Conformational Analysis of Some 1,4-Dioxepane Systems. 2.[1] Methoxy-1,4-dioxepanes

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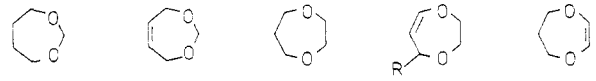
The conformational analysis of 5-methoxy-1,4-dioxepane (**15**), 2-methoxy-1,4-dioxepane (**16**), and 6-methoxy-1,4-dioxepane (**17**) has been carried out by means of molecular mechanics (MM2). Compound **15** shows one twist-chair (TC) form as the preferred conformer, while in **16** and in **17** there are three and four TC forms, respectively. These conformational preferences can be explained on the basis of the anomeric (**15** and **16**) and gauche effects (**17**) and are related to the available experimental data.

Introduction

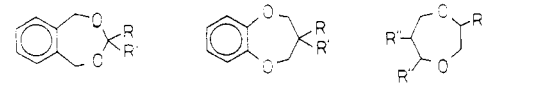
The conformational behavior of seven-membered rings that contain two oxygen atoms has been studied in recent years by means of various techniques. The results indicate that the conformational preferences of such rings are diverse and depend on factors such as the position of the oxygen atoms and the presence of double bonds, condensed aromatic rings, or substituents.

The saturated **1**[2] and **3**[3] rings show a complex conformational equilibrium between the chair/twist-chair (C/TC) and the boat/twist-boat (B/TB) families, the TC conformation being the most stable in both compounds.

The presence of double bonds and/or condensed aromatic rings introduces a greater rigidity in the ring, reduces the number of conformations in the pseudorotational equilibrium, and stabilizes the chair forms. Thus, it has been reported that compounds **6**,[4] **7**,[5] and **11**[6] exist as chair conformations while **2**[7] and **4**[4] show a preference for the twist boat, although in the latter, there is only a small difference between the chair and twist-boat energies.



1 2 3 4 R=H 6
5 R=OMe



7 R=R'=H
8 R=R'=Me
9 R=H; R'=Me
10 R=H; R'=OMe

11 R=R'=H
12 R=R'=Me
13 R=H; R'=Me
14 R=H; R'=X
X=F, OMe, Cl, Br, I

15 R=R''=H; R'=OMe
16 R=R''=H; R=OMe
17 R=R'=H; R''=OMe

Substituents modify the conformational preference of the dioxepine system depending on their type and number. Thus, for compound **5**[4] the chair conformation is the most stable. The 2,4-benzodioxepine derivative **9**, with a substituent at C-3, exists in a chair conformation, while **8** and **10**, with two substituents and one electronegative substituent at C-3, respectively, adopt the TB as the most stable conformation.[5] Finally, C-3 substituents on the 1,5-benzodioxepines **12–14** increase the preference for the TB conformation as the electronegativity of the substituent increases.[6c]

Although the influence of various substituents on the conformation of the above-mentioned unsaturated systems has been thoroughly studied, such is not the case for saturated rings **1** and **3**. Therefore, we have carried out the theoretical conformational study of 5-methoxy-1,4-dioxepane (**15**), 2-methoxy-1,4-dioxepane (**16**), and 6-methoxy-1,4-dioxepane (**17**). In this paper, we report on those studies and compare the theoretical data obtained for **15** and **16** with the observed experimental data.

Results and Discussion

Conformational analysis of **15**, **16**, and **17** has been carried out by means of the MM2 program of Allinger,[7a] using the twist-chair conformations of the 1,4-dioxepane[3] as starting points, since they are the most stable, and the influence of the OMe group on the energy of each conformer has been determined. So, the equatorial hydrogen at the C_5, C_2, or C_6 atom in the C1 conformation of 1,4-dioxepane has been substituted by the OMe group in order to obtain the C1 conformation of **15**, **16**, or **17**, respectively, and the equivalent substitution has been carried out in the 14 twist-chairs.

Also, in each conformer, we have considered the three possible rotamers due to the OMe group, as represented by the values of the ω_{6589} dihedral angles in **15**, ω_{3289} in **16**, and ω_{5689} in **17** (Figure 1). The geometries obtained for the conformations of **15** and **16** with the MM2 program have been recalculated with the PC version of the MM2-(85) program[7b] in oder to improve the study of the influence of the anomeric effect on such compounds.

(a) MM2 Results. 5-Methoxy-1,4-dioxepane (15). Table I shows the different contributions to the steric energy, the relative energies (kcal/mol), the value of the ω_{3458} and ω_{4589} dihedral angles and the conformational populations of the different conformers calculated for 5-methoxy-1,4-dioxepane (**15**). Attempts to calculate the rotamers and/or the conformers that are missing from the table were unsuccessful. The absence of TC2 and TC4 and of most of the g(+) rotamers is observed. The presence of the 5-OMe group breaks the degeneracy that existed among the conformations of the 1,4-dioxepane, and one predominant conformer (TC3anti, 79%) arises (Figure 2). Three less important conformations are observed. Two

