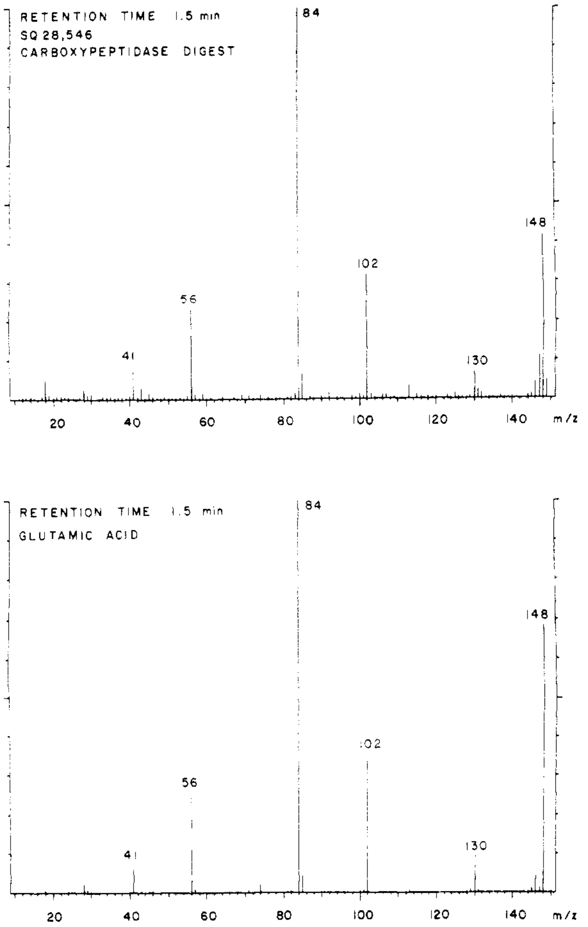
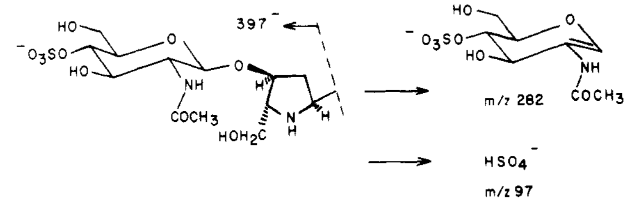


Figure 4. Thermospray LC/MS/MS spectra of (a) the carboxypeptidase digest of SQ 28546 and (b) glutamic acid.

ca. t_R 1.8 and 1.5 min. No other amino acids were seen by LC/MS. MS/MS spectra of the 106^+ and 148^+ ions matched those of the protonated molecule of authentic serine and glutamic acid (see Figure 4 for Glu). The absence of Thr or other amino acids released from the carboxy terminus supports the attachment of *N*-acetylglucosamine to threonine.

In a similar manner, mass spectral evidence established the attachment of sulfate to *N*-acetylglucosamine and showed its relation to 4-hydroxy-5-(hydroxymethyl)proline (bulgecinine). The FAB MS/MS spectrum of the 962^- parent of **1** defined the 397^- fragment. This ion was also evident from the FAB mass spectra of both **1** and **2**. Examination of this daughter established the fragmentation illustrated in Scheme III. Ions at *m/z* 282 and 97 were observed. As previously mentioned, the ion at *m/z* 97 was determined as HSO_4^- by high-resolution analysis while the *m/z* 282 fragment is due to sulfated *N*-acetylglucosamine. Comparison of the FAB MS/MS spectra of the 282^- and 397^- ions of **1** and **2** with those fragments from the related compound bulgecin (**4**) suggest a similar, if not identical, structure for these fragments. The negative FAB mass spectrum of bulgecin exhibited the $(M - H)^-$ ion at *m/z* 550. The MS/MS spectrum of this ion produced 397^- and 282^- fragments. Subsequent analysis of the 282^- fragment using FAB MS/MS indicated the 97^- daughter ion arises from this ionic species.

Scheme III



In conclusion, chemical and spectroscopic characterization of glycopeptides **1** and **2** show similarities to bulgecins; however, **1** and **2** are significantly larger peptides and contain two glucosamine residues. Both glycopeptides exhibit similar NMR and mass spectral features which have been examined in detail to define the structures shown. Mass spectral relations are best determined by using a combination of MS/MS with high-resolution analysis. The presence of structural features common to bulgecins and **1** and **2** are of biological interest. All of these compounds have been reported to potentiate the activity of β-lactam antibiotics. Furthermore, their coproduction with monobactams in broth cultures may be of interest from a biosynthetic standpoint.

