optimum structure for dodec-3Z-enolide is higher than in the 14-membered saturated rings. The geometric parameters have been determined for the most stable conformation of dodec-3Z-enolide and its electric charges have been localized.

REFERENCES

1. V. S. Abdukakharov, M. M. Kasymzhanova, G. S. Shakirzyanova, and A. A. Abduvakhabov, *Khim. Prir. Soedin.*, 568 (1990), p. 568.

2. V. S. Abdukakharov, M. G. Levkovich, G. S. Shakirzyanova, M. M. Kasymzhanova, and A. A. Abduvakhobov, in: Abstracts of Lectures at the First All-Union Conference on Theoretical Organic Chemistry [in Russian], Volgograd (1991), p. 318.
3. T. H. Keller, E. G. Neeland, S. Retting, J. Trotter, and L. Weiler, *J. Am. Chem. Soc.*, **110**, 7858 (1988).
4. J. P. Ounsworth and L. Weiler, *J. Chem. Educ.*, **64**, No. 7, 568 (1987).