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Analysis of the Conformational Preferences of (4*R*,5*R*)-4,5-Bis(alkylcarbamoyl)-1,3-dioxolanes

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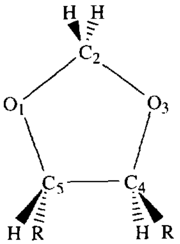
Abstract: The conformational preferences of several 4,5-bis(alkylcarbamoyl)-1,3-dioxolanes in *R,R* configuration were examined by FT-IR, ^{1}H-NMR, ^{13}C-NMR and computational methodologies. On the other hand, both the coupling of the ^{13}C satellite signals of dioxolane methine protons observed in ^{1}H-NMR spectra and the $^3J_{CH}$ coupling constants in the C-O-C-H segments observed in ^{13}C-NMR were consistent with the two low energy conformations derived from quantum mechanical calculations. These preferred conformations were envelope forms predicted to be ≈ 3.5 - 4 kcal/mol more stable than the twist forms.

The conformational analysis of five-membered rings has been a subject of intensive research for many years. Kilpatrick *et al.*[1] introduced the concept of pseudorotation to explain the puckered conformation of cyclopentane, which would be highly strained if it were held in a flat conformation. The dynamic puckering of cyclopentane has been extensively investigated by means of both experimental and computational techniques.[2] The results obtained in these studies indicate that whereas pseudorotation of cyclopentane occurs without appreciable energy change, the introduction of heteroatoms in the ring or the presence of substituents induces the appearance of significant energy barriers. Among five-membered rings, the pseudorotational equilibrium in furanose derivatives has been examined with particular insistence due to their key role in the molecular conformation and dynamics of nucleic acids.[3] The two stable puckerings of the furanose ring are the C_2'-*endo* and C_3'-*endo*, the preference for each of them being controlled by the steric and stereoelectronic effects of substituents. A survey of 178 crystal structures of nucleosides and nucleotides found the furanose ring in either one or the other of these two conformations.[4]

We are interested in the conformational behaviour of *trans*-4,5-disubstituted derivatives of 1,3-dioxolane (**1**). The elucidation of the conformational preferences induced by such a substitution pattern is very desirable since this structural unit is contained in several compounds of great biological and pharmacological interest. Thus, the 4,5-disubstituted 1,3-dioxolane ring is present in a novel class of orthosomycin oligosacharide antibiotics produced by fermentation of *Micromonospara Carbonaceae*.[5] The most widely studied component of this class of compounds is everninomicin D_1 which exhibits excellent in vitro and in vivo activities against *Gram*-positive bacteria and *Neisseria*, including strains resistant to β-lactams, macrolides, tetracyclines and rifamicins.[6] Studies of the structure-activity relationship in everninomicin D_1 indicate that the antibacterial activity is associated with the spiroortholactone structure containing the 1,3-dioxolane ring.[7] Despite the considerable progress achieved in the development of this type of antibiotics during the last years,[8-10] the conformation adopted by the substituted

1,3-dioxolane still remains unknown. More recently, 1,3-dioxolane derivatives linked at the 4 and 5 positions with the N-termini of amino acid residues were used for designing gramicidin channel analogues[11] suitable to model the gating processes occurring in biological systems.[11,12] It was found that the conformation and stereochemistry of the 1,3-dioxolane ring play a crucial role in the gating transition rate of such ring-linked gramicidin channels. On the other hand, certain *trans*-1,3-dioxolan-4,5-dicarboxylic acid derivatives have been recently used in our laboratory for the synthesis of novel optically active polyamides.[13]

In this work we have examined the conformation of a set of (4*R*,5*R*)-4,5-bis(alkylcarbamoyl)-1,3-dioxolanes (**2**-**4**). The dodecyl derivative (**2**) has been synthesized and analyzed by FT-IR and ^{1}H-NMR spectroscopies and a detailed conformational study of the methyl (**3**) and ethyl (**4**) derivatives as well as of the unsubstituted 1,3-dioxolane (**1**) has been performed by quantum mechanical methods. The main aim of the present study is to determine the conformational preferences of these compounds regarding both the influence of the amide side groups on the puckering of the ring and the reciprocal effect of the ring on the spatial orientation of the substituents. The latter point is particularly relevant for us because **2** is an appropriate model compound for the conformational analysis of the aforementioned polyamides, which is currently under course.



