Asian Journal of Chemistry Vol. 17, No. 2 (2005), 859–870

Quantitative Conformational Analysis of Dissymmetric Macrolides by Molecular Modelling

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Conformational analysis of dissymmetric macrolides was carried out using molecular modelling (molecular mechanics and molecular dynamics). Calculations indicate that each macrocycle presents eight families of preferential conformers. An important stereoselectivity of the complexed macrocycles was obtained. The Boltzmann distribution of the starting conformations can be used to predict the stereoselectivity of these reactions.

Key Words: Macrolide, Molecular mechanics, Molecular dynamics, Conformational analysis, Stereoselectivity.

INTRODUCTION

Conformational analysis in macrocyclic compounds has been studied since 1981 when Still and Galynker[1] published their investigations on the chemical consequences of conformation in macrocyclic compounds. Conformationally controlled reduction and alkylation reactions have been used to generate chiral centres on the macrocyclic skeleton of some macrolide antibiotics and their analogs[2]. The high stereoselectivity of these reactions can be rationalized by molecular mechanics calculations.

The conformational analysis of large ring compounds is difficult due to the large number of local energy minima. Vedejs and co-workers[3] solved this problem by introducing the concept of local conformation effect according to which the analysis can be limited to the immediate vicinity of the functional group. They used this method to explain the selectivity of epoxidation and osmylation reactions in 10-membered rings. Weiler and Keller[4] used the same method to rationalize the stereo-control of alkylation and reduction reactions of 14-membered β-ketolactones. Functionalized macrocycles have three-dimensional structures, which differ significantly from the normal rings in that sp^2 centres tend to lie perpendicular to the plane of the ring to minimize transannular

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non-bonded interactions. The reactions occur largely or perhaps exclusively from the peripheral face of the double bond[1]. Grée *et al.*[5] have also shown in some cases the existence of the remote stereocontrol induced by the tricarbonyl iron.

In this paper, we will study the α,β-unsaturated dissymmetric macrolides, which represent the binding structure for many antibiotic families of 12- to 22-membered rings ($n = n_1 + n_2$ and $n_2 = n_1 + 2$) (Fig. 1). Then, our object is to examine the relative importance of different contributions to total steric energy and to determine preferred conformations of non-complexed and complexed macrocycles. We will also try to evaluate the stereoselectivity of addition reactions carried out on functional groups appended to the tricarbonyl iron moiety.

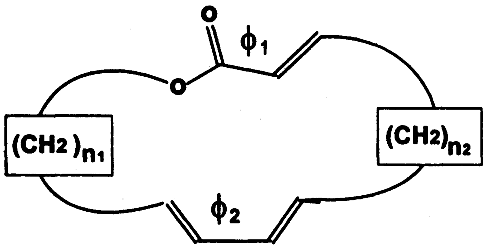

Fig. 1. Scheme of α,β-unsaturated dissymmetric macrolide

EXPERIMENTAL

Computational procedures

Calculations were carried out using molecular mechanics and molecular dynamics, with three software packages: PCM 6.1 for geometry optimization and calculations of energies[6], HyperChem 7.01 for conformational search[7] and TSAR 3.3 for statistical analysis[8]. The minimum energy geometries were located by minimizing energy with respect to all geometrical coordinates and without imposing any symmetry constraints. The molecular mechanics (PCM) is a method for structure determination, which uses a quantum mechanical (VESCF) π-system calculation in the iterative sequence and Allingers MM2 force field[9]. These calculations use the Monte Carlo simulations and the Metropolis algorithm[10]. The conformational searching method includes systematic and random conformational searches in both internal (torsion angle) and external (cartesian) coordinate 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. On the other hand, the stochastic or Monte Carlo search[11] generates starting geometries using random variations of molecular geometry.

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

RESULTS AND DISCUSSION

Energetic Considerations

Variation of the total strain energy: The conformational study is based on molecular mechanics. The calculation of energy has been done by the PCM software, with the following options: dp-dp (dipole-dipole), SCF (self-consistent field), RHF (restricted Hartree-Fock). 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 the relative stability of different studied macrocycles[13]. Fig. 2 presents an evolution of the strain energy per CH_2 group as a function of the total amount of methylene (n).