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Table I. Contributions to the Steric Energy, Relative Energy,[a] Conformational Population (%), and ω_{3458} and ω_{4589} Dihedral Angles of the Calculated Conformers of 5-Methoxy-1,4-dioxepane (15)

conformation	compression	bending	S bending	van der Waals	torsion	dipole	ω_{3458}	ω_{4589}	rel energy	population
TClanti	1.06	6.73	0.69	11.75	4.51	3.19	147.7	-77.2	2.88	0.61
TClg(-)	1.04	8.05	0.76	11.86	5.15	2.75	141.2	68.2	4.55	0.04
TC3anti	0.91	7.81	0.69	11.28	2.97	1.41	-81.7	-74.2	0.00	79.16
TC3g(+)	0.96	7.41	0.69	11.33	5.01	2.20	-80.3	-146.8	2.53	1.09
TC3g(-)	0.95	10.57	0.79	11.12	3.17	2.52	-116.8	-172.8	4.05	0.08
TC5anti	0.83	9.76	0.72	10.86	3.55	1.67	-55.3	-74.1	2.33	1.53
TC5g(+)	0.86	9.34	0.73	10.48	5.50	2.29	-56.0	-144.5	4.62	0.03
TC5g(-)	0.86	15.67	0.88	11.04	4.29	2.13	-71.8	116.1	9.81	0.00
TC6anti	0.88	9.77	0.75	11.42	3.18	1.52	-71.2	-73.4	2.46	1.24
TC6g(-)	0.95	15.07	0.93	11.70	3.72	3.19	-105.2	84.5	10.50	0.00
TC7anti	0.93	9.64	0.77	11.68	3.92	1.56	-59.8	-70.2	3.43	0.24
TC7g(-)	0.99	14.51	0.92	11.99	4.61	3.23	-91.3	75.5	11.18	0.00
TC8anti	0.82	10.62	0.73	11.11	4.26	1.30	-41.9	-79.0	3.79	0.13
TC9anti	0.91	9.55	0.75	11.38	2.56	1.56	-103.3	-72.7	1.65	4.86
TC10anti	0.98	7.33	0.67	11.41	4.60	1.88	-156.4	-72.1	1.81	3.69
TC10g(-)	0.98	8.45	0.75	11.20	6.16	1.97	179.6	68.4	4.46	0.04
TC11anti	1.06	6.39	0.69	12.43	4.99	1.63	144.9	-76.9	2.15	2.08
TC11g(+)	1.13	6.10	0.71	12.60	7.40	2.17	144.2	-169.8	5.05	0.01
TC11g(-)	1.07	8.34	0.78	12.75	5.38	1.56	136.4	68.5	4.82	0.02
TC12anti	1.01	6.61	0.66	11.68	4.95	1.82	162.0	-77.7	1.67	4.66
TC12g(-)	1.01	7.82	0.74	11.61	5.59	1.89	155.9	65.9	3.60	0.18
TC13anti	0.96	8.25	0.69	11.56	4.91	2.53	-176.8	-74.4	3.84	0.12
TC13g(-)	0.97	9.47	0.76	11.53	5.51	2.55	174.5	72.1	5.73	0.00
TC14anti	1.02	6.99	0.69	11.74	5.30	3.04	166.2	-75.9	3.73	0.14
TC14g(-)	1.02	8.70	0.76	11.84	5.76	2.74	156.6	69.7	5.76	0.00

[a] Relative energies are given in kilocalories/mole in relation to TC3anti.

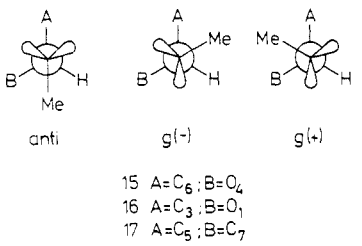

Figure 1. Rotamers around the C–OMe bond of compounds **15**, **16**, and **17** as a function of the dihedral angles ω_{6589}, ω_{3289}, and ω_{5689}, respectively.

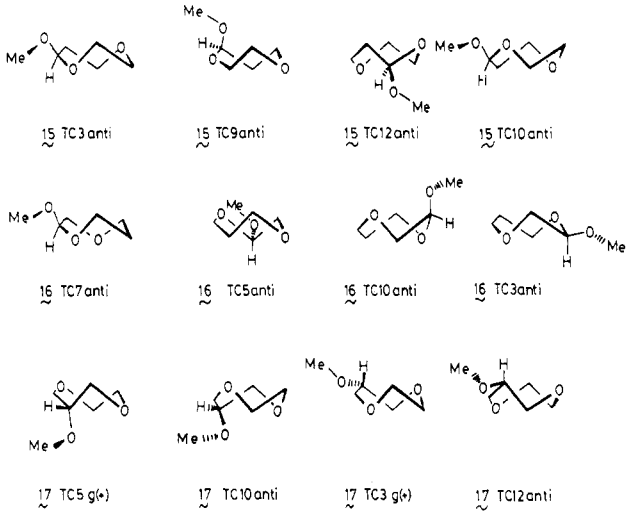

Figure 2. The four most stable conformers calculated for 5-methoxy-1,4-dioxepane (**15**) (top), 2-methoxy-1,4-dioxepane (**16**) (center), and 6-methoxy-1,4-dioxepane (**17**) (bottom).

of them (TC12anti, 4.66%, and TC10anti, 3.69%) (Figure 2) derive from the TC3 isoenergetic twist-chair in 1,4-dioxepane,[8] and the other one (TC9anti, 4.86%) (Figure 2) results from a higher energy twist-chair. Finally, the g(-) rotamer energies are higher than those of the corresponding anti rotamers.

