relative dipole moment change for different tautomers may vary considerably (e.g. m for 4-thioxopyridine increases by 46% in a medium of $\epsilon = 78.4$ when compared with $\epsilon = 1$, whereas for 4-mercaptopyridine the corresponding increase is only 18%). Such diverse variations of dipole moments invalidates the use of eq 12. When the multiplier in front of the dielectric constant function in eq 11 in LFER treatments is found empirically from the experimental data, it must be emphasized that this parameter varies with solvent. The calculated dependence of the dipole moment of the solutes on the dielectric constant function is nonlinear (cf ref 11d,e), and, moreover, the relationship between the dipole moments of the two tautomers is also not linear. Therefore, the use of eq 12 can lead only to a very qualitative description of the chemical phenomenon investigated. It follows that no "universal" single parameter solvent polarity scale[25-27,29-33] can exist for the description of chemical and physical processes.

The solvent reaction field can also have significant influence on the FMO energies of a solute molecule. However, FMO energy values for most of the structures in Table III are relatively insensitive to change in the dielectric medium. In general, the HOMO and LUMO energies of the C=X forms of tautomers are characterized by larger negative solvent shifts than those for the corresponding XH forms. For instance, the HOMO energy of 4-thioxopyridone is lowered by 1 eV and the LUMO energy of 4-pyridone by 0.55 eV, whereas the corresponding shifts for the XH forms are small positive numbers (0.1 and 0.17 eV, respectively). This observation is also reflected in the electron distributions of the molecules compared. The dipole moments of the C=X forms are altered more than those of the corresponding XH forms by the solvent reaction field. It appears that the charge redistribution in the heterocycles from the external field is due mainly to the frontier orbitals. Substantial relocalization of charge in these molecular orbitals in different dielectric media may lead to different reactivity in different dielectric media if we assume, for example, FMO theory.[34]

Several conclusions can be made on the basis of the results of the present investigation. First, our results indicate that the AM1 model[7] yields quite resonable results for the description of the prototropic equilibria, both for isolated molecules and for molecules in dielectric media (SCRF version). Secondly, the inclusion of the solvent reaction field in quantum-chemical theory is obligatory for accurate modeling of relative tautomer energies in solution. Thirdly, our results further indicate that a universal solvent polarity scale for LFER analysis is not justified. Finally, we observe that the orbitals most affected by the solvent reaction field in the substituted pyridines studied here are the frontier MO's.

Registry No. 2-Hydroxypyridine, 72762-00-6; 2(1*H*)-pyridone, 142-08-5; 2-aminopyridine, 504-29-0; 2(1*H*)-iminopyridine, 76959-52-9; 2-mercaptopyridone, 73018-10-7; 2(1*H*)-thioxopyridone, 2637-34-5; 2-methylpyridine, 109-06-8; 2(1*H*)-methylenepyridine, 34037-14-4; 3-hydroxypyridine, 109-00-2; 3(2*H*)-pyridone, 80618-81-1; 3-aminopyridine, 462-08-8; 3(2*H*)-iminopyridine, 80618-82-2; 3-mercaptopyridine, 16133-26-9; 3-(2*H*)-thioxopyridone, 76076-29-4; 3-methylpyridine, 108-99-6; 3(2*H*)-methylenepyridine, 123597-03-5; 4-hydroxypyridine, 626-64-2; 4(1*H*)-pyridone, 108-96-3; 4-aminopyridine, 504-24-5; 4-(1*H*)-iminopyridine, 29212-32-6; 4-mercaptopyridine, 4556-23-4; 4(1*H*)-thioxopyridone, 19829-29-9; 4-methylpyridine, 108-89-4; 4(1*H*)-methylenepyridine, 123597-04-6.

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Conformational Analysis of Some 1,4-Dioxepines by Molecular Mechanics (MM2)

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The conformational analyses of 2,3-dihydro-5*H*-1,4-dioxepine (**5**), 5-methoxy-2,3-dihydro-5*H*-1,4-dioxepine (**6**), and 6,7-dihydro-5*H*-1,4-dioxepine (**7**) have been theoretically studied by molecular mechanics, indicating a preference for a twist-boat conformation in **5** and for a chair in **6** and **7**. The stability of the different conformations is governed by the conjugation of the oxygen atoms with the π system, in **5** and **7**, and by this conjugation and the anomeric effect in **6**. The barrier for the chair ⇌ twist boat interconversion is 2.50 kcal/mol in **5** and 3.78 kcal/mol in **6**. The concordance between calculated and experimental coupling constants of **5** and **6** upholds these results.

Introduction

The conformational analysis of seven-membered rings has been the subject of special attention in recent years, and one in which molecular mechanics has emerged as a very powerful tool. The conformational behaviors of cycloheptane,[1] 1,3-dioxepane,[2] and 1,4-dioxepane[3] have been studied with different force fields, resulting in the finding that there exists in these compounds a complex confor-

