

Conformational Preferences of 2,3,3a,8a-Tetrahydrofuro[2,3-*b*]benzofuran. The Chemical Modifications Drive the Pseudorotational Preferences

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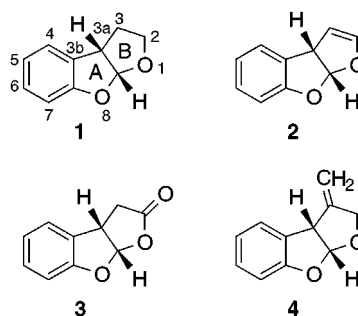
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Introduction

The conformational analysis of five-membered rings has been the subject of intensive research for many years. Fifty years ago, Kilpatrick et al.¹ introduced the concept of pseudorotation to explain the puckered conformation of cyclopentane. After this, the pseudorotation concept has been used to explain the conformational preferences of a large number of compounds.^{2,3} In this context, the furanose derivatives have been examined with particular insistence due to their key role in the molecular conformation and dynamics of compounds with biological interest.³

2,3,3a,8a-Tetrahydrofuro[2,3-*b*]benzofuran (**1**) is the parent compound of an important number of natural products with both toxic and therapeutic properties.^{4–7} Thus, **1** is present in a metabolite denoted aflatoxin B₁, which is produced by *Aspergillus flavus* and is able to contaminate different types of foods.⁵ On the other hand, **1** is also a constituent of semiglabin⁶ and microminutinin,⁷ which have been successfully applied in antimalarial therapies. These tricyclic compounds consist of two fused furan rings, which we will denote A and B, with the A ring in turn fused to a benzene. It is worth noting

that the fused rings introduce a conformational stiffness in these compounds, which should exercise a strong influence in their pseudorotational preferences. Despite their chemical and pharmacological interest, the molecular structure of **1** and its derivatives has been scarcely investigated by semiempirical calculations.⁸ The present work describes the results of a quantum mechanical study about the conformational preferences of **1** in the gas phase, aqueous solution, and chloroform solution. Furthermore, the study has been extended to 3a,8a-dihydrofuro[2,3-*b*]benzofuran (**2**), 2,3,3a,8a-tetrahydro-2-oxofuro[2,3-*b*]benzofuran (**3**), and 2,3,3a,8a-tetrahydro-3-methylenefuro[2,3-*b*]benzofuran (**4**), which are three of the most important derivatives of **1**. The results reveal that the incorporation of an endocyclic or exocyclic double bond provides drastic changes in the conformational preferences of these tricyclic compounds.



Methods

The conformations of the five-membered rings were defined using the Altona–Sundaralingam puckering parameters:⁹ the phase angle of pseudorotation (*P*) and the puckering amplitude (τ_m). These parameters are defined according to

$$P = \text{ATAN}[(\tau_1 + \tau_4 - \tau_0 - \tau_3)/(b\tau_2)] \quad (1)$$

$$\tau_m = \tau_2/(\cos P) \quad (2)$$

where $b = 3.077683537$, ATAN is the arctangent function, and τ_0 , τ_1 , τ_2 , τ_3 , and τ_4 are the endocyclic torsion angles.

The minimum energy conformations of **1–4** were obtained with the Gaussian 94 computer program¹⁰ using the following procedure. First, all the possible structures with envelope conformations in the A and B rings were generated by varying the phase *P* at a fixed value of τ_m . These conformations were optimized at the HF/3-21G level,¹¹ the resulting structures being subsequently reoptimized at the HF/6-31G(d) level.¹² Single-

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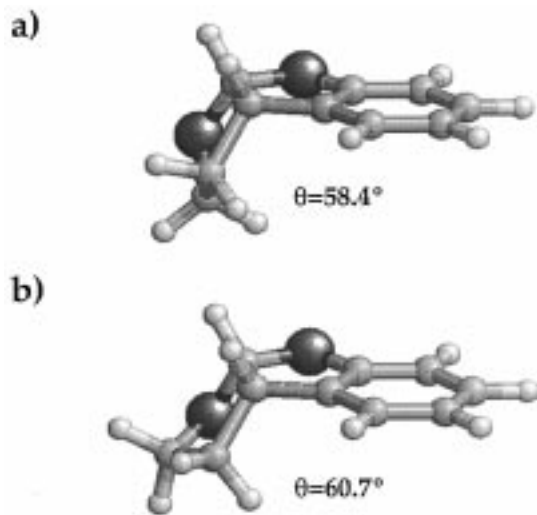


