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Conformational Analysis of the 14-Membred Unsymmetrical Macrodiolides Using Quantum and Molecular Mechanics, Implication in the Colletallol Behavior

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ABSTRACT

Conformational analysis of the 14-membred unsymmetrical macrodiolides (m=2, n=4) has been carried out using hybrids molecular mechanics and quantum calculations at different levels. A new MM2 and MM3 torsional parameters of the missing 5-2-3-6 dihedral type were proposed. The results indicate that the C3-C2-C1-O3 dihedral can adopt both the s-trans and s-cis form, while the C10-C9-C8-O4 has a clear preference for the s-cis form. The same anti-dihedral angle C4-C5-C6-C7, around 150°, and gauche dihedral angle C10-C11-C12-O1, around 48°, characterize the conformational states of all the investigated compounds. The presence of substituents (including methyl groups), have a significant impact on the conformational behavior of the ring, leading (depending on its configuration) to favoring a certain type of conformations, like in the collectallol. In conjunction with that, the revise of cyclotetradecane conformational behavior, by the use of polar map, which is a convenient tool to identify and compare the conformations, reveal that it is richer on conformational diversity than that reported in the literature.

Keywords: Colletallol, Conformational analysis, ab initio, Molecular mechanics

INTRODUCTION

14-membered α,β -unsaturated macrodiolides are common in nature, and their physiological effects are multiform. To mention just a few examples, colletoketol (still called Grahamimycine A) is particularly interesting [1]. Mac Millan and Simpson [2], have elucidated absolute configuration (2R, 8R, 10R) of natural product. This compound is active against 36 kinds of bacteria, eight kinds of blue-green algae, two kinds of green algae and five variety of fungus [3]. Others compounds like Colletallol or Colletol have antibacterial property [4].

In the field of the conformational analysis, we report the work of Keller et al. [4] on 14-membred macrolides [5]. They have studied seven kinds of 14-membred macrolides using X-ray crystallography and MM2 molecular mechanics calculation. Using Dale's nomenclature [6], they have found that (3434) conformation having exterior substituents should be the lowest energy conformation of a 14-membred macrolide. In general, large-ring compounds have several conformations that easily interconvert by pseudo rotation involving very low barriers, generally inaccessible by NMR [7]. Macrocycles are capable of existing in a number of stable conformations, but only a few of these are of low enough energy to be appreciably populated at room temperature [8]. Probe the conformations of large rings have included the use of 13C and 1H NMR spectroscopy [9], NOEDS [10] and IR [11-13]. However, the most successful technique has been X-ray crystallography [14]. According to Dunitz conclusion "any conformation observed in a molecular crystal cannot be far from an equilibrium structure of the isolated molecules although it has nothing to say about the energy difference between them" [15].

Objective of this paper

Our objective is to aid in the conformational analysis of the 14-membred rings. We therefore, performed conformational search on Cyclotetradecane 1, and a 14-membred unsymmetrical α , β -unsaturated macrodiolide 2 (Figure 1). Then we were focused on selected minima of 2 and its substituted derivatives, employing molecular mechanics: MMX [16], MM2 [17] (as incorporated in the Tinker package 7.1, with our additional 5-2-3-6 dihedral constants V1=-0.405; V2=11.100; V3=0.000), MM3 [18] (as incorporated in the Tinker package. 1, with our additional 5-2-3-6 dihedral type constants, V1=1.063; V2=10.000; V3=0.000. as provided by Prof. Allinger NL), H-MM+ [19] (as implemented in hyperchem 7.5 package, 2003). In conjunction with semi-empirical AM1 [20], *ab initio* and DFT at different level of calculation, compared with available X-ray data found in the literature [21-25].



Figure 1: (a) Model of unsymmetrical 14 membered macrodiolides 2, (b) Substituted derivatives of 2 (R1=OH, R2=R3=Me), corresponding to the collectable and its stereoisomers

Definition of polar maps

Polar maps (Figure 2a) are circular graphs, which plot the magnitude and sign of the endo-cyclic dihedral angles (values between 180° and 180°), versus the bond number [26,27]. The concentric circles representing the dihedral angles [5]. For clarity throughout the polar map, the dihedral angles-axis origin point is fixed at -300°. Polar maps of the invert are polar maps of the enantio-conformers (all the dihedral angles with opposite signs). The labeled "Abs" polar maps (Figure 2b) are polar maps, with absolute values of the torsions (values between 0° and 180°). This "Absolute" polar map allows immediately identifying the enantiomers [28-30].



Figure 2: (a) Example of polar map, (b) Absolute polar map, related to (a)

Atoms numbering and conformational notations

In this work, we have adopted the atoms numbering by group of the same element (Figure 3). Concerning the Cyclotetradecane, we have used the modified Dale's nomenclature, according to Goto [31], to designate different conformations, and when it is possible, we have extended this nomenclature to the unsymmetrical 14-membred macrodiolide. To unify the polar map reading, we suggest the use of the absolute values of the dihedral angles instead of the real values, this transformation leads to the absolute polar map. The identification of two enantio-conformers is facilitated by the use of the absolute polar map. Concerning the unsymmetrical 14-membred macrodiolide, due to the presence of two-enone functionality (C=C-C=O), involving specific type of conformations (s-cis, s-trans), that can be dispatched on families, and to distinguish different conformational families, we use in this work, acronyms constituted of 3 letters [32-35].