Table I shows that the E_B and E_T contributions determine the energy differences between the conformers. The conformers with an elevated E_B have a clearly axial OMe group, establishing strong transannular steric interactions which are relaxed by a deformation of the intrannular bond angles. On the other hand, the high E_T value is mostly due to the ω_{3458} and ω_{4589} angles, which are the central dihedral angles of the C–O–C–O–C moiety affected by the anomeric effect. This effect can be understood as the preference of such angles for a g(+) or g(-) conformation and leads to the greater stability of the axial conformer of the 2-methoxytetrahydropirane.[9] This conformational behavior is thought to be governed by a combination of two factors: (i) dipole–dipole interactions between a C–O polar bond and the dipolar moment resulting from the lone pairs of the adjacent oxygen,[10] and (ii) stereoelectronic interaction between the lone pair of an oxygen and the σ^*_{C-O} adjacent orbital (called n-σ^*).[11] Unfortunately, the relative importance of each contribution is difficult to assess quantitatively and is still a matter for discussion and investigation.

The treatment of the anomeric effect in the original MM2 force field[7a] was not exact, especially with regard to bond angles and bond lengths. Recently, Allinger[12] has provided a new scheme of parameterization involving a redetermination of l_0 for the O–C–O bonds as a function

(8) Four energetically different twist chairs have been found whose relative energies defined with respect to the most stable conformation are: TC3 (TC5, TC10, TC12), 0.0 kcal/mol; TC4 (TC11), 1.16 kcal/mol; TC1 (TC7, TC8, TC14), 1.53 kcal/mol; and TC2 (TC6, TC9, TC13), 1.56 kcal/mol. See ref 3.

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Table II. Contributions to the Steric Energy, Relative Energy,[a] Conformational Population (%), and ω_{7128} and ω_{1289} Dihedral Angles of the Calculated Conformers of 2-Methoxy-1,4-dioxepane (16)

conformation	compression	bending	S bending	van der Waals	torsion	dipole	ω_{7128}	ω_{1289}	rel energy	population
TClanti	1.08	6.80	0.71	11.92	4.22	3.31	145.3	-76.2	1.96	1.21
TClg(+)	1.16	6.34	0.72	12.06	6.66	4.11	144.3	-165.5	4.98	0.00
TClg(-)	1.06	8.83	0.80	12.29	4.59	2.94	137.2	67.6	4.44	0.02
TC2anti	1.03	8.00	0.71	11.76	4.49	2.77	163.2	-77.5	2.67	0.36
TC2g(-)	1.01	9.23	0.78	11.65	5.16	2.73	157.3	63.6	4.49	0.02
TC3anti	0.98	6.77	0.64	11.48	5.28	1.88	-178.3	-75.1	0.96	6.58
TC3g(-)	0.99	7.90	0.72	11.44	5.78	2.24	173.4	71.2	3.01	0.20
TC4anti	1.05	6.43	0.68	12.41	5.79	1.68	161.1	-77.0	1.98	1.16
TC5anti	1.02	6.59	0.66	11.59	4.14	2.18	145.0	-77.5	0.11	27.74
TC5g(-)	1.02	7.71	0.74	11.76	4.70	2.18	138.4	68.3	2.02	1.10
TC7anti	0.96	7.82	0.71	11.57	2.98	2.02	-85.9	-74.7	0.00	33.32
TC7g(-)	1.03	10.07	0.82	11.39	3.31	3.20	-121.3	72.2	3.74	0.60
TC8anti	0.95	10.69	0.81	11.49	4.02	1.75	-41.9	-75.5	3.65	0.07
TC8g(+)	0.97	10.09	0.81	11.81	5.78	2.21	-43.7	-138.2	5.60	0.00
TC9anti	0.79	11.51	0.76	10.81	3.02	1.99	-56.8	-72.5	2.80	0.29
TC9g(+)	0.82	11.03	0.77	10.78	5.19	2.36	-57.8	-158.8	4.88	0.01
TC10anti	0.91	8.47	0.72	11.16	3.03	2.00	-70.6	-72.8	0.22	23.14
TC10g(-)	0.97	13.27	0.89	11.29	2.93	2.38	-94.1	97.1	5.66	0.00
TC11anti	0.99	8.98	0.79	12.06	4.29	1.38	-59.1	-68.9	2.57	0.42
TC12anti	0.82	10.36	0.72	8.80	3.66	1.72	-38.6	-79.7	2.01	1.12
TC12g(-)	13.18	21.53	1.54	8.65	3.82	2.13	-63.4	75.8	24.78	0.00
TC13anti	0.93	9.76	0.77	11.04	2.18	2.98	-102.1	-71.8	1.60	2.23
TC13g(+)	0.99	9.63	0.81	11.00	4.30	3.61	-98.9	-159.2	4.27	0.02
TC14anti	1.02	7.80	0.72	11.47	3.81	3.46	-150.9	-70.5	2.21	0.80
TC14g(-)	0.99	8.90	0.78	11.12	5.18	2.67	-167.4	73.3	3.56	0.08

[a] Relative energies are given in kilocalories/mole in relation to TC7anti.

of the torsional angles around them. This modification is incorporated in the MM2(85)[7b] version and leads to better results than the original version, in molecules with this type of effect.