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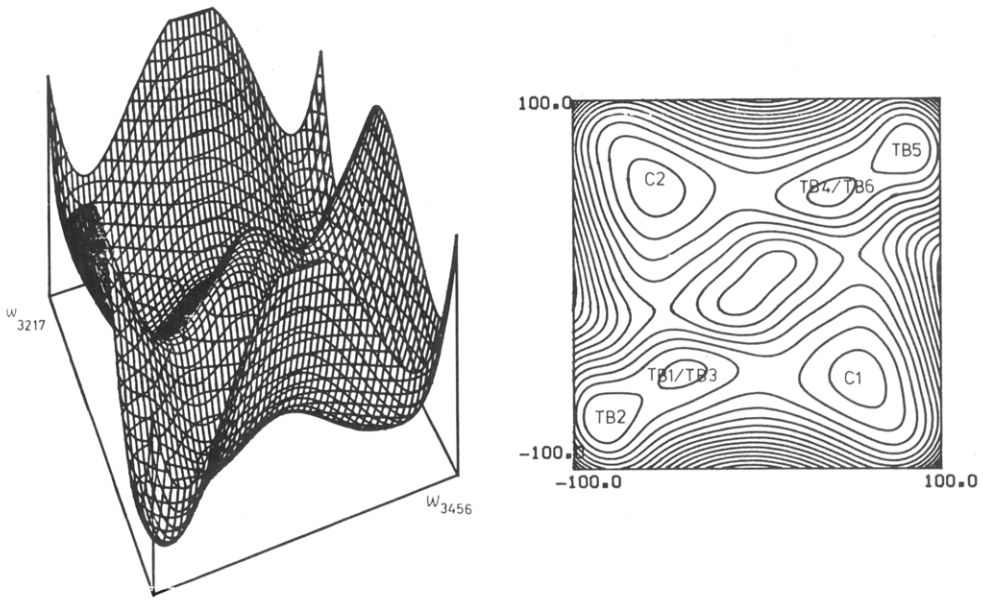
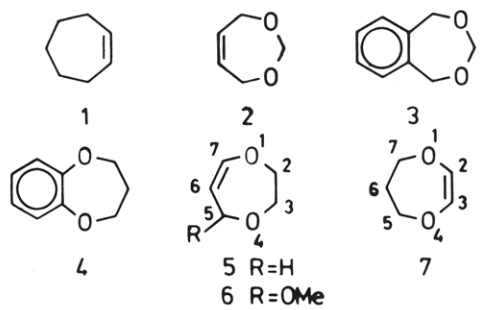


Figure 1. Calculated potential energy surface for 2,3-dihydro-5*H*-1,4-dioxepine (**5**) as a function of the dihedral angles ω_{3456} and ω_{2176}. The separation between lines is 1 kcal/mol.

mational equilibrium between the chair, twist-chair, boat and twist–boat forms, with the twist-chair being the most favored conformation.

The presence of a double bond in the ring considerably reduces the number of possible conformations. Thus, the chair[4] has been described as the most stable form for cycloheptene (**1**), while the twist-boat is considered the most stable form for 4,7-dihydro-2*H*-1,3-dioxepine (**2**)[5] as well as for 2,4-benzodioxepine (**3**).[5c,6] In contrast, the 1,4-dioxepine systems have barely been studied up to the present. Some 1,5-benzodioxepine derivatives, **4**, which have been studied by NMR, have exhibited preferences for the chair or twist-boat conformations, depending upon the C-3 substituent.[7] 2,3-Dihydro-5*H*-1,4-dioxepine (**5**) has been described,[8] although its conformational behavior has not been studied; 6,7-dihydro-5*H*-1,4-dioxepine (**7**) has not yet been synthesized, nor has its theoretical conformational behavior been analyzed.



In this paper we describe the MM2 results on the conformational analysis of 2,3-dihydro-5*H*-1,4-dioxepine (**5**) and of 5-methoxy-2,3-dihydro-5*H*-1,4-dioxepine (**6**) and compare the results obtained with the experimental data available for these compounds. In the same way, we present a theoretical conformational study of 6,7-dihydro-5*H*-1,4-dioxepine (**7**).

Results and Discussion

The conformational analysis of compounds **5** and **7** has been carried out according to the methodology described by Osawa:[1c] (i) calculation of the torsional energy surface representing the pseudorotational movement of these compounds by using either the one- or two-bond drive technique within the MM2[9a] program, and (ii) full characterization of the stationary points by using the BIGSTRN-3[9b] program implemented with all MM2 parameters. Eigenvector distortion of the energy maxima (BIGSTRN-3) was applied for obtaining the energy minima connected by the maxima.

The study of compound **6** has been carried out by the MM2 program, using the conformers of **5** as the starting points and taking into consideration the different rotamers of the 5-OMe group.

The $^3J_{HH}$ coupling constants between neighboring protons through the C–C bond have been calculated according to the generalization of the Karplus equation carried out by Haasnoot.[10] The vinylic $^3J_{HH}$ and $^4J_{HH}$ (allylic) constants have been calculated with the Garbisch equation.[11] In both cases these constants have been calculated for each the conformers and the individual values have been averaged in accordance with the conformational populations, so as to compare them with the values observed experimentally.