Figure 3: Atom numbering (by groups of same atoms), the numbering in the nomenclature is not the same as used in the molecular drawing

The first letter (A or F) indicate the relative orientation of the two carbonyl oxygen atoms to each other (Figures 4c and 4d), the second letter C or T indicate respectively the s-cis or s-trans form for the heptenoic part of the ring (Figure 1b), the third letter (C or T) indicate respectively the s-cis or s-trans form for the pentenoic part of the ring. Subsequently we obtain, eight conformational types regrouped in families (Table 1) [36-38].



Figure 4: Definitions of acronyms used to differentiate conformational families. (a) C: S-CIS, (b) T: S-TRANS, (c) F: Facing, (d) A: Antipodal

Table 1: Conformational cla	iss numbering and	related acronyms
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Family number	1	2	3	4	5	6	7	8
Acronyms	FTT	ATT	FCC	ACC	FTC	ATC	FCT	ACT

METERIALS AND METHODS

Meterials

During this work we have used the following software: (1) HyperChem version 7.52 [23,39] for conformational search, and AM1 calculations, (2) Gamess version 6.0 [24,40] for RHF/6-31G* optimizations on selected minima, (3) Gaussian 09 [25,41], for RHF/6-31G**, B3LYP/6-31G**, MP2/6-31G** and MP2/6-31++G** optimizations, PCM 5.0 [42] for the MMX optimizations. Tinker [42] version 7.1 for MM2 and MM3 optimizations and analysis. (4) Chembio3D 11.0 [32d] as an interface in the visualization of the optimized structures with the ChemCraft 1.6 [33] (For the visualization of the Games output files).

METHODS OF CALCULATIONS

Conformational search

The conformational search, for the two macro cycles 1 and 2, was performed under the following conditions: Starting from an MM+ optimized structure (Figures 5 and 6), we have selected all the single bonds, belonging to the ring, as rotors. This implies the use of 14 rotatable bonds for 1 and 12 rotatable bonds for 2. The starting conformations for the two macrocycles are successively represented in Figures 2 and 3. Initial conformations are generated by the usage directed procedure, which consists to use the lowest energy previously found conformation that has not already been used. Once all previously found conformations have been used, it cycles through them again. In order to sweep the widest conformational space, we have taken a very large window (30 kcal/mol). The total number of conformations to retain was set to 2000. The termination condition for conformational search was set to MaxTries=60000, MaxOpts=50000. Setup range was set to default (for ring torsion flexing \pm 30 to \pm 120). In the case of the Cyclotetradecane, 1421 optimized single conformations cause of the lack of new conformations for 4 successive hr. The effective number of recorded conformations are set 3836 unique conformations, after 73 h of running on pc time.



Figure 5: Starting conformation in the conformational search procedure for the cyclotetradecane 1, (a) Side view, (b) Top view, (c) Polar map

(a) (b) (c)

Figure 6: Starting conformation in the conformational search procedure for 2, (a): Side view, (b) Top view, (c): Polar map

Geometry optimizations

The optimizations on selected minima was performed under the following conditions

MM+ (bond dipoles, RMS=0.01 kcal/mol.Å), (2) MMX (all the lone pairs deleted, considering dipole-dipole interaction, RHF-SCF calculations, C and O atoms belonging to the enoate part considered as π atoms RMS=0.01 kcal/mol.Å), (3) R-HF/6-31G* (tight convergence criteria, nstep=100), (4) R-HF/6-31G** and MP2-6-31G** (tight convergence criteria), (5) B3LYP-631G** (default option) (Figure 7) MM2 and MM3 (RMS Gradient per Atom Criterion=0.001 kcal/mol.Å).



Figure 7: The MM2 and MM3, missing atom types, (5=H, 2=Csp2, 3=Csp2 (Carbonyl), 6=Osp3)

For the purpose of the determination of torsional missing parameters, it was necessary to perform a high level MP2/6-311++ G^{**} optimizations (opt=tight convergence criteria), on a set of acrylate molecules used as test molecules, in particular the meta acrylate MA, and the methyl trans crotonate acrylate MCA, for witch confrontation with available experimental data [26-30] were discussed.

Revise of cyclotetradecane

RESULTS AND DISCUSSION

Thomas Keller et al. [4], have reported six conformations in the range of 5 Kcal/mol above the global minimum (G.M). The following order: [3434]; [3345]; [347]; [343'4'] and [3'3'4'4'] using modified Dale's nomenclature, where the primed numbers designate bonds between pseudo corner atoms, and the asterisk a gathered "fused corner" [43-46] bond.

Side view	Top view	Polar maps		ΔE	
			Invert	Abs	(kcal/mol)
Mar 18	++++	NZ			0.0
[3434]	手手			A	(G.M)
	A L L .	1		1	
The	THA				1.08
[3344]	专业主		- T		
		2	3	2 & 3	
2 x	tt				1.47
	Fat		ZA		NEW
[1;331;33]		4	5	4 & 5	
[133133]					
the po	++++	23			2.156
[1 _g 3334'] ^a	The	A B			
[1'3334']		6	7	6&7	
N may	744				2.415
	FAF	TAS .			
[1t3 3 43]	1.1	8	9	8 & 9	
[13'3'43]					

(a) (3335) *According to Keller, designation. (b) According to Goto

As evoked previously, our conformational search, lead to the same GM that is the well-known (3434) conformation, however this search leads to 32 different conformations in the range of 5 kcal/mol (Tables 2a and 2b), instead of 6 conformations as mentioned in the literature. (New conformations are labeled "NEW").

