A Conformational Exploration of Dissymmetric Macrolides Antibiotics

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Conformational analysis of the macrolides from 12 to 22 links was carried out using molecular mechanics. Calculations indicate that each studied macrocycle presents eight families of preferential conformers. They result from the combination of the conformations of the two systems diene and α, β-unsaturated ester. Among these conformers three families (F5, F6 and F3) have the lowest energy. The two families F5 and F6 adopt an s-cis conformation of the ester function and s-trans of the diene system with a pseudo-parallel arrangement of the two systems for the first family and a pseudo-antiparallel for the second. The third family F3 presents a s-trans conformation for the two systems. An important stereoselectivity of the complexed macrocycles was obtained.

Key Words: macrolide, molecular mechanics, conformational analysis, and tricarbonyliron.

Introduction

Macrolide antibiotics play a therapeutically important role, particularly the emergence of new pathogens. Among these products of major importance are macrocyclic antibiotics. The macrolide antibiotic family (14-, 15-, 16- membered ring derivates) shows a wide range of characteristics (antibacterial spectrum, side effects). The most commonly used macrolides are erythromycin and josamycin. Because of their biological interest many synthesis methods have been elaborated[1].

Molecular structure studies of these molecules show the existence of two parts[2]. The first one is a macrocyclic system from 12 to 40 links with several asymmetric centres and the lactone. The second part is a sugar.

Still et al.[3,4] demonstrated that conformational properties of medium and large rings have profound consequences on the stereochemical course of their chemical reactions. More precisely, the macrocycles having a double bond (C=C, C=O), with substitutents in a perfect position adopting preferred conformations. Peripheral attack of external reagents would occur largely from the less hindered peripheral face of the Π-system. This allows a highly stereoselective formation of new asymmetric centres. In this case, a substitute applies remote stereocontrol by conformational stability of a macrocycle. Grée et al. have shown also in some cases the existence of the remote stereocontrol induced by the tricarbonyliron [5]. In this paper we will study

the α,β-unsaturated macrolides which represent the binding structure for many antibiotic families of 12- to 22- membered rings (Fig. 1). Our object is to examine the relative importance of different contributions to total steric energy, and to determine preferred conformations of non-complexed macrocycles. Then we will also try to evaluate the stereoselectivity of additions reactions carried out on functional groups appended to the tricarbonyliron moiety.
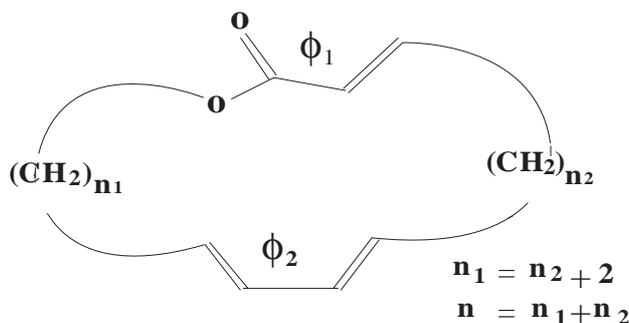
Figure 1. Scheme of α,β-unsaturated dissymmetric macrolide.

Calculations

Calculations were carried out using molecular mechanics and molecular dynamics, with two software packages, Alchemy II[6] and TSAR[7], implemented a Data General Computer and P.C.M 5.9 [8] a P.C. The minimum energy geometries were located by minimising energy with respect to all geometrical coordinates and without imposing any symmetry constraints. This method for structure determination uses a quantum mechanical (VESCF) Π-system calculation in the iterative sequence and Allinger's MM2 force field [9]. These calculations use the "Monte Carlo" simulations and the Metropolis algorithm. The conformational searching method included systematic and random conformational searches in both internal (torsion angle) and external (Cartesian) coordinates frames. Systematic searches are typically conducted by alternating torsional angles and operate by generating all combinations of selected values for some or all possible torsional angles to produce starting geometries distributed throughout a conformational space. The stochastic or Monte Carlo[10] searches, on the other hand, generate starting geometries using random variations of molecular geometry. Then, based on these calculations and the Boltzmann distribution[11], our objective is to find all of these low-energy conformers.

Energetic Considerations

1-Variation of the total strain energy

Conformational study is based on molecular mechanics. We will use the entire steric energy to compare the thermodynamic stability of conformation isomers of the same compound. The strain energy will be used for a comparison of relative stability of different studied macrocycles[12]. Figure 2 presents an evolution of the strain energy per CH_2 group as a function of the total amount of methylene (n).