2,3-Dihydro-5*H*-1,4-dioxepine (5). As expected, the presence of a double bond introduces considerable rigidity into the ring and reduces substantially the number of conformations that can participate in the pseudorotational equilibrium of **5**, in comparison to 1,4-dioxepane.[3] The representation of the pseudorotational surface as a function of the two internal dihedral angles ω_{3456} and ω_{3217} is shown

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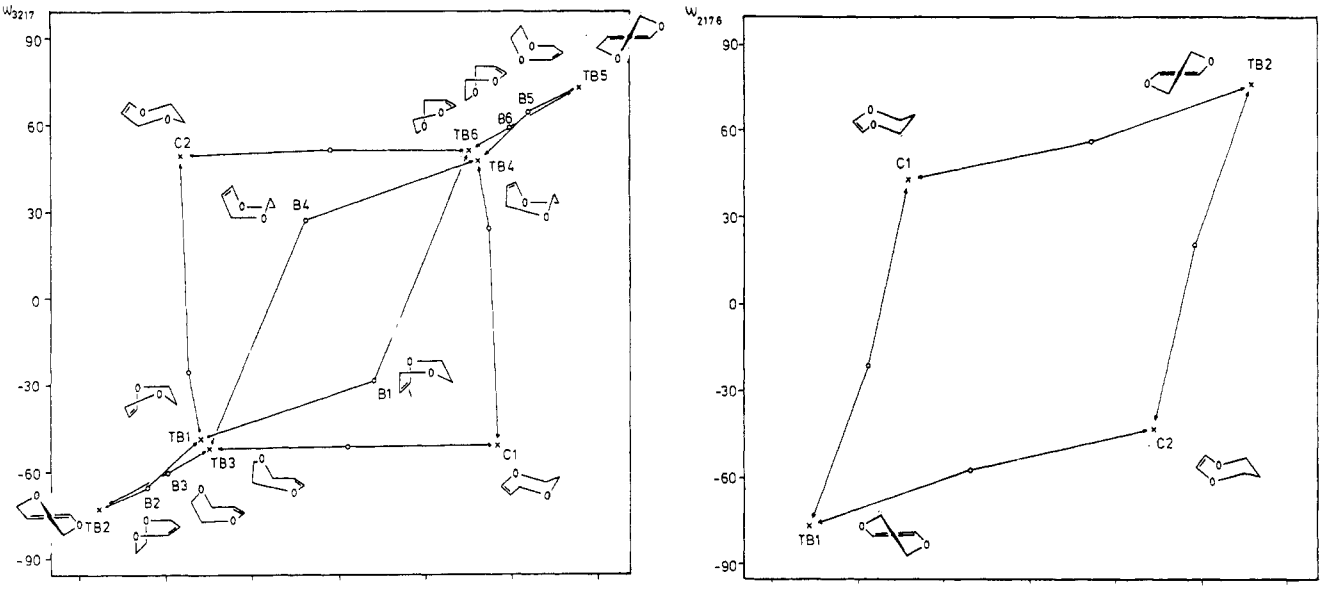

Figure 2. Schematic representation of the pseudorotational equilibria of 2,3-dihydro-5*H*-1,4-dioxepine (**5**, left) and of 6,7-dihydro-5*H*-1,4-dioxepine (**7**, right). × and ○ represent the maximum and minimum energetics, respectively.

Table I. Intraannular Dihedral Angles and Relative Energies[a] (kcal/mol) Calculated for the Most Significative Conformations of the Dioxepines 5 and 7

compd	conformation	ω_{1234}	ω_{2345}	ω_{3456}	ω_{4567}	ω_{1765}	ω_{2176}	ω_{3217}	rel *E*
5	C1	86.9	-88.5	55.1	-22.1	3.5	17.2	-50.6	0.49
5	C2	-86.9	88.5	-55.1	22.1	-3.5	-17.2	50.6	0.49
5	TB1	-36.1	94.8	-48.5	-13.1	-2.8	64.4	-48.4	4.74
5	TB2	53.1	34.5	-83.1	42.6	6.1	17.5	-72.9	0.00
5	TB3	90.0	-30.1	-44.9	57.6	-2.8	-3.7	-52.5	0.76
5	TB4	36.1	-94.8	48.5	13.1	2.8	-64.4	48.4	4.74
5	TB5	-53.1	-34.5	83.1	-42.6	-6.1	-17.5	72.9	0.00
5	TB6	-90.0	30.1	44.9	-57.6	2.8	3.7	52.5	0.76
5	B1	-59.9	66.3	11.9	-58.5	-1.4	66.5	-27.9	7.78
5	B2	-7.4	82.3	-66.1	2.5	1.0	56.2	-64.8	5.51
5	B3	80.0	-8.2	-60.2	55.6	0.3	2.3	-60.3	0.91
5	B4	59.9	-66.3	-11.9	58.5	1.4	-66.5	27.9	7.78
5	B5	7.4	-82.3	66.1	-2.5	-1.0	-56.2	64.8	5.51
5	B6	-80.0	8.2	60.2	-55.6	-0.3	-2.3	60.3	0.91
5	C1 ⇄ TB3	100.1	-66.0	3.0	25.2	-0.9	1.9	-51.3	2.50
5	C1 ⇄ TB4	49.9	-98.0	52.1	7.5	-1.3	-43.1	24.9	5.09
5	C2 ⇄ TB6	-100.1	66.0	-3.0	-25.2	0.9	-1.9	51.3	2.50
5	C2 ⇄ TB1	-49.9	98.0	-52.1	-7.5	1.3	43.1	-24.9	5.09
7	C1	0.0	9.8	-43.4	82.7	-82.7	43.4	-9.8	0.00
7	C2	0.0	-9.8	43.4	-82.7	82.7	-43.4	9.8	0.00
7	TB1	10.2	28.5	-77.3	42.4	42.4	-77.3	28.5	0.31
7	TB2	-10.2	-28.5	77.3	-42.4	-42.4	77.3	-28.5	0.31
7	C1 ⇄ TB1	2.3	1.6	-56.8	92.3	-44.3	-20.9	35.7	3.78
7	C1 ⇄ TB2	-2.3	-35.7	20.9	44.3	-92.3	56.8	-1.6	3.78
7	C2 ⇄ TB1	2.3	35.7	-20.9	-44.3	92.3	-56.8	1.6	3.78
7	C2 ⇄ TB2	-2.3	-1.6	56.8	-92.3	44.3	20.9	-35.7	3.78

