A New Systematization of the Conformational Behavior of Seven-Membered Rings. Isoclinal Anomeric and Related Orientations[1]

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The chair and twist-chair conformations of seven-membered rings are classified as a function of the signs of their endocyclic torsion angles. The conformational analysis (MM3) of the methoxy- and methyloxepanes **1**−**6** used as patterns allows the study and classification of the different types of hydrogen orientation in the seven-membered saturated heterocycles. General principles are established, allowing the prediction of the stability of the different twist-chair conformations as a function of the substituent type, its position in the ring, and the type of hydrogen atom that has been substituted. These results are extended to the 1,4-dioxepane derivatives **7**−**13** and are compared with experimental data.

Introduction

Conformational analysis of six-membered rings has progressed spectacularly in the last 30 years,[2] and in consequence, really complex processes such as the anomeric[3] and gauche[4] effects are now known. In six-membered rings, the conformational study is restricted to chair conformations because the twist-boat forms have higher energies.

The more flexible seven-membered rings occur in complex pseudorotational equilibria among several conformations. The absence of significant pseudorotational barriers and the existence of conformations of similar energy make its study very difficult by means of experimental techniques. Theoretical methods, especially molecular mechanics,[5] have proved to be powerful tools. Thus, several force fields have been used to study cycloheptane,[6] oxepane,[7] thiepane,[8] perhydroazepine,[9] 1,3-dioxepane,[10] 1,4-dioxepane,[11] and 1,4-oxathiepane.[8]

The introduction of a double bond or a condensed benzene ring produces the necessary rigidity in the ring in order to freeze the conformational equilibria at a low temperature. Dynamic nuclear magnetic resonance becomes the most important tool for studying the conformational behavior of such systems. Several 4,7-dihydro-2*H*-1,3-dioxepine,[12] benzooxepines,[13−15] or benzodioxepines[16−19] derivatives have been studied by means of this technique. They show preference for a chair or a twist-boat conformation, depending on the heterocycle at issue, and the orientation, nature, and number of substituents.

The anomeric effect[3] can be defined as the preference for a gauche conformation of the dihedral angles centered in the C−X−C−Y−C fragment. It is responsible for the axial orientation of electronegative C-2 substituents in six-membered heterocycles. This effect has been explained via electrostatic interactions[20−23] and molecular orbital interactions,[24−26] but the discussion over which

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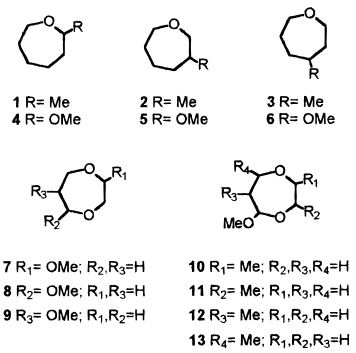
cause prevails still continues. In seven-membered rings the anomeric effect can stabilize conformations different from the ones preferred by the heterocyclic system and even produce a change in the ring conformation preference.[14,27]

The conformational preference of the X−C−C−Y moiety by a synclinal orientation is attributed to the gauche effect.[4] This effect can be attractive, repulsive, or negligible depending on the nature of the atoms X and Y,[28] and its origin has been attributed to interactions between bonding and nonbonding oribitals.[29] The gauche effect is responsible for the greatest stability of the gauche conformation of 1,2-dimethoxyethane[30] and polyoxyethylene.[31] Because of their greater flexibility, seven-membered rings are very suitable substrates for the study of this conformational effect and the interactions that take place between orbitals. Thus, for instance, in 3-substituted 1-benzooxepines[13] the gauche effect is attractive for the atom pairs O/O and O/F.

The consequences of the anomeric effect and the gauche effect in seven-membered heterocycles have been studied[32,33] but not systematized. The relationship between the spatial orientation of the hydrogen atom being substituted, the nature of the substituent, and the stability of the conformation of the ring is not as well-known as in six-membered rings. The systematization of this relationship would allow the establishment of general principles related to the conformational behavior of saturated seven-membered heterocycles.

The aim of this paper is to establish general principles that permit the systematization of the conformational behavior of seven-membered rings, and oxygenated seven-membered rings have been taken as patterns. First of all, the classification of hydrogen atoms in oxepane is addressed, and then the theoretical study of the monosubstituted oxepanes **1**−**6** is carried out by means of



molecular mechanics. The theoretical conformational behavior of such compounds allows the establishment of principles with a predictive nature, and these are extended to 1,4-dioxepane derivatives. Finally, the results obtained are compared with those reported for molecules **7**−**9** and with the new molecules **10**−**13**.

Nomenclature of Conformations in Seven-Membered Rings. Several methods have been described for characterizing the symmetrical conformations of cycloalkanes, and they can be applied to heterocyclic systems with certain restrictions. The first one is attributed to Hendrickson[34] and represents the axis or symmetry plane as a horizontal line and the signs of the endocyclic torsion angles above and beneath it. This type of nomenclature allows the chair (**C**), twist-chair (**TC**), boat (**B**), and twist-boat (**TB**) conformations and their inverted ones to be easily distinguished, but it is not very useful when several conformations of the same type need to be distinguished.

Another more recent notation is attributed to Díez et al.[35] who denote the previous conformations by means of the symbols **C**, **TC**, **B**, and **TB**, followed by the number of the atom located on the axis or symmetry plane of the ring between brackets. Thus, the notation **C(1)** shows a chair conformation in which the symmetry plane contains the atom 1 of the ring and bisects the C_4-C_5 bond. The notation **C′(1)** is used for the inverted chair conformation of **C(1)**.

A third type of notation, attributed to Foces-Foces et al.,[36] takes as a reference the bond bisected by the element of symmetry instead of the atom located on it. Conformations are named by adding a superscript on the right-hand side showing the endocyclic torsion angle (named as τ_0, τ_1, ..., τ_6) bisected by the element of symmetry, and as subscript the sign of the first torsion angle of the ring. Thus, $\mathbf{C}_{-}^{1}$ indicates a chair conformation in which the τ_0 torsion angle is negative and with a symmetry plane bisecting the C_2-C_3 bond, and the notation $\mathbf{C}_{+}^{1'}$ shows the inverted chair conformation of the previous one.

The problem with these last two notations is that they do not show prompt information on the signs of endocyclic torsion angles, which, from a practical point of view, allow a more rapid identification of the conformation under study. Unlike Hendrickson's notation, they are more complete, allowing the diverse conformations of the same type to be distinguished.

We have previously characterized[7−9,11,27] the conformations of several seven-membered heterocyclic systems, by means of the signs of the endocyclic torsion angles of the different chair and twist-chair conformations, naming them **C1**, **TC1**, ..., **C14**, **TC14**. Figure 1 represents the notation used and the equivalences with Díez and Foces-Foces' notations for the oxepane ring. It is necessary to point out that the majority of the conformations do not show any symmetry due to the presence of the heteroatom. This problem has been solved with the consideration of the existence of a symmetry pseudoaxis or pseudoplane (symmetry elements that do exist in cycloheptane but do not in oxepane due to the presence of oxygen) with the objective of being able to apply the aforementioned notations. The following are noticed:

(1) **C1** is the chair conformation in which the endocyclic torsion angle ω_{1234} (defined by the $O_1-C_2-C_3-C_4$ atoms)

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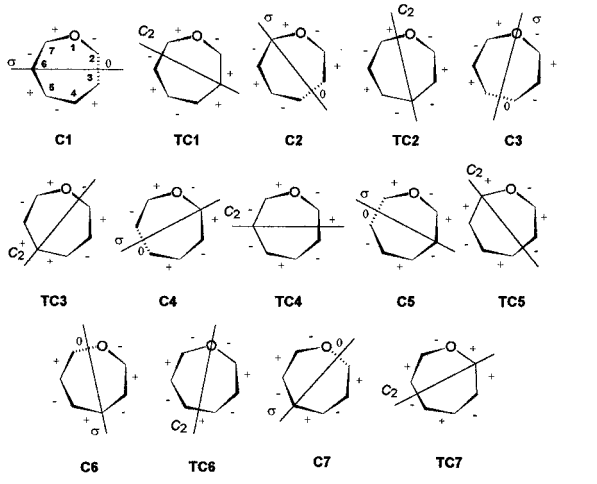

a	C1	TC1	C2	TC2	C3	TC3	C4	TC4	C5	TC5	C6	TC6	C7	TC7
b	C'(6)	TC(3)	C(7)	TC'(4)	C('1)	TC(5)	C(2)	TC'(6)	C'(3)	TC(7)	C(4)	TC'(1)	C'(5)	TC(2)
c	$C_s^{1'}$	TC_2^{5}	C_s^{2}	$TC_s^{6'}$	C_s^{3}	$TC_2^{6'}$	C_s^{4}	$TC_1^{1'}$	C_s^{5}	TC_2^{2}	C_s^{6}	TC_2^{3}	$C_s^{7'}$	TC_s^{4}

Figure 1. Representation of the pseudorotation in the **C/TC** family in oxepane. The notations σ and C_2 denote the symmetry plane (or pseudoplane) and binary axis (or pseudoaxis) for each conformation, respectively. The sign of the endocyclic torsional angles for each conformation is represented as positive (+), negative (−), or zero (0) behind the central bond of the torsional angle. The equivalence between the notation used in this paper and notations defined by Díez[35] and by Foces-Foces[36] is given in lines a, b, and c, respectively.

has a value of 0° and the angle ω_{2345} is positive. The rest of the endocyclic torsion angles alternate the value of their sign.

(2) Pseudorotation takes place in such a way that the pseudoelement of symmetry goes clockwise and, hence, in **C2** the angle ω_{2345} in 0°, while ω_{1234} has a positive value.

(3) In the conformation **TC1**, located between **C1** and **C2**, the torsion angles ω_{1234} and ω_{2345} have positive values. The difference between two **TC** consecutive conformations in the pseudorotational pathway is the sign of just one torsion angle. Thus, it is necessary to change only the sign of the torsion angle ω_{2345} to go from **TC1** to **TC2**; to go from **TC2** to **TC3** the sign of ω_{3456} has to be changed, etc. In addition, each twist-chair differs only in the sign of one torsion angle from the chair which precedes it and from the chair which follows it in the pseudorotational progression.

(4) In the chair conformations, the symmetry plane (or pseudoplane) bisects the central bond of the torsion angles whose value is 0°, while in the twist-chair conformation, the C_2 symmetry axis (or pseudoaxis) goes through the atom located among the two torsion angles with identical sign. Hydrogens linked to this atom have been defined as isoclinal hydrogens by Hendrickson.[37]

(5) For these compounds, 14 **C** and 14 **TC** forms occur. **C8**, **TC8**, ..., **C14**, **TC14** conformations are the inverted forms of the **C1**, **TC1**, ..., **C7**, **TC7** conformations, respectively, and accordingly the values of their endocyclic torsion angles are of opposite sign.

