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Résumé : L'analyse conformationelle des macrolides de 22 chaînons a été réalisée en utilisant la modélisation moléculaire (mécanique moléculaire et dynamique moléculaire). Les résultats indiquent que les macrocycles étudiés présentent chacun huit types de conformations préférentielles. Ces dernières résultent de la combinaison des conformations des deux systèmes diène et ester α, β -insaturé. Une mobilité conformationelle importante a été obtenu pour les macrocycles (22) non complexés. Avec la présence du fer tricarbonyle le nombre des conformations a été réduit.

Abstract: Conformational analysis of macrolides with 22-ring membered has been carried out using molecular modeling (molecular mechanics and molecular dynamics). The results indicate that each investigated macrocycles present eight types of preferential conformations. They result of the combination of two systems diene and ester α,β-unsaturated. A high conformational mobility of no complexed macrocycles (22) was obtained. In presence of tricarbonyliron, the number of the privileged conformations was reduced.

INTRODUCTION

Biological importance of macrolides, presenting for the most an anti-bacterial activities and their medical use has swiped away [1] , recently an increasing interest for the study of these molecules [2] .

Among these products which have a major importance, the macrocyclic antibiotics on account of their biological interest a large number of synthesis methods were elaborated [3]. Structure elucidation of a large number of obtained molecules shows the existence of two parts[4]. The first one is a macrocyclic system from 12 to 40 links with several asymmetric centers and lactone function; the second 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.

Grée et al. [6] have shown also in some cases the possibility of a stereochemical control induced by tricarbonyliron. So, our objective is to verify if this notion can be extended for cycles with large size. In this paper we propose to study the 22-membered macrocycle α,β-unsaturated in a view to determine the most privileged conformations and the influence of $Fe(CO)_3$ on conformational mobility of these macrocycles.
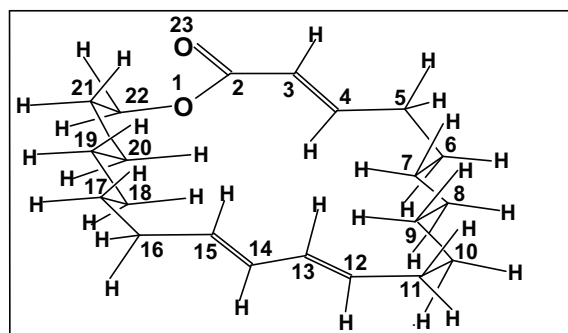
RESULTS AND DISCUTION

In our study, the principal method which we have used 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.

These calculations were carried out with three software packages P.C.M.6.1 [9] for geometry optimization and calculations of energies, HyperChem 7.01 [10] for conformational search and molecular dynamics. Chem3D (7.0) [11] for structural representation. They use "Monte-Carlo" simulations type and Metropolis algorithm. Computer times require some hours for conformational investigation and a few minutes for energetic minimization on P.C.

The minimization algorithms used repeatedly in the calculation of the privileged conformation are in the following order: steepest-descent, conjugated gradient and Newton-Raphson. The calculation procedures were stopped when the minimal energy obtained became constant.

We also used the molecular dynamics (HyperChem) for the conformational research, with the following options: 1000°K, in vacuo, step size: 0.001ps, relaxation time: 0.1ps. Then our objective is to search the privileged conformations. Based on these calculations and the Boltzmann distribution [12], our aim was to find all these low-energy conformers.

In this part of our work we have undertake a conformational study of macrocycle 22, symmetrical which we will design 22s Fig. 1 (a), dissymmetrical which we will design 22d Fig. 1 (b) complexed and no complexed with $Fe(CO)_3$.
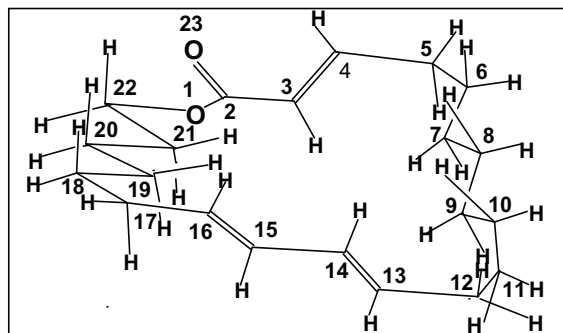
(a)   **(b)**

Fig. 1: Molecular structures of privileged conformers of macrocycles 22s (a) and 22d (b)

Detailed study of macrocycle geometries that have the lowest energies of this macrocycle shows that these macrolides possess three main structural characters: diene system, α,β-unsaturated ester group and two saturated chains. Thus we have obtained eight types of conformations which are present in the majority of cases in 3 Kcal/mol energetic ranges above an entire minimum. The conformation types are classed from 1 to 8 [13, 14].

