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CONFORMATIONAL ANALYSIS AND STEREOCHEMICAL CONTROL IN MACROLIDES BY MOLECULAR MECHANICS AND BOLTZMANN DISTRIBUTION

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ABSTRACT

The Conformational analysis and stereochemical control of 20-Membered Macrolides were investigated using molecular mechanics calculations, PM3 semi-empirical method, and Boltzmann distribution. The results indicate that these macrocycles have a high degree of conformational flexibility. However, in the presence of tricarbonyliron, the number of favorable conformations was reduced to only four. The study also revealed significant diastereoselectivity (73:27) in B-type complexed macrolides. Furthermore, it was observed that the methyl group in position α_2 had a local conformational effect that increased the diastereoselectivity of alkylation reactions. The high diastereoselectivity observed was attributed to the combination of stereochemical remote control with $Fe(CO)_3$ and local control by the methyl group.

Keywords: Macrolide, Molecular mechanics, PM3, Boltzmann distribution, Stereoselectivity

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1. INTRODUCTION

The medical significance of macrolides has generated considerable interest in studying and synthesizing these molecules [1,2]. Their structures consist of a macrocyclic system of 12 to 40 members with several centers of asymmetry and a lactone function, as well as a sugar component. In recent years, a new class of antibiotics, including clarithromycin, azithromycin, and josamycin, has been developed to improve the antimicrobial spectrum and address antibiotic resistance in bacteria [4].

However, the synthesis of macrolides presents challenges, particularly with regard to remote stereochemical control over long distances. Stereoselectivity observed in reactions on macrocycles has been rationalized by Still et al. [5,6] based on the work of Anet [7] on NMR studies and Allinger [8] with molecular mechanics calculations. Additionally, Grée et al. have experimentally demonstrated the possibility of stereochemical control induced by tricarbonyl iron in some cases [9,10].

The aim of our study is to investigate the extent to which this notion can be extended to very large rings (20 members). We have selected macrolactones containing a butadiene tricarbonyl iron unit as our model compounds and propose to examine the various factors that influence the stereoselectivity of alkylation reactions.

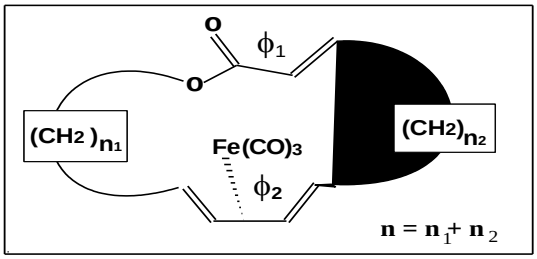
2. CALCULATIONS AND RESULTS

Computational chemistry is a field that utilizes computer modeling to solve complex chemical problems by using theoretical chemistry methods and powerful computer programs. In the pharmaceutical industry, computational chemistry plays a crucial role in various aspects of drug design, including lead identification and optimization, and target selection. This method has become increasingly popular due to its ability to save time and costs before moving onto experimental stages. Our study employs two calculation methods, namely Molecular Mechanics and the semi-empirical method PM3. Molecular Mechanics is the preferred method for large molecules and is based on the Allinger force field. We performed calculations using HyperChem 8.08 and Chem3D on a HP Z620 workstation, searching for energetically stable structures via a random walk among all possible conformations. Our goal

was to determine the energetically preferred conformations, utilizing both energetic and geometrical considerations, and using the Boltzmann distribution through statistical calculations to determine the most likely conformers to exist.

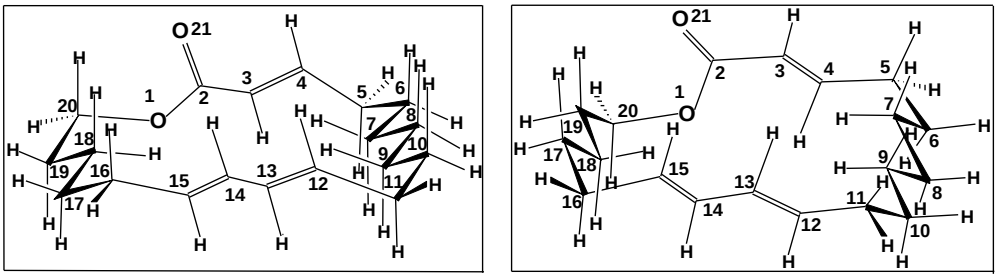
2.1 Study of 20-membered macrocycles

This section of our research involved investigating the conformational properties of the 20-membered macrocycles (Scheme 1), which serve as the fundamental structure for numerous antibiotic macrolides. We examined both symmetrical designs, such as 20s (n1 = n2 = 6), and dissymmetrical designs, such as 20d (n1 = 5, n2 = 7), in their uncomplexed and complexed states with Fe(CO)3. Additionally, we introduced substituents into the complexed macrocycles to observe how their positioning affected their conformational stability.