The analysis of the geometry of all the conformers, even TC2 and TC4, using Dreiding models, has permitted us to rationalize the results found on the basis of the two above considered effects. So in TC2, the 5-OMe group has an equatorial orientation with an angle ω_{3458} close to 180° and the anomeric effect destabilizes this twist-chair causing it to pseudorotate toward TC1 or TC3. In contrast, in TC4 the angle ω_{3458} is almost a g(+) conformation, but the 5-OMe axial group creates strong steric interactions with O_1 and C_3 and destabilizes it.

In the most stable conformation, TC3anti, the two above-mentioned effects combine in such a way as to minimize the total sum: the OMe group has a markedly equatorial character and both angles ω_{3458} and ω_{4589} approximate the g(-) conformation necessary for stabilization by the anomeric effect. In the other conformations (TC10anti and TC12anti), the angle ω_{3458} is nearly 180° (-156° in TC10anti and 162° in TC12anti) and therefore the anomeric effect elevates the energies.

The anomeric effect also seems to be responsible for the absence of the g(+) rotamers in some conformations, (ω_{4589} is nearly 180° in g(+) rotamers), as well as for their high energy when they do exist. Finally, the higher energy of the g(-) rotamers relative to the anti conformations is a consequence of the greater steric interactions between the OMe group and the ring, in the former.

2-Methoxy-1,4-dioxepane (16). Table II shows the contributions to the steric energy, the relative energies (kcal/mol) defined in relation to the most stable conformation (TC7anti), the values of the ω_{7128} and ω_{1289} dihedral angles and the conformational populations of the calculated conformers of 2-methoxy-1,4-dioxepane (16).

The conformational behavior of **16** is similar to that of its isomer **15**. On the one hand, the presence of the 2-OMe group gives rise to four predominant conformations (TC7anti, 33%; TC5anti, 27,7%; TC10anti, 23,1%; TC3anti, 6.5%) (Figure 2). On the other, the absence of the TC6 conformer and of most of the g(+) rotamers and a higher energy for g(-) rotamers is observed.

As in the previous case, the E_B energy, interpreted as an axial or equatorial orientation of the OMe group, and the E_T energy, due to the ω_{7128} and ω_{1289} dihedral angles as modified by the anomeric effect, are the components that control the energy differences between conformers.

The Dreiding models shows that in TC6 the OMe group is equatorial and the ω_{7128} dihedral angle is nearly 180°. Consequently, the anomeric effect destabilizes this conformation. In the g(+) rotamers, the ω_{1289} dihedral angle is also nearly 180° so that the anomeric effect also destabilizes them. Furthermore, as in **15**, the g(-) rotamers present a greater steric interaction with the ring than do the anti ones.

The stabilities of the twist chairs of **16** are also governed by these two factors. Thus, in TC7anti, the orientation of the 2-OMe group is markedly equatorial and ω_{7128} = -85°; therefore E_B and E_T are low. It is the most stable conformer, although TC7 is not one of the preferable conformers of 1,4-dioxepane itself. In TC10anti, the 5-OMe group is axial but the angle ω_{7128} = -70°, a value close to a g(-) conformation, so it is the third most important conformer. In contrast, in TC5anti and TC3anti the 2-OMe is clearly equatorial, but ω_{7128} has nearly an antiperiplanar disposition (-178° in TC3anti and 145° in TC5anti). The absence of important steric interactions and the destabilization due to the anomeric effect combine in such a way that these conformers are, respectively, the second and the fourth of the conformational population.

It must be reiterated that the most stable conformer of **16** is a twist-chair that does not correspond to the most stable conformers of 1,4-dioxepane. However, it has been reported that the conformational consequences of the anomeric effect in seven-membered rings are different from those in six-membered rings. Thus, in the latter case, the anomeric effect produces a preference for the axial orientation of the substituents but it does not affect the ring preference, while it can modify the conformational preference of the seven-membered ring. This has been observed with 2-methoxy-1-benzoxepine (TB) relative to the

Table III. Contributions to the Steric Energy, Relative Energy[a] and Conformational Population (%) of the Calculated Conformers of 6-Methoxy-1,4-dioxepane (17)