For types (2, 4, 6, 8) the two planes of two conformational sites diene and ester function α,β-unsaturated were pseudo-parallels; But for types (1, 3, 5,7) the two planes of the two sites are pseudo-antiparallels [15,16]. We remark also that for two conformations which we distinguish by the arrangement between the two systems, the dipolar moment values are higher for pseudo-parallel arrangement and lower in the opposite case (for the macrocycle 22s $\mu(T2)= 2.29$ Debye and $\mu(T1)= 1.97$ Debye).

In 1Kcal/mol difference the macrocycle 22d is characterized by the first conformer type 3 which is the most favorable with 20.1%. Then the macrocycle 22s is presented preferably in the type T4 (17.9%) and type T3 (17.5%) conformations. The percentages of other conformations types are listed in table (1)

The conformer's populations rates of macrocycle 22d are lightly greater than these of macrocycle 22s. For the most privileged conformer geometry the ester system α,β-unsaturated has a s-trans conformation with an angle ϕ_1: O23-C2-C3-C4 = 179.6° for macrocycle 22d and ϕ_1: O23-C2-C3-C4 = 170.3° for cycle 22s. The diene system has a s-trans conformation with a torsion angle ϕ_2:C13-C14-C15-C16 = 172.4° for 22d and ϕ_2:C12-C13-C14-C15 = 177.2° for 22s (Fig. 1).

The two planes systems ester and diene are parallel between themselves. These macrocycles have a very high conformational mobility. However mobility of dissymmetric cycles is lightly less important than that of symmetric cycles. They present large privileged conformations that not allow a priori the diastereoselection previsions for envisaged reactions.

This is in good agreement with Still's work, on macrocycle 17 (cycloheptadecane), which yields many different products [17].

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

Macrolide	22 symmetric			22 dissymmetric		
	Type	ΔE	%	Type	ΔE	%
To 1 kcal/mol	4	0.00	17.9	3	0.00	20.1
	3	0.08	17.5			
	5	0.36	16.4			
To 2 kcal/mol	6	1.47	12.5	4	1.06	15.6
				5	1.49	14.0
				8	1.86	12.8
Sup to 2 kcal/mol	7	2.47	09.8	6	2.68	10.5
	8	2.69	09.3	7	2.80	10.2
	1	2.75	09.2	2	2.93	09.9
	2	3.55	07.5	1	4.43	06.9

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

After that we have studied the exerted effect by tricarbonyliron on conformational mobility of these macrocycles. We note 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 22 show that tricarbonyliron has a considerable influence on cycles because the number of possible conformations was reduced to four types.

In 1 Kcal/mol energetic difference, the complexed macrocycle 22s show three privileged conformations and only one privileged conformation for 22d. The peopling rate of the most stables conformers was increased for complexed macrocycles compared with these without tricarbonyliron (table 2).

Table 2: Energetic difference and Boltzmann population of different conformational types for every complexed macrocycle.

Macrolide	22 symmetric			22 dissymmetric		
	Type	ΔE	%	Type	ΔE	%

to 1 kcal/mol	1	0.00	28.1	8	0.00	36.2
	7	0.16	27.0			
	8	0.63	24.1			
Sup to 1 kcal/mol	2	1.23	20.8	7	1.96	22.5
				2	2.04	22.0
				1	2.59	19.3

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

For macrocycle 22d which was presented with a peopling rate 20.1% without complexant, become peopled with 36.2% rate in presence of Fe(CO)₃. We remark also that macrocycles 22s and 22d will be presented respectively in T1 type with 28.5% and T8 type with 36.2% 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 0.69° and 2.74° for 22s macrocycle and between 4.8 and 11.0° for 22d macrocycle. The lower deviations of registered dihedral angles compared with normal values were imposed essentially by a cyclic chain.