[a] The relative energies have been defined with respect to the most stable conformation of each compound: TB2/TB5 for **5** and C1 for **6**.

in Figure 1, using an interval of 10° in the driver. This particular representation was chosen because it is the one that contains the greatest number of stationary points. Nevertheless, a careful analysis of the surface shows that it is discontinuous, as some of its points of minimum energy correspond to several different conformations of the ring (TB1/TB3 and TB4/TB5). Eight different energetic minima are found, and 10 saddle points connect these minima. The geometry analysis of these minima, using Dreiding models, reveals that two of them are chair conformations of equal energy (C1 and C2), while the remaining six are isoenergetic twist-boat forms in pairs TB1/TB4, TB2/TB5, and TB3/TB6. These twist-boat conformations take part in a closed pseudorotational pathway consisting of two isoenergetic boat forms (B1/B4) and four isoenergetic envelope forms in pairs (B2/B5 and B3/B6), which are the transition states in the circuit. Finally, each chair form is transformed through two different transition states in two twist–boat forms, completing the total of 10 transition states.

Figure 2 presents schematically the complete pseudorotational equilibrium of **5** as a function of the internal dihedral angles ω_{3456} and ω_{3217}. Table I summarizes the internal dihedral angles for each of the stationary states mentioned, together with the relative energy (kcal/mol) defined in relation to the more stable conformer (TB2/TB5).

The differences in energy among different conformations cannot be explained on the basis of a single factor, as in the case of 1,4-dioxepane.[3] An analysis of the different contributions to the steric energy calculated for each conformation shows that two main factors affect the sta-

Table II. Intraannular Bond Angles, Deviation of the "Natural" Values (in Parentheses), and Root-Mean-Square of the Energetically Different Stationary Points of the Dioxepines 5 and 7

compd	conformation	θ_{123}	θ_{234}	θ_{345}	θ_{456}	θ_{567}	θ_{176}	θ_{217}	σ_{ms}
5	C1	113.6 (6.2)	108.9 (1.5)	112.9 (6.1)	117.1 (7.6)	130.7 (8.7)	132.2 (8.0)	120.2 (9.4)	3.93
5	TB1	113.5 (6.1)	110.6 (3.2)	111.8 (5.0)	115.1 (5.6)	125.5 (3.5)	126.0 (1.8)	115.7 (4.9)	2.51
5	TB2	113.9 (6.5)	115.1 (7.7)	114.2 (7.4)	110.5 (1.0)	124.7 (2.7)	128.3 (4.1)	116.7 (5.9)	3.13
5	TB3	111.1 (3.7)	114.7 (7.3)	115.6 (8.8)	115.5 (6.0)	125.8 (3.8)	128.8 (4.6)	117.7 (6.9)	3.38
5	B1	114.8 (7.4)	113.4 (6.0)	115.0 (8.2)	115.6 (6.1)	120.6 (−1.4)	122.7 (−1.5)	114.7 (3.9)	2.91
5	B2	115.1 (7.7)	113.5 (6.1)	112.4 (5.6)	114.7 (5.2)	125.7 (3.7)	127.1 (2.7)	115.4 (4.6)	2.85
5	B3	112.1 (4.7)	116.7 (9.3)	116.2 (9.4)	113.6 (4.1)	125.6 (3.6)	128.7 (4.3)	117.7 (6.9)	3.58
5	C1 ⇄ TB3	110.8 (3.4)	109.9 (2.5)	115.8 (9.0)	121.0 (11.5)	131.3 (9.3)	130.6 (6.2)	117.4 (6.6)	5.09
5	C1 ⇄ TB4	116.4 (9.0)	109.9 (2.5)	110.9 (4.1)	114.5 (5.0)	127.8 (5.8)	130.3 (5.9)	120.6 (9.8)	3.46
7	C1	133.7 (9.3)	133.7 (9.3)	120.9 (10.1)	113.3 (5.9)	109.9 (0.4)	113.3 (5.9)	120.9 (10.1)	4.27
7	TB1	128.0 (3.6)	128.0 (3.6)	115.3 (4.5)	113.1 (5.7)	114.6 (5.1)	113.1 (5.7)	115.3 (4.5)	2.57
7	C1 ⇄ TB1	132.0 (7.6)	130.7 (6.3)	117.1 (6.3)	109.4 (2.0)	112.3 (2.8)	116.9 (9.5)	122.1 (11.3)	3.82

bility of each stationary state: (i) torsional energy of the dihedral bond angles, and (ii) bending energy of the ring bond angles.

The influence of the torsional energy component seems to be predominant and is fundamentally due to the contribution of the dihedral angles formed by the C-6, C-7, O-1, and C-2 atoms on one hand and the C-2, O-1, C-7, and H-7 atoms on the other; these dihedral angles exhibit a strong preference for coplanarity. This conformational preference is a consequence of the conjugation of one of the electronic lone pairs on the O-1 atom with the π cloud of the double bond between C-6 and C-7, exactly as has been described for the enolic ethers.[12] Although this conjugation is not properly treated in the force field, it is implicitly considered in the torsional constants of the dihedral angles mentioned. These angles produce an energy minimum when they acquire a value of 0° or 180° (necessary for the conjugation to be effective) and provoke a rapid increase of the torsional energy on diverging from these values. The most favored conformation from the torsional point of view would be B3(B6) (ω_{2176} = 2.4°) while the least favored is B2(B5) (ω_{2176} = 66.5°).