The presence of the heteroatom, besides considerably diminishing the symmetry of the ring, causes distortions in its geometry due to the differences in the C−C and C−O bond lengths and the θ_{C-O-C} and θ_{C-C-C} bond angles, and the torsion angles rarely obtain the value 0°. Thus, those forms in which one torsion angle has a value adequately close to 0° are considered as chair (in general, the value ±8° spans the interval of all the compounds we have studied).

A quantitative description of the conformations of the ring is achieved with its puckering parameters. Such parameters were introduced by Cremer and Pople,[38] and two amplitude parameters (q_2 and q_3) and two phase angles (ϕ_2 and ϕ_3) are necessary to obtain a complete description of a seven-membered ring conformation. Some relationships between the puckering parameters and the type of conformation[39] and between the puckering parameters and the endocyclic torsion angles[35] have been described. Table 1 shows the puckering parameters of the main conformers of oxepane calculated by means of the CONPUCK[40] program. The equivalence between isoenergetic conformations (for which both amplitude parameters are identical) and enantiomeric conformations (with phase angles differing in 180°) are observed.

Orientation of Hydrogen Atoms. In addition to the axial and equatorial orientations, the hydrogens in cycloheptane can be located in an isoclinal position.[37] When an isoclinal hydrogen is substituted in cycloheptane, steric interactions intermediate between those of an axial and those of an equatorial hydrogen are to be expected. For example, the increment in energy due to the introduction of a methyl group in the twist-chair conformation has been calculated for methylcycloheptane:[41] equatorial Me, ±0.01 kcal/mol; axial Me, 1.43−4.88 kcal/mol; isoclinal Me, 0.03 kcal/mol.

The relationships between the orientation of hydrogen atoms and the sign and magnitude of endocyclic torsional angles that flank them[42] are also well-known. In short, viewed clockwise, a hydrogen atom with a β-orientation is axial if the α_1 and α_2 torsion angles have the signs (+,−), (0,+), or (0,−), is equatorial if the signs are (−,+), (+,0), or (−,0), and is isoclinal if the two torsion angles are equal in sign and magnitude. Nevertheless, this criterion is not enough for the classification of the hydrogen atoms of heterocyclic systems.[43] As an example, Table 2 shows the values of the endocyclic α_1 and α_2 torsion angles that flank the β-orientated hydrogen atoms H-2, H-3, and H-4 of oxepane (the three different substitution positions in this compound), calculated by means of the MM3 force field[44] for the 14 twist-chair conformations. According to the previous criterion,[42] the following are observed:

(a) Some conformations occur in which the hydrogen atoms are flanked by angles $\alpha_1 > 0$ and $\alpha_2 < 0$ and, hence, can be classified as axial (see Figure 2). Hydrogens H-2 in twist-chair **TC8**−**TC13**, H-3 in **TC2**−**TC7**, and H-4 in **TC10**−**TC1** belong to this type.

(b) In another series of conformations $\alpha_1 < 0$ and $\alpha_2 > 0$ are achieved. Such is the case of H-2 in the conformation **TC1**−**TC6**, H-3 in **TC9**−**TC14**, and H-4 in the twist-

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Table 1. Puckering Parameters[a] for the TC, B, and TB Conformers of Oxepane Calculated Using the CONPUC[40] Program from the MM3-Optimized Coordinates of Each Conformer

conformer	q_2	q_3	ϕ_2	ϕ_3	conformer	q_2	q_3	ϕ_2	ϕ_3
TC1	0.533	0.657	63.49	322.97	**TC8**	0.533	0.657	243.54	142.99
TC2	0.471	0.692	138.24	348.14	**TC9**	0.471	0.692	318.24	168.14
TC3	0.471	0.692	221.76	11.86	**TC10**	0.471	0.692	41.76	191.86
TC4	0.533	0.657	296.48	37.03	**TC11**	0.533	0.657	116.46	217.01
TC5	0.548	0.655	11.93	61.95	**TC12**	0.548	0.655	191.97	241.97
TC6	0.577	0.647	90.00	90.00	**TC13**	0.577	0.647	270.00	270.00
TC7	0.548	0.655	168.03	118.03	**TC14**	0.548	0.655	348.03	298.03
B1	1.164	0.025	25.19	321.29	**B8**	1.164	0.025	205.19	141.29
TB3	1.151	0.000	90.00	270.00	**TB10**	1.151	0.000	270.00	90.00
B6	1.164	0.025	154.81	218.71	**B13**	1.164	0.025	334.81	38.71

[a] Amplitude parameters (q_2 and q_3) are given in Å and phase angles (ϕ_2 and ϕ_3) in degrees.

Table 2. Intraannular Dihedral Angles Outflanking H-2, H-3, and H-4 and Hydrogen Character in the 14 TC Conformers of Oxepane

	H-2					H-3					H-4				
conformer	α_1[a]	α_2[a]	character	β_1[a]	β_2[a]	α_1[b]	α_2[b]	character	β_1[b]	β_2[b]	α_1[c]	α_2[c]	character	β_1[c]	β_2[c]
TC1	−98.3	42.3	**e**	141.7	161.8	42.3	35.7	$\mathbf{i_g}$	−80.4	158.8	35.7	−82.4	**a**	−87.1	40.6
TC2	−82.8	88.7	**e**	158.7	−153.6	88.7	−37.5	**a**	−34.9	85.8	−37.5	−35.8	**i**	−160.3	86.6
TC3	−65.9	74.4	**e**	174.5	−166.2	74.4	−82.5	**a**	−50.4	42.3	−82.5	35.8	**e**	155.7	158.0
TC4	−80.7	54.5	**e**	159.4	173.9	54.5	−69.1	**a**	−68.6	54.2	−69.1	82.4	**e**	171.0	−157.8
TC5	−100.0	72.6	**e**	141.6	−169.7	72.6	−52.1	**a**	−50.2	70.7	−52.1	68.8	**e**	−174.2	−169.3
TC6	−40.3	89.2	**e**	−161.6	−150.6	89.2	−69.2	**a**	−35.9	55.9	−69.2	50.6	**e**	168.8	172.7
TC7	52.3	32.9	$\mathbf{i_a}$	−71.7	156.4	32.9	−83.3	**a**	−90.6	40.5	−83.3	68.8	**e**	165.8	−171.2
TC8	98.3	−42.3	**a**	−25.8	81.9	−42.3	−35.7	$\mathbf{i_f}$	−164.8	86.5	−35.7	82.4	**e**	−158.1	−155.7
TC9	82.8	−88.7	**a**	−42.5	36.1	−88.7	37.5	**e**	149.7	159.5	37.5	35.8	**i**	−85.0	158.7
TC10	65.9	−74.4	**a**	−59.4	49.8	−74.4	82.5	**e**	165.9	−157.9	82.5	−35.8	**a**	−40.8	87.3
TC11	80.7	−54.5	**a**	−44.0	70.0	−54.5	69.1	**e**	−176.9	−168.9	69.1	−82.4	**a**	−55.1	41.9
TC12	100.0	−72.6	**a**	−24.5	51.5	−72.6	52.1	**e**	165.6	174.0	52.1	−68.8	**a**	−70.7	54.1
TC13	40.3	−89.2	**a**	−84.2	34.8	−89.2	69.2	**e**	151.7	−171.4	69.2	−50.6	**a**	−53.5	72.1
TC14	−52.3	−32.9	$\mathbf{i_f}$	173.4	−87.3	−32.9	83.3	**e**	−154.9	−155.1	83.3	−68.8	**a**	−40.8	55.2

[a] $\alpha_1 = \omega_{3217}$, $\alpha_2 = \omega_{1234}$, $\beta_1 = \omega_{H217}$ (H−C−O−C dihedral angle), $\beta_2 = \omega_{H234}$ (H−C−C−C dihedral angle). [b] $\alpha_1 = \omega_{1234}$, $\alpha_2 = \omega_{2345}$, $\beta_1 = \omega_{H321}$ (H−C−C−O dihedral angle), $\beta_2 = \omega_{H345}$ (H−C−C−C dihedral angle). [c] $\alpha_1 = \omega_{2345}$, $\alpha_2 = \omega_{3456}$, $\beta_1 = \omega_{H432}$ (H−C−C−C dihedral angle), $\beta_2 = \omega_{H456}$ (H−C−C−C dihedral angle).

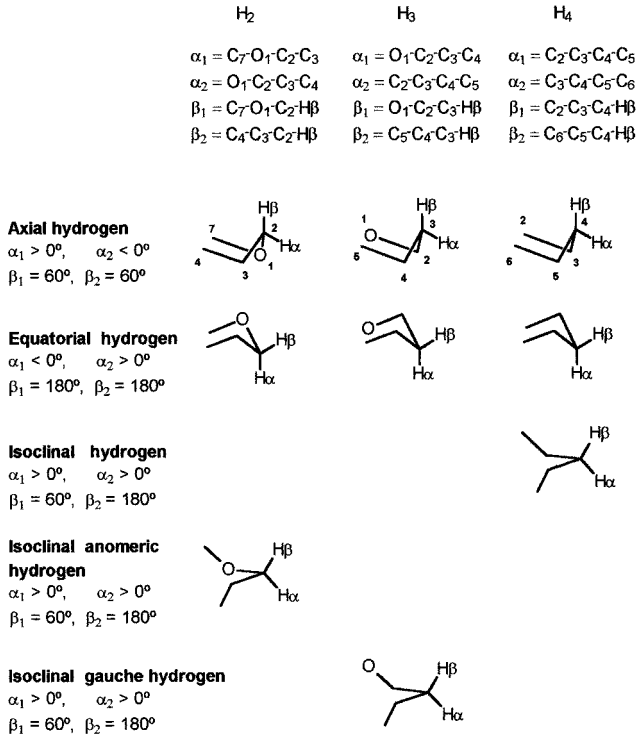


Figure 2. Hydrogen character of H-2, H-3, and H-4 hydrogen atoms of oxepane, defined as a function of both α and β angle types.

chairs **TC3**−**TC8** where such hydrogen atoms have an equatorial character.

(c) Finally, in some conformations the α_1 and α_2 torsion angles are of equal sign but different magnitude, and therefore, such hydrogen atoms cannot be considered as strictly isoclinal as Hendrickson proposes.[37] The reason for the irregularity in the magnitude of torsion angles lies in the strain produced by the oxygen atom. Should this irregularity be the only difference with regard to an isoclinal hydrogen, such hydrogen atoms could be considered as isoclinal. Nevertheless, the two geminal hydrogens of these conformations are not equivalent, since the substitution of each one leads to opposite results in the stabilization or destabilization of the twist-chair. It seems necessary to look for more general principles that allow the description of the hydrogen atom orientation in seven-membered heterocycles.

Computational Methodology. The conformational analysis has been carried out by means of Allinger's MM3 force field.[44] The MM3(92)[45] program includes the parametrization for a wide range of organic compounds. In the parametrization for alcohols and ethers,[46] special attention has been paid to the gauche and anomeric effect. The structures and relative energies of the different conformers of compounds like dimethoxymethane, 1,3-dioxolane, 1,3,5,7-tetraoxocane, and 2-methoxytetrahydropyrane, in which the anomeric effect plays an important role, can be adequately reproduced with this force field. Furthermore, some compounds in which there exists a O−C−C−O moiety, like 1,2-dimethoxyethane, 1,2-dimethoxypropane, and 1,2-dimethoxy-2-methylpropane, have been used to test the suitability of this force field in compounds affected by gauche effect.