(**1**) **R** = -H
(**2**) **R**= -CONH-$(CH_2)_{11}$-CH_3
(**3**) **R**= -$CONHCH_3$
(**4**) **R**= -CONH CH_2CH_3

RESULTS AND DISCUSSION

The pseudorotational model[14,15] was used for the description of the conformation of the ring by making use of only two parameters. According to Altona and Sundaralingam,[14,16] these parameters are τ_m (the puckering amplitude) and P (the pseudorotational phase angle). The parameter P describes the specific puckering state of the ring, which in turn depends on the values of all the five endocyclic torsional angles (τ_0 through τ_4). Thus, P is of extreme practical importance as it reduces a set of interrelated variables (τ_i) to a single parameter. Both P and τ_m can be calculated from the endocyclic torsional angles τ_i by the following formulae:

$$P = \text{arctg}\ [(\tau_1+\tau_4 - \tau_0 - \tau_3) / (3.077683\ \tau_2)] \qquad [1]$$
$$\tau_m = \tau_2/(\cos P) \qquad [2]$$

where τ_i (i= 0, 1, 2, 3 and 4) are the ring dihedral angles. Although P ranges form 0° to 360°, it does not correspond to any single torsional angle; it is merely a mathematical convention used to describe the cyclic pathway for interconversion between the possible envelope and twist conformations of 5-membered rings. On the other hand, Altona and Sundaralingam[14,16] proposed a relationship to derive the endocyclic torsional angles from P and τ_m:

$$\tau_i = \tau_m\ [\cos(P+144\ (i-2)] \qquad [3]$$

where i=0, 1, 2, 3 and 4, and the dihedral angles of the 1,3-dioxolane ring denoted by τ_i are the following: τ_0=<C4-C5-O1-C2; τ_1=<C5-O1-C2-O3; τ_2=<O1-C2-O3-C4; τ_3= <C2-O3-C4-C5; τ_4=<O3-C4-C5-O1.

Experimental data in five-membered rings reveal that P is usually restricted to certain preferred angle regions.[17] For example in nucleosides such intervals are the so called north region (P= 0° to 36°) and south region (P≈ 144° to 180°). Consequently, in order to make a complete exploration of the pseudorotational wheel of 1,3-dioxolane derivatives, the degrees of freedom of the ring must be restricted in some extent. In the present work the pseudorotational movement was driven by keeping the ring torsion angles τ_2 and τ_3 frozen, while all other geometrical parameters were optimized. By this means, an estimation of the energy of the all 20 possible conformations of the 1,3-dioxolane derivatives is feasible.[3] The selection of such a model has been criticized by some authors since it tends to overestimate the conformational energies.[18-20] Levitt and Warshell nicely demonstrated that the pseudorotational movement of a five-membered ring can be obtained by varying only one dihedral angle and optimizing the rest of the molecule.[20] However this method is scarcely applied due to extensive computation requirements. Conversely, the model based on two frozen endocyclic angles has been currently used for predictive purposes since it provides reasonable estimations of the pseudorotational barrier at relatively low computational costs.[3]

The performance and applicability of the AM1 Hamiltonian[21] for the conformational analysis of cyclic systems like **3** and **4** was evaluated by computing the pseudorotational profile of **1** at two different theoretical levels. These were the ab initio MP2/6-31G(d)//HF/6-31G(d)[22,23], where the level of energy evaluation and geometry optimization are indicated before and after the double slash respectively, and the semiempirical AM1. *Figure 1* shows the relative conformational energies computed with the two methods plotted against the pseudorotational movement.

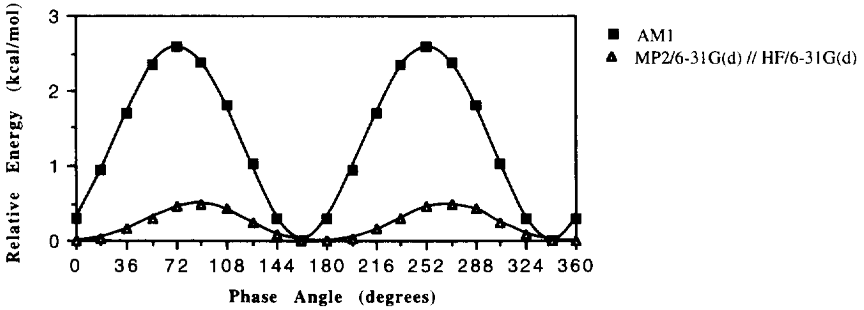


Figure 1. Representation of the variation of the relative conformational energy of **1** during the pseudorotational movement.