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Registry No. SQ 28504, 96827-99-5; SQ 28546, 96828-00-1.

Di- and Trisubstituted γ-Lactones. Conformational Study by Molecular Mechanics Calculations and Coupling Constant Analysis

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A conformational study on di- and trisubstituted γ-butyrolactones has been performed using molecular mechanics (MM) calculations and analysis of coupling constants through an empirically generalized Karplus equation. Our results corroborate the existence of only two envelope conformations for every compound. Calculated coupling constants reproduce experimental values with a global root-mean-square (rms) deviation of 0.93 Hz.

The γ-lactone system possesses great importance in natural product chemistry. The existence of several metabolites having as constitutional unit the γ-butyrolactone ring **1**, such as eldanolide, **2**, litsenolides **3**, and antimycinones **4**, has generated an enormous interest on the synthesis and configurational assignments of variously

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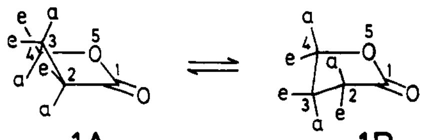
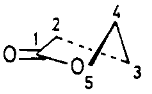
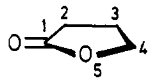
substituted γ-butyrolactone rings.



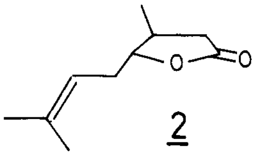
1A 1B



1T



1P



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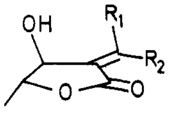

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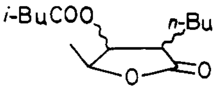

4

^1H NMR is one of the most widely used techniques for configurational assignment, owing to the correlation between vicinal coupling constants (J's) and H–C–C–H dihedral angles. It is usually considered that dihedral angles, in pentacyclic systems, are determined by the relative configuration existing at both carbon atoms. However, in this article we try to show how molecular conformation(s) is(are) the main factor(s) controlling dihedral angles.

The original Karplus equation, $J = 8.5 \cos^2 \theta - 0.3$ ($0° < \theta < 90°$), $J = 9.5 \cos^2 \theta - 0.3$ ($90° < \theta < 180°$), has been used to determine the configuration of some nonfused γ-lactones.[1-4] In those cases, coupling constants of cis-oriented protons had generally a value of 9 Hz whereas those for the trans-oriented protons were about 2–4 Hz. This generalization has been widely utilized in configurational assignment.[4] However, Mori[5] found that the isomers of blastmycinone (trans,trans relationship in 4) having cis,trans, trans,cis, and cis,cis relationships on the C_2–C_3–C_4 fragment of 4 showed "rather unusual results", i.e., trans coupling constants were larger than cis.

The combination of force field calculations, that allow one to know the preferred conformations of a molecule, with a Karplus-type equation is being currently used in coupling constant analysis.[6-8] de Leeuw et al.[6,7] found the conformational equilibrium and behavior in some cases, including five-membered rings (mainly furanosic type sugars),[6] by analizing its ^1H NMR, while Ōsawa[8] prefers a different approach: the determination of all possible conformers of the target molecule by molecular mechanics (MM) and then calculation of the weighted coupling constants from their MM-calculated geometries. In this article we apply the latter combination to determine the most stable conformation and the different H–C–C–H coupling constants for all the possible relative configurations of several di- and trisubstituted γ-butyrolactones in order to establish unambiguously the exact J values for each class of compounds.

Results and Discussion

Computational Technique. Program MM2[9] was used throughout all this work for the computation of the geometry and the energy of each conformer. The calculation of averaged coupling constants was undertaken using program 3JHH[10] which, in turn, is based on Altona's generalized Karplus equation.[11] This equation uses as variables the H–C–C–H dihedral angle, the number of substituents on the fragment and their electronegativities, and the configuration on the C–C fragment.

The knowledge of the number of possible conformers for a given molecule, their geometry and relative populations (mole fraction), allows us to obtain J_{calc} by application of (eq 1). Comparison of the observed and calculated J's

$$J = \sum_{i=1}^{m} n_i J_i \qquad (1)$$

m = number of conformers, n = mole fraction

will provide information about the correctness of the configurational assignment and even about the conformational preference.