(45) The MM3(92) program is available from the Technical Utilization Corporation, Inc., 235 Glen Village Court, Powell, OH 43065.

(46) Allinger, N. L.; Rahman, M.; Lii, J. H. *J. Am. Chem. Soc.* **1990**, *112*, 8293.

4: A=O1, B= C3 **7**: A=C3, B= O1 **10**: A=C6, B= O4
5: A=C2, B=C4 **8**: A=C6, B=O4 **11**: A=C6, B=O4
6: A=C3, B=C5 **9**: A=C5, B=C7 **12**: A=C6, B=O4
13: A=C6, B=O4

Figure 3. C−OMe rotamers defined as a function of the torsion angle ω_{12OMe} for **4**, ω_{23OMe} for **5**, ω_{34OMe} for **6**, ω_{32OMe} for **7**, ω_{45OMe} for **8** and **10**−**13**, and ω_{56OMe} for **9**.

The oxepane **TC** conformations previously reported[7] are used as starting points, and the β-oriented[47] hydrogens of C-2, C-3, and C-4 atoms of the ring have been substituted to obtain the **TC** conformations of compounds **1**−**6**. The rotamers due to the methoxy group have been considered and named as **anti**, **g(+)**, and **g(−)** according to the value of the ω_{12OMe}, ω_{23OMe}, and ω_{34OMe} torsion angles in compounds **4**, **5**, and **6**, respectively (Figure 3).

Oxepane shows a **B/TB** family in which the lowest energy boat form is only 2.6 kcal/mol[7] higher in energy than the most stable twist-chair (**TC5**, **TC7**, **TC12**, and **TC14**) conformations. Due to this small energy difference, it is possible that boat or twist-boat conformations could become more stable than chair or twist-chair conformations with the appropriate substitution. Calculations carried out on this pseudorotational family for compounds **1**−**6** show that such types of conformations do not make an important contribution to the description of the conformational properties of these molecules, since they have higher energies than those of the twist-chair conformations. This fact seems to be due to the following two factors: (i) In the boat or twist-boat conformations, the steric interactions appearing between the substituents and the rest of the ring atoms are superior to those of twist-chair conformations, owing to the fact that in a boat form the ring is folded more. (ii) The number of twist-chair conformations is sufficiently large to accommodate the substituent in an appropriate position so that the energy of one of them will be very inferior to that of any boat or twist-boat conformations. For this reason, the following discussion is based only on twist-chair conformations. Nevertheless, the results found for all the conformations, including the boat and twist-boat forms, are collected in the Supporting Information of this paper.

We have previously reported[27] the conformational behavior of compounds **7**−**9** using Allinger's MM2 force field.[48] Although it is a different force field, its parametrization for alcohols and ethers[49] and the corrections made for the anomeric effect[50] lead to good results for these types of compounds. Conformational analysis of methoxy-1,4-dioxepanes was carried out by substituting the hydrogen atoms H-2, H-5, and H-6′ (equatorial in the conformation **TC1**) in 1,4-dioxepane[11] by the corresponding OMe group. The rotamers due to the OMe group were named as **anti**, **g(+)**, and **g(−)** according to the values of the torsional angles ω_{32OMe}, ω_{65OMe}, and ω_{56OMe} in compounds **7**, **8**, and **9**, respectively (Figure 3). The conformers found for each compound have been recalculated using the MM3 force field, and here we present the results obtained.

Substitution of a suitable hydrogen for a methyl group in the 5-methoxy-1,4-oxepane **8** allows the generation of the different **TC** conformations of each *cis*/*trans* isomer of compounds **10**−**13**. As in oxepane, the **B/TB** manifold of 1,4-dioxepane conformations does not seem to be important in the conformational behavior of their derivatives due to the higher energies of this type of conformation in relation to **TC** conformers.

Methoxy- and Methyloxepanes: Classification of the Hydrogen Atoms in a Seven-Membered Heterocycle. Oxepane derivatives **1**−**6** have been taken as patterns in order to classify the several orientations of a hydrogen in a heptagonal heterocycle. In addition to the endocyclic α_1 and α_2 angles, Table 2 shows the β_1 and β_2 torsion angles formed by hydrogen atoms, the carbon to which they are linked, and the two adjacent atoms of the ring (Figure 2). In cyclohexane, both β angles have a value of 180° for the equatorial hydrogens and 60° for the axial ones. In cycloheptane, the two angles come closer to 180° and 60° for the equatorial and axial hydrogens, respectively. When a hydrogen is isoclinal, one of the β angles comes near to 180° and the other one to 60°. This criterion can also be used to classify the hydrogen atoms, since it does not contradict that of Bucourt.[42] Nevertheless, the nature of such β angles is important in determining the effect that the substitution of a hydrogen atom has on ring conformation. In this respect, β angles define the character of a hydrogen atom with greater precision, since some predictions can be made on what will occur to the ring when a hydrogen is substituted. According to this criterion, the various types of oxepane hydrogens are as follows:

(a) Axial Hydrogen (a) (Figure 2). $\alpha_1 > 0$, $\alpha_2 < 0$ is achieved in them, and the angles β_1 and β_2 also have absolute values ranging from 40° to 80° in most cases. In all cases the substitution of an axial hydrogen leads to an important increase of the steric interaction with the ring. Table 3 shows the relative energies and the conformational populations of oxepanes **1**−**6**, which have been arranged according to the four isoenergetic groups of oxepane.[7]

In the three methyl derivatives **1**−**3**, the introduction of a methyl group destabilizes the twist-chair conformations. The twist-chair conformations **TC8** and **TC13** in compound **1** and **TC6** in compound **2** have not been found, probably due to strong steric interactions between the 2-Me and 3-Me groups and the ring atoms. Such conformations pseudorotate to the most stable ones: **TC7** and **TC14** in compound **1** and **TC7** in compound **2**.

The magnitude of the steric interactions depends on the substitution position. The difference between the relative energies of the twist-chair conformations of the substituted compounds and those of oxepane (ΔE, conformational steric energy of the substituent; i.e. ΔE = rel E of **TC3** in **1** − rel E of **TC3** in oxepane, Table 3) has been worked out to obtain a measure of the influence of the methyl group on conformational energy. Strictly speaking, oxepane and its derivatives have independent relative energy ranges, and so the ΔE value has no quantitative meaning. Nevertheless, there is considerable similarity between the puckering parameters of the diverse conformations of compounds **1**−**6** and those of the **TC** conformations of oxepane. In view of this fact, we think that, to a certain extent, ΔE shows the conforma-

(47) The β face of oxepane has been considered as that which contains the equatorial hydrogen of C-2 in the **TC1** conformation. Once determined, such a criterion has been followed in the substitution of the hydrogen atoms H-2, H-3, and H-4 in the different conformations.

(48) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127.
(49) Allinger, N. L.; Chang, S. H. M.; Glaser, D. H.; Honig, D. *Isr. J. Chem.* **1980**, *20*, 51.
(50) Norskov-Lauritsen, L.; Allinger, N. L. *J. Comput. Chem.* **1984**, *5*, 326.

Table 3. Relative Energies (rel *E*, kcal/mol), Corrected Energies (Δ*E*, kcal/mol), and Conformational Populations (pop., %) Calculated for Oxepane, Methyloxepanes 1−3, and Methoxyoxepanes 4−6

		oxepane			**1**			**4**				**2**			**5**				**3**			**6**		
conformer	rotamer	rel *E*	pop.	H-2	rel *E*	pop.	Δ*E*	rel *E*	pop.	Δ*E*	H-3	rel *E*	pop.	Δ*E*	rel *E*	pop.	Δ*E*	H-4	rel *E*	pop.	Δ*E*	rel *E*	pop.	Δ*E*
TC5	**anti**	0.00	15.4	**e**	0.00	44.8	0.00	3.45	0.2	3.45	**a**	1.17	5.3	1.17	1.78	0.7	1.78	**e**	0.00	37.3	0.00	0.47	7.2	0.47
	g(+)							3.06	0.3	3.06					4.87	0.0	4.87					2.35	0.3	2.35
	g(−)							0.45	26.7	0.45					1.44	1.2	1.44					0.26	10.2	0.26
TC7	**anti**	0.00	15.4	**i_a**	1.42	4.1	1.42	2.83	0.5	2.83	**a**	2.60	0.5	2.60	0.01	13.2	0.01	**e**	0.18	27.5	0.18	0.00	15.8	0.00
	g(+)							4.57	0.0	4.57												2.00	0.5	2.00
	g(−)							0.00	57.1	0.00					0.48	5.9	0.48					0.03	15.1	0.03
TC12	**anti**	0.00	15.4	**a**	4.62	0.0	4.62	6.93	0.0	6.93	**e**	0.00	38.3	0.00	0.00	13.4	0.00	**a**	2.09	1.1	2.09	0.54	6.3	0.54
	g(+)							12.14	0.0	12.14					2.42	0.2	2.42					8.14	0.0	8.14
	g(−)							4.27	0.0	4.27					0.27	8.4	0.27					0.96	3.1	0.96
TC14	**anti**	0.00	15.4	**i_f**	0.75	12.6	0.75				**e**	0.40	19.4	0.40	0.61	4.8	0.61	**a**	1.64	2.3	1.64	1.51	1.2	1.51
	g(+)							4.98	0.0	4.98					2.74	0.1	2.74					8.31	0.0	8.31
	g(−)							1.90	2.3	1.90					0.00	13.4	0.00					1.42	1.4	1.42
TC2	**anti**	0.70	4.7	**e**	0.91	9.6	0.21	4.71	0.0	4.01	**a**	2.68	0.4	1.98				**i**	1.35	3.6	0.65	1.69	0.9	0.99
	g(+)							4.43	0.0	3.73												3.93	0.0	3.23
	g(−)							1.85	2.5	1.15					2.99	0.1	2.29					1.10	2.5	0.40
TC3	**anti**	0.70	4.7	**e**	0.92	9.4	0.22				**a**	2.50	0.6	1.80	2.10	0.4	1.40	**e**	1.07	6.1	0.37	0.87	3.7	0.17
	g(+)							4.75	0.0	4.05												3.61	0.0	2.91
	g(−)							2.37	1.1	1.67					2.23	0.3	1.53					1.45	1.3	0.75
TC9	**anti**	0.70	4.7	**a**	4.67	0.0	3.97	6.13	0.0	5.43	**e**	1.03	6.7	0.33	0.49	5.8	−0.21	**i**	1.38	3.6	0.68	0.70	4.8	0.00
	g(+)							13.02	0.0	12.32					3.38	0.0	2.68					3.92	0.0	3.22
	g(−)							3.36	0.2	2.66					0.90	2.9	0.20					1.33	1.6	0.63
TC10	**anti**	0.70	4.7	**a**	4.19	0.0	3.49	4.98	0.0	4.28	**e**	1.02	6.8	0.32	1.01	2.4	0.31	**a**	3.39	0.1	2.69	2.20	0.4	1.50
	g(+)							10.73	0.0	10.03					2.90	0.1	2.20					3.91	0.0	3.21
	g(−)							2.11	1.6	1.41					1.09	2.1	0.39					1.76	0.8	1.06
TC1	**anti**	0.75	4.4	**e**	1.01	8.2	0.26	4.35	0.0	3.6	**i_g**	1.07	6.3	0.32	0.29	8.2	−0.46	**a**	3.05	0.2	2.30	2.58	0.2	1.83
	g(+)							4.58	0.0	3.83					2.17	0.3	1.42					8.51	0.0	7.76
	g(−)							1.48	4.6	0.73					0.87	3.1	0.12					3.02	0.1	2.27
TC4	**anti**	0.75	4.4	**e**	0.89	9.9	0.14	5.00	0.0	4.25	**a**	2.50	0.5	1.75	1.54	1.0	0.79	**e**	0.86	8.7	0.11	0.94	3.2	0.19
	g(+)							4.97	0.0	4.22					6.43	0.0	5.68					2.70	0.2	1.95
	g(−)							2.06	1.8	1.31					1.98	0.5	1.23					1.03	2.8	0.28
TC8	**anti**	0.75	4.4	**a**							**i_f**	1.34	3.9	0.59	1.26	1.6	0.51	**e**	1.03	6.5	0.28	1.00	2.9	0.25
	g(+)														3.99	0.0	3.24					3.46	0.0	2.71
	g(−)														0.73	3.9	−0.02					0.48	6.9	−0.26
TC11	**anti**	0.75	4.4	**a**	4.97	0.0	4.22				**e**	0.82	9.5	0.07	1.15	1.9	0.40	**a**	2.79	0.3	2.04	1.03	2.8	0.28
	g(+)							11.09	0.0	10.34					3.36	0.0	2.61							
	g(−)							3.26	0.2	2.51					0.98	2.5	0.23					1.30	1.8	0.55
TC6	**anti**	1.58	1.1	**e**	2.12	1.3	0.54				**a**				3.90	0.0	2.32	**e**	1.58	2.6	0.0	1.77	0.8	0.19
	g(+)							5.12	0.0	3.54												4.15	0.0	2.57
	g(−)														3.38	0.0	1.80					2.07	0.5	0.49
TC13	**anti**	1.58	1.1	**a**				5.43	0.0	3.85	**e**	1.81	1.8	0.23	1.74	0.7	0.16	**a**	3.70	0.1	2.12	2.76	0.1	1.18
	g(+)							4.98	0.0	3.40					3.64	0.0	2.06							
	g(−)							2.67	0.6	1.09					1.63	0.8	0.05					2.46	0.2	0.88