Ab initio calculations indicate that there are two low energy regions at approximately P≈ 162-180° and P≈ 342-360°, which are equivalent. These regions are near to the C_2-*endo* and C_2-*exo* envelope conformations respectively, which are shown in *Figure 2a*. The pseudorotational barrier for conversion from C_2-*endo* to C_2-*exo* is 0.5 kcal/mol, which is fully consistent with the small barriers indicated by far-infrared[24] and microwave[25] measurements. These unfavoured energy regions are near to the twist conformations, which are also displayed in *Figure 2b*. The present results are in excellent agreement with those recently published by Shem et al.[26] and Norskov-Lauritsen et al.[27] who predicted the envelope forms of **1** to be 0.36 and 0.52 kcal/mol lower in energy than the respective twist forms. However, the same authors found that the twist form explains better electron diffraction results so that a model consisting of a mixture of twist (65%) and envelope (35%) conformations provides the best comparison with experimental data.[26] Thus it seems that the MP2/6-31G(d)//HF/6-31G(d) calculations slightly overestimate the stability of the envelope form. The semiempirical energy profile is also displayed in *Figure 1*. Comparison between ab initio and semiempirical results indicates that the stabilities of the envelope forms are much more overestimated by the latter method since a much larger energy jump between the minima (2.6 kcal/mol) is predicted by AM1. Nevertheless semiempirical and ab initio calculations provide a similar representation of the pseudorotational movement from a qualitative point of view, since positions of minima and maxima determined by both methods are coincident.

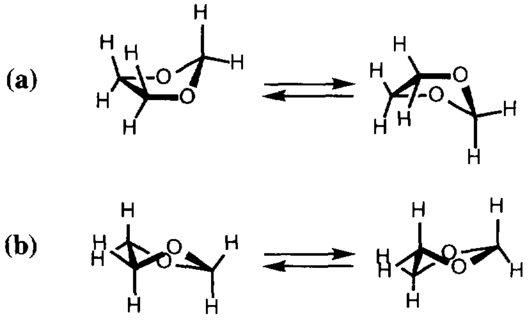


Figure 2. Representation of the envelope (a) and twist (b) forms of **1**.

In order to obtain experimental evidence on the influence of the amide groups on conformation of the 1,3-dioxolane ring, compound **2** has been synthesized and subjected to spectroscopic analysis. Firstly, possible intramolecular hydrogen bonding between amide hydrogens and either annular or carbonyl oxygen atoms was investigated by FT-IR in $CHCl_3$ solution within a range of concentrations from 0.25 to 10%. We have focused our attention on the stretching frequencies of the proton donating (N-H) and accepting (C=O and C-O) groups. The involvement of such groups in hydrogen bonds should be denoted by the shift to lower frequencies of their corresponding unassociated stretching vibrations. However, FT-IR spectra of **2** exhibit sharp absorptions at 3423 (N-H), 1676 (C=O) and 1090 (C-O) cm^{-1} typical of the free state. Furthermore, their positions were found to be unaffected by concentration indicating that no hydrogen bond mediated aggregation of **2** must take place under the conditions used. Unfortunately no precedents of 1,3-dioxolanes bearing amide groups are found in the literature . The present system can be compared with *N*-(*n*-alkyl)-D-gluconamides,[28] where one hydroxyl group of the D-glucose moiety is located at three bonds from the N-H amide group. The crystal structure of such compounds shows intramolecular hydrogen bonding between OH and NH groups. Although in compounds **2-4** the ether group of the 1,3-dioxolane ring is also at three bonds from the NH group, the geometric constraints imposed by the cycle precludes the formation of intramolecular hydrogen bonds.