The strain energy per CH_2 group is relatively higher for macrocycle 12 (n = 4) (E(st/n) = 0.56 Kcal/mol). The variation of E(strain/n) as a function of the entire number of methylene is similar to that obtained in anterior works concerning cycloalcanes studies C_4-C_{12} [13]. An important decrease in the strain

energy per CH_2 group from n = 4 to n = 6 confirms perfectly the limit between the two classes of medium and large rings, as was mentioned in the literature[14]. In line with the above conclusions, the rate of cyclization increases with the size of the ring[14,15]. This is in good agreement with our results, which indicate that an evolution of strain energy per CH_2, group is opposite to the size of the ring.
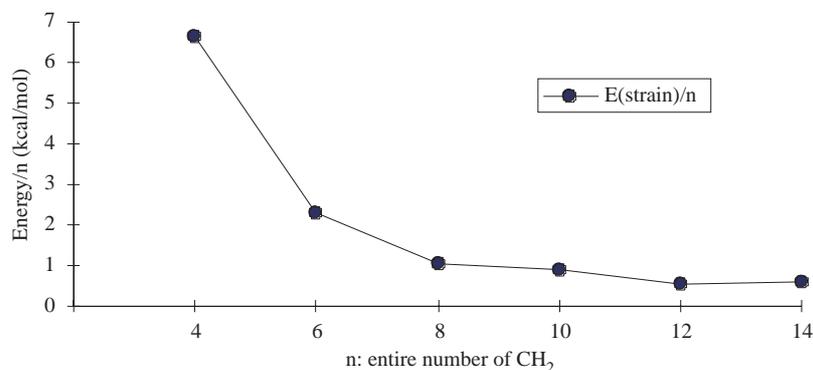
Figure 2. Evolution of the strain energy by (CH_2) group as a function of the entire number of methylene (n).

2-Contributions of different features to steric energy

The steric energy calculated[13] from the sum of different contributions such as stretching, bending, torsional, VanderWaals, and electrostatic energies:

E(steric) = E(stretch) + E(bend) + E(tors) + E(vdw) + E(electr) + …..

We will investigate their contributions and influences on steric energy. Figure 3 presents the contribution of different component energies to the total steric energy of the most stable conformers.
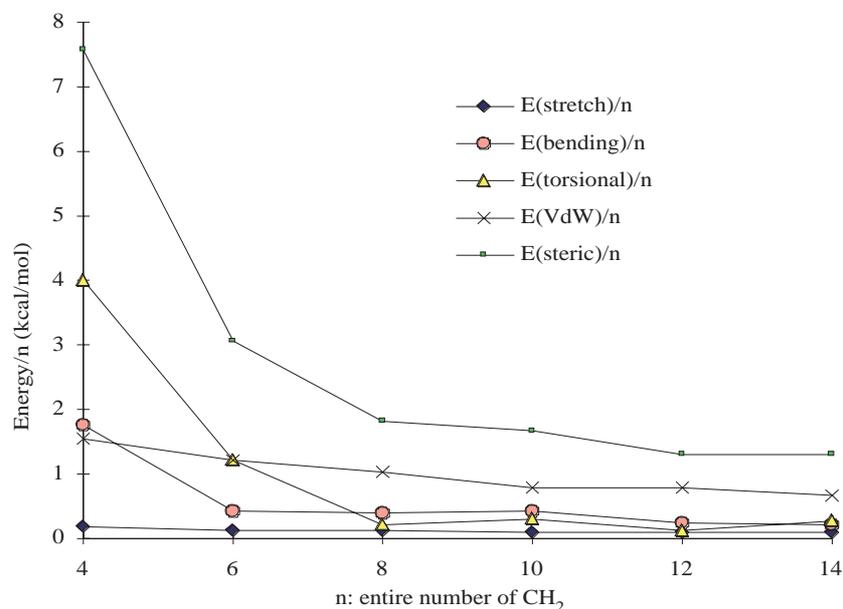
Figure 3. Contribution of different componantes to the total steric energy of the most stable conformers.