Figure 1. Minimum energy conformations of **1**. The structures differ in the conformation of the B ring: C₂-exo (a) and C₂-endo (b). The interplanar angle θ (see text) is displayed.

point calculations at the MP2/6-31G(d) level were performed on the HF/6-31G(d) minima, which were characterized as such from frequency analyses.

The solvent may exercise a large influence on the conformational properties of five-membered rings.^{3c,13} The effects of both water and chloroform solvents in the conformational energies of the compounds under study were investigated using the AM1 semiempirical optimized version^{14,15} of the self-consistent reaction field (SCRF) developed by Miertus, Scrocco, and Tomasi.¹⁶ According to this method, the free energies of solvation (ΔG_{sol}) are determined from the addition of electrostatic, van der Waals, and cavitation contributions. The cavitation term was determined using Pierotti's scaled particle theory, while the van der Waals component was evaluated using a linear relation with the solvent-excluded surface area.^{14,15} The electrostatic contribution was determined using the solvent reaction field developed by Miertus, Scrocco, and Tomasi.¹⁶

Results and Discussion

Two minimum energy conformations, which are displayed in Figure 1, were characterized for **1**. The A ring presents a planar conformation in the two minima, whereas the B ring shows distinct envelope conformations. Furthermore, the mean plane of the B ring in each minimum forms an interplanar angle θ of about 58–61° with the benzene and A rings. The endocyclic dihedral angles of the B ring, the derived pseudorotational parameters, and the relative energies computed in the gas phase are listed in Table 1 for the two minimum energy conformations. The B ring of the lowest energy minimum presents a C₂-exo conformation with pseudorotational parameters $P = 124.7^\circ$ and $\tau_m = 38.3^\circ$. Conversely, in the second minimum, the B ring shows a C₂-endo conformation with $P = -43.2^\circ$ and $\tau_m = 37.5^\circ$. The population of the latter minimum is expected to be negligible in the conformer distribution of **1** since it is 3.3 kcal/mol less favored than the lowest energy minimum.

Table 1. Endocyclic Torsion Angles of the B ring (τ_i , $i = 0-4$; in Degrees), Pseudorotational Parameters (P and τ_m ; in Degrees), Relative Energies in the Gas Phase (ΔE ; in kcal/mol), Free Energies of Solvation in Aqueous and Chloroform Solution (ΔG_{sol} ; in kcal/mol), and Conformational Free Energies (ΔG_{conf} ; in kcal/mol) of the Minimum Energy Conformations Predicted for **1** and the One of the Investigated Twist Conformations

	C ₂ -exo	C ₂ -endo	C ₃ -exo-C _{3a} -endo
τ_0 (C2-O1-C8a-C3a)	-21.8	27.3	-23.0
τ_1 (O1-C8a-C3a-C3)	-2.0	-5.8	21.3
τ_2 (C8a-C3a-C3-C2)	22.4	-15.3	-12.1
τ_3 (C3a-C3-C2-O1)	-35.6	31.6	0.0
τ_4 (C3-C2-O1-C8a)	36.8	-37.9	14.4
P^a	124.7	-43.2	-175.0
τ_m^a	38.3	37.5	22.2
$\Delta E(\text{HF}/6-31\text{G}(\text{d}))$	0.0	2.8	3.0
$\Delta E(\text{HF}/6-31\text{G}(\text{d}))^b$	0.0	2.3	3.2 ^c
$\Delta E(\text{MP2}/6-31\text{G}(\text{d}))$	0.0	3.7	3.8
$\Delta E(\text{MP2}/6-31\text{G}(\text{d}))^b$	0.0	3.3	4.0 ^c
$\Delta G_{\text{sol}}^{\text{H}_2\text{O}}$	-5.1	-5.9	-5.3
$\Delta\Delta G_{\text{conf}}^{\text{H}_2\text{O}}$	0.0	2.5	3.8
$\Delta G_{\text{sol}}^{\text{CHCl}_3}$	-9.2	-9.4	-9.2
$\Delta\Delta G_{\text{conf}}^{\text{CHCl}_3}$	0.0	3.1	4.0