tional energy variation due to the substituent and can be helpful in the following discussion.

When ΔE is calculated, an axial 2-Me group introduces a very high destabilization ranging from 3.49 (**TC10**) to 4.62 (**TC12**) kcal/mol. On the other hand, the ΔE value for the axial 3-Me group is less, ranging from 1.17 (**TC5**) to 2.60 (**TC7**) kcal/mol and is intermediate for a 4-Me group, between 1.64 (**TC14**) and 2.69 (**TC10**) kcal/mol. The reason for this difference must be sought in the type of steric interaction which appears. An axial 2-Me group is in a gauche position in relation to the atoms C-4 and C-7, and the interaction with the latter is greater due to the lesser C−O bond length and the lesser C−O−C bond angle. Some H,Me-1,3-syn$_O$diaxial interactions appear (those between both a diaxial H and Me through an oxygen atom) between the methyl group and the β-oriented hydrogen of C-7. An axial 3-Me group gives interactions with C-5 and O-1. The absence of hydrogens in the oxygen atom weakens the interactions. Finally, a 4-Me group shows an intermediate situation: the interaction takes place between the methyl group and two carbon atoms, C-2 and C-6, and does not take place through the heteroatom.

As can be seen, the nature of the β angles determines the magnitude of steric interactions. If one of them is of the H−C−O−C type (2-methyloxepane), the hydrogen substitution produces strong steric interactions; if an angle is of the H−C−C−O type (3-methyloxepane), the steric interactions will be considerably weaker. Finally, in the substitution of a hydrogen in which both β angles are of the H−C−C−C type (4-methyloxepane), the steric interactions are intermediate between the two previous cases.

The introduction of an alkoxy group in the molecule complicates the conformational behavior. This is due to the presence of the O−C−C−O or C−O−C−O−C moieties whose conformational preference is governed by the gauche and the anomeric effects when a methoxy group is located in C-3 and C-2, respectively. If those effects are not present, the steric interactions control the conformational behavior. Such is the case of 4-methoxyoxepane **6**, in which an axial OMe group destabilizes the conformation. The estimated value for ΔE ranges from 0.28 to 1.83 kcal/mol, somewhat less than that of a 4-Me group since the methoxy group leads to less steric interactions.[51] The rotamer **g(+)** always has the greatest energy since the methoxy group bisects the C-3 and C-4 atoms of the ring.

In compound **5**, the gauche effect stabilizes the axial position. Thus, the **TC7anti** conformation has a relative energy of only 0.01 kcal/mol in spite of the methoxy group being axial. It is as important as **TC12** and **TC14**, in which the steric interactions are weaker. The estimated ΔE value ranges from 0.01 (**TC7anti**) to 1.8 (**TC6g(−)**) kcal/mol, which is inferior to that of a 3-Me group, not only because of the lesser steric interactions of a 3-OMe but also for the additional stabilization due to the gauche effect. Again, rotamers **g(+)** are more destabilized because the methoxy group bisects the atoms C-2 and C-4.

The axial position of a 2-OMe group is stabilized by the anomeric effect. The ΔE value ranges between 1.09 (**TC13g(−)**) and 4.27 (**TC12g(−)**) kcal/mol, markedly inferior to the value of the 2-Me group. Such a stabilization reveals the greater importance of the conformations in which the methoxy group is axial when they are compared with the corresponding 2-Me derivative ones. Nevertheless, no conformation in which the methoxy group is axial is important in the conformational equilibrium, in spite of the anomeric effect. This is due, as will be seen later, to another type of spatial orientation in which the methoxy group is favored much more. The exo anomeric effect[52] is responsible for the high energy of **anti** rotamers in which the O_1-C_2-O-Me angle is close to 180°. The high energy of rotamers **g(+)** should again be attributed to the greater steric interactions.

(b) Equatorial Hydrogen (e) (Figure 2). $\alpha_1 < 0$, $\alpha_2 > 0$ is observed for them, and the β_1 and β_2 angles have absolute values greater than 150° in most cases. Thus, the substitution of an equatorial hydrogen for an alkyl group gives rise to quite stable conformations due to the fact that the location of such an alkyl group is almost antiperiplanar in relation to the ring atoms. It can be observed (Table 3) that, in compounds **1**−**3**, the most stable conformation belongs to the group of the twist-chair conformations of lowest energy in the unsubstituted ring: 2-methyloxepane (**1**), **TC5** (rel E = 0.00 kcal/mol, pop. = 44.8%); 3-methyloxepane (**2**), **TC12** (rel E = 0.00 kcal/mol, pop. = 38.3%) and **TC14** (rel E = 0.40 kcal/mol, pop. = 19.4%); and 4-methyloxepane (**3**), **TC5** (rel E = 0.00 kcal/mol, pop. = 37.3%) and **TC7** (rel E = 0.18 kcal/mol, pop. = 27.5%). The ΔE values for equatorial methyl groups in oxepane range between the following: 2-Me 0.00−0.54 kcal/mol, 3-Me 0.00−0.40 kcal/mol, and finally, 4-Me 0.00−0.37 kcal/mol. In general, a greater increment implies a greater deviation of β angles from the value of 180°.

In the methoxy derivatives, the gauche and anomeric effect introduce an additional destabilization when 3-OMe and 2-OMe are located in an equatorial orientation, respectively. The influence of a 4-OMe group over the conformational energy in compound **7** is a consequence of the steric interactions.

Firstly, if the substitution takes place in C-4, the results are similar to those observed in alkyloxepanes since the two heteroatoms are sufficiently separated for conformational effects not to appear. Thus, the most stable conformations of 4-methoxyoxepane (**6**) are the twist-chairs **TC5** and **TC7** in which the methoxy group is equatorial (the sum of the conformational populations of all three rotamers is nearly 50%). Such twist-chair conformations are also the most stable ones in oxepane. An equatorial 4-OMe group leads to an energy change (ΔE) in the ring conformation, which ranges between −0.26 kcal/mol in the conformation **TC8g(−)** and 0.26 kcal/mol for **TC5g(−)**.

Moreover, the most stable conformations of 3-methoxyoxepane (**5**) belong to the more stable ones of oxepane, and in two of them (**TC12anti** and **TC14g(−)**), the methoxy group is equatorial. It seems that the steric interactions are more important when it comes to determining which are the most stable conformations. The introduction of an equatorial 3-OMe group leads to a

(51) The free-energy differences between equatorial and axial methyl and methoxy groups in cyclohexane are respectively 1.74 kcal/mol (Booth, H.; Everett, J. *J. Chem. Soc., Chem. Commun.* **1976**, 278) and 0.75 kcal/mol (Schneider, H. J.; Hoppen, V. *Tetrahedron Lett.* **1974**, 579).

(52) (a) Lemieux, R. V.; Pavia, A. A.; Martin, J. C.; Watanabe, K. H.; *Can. J. Chem.* **1969**, *47*, 427. (b) Pérez, S.; Marchessault, R. H. *Carbohydr. Res.* **1978**, *65*, 114. (c) Booth, H.; Khedahair, K. A.; Readshow, S. A. *Tetrahedron* **1987**, *43*, 4699.

conformational energy change (ΔE) ranging between −0.21 kcal/mol in **TC9anti** and 0.31 kcal/mol in **TC10anti**.

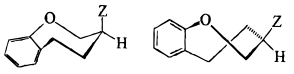
Finally, the introduction of an electronegative group in C-2 leads to an anomeric effect in the molecule according to the C−O−C−O−C moiety. Related to ring stability, in all the conformations in which the methoxy groups is equatorial, a remarkable increment in energy is observed with regard to the methyl derivatives. This is caused by the value close to 180° for the $C_7-O_1-C_2-$OMe angle. The energy change (ΔE) introduced in the ring by an equatorial 2-OMe group is between 0.45 kcal/mol for the conformation **TC5g(−)** and 1.67 kcal/mol for the conformation **TC3g(−)**. The relatively high stability of the conformation **TC5g(−)** must be attributed to a stabilization by exo anomeric effect.

