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CONFORMATIONAL ANALYSIS IN 18-MEMBERED MACROLIDE ANTIBIOTICS BASED ON MOLECULAR MECHANICS.

ANALYSE CONFORMATIONNELLE DES MACROLIDES ANTIBIOTIQUES A 18 CHAINONS BASEE SUR LA MECANIQUE MOLECULAIRE.

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ABSTRACT

Conformational analysis of macrolides with 18-ring membered has been carried out using molecular mechanics calculations and molecular dynamics. A high conformational mobility of no complexed macrocycles has been obtained and an important stereoselectivity has been observed for the complexed macrocycles. For 18d macrolide, which was presented by a privileged conformer with 20.1% without complex, was populated with 50.1% in presence of $Fe(CO)_3$. For the most privileged conformer geometry; the α,β-unsaturated ester group has an s-cis conformation with a torsion angle ϕ_1: O19-C2-C3-C4 = 14.5° for macrocycle 18d macrolide and ϕ_1: O19-C2-C3-C4 = 25.0° for 18s macrolide. The diene group has an s-trans conformation with a torsion angle ϕ_2:C11-C12-C13-C14 = 169.4° for 18d macrolide and ϕ_2:C10-C11-C12-C13 = 179.5° for 18s macrolide.

RESUME

L'analyse conformationnelle des macrolides à 18 chaînons a été réalisée par des calculs de mécanique moléculaire et de dynamique moléculaire. Une mobilité conformationnelle élevée a été obtenue pour les macrocycles non complexés et une stéréosélectivité importante a été observé pour les macrocycles complexés. Pour le macrolide 18d, qui a été présenté par un conformère privilégié avec 20.1% sans complexe, est devenu 50.1% en présence de $Fe(CO)_3$

Pour la géométrie du conformère le plus privilégiée; le système d'ester α,β-insaturé, a une conformation s-cis avec un angle de torsion ϕ_1 : O19-C2-C3-C4 = 14.5° pour le macrolide 18d et ϕ_1 : O19-C2-C3-C4 = 25.0° pour le macrolide 18s. Le système diène a une conformation s-trans avec un angle de torsion ϕ_2 : C11-C12-C13-C14 = 169.4° pour macrolide 18d et ϕ_2:C10-C11-C12-C13 = 179.5° pour macrolide 18s.

1 INTRODUCTION

Macrolide antibiotics have been the focus of widespread research due to increasing bacterial resistance [1, 2]. There have been significant synthetic and theoretical efforts to generate new core structures to address this challenge [3].

Structure elucidation of a large number of obtained molecules[4] actually shows the existence of two parts. The first one is a macrocyclic system from 12 to 40 links with several asymmetrical centers and lactone function; the second one is a sugar part. The two main classes of these macrolides are presented by Erythromycin A which is an active antibiotic against a large number of bacteria, the Amphotericin B which presents a strong anti-fungal.

Still et al[5] have shown that conformational properties of middle and large size (8 to 14 atoms) might induce a diastereoselection phenomenon for the reactions carried out on these compounds. More precisely macrocycles which have a double bond (C=C, C=O) and substitutes correctly situated adopt privileged conformations. Peripheral attack of the reactive by the less hindered face of π-system conduct to a higher stereoselective formation of a new asymmetrical center. Grée et al [6] have also shown in some cases the possibility of a stereochemical control induced by tricarbonyliron. Our objective is therefore to verify if this notion can be extended for cycles with large size. In the present paper, we propose to study the 18-membered α,β-unsaturated macrocycle with the view to determine the most privileged conformations and the influence of $Fe(CO)_3$ on conformational mobility of these macrocycles.

2 COMPUTATIONAL PROCEDURES

In the present study, the main method of calculation is Molecular Mechanics. This is considered as the most adapted method for larger molecules[7]. Programs that we have used are based on Allinger force field [8]. This method for structure determination includes a quantum mechanical (VESCF) π-system calculation in the iterative sequence. They use "Monte-Carlo" simulation type and Metropolis algorithm.

These calculations were carried out with three software packages P.C.M. (6.1)[9] for geometry optimization and calculations of energies, HyperChem (7.1)[10] for conformational search by molecular dynamics and Chem3D (7.0) [11] for structural representation.

Our objective then, is to look for the privileged conformations, on the basis of energy and geometric considerations with statistical calculations using Boltzmann distribution [12].

In this part of our work, we have undertake a conformational study of macrocycle 18 (figure 1), symmetrical which we will design 18s ($n_1 = n_2 = 5$), dissymmetrical which we will design 18d ($n_1 = 4$, $n_2 = 6$) complexed and no complexed with $Fe(CO)_3$.