conformation	compression	bending	S bending	van der Waals	torsion	dipole	rel energy	population
TClanti	0.95	6.46	0.51	11.27	6.95	1.26	1.55	1.16
TClg(+)	0.95	6.45	0.57	11.27	6.97	1.26	1.94	0.61
TClg(-)	0.97	7.42	0.64	11.23	7.09	2.02	3.86	0.02
TC2anti	0.95	7.67	0.59	11.26	6.29	1.21	2.44	0.26
TC2g(+)	0.94	7.61	0.58	11.20	6.31	1.17	2.28	0.34
TC2g(-)	0.94	8.44	0.66	11.03	6.55	1.76	3.85	0.02
TC3anti	0.96	6.17	0.55	11.23	6.66	0.64	0.69	5.04
TC3g(+)	0.95	6.09	0.55	11.05	6.05	0.85	0.02	15.60
TC3g(-)	0.96	7.39	0.63	11.17	6.99	0.86	2.48	0.24
TC4anti	0.98	5.98	0.58	11.71	6.47	0.73	0.83	3.97
TC4g(+)	0.98	5.91	0.58	11.93	7.09	0.62	1.59	1.10
TC4g(-)	0.95	7.59	0.65	11.48	7.15	0.25	2.55	0.22
TC5anti	0.93	6.59	0.58	10.84	6.16	1.25	0.83	3.97
TC5g(+)	0.91	7.10	0.60	10.53	5.51	0.88	0.00	16.13
TC6anti	0.79	9.29	0.62	10.05	4.87	1.87	1.96	0.59
TC6g(+)	0.80	9.56	0.64	10.21	4.89	1.94	2.51	0.23
TC7anti	0.94	7.16	0.61	10.69	5.53	2.86	2.27	0.35
TC7g(+)	0.96	6.88	0.61	10.99	5.95	3.03	2.88	0.12
TC7g(-)	0.94	8.75	0.68	10.97	6.75	1.27	3.83	0.02
TC8anti	0.96	6.86	0.61	10.99	5.96	3.03	2.88	0.12
TC8g(+)	0.93	7.24	0.61	10.67	5.50	2.85	2.27	0.12
TC8g(-)	0.94	8.73	0.68	10.97	6.76	1.27	3.83	0.02
TC9anti	0.80	9.58	0.64	10.32	4.88	1.94	2.51	0.23
TC9g(+)	0.79	9.26	0.63	10.06	4.88	1.87	1.96	0.59
TC10anti	0.92	7.09	0.60	10.52	5.52	0.89	0.00	16.13
TC10g(+)	0.93	6.61	0.58	10.85	6.14	1.25	0.84	3.94
TC11anti	0.99	5.90	0.58	11.92	7.10	0.62	1.59	1.10
TC11g(+)	0.98	5.89	0.57	11.71	6.46	0.74	0.83	3.96
TC11g(-)	0.96	7.58	0.65	11.50	7.13	0.26	2.55	0.22
TC12anti	0.95	6.05	0.55	11.05	6.11	0.83	0.02	15.60
TC12g(+)	0.96	6.19	0.56	11.24	6.63	0.64	0.69	5.03
CT12g(-)	0.96	7.39	0.63	11.17	7.01	0.86	2.49	0.24
TC13anti	0.94	7.59	0.58	11.19	6.33	1.17	2.28	0.34
TC13g(+)	0.95	7.74	0.59	11.25	6.23	1.21	2.45	0.26
TC13g(-)	0.94	8.39	0.66	11.04	6.58	1.76	3.85	0.02
TC14anti	0.95	6.44	0.56	11.26	6.99	1.26	1.94	0.61
TC14g(+)	0.95	6.48	0.56	11.22	6.47	1.39	1.56	1.16
TC14g(-)	0.97	7.66	0.64	11.22	6.92	2.02	3.90	0.02

[a] Relative energies are given in kilocalories/mole in relation to TC5g(+) (TC10anti).

1-benzoxepine (C)[13] and with 5-methoxy-2,3-dihydro-5*H*-1,4-dioxepine (**5**) (C) in constrast to 2,3-dihydro-5*H*-1,4-dioxepine (**4**) (TB);[4] and now in **16** (TC7) relative to **3** (TC3), although to a lesser degree since the preferred conformation is still a TC.

6-Methoxy-1,4-dioxepane (17). Table III shows the different energetic contributions of the conformers calculated for the compound **17** together with the conformational populations and the relative energy.

The conformational behavior of 6-methoxy-1,4-dioxepane has turned out to be slightly different from that of the isomers **15** and **16**. All of the twist-chairs and all of the g(+) rotamers have been found, with only some g(-) rotamers missing. However, the 6-OMe group modifies the conformational preferences of **17** with respect to those of **5**, as occurs in **15** or in **16**. But, due to the symmetry of 6-methoxy-1,4-dioxepane, energetically degenerated conformations still exist. So, as preferred conformers we have found four isoenergetic twist chairs in pairs (TC5g(+) and TC10anti, 16.13%; TC3g(+) and TC12anti, 15.6%) (Figure 2) that derive from the more stable TC of 1,4-dioxepane. Variations in the values of the contributions to the steric energy of the conformers of **17** are not as important as in **15** or **16**; nevertheless, conformational behavior of **17** can be explained in accordance with the following two effects: (i) The steric interactions between the ring and the OMe group when this is axial play an important role, but in the two most stable conformers (TC5g(+) and TC10anti) the 6-OMe group is axial, while in the other two (TC3g(+) and TC12anti) the 6-OMe has a clearly equatorial character. (ii) Concurrently, the molecule has three O–C–C–O moieties (O_1–C_2–C_3–O_4; O_4–C_5–C_6–O_8; O_1–C_7–C_6–O_8) which show preference for a g(+) or g(-) conformation due to the so-called "gauche" effect.[14-18] This effect presents a rotational barrier around the central C–C bond of the X–C–C–Y groups and can be attractive, negligible, or repulsive[14] depending on the nature of the two heteroatoms in the gauche disposition. A preference for the gauche conformation has been observed when X and Y are atoms or small electronegative atomic groups (O, F, CN) and has been interpreted to arise from interactions between

Table IV. ω_{1234}, ω_{4568}, and ω_{1768} Dihedral Angles of the TC5g(+), TC10anti, TC3g(+), and TC12anti Conformations of 6-Methoxy-1,4-dioxepane (17)

conformation	ω_{1234}	ω_{4568}	ω_{1765}
TC3g(+)	75.4	150.1	151.7
TC5g(+)	74.6	40.7	-100.0
TC10anti	-74.6	100.2	-40.8
TC12anti	-75.2	152.3	148.9