^a P and τ_m correspond to the phase angle of pseudorotation and the puckering amplitude, respectively, which are defined by $P = \text{ATAN}[(\tau_2 + \tau_4 - \tau_1 - \tau_3)/(\tau_2 \cdot 3.077683)]$ and $\tau_m = \tau_0/\cos P$. ^b Zero point energy (ZPE) and thermal corrections calculated at the HF/6-31G(d) level are included. ^c The negative frequency was not considered for the calculation of ZPE and thermal corrections.

Some structures with a twist conformation in the B ring were computed from geometry optimizations but fixing one endocyclic dihedral angle. Table 1 includes the results obtained for the C₃-exo-C_{3a}-endo conformation as a representative example. This conformation, which is unstabilized by 4.0 kcal/mol, was characterized as a transition state by frequency analysis. In all cases, an unfavorable high energy was predicted for the twist conformations. These results suggest that the pseudorotational preferences in **1** can be defined by one state characterized by fully planar and C₂-exo conformations for the A and B rings, respectively.

The ΔG_{sol} values in both aqueous and chloroform solutions for the two minima and the transition state are listed in Table 1. Furthermore, the conformational free energy differences ($\Delta\Delta G_{\text{conf}}$) in solution, which were estimated by adding $\Delta\Delta G_{\text{sol}}$ to the gas-phase energy computed at the highest level of theory, are also included in Table 1. Results indicate that water tends to stabilize the C₂-endo form by about 0.8 kcal/mol, whereas the unfavorable energy of the twist conformations remains unaltered. However, despite its stabilization, the population predicted in aqueous solution for the C₂-endo conformation is lower than 1.5%. On the other hand, the influence of the bulk chloroform in the conformational properties of **1** seems to be almost negligible. It is worth noting that the solvation of **1** is more favorable in chloroform than in water, the partition coefficient for the transfer to the organic solvent from water being positive ($\log P_{\text{CHCl}_3/\text{H}_2\text{O}} \approx 14-16$).

Geometry optimizations at the HF/6-31G(d) level lead to only one minimum energy conformation for **2-4** (see Figure 2) since the presence of either an endocyclic or exocyclic double bond increases the stiffness of the B ring. In all cases, the interplanar angles θ are close to that predicted for **1**, suggesting that chemical modifications have a small influence in the "folded"-shaped conformation of this family of compounds. However, a detailed inspection of Figure 2 reveals that all the compounds

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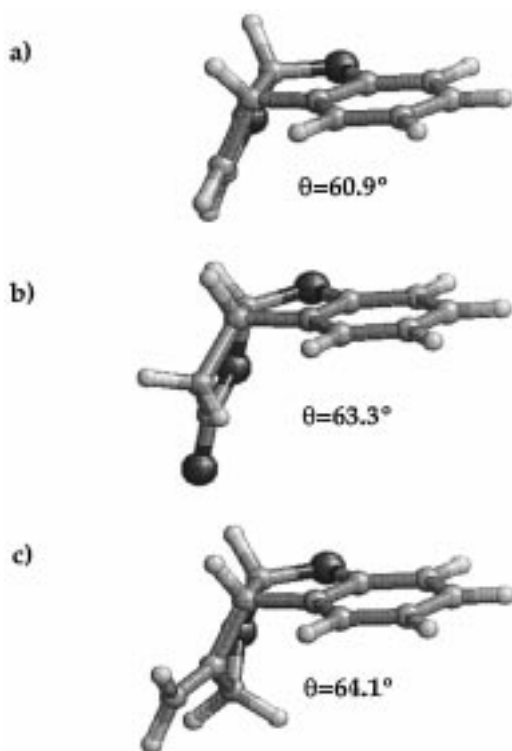


Figure 2. Minimum energy conformations of **2** (a), **3** (b), and **4** (c). The interplanar angle θ (see text) is displayed.

present different conformations in the B ring. The endocyclic dihedral angles and the pseudorotational parameters of the B ring for the minimum energy conformations of **2–4** are listed in Table 2.