We remark also that for two adjoining macrolides the torsional energy is lower for (m) pair (m = n/2) as in the case of the strain energy for n ⩾ 6. This can be explained by the favourable torsional

angles. All methylene groups are in the anti position in a conformation composed with two long parallel chains. For n $\geqslant$ 6 the v der Waals' constraint is the major contribution, taking into account the number of supplemental interactions created by the transannular hydrogen atoms. It attains a maximum for macrocycle 20 (E(VdW) = 9.52 Kcal/mol). For the macrolides (n $\geqslant$ 6), the torsional energy E(Φ/n) is lower than the van der Waals energy. Rings are less strained, the size of the ring allows more anti-alignment of methylene groups. In such a case, the energy gauche-form is 0.8 Kcal/mol[13] superior to the anti-form. However, the stretching contribution E(l)/n is lower and stays appreciably constant. Bond lengths are not very different from reference values. For the bending energy, this contribution does not differ strongly between them. The C-C-C angle is not influenced by the length of a cyclic chain and stays close to the normal tetrahedral valence 109° [16].

For the macrolide 12 (n = 4), the torsional energy contribution is superior to that of van der Waals'. E(Φ/n) = 4.01 Kcal/mol represents alone 53% of the total steric energy. This is essentially due to unfavourable torsional angles because it is not possible to obtain the perfectly altered conformation on a majority of C-C bonds, as is the case with other macrocycles. In conclusion, the contribution of the Van der Waals' energy E(VdW/n) is higher in all examined macrocycles in their stable conformers (n $\geqslant$ 6). Its variation as function of (n) is, in general, proportional to a resultant of the bending and torsional constraint. In each ring, a compromise was established between the torsional, bending and Van der Waals energies in order that each molecule adopts the conformation which corresponds to the minimal total steric energy[17].

3- Geometrical and statistical study

The conformation searching operation was as follows: a crude starting geometry is produced and its structure is optimised by the molecular mechanics energy minimisation. The resulting minimum energy conformer is then compared with previously found conformers to test for possible duplication. If the conformer thus generated is a previously undiscovered one, it is added to an accumulating list of unique conformers, and the cycle is then repeated by obtaining a new crude starting geometry energy minimisation etc. When all given starting geometries have been used or when new minima cease to be found the search is terminated. Although several calculations were carried out in the conformational search we cannot be sure that other low energy conformers were not overlooked in some instances. This is in agreement with Still's work[3].

Conformational analysis using the statistical analysis software TSAR[7] (Tools for structure activity relationships) has led to an important number of conformers. Thus, the conformer number to explore is N^m, where N is the rotator number and m defines the angular increment (360/m). For the macrocycle 20 e.g., the TSAR program, which was executed over 100 hours, declined 20425 conformers registered from 1 to 32538. Missed conformers are those for which a re-closing of the cycle has become impossible or for which steric interactions were too strong. Thus, we have grouped conformers with identical structure (energetic differences are due to low altering of atoms, in particular on a level with hydrogen atoms). This previous study shows the existence of different conformers in a narrow energetic domain. Effectively the first 60 molecules with the lowest energies are situated in the energetic domain 14.88 $\leqslant$ E $\leqslant$ 17.85 Kcal/mol.

A visual analysis of the first conformers shows that macrocycles possess three structural characters: the diene system, the α, β-unsaturated ester group and the two saturated chains. As these two chains do not intervene in the reactivity problem that interests us, the conformation of these two chains is not to be taken as an important characteristic and will be ignored in our following reasoning. Finally, we found eight main conformational families for each set studied (Figure 4). Conformational the families (2,4,6,8) have the two

plans of the two sites: diene and α, β-unsaturated ester pseudo-parallels. For the rest of families (1,3,5,7) the two plans are pseudo-antiparallels.
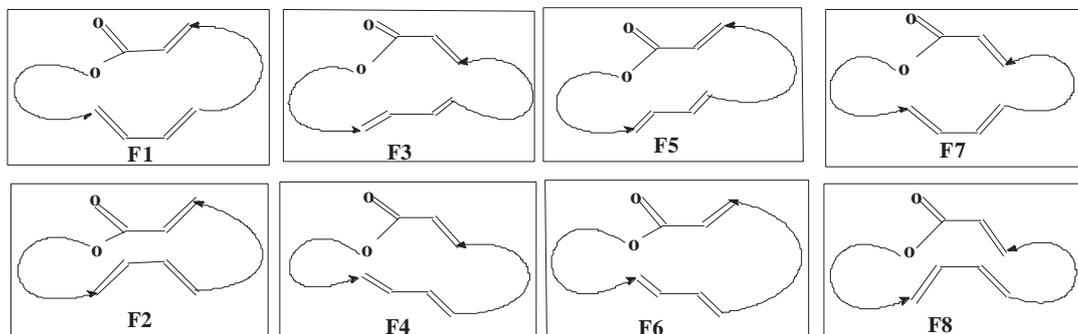
Figure 4. main conformational families.