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bonding and antibonding orbitals[15] and is the cause of the gauche conformation of 1,2-dimethoxyethane[16] and of polyoxyethylene.[17] It has also been studied in 5-substituted 1,3-dioxanes[18] and in 1,5-benzodioxepines.[5]

Although there is a gauche effect in **15** and **16** due to the O_1–C_2–C_3–O_4 moiety, it seems negligible relative to the anomeric effect. However, the presence of three moieties with this conformational preference in **17** and the absence of the anomeric effect makes the gauche effect an important factor governing the energy differences between conformers. Table IV shows the values of the ω_{1234}, ω_{4568}, and ω_{1768} dihedral angles of the TC5g(+), TC10anti, TC3g(+), and TC12anti conformers. In the two first conformations the mentioned dihedral angles are nearer to 60° than in the last two. Thus (Table III) the torsional contribution is low in TC5g(+) and TC10anti and, although their OMe groups are axial (E_B elevated), they are the most stable conformations. On the contrary, in TC3g(+) and TC12anti, the OMe is equatorial but the E_T component is high because of the gauche effect and these are, respectively, the third and fourth highest conformers in stability.

Finally, the higher steric repulsions seem to be the only cause of the absence of some g(−) rotamers and of the higher energy of these rotamers relative to the anti or g(+) ones.

(b) ^{1}H NMR Results. Chemical shifts and coupling constants of **15** and **16** have been determined using the following techniques: ^{1}H NMR, ^{13}C NMR (homodecoupling and DEPT), 2D C–H correlation, 2D COSY, and 2D NOESY. We refer to hydrogen atoms as H-2, H-2′, according to the carbon atoms to which they are bonded, indicating as H-2′ the C-2 hydrogen atom that is cis to the methoxy group.

5-Methoxy-1,4-dioxepane (15). In the ^{1}H NMR spectrum of 5-methoxy-1,4-dioxepane H-5 (4.69 ppm), H-6 (2.16 ppm), and H-6′ (1.98 ppm) signals can be clearly observed, assignment being confirmed by irradiating H-5 and by the $J_{5,6}$ and $J_{5,6'}$ coupling constants. At 3.97 and 3.47 ppm the signals of two geminal protons appear that have been assigned to H-3′ and H-3, respectively, on the basis of the following reasoning: (i) the proximity of the OMe group should cause a greater chemical shift difference between the C-3 hydrogens than between those of C-2 or C-7 and (ii) there is (2D NOESY) a quadrupolar coupling between H-6′ and H-3′. The coupled multiplets at 3.81 and 3.39 ppm (and at 3.60 and 3.51 ppm) integrate to two hydrogens, and the 2D CH correlation demonstrates that each signal corresponds to one of the C-2 hydrogen atoms and one at C-7. In the first multiplet, H-7′ can be identified and this, together with the 2D COSY spectrum, has allowed us to assign the relative chemical shifts of H-2, H-2′, and H-7′.

Table V shows $^3J_{HH}$ experimental and theoretical coupling constants between neighboring protons in compound **15**. The theoretical constants have been calculated, according to the generalization of the Karplus equation carried out by Haasnoot,[19] for each one of the conformers, and their values have been averaged, according to the conformational populations, in order to compare them with those observed experimentally. As can be seen, the concordance between the theoretical and the experimental values is excellent (σ_{ms} = 0.70). Finally, it can be added that in **15**, 2D NOESY quadrupolar couplings between H-6′ and H-3′ (vide supra) and between H-5 and H-7 are observed, indicating their spatial proximity. This fact is in accordance with the distances calculated by means of the MM2(85) program between the hydrogen pair in the TC3anti conformer (2.36 and 2.78 Å respectively).

Table V. Theoretical and Experimental $^3J_{HH}$ Coupling Constants of 5-Methoxy-1,4-dioxepane (15) and 2-Methoxy-1,4-dioxepane (16)

	15		16	
coupling	J_{cal}	J_{exp}	J_{cal}	J_{exp}
H-2, H-3	1.86	1.62	3.29	4.08
H-2, H-3′	8.52	9.29	8.21	7.35
H-2′, H-3	3.51	3.27	–	–
H-2′, H-3′	1.12	1.36	–	–
H-5, H-6	5.22	5.67	4.71	5.37
H-5, H-6′	8.66	7.83	3.81	2.58
H-5′, H-6	–	–	9.79	10.32
H-5′, H-6′	–	–	3.47	3.96
H-6, H-7	1.23	1.64	3.87	3.88
H-6, H-7′	7.21	6.20	9.44	9.86
H-6′, H-7	8.93	9.35	4.58	4.74
H-6′, H-7′	1.34	2.20	2.87	2.47
	σ_{ms} = 0.70		σ_{ms} = 0.64	

2-Methoxy-1,4-dioxepane (16). The 2-methoxy-1,4-dioxepane ^{1}H NMR spectrum shows the signals of H-2 (4.69 ppm), H-3 (3.47 ppm), and H-3′ (3.97 ppm) which can be clearly identified on the basis of their chemical shifts and coupling constants. H-6 and H-6′ are observed at 2.04 and 1.73 ppm, respectively, and have been assigned by means of their coupling constants with protons at C-5 and C-7; H-5 and H-5′ appear at 4.02 and 3.55 ppm, respectively, and H-7 and H-7′ at 4.04 and 3.68 ppm. The assignment of the chemical shifts has been achieved as follows: (i) There is a long-range *w* coupling between the signals at 3.68 and 4.04 ppm ($J_{5,7}$ = 1.15 Hz), which shows the markedly equatorial character of H-5 and H-7 and, consequently, the axial character of H-5′ and H-7′. (ii) The existence of a NOE effect (2D NOESY and NOE difference) between the signal at 3.55 ppm and that of the H-3′ shows the spacial proximity between them and confirms the axial orientation of both hydrogens. (iii) H-7′ must be more deshielded than its geminal H-7 because it is cis to the 2-OMe group, as was proposed for H-3 and H-3′ of 5-methoxy-1,4-dioxepane (**15**).