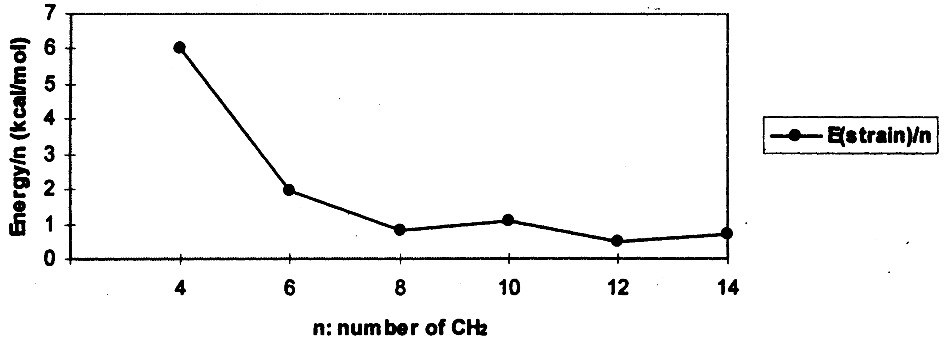

Fig. 2. Evolution of the strain energy by CH_2 group as a function of the number of methylene (n)

The strain energy per CH_2 group is relatively higher for macrocycle 12 (n = 4) (E(st/n) = 6.01 kcal/mol). The variation of E(strain/n) as a function of the entire amount of methylene is similar to that obtained in anterior works concerning cycloalkanes studies[14] C_4-C_{12}. An important decrease in the strain energy per CH_2 group from n = 4 to 6, confirms perfectly the limit between the two classes of medium and large rings, as was mentioned in literature. In line with the above conclusions, the rate of cyclization increases with the size of the ring[15, 16]. 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.

Contributions of different features to steric energy: The steric energy is calculated[14] from the sum of different contributions such as stretching, bending, torsional, Van der Waals and electrostatic energies:

$$E(steric) = E(stretch) + E(bend) + E(tors) + E(vdw) + E(electr) \ldots$$

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

For two successive macrolides, the torsional energy is lower for a number of methylene groups (n) equal to twice an even (n = 2m) as in the case of the strain energy for $n \geq 6$. This can be explained by the favourable torsional angles. All methylene groups are in the anti position in a conformation composed with two

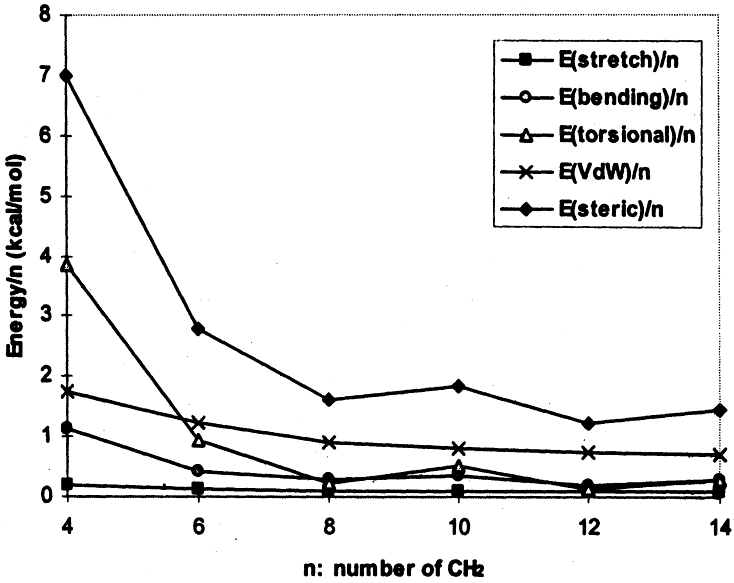

Fig. 3. Contribution of different components to the total steric energy of conformers

long parallel chains. For n ≥ 6 the Van der Waals constraint is the major contribution, taking into account the number of supplementary interactions created by the transannular hydrogen atoms. For the larger macrolides (n ≥ 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 easily a staggered conformation methylene group. In such a case, the energy of the Gauche-form is 0.8 kcal/mol[14] greater than that of the anti-form. However, the stretching contribution E(stretch)/n is lower and remains appreciably constant. Bond lengths are not very different from reference values. For the bending energy, this contribution does not differ strongly between the various macrolides. The C—C—C angle is not influenced by the length of a cyclic chain and stays close to the normal tetrahedral valence angle 109°[17].