Scheme 1

The 20-membered macrocycles (Scheme 1) studied in this research have been found to possess three primary structural features: the diene conformation, the conformation of the α,β-unsaturated ester function, and the conformation of the two lateral carbon chains [27-29]. By analyzing the obtained conformers based on these two structural features, we have identified eight conformational types, each characterized by a specific geometry and an average energy [30, 31]. These types are designated 1 through 8, and for types 2, 4, 6, and 8, the two planes of the diene and α,β-unsaturated ester function are pseudo-parallel (with pseudo-symmetry of the finite group, C2v). Conversely, for types 1, 3, 5, and 7, the two planes of the two sites are pseudo-antiparallel (with pseudo-symmetry of the finite group, C2h). These conformational types are present in the majority of cases within an energy range of 4 kcal/mol above the global minimum.



(a) Type 5; ΔE = 0.00 kcal/mol (b) Type 4; ΔE = 0.81 kcal/mol

Fig 1. The two preferred conformations of macrocycle 20d

In a range of 1 kcal/mol the macrocycle 20d is characterized by a first most preferred conformation of type 5 (figure 1-a) with a rate of 22.4%, followed by type 4 (figure 1-b) with 18.4% and type 3 (15.1%). While the macrocycle 20s occurs preferentially in the conformations: type 6 (19.8%), type 5 (17.5%) and type 3 (15.7%). The percentages of the other conformational types are recorded in Table (1). The population rate of the preferred conformer of the 20d macrocycle is slightly higher than that of the 20s macrocycle.

Table 1. Boltzmann population for different conformational types

Macrolide	20 symmetric ($n_1 = n_2 = 6$)			20 dissymmetric ($n_1 = 5, n_2 = 7$)		
	Type	ΔE	%	Type	ΔE	%
at 1 kcal/mol	6	0.00	19.8	5	0.00	22.4
	5	0.50	17.5	4	0.81	18.4
	3	0.96	15.7	3	1.52	15.1
to 2 kcal/mol	4	2.06	12.0	8	2.93	11.0
Above 2	1	2.32	11.3	2	3.52	09.5
kcal/mol	2	3.43	08.6	7	3.65	09.2
	7	3.97	07.6	1	4.38	07.7
	8	4.03	07.5	6	5.13	06.4

ΔE: deviation from the global minimum %: Boltzmann population

For the preferred conformer geometry; the ester α, β-unsaturated system has an s-cis conformation with an angle ϕ_1:O21-C2-C3-C4= 34.0° for the 20d macrocycle and ϕ_1(O21-C2-C3-C4)= 25.1° for the 20s ring (Table 1). The diene system has an s-trans conformation with a twist angle ϕ_2(C12-C13-C14-C15)= 177.3° for 20d and

ϕ_2(C11-C12-C13-C14)=179.4° for 20s. The two ester and diene systems are parallel to each other.

These macrocycles have a very high conformational mobility. They present many preferred conformations that do not allow a priori predictions of diastereoselection for the considered reactions. This is in agreement with the work of Saunders et al who show that the 17-membered rings present many preferred conformations [32].

2.2 Introduction of the tricarbonyl iron

We are going to study the effect of the tricarbonyl iron $Fe(CO)_3$ on the conformational mobility of these macrocycles. The organometallic complexes obtained by reaction between an organic species and a species carrying a transition metal atom, constitute intermediates very much used in organic synthesis [33] insofar as the complexation generally involves the modification of the electronic and steric properties of the organic species. The complex obtained must however present all the conditions required for thermal and chemical stability and mobility in order to be able to easily decomplex the organic species under mild conditions. In this complexing agent the iron forms coordination bonds with the delocalized electrons (Π) of the ring diene system and prevents the rotation of the two double bonds around the bond σ.

The results of the conformational analysis of the two complexed 20-chain macrocycles show that the tricarbonyl iron has a considerable influence on the rings because the number of possible conformations was reduced to four. Within an energy gap of 1 kcal/mol, the 20s and 20d complexed macrocycles show two preferred conformations. The settlement rate of the most stable conformers increased for the complexed macrocycles compared to those without tricarbonyl iron (Table 2).