Table V shows the $^3J_{HH}$ experimental and calculated coupling constants of **16**. The concordance between the values is better (σ_{ms} = 0.64) than that of 5-methoxy-1,4-dioxepane (**15**) and comparable to that described by Haasnoot.[19]

On the other hand, the $J_{5,7}$ long-range coupling constant requires that H-5, C-5, C-6, C-7, and H-7 lie in the same plane forming a *w*, which is a frequent situation in a more rigid six-membered ring; nevertheless, in the three preferred conformations of the ring (TC7anti, TC5anti, and TC10anti) the five mentioned atoms are in an arrangement very nearly appropriate for effective long-distance coupling. Finally, the calculated distance between H-3′ and H-5′ in the TC5anti and TC7anti conformations are 2.41 and 2.20 Å, respectively, sufficient to explain a NOE effect.

Whereas the synthesis of the 6-hydroxy-1,4-dioxepane has been carried out,[20] the 6-methoxy-1,4-dioxepane has not been prepared. The NMR data of the former compound and the symmetry of the latter lead us to expect that in the ^{1}H NMR spectra of **17**, only a coupling constant between the hydrogen atoms of C-5 and C-7 or C-6 would be observed so that a correlation between the experimental and theoretical data would be impossible. For this reason we did not study it.

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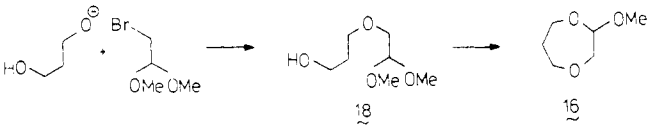
Scheme I



Conclusions

The theoretical conformational analysis of 5-methoxy-1,4-dioxepane (**15**), 2-methoxy-1,4-dioxepane (**16**), and 6-methoxy-1,4-dioxepane (**17**) shows a single TC3anti preferred conformation in **15**, while in **16** and **17** there are three (TC7anti,TC5anti, and TC10anti) and four (TC5g-(+), TC10anti, TC3g(+), and TC12anti) stable conformers, respectively. The observed conformational preferences can be explained on the basis of steric or stereoelectronic effects (anomeric in **15** and **16** and gauche in **17**). There is a good correlation between the experimental and calculated vicinal coupling constants in **15** and **16**, which supports the results presented. Moreover, in both cases the observed NOE effects can be explained if the calculated predominant conformations are assumed. Finally, in **16** there is a long-distance *w* coupling, compatible with the three calculated preferred conformations.

The conformational behavior of **15** and **16** shows two consequences of the anomeric effect in seven-membered rings: (i) The substituents affected by this effect do not necessarily adopt an axial conformation as they do in six-membered rings. (ii) The anomeric effect, as it has been previously described, can change the preferred conformation of seven-membered rings but does not modify the conformation in six-membered rings.

Experimental Section

NMR spectra were recorded on a Bruker AM-300 or WP-80CW spectrometer 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.

TLC was performed on silica gel G (Merck), with detection with iodine, using mixtures of ether–hexane as developing solvent.

5-Methoxy-1,4-dioxepane (**15**) has been synthesized previously by us,[21] but in this paper we describe its high-resolution NMR spectroscopic properties. 2-Methoxy-1,4-dioxepane has not been described previously and herein we describe its synthesis and structure (Scheme I).

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5-Methoxy-1,4-dioxepane 15: ^1H NMR (300 MHz) ($CDCl_3$) 4.69 (dd, 1 H, $J_{5,6}$ = 5.67 Hz, $J_{5,6'}$ = 7.83 Hz, H-5), 3.97 (m, 1 H, $J_{2,3'}$ = 9.29 Hz, $J_{2',3'}$ = 1.36 Hz, $J_{3,3'}$ = 13.52 Hz, H-3'), 3.79 (m, 1 H, $J_{6,7'}$ = 6.2 Hz, $J_{6',7'}$ = 2.2 Hz, $J_{7,7'}$ = 12.55 Hz, H-7'), 3.72 (m, 1 H, $J_{2',3'}$ = 1.36 Hz, $J_{2',3}$ = 3.27 Hz, H-2'), 3.56 (m, 1 H, $J_{2,3}$ = 1.62 Hz, $J_{2,3'}$ = 9.29 Hz, H-2), 3.54 (m, 1 H, $J_{6',7}$ = 9.35 Hz, $J_{6,7}$ = 1.64 Hz, $J_{7,7'}$ = 12.55 Hz, H-7), 3.47 (m, 1 H, $J_{2,3}$ = 1.62 Hz, $J_{2',3}$ = 3.27 Hz, $J_{3,3'}$ = 13.52 Hz, H-3), 3.32 (s, 3 H, OMe), 2.16 (m, 1 H, $J_{5,6}$ = 5.67 Hz, $J_{6,7}$ = 1.64 Hz, $J_{6,7'}$ = 6.2 Hz, $J_{6,6'}$ = 15.8 Hz, H-6), and 1.98 (m, 1 H, $J_{5,6'}$ = 7.83 Hz, $J_{6',7}$ = 9.35 Hz, $J_{6',7'}$ = 2.2 Hz, $J_{6,6'}$ = 15.8 Hz, H-6'); ^{13}C NMR ($CDCl_3$) 102.04 (C-5), 71.46 (C-2), 65.68 (C-7), 64.34 (C-3), 54.92 (OMe), and 38.27 (C-6).