For macrolide 12 (n = 4), the torsional energy contribution is greater than that of Van der Waals. E (Φ/n)= 3.86 kcal/mol represents 54.9% of the total steric energy. This is essentially due to unfavourable torsional angles because it is not possible to obtain the perfectly altered conformation of a majority of C—C bonds, as is the case with other macrocycles. In conclusion, the contribution of the Van der Waals energy E (V dW/n) is higher in all examined macrocycles in their stable conformers (n ≥ 6). Its variation as a function of (n) is, in general, proportional to a resultant of the bending and torsional constraint. In each ring, the minimum total energy is a compromise between the torsional, bending and Van der Waals energies[18].

Geometrical and statistical study: The conformation searching operation was as follows: a crude starting geometry is produced and its structure is optimized by molecular mechanics energy minimization. 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 minimization 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[1].

Conformational analysis using the statistical analysis software TSAR[8] has led to an important number of conformers. Thus, the conformer number to explore is N^x, where N is the number of rotators and x defines the angular increment (360/x). For the macrocycle 20, *e.g.*, the TSAR program, which was executed over 100 h, generated 20420 conformers numbered from 1 to 32533. Missing conformers are those for which a ring closure of the cycle has become impossible or for which steric interactions were greater than a threshold 6 kcal/mol. 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. Effectively, the first 60 molecules with the lowest energies are situated in the energetic domain $15.61 \leq E \leq 18.75$ kcal/mol). Therefore this study shows the existence of different conformers in a narrow energetic domain.

The most stable structures can be characterized by three structural characters: the diene system, the α,β-unsaturated ester group and the two saturated chains. Since these two chains do not intervene in the reactivity problem that interests us, we shall not take their conformation into account by doing this[19, 20]. We found eight main conformational families for each set studied (Fig. 4). Conformational 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 the families (1,3,5,7) the two plans are pseudo-antiparallels.

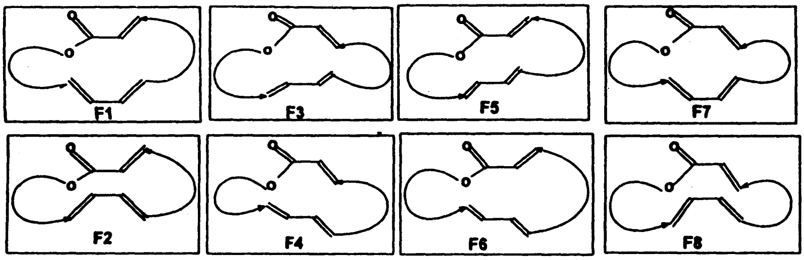

Fig. 4. Main conformational families

The Boltzmann population at normal temperature and relative energies with respect to the most stable family are listed in Tables 1a and 1b. Similarly, the Boltzmann population at normal temperature has been evaluated and given in these tables. It appears that two conformational families, F5 and F6 are preferred. In an energy gap of 2 kcal/mol, we have 7 conformational families for macrolide 22, 4 families for macrolides 12, 18, 20 and only 3 families for macrolides 14, 16.

TABLE-1a
RELATIVE ENERGIES AND BOLTZMANN POPULATION FOR DIFFERENT CONFORMATIONAL FAMILIES (12 TO 16)

n	4			6			8		
Macrolide	12			14			16		
	Family	ΔE	%	Family	ΔE	%	Family	ΔE	%
to 1 kcal/mol	5	0.00	18.6	6	0.00	19.4	5	0.00	19.9
				3	0.52	17.1	3	0.25	18.7
				4	0.90	15.6			
to 2 kcal/mol	6	1.17	14.0				6	1.10	15.2
	2	1.27	13.6						
	1	1.62	12.5						
Sup to 2 kcal/mol	8	2.17	11.0	5	2.15	11.5	1	2.45	10.9
	4	2.23	10.8	1	2.16	11.5	4	2.46	10.9
	3	2.52	10.1	7	2.52	10.5	8	3.03	9.5
	7	2.79	9.4	2	4.08	7.2	7	4.01	7.5
				8	4.15	7.1	2	4.04	7.4

ΔE: Relative steric energies to the absolute minimum %: Boltzmann population.