Side view	Top view			ΔΕ	
			Invert	Abs	(kcal/mol)
	+++				3.050
[115 4 5 5], [נע]	e [10	11	10 & 11	
and a	the state				3.200 NEW
[1t 3 4*4 3]		12	13	12 & 13	
and the second					3.230 NEW
[43*4'4']		14	15	14 & 15	
[2444]	+++	16			3.245 NEW
000000 000000	to the total				3.304 NEW
[33'4'4']		17	18	17 & 18	
To the	t t				3,418 NEW
[34'3'4']	. 20 .	19	20	19 & 20	

Table 2b: Compound 1: conformations, with 3.00 kcal/mol<\EMM+<3.42 kcal/mol

(a)*. According to Thomas Keller designation



Table 2c: Cyclotetradecane: (conformation n° 64, plus the most strained conformation (MSC))

For the definition of 1t (Figures 10c-10e)

At 5,040 kcal/mol above the GM, the conformation with Dale's designation, [3'3'4'4'] revealed by Keller et al. [4] to be the sixth low local minimum, is in this study, actually the 32^{nd} conformer. The window of the explored conformational space is situated in the range from 17.46 kcal/mol to 44.47 kcal/mol, over this range wrong conformations are generated, that is contain wrong hybridization. In Figure 8a, we have represented the variation of the number of recorded conformations as a function of the relative MM+ total energy. It shows a normal distribution like curve with a point of inflexion, characterizing a maximum number of conformations at 8.09 kcal/mol above the GM (maximization of the entropy), with a small number of conformations near the GM and also a small number near the most strained conformation MSC. This reading is revealed by the conformational distribution all over the 1421 true conformations generated by the conformational search (Figure 8b).



Figure 8: (a) Plot of the variation of the number of conformations versus relative MM+ total energy, (b) Plot of the conformational distribution with relative MM+ total energy

In particular, the global minimum [3434] (Figure 9b), is characterized by a double occurrence of the dihedrals with $\pm 62.7^{\circ}, \pm 57.2^{\circ}$ and $\pm 175.5^{\circ}$ values, and the single presence of $\pm 171^{\circ}$. From the global minimum to the most strained conformation (Table 3), it is outward that, in the nine first conformations (ΔE <2.5 kcal/mol), dihedral angles in the range from -47.7° to +47.7°, are not present. Another range do not occur in this nine first low energy conformations, that is from 103° to 166° and from -166° to -103°. Through the energy increasing, values between -40° and 40°, begin to appear from at ΔE =8 kcal/mol. This effect indicate that the conformations where occur syn-periplanar forms are quasi nonexistent in the cyclotetradecane.



Figure 9: Dihedral distribution, (a) Over the total number of recorded conformations (b) GM



Table 3: Evolution of dihedral frequency with the relative MM+ energy increasing

Local structure occurrence frequency composed of three and four contiguous dihedral angles

For the purpose of the simplification, all of the dihedral angles are divided into four groups: gauche (g), $1^{\circ}-119^{\circ}$; minus gauche (g-); $-1^{\circ},-119$; anti (a); $120^{\circ}-180^{\circ}$ and minus anti (a-) $-120,-180^{\circ}$ [13].

Occurrence of three contiguous dihedrals

Six local, three contiguous dihedral angles, occur within 3 kcal/mol. In comparison with the results related to the cycloheptadecane reported in reference [34], (aaa), (aga), (aga-) and (gg-g) arrangement do not occurs within 3 kcal/mol. As reported in reference [32], local (gag-) arrangement do not occurs within 3 kcal/mol, in this case (ring smaller than cycloheptadecane). Its first appearance is 5.56 kcal/mol above G.M. The ggg- arrangement occurs only once within 3 kcal/mol (Table 4).

Dihedral pattern	1 kcal/mol	2 kcal/mol	3 kcal/mol	First entrance
aaa	0	0	0	4.47
aag	6	6	12	0
aga	0	0	0	3.2
gag	4	8	16	0
gag-	0	0	0	5.56
agg	9	13	24	0
agg-	0	0	3	2.15
ggg	0	2	4	1.46
ggg-	0	0	1	2.15
00-0	0	0	0	4 59

Table 4: Distribution of three contiguous dihedral angle
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Occurrence of four contiguous dihedrals

Considering the distribution of four contiguous dihedral angles, it appears 26 nonequivalent arrangement (25 reported in reference [13], for the cycloheptadecane). The agga arrangement is the most frequent one. Apart from this, only three other arrangements are significantly populated, that is aagg, gaag- and aggg. The "aaaa" arrangement begins to appear from 8.15 kcal/mol above the GM and has a particular long-limbed conformation (Figure 10), the so called CCCCC conformation (C meaning chair) (Table 5).

Dihedral pattern	1 kcal/mol	2 kcal/mol	3 kcal/mol	First entrance
aaaa	0	0	0	8.15
aaag	0	0	0	4.47
aaga	0	0	0	3.2
aagg	2	2	4	0
aagg-	0	0	0	3.23
agag	0	0	0	3.23
agag-	0	0	0	6.32
aagg-	0	0	0	3.23
aggg	0	2	4	1.46
aggg-	0	0	1	2.15
agga	4	6	11	0
agg-a	0	0	1	3.05
agg-g	0	0	0	4.59
ag-gg	0	0	0	4.02
gaag	0	0	0	4.03
gaag-	2	2	4	0
gagg	0	0	0	4.03
gagg-	0	0	2	2.41
gag-g	0	0	0	7.43
g-agg	0	0	0	5.56
gggg	0	0	0	12.95
gggg-	0	0	0	6.63
ggg-g	0	0	0	7.69
ggg-g-	0	0	0	4.47
gg-gg-	0	0	0	15.1
00-0-0	0	0	0	5.86