(c) Isoclinal Hydrogen (i) (Figure 2). Hydrogen on C-4 can be considered as isoclinal when the α_1 and α_2 torsion angles have the same sign, that is, in the conformations **TC2** and **TC9**. The small differences between α_1 and α_2 (less than 2°) are due to the strain caused by oxygen in the ring geometry. Furthermore, β_1 and β_2 angles are both of the same type, one of them having a value close to 180° and the other one to 60°. The two geminal hydrogens[53] are of equal character and are practically equivalent from a conformational point of view. On carrying out the substitution of one of these hydrogens, the ΔE values are 0.63−0.68 kcal/mol for a 4-Me group and 0.0−0.4 kcal/mol for a 4-OMe group. Steric interactions are in both cases intermediate between those corresponding to axial and equatorial substituents.

(d) Gauche Isoclinal Hydrogen (i_g) (Figure 2). As in isoclinal hydrogens, the two intraannular α_1 and α_2 torsion angles have the same sign, although the differences between their values (to the order of 7°) are greater. One of the β angles is antiperiplanar, and the other one is gauche. The difference from isoclinal hydrogens is based on the different nature of the β_1 and β_2 angles. Specifically, β_2 is of the H−C−C−O type while β_2 is of the H−C−C−C type. When the β_1 angle has a value close to 60°, the hydrogen is named $\mathbf{i_g}$. For its geminal one, the β_1 angle has a value close to 180°. The result is that the two geminal hydrogen are not equivalent. Thus, for 3-methyloxepane **2**, an $\mathbf{i_g}$ orientation is found in the conformation **TC1** in which the methyl group is gauche in relation to O-1 and antiperiplanar related to C-5. In conformation **TC8**, the methyl group lies antiperiplanar to O-1 and gauche to C-5. The absence of hydrogen makes the steric interactions smaller with the oxygen atom than with the carbon one, and this is the cause of the difference in stability between the conformations **TC1** and **TC8**. The ΔE value calculated for the substitution by a methyl group of an $\mathbf{i_g}$ hydrogen is 0.32 kcal/mol (**TC1**) while its geminal one is 0.59 kcal/mol (**TC8**). It is observed that the steric interactions caused by a 3-Me group in an $\mathbf{i_g}$ orientation are smaller than those caused by an isoclinal 4-Me group, but these are comparable to the 3-Me group geminal to $\mathbf{i_g}$.

The $\mathbf{i_g}$ orientation is ideal for a 3-OMe substituent since its steric interactions are small and a stabilization by gauche effect takes place. The substitution of the geminal hydrogen to $\mathbf{i_g}$ is disfavored by both a higher steric interaction and a destabilization by gauche effect. It is because of this that **TC1anti** has a conformational population of 8.2% while **TC8anti** is only 1.6% of the pseudorotational equilibrium. In the axial orientation, the 3-OMe group is also stabilized by gauche effect; nevertheless, the higher steric interactions in such an orientation favor $\mathbf{i_g}$ most. However, the stabilization caused by gauche effect is not enough to turn the **TC1anti** conformation into the most stable one, since this twist-chair does not belong to the most stable oxepane group. The ΔE value for a 3-OMe is −0.46 kcal/mol if the orientation is $\mathbf{i_g}$, whereas the ΔE value is 0.51 kcal/mol for the geminal hydrogen. It must be pointed out that the value for the former is markedly smaller than that of an isoclinal 4-OMe group.

The fact that the $\mathbf{i_g}$ orientgation is the most favored one when an attractive gauche effect appears is in accordance with the results reported on 3-substituted 1-benzooxepines. 1-Benzooxepine[13] exists as the chair form **14C**. The preferred conformations of 3-fluoro- and 3-methoxy-1-benzooxepine[13] are chairs in which the substituent is located in an axial orientation (**14Ca**).



14C: Z = H
14Ca: Z = F, OMe
14TB: Z = F, OMe

Nevertheless, for both compounds the twist-boat conformation **14TB** is detected in solution. In the latter the substituent is gauche in relation to the heterocyclic oxygen atom and antiperiplanar with regard to C-5, i.e. it adopts an $\mathbf{i_g}$ orientation. Such a twist-boat conformation is not preferred by the molecule, but the fact that it is detected confirms the previous reasoning.

(e) Anomeric Isoclinal Hydrogen (i_a) (Figure 2). This type of orientation appears in the carbon atom next to an oxygen when both α_1 and α_2 angles have the same sign. The difference in value between the α angles increases, by the order of 20°, due to the greater proximity of the heteroatom. The nature of the β angles is different: β_1 is of the H−C−O−C type, and β_2 is of the H−C−C−C type. All this leads to the greater difference between the isoclinal geminal hydrogens.

Anomeric isoclinal $\mathbf{i_a}$ is the orientation in which the β_1 angle has a value close to 60° and the β_2 angle is near 180°. The steric interactions appearing when this hydrogen is substituted by a methyl group are greater than those appearing when the substitution is made in the geminal hydrogen. Thus, the **TC7** conformation of 2-methyloxepane (**1**) is only 4% of the pseudorotational equilibrium, while **TC14** has a conformational population of 12%. The energy increment due to a 2-Me group is 1.42 kcal/mol for an $\mathbf{i_a}$ hydrogen, very superior to that of an isoclinal orientation. The ΔE value for its geminal hydrogen is 0.75 kcal/mol, comparable to that of an isoclinal 4-Me group or to a 3-Me geminal to $\mathbf{i_g}$.

The introduction of a 2-OMe group causes an anomeric effect in the molecule due to the $C_7-O_1-C_2-$OMe grouping. If 2-OMe adopts an anomeric isoclinal orientation, a stabilization of the conformation takes places due to the fact that the β_1 angle adopts a gauche arrangement (endo anomeric effect). Such a stabilization by anomeric effect is also produced in the axial orientation. Nevertheless, due to the smaller steric interactions in the $\mathbf{i_a}$ orientation, it is the arrangement preferred by a 2-OMe

(53) The α hydrogen atom of C-4 in **TC2** conformation is equivalent to the β atom of C-4 in conformation **TC9**, since both are inverted twist-chair conformations.

Table 4. Spatial Orientation of Hydrogen Atoms in Flexible Cyclic Forms as a Function of the α and β Angles

			β_1			β_2		
spatial orientation	α_1	α_2	HCOC	HCCO	HCCC	HCOC	HCCO	HCCC
equatorial (**e**)	(+)	(−)	**a**	**a**	**a**	**a**	**a**	**a**
axial (**a**)	(−)	(+)	**g**	**g**	**g**	**g**	**g**	**g**
isoclinal (**i**)	(+)	(+)	**g**			**a**		
			a			**g**		
				g			**a**	
				a			**g**	
					g			**a**
					a			**g**
anomeric isoclinal ($\mathbf{i_a}$)	(+)	(+)	**g**				**a**	
			g					**a**
gauche isoclinal ($\mathbf{i_g}$)	(+)	(+)		**g**				**a**
false isoclinal l($\mathbf{i_f}$)	(+)	(+)	**a**				**g**	
			a					**g**
				a				**g**

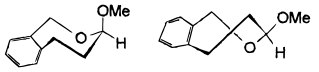
Table 5. MM3 Relative Energies (kcal/mol) and Spatial Orientations[a] of Hydrogen Atoms in All the 14 TC Conformers of 1,4-Dioxepane

		hydrogen atom									
conformer	rel *E*	H-2[b]	H-2′	H-3	H-3′	H-5	H-5′	H-6	H-6′	H-7	H-7′
TC3	0.00	**e**	**a**	**a**	**e**	$\mathbf{i_a}$	$\mathbf{i_f}$	**a**	**e**	**e**	**a**
TC5	0.00	**e**	**a**	**a**	**e**	**a**	**e**	**e**	**a**	$\mathbf{i_f}$	$\mathbf{i_a}$
TC10	0.00	**a**	**e**	**e**	**a**	$\mathbf{i_f}$	$\mathbf{i_a}$	**e**	**a**	**a**	**e**
TC12	0.00	**a**	**e**	**e**	**a**	**e**	**a**	**a**	**e**	$\mathbf{i_a}$	$\mathbf{i_f}$
TC4	1.10	**e**	**a**	**a**	**e**	**a**	**e**	**i**	**i**	**e**	**a**
TC11	1.10	**a**	**e**	**e**	**a**	**e**	**a**	**i**	**i**	**a**	**e**
TC1	2.21	**e**	**a**	$\mathbf{i_f}$	$\mathbf{i_a}$	**e**	**a**	**a**	**e**	**e**	**a**
TC7	2.21	$\mathbf{i_a}$	$\mathbf{i_f}$	**a**	**e**	**a**	**e**	**e**	**a**	**a**	**e**
TC8	2.21	**a**	**e**	$\mathbf{i_a}$	$\mathbf{i_f}$	**a**	**e**	**e**	**a**	**a**	**e**
TC14	2.21	$\mathbf{i_f}$	$\mathbf{i_a}$	**e**	**a**	**e**	**a**	**a**	**e**	**e**	**a**
TC2	1.48	**e**	**a**	**a**	**e**	**e**	**a**	**a**	**e**	**e**	**a**
TC6	1.48	**e**	**a**	**a**	**e**	**a**	**e**	**e**	**a**	**a**	**e**
TC9	1.48	**a**	**e**	**e**	**a**	**a**	**e**	**e**	**a**	**a**	**e**
TC13	1.48	**a**	**e**	**e**	**a**	**e**	**a**	**a**	**e**	**e**	**a**

[a] Spatial orientation has been defined according to the nature and value of the β angle for each hydrogen. [b] H-2 is the β-oriented hydrogen atom bonded to C-2, which is equatorial in the **TC1** conformation.

group, and therefore, the **TC7g(−)** conformation is the most stable one (rel *E*:0.00 kcal/mol, 57% of the conformational population). The relative energy of the conformation **TC14g(−)** is 1.90 kcal/mol due to the lack of stabilization by anomeric effect (the 2-OMe group is $\mathbf{i_f}$-oriented) in spite of the steric interactions being markedly less.

The stabilization of the $\mathbf{i_a}$ arrangement preferred in electronegative groups affected by the anomeric effect agrees with the fact previously described that, in 3-methoxy-2-benzooxepine, the conformation represented by **15TB** is stabilized. In this twist-boat the methoxy group



15Ca **15TB**

is antiperiplanar with regard to C-5 and gauche to C-1, that is, it has an $\mathbf{i_a}$ orientation. The anomeric effect stabilizes the twist-boat conformation in which the steric interactions are smaller than those in the **15Ca** conformation. For these two reasons, the twist-boat conformation acquires some importance in spite of not having been detected in the base ring.

(f) False Isoclinal Hydrogen ($\mathbf{i_f}$). This is the name given to the geminal hydrogens of the $\mathbf{i_g}$ and $\mathbf{i_a}$ ones. In them the two torsion angles α have the same sign, and the β_1 angle, which is of the H−C−C−O or the H−C−O−C type, has a value close to 180°. In general, the steric interactions which appear on substituting an $\mathbf{i_f}$ hydrogen are similar to the ones corresponding to an **i** atom. On introducing an electronegative group, some destabilizing interactions appear. That is why they are not equivalent to their geminal ones and hence the name of false isoclinal hydrogen.