The conformation of the dioxolane moiety in compound **2** was investigated by ^{1}H-NMR in $CDCl_3$ solution within the temperature range 253-323 K. Since the protons attached to C4 and C5 are magnetically equivalent, we used the ^{13}C satellites of their signal at 4.6 ppm for coupling constants measurements. The method had proven to be successful in the conformational analysis of 2,3-disubstituted 1,4-dioxanes.[29] *Figure 3* shows the whole ^{1}H-NMR spectrum of **2** at 295 K together with its 4-5 ppm region duly enhanced as to make apparent the ^{13}C satellites of the methine peak. The coupling constant observed for C4 and C5 protons was 5.9 Hz and its dependence on temperature was found to be practically negligible (less than 0.2 Hz throughout the examined temperature range). This behavior is fully consistent with a conformational pattern involving the occurrence of preferential arrangements for the dioxolane ring. In order to obtain a more precise description of the conformational preferences of **2**, a ^{13}C-NMR spectrum of the same sample was performed without proton decoupling. *Figure 4* shows the proton coupled ^{13}C-NMR spectrum together with its central signal due to the coupling between C2 and the protons on C4 and C5 carbons. The observed ${}^{3}J_{CH}$ coupling constant was 2.45 Hz.

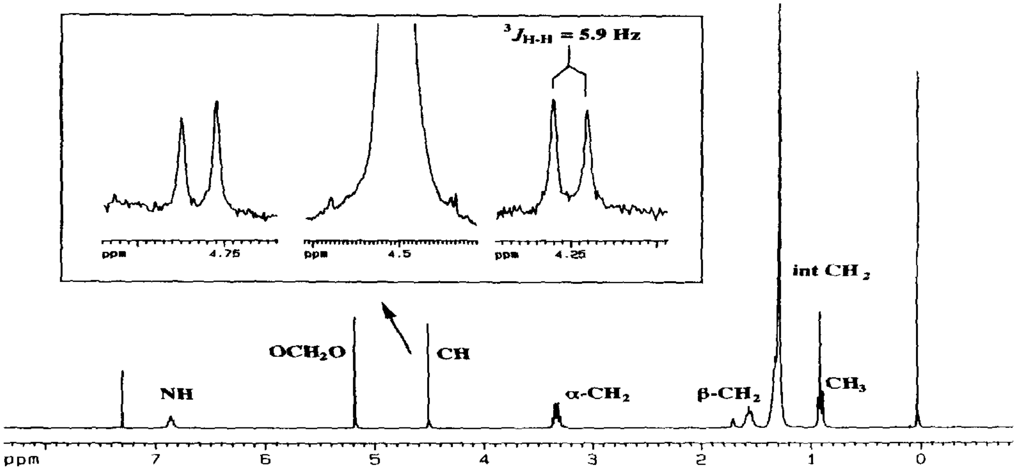


Figure 3. The ^{1}H-NMR spectrum of (4*R*,5*R*)-4,5-bis(dodecylcarbamoyl)-1,3-dioxolane (**2**) observed in CDCl$_3$ solution. Inset: ^{13}C satellites of the peak at 4.6 ppm assigned to the methine protons.