Table 5: Distribution of four contiguous dihedral angles



Figure 10: Local arrangements

(a) Two same signed gauche bonds: g+g+, (g-g-) Vt, (b) Two opposed signs gauche bonds: g+g-, (g-g+) V, (c) One gauche bond flanked by two gauche bonds with opposite signs: g-g-g+, (g+g+g-): 1(c) g+g-g+, (g-g+g-): 1c; gauche bond flanked by two gauche bonds same signs (c: cruised form), (d) g+g+g+, (g-g-g-): 1t; gauche bond by two gauche bonds with same sign (twested), (e) aga, "fused corner" [35], the g is counted twice this is indicated by an asterisk *, (f) Pseudo corner: ag+g-a, (ag-g+a) (g), Corner: ag+g+a (ag-g-a), (h) [CCCCC] conformation.

$MM+\ conformational\ exploration\ of\ the\ (E,E)-dioxacyclotetradeca-3,9-diene-2,8-dione\ (A\ model\ of\ unsymmetrical\ 14-membred\ macrodiolide)$

 $(E,E)-\alpha,\beta$ -unsaturated-14 membered macrodiolides model is represented in Figure 11a (R1=R2=R3= H). For analysis simplification, one can split the molecule into two parts (Figure 11b).



Figure 11: Compound 2: Splitting of the molecule on heptenoic and pentenoic parts

Replacement of CH_2 -group by hetero-atoms, such as oxygen, does not disturb the conformation of skeleton and it prefer a position next to corner atom. This position leads to a reduction of trans-annular interactions caused by the hydrogen atoms pointing into the ring (Figure 12a) [36-45]. As mentioned in references [8,11], sp2 centers are perpendicular to the plane of the ring (Figure 12b). In addition, sp2 hybridized carbon atoms have the tendency to occupy non-corner positions, this was established by dipole moment measurements, IR, NMR spectroscopy [47-50], and molecular mechanics calculations [6,38,39]. It is obvious that a double bond in a macrocyclic ring immobilizes four adjacent carbon atoms and no strain-free conformations can be found [6a].



Figure 12: (a) Trans-annular interactions, caused by the hydrogen atoms pointing into the ring, (b) Minimization of the trans-annular interactions by the perpendicular disposition of the C=O group to the plane of the ring [8,11]

The G.M. of 2, (Figures 13b and 13c) can be correlated with the 227^{th} conformation of 1 (Figure 13a) which is 7.15 kcal/mol above the GM. Indeed the two structures have the same polar map (Figure 13d). The classical and the modified Dale's nomenclature are not appropriate to identifying this conformation. In this case it is more convenient to use the modification introduced by Goto, [31]. In this modification, Goto introduce the definition of the fused corner gauche bond, flanked by two anti-bonds on both sides. In Figure 13a, the dark atoms represent corner positions, and the green colored bond represents the fused corner. The designation of this conformation will be [1(3*3)'35'].



Figure 13: (a) The 227th conformation of the cyclotetradecane (Relative energy=7.15 kcal/mol, black colored atom represent corner or pseudo corner position, green colored bond represent the fused corner according to Bernardinelli, definition [45]), (b) Compound 2: GM top view (ChemCraft), (c) Compound 2: GM side view (ChemBio), (d) Same polar map for, related to (a) and (b)

Principal conformational types

As mentioned previously, eight conformational types can be expected. Minima representing each type (categorized by its 3 letters acronym) are shown in Figure 14, organized according to their increasing of the relative MM+ total energy in the HCS conformational file. The MM+ global minimum (GM), belong to the ATC family (type 6).



Figure 14: Compound 2: Modified Dale's nomenclature, according to Goto, [31] of the eight conformations representing 8 families. (Between brackets, capital letters label the name of the family)

MM2/MM3 parameterization of the missing 5-2-3-6 dihedral angle

Because of the occurrence of the new functional grouping "enoate", we first carried out comparative calculations, on the small fragment: methylprop-2-enoate (Methyl Acrylate: MA). As referring to this results (Table 6), the energetical gap between the two conformers, s-cis and s-trans vary from -2.03 kcal/mol to +0.57 kcal/mol, conducting to a contradictory conclusion, concerning the relative stability between the two conformers. The s-trans conformer is more stable according to MMX and the generalized MM2 incorporated successively, in the CS-Chem3D package 8.0 [32b] and 9.0[32c], whereas AM1 and HF/6-31G** leads to a preference for the s-cis conformation (Scheme 1).

	Etrans-Ecis (kcal/mol)	Program
MMX	-0.4	PCM5.0
MM+	0.26	HC-752
R-HF/6-31G**	0.58	HC-752
AM1	0.42	HC-752
CSMM2 Chem3D 7.0	0.27	CS2000
CSMM2 Chem3D 8.0	-2.03	CS2004
CSMM2 Chem3D 9.0	-1.97	CS2005
ChemBio3D 11.0	-1.88	CS2007

C. LL. Z. M. AL. L L. A.		1.66 1	
i anie 6. Methyl acrylate	A (WIA) S.Trans/S.cis energy	difference according to	different method of calcillation
	\mathcal{L}	uniter chece, according to	and the method of calculation
		/ 8	



Scheme 1: Enone part: Definition of the S-cis/S-trans forms

In another hand MM+, and generalized CSMM2 incorporated in older CS-Chem3D package version 7.0 [32a] gives a preference for s-cis conformer with a relative energy for s-trans close to 0.27 Kcal/mol. The chem3D CSMM2 results vary drastically from one version to another. This difference is due essentially to the low quality of the (5-2-3-6) MM2 type dihedral parameters (V1, V2 and V3).