TABLE-1b
RELATIVE ENERGIES AND BOLTZMANN POPULATION FOR DIFFERENT CONFORMATIONAL FAMILIES (18 TO 22)

n	10			12			14		
Macrolide	18			20			22		
	Family	ΔE	%	Family	ΔE	%	Family	ΔE	%
to 1 kcal/mol	6	0.00	20.1	5	0.00	22.4	6	0.00	15.5
	3	0.37	18.3	4	0.81	18.4	5	0.06	15.2
	4	0.90	16.1	3	1.52	15.1	8	0.43	13.9
							4	0.64	13.2
							3	0.76	12.9
to 2 kcal/mol	8	1.90	12.6	8	2.93	11.02	7	1.37	11.1
							2	1.50	10.7
Sup to 2 kcal/mol	5	3.03	9.6	2	3.52	9.5	1	3.00	7.5
	1	3.61	8.3	7	3.65	9.2			
	7	3.66	8.2	1	4.38	7.7			
	2	4.54	6.7	6	5.13	6.4			

ΔE: Relative steric energies to the absolute minimum %: Boltzmann population.

Dihedral angles of the ester (Φ_1) and diene (Φ_2) systems are summarized in Table-2. For the first system, the values of dihedral angles Φ_1 vary between 2.43 and 34°. For example, for the macrocycle 14 (Fig. 5), Φ_1 : O_{15}-C_2-C_3-C_4 = 20.7°. Therefore, 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.

TABLE-2
DIHEDRAL ANGLES IN DEGREES OF THE MOST STABLE CONFORMERS FOR EACH MACROCYCLE

n	4	6	8	10	12	14
Macrolide	12	14	16	18	20	22
Ester (Φ_1)	24.0	20.7	29.6	15.0	34.0	2.43
Diene (Φ_2)	152.3	171.0	175.3	169.4	177.3	178.30

Concerning the second system, values of Φ_2 are in a majority of cases close to a dihedral angle value of an aliphatic diene system. For example, the macrocycle 14 (Fig. 5), Φ_2 : C_9-C_{10}-C_{11}-C_{12} = 171°. The low deviation noted is due essentially to the 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, *a priori*, permit one to foresee a diastereoselection for the reactions between the two groups. This is in good agreement with Still's work[21], on macrocycle 17 (cycloheptadecane), which yields many different products.

Finally, for all macrocycles, the most preferential conformers depend on the number of methylene groups (n), which are either when this number is twice even number (n = 2m), belongs to the F5 family, but for (n) is not twice an even number, it belongs to the F6 family (Fig. 5).

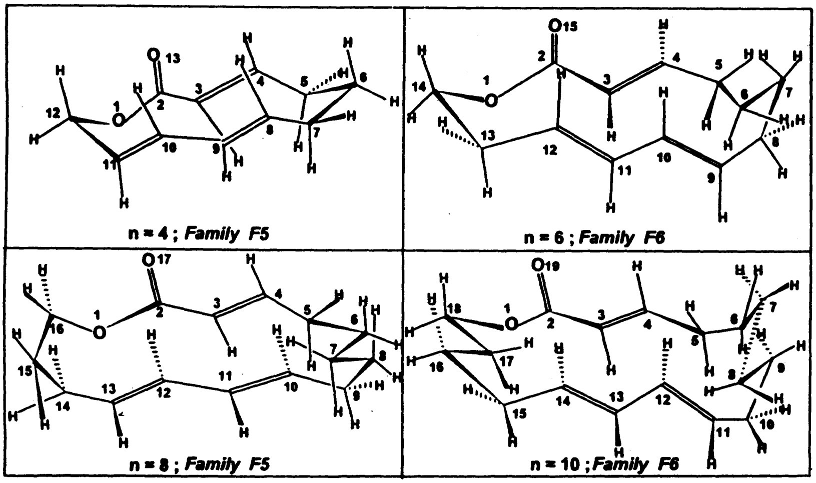

Fig. 5. Molecular structures of different macrocycles (n = 4 to n = 10)

Introduction of tricarbonyl iron 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 based on this element, in particular, complexes of dienes with iron tricarbonyl, constitute intermediate compounds usually used in organic synthesis[22].