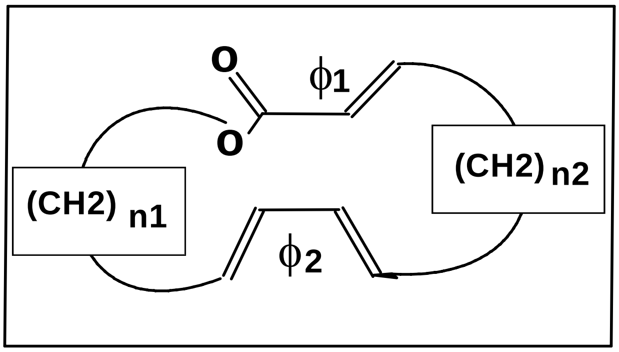

Figure 1: α,β-unsaturated macrolide.

3 RESULTS AND DISCUSSION

The most stable structures can be characterized by three structural characters: the diene group, the α,β-unsaturated ester group and the two saturated chains. Thus we have obtained eight types of conformations, which are present in the majority of cases in 6 Kcal/mol energetic range above an entire minimum. The conformation types are classed from 1 to 8 [13, 14,15].

For types (2, 4, 6, 8) the two planes of two conformational sites diene and α,β-unsaturated ester group were pseudo-parallels; but for types (1, 3, 5, 7) the two planes of the two sites are pseudo-antiparallels.

We conclude also, that for the two conformations, which we distinguished by the arrangement between the two sites, the dipolar moment values are higher for pseudo-parallel arrangement and lower in the other case (i.e. for the macrocycle 18s $\mu(T2) = 2.17$ D and $\mu(T1) = 1.97$ D.

In 1Kcal/mol difference the macrocycle 18d is characterized by the first conformer type 6, which is the most favorable with 20.1% rate followed by a type 4 with 18.3%. Then the macrocycle 18s is presented preferably in the type T5 (17.2%) and type T3 (15.0%) conformations.

The percentages of other conformation types are listed in table (1). The conformer's populations rates of macrocycle 18d are lightly greater than these of macrocycle 18s. For the most privileged conformer geometry; the α,β-unsaturated ester group has an s-cis conformation with an angle ϕ_1: O19-C2-C3-C4 = 14.5° for macrocycle 18d and ϕ_1: O19-C2-C3-C4 = 25.0° for cycle 18s. The diene group has an s-trans conformation with a torsion angle ϕ_2:C11-C12-C13-C14 = 169.4° for 18d and ϕ_2:C10-C11-C12-C13 = 179.5° for 18s. The two systems ester and diene are parallel between themselves. These macrocycles have a very high conformational mobility.

However the mobility of dissymetric macrocycles is lightly less important than that of symmetric macrocycles.

They present many privileged conformations that do not a priori one foresee a diastereoselection for envisaged reactions. This is in agreement with Still's works on macrocycle 17, which yields many different conformations[16].

Table 1: Energetic difference and Boltzmann population for different conformationals types.

Macrolide	18 symmetric ($n_1 = n_2 = 5$)			18 dissymmetric ($n_1=4$, $n_2= 6$)		
	Type	ΔE	%	Type	ΔE	%
To 1 kcal/mol	5	0.00	17.2	6	0.00	20.1
	3	0.58	15.0	4	0.37	18.3
	4	0.84	14.1	3	0.90	16.1
To 2 kcal/mol	6	1.07	13.3	8	1.90	12.6
	1	1.89	10.9			
	8	1.90	10.9			
Sup to 2 kcal/mol	7	2.06	10.5	5	3.03	9.6
	2	3.05	08.2	1	3.61	8.3
				7	3.66	8.2
				2	4.54	6.7

ΔE: Energetic difference to the absolute minimum %: Boltzmann population

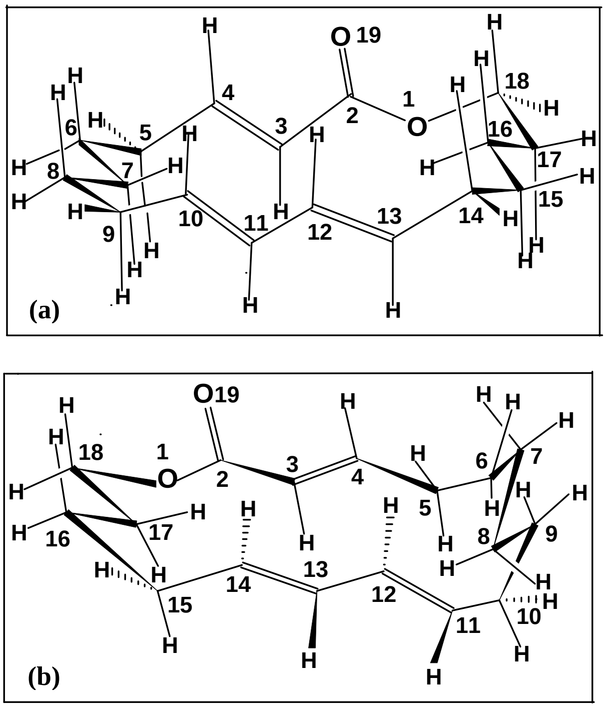

Figure 2: Privileged conformers of macrocycles 18s (a) and 18d (b)