Table 2. Boltzmann population for different conformational types

Macrolide	20 symmetric ($n_1 = n_2 = 6$)			20 dissymmetric ($n_1 = 5, n_2 = 7$)		
	Type	ΔE	%	Type	ΔE	%
at 1 kcal/mol	1	0.00	33.0	1	0.00	40.2
	2	0.92	26.4	2	1.71	26.5
above 1	8	1.79	21.3	7	3.16	18.6
kcal/mol	7	2.20	19.3	8	4.13	14.7

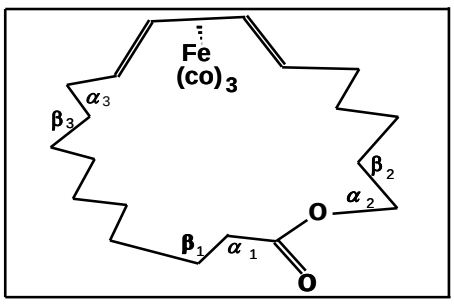
For the macrocycle 20d for example, which was presented with a settlement rate of 22.4% without complexing agent, becomes settled with a rate of 40.2% in the presence of $Fe(CO)_3$ (Table 2). The latter is presented preferentially in the conformations, type1 (40.2%) and type 2 (26.5%), the first type1 having the same conformation as that obtained by X-ray [34]. The diene system is fixed in the s-cis conformation for all preferential conformations. The value of the dihedral angle of the diene system is between 1.52° and 15.36° for ring 20s and between 1.79° and 30.30° for the ring 20d.

The presence of the tricarbonyl iron imposes a minimum of steric modifications and introduces an element of asymmetry. This creates an environment that favors discrimination between the two faces of the macrocycle, thus increasing the proportion of peripheral attack.

This reasoning is found in methyl acetates with fluorite, where metal-fluorine and oxygen interactions create steric hindrance around one of the two faces of the enolate then producing a diastereofacial selectivity of (94.6 : 5.4) [35]. The lactone function and the complexed diene are almost perpendicular to the mean plane of the ring. This is in agreement with the work of Still et al who state that the addition of CH_3I takes place on the exposed side, by peripheral attack [5,6].

2.3 Introduction of substituents

In order to study the role that a new substituent can play on the stereochemical control we introduced a methyl in various positions (Scheme 2). The introduction of the substituent shows that the order of types is variously modified depending on the position of the methyl in the carbon chain and the position of the methyl relative to $Fe(CO)_3$.



Scheme 2

Type 2 represents in most cases the preferred conformer in a conformation (endo or exo) except for the substitution β_1 where it is in second position in the 'exo' case, with a low energy gap of 0.13 kcal/mol compared to the preferred conformer. In second place comes type 1, like the case of unsubstituted complexed macrolactones. The most influential position is α_3 (endo) for which the energy difference between the absolute minimum (type 1) and the second minimum (type 2) is the largest (1.75 kcal/mol) giving a probability to the majority type 1 of the order of 37.9%, while this difference is only 0.26 kcal/mol in the case of the unsubstituted complexed macrolactone with a rate of 31.4%.

Similarly, the positions β_3 (endo) and α_2 (endo) also have an influence because the preferred conformers are also in the majority (36.9% and 33.7% respectively)

In conclusion, it appears from this study on the complexed ring 20d that the stereochemical control is all the more effective as the methyl is close to the center of asymmetry.

It seems that the role of this substituent is not limited to the conformational stabilization of the ring, but also linked to a local conformational control. This is in agreement with previous work [5] concerning the 11, 12 and 13 membered rings for which only one form of local conformational control is used to explain the observed diastereoselectivity. These results also confirm the hypothesis of Vedejs who, in order to arrive at a simple model of stereochemical control, he neglected the effect of distant substituents compared to those located near this site [36].

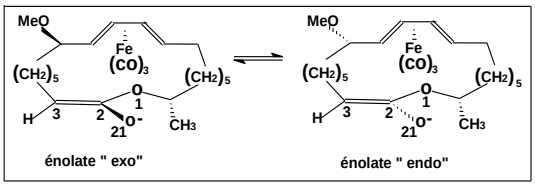
2.4 Study of complexed macrocyclic models of type B

Here we consider the case of a B-type macrocycle 20, after alkylation it carries a methyl substituent at the (α_1) position of the lactone, a methoxy substituent at the α_3 position of the diene and another methyl at the α_2 position of the oxygen (Scheme 4). The purpose of this section is to investigate the influence of the local conformational control provided by the additional methyl on the diastereoselectivity of the alkylation reaction. The formation of the enolate intermediate is stereoselective and leads to the derivative of Z geometry (Scheme 3). Attempts to trap the enolate of the same type failed experimentally [37].