The coplanarity preference of such groups is so great that in some conformations small dihedral angles are obtained at the cost of considerable deformation of the bond angles of the ring, with the result that the bending energy assumes second rank in importance. The intrannular bond angles, the deviation from the "natural" value of these angles, and the value of σ_{ms} of these deviations, calculated for each of the energetically different conformations, are shown in Table II. In general, it can be observed that the average deviation is great in all cases.

The chair conformation undergoes a great deviation of all angles, which makes the chair very flattened and permits an acceptable degree of coplanarity for the C-2, O-1, C-7, and C-6 (ω_{2176} = 17.2°). In the TB1 conformation the average deviation of the bond angle is lowest (σ_{ms} = 2.51); nevertheless, the torsional contribution to its steric energy is so high (ω_{2176} = 64.4°) that it is converted into the conformer with the greatest energetic content.

The two factors mentioned above combine in such a way so as to minimize the total sum in the two most stable conformers, TB2 and TB5: the torsional contribution is small because the angle ω_{2176} is small (17°) and the bending contribution (σ_{ms} = 3.13) takes on a medium value.

The nonbonding interactions seem to be unimportant, due to the low number of hydrogen atoms that can interact; there is only one hydrogen atom at each C-6 and C-7 position, and it assumes a markedly equatorial disposition in all conformations. Such contributions take on the highest values in the conformations B1 and B4, but they are mainly due to the interactions between carbon atoms (C-3 and C-6 or C-7).

Finally, two atoms of the ring exchange their relative positions with regard to a hypothetical equatorial plane of the ring in the transformations between chair and twist-boat forms. The difference in energy between both transition states is due, once again, to the degree of conjugation of the O-1 atom with the π system.

In the C1 ⇄ TB3 transition, the O-4 atom moves upward with regard to the equatorial plane, while C-5 dips below the plane; this adjustment allows the dihedral angle to adopt a low value, with the result that the torsional contribution will be very small and the total energy low. On the other hand, in the C1 ⇄ TB4 transition, the atom that rises is C-2, and the one that descends is O-1; the dihedral angle ω_{2176} thus acquires a high value, and conjugation between the electronic pair and the π system is not possible. As a result, the torsional contribution will be large and the torsional energy of this transition state will also be high.

6,7-Dihydro-5*H*-1,4-dioxepine (7). The conformational behavior of the dioxepine 7 is even simpler than that of its isomer 5. For this compound, only four energetic minima have been found, which interchange through another four maxima, forming a closed pseudorotational pathway. Two of the conformations of minimal energy correspond to the chair forms (C1 and C2), and the other two are twist-boat forms (TB1 and TB2). Such simple behavior is surprising; nevertheless, 1,5-benzodioxepine (4) and its derivatives, in which the benzene ring would introduce a rigidity comparable to the double bond, show preference for conformations equivalent to the chair or the twist-boat conformation of 7.

The complete pseudorotational pathway as a function of the intraannular dihedral angles ω_{3456} and ω_{2176} is represented in Figure 2, together with the geometry of the conformers. Table I shows the intraanular dihedral angles for each of the stationary points, together with the relative energy (kcal/mol) expressed in relation to the more stable conformations (C1/C2).

As was found in the case of compound 5, the difference in energy between the different conformations depends mainly on the torsional and bending contributions, the former being more important than the latter. In this case, the torsional contribution is due to the dihedral angles formed by the C-7, O-1, C-2, and C-3; C-7, O-1, C-2, and H-2; C-5, O-4, C-3, and C-2; and C-5, O-4, C-3, and H-3 atoms. The value of these dihedral angles should be near to 0° so that the electronic pairs of O-1 and O-4 can conjugate with the π bond, since the compound is a double enol ether.

From this point of view, the C1 and C2 conformations are the most favored because, in these forms, the dihedral angles mentioned above assume values near 0° (ω_{3217} = 9.8°

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Table III. Calculated Conformations, Their Relative Energies,[a] and Conformational Populations (percent) of 5-Methoxy-2,3-dihydro-5*H*-1,4-dioxepine (6)

conformation	rel *E*	popn
C1-g(+)	2.02	1.23
C1-g(−)	2.16	0.96
C2-g(+)	0.00	37.32
C2-g(−)	2.21	0.88
TB1-g(+)	3.73	0.06
TB1-g(−)	6.54	0.00
TB2-anti	1.96	1.34
TB2-g(+)	0.53	15.04
TB2-g(−)	7.61	0.00
TB3-anti	1.69	2.13
TB3-g(+)	0.28	23.05
TB4-anti	7.91	0.00
TB4-g(+)	6.15	0.00
TB4-g(−)	5.89	0.00
TB5-anti	2.76	0.34
TB5-g(+)	0.71	11.19
TB5-g(−)	1.52	2.83
TB6-anti	3.30	0.14
TB6-g(+)	1.49	2.98
TB6-g(−)	2.62	0.44

[a] Relatives energies are defined with respect to the most stable conformation, C2-g(+).

and $\omega_{2345} = -9.8°$). However, for this to occur, the bond angles have to open considerably, causing the chair to be considerably flattened, in which case the bending contribution becomes important ($\sigma_{ms} = 4.27$). In the TB1 and TB2 conformations, on the other hand, the deformations of the bond angles are small ($\sigma_{ms} = 2.57$) but the torsional contribution is great, since the dihedral angles mentioned acquire a high value ($\omega_{2345} = \omega_{3217} = 28.5°$ in TB1). The result is that the conjugation in TB1 of the pairs of electrons of O-1 and O-4 with the π bond is not very effective.