Table 4 shows the criteria discussed for the classification of hydrogen atoms in oxygenated seven-membered heterocycles as a function of the endocyclic α angle signs and the nature and value of β angles. Thus, we consider as axial or equatorial hydrogens those in which both β angles acquire a gauche or antiperiplanar conformation, respectively. Such types of hydrogens are similar to the axial or equatorial ones of a chair conformation in a six-membered ring. The nature of the β angles determines only the magnitude of the steric or steroelectronic effects that appear when they are substituted.

Methoxy-1,4-dioxepanes 7−9. With the objective of checking the previous reasoning on types of hydrogens in seven-membered rings, the conformational behavior of methoxy-1,4-dioxepanes **7**−**9** in the MM3 force field will be analyzed.

In 1,4-dioxepane[11] there exist four isoenergetic twist-chair conformations (**TC3**, **TC5**, **TC10**, and **TC12**) whose conformational populations total a little more than 80% of the pseudorotational equilibrium. In general, the most important conformations of 1,4-dioxepane derivatives correspond to those of the basic ring. Only the appearance of important steric and/or stereoelectronic effects will modify this fact and stabilize other different twist-chair forms. Table 5 summarizes the character of all the 1,4-dioxepane hydrogen atoms in each of the 14 twist-chair conformations, in accordance with the previous

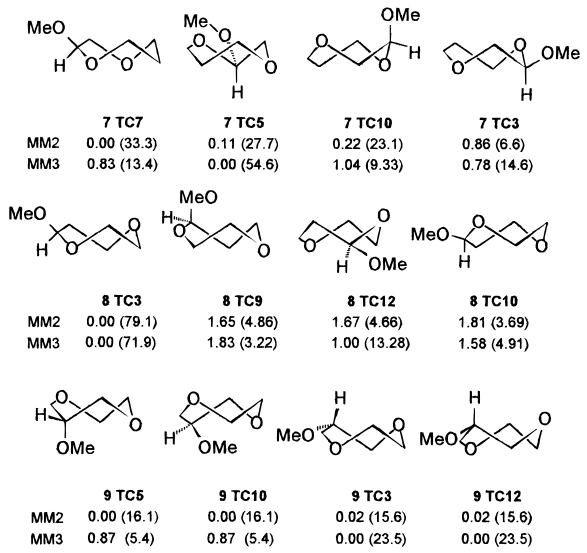


Figure 4. The four most stable conformers calculated for compounds **7**−**9**. MM2[27] and MM3 relative energies (kcal/mol) and conformational populations (in parentheses, %) are shown.

reasoning, together with the relative energies of each twist-chair conformation. Figure 4 shows the four most important conformations of compounds **7**−**9** together with their relative energies and conformational population. The previously reported[27] MM2 results are appended for comparison with those obtained with the MM3 force field (Supporting Information contains Table VII with the MM3 results for all the conformers of these compounds). The most important conformation for 5-methoxy-1,4-dioxepane (**8**), superior to all the others, is **TC3**, whose conformational population is 71.9%. The great importance of this conformation is the consequence of the spatial orientation of the methoxy group, which has substituted a hydrogen of the $\mathbf{i_a}$ type (H-5, Table 5). The remaining conformations are less important, and also their relative energies are dependent on the force field used. The **TC9** conformation, in which the methoxy group is axial (Table 5), acquires some importance in spite of 1.5 kcal/mol being the relative energy of this twist-chair in the 1,4-dioxepane (both force fields are concordant in this value). The anomeric effect has to compensate this energy difference. It has to be pointed out that the **TC10** conformation, with the methoxy group in a $\mathbf{i_f}$ orientation, has a much greater energy. Finally, the importance of the **TC12** conformation with the equatorial methoxy group is due to the small steric interactions and, probably, to a strong stabilization by the exo anomeric effect.

The hydrogen H-2 of 1,4-dioxepane does not acquire an $\mathbf{i_a}$ orientation in any of the more stable twist-chair conformations (Table 5). The $\mathbf{i_a}$ orientation appears in **TC7** which thus becomes the most important conformation of 2-methoxy-1,4-dioxepane (**7**) within the MM2 force field.[27] The anomeric effect compensates for the relative energy of **TC7** in 1,4-dioxepane and produces a change in the ring conformational preference. **TC7** conformation of **7** is not the most stable one within the MM3 force field because **TC7** of 1,4-dioxepane is the most energetic one in this force field (2.21 kcal/mol). Nevertheless, its conformational population is important, the stabilization by anomeric effect being observed. Conformers **TC5** and **TC3** have an equatorial methoxy group, and their importance is due only to the small steric interactions and to a stabilization by exo anomeric effect. Finally, in

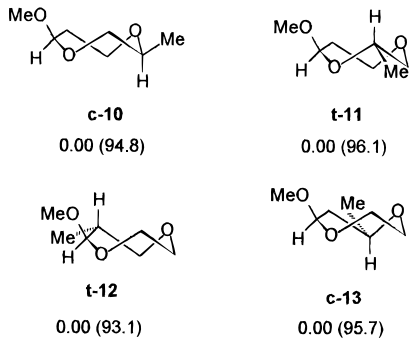


Figure 5. The **TC3** conformation of compounds *c*-**10**, *t*-**11**, *t*-**12**, and *c*-**13**. In all of them the 5-OMe and Me groups have $\mathbf{i_a}$ and **e** orientations, respectively. MM3 relative energies (kcal/mol) and conformational populations (in parentheses, %) are shown.

the **TC10** conformations the stabilization of an axial methoxy group can be observed.

The most stable conformers of 6-methoxy-1,4-dioxepane (**9**) belong to the more stable conformation group of the pattern compound. In the conformational behavior of this compound intervene the steric interactions of the methoxy group and the gauche effects that appear between the oxygen of the substituent and each of the oxygen atoms of the ring. There is no $\mathbf{i_g}$ orientation in the molecule, and the methoxy group, hence, tends to adopt an axial orientation as a consequence of both gauche effects. When this group is axial, greater steric interactions appear. The most favored conformations in the MM2 force field are those in which the methoxy group is axial (**TC5** and **TC10**). The steric interactions seem to dominate in the MM3 force field since there is a preference for conformations in which the methoxy group is equatorial.

5-Methoxy-X-methyl-1,4-dioxepanes 10−**13.** Our study has been extended to 1,4-dioxepane compounds with two substituents, such as 5-methoxy-2-, -3-, -6-, and -7-methyl-1,4-dioxepanes **10**−**13**. Two different types of behavior have been found for these disubstituted derivatives, depending on the ring configuration.

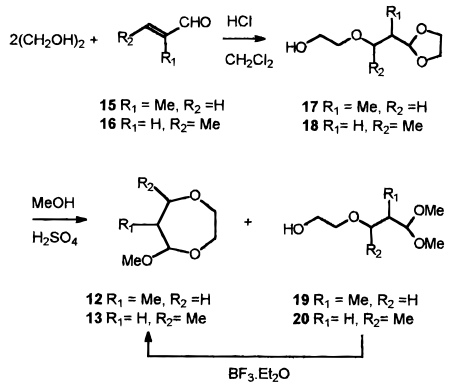
Firstly, a predominant conformer exists in one of the isomers of each compound. Such is the case of compounds *c*-**10**, *t*-**11**, *t*-**12**, and *c*-**13** in which the **TC3** conformation (Figure 5) has a conformational population of 95%. The reason for the great stability of this conformer in the aforementioned isomers has to be explained by the orientation shown by the methoxy and methyl groups in each compound. In all of them the 5-OMe group is of the $\mathbf{i_a}$ type in **TC3** (Table 5, H-5), which produces a great stabilization by anomeric effect. Moreover, Table 5 shows that the hydrogen atoms H-2, H-3′, H-6′, and H-7 are equatorial in **TC3**. These are the hydrogens that are substituted for the methyl group to obtain each of the compounds *c*-**10**, *t*-**11**, *t*-**12**, and *c*-**13**. Consequently, the methyl group does not introduce any important interaction, and **TC3** becomes the most important, almost unique, conformer of these compounds.

Secondly, a mixture of four or even five important conformations of similar energy exists for the other isomer of each of the aforementioned compounds. Table 6 summarizes the MM3 results obtained for compounds *t*-**10**, *c*-**11**, *c*-**12**, and *t*-**13** (Table VIII of Supporting Information contains the results for all the conformers). In this case, the hydrogen atoms H-2′, H-3, H-6, and H-7′ are axial in the **TC3** twist-chair, from which the methyl

Table 6. MM3 Relative Energies (kcal/mol) and Conformational Populations (%, in Parentheses) Calculated for Some Conformers of Compounds *t*-10, *c*-11, *c*-12, and *t*-13

conformer	*t*-**10**	*c*-**11**	*c*-**12**	*t*-**13**
TC3anti	1.54 (4.06)	4.16 (0.05)	1.29 (3.31)	1.63 (2.07)
TC5anti	6.76 (0.00)	5.08 (0.01)	0.87 (6.81)	2.10 (0.94)
TC10anti	0.68 (17.37)	0.57 (20.96)	0.17 (22.02)	0.05 (30.10)
TC12anti	0.00 (55.12)	0.00 (55.44)	0.44 (13.88)	0.00 (32.69)
TC11anti	1.06 (9.14)	0.92 (11.76)	0.59 (10.92)	0.69 (10.06)
TC6anti	3.20 (0.25)	6.19 (0.00)	0.59 (10.84)	1.11 (4.99)
TC9anti	0.92 (11.65)	1.12 (8.33)	0.00 (29.50)	0.34 (17.24)
TC13anti	2.56 (0.73)	2.26 (1.21)	3.08 (0.16)	

Scheme 1



group gives rise to a great destabilization of this conformation. Thus, in these isomers a mixture of several conformations of similar energy exists, and between them **TC3** has limited importance. In all of them, the **TC9** conformer, the second one in stability in 5-methoxy-1,4-dioxepane (**8**), acquires certain importance. In such a conformation, the 5-OMe group is axial and a stabilization by anomeric effect exists, and moreover, the methyl group is equatorial. Nevertheless, the steric interactions of the axial 5-OMe and the fact that the conformation **TC9** is not one of the most important ones of 1,4-dioxepane prevent this twist-chair form from being the most stable in these compounds. In the remaining conformations, the tendency is for the two substituents to occupy orientations in which the steric interactions are small. Thus, for example, in the **TC12** conformer of the compounds *t*-**10** and *c*-**11** and **TC11** of the compound *t*-**13**, both substituents adopt equatorial orientation while the methyl group is equatorial and methoxy group is $\mathbf{i_f}$ in the conformation **TC10** of the four compounds.