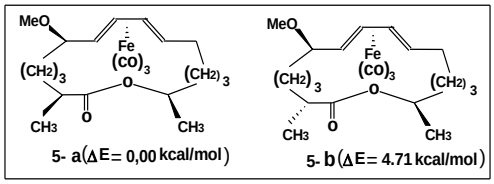
This result is similar to that of 2-alkoxy esters, which provide enolates with a preferred Z geometry [35]. Following the work of Still et al [5-6], and Takahashi et al. [38-39] the

addition of CH_3I is then performed on the free face, by peripheral attack.

The enolate of Z geometry exists in two preferred conformations "exo" and "endo" (scheme 3) with the torsion angle of the exo configuration: O21-C2-C3-H(3) = 0.28°



Schema 3



Schema 4

The two enolates "exo" and "endo" give the majority diastereomer (5-a) and the minority diastereomer (5-b), respectively (Scheme 4). The two methyl groups are cis to each other for the more stable diastereomer; this result is in agreement with the previously mentioned work on other smaller lactones [5]. These groups are "exo" to the $Fe(CO)_3$ group for the majority diastereomer.

The reaction proceeds preferentially via the "exo" form of the enolate (Scheme 3); the preferred diastereomer type 5-a (Scheme 4; Figure 2) has the same conformation as that found by X-ray [37]. It is in the majority with 73%, the other type 5-b is in much lower proportion with 27%.

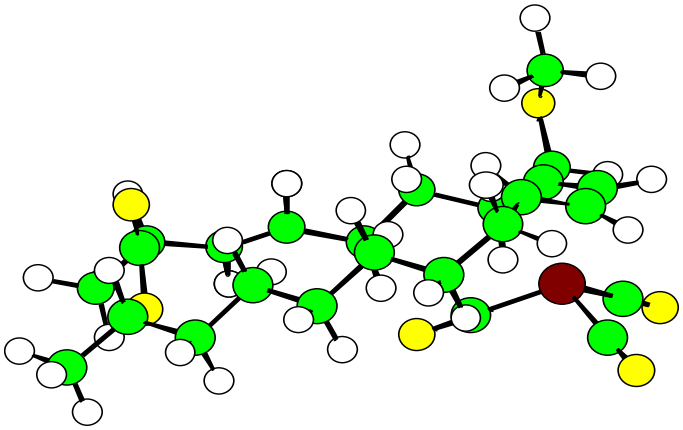


Fig.2. Preferred conformation (Type B) of complexed macrocycle 20 (Chem 3D Pro)

Our study of type B complexed macrolactones revealed a significant diastereoselectivity (73:

27). The methyl in the position α_2 increases, probably by a local conformational control, the diastereoselectivity of the alkylation reactions.

The high diastereoselectivity found for complexed macrolactones of type B is rationalized using Still's work; Methyl at α_2 favors by steric interaction a conformation of the enolate intermediate (Z); It increases the diastereoselectivity of the alkylation reaction for 20-membered macrocycles by local control.

For smaller rings (≤ 14 members), [5-6] the alkylation reaction is highly stereoselective under only local steric control. This grouping alone does not explain the high diastereoselectivity observed in the case of macrocyclic complexes of type B compared to the uncomplexed diene. For these compounds, it is established that a long range stereochemical control, induced by the tricarbonyl iron, operates in a significant way. These two factors add up to a highly stereoselective reaction under double control.

3. CONCLUSION

The computational calculations conducted in this study revealed that macrocycles with 20 symmetrical and dissymmetrical chains display a remarkable degree of conformational mobility, with numerous preferred conformations that make it challenging to predict diastereoselection in the reactions under consideration. Conversely, the complexed macrocycles with tricarbonyl iron exhibited limited preferred conformations, suggesting a significant influence of the $Fe(CO)_3$ group. This group introduced asymmetry and a substantial steric effect that increased the proportion of peripheral attack and rigidified the backbone, including the diene system, which remained frozen in an s-cis conformation, thereby reducing the conformational mobility of the rings. Notably, the B-type complexed macrolactones exhibited a high degree of diastereoselectivity, resulting from the combined effect of local control by the methyl (α_2) group and long-range control by $Fe(CO)_3$. Moreover, this study extended the diastereoselection phenomena observed in medium-sized rings to very large rings (>14 members).

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