This compound should be expeced to present a B/TB family equivalent to that of **5** formed by six boats and another six twist-boats. When the molecular models of these conformations are examined, the absence of a flexible family can be understood. In all the conformations, the values of the dihedral angles ω_{2345} and ω_{3217} are less favorable than in TB1 or TB2 because, although one of them approaches 0°, the other moves considerably farther away. A situation similar to that of the chair forms is to be expected only in the boats that can be obtained by inverting C1 and C2, on condition that these boats are sufficiently flattened for the conjugation of the π bond and the O-1 and O-4 atoms to be efficient, as in the case of the chairs. Even so, in these cases C-6 would remain too close to the double bond, and nonbonding interaction would appear between C-6 and C-2 or C-3. To partially alleviate these repulsions, the boats would twist to TB1 or TB2 or would flip into a chair.

Finally, in the C $\rightleftarrows$ TB transitions, an oxygen atom and the vicinal sp^3 carbon change their positions relative to the equatorial plane of the molecule. In the C1 $\rightleftarrows$ TB1 transition, O-1 moves upward from below the plane and C-7 moves downward from above the plane. The movement of these atoms causes an interruption of the conjugation between O-1 and the π system ($\omega_{3217} = 75°$), with the result that its energy is greater than the conformations that it interconverts.

5-Methoxy-2,3-dihydro-5*H*-1,4-dioxepine (6). The conformational analysis of the compound **6** has been carried out, taking into consideration the influence of the methoxy group on the conformation of the ring. Thus the eight conformers of the dioxepine **5** have been analyzed, substituting the equatorial hydrogen of C-5 in **C1** by a methoxy group and carrying out the equivalent substitution in the other conformers. On the other hand, the methoxy group can give rise to three rotamers around the C_5–O_8 bond which have been defined according to the value of the dihedral angle ω_{4589} (Figure 3). Table III lists the conformational populations together with the relative energies calculated for each of the conformations found. Attempts made to calculate the rotamers that are missing from the table have proven unsuccessful.

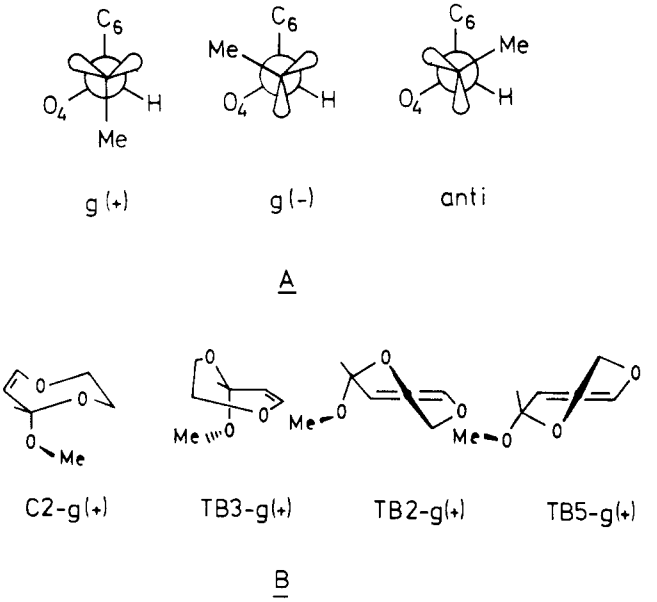


Figure 3. (a) Rotamers around the O_4–C_5–O_8–C_9 bond of 5-methoxy-2,3-dihydro-5*H*-1,4-dioxepine (**6**). (b) Four more stable conformations of 5-methoxy-2,3-dihydro-5*H*-1,4-dioxepine (**6**).

Table IV. Theoretical and Experimental Coupling Constants of 2,3-Dihydro-5*H*-1,4-dioxepine (5) and of 5-Methoxy-2,3-dihydro-5*H*-1,4-dioxepine (6)

	5		6	
coupling	J_{exp}	J_{calc}	J_{exp}	J_{calc}
$J_{2,3}$	*a*	2.89	0.8	2.37
$J_{2,3'}$	*a*	5.41	5.6	5.46
$J_{2',3}$	*a*	6.56	7.8	6.64
$J_{2',3'}$	*a*	2.90	1.12	2.43
$J_{5,6}$	3.9	4.41	3.9	4.76
$J_{5',6}$	3.9	4.41		
$J_{5,7}$	1.5	0.9	0.0	−0.8
$J_{5',7}$	1.5	0.9		

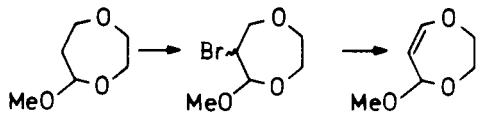
[a] Unresolved coupling constants.