In order to predetermine the 5-2-3-6 qualitative torsional parameters for both MM2 and MM3 force fields, we have used the Tinker [42] software package. Indeed these parameters are missing in the MM2 and MM3 parameters files.

In the literature, different experimental data were reported, approving the stability of the s-cis conformer. Dulce and Faria has performed a Raman and IR of liquid and solid methyl acrylate and its deuterated analogue [37]. The results of this study indicate an energy difference of 0.45 kcal/mol.

In another study, on MA, by a joint analysis of gas electron, diffraction data and rotational constants, Egawa [38] has reported a coexistence of the s-cis and s-trans at room temperature, in ratio of 67:33, involving an energy difference of about 0.67 kcal/mol. Thus according to experimental data, the difference in energy is between 0.45 and 0.67 kcal/mol in the case of MA.

In a related study on methyl trans-crotonate MC, Dulce and Faria [39] has likewise performed Raman and infrared spectra of liquid and solid, from variable temperature studies. It was reported that the molecules exist as a mixture of the s-cis and s-trans forms, with the s-cis being more stable than the s-trans form by 0.63 kcal/mol. This finding was established by Virdi, et al, [40] computationally in a spectroscopic and quantum chemical study.

The starting point to parameterize the (5-2-3-6) dihedral angle is the methyl acrylate MA. Initially, a test values of the missing parameters, were introduced to reproduce the R-HF/6-31G** ($\Delta E=0.5781$ kcal/mol) for the MA, and then these values was refitted to reproduce the HF/MP2/6311++G**, values (Figure 15), for a set of acrylic esters held to be test molecules. The refitting process leads to the values:





Figure 15: A set of acrylic esters: S-trans/S-cis energy difference, using three computational methods

In Figure 15, we have used three methods MM2, MM3 with our parameterization, and the MP2/6-31++G** to evaluate the variation of $\Delta E_{trans/cis}=E_{trans}-E_{cis}$ with different acrylic esters (from 1 to 9, where 1 correspond to the MA and 5 correspond to the MC). Globally there is a congruency between the three methods to give a preference to the s-cis form, with relative steric energy between 0.45 and 0.65 kcal/mol. MM3 force field results, are more similar to the MP2/6-311++G**, than the MM2 results. The average deviation of $\Delta E_{trans/cis}$ calculated with MM3 and MM2, in relation with $\Delta E_{trans/cis}$ calculated with MP2, are respectively, $\Delta (\Delta E)_{MM3} = |\Delta E_{MM3} - \Delta E_{MP2}|$ around 0.035 kcal/mol and, $\Delta (\Delta E)_{MM2} = |\Delta E_{MM2} - \Delta E_{MP2}|$ around 0.075 kcal/mol.

Particularly $\Delta E_{trans/cis}$ for the MC, for which $\Delta E_{trans/cis}$ experimental is about 0.63 kcal/mol, we find a good agreement between the three methods and the experimental value. The new torsional parameters will be in use, in the continuation of this work.

Regarding the ester part (Scheme 2), it was established that the s-trans form is more stable than the s-cis form by around ~ 3.0 kcal/mol and thus it can be ignored [45-50]. Concretely, the first appearance of the ester s-cis form, correspond to the 63th conformer in the file list (4.23 kcal/mol above the GM). The 342nd conformer (11 kcal/mol above the GM) correspond to the first entrance of two esters in s-cis form Scheme 2.



Scheme 2: Ester part: Definition of the S-trans/S-cis forms

Unsymmetrical 14-membred macrodiolide, QM/MM study

Compound 1: (E,E)-dioxacyclotetradeca-3,9-diene-2,8-dione (R1=R2=R3=H).

We have selected minima from each family, from the type 1, to the type 8. Therefore, we performed optimization on each selected conformation, using sequentially different variant molecular mechanics force fields. Semi empiric AM1, HF/6-31G**, B3LYP/6-31G** and finally MP2/6-31G** (exclusively for FCC, FTC and ATC) were used in order to compare the results (Table 7a) and subsequently validate the suggested parameterization. In Table 7b, we have reordered the conformations, from the most stable to the less stable, according to each used method [51].

Qualitatively, we note that, three conformations, belonging to the ATC, FCC and FTC families, are among the favored conformations, regardless of the computational method, except for the AM1 method, where the ATC type conformer share the position of privileged conformer with the FTT type conformer. The difference between ab initio and MM methods is, in the label of the privileged conformer [52]. It is the ATC type for the MM methods, while it became the FCC type conformer for the two last ab initio methods, which includes electronic correlation (MP2/6-31G** and B3LYP/6-31G**). The HF/6-31G** and MM2 methods, leads equality to the ATC and FCC type conformers [53-55].