1,1-Dimethoxy-2-(3-hydroxypropoxy)ethane (18). In a two-necked round-bottomed flask fitted with a reflux condenser and a dropping funnel are placed 150 mL of dry toluene and 0.13 mol of metallic Na, and the mixture is heated and stirred until the Na melts. Toluene is separated, and 150 mL of dry dioxane and, overall, 0.13 mol of 1,3-propanediol are add. The mixture is refluxed for 24 h, and, then, 0.23 mol of bromoacetaldehyde dimethyl acetal is added dropwise. After 36 h under reflux, the mixture is cooled, filtered, and concentrated, and the residue is dissolved in chloroform and washed with water. The organic layer is separated, dried over sodium sulfate, filtered, and concentrated. Distillation of the residue in vacuo yielded (bp 108–115 °C/16 Torr) 7 g (21%) of 1,1-dimethoxy-2-(3-hydroxypropoxy)ethane (**18**): ^1H NMR (80 MHz) ($CDCl_3$) 4.42 (t, 1 H, J = 5 Hz, CH), 4.8–3.4 (m, 7 H, OCH_2, OH), 3.34 (s, 6 H, OCH_3), and 1.60 (m, 2 H, $CH_2CH_2CH_2$); IR (KBr, film) 3440, 2920, 2850, 2820, 1460, 1440, 1375, 1360, 1320, 1270, 1245, 1190, 1115, 1050, 965, 910, 845, 750, and 580 cm^{-1}.

2-Methoxy-1,4-dioxepane (16). A 1.9-g portion of **18** is dissolved in 20 mL of dry ether, and a few drops of $Et_2O{\cdot}BF_3$ are added. The mixture is kept at room temperature for 22 h and washed with K_2CO_3 (10%), and the organic layer is dried over sodium sulfate, filtered, and concentrated. The residue is purified by column chromatography with ether–hexane (1:5 v/v), yielding 0.14 g (9%) of 2-methoxy-1,4-dioxepane (**16**): ^1H NMR (300 MHz) ($CDCl_3$) 4.67 (dd, 1 H, $J_{2,3}$ = 4.08 Hz, $J_{2,3'}$ = 7.35 Hz, H-2), 4.04 (m, 1 H, $J_{5,6}$ = 5.37 Hz, $J_{5,6'}$ = 2.58 Hz, $J_{5,7}$ = 1.15 Hz, $J_{5,5'}$ = 12.0 Hz, H-5), 4.02 (m, 1 H, $J_{6,7'}$ = 9.86 Hz, $J_{6',7'}$ = 2.47 Hz, $J_{7,7'}$ = 12.7 Hz, H-7'), 3.68 (m, 1 H, $J_{5,7}$ = 1.15 Hz, $J_{6,7}$ = 3.88 Hz, $J_{6',7}$ = 4.74 Hz, $J_{7,7'}$ = 12.7 Hz, H-7), 3.55 (m, 1 H, $J_{5',6}$ = 10.32 Hz, $J_{5',6'}$ = 3.96 Hz, $J_{5,5'}$ = 12.0 Hz, H-5'), 3.38 (s, 3 H, OMe), 2.04 (m, 1 H, $J_{5,6}$ = 5.37 Hz, $J_{5',6}$ = 10.32 Hz, $J_{6,7}$ = 3.88 Hz, $J_{6',7'}$ = 9.81 Hz, $J_{6,6'}$ = 15.6 Hz, H-6), and 1.73 (m, 1 H, $J_{5,6'}$ = 2.58 Hz, $J_{5',6'}$ = 10.32 Hz, $J_{6',7}$ = 4.74 Hz, $J_{6,6'}$ = 15.6 Hz, H-6'); ^{13}C NMR ($CDCl_3$) 101.93 (C-2), 73.40 (C-3), 72.60 (C-7), 61.10 (C-5) 55.28 (OMe), and 32.74 (C-6); MS (70 eV) m/z (%) $(M-1)^{\cdot+}$ 131 (<1), 104 (10), 101 (5), 74 (2), 73 (3), 72 (7), 71 (26), 61 (56), 59 (3), 58 (4), 59 (6), 45 (43), 44 (25), 43 (37), 42 (100), and 41 (45); IR (KBr, film) 2955, 2912, 2841, 1469, 1451, 1424, 1382, 1356, 1326, 1276, 1257, 1230, 1196, 1172, 1126, 1096, 1063, 1017, 958, 940, 912, 848, 779, and 585 cm^{-1}.

Registry No. **15**, 112853-53-9; **16**, 129708-83-4; **17**, 129708-84-5.