The presence of tricarbonyliron motif imposes minimum steric modifications, introduce an asymmetric element. So, this creates a favorable environment to discrimination between two faces of macrocycles increasing thus a peripheral attack proportion (Fig. 2). This reasoning was found again in methyl acetates with fluorine containing auxiliaries where intramolecular interaction Li….F create a steric hindrance around one of two faces causing a diastereofacial selectivity of 94.6: 5.4 [18] .

The lactone function and complexed diene were practically perpendicular at medium plane of the cycle. This is in good agreement with Still et al., who affirmed that the addition of CH₃I on enolate, was carried out by a peripheral attack on this face [5].

The study carried out by Ley [19] on Fe(CO)₃ complexes has shown that the presence of complexant which has an important steric effect, induced a diastereoselectivity of addition reactions.
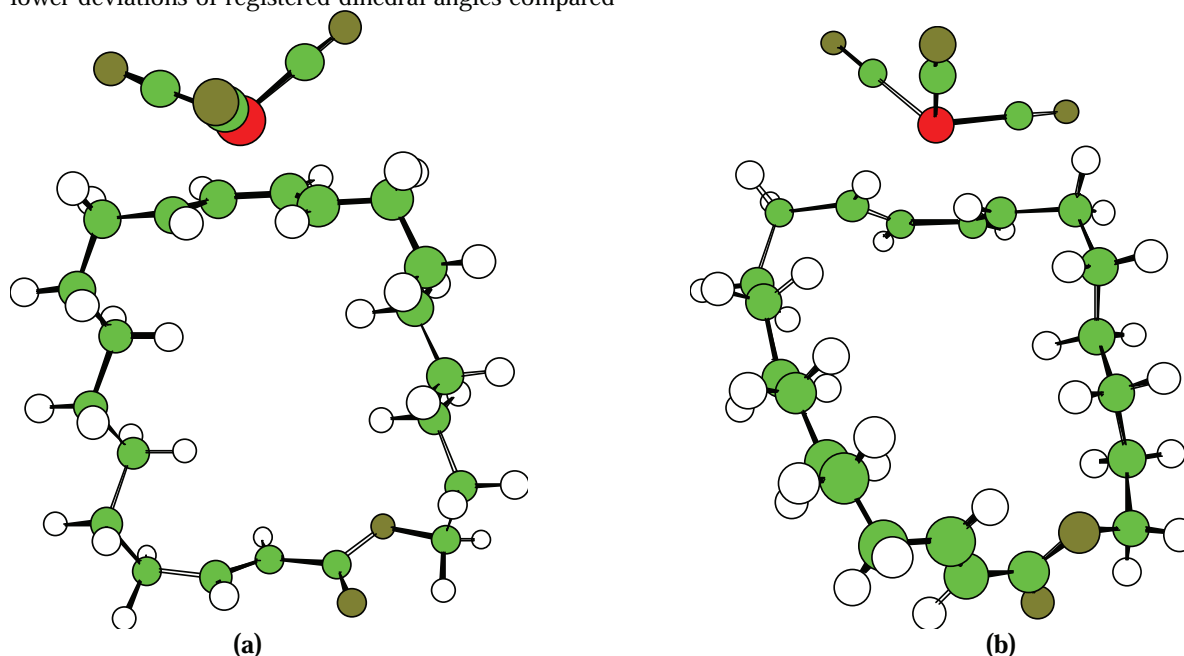

(a)　　　　　　　**(b)**

Fig.2: molecular structures of privileged conformations of complexed macrocycles 22s (a), 22d (b) (Chem 3D [11])

CONCLUSION

We conclude that the study that we have carried out shows the existence of a very high conformational mobility increasing in a majority of non complexed macrolides. The tricarbonyliron introduction in a skeleton permitted to fix the function diene in 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 a result of tricarbonyliron control effect. This last factor constitutes a tool of the stereochemical remote control, which permits us to foresee a priori the phenomenon of the stereoselectivity for envisaged reactions

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