Conformation	1	2	3	4	5	6	7	8
Family	FTT	ATT	FCC	ACC	FTC	ATC	FCT	ACT
H-MM+	2.29	2.26	1.24	1.4	0.63	0	3.45	2.97
MMX	1.02	1.51	0.51	3.21	0.17	0	1.84	1.66
MM2	2.71	2.96	0.06	0.68	0.35	0	2.7	2.73
MM3	3.32	3.88	0.86	1.25	1.05	0	3.91	4.1
AM1	0.09	0.66	0.27	0.97	0.36	0	1.59	1.71
R-HF/6-31G*	1.97	2.24	0.09	0.67	0.38	0	3.35	3.22
R-HF/6-31G**	1.96	2.14	0.04	0.71	0.31	0	3.14	3.11
MP2/6-31G**	2.42	3.81	0	0.96	0.95	0.99	4.18	3.39
B3LYP/6-31G**	2.71	2.33	0	1.14	0.55	0.53	3.17	2.85

All of these eight conformations are characterized by the same anti-dihedral C(4)-C(5)-C(6)- C(7), around 150°, and a same gauche dihedral angle C(10)-C(11)-C(12)-O(1), around 48°. Globally, we note the fitting between the MM2 and HF/6-31G** tendency

H-MM+	ATC	FTC	FCC	ACC	FTT	ATT	ACT	FCT
MMX	ATC	FTC	FCC	FTT	ATT	ACT	FCT	ACC
MM2	ATC	FCC	FTC	ACC	FCT	FTT	ATT	ACT
MM3	ATC	FCC	FTC	ACC	FTT	ATT	FCT	ACT
AM1	ATC	FTT	FCC	FTC	ATT	ACC	FCT	ACT
HF/6-31G*	ATC	FCC	FTC	ACC	ATT	FTT	ACT	FCT
HF/6-31G**	ATC	FCC	FTC	ACC	ATT	FTT	ACT	FCT
MP2/6- 31G**	FCC	FTC	ATC	ACC	FTT	ATT	ACT	FCT
B3LYP/6- 31G**	FCC	ATC	FTC	ACC	ATT	FTT	ACT	FCT

Table 7b: Reordering of the conformations, according to H-MM+ results

Why the FTC, ATC more stable than FCT, ACT conformers?

Analysis of different contributions to the MM3 total energy (Figure 16), show a very close linkage and consistency, in variation, between the torsional and the total energy. Thus we can depict the relative stability of each conformer in relation with each other, in terms of torsional energy. We can split the eight conformations in to two groups, with the first group as of relative low torsional energy (FCC, ACC, FTC and ATC) characterized by the third letter "C" and the second group with a relative high torsional energy (FTT, ATT, FCT and ACT) characterized by the third letter "T". Consequently we can assume that the pentenoic part of the dilactone, prefer the S-cis form. An overview on the breakdown of the MM3 torsional energy, over each atom of the ring (Figure 17), shows that the torsional energy of the C2=C3-C4-C5 dihedral angle is lowest for the, FTT, ATT, FTC and ATC conformers, characterized by the second letter "T" i.e., the heptenoic fragment in s-trans form. In fact the dihedral angle adopt an optimal anticlinal value, around 120° according to B3LYP/6-31G** calculations (Table 8), while it is less anticlinal, tending to the (more strained) synclinal form, in the FCT and ACT conformers. This is the principal origin of the relative stability of the conformer FTC and ATC in relationship with the FCT and ACT conformers (Figure 18) [55-58].



Figure 16: Compound 1: MM3 contributions to the total potential energy for the conformations representing the 8 principal conformational families



Figure 17: Compound 1: Breakdown of the MM3 torsional energy over each atom the ring for the conformations representing the 8 principal conformational families



Figure 18: Conformations, figuring among the three most stable conformers, regardless of the method of calculation, (a) [15'35'], (b) [1(3*3)'3'5'], (c) [1(3*3)'35']

Table 8: Compound 2: C4-C5-C6-C7 to	orsion values according to each used method
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Туре	Acronyms	MM3	MM2	RHF/6-31G**	B3LYP/6- 31G**	MP2/6-31G**
1	FTT	-146	-140.9	-126,9	-124,3	-118.6
2	ATT	148.7	142	133,2	130,9	125.7
3	FCC	-158	-157.2	-148,5	-147,1	-144.9
4	ACC	147.5	145	135,2	133,5	130
5	FTC	-153	-150.4	-143,2	-142,1	-137.4
6	ATC	153.7	152.4	140,8	140,3	135.2
7	FCT	151.5	146.8	138,9	146,7	141.3
8	ACT	151.2	145.6	141,3	137,1	118

Concerning the other contributions to the total energy, we relive the low bond stretching contribution for the 3 privileged conformations, that is, the FCC, FTC and ATC Figure 19a. The ACC conformation is the highest stretched conformation. The same tendency is perceived for the Van Der Waals and the angle bending contributions Figures 19b and 19c [59,60].

The dipole-dipole interaction is significantly different. Globally it is low for the antipodal conformations, and is high for the frontal neighboring conformations, Figure 19d. The FCC conformation is characterized by its closest and parallel carbonyl groups. Consequently its Edp-dp is high.





Figure 19b



Figure 19: Van Der Waals and the angle bending contributions

Substituents effect

The (6R, 11R, 14R)-Colletallol 2a, and its stereoisomers 2b, and 2c, (Figure 20), were used to examine computationally, the substituent effect on the conformational properties of the unsymmetrical 14-memebred macrodiolides under study. The same methods (MMX, MM2, MM3, HF/6-31G*, B3LYP/6-31G**) were used.