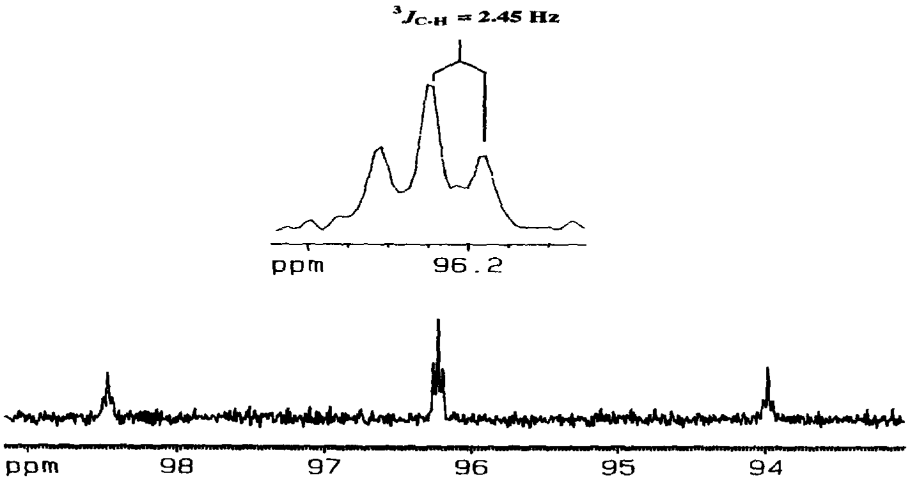


Figure 4. Proton coupled ^{13}C-NMR spectrum of (4*R*,5*R*)-4,5-bis(dodecylcarbamoyl)-1,3-dioxolane (in CDCl$_3$ at 298 K) in the region of the C-2 signal. Inset: central signal as a triplet due to the ${}^{3}J_{C\text{-}H}$ between ^{13}C2-O3-C4-^{1}H and ^{13}C2-O1-C5-^{1}H.

In spite of the poor performance of computational methods to reproduce the pseudorotation of **1**, Hildebrandt and co-workers[26] found that such methods give a satisfactory description of the conformational preferences of substituted derivatives. Therefore the pseudorotational model of **3** was computed at the AM1 level in order to relate NMR data with the conformational parameters of the ring. The two ring torsion angles τ_2 and τ_3 were kept frozen while all other degrees of freedom were optimized and no constraints were applied to the rotation of substituents. The resulting energy profile shown in *Figure 5* contains two low energy regions located around P=162° and 342°, *i.e.*, the envelope region. As can be expected from the molecular symmetry of the system, the two minima are equivalent and isoenergetic. This equivalence has been reached by performing an extensive conformational search at each value of P. Thus, different orientations of the whole side chain with respect to the ring were investigated in each case. On the other hand, the twist form was predicted to be 3.8 kcal/mol less favoured than the envelope form, although according to calculations made on **1**, this value is expected to be overestimated.

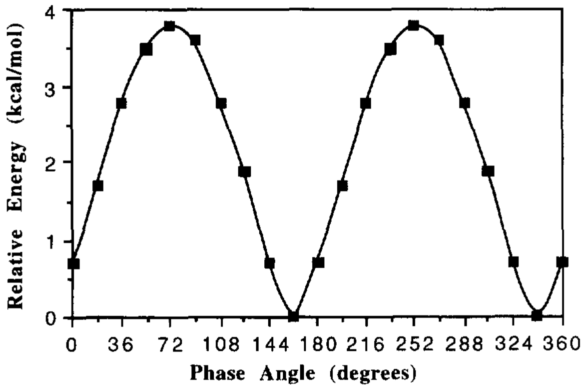


Figure 5. Representation of the variation of the relative conformational energy of **3** during the pseudorotational movement at the semiempirical AM1 level.

Comparison with results obtained for **1** indicates that substituents increment in about 1 kcal/mol the energy between the twist and the envelope forms. The two equivalent conformations corresponding to the two equivalent minima are depicted in *Figure 6*.

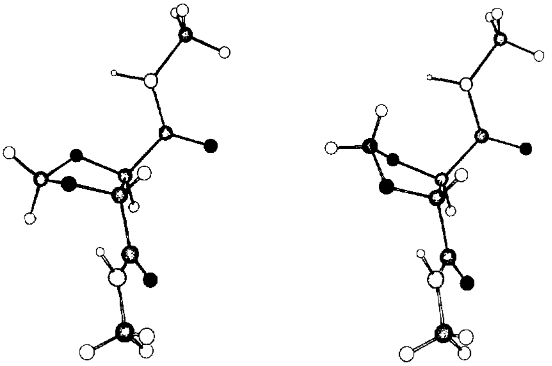


Figure 6. Representation of the minimum energy conformations C_2-*endo* (left) and C_2-*exo* (right) of **3**.