Conformers in each macrocycle with relative energies and their Boltzmann population at normal temperature[11] are listed in Tables 1a and 1b. Three conformational families, F5, F6 and F3, are preferred. In an energy window of 2 Kcal/mol, we have 5 conformational families for macrolide 22, 4 families for macrocycle 20, 3 families for macrolides 12,16,18 and only 1 family for macrocycle 14.

Table 1a. energetic difference and Boltzmann population for different conformational families (12 to 16)

n	4			6			8		
Macrocycle	12			14			16		
	family	ΔE	%	Family	ΔE	%	family	ΔE	%
	5	0.00	18.8	6	0.00	26.6	5	0.00	19.6
	1	1.39	13.4	3	2.29	15.2	4	1.37	14.0
	4	1.69	12.5	2	2.44	14.7	6	1.83	12.5
Sup to 1 kcal/mol	8	2.02	11.5	4	2.98	12.9	7	2.04	11.9
	2	2.14	11.2	5	3.79	10.6	8	2.17	11.5
	6	2.15	11.1	1	4.25	09.5	3	2.21	11.4
	3	2.28	10.8	8	5.65	06.7	1	2.68	10.2
	7	2.29	10.8	7	7.86	03.9	2	3.28	08.8

Δ E: Energetic difference to the absolute minimum   %: Boltzmann population.

Table 1b. energetic difference and Boltzmann population for different conformational families (18 to 22)

n	10			12			14		
Macrocycle	18			20			22		
	family	Δ E	%	family	Δ E	%	family	Δ E	%
to 1 kcal/mol	6	0.00	21.4	3	0.00	17.5	3	0.00	18.3
	3	0.64	18.3	5	0.28	16.4	4	0.18	17.6
				4	0.29	16.3			
	5	1.64	14.4	6	1.55	12	6	1.66	12.3
	4	2.68	11.2	2	2.16	10.4	7	1.70	12.1
Sup to 1 kcal/mol	8	3.38	09.4	7	2.17	10.3	8	1.81	11.8
	7	3.39	09.4	1	2.74	09.0	5	1.95	11.4
	1	3.47	09.2	8	3.14	08.2	2	3.21	08.4
	2	4.72	06.8				1	3.37	08.1

Δ E: Energetic difference to the absolute minimum   %: Boltzmann population.

Thus, is the last macrolide which has the lower conformational mobility. The preferential conformer has 26.6% of the Boltzmann population. Dihedral angles of the diene and ester systems are summarised in Table 2. For the first system, the values of dihedral angles $\Phi 1$ of the F3 family are close to $180°$ for large macrocycles with $n \geqslant 12$.

Table 2. Dihedral angles values of the most stable conformers for each macrocycle.

n	4	6	8	10	12	14
Macrocycle	12	14	16	18	20	22
Ester ($\phi 1$)	s-cis 51	s-cis 23.2	s-cis 5.6	s-cis 12.2	s-trans 171.9	s-trans 166.5
Diene ($\phi 2$)	s-trans 149.1	s-trans 166.1	s-trans 176.8	s-trans 177.5	s-trans 174.7	s-trans 166

For rings with $n \leqslant 10$, dihedral angle differs slightly to normal values of s-cis conformation of α, β-unsaturated ester system. This is due to the strains of the ring. Concerning the second system, values of $\Phi 2$ are in a majority of cases close to a dihedral angle value of an aliphatic diene system. The low deviation noted is due essentially to van der Waals' repulsions between the hydrogen atoms of lateral chains and the constraint of a binding structure of a ring that imposes geometrical parameters for obtaining the lowest energetic conformer.

The calculations carried out showed that these non-complexed macrocycles have a high conformational mobility. They also present many preferred conformers that do not permit, a priori, one to foresee a diastereoselection for envisaged reactions. This is in good agreement with Still's work on macrocycle 17 (cycloheptadecane), which presents many preferred conformers [18]. Finally, for macrocycles with $n \leqslant 10$, a conformation of the ester group is cisoide, and that of diene system is transoide for two families (F5 and F6) but the arrangement between these systems is a function of the parity of m. For even m, the strain constraints of methylene groups oblige the two systems to adopt a pseudo-parallel arrangement for the F6 family which is more favourable than the pseudo-antiparallel arrangement for the F5 family. For uneven m, from $n = 12$, the large size of the rings allows the F3 family to be the most stable. Thus, for $n \leqslant 10$, the most preferential conformer for rings with m even 5m = n/2) belongs to the F5 family, then for (m) uneven it belongs to the F6 family. For $n \geqslant 12$, only one family, F3, has the preferred conformer (Figure 5).