^{1}H NMR Results. Scheme 1 shows the synthesis of compounds **12** and **13**. The separation of the two *cis*/*trans* isomers of these two compounds has been attempted, but only the major isomer of each compound has been isolated in sufficient quantity to achieve a detailed study of the vicinal coupling constant. The synthesis of the *cis*/*trans* isomers of compounds **11** has been previously described by us,[54] and recently we have reported a highly diastereoselective synthesis of *trans*-**11**.[55] Experimental coupling constants have been compared with the theoretical ones obtained through the Haasnoot equation[56] from the coordinates and the conformational populations calculated with the MM3 force field.

Table 7. Experimental and Calculated (MM3) $^3J_{HH}$ Coupling Constants for Compounds *t*-11, *t*-12, and *c*-13

	t-**11**		*t*-**12**		*c*-**13**	
constant	J_{exp}	J_{cal}	J_{exp}	J_{cal}	J_{exp}	J_{cal}
$J_{2,3}$			1.79	1.81	1.50	1.79
$J_{2,3'}$			9.45	7.49	10.31	7.59
$J_{2',3}$	1.26	1.58	3.03	2.95	1.80	2.94
$J_{2',3'}$	9.06	8.51	1.76	1.84	1.40	1.77
$J_{5,6}$	6.06	5.71			6.02	5.52
$J_{5,6'}$	8.30	9.32	7.33	7.92	8.52	9.54
$J_{6,7}$	1.12	0.59			1.03	1.18
$J_{6,7'}$	5.30	7.05			8.77	8.66
$J_{6',7}$	10.40	9.49	10.50	8.25		
$J_{6',7'}$	2.00	0.78	3.33	1.60		
σ_{ms}	0.95		1.32		1.13	

The configurational assignment of these compounds has been carried out by means of their coupling constant. Thus the acetalic proton of compound **12** appears as a doublet at 4.20 ppm with a $J = 7.33$ Hz in the *trans* isomer, while it resonates at 4.50 ppm in the *cis* isomer with a $J = 3.8$ Hz. The coupling constants $J_{5,6}$ and $J_{5,6'}$ of the major isomer of **13** are characteristic of a *cis* configuration. Finally, the assignment of the signals of the hydrogen atoms of C-2 and C-3 and the *trans* configuration of compound **11** are based on the fact previously described by us[27] that the proton of C-3, which is located *cis* with respect to the methoxy group, resonates at a markedly lower field than its geminal one. Table 7 shows the experimental and theoretical coupling constants of compounds *t*-**11**, *t*-**12**, and *c*-**13**. The concordance between them is excellent, especially in *t*-**11** for which the σ_{ms} is 0.95. In *t*-**12** and *c*-**13** the σ_{ms} is higher, but it has to be kept in mind that the Karplus equation generalized by Haasnoot[56] was developed for six-membered rings and that the presence of several substituents in the system introduces a greater deviation between the theoretical and experimental values.

Conclusions

The different hydrogen atoms of oxepane have been classified according to the α and β angle types. The different nature of the β angles determines the interaction values which appear when the hydrogen atom is substituted, affecting both the steric interactions and the conformational effects that could be present.

The magnitude of the steric interactions generated by an axial substituent depends on its position in relation to the heteroatom being greater in the α position than in the γ one, and the latter greater than in the β one. In general, the steric interactions generated by an axial substituent are strong enough to destabilize the ring conformation, converting it into one of the most disfavored ones. The magnitude of the steric interactions is also different according to the isoclinal orientation adopted by the substituent, following the order $\mathbf{i_a} > \mathbf{i} \simeq \mathbf{i_f} > \mathbf{i_g}$. In all these cases, the steric interactions in these orientations are markedly less than those of an axial substituent and, can be adopted easily by substituents. The most favored orientation from a steric point of view is the equatorial one as was to be expected.

The presence of an anomeric effect in the molecule causes the substituent to show a great preference for an $\mathbf{i_a}$ orientation as a consequence of the stabilization by such an effect in this orientation and the small steric interactions. The axial orientation, adopted by a sub-

(54) Espinosa, A.; Gallo, M. A.; Campos, J. *An. Quim.* **1983**, *C79*, 210.
(55) Espinosa, A.; Gallo, M. A.; Campos, J.; Gómez, J. A. *Synlett* **1995**, *11*, 1119.
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stituent in six-membered rings when the anomeric effects exists, is not the most favored one in the heptagonal systems due to the existence of the $\mathbf{i_a}$ orientation type. A substituent will adopt an axial orientation should the anomeric isoclinal one not exist.

Finally, should an attractive gauche effect exist, the orientation preferred is that of the $\mathbf{i_g}$ type, since in it the stabilization due to the gauche effect and the stabilization due to some small steric interactions are again associated. Again, the axial orientation is not the most favored one, and it would be adopted by this type of substituent only if the $\mathbf{i_g}$ did not exist. On the other hand, should the gauche effect be repulsive or negligible, the orientation preferred by the substituent would be the equatorial one, as in a six-membered ring.

With regard to the ring conformation, the conformations preferred by the several derivatives are usually the most stable ones in the base ring. The steric interaction and the gauche effect do not involve a stabilization sufficient to cause the conformers not preferred by the unsubstituted compound to become the most stable ones of the derivative. The anomeric effect can stabilize conformations that are different from the ones favored by the parent compound. Two requirements are needed for this to happen: (i) that the energy difference between the most stable conformation of the ring and that undergoing stabilization is not too high and (ii) that an $\mathbf{i_a}$ orientation between the most stable conformations of the ring does not exist.

The classification of the different types of hydrogen in the oxepane can be easily extended to other types of oxygenated heterocyclic systems. Also, the conclusions about the preference of the substituent for each type of orientation seem to be general. At present, we are performing molecular mechanics calculations in saturated seven-membered heterocycles with different heteroatoms and substituents. From these studies, we hope to extend the rules presented in this paper to other systems. The conclusions derived from this study depend on the quality of the force field used. The MM3 force field seems to give good results in the anomeric and gauche effect.

Experimental Section

NMR spectra were recorded on an 300.13 MHz ^{1}H and 75.78 MHz ^{13}C NMR Bruker AM-300 and 80 MHz Bruker WP-80CW spectrometers in $CDCl_3$ solutions using TMS as the internal standard, and peaks are reported in ppm (δ). The infrared spectra (IR) were recorded on a Perkin-Elmer 782 instrument connected to a 3600 Data Station as a neat film over KBr. The mass spectra were obtained using a Hewlett-Packard 5988A spectrometer at 70 eV, carrying out injection through a 5890 gas chromatograph. Analytical thin-layer chromatography (TLC) was done on Merck silica gel F-254 plates with detection with iodine, using a mixture of ether−hexane as developing solvent. For normal column chromatography Merck silica gel 60 was used with a particle size 0.063−0.200 mm (70−230 mesh ASTM). For flash chromatography Merck silica gel 60 was used with a particle size 0.040−0.063 mm (230−400 mesh ASTM). Semipreparative GC was performed on a Perkin-Elmer 8410 apparatus with a 4 mm × 2 m 10% carbowax 20M in a Chromosorb w column.

Preparation of 2-[2-(2-Hydroxyethoxy)alkyl]-1,3-dioxolane. General Procedure. A two-phase mixture of the α,β-unsaturated aldehyde (0.734 mol), ethylene glycol (210 mL, 3.67 mol), concentrated HCl (2 mL), and CH_2Cl_2 (143 mL) was distilled through a Vigreux column which was fitted with a Clevenger adapter until no more aqueous phase separated in the distillate. Then, the homogeneous mixture was made alkaline (KOH/MeOH), and the solvent was rotaevaporated off. The residue was subjected to fractional distillation, giving the excess of glycol used and the 2-[2-(2-hydroxyethoxy)alkyl]-1,3-dioxolane.

2-[2-(2-Hydroxyethoxy)-1-methylethyl]-1,3-dioxolane (17). It was obtained (40%) from methacrolein **15**; bp 137−38 °C/20 mmHg (lit.[57] bp 133 °C/14 mmHg). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 4.8 (d, J = 4.5 Hz, 1H, H-2), 3.94−3.78 (m, AA′BB′ system, cyclic OCH_2CH_2O moiety), 3.70−3.46 (m, 5H, H-2′, acyclic OCH_2CH_2O moiety), 3.39 (dd, J = 6.1, 9.4 Hz, H-2′), 2.7 (br s, 1H, OH), 2.09−1.96 (m, 1H, H-1′), 0.94 (d, J = 7 Hz, 3H, Me). ^{13}C NMR (75.78 MHz, $CDCl_3$): δ 105.52 (C-2), 72.52 (C-4′), 72.15 (C-2′), 65.06 and 64.95 (C-4 and C-5), 61.60 (C-4′), 37.44 (C-1′), 11.46 (Me). MS: *m/e* 176 ($M^{\bullet+}$, <1), 145 (1), 115 (3), 99 (5), 73 (100). IR (film): 3416, 2883, 1462, 1403, 1122, 948 cm^{-1}. HRMS (CI): calcd for $C_8H_{17}O_4$ (M + 1) 177.1127, found 177.1125.

2-[2-(2-Hydroxyethoxy)propyl]-1,3-dioxolane (18). It was obtained (61%) from crotonaldehyde **16**; bp 132−34 °C/19 mmHg (lit.[58] bp 139 °C/17 mmHg, as a mixture with other compounds). ^{1}H NMR (80 MHz, $CDCl_3$): δ 4.98 (t, J = 5 Hz, 1H, H-2), 4.00−3.64 (m, AA′BB′ system, 8H, OCH_2CH_2O moieties), 3.46−3.40 (m, 1H, H-2′), 1.93 (ddd, J = 4.5, 14 Hz, 1H, H-1′), 1.18 (d, J = 6.2 Hz, 3H, Me). ^{13}C NMR (20 MHz, $CDCl_3$): δ 102.86 (C-2), 72.71 (C-2′), 69.75 (C-4′), 64.93 and 64.67 (C-4 and C-5), 62.91 (C-5′), 20.26 (Me). MS: *m/e* 161 [(M − Me)$^{\bullet+}$, <1], 145 (<1), 115 (2), 99 (15), 73 (100). IR (film): 3455, 2972, 1461, 1412, 1217, 947 cm^{-1}. HRMS (CI): calcd for $C_8H_{17}O_4$ (M + 1) 177.1127, found 177.1131.

Reaction of Transacetalization of 2-[2-(2-Hydroxyethoxy)alkyl]-1,3-dioxolanes with Methanol. General Procedure. A 0.06 mol sample of 2-[2-(2-hydroxyethoxy)alkyl]-1,3-dioxolane was dissolved in 44 mL of MeOH, which contained the appropriate amount of sulfuric acid to produce 1% in the final concentration. The mixture was left for 22−24 h at rt, basified (KOH/MeOH), and concentrated. The residue was dissolved in chloroform (100 mL) and washed with water (2 × 20 mL). The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated, giving by distillation and/or column chromatography the *cis*/*trans* mixture of 5-methoxy-X-methyl-1,4-dioxepane and 3-(2-hydroxyethoxy)-1,1-dimethoxyalkanes. The major isomer of the 5-methoxy-X-methyl-1,4-dioxepane was isolated by GLC.