Figure 20: Colletallol 2a, and two of its unnatural stereoisomers, 2b and 2c

Compound 2a: (6R, 11R, 14R)-colletallol

All methods used (Table 9), leads to the same minimum, belonging to the FCC family. In the literature, X-Ray structure [43-45] of 2a obtained by Hervé Dumartin in 1993, was identical to this minimum. Unfortunately, we do not have actually the detailed structural data for comparison except selected dihedral angles reported as underlying data in reference [46]. The FTC conformer is the second minimum according to all methods, except AM1, which is entirely different, with ACT and FCT, equivalently as second minima. However, if we refer to HF/6-31G* and MM3, the ATC conformer is equally the second minimum with the FTC type. The second minimum is dependent with the computational method. We note the obvious equivalence, between the MM3 and HF/6-31G* energy tendency. This Remarque is more valuable for the two stereoisomers 2b and 2c.

Table 9: Compound 2: C2-0	C3-C4-C5 torsion values a	according to each used method
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Туре	Acronyms	MM3	MM2	RHF/6- 31G**	B3LYP/6- 31G**	MP2/6- 31G**
1	FTT	98	94.1	115.3	117.4	116
2	ATT	118.2	117.6	128.6	122.8	113.6
3	FCC	75.5	70	83.4	85.8	84.8
4	ACC	98.4	105.6	112.1	110.9	116
5	FTC	-113	-121	-129.2	-122.3	-112.2
6	ATC	-96.2	-88.4	-106.9	-109.1	-105.6
7	FCT	-70.9	-72.6	-91.8	-84.5	-88.9
8	ACT	-70.6	-72.2	-86.5	-89.7	-107.7

In the FCC and FCT families, the two Methyl groups are equatorial or pseudo equatorial and are in opposite sides relative to their respective nearest carbonyl oxygen atoms Table 10. This preference is explained by the stabilizing syn-periplanar (I, II) of the Hydrogen atom in relationship to the -COCH=CH- moiety (Figure 21).

Types	1	2	3	4	5	6	7	8
Methods	FTT	ATT	FCC	ACC	FTC	ATC	FCT	ACT
H-MM+	1.9	2.15	0	1.39	0.37	0.45	2	2.15
MMX	1.59	2.54	0	3.62	0.5	1.67	1.09	2.87
MM2	1.70 ^(H)	4.24	0	1.57	0.68	1.31	2.77	4.20 ^(H)
MM3	3.1	4.13	0	1.51	0.16	0.19	5.97	3.1
AM1	1.36	2.31	0	2.7	0.97	0.59	0.52	2.31
HF/6-31G*	3.09	4.26	0	1.39	0.31	0.45	3.51	4.76
B3LYP/6-31G**	2.59	4.72	0	2.32	0.17	3.26	2.73	5.26

Table 10: Compound 2a: relative energy according to each used method



Figure 21: Isopropylethenoate: (C-C-O-C dihedral scan at B3LYP/6-31G** level)

The relationship of the axial hydroxyl OH, to the C=C double bond, is anti-periplanar (around 155.2° B3LYP/6-31G**), corresponding to the local minimum II (Figure 21) in the FCC conformation, whereas it is a favorable, syn-periplanar (around 4.2°) in the FTC conformation corresponding to the global minimum I (Figure 22).

The conjunction of three factors that drags the FCC and FTC conformers from the second and third rank in the substituted macrodiolide to the first rank in the case of 2a.



Figure 22: Pent-3-enol: C=C-C-OH dihedral scan at B3LYP/6-31G** level

^(H): MM2 is unique to give, relative stable conformations containing hydrogen bond, belonging to the FTT type, (Figures 23c and 23 d), in contradiction with MM3, and ab initio methods.

Compound 2b (6R, 11S, 14R)-colletallol

2b and 2c are unnatural stereoisomers of the colletallol. The X-Ray structure [44,45] of the stereoisomer 2b belongs to the FTC type (Figure 23b). As for 2a, the two are in opposite side relative to their nearest carbonyl Osp2. The hydroxyl OH group is anti periplanar in relationship to C=C group [61,62].

The GM, is FCC like type (Figure 23a), according to all methods used (Table 11) except for MM+ which leads equivalently to the FCC and FTC conformers. FTC like conformer (corresponding to the experimental structure) is the second lowest strained for MMX (0.17), MM3 (0.39), HF/6-31G*(0.54) and B3LYP/6-31G** (0.92).

In the FCC conformer, OH is pseudo-axial, in synclinal (around -27.5°) relationship to the C=C group, corresponding to 1 kcal/mol, higher than the global minimum I (Figure 22). The FTC conformer is characterized by, an equatorial OH, in anti-clinal (around 121.5° -BLYP/6-31G**) relationship to the C=C group corresponding to the local conformation II (Figure 24).



Figure 23: Compound 2a: a) GM belonging to the FCC family, according to the used methods, in agreement with the X-ray structure, b) (3) 2nd minimum (FCT family), c) FTT family according to MM2 (top view) d) side view (from left)

The two conformers FCC and FTC may probably coexist, in a ratio of 67:33. The crystalline structure do not correspond necessarily to the GM. The OH conformation is more stabilizing for the FTC than for FCC.