The conformation of the B ring in **2** is almost planar, as should be expected from the presence of the endocyclic double bond C2=C3. This planarity is clearly indicated by the small amplitude of the puckering ($\tau_m = 5.2^\circ$), even though the value of the phase angle ($P = -179.7^\circ$) could suggest a C₃-exo-C_{3a}-endo conformation. Thus, the influence exerted by the endocyclic double bond in the conformation of the B ring seems to be similar to that expected from a fourth fused ring. On the other hand, the pseudorotational parameters $P = 64^\circ$ and $\tau_m = 18.0^\circ$ for the B ring of **3** indicates a C_{8a}-exo-O₁-endo form. The exocyclic double bond in C2 also induces a distinctive feature in the A ring. This is an envelope C_{8a}-exo conformation with $P = 130.3^\circ$ and $\tau_m = 15.0^\circ$. The value of amplitude indicates that the puckering of the A ring is flattened relative to that of the B ring in the minimum

Table 2. Endocyclic Torsion Angles of the B ring (τ_i , $i = 0-4$; in Degrees), Pseudorotational Parameters (P and τ_m ; in Degrees), and Free Energies of Solvation in Aqueous and Chloroform Solution (ΔG_{sol} ; in kcal/mol) of the Minimum Energy Conformations Predicted for **2–4**

	2	3	4
τ_0 (C2–O1–C8a–C3a)	-5.2	7.9	-17.2
τ_1 (O1–C8a–C3a–C3)	4.1	-15.6	-2.7
τ_2 (C8a–C3a–C3–C2)	-1.7	17.1	19.7
τ_3 (C3a–C3–C2–O1)	1.4	-13.5	-30.1
τ_4 (C3–C2–O1–C8a)	4.3	3.6	29.8
P^a	-179.7	64.0	122.7
τ_m^a	5.2	18.0	31.8
conformation	planar	C _{8a} -exo-O ₁ -endo	C ₂ -exo
$\Delta G_{\text{sol}}^{\text{H}_2\text{O}}$	-4.8	-7.2	-5.4
$\Delta G_{\text{sol}}^{\text{CHCl}_3}$	-9.7	-11.0	-10.4

^a P and τ_m correspond to the phase angle of pseudorotation and the puckering amplitude, respectively, which are defined by $P = \text{ATAN}[(\tau_2 + \tau_4 - \tau_1 - \tau_3)/(\tau_2 3.077683)]$ and $\tau_m = \tau_0/\cos P$.

energy conformations of **1**. Thus, τ_m values generally range from 35° to 45° , yielding an average value of 39° .^{2,3,9} The B ring of **4** presents a C₂-exo conformation characterized by $P = 122.7^\circ$ and $\tau_m = 31.8^\circ$, which is similar to that predicted for **1**. On the other hand, the ΔG_{sol} values in aqueous and chloroform solutions computed for the minimum energy conformations of **2–4** are listed in Table 2. The three compounds present positive partition coefficients for the transfer to the organic solvent from water ($\log P_{\text{CHCl}_3/\text{H}_2\text{O}} \approx 15-19$), showing a behavior similar to that predicted for **1**.

Conclusions

Compound **1** and its derivatives present a "folded"-shaped conformation characterized by an interplanar angle θ of about 60° . However, the introduction of a double bond in **1** introduces drastic changes in the pseudorotational preferences depending on both its exocyclic or endocyclic nature and its position. The small number of minima characterized for the compounds investigated indicate that they are quite rigid, as should be expected from the presence of fused rings. Accordingly, the conformational preferences of **1** and its derivatives can be explained by a one-state rather than a two-state equilibrium like compounds without fused rings.^{2,3,9}

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