Introduction of tricarbonyliron moiety

The development of organometallic reagents derived from transition metals has been particularly successful and has had a deep effect on synthetic planning. The high natural abundance and ready accessibility of iron has resulted in the development of a wide and varied organometallic chemistry. These complexes constitute an intermediate compound usually used in organic synthesis[19]. The obtained complex must present all requisite conditions of thermal and chemical stability and mobility in order to have an efficient decomplexation. We note that the organometallic complex may intervene both by high steric hindress and introducing rigidity in the structure. Tables 3a and 3b summarise conformational families of complexed macrocycles with the tricarbonyliron moiety, with relative energy less and more than 1 Kcal/mol, and the probability of each conformer calculated using the Boltzmann distribution.

Macrocycle 12 (n = 4) : Family 6

Macrocycle 14 (n = 6) : Family 5

Macrocycle 16 (n = 8) : Family 6

Macrocycle 18 (n = 10) : Family 5
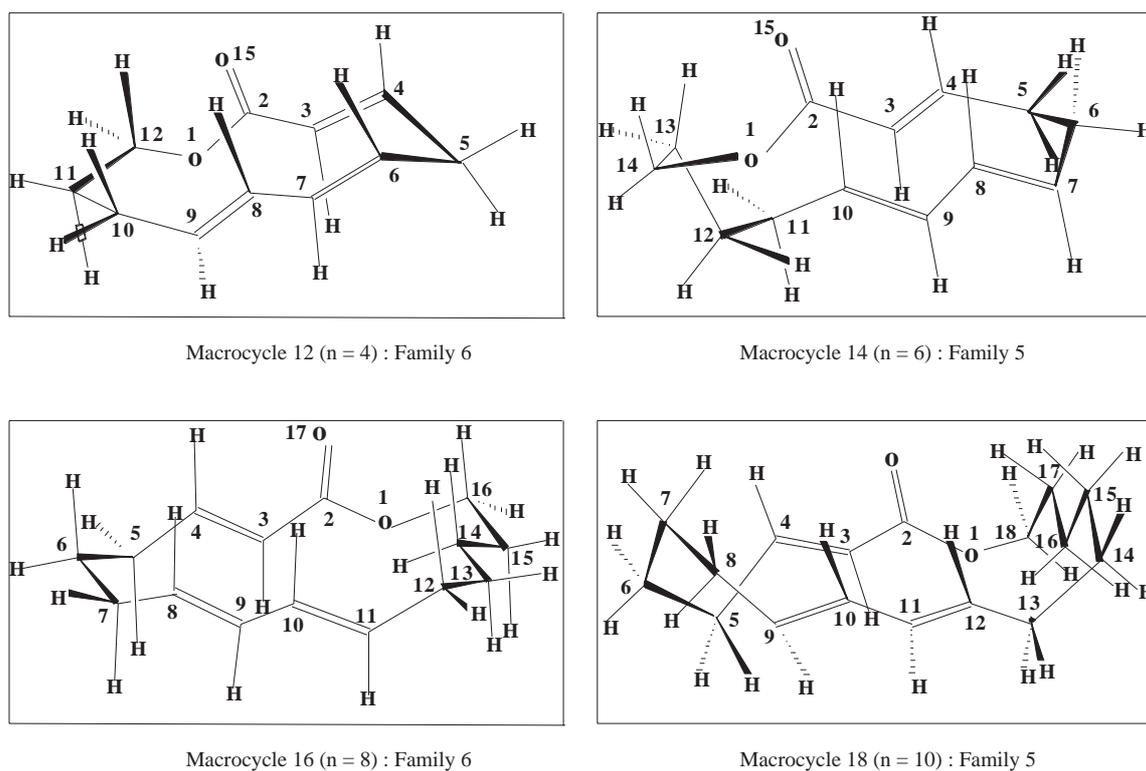
Figure 5. Molecular structures of different macrocycles.