The presence of the methoxy group breaks the degeneracy that existed among the conformations of the dioxepine **5**, and four predominant conformations (C2-g(+), TB3-g(+), TB2-g(+) and TB5-g(+)) are observed. These correspond to the three more stable conformers of the ring, although the order of stability has been altered. The factor that controls the difference in stability among these conformations is the anomeric effect, understood as the tendency of the C_3–O_4–C_5–O_8–C_9 moiety to assume a "gauche" conformation about the O_4–C_5–O_8 bonds. Thus, the C2-g(+) conformer (Figure 3) is the most stable since it places the methoxy group axial ($\omega_{3458} = 78°$) and the angle $\omega_{4589} = 77°$, as a result of which both angles are near to a g(+) conformation. In the other conformations, the situation is less favorable.

The anomeric effect also seems to be responsible for the absence of anti rotamers in some conformations (ω_{4589} is near 180° in anti rotamers), as well as for the high energy of these rotamers when they do exist.

Finally, Table IV shows the theoretical and experimental coupling constants for 2,3-dihydro-5*H*-1,4-dioxepine (**5**)

Scheme I



8 9 6

and 5-methoxy-2,3-dihydro-5*H*-1,4-dioxepine (**6**). It can be observed that the concordance is good in the case of **6**; although the value of the $\sigma_{ms} = 1.07$, the Karplus equation has been developed for six-membered rings, and even for these systems, the value of $\sigma_{ms} = 0.7$. Unfortunately, the coupling constants of the O–CH_2–CH_2–O grouping in **5** are unresolved in its ^{1}H NMR spectrum (300 MHz); nevertheless, there exists a concordance between the experimental and calculated $J_{5,6}$ and $J_{5,7}$ constants. These agreements uphold the calculations performed.

Conclusions

The conformational behavior of the **5**, **6**, and **7** dioxepines has been studied by MM2 calculations. The number of total conformations is reduced due to the presence of a double bond. In the case of **5**, two chairs and a closed pseudorotational pathway in which six TB conformations are the energetic minima are found, separated by six other B forms, which are the transition states. For **7**, a pseudorotational pathway is found that is formed by four minima (two C and two TB) and four maxima which are the transition states for the C $\rightleftarrows$ TB interconversion. Compound **5** shows preference for the TB conformation while its isomer **7** prefers the C form. The difference in stability among the conformations has been explained on the basis of the capacity of the electronic pairs of the ring oxygens to conjugate with the π bond. The energies of the C $\rightleftarrows$ TB transition states are also governed by this same conjugation. The barrier for this interconversion is 2.50 kcal/mol for the former compound and 3.78 kcal/mol for the latter. In contrast, compound **6** adopts as its preferred conformation a C form in which the methoxy group is axial, and whose greater stability is attributed to the anomeric effect. The concordance between the theoretical and experimental coupling constants of **5** and **6** compounds upholds the results presented.

Experimental Section

NMR spectra were recorded on a Bruker AM-300 spectrometer in $CDCl_3$ solutions using TMS as internal standard. The infrared spectra (IR) were recorded on a Perkin-Elmer 782 spectrometer connected to a 3600 data station, as a neat film over KBr. The mass spectra were obtained by using a Hewlett-Packard 5988A spectrometer at 70 eV, carrying out injection through a 5890 gas chromatograph.

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

2,3-Dihydro-5*H*-1,4-dioxepine (**5**) has been previously reported;[8] nevertheless, we describe herein its spectroscopical properties: ^{1}H NMR (300 MHz), ^{13}C NMR (75.4 MHz), MS, and IR.

5-Methoxy-2,3-dihydro-5*H*-1,4-dioxepine (**6**) synthesis has been carried out as indicated in Scheme I from 5-methoxy-1,4-dioxepane (**8**), previously reported by us.[13]

2,3-Dihydro-5*H*-1,4-dioxepine (5): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.31 (dt, 1 H, $J_{6,7} = 7.6$ Hz, $J_{5,7} = J_{5',7} = 1.56$ Hz, H-7), 4.69 (dt, 1 H, $J_{6,7} = 7.6$ Hz, $J_{5,6} = J_{5',6} = 4.30$ Hz, H-6), 4.16 (dd, 2 H, $J_{5,6} = J_{5',6} = 4.30$ Hz, $J_{5,7} = J_{5',7} = 1.56$ Hz, H-5 and H-5'), 4.05 (m, 2 H, H-3 and H-3'), and 3.77 (m, 2 H, H-2 and H-2'); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 146.99 (C-7), 121.59 (C-6), 105.94 (C-5), 71.89 (C-2), and 68.00 (C-3); IR (film) 3030, 2930, 2900, 2840, 1650, 1435, 1375, 1310, 1275, 1210, 1160, 1090, 1015, 980, 895, 880, 830, and 730 cm^{-1}; MS, m/z (%) 101 ((M + 1)$^{\bullet+}$, 2), 100 (57), 99 (37), 73 (32), 71 (14), 70 (2), 69 (14), 57 (3.8), 56 (4.8), 55 (18.5), 45 (32), 44 (44), 43 (100), 42 (50), 41 (38.5), 40 (32), and 39 (57).