The obtained complex must present all requisite conditions of thermal and chemical stability and should allow an efficient decomplexation. We note that the organometallic complex may intervene both by high steric hindrance and introducing rigidity in the structure. Tables 3a and 3b summarize 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.

TABLE-3a

RELATIVE ENERGIES AND BOLTZMANN POPULATION FOR DIFFERENT CONFORMATIONAL FAMILIES OF THE COMPLEXED MACROCYCLES (12 TO 16)

n Macrolide	4 12			6 14			8 16		
	Family	ΔE	%	Family	ΔE	%	Family	ΔE	%
to 1 kcal/mol	1	0.00	32.9	1	0.00	34.5	1	0.00	30.5
	2	0.49	19.2				8	0.58	26.4
	7	1.86	21.0	8	1.76	22.5	2	1.30	22.2
Sup to 1 kcal/mol	8	2.75	16.9	2	1.90	21.7	7	1.55	20.9
				7	1.96	21.4			

ΔE: Relative steric energies to the absolute minimum %: Boltzmann population.

TABLE-3b

RELATIVE ENERGIES AND BOLTZMANN POPULATION FOR DIFFERENT CONFORMATIONAL FAMILIES OF THE COMPLEXED MACROCYCLES (18 TO 22)

n Macrolide	10 18			12 20			14 22		
	Family	ΔE	%	Family	ΔE	%	Family	ΔE	%
to 1 kcal/mol	1	0.00	45.8	1	0.00	40.2	8	0.00	36.2
	7	4.04	23.5	2	1.71	26.5	7	1.96	22.5
Sup to 1 kcal/mol	8	4.30	18.4	7	3.16	18.6	2	2.04	22.0
	2	5.39	13.5	8	4.13	14.7	1	2.59	19.3

ΔE: Relative steric energies to the absolute minimum %: Boltzmann population.

The majority of complexed macrolides with relative energy less than 1 kcal/mol present one preferred conformer. The probability of the most stable conformers has increased in the case of complexed macrocycles compared with non-complexed rings. Macrocycle 20, which was presented by a preferred conformer with 22.4% without complexant, was populated with 40.2% in presence of $Fe(CO)_3$. For all preferred conformers the dienic system has been fixed in a *s-cis*-conformation by reason of the presence of the tricarbonyl iron. A value of a dihedral angle of the dienic system (Φ_2) is comprised between 1.79 and 11.30° (Table- 4).

TABLE-4
DIHEDRAL ANGLES IN DEGREES OF THE MOST STABLE CONFORMERS FOR EACH COMPLEXED MACROCYCLE

n Macrolide	4 12	6 14	8 16	10 18	12 20	14 22
Ester (Φ_1)	31.57	24.12	26.20	28.22	12.92	174.70
Diene (Φ_2)	11.13	8.39	11.30	9.60	1.79	11.08

For example, in the macrocycle 20, its structure obtained by calculation is similar to the one obtained by X-ray diffraction[23]. We remark a good agreement between the calculated and experimental values, the gap varies from 0.01 to 0.07 Å for distances and from 0.1 to 5.1° for angles (Tables 5a and 5b)

TABLE-5a
BOND LENGTHS IN Å

Atoms a—b	Distance (RX)	Distance (MM)	Gap
O_1—C_{19}	1.45	1.41	0.04
O_1—C_1	1.34	1.35	0.00
O_2—C_1	1.21	1.21	0.00
C_1—C_2	1.45	1.36	0.09
C_2—C_3	1.30	1.34	0.04
C_3—C_4	1.51	1.51	0.00
C_4—C_5	1.53	1.54	0.01
C_5—C_6	1.53	1.54	0.01
C_6—C_7	1.51	1.54	0.03
C_7—C_8	1.52	1.54	0.02
C_8—C_9	1.53	1.54	0.01
C_9—C_{10}	1.53	1.54	0.01
C_{10}—C_{11}	1.50	1.51	0.01
C_{11}—C_{12}	1.41	1.34	0.07
C_{12}—C_{13}	1.38	1.48	0.10
C_{13}—C_{14}	1.43	1.34	0.09
C_{14}—C_{15}	1.50	1.51	0.01
C_{15}—C_{16}	1.52	1.54	0.02
C_{16}—C_{17}	1.52	1.54	0.02
C_{17}—C_{18}	1.53	1.54	0.01
C_{18}—C_{19}	1.51	1.54	0.03
O_3—C_{20}	1.15	1.55	0.00
Fe—C_{20}	1.79	1.84	0.05