Table 3a. Energetic difference and Boltzmann population for different conformational families. (12 to 16)

n	4			6			8		
Macrocycle	**12**			**14**			**16**		
	family	Δ E	%	family	Δ E	%	family	Δ E	%
to 1 kcal/mol	2	0.00	29.2	2	0.00	40.3	2	0.00	27.6
	1	0.58	25.3	1	0.87	32.6	1	0.12	26.8
	8	0.90	23.4				3	0.14	26.7
Sup to 1 kcal/mol	7	1.15	22.1	8	3.81	16.0	4	1.57	18.9
				7	5.28	11.2			

Δ E: Energetic difference to the absolute minimum   %: Boltzmann population.

Table 3b. Energetic difference and Boltzmann population for different conformational families. (18 to 22)

n	10			12			14		
Macrocycle	**18**			**20**			**22**		
	family	Δ E	%	family	Δ E	%	family	Δ E	%
to 1 kcal/mol	8	0.00	31.7	2	0.00	26.6	8	0.00	30.5
	7	0.08	31.1	7	0.27	24.9	7	041	27.6
				1	0.35	24.4			
				8	0.42	0.24			
Sup to 1 kcal/mol	1	1.17	23.9				1	1.35	22.0
	2	3.57	13.3				2	1.77	19.9

Δ E: Energetic difference to the absolute minimum   %: Boltzmann population.

The majority of complexed macrolides with relative energy less than 1 Kcal/mol present two preferred conformers. The probability of the most stable conformers has increased in the case of complexed macrocycles compared with non-complexed rings. Macrocycle 14, which was presented by a preferred conformer with 26.6% without complexant, was populated with 40.3% in presence of $Fe(CO)_3$. For all preferred conformers the dienic system has been fixed in an s-cis conformation by reason of the presence of the tricarbonyliron. A value of a dihedral angle of the dienic system ($\Phi 2$) is comprised between 1.6 and 17.6 ° (Table 4). For example, in the macrocycle 20, its structure obtained by calculation is in good agreement with that obtained by RX[20].

Table 4. Dihedral angles values of the most stable conformers for each complexed macrocycle.

n	4	6	8	10	12	14
Macrocycle	12	14	16	18	20	22
Ester $\alpha,\beta-$	s-cis	s-cis	s-cis	s-trans	s-cis	s-trans
unsaturated ($\phi 1$)	51.9	16.4	25.5	177.6	34.0	177.5
Diene ($\phi 2$)	s-cis	s-cis	s-cis	s-cis	s-cis	s-cis
	08.8	16.1	17.6	01.6	05.1	03.5

The results of the conformational analysis of these complexed macrocycles show that the tricarbonyl-iron has a wide influence on the ring, because the number of conformers was reduced to four (Tables 3a and 3b). For all preferred conformers we found that the lactone function and the complexed diene are practically perpendicular to the medium plan of the ring. The lactone face was pointed towards the exterior of the ring, so the two faces of the enolate are diastereotopic. This was also found in methyl acetates with fluorine-containing auxiliaries where metal fluorine interaction causes a steric hindrance around the *si* face of enolate. This realises an effective discrimination between enolate faces in a ratio of up to 92:8 [21]. Therefore, stereoselectivity is a result of two principles: the tricarbonyliron stabilises a ring under one or several preferential conformations and the addition of the reagent has been carried out by the less hindered face. This is in good agreement with Still[4] and Takahashi[22], who affirmed that the addition of CH_3X on enolate carried out by a peripheral attack on this face. This is due to a part of the tricarbonyliron, which has introduced an asymmetric element, and a steric effect that has increased the proportion of the peripheral attack. Our recent study[23,24] and Ley's work[25] on the complexes of $Fe(CO)_3$ show that the presence of this organometallic ligand induces a diastereoselectivity of addition reactions.

Conclusion

The conformational analysis of the dissymetric macrolides has been studied by molecular mechanics calculations. These results show the existence of high conformational mobility in the majority of non-complexed dissymetric macrolides. Calculations have allowed us to group them into conformational families and then to reduce the number of preferred families further by the introduction of the tricarbonyliron in the structure. In all non-complexed preferred conformers, the dienic system adopts a transoide conformation, then the ester system adopts a cisoide conformation for n $\leqslant$ 10 and a transoide conformation for n > 10. For macrolides with n $\leqslant$ 10, the preferred conformer belongs to the F5 family when m is even and the F6 family when m is odd. As for n > 10, this belongs to the F3 family.

Finally the obtained diastereoselectivity for complexed macrolides is the result of the stereochemical control effect of the tricarbonyliron. It has introduced an asymmetric element, an important steric effect

increasing a peripheral attack proportion, and has contributed to the rigidity of the structure. 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.

Acknowledgements

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