6-Bromo-5-methoxy-1,4-dioxepane (9). **8** (5.2 g) was dissolved in 52 mL of anhydrous ethyl ether and placed in a three-necked round-bottomed flask fitted with a reflux condenser, a dropping funnel, and a capillary for the entry of nitrogen, and 1.5 mL of bromine was added dropwise under a nitrogen flow. The solution was stirred until the bromine color disappeared. Then, 9.6 g of anhydrous K_2CO_3 was added, and the stirring was continued for about 5 h. The solution was filtered and concentrated, and the residue was distilled in vacuo to yield 3.98 g (bp 68–72 °C/12 Torr). This fraction was chromatographed on a silica gel column. Elution with a mixture of ether:hexane (1:6 v/v) yielded 2.06 g of **9** (26%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.78 (d, 1 H, $J_{5,6'} = 6.8$ Hz, H-5), 3.98 (m, 1 H, $J_{2',3'} = 2.4$ Hz, $J_{2,3'} = 8.1$ Hz, and $J_{3,3'} = 13.4$ Hz, H-3'), 4.0–3.95 (m, 2 H, H-6' and H-7'), 3.87 (dd, 1 H, $J_{7,7'} = 13$ Hz and $J_{6',7} = 9$ Hz, H-7), 3. 74 (m, 1 H, $J_{2',3'} = 2.4$ Hz, $J_{2',3} = 3.7$ Hz, and $J_{2,2'} = 12.6$ Hz, H-2'), 3.66 (m, 1 H, $J_{2,3} = 2.2$ Hz, $J_{2,3'} = 8.1$ Hz, and $J_{2,2'} = 12.6$ Hz, H-2), 3.56 (m, 1 H, $J_{2,3} = 2.2$ Hz, $J_{2',3} = 3.7$ Hz, and $J_{3,3'} = 13.4$ Hz, H-3), and 3.41 (s, 3 H, –OCH_3); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 107.87 (C-5), 72.92 (C-7), 71.41 (C-3), 65.43 (C-2), 55.81 (–O–CH_3), and 52.07 (C-6); IR (film) 2958, 2915, 2869, 2841, 1454, 1377, 1320, 1294, 1266, 1242, 1212, 1198, 1146, 1109, 1078, 1061, 1001, 958, 923, 871, 829, 739, 645, 624, and 571 cm^{-1}; MS, m/z (%) 212 (M$^{\bullet+}$, 2), 210 (1), 181 (4), 179 (4), 168 (1), 167 (1), 166 (1), 152 (2), 151 (1), 150 (3), 149 (1), 138 (3), 137 (5), 136 (3), 135 (5), 109 (8), 108 (27), 107 (10), 106 (26), 105 (3), 104 (12), 95 (3), 93 (3), 87 (16), 74 (10), 73 (100), 71 (68), 61 (10), 45 (10), 44 (3), and 43 (11).

5-Methoxy-2,3-dihydro-5*H*-1,4-dioxepine (6). KOH (10.9 g) in 30 mL of anhydrous methanol was dissolved in a flask fitted with a reflux condenser and a capillary for the entry of nitrogen. **9** (14.36 g) was added to this solution, and this mixture was heated under reflux for 4 h, under a continuous nitrogen flow, cooled, and poured into 100 mL of water. The aqueous layer was extracted with chloroform (3 × 30 mL). The organic extracts were combined, dried over sodium sulfate, filtered, and concentrated. The residue was distilled in vacuo, under a nitrogen flow, to yield 6.99 g (79%) of **7** (bp 92–93 °C/50 Torr): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.17 (d, 1 H, $J_{6,7} = 8.26$ Hz, H-7), 5.01 (d, 1 H, $J_{5,6} = 3.91$ Hz, H-5), 4.56 (dd, 1 H, $J_{5,6} = 3.91$ Hz and $J_{6,7} = 8.26$ Hz, H-6), 4.29 (m, 1 H, $J_{2',3'} = 0.8$ Hz, $J_{2,3'} = 5.6$ Hz, and $J_{3,3'} = 13.8$ Hz, H-3'), 4.12 (m, 1 H, $J_{2',3'} = 0.8$ Hz, $J_{2',3} = 7.8$ Hz, and $J_{2,2'} = 12.6$ Hz, H-2'), 4.01 (m, 1 H, $J_{2,3} = 1.12$ Hz, $J_{2',3} = 7.8$ Hz, and $J_{3,3'} = 13.8$ Hz, H-3), 3.74 (m, 1 H, $J_{2,3} = 1.12$ Hz, $J_{2,3'} = 5.6$ Hz, and $J_{2,2'} = 12.6$ Hz, H-2), and 3.36 (s, 3 H, –O–CH_3); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 144.99 (C-7), 103.83 (C-5), 99.89 (C-6), 73.47 (C-2), 63.35 (C-3), and 54.55 (–OCH_3); IR (film) 3057, 2958, 2932, 2832, 1662, 1517, 1451, 1420, 1389, 1346, 1310, 1265, 1184, 1147, 1134, 1093, 1065, 1040, 998, 947, 890, 850, 752, and 575 cm^{-1}; MS, m/e (%) 130 (M$^{\bullet+}$, 14), 129 (67), 116 (5), 115 (75), 100 (8), 99 (47), 87 (7), 86 (5), 85 (100), 73 (36), 71 (41), 69 (73), 58 (40), 55 (13), 54 (7), 53 (6), 45 (33), 43 (38), and 42 (26).

Registry No. **5**, 4040-81-7; **6**, 123290-24-4; **7**, 123290-25-5; **8**, 112853-53-9; **9**, 123290-26-6.

(13) Espinosa, A.; Gallo, M. A.; Campos, J. *An. Quim.* **1983**, *79C*, 210.