Experimental NMR data obtained for compound **2** were used to test the results arising from AM1 calculations. Coupling constants for methine protons in the (4*R*,5*R*)-4,5-bis(alkylcarbamoyl)-1,3-dioxolanes were predicted by using the empirical generalization of the Karplus equation,[30] where the calculated values were found to span from 0 to 10.2 Hz for the H-C4-C5-H torsion angle ranging from 0 to 180°. Values of 5.6 and 5.9 Hz were obtained for torsion angles of 124.2° and 126.0°, which are those corresponding to the minimum energy conformers at P=162° and 342° respectively. The averaged coupling constant is in excellent agreement with the experimental value (5.9 Hz) and correlates well with the fact that the two preferred envelope conformations are equivalent. Similar results have been recently reported[31] for a rigid 4,5-bis(carbamoyl)-1,3-dioxolane substituted with a phenyl group in the annular C2. The ^{1}H-NMR observed coupling constant and the X-ray estimated H-C4-C5-H angle for this compound were 6.2 Hz and 123° respectively . On the other hand, the Karplus relationship for the $^3J_{CH}$ in ^{13}C-O-C-^{1}H segments developed for the study of conformations in oligosaccharides[32] has been used for the estimation of C2-O3-C4-H and C2-O1-C5-H dihedral angles. Since the rate of internal pseudorotation in the ring between the two most stable conformers is fast on the NMR time-scale, the hypothetical averaged coupling constant for these two conformations (142.3° and 97.4°) should be 2.67 Hz, the upper and lower values being 4.5 and 0.7 Hz respectively. This value turns to be very close to the experimental value of 2.45 Hz. Thus, the conformation of the 1,3-dioxolane ring in these model compounds can be interpreted in terms of a rapid equilibrium between the two equivalent envelope conformations. On the other hand, the ^{1}H-^{1}H and ^{1}H-^{13}C coupling constants predicted for the two twist conformations were 1.2 Hz and 5.3 Hz respectively, which are in disagreement with our experimental data.

In order to ensure that the puckering preferences of the ring are not significantly affected by the length of the alkyl chain in the substituents, the conformational behavior of **4** was investigated. The analysis was limited to those forms with P= 72°, 162°, 252° and 342°. Results were parallel to those obtained in the analysis of **3** with the lowest energy structures being those with P=162° and 342°; these forms are 4.0 kcal/mol preferred over the twist forms.

The conformational preferences displayed by **2**, **3** and **4** may be explained in terms of the so-called *gauche* effect,[33] which is the tendency of the O-C-C-O and O=C-C-O sequences to prefer *gauche* over *trans* or *cis* conformations. The stereoelectronic *gauche* effect is known to be common to a wide assortment of compounds like polyoxides,[34] carbohydrates[35] and furanose derivatives.[4] The averaged value of the O=C-C-O dihedral angles for the two lowest energy conformers of compounds **3** and **4**, *i.e.* those with P=162° and 342°, is ≈ 124°. In these conformers, the two O=C-C-O dihedral angles adopt a *gauche* orientation, while the ring dihedral angle O-C-C-O has a *cis* conformation. According to this, the favourable bond-antibond interactions are emphasized in the former sequence.[36] On the contrary, in conformers with P=72° and 252°, the *gauche* conformation is adopted by the O-C-C-O sequence while the two O=C-C-O angles are arranged in *trans*. In view of this, the higher stability of conformers with P=162° and 342° may be accounted on the basis of *gauche* effects exclusively. It seems that the strong tendency displayed by the O=C-C-O sequence to adopt a *gauche* arrangement is the main factor inducing these dioxolane derivatives to prefer the envelope conformation.

In support of our conclusions, a survey of crystal structures of 1,3-dioxolane derivatives included in the Cambridge Structural Data Base[37] was performed. Unfortunately, no compound of this type with substituents containing amide groups is described. However, five 1,3-dioxolane derivatives[38-41] substituted at the 4 and 5 positions were found, whose conformational features in connection with this work are shown in Table 1. The dihedral angles of three of these compounds[39,40] correspond to envelope forms having phase angles, P, similar to those found in calculations of **3** and **4**. This is particularly remarkable in MOEURK, an *O*-acetyleurekanate in which the substituent at C5 is a methoxycarbonyl group, which is the most similar to the compounds investigated in the present work. In both SOYHOD and SOUHUJ, the dioxolane cycle is fused to a trisubstituted cyclopentane. Conversely, the phase angle for the preferred conformation is near to 72° in BELJAD and OLGOSE, which are compounds containing the dioxolane ring fused to a tetrahydropiran ring. Apparently, it is the conformation of the six-membered ring which largely determines the stability of the whole structure in these cases.