TABLE-5b

VALENCE ANGLES IN (°)

Atoms a—b—c	Distance (RX)	Distance (MM)	Gap
Fe—C$_{20}$—O$_{3}$	178.2	179.1	0.9
Fe—C$_{21}$—O$_{4}$	179.1	179.3	0.2
O$_{1}$—C$_{1}$—O$_{2}$	122.6	121.5	1.1
O$_{1}$—C$_{1}$—C$_{2}$	112.0	113.2	1.2
O$_{2}$—C$_{1}$—C$_{2}$	125.3	125.2	0.1
C$_{1}$—C$_{2}$—C$_{3}$	122.9	125.1	2.2
C$_{2}$—C$_{3}$—C$_{4}$	126.6	123.6	3.0
C$_{3}$—C$_{4}$—C$_{5}$	112.1	112.2	0.1
C$_{4}$—C$_{5}$—C$_{6}$	114.6	114.4	0.2
C$_{5}$—C$_{6}$—C$_{7}$	115.3	113.9	1.4
C$_{6}$—C$_{7}$—C$_{8}$	113.3	111.5	1.8
C$_{7}$—C$_{8}$—C$_{9}$	115.4	112.6	2.8
C$_{8}$—C$_{9}$—C$_{10}$	113.9	113.7	0.2
C$_{9}$—C$_{10}$—C$_{11}$	113.2	111.7	1.5
C$_{10}$—C$_{11}$—C$_{12}$	122.6	125.1	2.5
C$_{11}$—C$_{12}$—C$_{13}$	120.3	123.8	3.5
C$_{12}$—C$_{13}$—C$_{14}$	119.0	124.1	5.1
C$_{13}$—C$_{14}$—C$_{15}$	120.9	125.2	4.3
C$_{14}$—C$_{15}$—C$_{16}$	114.5	112.9	1.6
C$_{15}$—C$_{16}$—C$_{17}$	115.0	114.3	0.7
C$_{16}$—C$_{17}$—C$_{18}$	111.9	112.4	0.5
C$_{17}$—C$_{18}$—C$_{19}$	113.4	112.3	1.1
O$_{1}$—C$_{19}$—C$_{18}$	106.5	108.8	2.3

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 ester function and the complexed diene are practically perpendicular to the average plane of the ring. The ester 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 interior face of enolate. This realizes an effective discrimination between enolate faces in a ratio[24] of up to 92 : 8. Therefore, stereoselectivity is a result of two principles: the tricarbonyl iron stabilizes 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 *et al.*[1, 2] and Takahashi *et al.*[25], who affirmed that the addition of CH_3X on enolate was carried out by a peripheral attack on this face. This is due to a part of the tricarbonyl iron, which has introduced an asymmetric element and a steric effect that has increased the proportion of the peripheral attack. Our recent study[26–28] and Ley and Cox's work[29] 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 dissymmetric macrolides has been studied by molecular modelling. These results show the existence of high conformational mobility in the majority of non-complexed dissymmetric 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 tricarbonyl iron in the structure. In all non-complexed preferred conformers, the dienic system adopts a transoid conformation, and then the ester system adopts a cisoid conformation. For all macrolides, the preferred conformer appertains to the F_5 family when m is even and the F_6 family when m is odd.

Finally the obtained diastereoselectivity for complexed macrolides is the result of the stereochemical control effect of the tricarbonyl iron. 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.

ACKNOWLEDGEMENT

The authors thank Professor R. Grée of the University of Rennes-1 (France) for scientific discussions on this work.

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(*Received*: 19 May 2004; *Accepted*: 8 December 2004) AJC-4018