5-Methoxy-6-methyl-1,4-dioxepane (12). It was obtained (6%, *cis*/*trans* 25/75) from 2-[2-(2-hydroxyethoxy)-1-methylethyl]-1,3-dioxolane (**17**). ^{1}H NMR (300.13 MHz, $CDCl_3$, *trans* isomer): δ 4.20 (d, J = 7.33 Hz, 1H, H-5), 4.02 (ddd, J = 1.79, 9.45, 13.42 Hz, 1H, H-3′), 3.71 (ddd, J = 1.76, 3.03, 12.58 Hz, H-2′), 3.57 (ddd, J = 1.79, 9.45, 12.58 Hz, 1H, H-2), 3.55−3.49 (m, 2H, H-7, H-7′), 3.46 (ddd, J = 1.79, 3.03, 13.42 Hz, 1H, H-3), 3.34 (s, 3H, OMe), 2.11 (m, J = 3.33, 7.21, 7.33, 10.5 Hz, 1H, H-6), 0.92 (d, J = 7.21 Hz, 3H, Me). ^{13}C NMR (75.78 MHz, $CDCl_3$, *trans* isomer): δ 108.33 (C-5), 72.53 (C-7), 71.28 (C-3), 64.55 (C-2), 55.39 (OMe), 43.35 (C-6), 15.45 (Me). ^{13}C NMR (75.78 MHz, $CDCl_3$ *cis* isomer): δ 105.79 (C-5), 71.34 (C-7), 71.49 (C-3), 66.47 (C-2), 55.78 (OMe), 40.13 (C-6), 12.67 (Me). MS (*trans* isomer): *m/e* 146 ($M^{\bullet+}$, <1), 115 (9), 101 (1), 86 (8), 73 (100), 57 (9). MS (*cis* isomer): *m/e* 146 ($M^{\bullet+}$, <1), 115 (7), 101 (4), 86 (20), 73 (100). IR (film, *cis*/*trans* mixture): 2940, 2882, 1464, 1299, 1245 cm^{-1}. HRMS (CI): calcd for $C_7H_{15}O_3$ (M + 1) 147.1021, found 147.1021.

3-(2-Hydroxyethoxy)-1,1-dimethoxy-2-methylpropane (19). It was obtained (44%) from 2-[2-(2-hydroxyethoxy)-1-methylethyl]-1,3-dioxolane (**17**). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 4.19 (d, J = 6.26 Hz, 1H, H-1), 3.67 and 3.48 (m, AA′BB′ system, OCH_2CH_2O), 3.45 (dd, J = 5.25, 9.33 Hz, 1H, H-3), 3.33 (dd, J = 6.14, 9.33 Hz, 1H, H-3′), 3.32 (s, 6H, OMe), 2.38 (br s, 1H, OH), 2.02 (m, J = 5.25, 6.14, 6.92 Hz, 1H, H-2), 0.92 (d, J = 6.92 Hz, 3H, Me). ^{13}C NMR (75.78 MHz, $CDCl_3$): δ 106.61 (C-1), 72.61 (C-3), 72.12 (C-5), 61.66 (C-6), 54.40 and 54.38 (OMe), 36.61 (C-2), 12.28 (Me). MS: *m/e* 146 ($M^{\bullet+}$, <1), 115 (5), 101 (1), 87 (4), 75 (100), 73 (8). IR (film): 3446, 2937,

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2882, 1382, 948 cm^{-1}. HRMS (CI): calcd for $C_8H_{19}O_4$ (M + 1) 179.1283, found 179.1276.

5-Methoxy-7-methyl-1,4-dioxepane (13). It was obtained (11%, *cis*/*trans* mixture 72/28) from 2-[2-(2-hydroxyethoxy)-propyl]-1,3-dioxolane (**18**). ^1H NMR (300.13 MHz, $CDCl_3$, *cis* isomer): δ 4.68 (dd, J = 6.02, 8.52 Hz, 1H, H-5), 4.02 (ddd, J = 1.40, 10.31, 13.54 Hz, 1H, H-3′), 3.78−3.67 (m, 2H, H-7, H-2′), 3.58 (ddd, J = 1.50, 10.31, 11.85 Hz, 1H, H-2), 3.44 (ddd, J = 1.50, 1.80, 13.54 Hz, 1H, H-3), 3.31 (s, 3H, OMe), 2.07 (ddd, J = 1.03, 6.02, 15.66 Hz, 1H, H-6), 1.94 (ddd, J = 8.52, 8.77, 15.66 Hz, 1H, H-6′), 1.16 (d, J = 6.43 Hz, 3H, Me). ^{13}C NMR (75.78 MHz, $CDCl_3$, *cis* isomer): δ 101.04 (C-5), 71.58 (C-7), 70.44 (C-2), 63.72 (C-3), 54.80 (OMe), 44.93 (C-6), and 23.01 (Me). ^{13}C NMR (75.78 MHz, $CDCl_3$, *trans* isomer): δ 103.27 (C-5), 71.94 (C-7), 70.76 (C-2), 67.82 (C-2), 55.53 (OMe), 44.23 (C-6), 21.99 (Me). MS (*cis* isomer): *m*/*e* 146 ($M^{\bullet+}$, <1), 115 (5), 101 (11), 87 (7), 73 (100). MS (*trans* isomer): *m*/*e* 146 ($M^{\bullet+}$, 1), 115 (10), 101 (10), 87 (5), and 73 (100). IR (film, *cis*/*trans* mixture): 2949, 2895, 1444, 1383, 1296, 1241 cm^{-1}, HRMS (CI): calcd for $C_7H_{15}O_3$ (M + 1) 147.1021, found 147.1022.

3-(2-Hydroxyethoxy)-1,1-dimethoxybutane (20). It was obtained (64%) from 2-[2-(2-hydroxyethoxy)propyl]-1,3-dioxolane (**18**). ^1H NMR (80 MHz, $CDCl_3$): δ 4.61 (dd, J = 5.0, 6.5 Hz, 1H, H-1), 3.75−3.50 (m, 5H, H-3, OCH_2CH_2O moiety), 3.35 (s, 3H, OMe), 2.7 (br s, 1H, OH), 1.85−1.65 (m, 2H, H-2, H-2′), 1.18 (d, J = 6 Hz, 3H, Me). ^{13}C NMR (20 MHz, $CDCl_3$): δ 102.28 (C-1), 72.52 (C-3), 69.90 and 61.86 (OCH_2CH_2O moiety), 52.83 and 52.72 (OMe), 39.84 (C-2), 19.98 (Me). MS: *m*/*e* 146 [$(M - MeOH)^{\bullet+}$, <1], 131 (3), 115 (6), 101 (12), 75 (97), 73 (5), 45 (100). IR (film): 3458, 2936, 2836, 1378, 964 cm^{-1}. HRMS (CI): calcd for $C_8H_{19}O_4$ (M + 1) 179.1283, found 179.1285.

Intramolecular Cyclization of 3-(2-Hydroxyethoxy)-1,1-dimethoxyalkane with BF_3·Et_2O. General Procedure. 3-(2-Hydroxyethoxy)-1,1-dimethoxyalkane was dissolved in anhydrous diethyl ether (1 g of starting material in 10 mL of ether), a few drops of boron trifluoride etherate were added, and the solution was kept at rt for 1 day. It was then washed with a K_2CO_3 solution (10%) to remove the acid, and the organic layer was dried ($MgSO_4$). After filtration and concentration, the residue was purified by column chromatography. 5-Methoxy-6-methyl-1,4-dioxepane (**12**) was obtained (33%, *cis*/*trans* mixture, 23/77) from 3-(2-hydroxyethoxy)-1,1-dimethoxy-2-methylpropane (**19**). 5-Methoxy-7-methyl-1,4-dioxepane (**13**) was obtained (69%, *cis*/*trans* mixture, 80/20) from 3-(2-hydroxyethoxy)-1,1-dimethoxybutane (**20**).

Intramolecular Cyclization of 3-(2-Hydroxyethoxy)-1,1-dimethoxyalkane Using Ph_3P/CCl_4.[55] 5-Methoxy-3-methyl-1,4-dioxepane (**11**) was obtained (85%, *cis*/*trans* mixture, 14/86) from 3-(2-hydroxypropoxy)-1,1-dimethoxypropane. ^1H NMR (300.13 MHz, $CDCl_3$, *trans* isomer): δ 4.68 (dd, J = 6.06, 8.30 Hz, 1H, H-5). 4.16 (m, J = 1.26, 6.58, 9.06 Hz, 1H, H-3′), 3.78 (ddd, J = 2.00, 5.30, 12.50 Hz, 1H, H-7′), 3.66 (dd, J = 1.26, 12.3 Hz, 1H, H-2′), 3.53 (ddd, J = 1.12, 10.40, 12.50 Hz, 1H, H-7), 3.34 (s, 3H, OMe), 3.23 (dd, J = 9.06, 12.30 Hz, 1H, H-2), 2.17 (m, J = 1.12, 5.30, 6.06, 12.50 Hz, 1H, H-6), 2.01 (m, J = 2.00, 8.30, 10.40, 12.50 Hz, 1H, H-6′), 1.05 (d, J = 6.58 Hz, 3H, Me). ^{13}C NMR (75.78 MHz, $CDCl_3$, *trans* isomer): δ 101.13 (C-5), 76.07 (C-2), 68.52 (C-3), 65.38 (C-7), 55.18 (OMe), 38.80 (C-6), 17.80 (Me). ^{13}C NMR (75.78 MHz, $CDCl_3$, *cis* isomer): δ 101.50 (C-5), 76.07 (C-2), 68.05 (C-3), 65.41 (C-7), 54.45 (OMe), 38.36 (C-6), 17.02 (Me). MS (CI, *cis*/*trans* mixture): *m*/*e* 147 [$(M + 1)^{\bullet+}$, 1], 115 (100), 87 (9), 73 (25), 72 (22), 71 (53), 59 (22), 57 (10). HRMS (CI): calcd for $C_7H_{15}O_3$ (M + 1) 147.1021, found 147.1022. 5-Methoxy-6-methyl-1,4-dioxepane (**12**) was obtained (50%, *cis*/*trans* mixture, 6/94) from 3-(2-hydroxyethoxy)-1,1-dimethoxy-2-methylpropane (**19**). 5-Methoxy-7-methyl-1,4-dioxepane (**13**) was obtained (80%, *cis*/*trans* mixture, 91/9) from 3-(2-hydroxyethoxy)-1,1-dimethoxybutane (**20**).

Supporting Information Available: Tables I−VI containing the endocyclic torsion angles, steric energies, relative energies, conformational population, and puckering parameters for the **TC** and **B**/**TB** conformations of compounds **1**−**6**, calculated from the MM3 optimized coordinates; Tables VII and VIII containing relative energies (MM3) and conformational population of compouds **5**−**11**; and ^{13}C NMR spectra of compounds for which no elemental analysis was obtained (17 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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