Name[(a)]	τ_0	τ_1	τ_2	τ_3	τ_4	P[(b)]	τ_m[(b)]	**Ref.**
1[(c)]	-22.8	38.5	-38.6	22.9	0.0	162.1	40.6	This work
3[(c)]	-22.9	37.1	-37.2	22.9	0.0	162.0	39.1	This work
4[(c)]	-22.9	37.2	-37.2	22.8	0.0	162.0	39.1	This work
MOEURK[(d)]	33.3	-41.6	32.7	-11.2	-13.6	322.5	41.2	38
BELJAD[(e)]	-34.2	14.4	12.6	-33.2	41.5	72.5	42.0	39
OLGOSE[(f)]	-36.0	15.6	13.4	-35.1	44.1	72.5	44.6	40
SOYHOD[(g)]	-13.5	28.5	-33.2	23.8	-6.1	173.2	33.4	41
SOUHUJ[(h)]	-20.0	26.4	-38.1	24.4	-2.7	162.6	39.9	41

Table 1. Dihedral angles and pseudorotational parameters of the 1,3-dioxolane derivatives in both Energy Minima and Crystals. (a) Named in the text with their code in the Database. (b) P and τ_m denote the phase angle and the puckering amplitude respectively, which were determined using equations 1 and 2. (c) Only the lowest-energy conformations of **1**, **3** and **4** with P around 162° are listed. Conformers with P around 342° have the same values for all the dihedral angles (±0.5°) but with the sign inverted. Dihedral angles τ_2 and τ_3 were kept fixed during the optimization procedure. (d) Metil *O*-acetyleurekanate. (e) and (f) 1,3-dioxolane rings fused to a ciclopentane. (g) and (h) 1,3-dioxolane rings fused to a tetrahydropiran ring.

At this stage, the influence of the ring puckering on the spatial orientation of the substituents was evaluated by analyzing the conformational preferences of the dihedral angles N-(C=O)-C4-C5 and N-(C=O)-C5-C4, referred as χ_1 and χ_1'. In a first step, the continuous variation of χ_1 and χ_1', independently considered, was examined throughout the whole pseudorotational wheel of compound **3**. As shown in *Figure 7a*, a wide range of values is allowed for both angles indicating that the energy barriers implied in the rotation of (C=O)-C4 and (C=O)-C5 bonds must be small. Although the two angles are unlike each other throughout the whole pseudorotational movement, both approach the *gauche* conformation at P=162° and 342°, which are the phase angles for the two energy minima of the structure (see *Figure 5*).

In a second step, the energy of compound **3** was computed as a function of χ_1 and χ_1'. This analysis was confined to discrete χ_1 values spaced at 30° intervals within the range 0-360° while the conformation of the ring was fixed at the energy minimum corresponding to P=162°. Two cases were considered: *i)* $\chi_1 = \chi_1'$ and *ii)* $\chi_1 = -\chi_1'$. The energy profiles resulting for both cases are compared in *Figure 7b*, which clearly shows that conformations for case *i)* are more stable at any value of χ. Two minima at χ_1=90° and χ_1=-90°, the latter unfavoured in about 3.5 kcal/mol with respect to the former, were found in both cases. These results reveal that the preferred arrangement around the (C=O)-C bond is not far from the ideal *gauche* conformation.