After that, we have studied the exerted effect of tricarbonyliron on conformational mobility of these macrocycles. We noted that organometallic complex can intervene by a very high steric hindrance and also introducing an important rigidification of skeleton. The results of conformational analysis of two complexed macrocycles 18 show that tricarbonyliron has a considerable influence on cycles because the number of possible conformations was reduced to four types [17, 18, 19].

In 1 Kcal/mol energetic difference, the complexed macrocycle 18s shows three privileged conformations and only one privileged conformation for 18d.

The peopling rate of the most stable conformers was increased for complexed macrocycles compared with these without tricarbonyliron (Table 2).

For macrocycle 18d, which was presented by a preferred conformer with 20.1% without complex, was populated with 50.1% in presence of $Fe(CO)_3$. We remark also that macrocycles 18s and 18d were presented respectively in T1 type with 28.5% and T8 type with 50.1% for the most privileged conformers.

Dienic system was fixed in s-cis conformation for all preferential conformations. The dihedral angle value of dienic system was comprised between 1.0 and 5.4° for 18s cycle, between 4.1 and 13.9° for 18d cycle. The lower deviations of registered dihedral angles compared with normal values were imposed essentially by a cyclic chain.

The presence of tricarbonyliron motif imposes a minimum steric modifications, introduces an asymmetric element. So, this creates a favorable environment to the discrimination between two faces of macrocycles, which leads to the increase of a peripheral attack (Figure 3)

Table 2: Energetic difference and Boltzmann population of different conformational types of complexed macrocycles.

Macrolide	18 symmetric ($n_1 = n_2 = 5$)			18 dissymmetric ($n_1 =4$, $n_2 = 6$)		
	Type	ΔE	%	Type	ΔE	%
to 1 kcal/mol	1	0.00	28.5	8	0.00	50.1
	8	0.30	26.5			
	7	0.54	25.1			
Sup to 1 kcal/mol	2	1.47	19.9	7	4.04	18.8
				1	4.30	17.6
				2	5.39	13.5

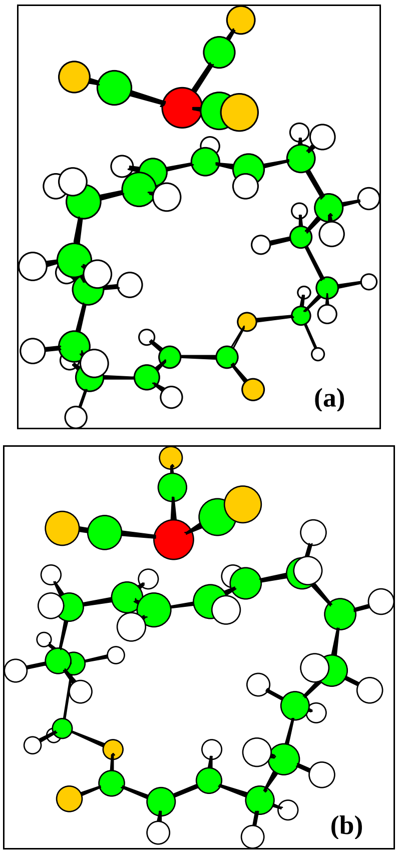

Figure 3: Privileged conformations of complexed macrocycles 18s (a) and 18d (b)

Again this reasoning was found again in methyl acetates with fluorine containing auxiliaries where intramolecular interaction Li….F creates a steric hindrance around one of two faces causing a diastereofacial selectivity of 94.6: 5.4[20]. The lactone function and complexed diene were practically perpendicular at medium plane of the cycle. This is in agreement with Still's works that affirm that CH_3I addition will be executed on the clear face by peripheral attack [5]. The study carried out by Ley [21] on $Fe(CO)_3$ complexes have shown that the presence of complex, which has an important steric effect, induced a diastereoselectivity in addition reactions.

4 CONCLUSION

Our study then, shows the existence of a very high conformational mobility increasing in a majority of no complexed macrolides.

The tricarbonyliron introduction in a skeleton has permitted to fix the function diene in an s-cis conformation. This has introduced an asymmetric element, an important steric effect increasing the peripheral attack proportion. The observed diastereoselectivity for complexed macrolides is the result of tricarbonyliron control effect. Consequently, this complex of iron constitutes a tool of remote stereochemical control, which permits to foresee the diastereoselectivity of alkylation reactions.

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