Figure 24: Compound 2b: a) Privileged conformer, according to all the used methods, b) Privileged conformer according to MM+ (0.05 kcal/mol), corresponding to the X-RAY structure, and second minimum according to the used methods, except AM1 (Table 11)

 Table 11: Compound 2b: Relative energy according to each used method

Types	1	2	3	4	<u>5</u>	6	7	8
Method	FTT	ATT	FCC	ACC	FTC	ATC	FCT	ACT
H-MM+	1.78	2.6	0	1.42	0.05	<u>0.5</u>	2.09	2.99
MMX	1.04	2.96	0	3.64	0.17	1.88	1.13	3.77
MM2	4.7	4.35	0	2.49	1.41	1.59	2.82	4.58
MM3	3.61	4.49	0	1.99	0.39	1.2	3.56	4.65
AM1	0.77	1.27	0	1.59	0.66	1.16	0.53	0.85
HF/6-31G*	3.63	4.66	0	1.89	0.54	1.34	3.57	4.52
B3LYP/6- 31G**	2.81	4.7	0	3.08	0.92	2.89	2.62	4.05

Compound 2c: (6R, 11R, 14S)-colletallol

Apart from MMX, and AM1, which leads to ACT (type 8), all the methods used (Table 12), give the ATC (type 6) as GM (Figure 25), in agreement with the X-ray structure reported in the literature [43,45]. As in the case of compounds 2a and 2b, the two Me are in opposite side in relationship to their nearest carbonyl Oxygen atoms. The OH group is pseudo axial, in a favorable syn-periplanar relationship (around 14°) to the C=C group. By way of indication, MMX and AM1 give the same ACT conformation as GM, followed by the ATT, and the ATC conformer. As for 2a and 2b, the MM3 and HF/3-31G*, show an equivalent leaning for the compound 2c. In this last case, we report the distinction of the B3LYP/6-31G**, to give the ATT (type 2) as the second minimum, with a little 0.14934 kcal/mol, above the GM. Table 13 show the comparison between the torsion values from the literature selected in reference [44], with data taken from computational procedures achieved in this work. B3LYP/6-31G** values agree perfectly with experimental data, the maximum difference is about 4°. While the MM (MM+, MM2 and MM3) torsion values are similarly, quite different from the experimental values (mean deviation of 12°), in particular the 01-C1-C2-C3 torsion, which is slightly gauche (19°), but in the MM result it is strictly eclipsed (about 0°).



Figure 25: Compound 2c: ATC conformation, corresponding to the X-Ray structure and the GM, according to the used methods except for MMX and AM1 (Table 12)

Table 12: Co	ompound 2c:	relative energy	according to e	ach used method
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Types	1	2	3	4	5	<u>6</u>	7	8
Method	FTT	ATT	FCC	ACC	FTC	ATC	FCT	ACT
H-MM+	1.41	1.33	0.53	1.5	1.2	0	2.88	0.94
MMX	1.33	0.33	0.95	2.79	1.75	0.53	3.65	0
MM2	1.93 ^(H)	2.38	0.01	1.48	1.01	0	2.79	1.51
MM3	3.75	2.99	1.86	1.76	2.33	0	6.29	3.37
AM1	1.16	0.25	0.84	1.3	2.1	0.42	0.69	0
HF/6-31G*	3.82	2.98	1.81	1.41	2.48	0	6.08	3.38
B3LYP/6- 31G**	2.62	0.15	1.45	1.13	2.17	0	5.44	1.15

(H): Contain Hydrogen bond

Table 13: Compound 2c: conformation [1(3*3)'35'], comparison between experimental [44] and computed torsion values (in

degrees)

	Exp	MM+	MM2	MM3	HF/6- 31G*	B3LYP/6- 31G**	MP2/6- 31G**
C10-C11	-111	-107	-106	-110	-109	-108	-107
C12-C11	44	46	45	49	47	45	41
C1-C2	19	-2	-2	0	10	16	26
C3-C4	-113	-82	-82	-96	-94	-109	-101
C5-C6	142	152	150	154	145	141	135
C7-O2	-80	-66	-66	-67	-80	-81	-59
Mean errors	0	13	22.69	11.17	6	2.17	9

CONCLUSION

The Cyclotetradecane 1 conformational analysis, via a conformational search, show that the number of conformations, at room temperature, within 5 kcal/mol above the GM, is greater than mentioned in the literature [5]. New conformations identified by unique polar map and absolute map, were proposed in this work in this range.

In another hand, the conformational search, on unsymmetrical 14-memebred macrodiolide model 2, shows that one can split conformations on families demarcated by acronyms. On the way, eight principal types of conformations was well-defined, on basis of the local enone conformation, and the relationship of each carbonyl oxygen atom to each other.

The Q/MM comparative study, show that, among the eight selected minima, representing the defined classes, three are always of low energy, whatever the computational used method. These are the ATC, FCC and the FTC classes, characterized by the pentenoic fragment in s-cis form.

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Among these three conformers, the GM depend on the computational method. We think that, the principal cause for the relative stability of the ATC and FTC conformers, as opposed to the ACT and FCT conformers, is the relative stabilization of the C2-C3-C4-C5 dihedral angle, which is anticlinal close to the optimal value 120° in the two former conformers (Table 9), while it is synclinal in the latest conformers. Regarding the substituent effect, the methyl exhibits an obvious effect to turn the vicinal carbonyl oxygen atom on its opposite side. Thus, two related trans methyl group (R,R or S,S) implies the promotion of the types 2, 4, 6 and 8, while two cis methyl group (R,S or S,R) involve the promotion of the types 1, 3, 5 and 7. The qualitative comparison with x-ray structures, show that molecular mechanics, despite the fact that it is based on parameterization, is still, a reliable tool to predict quickly the conformational preference of organic molecules, particularly for macrocycles if correctly parameterized, compared to semi empiric AM1 and quantum mechanics, at different levels of theory. However, the molecular mechanics (MM+, MM2, and MM3) do not reproduce the experimental torsions values. The best method to reproduce is the DFT method, best than the MP2 with same basis set.

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NOTES

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