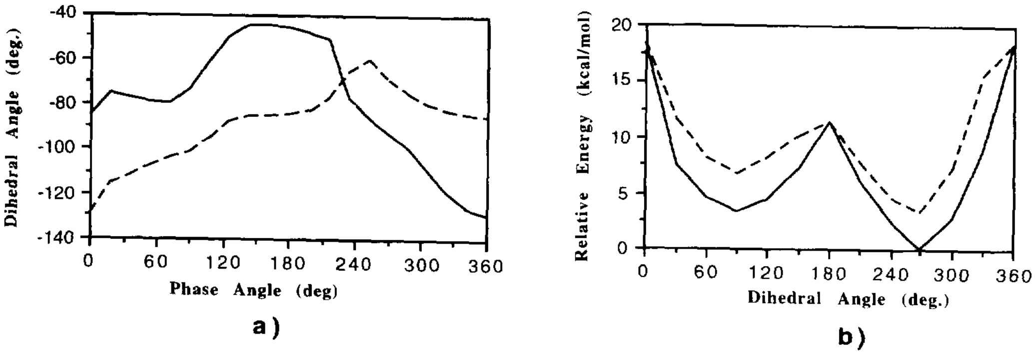


Figure 7. Effect of the ring puckering on the conformation of the attached groups: (a) Representation of the variation of the χ_1 (solid line) and χ_1' (broken line) angles during the pseudorotational movement of **3**; (b) Representation of the variation of the energy relative to the lowest energy conformation of **3** during the rotation around the (C=O)-C bond. The following constraints were applied $\chi_1=\chi_1$' (solid line) and $\chi_1=-\chi_1$' (broken line).

In summary, it can be concluded from this study that the nature of the alkyl chains attached to the carbamoyl groups at the **4** and **5** positions in 1,3-dioxolane in *R,R* configuration, does not modify the intrinsic conformational preferences of the cycle. On the contrary, the influence of the cycle on the spatial orientation of the substituents appears to be determinant. Furthermore, the dihedral angle (C=O)-C4-C5-(C=O) in the low energy conformers of **3** and **4**, *i.e.* those at P=162° and 342°, is -122° and -129° respectively. In aliphatic polyamides, the polymethylene segments connecting the amide groups usually adopt a fully extended conformation[42] with all the backbone dihedral angles taking values near to 180°. Our results lead to anticipate that a dioxolane ring inserted in a polyamide chain will induce a change in the backbone dihedrals of approximately 60°. Such a change would result in an unusual structure characterized by a slight kink at every repeating unit of the polymer chain.

EXPERIMENTAL

Synthesis and spectroscopy

Compound **2** was obtained from bis(pentachlorophenyl) 2,3-*O*-methylene-L-tartrate[13] by reaction with dodecylamine in excess. The crude product was purified by repeated crystallization. The FT-IR spectra were recorded in $CHCl_3$ solution on a Perkin-Elmer 2000 apparatus at room temperature. Sixty four scans at a resolution of 4 cm^{-1} were collected and signals averaged for each concentration. ^{1}H-NMR spectra were recorded at room temperature on a Bruker AMX 300 spectrometer, in $CDCl_3$ solution using $Si(CH_3)_4$ as internal reference. The carrier frequency was 300.13 MHz and the spectral width was 4132 Hz. The number of transients was 1280 and the number of data points was 32 K. The angle was 90° (9.5 μs). A sample concentration of 1% w/v was used at different temperatures (from 253 K to 323 K in increments of 10 K). 75.5 MHz ^{13}C-NMR spectra were obtained without proton decoupling at the same concentration . The number of transients was 94,000 and the number of data points was 32 K. The spectra were acquired with a flip angle of 90° (4 μs) and were processed without exponential multiplication (LB=0).

Computational Procedure

An accurate description of the conformations of the 1,3-dioxolane ring would need five torsion angles named τ_0, τ_1, τ_2, τ_3 and τ_4, corresponding to the following dihedral angles: τ_0=<C4-C5-O1-C2; τ_1=<C5-O1-C2-O3; τ_2=<O1-C2-O3-C4; τ_3= <C2-O3-C4-C4; and τ_4=<O3-C4-C5-O1. The pseudorotational model was used to describe the ring conformation and the ring movement was followed by the variation of the phase angle from 0° to 360°. Rotation around the (C=O)-C bond was represented by the dihedral angles N-(C=O)-C4-C5 and N-(C=O)-C5-C4, named χ_1 and χ_1' respectively.

Calculations at both ab initio MP2/6-31G(d) and semiempirical AM1 levels were performed for compound **1**. The molecular geometries were optimized at the HF/6-31G(d) level in ab initio calculations. The semiempirical method AM1 was used to carry out the calculations for **3** and **4**. The positions of the energy minima were located with a gradient method. A molecular mechanics correction was applied to the amide bond in the geometry optimizations by using the MMOK option.

Ab initio calculations were performed using Gaussian-92.[43] Semiempirical calculations were performed with the MOPAC program.[44] All calculations were performed on the IBM 3090/600 of the CEntre de Supercomputació de CAtalunya (CESCA) and on a workstation RI-4000 at our laboratory.

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