Conformational Analysis. γ-Butyrolactone (1). Semiempirical quantum chemical calculations[12] (CNDO/2 and PCILO) on **1** indicate that **1T** is the most stable conformer. The unit O_5–C_1(O)–C_2 is planar and C_3 is close to this plane, while C_4 is out of the plane. This situation produces an important torsion around the O_5–C_1 bond (from 10° to 17° under CNDO/2). Although PCILO calculations are recognized to be the best quantum chemical calculations on conformational analysis,[13] some doubt can be cast on the correctness of such calculations in the case of 1, because PCILO predicts the second most stable conformer of 1 to be **1P** with all bonds eclipsed.[12]

These results are clearly in disagreement with the known tendency of esters to have the C–O–CO–C fragment coplanar, although with a rotational barrier smaller than that in an amide.[14]

Mathieson[15] already pointed out that 1 exists only in one conformation, which is degenerate, having four atoms (C_4–O_5–C_1–C_2) in one plane and the fith atom (C_3) out of

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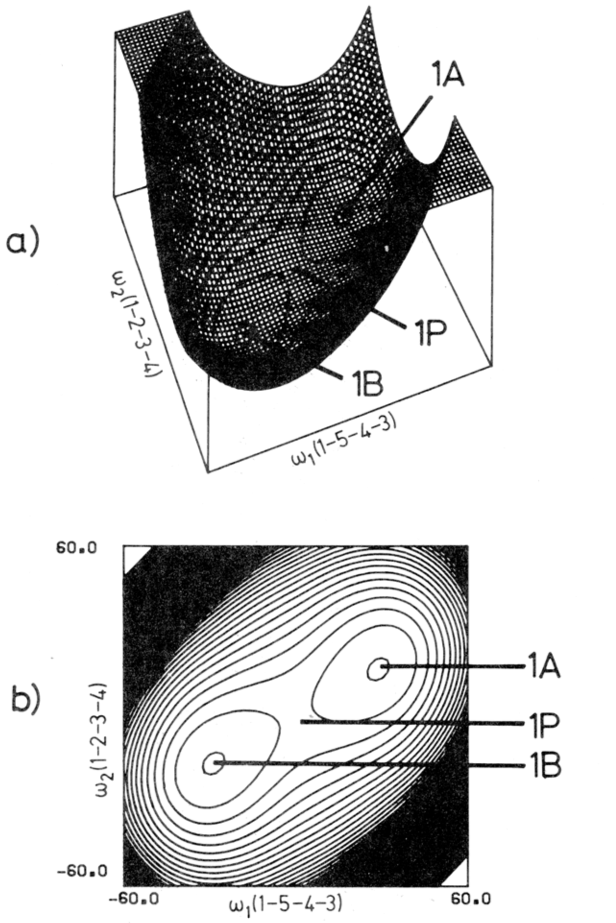


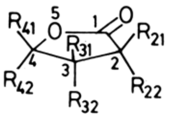
Figure 1. Torsional energy surface of γ-butyrolactone, 1, as calculated by MM2: (a) three-dimensional representation (Contour lines separation is 1.0 kcal/mol); (b) contour map (Line separation is 1.0 kcal/mol.).

Table I. Endocyclic Dihedral Angles (in deg) and Relative Energy (in kcal/mol) for the Stationary Points of 1 as Obtained by BIGSTRN-3

conformer	endocyclic dihedral angles[a]	energy
1P	0.0, 0.0, 0.0, 0.0, 0.0	1.16
1A (and **1B**)[b]	28.9, −28.3, 16.6, 2.9, −20.9	0.00

[a] Endocyclic dihedral angles are given in the following sequence: 1–2–3–4, 2–3–4–5, 3–4–5–1, 4–5–1–2, 5–1–2–3 (see structure **1** for numbering). [b] **1B** has opposite signs in dihedral angles.

Chart I



	R_{21}	R_{22}	R_{31}	R_{32}	R_{41}	R_{42}
5c	Me	H	Me	H	H	H
t	Me	H	H	Me	H	H
6c	Me	H	OH	H	H	H
t	Me	H	H	OH	H	H
7c	Me	H	H	H	Me	H
t	Me	H	H	H	H	Me
8c	H	H	Me	H	Me	H
t	H	H	Me	H	H	Me
9c	H	H	OH	H	Me	H
t	H	H	OH	H	H	Me
10cc	Me	H	Me	H	Me	H
tt	Me	H	H	Me	Me	H
ct	Me	H	Me	H	H	Me
tc	Me	H	H	Me	H	Me
11cc	Me	H	OH	H	Me	H
tt	Me	H	H	OH	Me	H
ct	Me	H	OH	H	H	Me
tc	Me	H	H	OH	H	Me
12cc	Me	H	OAc	H	Me	H
tt	Me	H	H	OAc	Me	H
ct	Me	H	OAc	H	H	Me
tc	Me	H	H	OAc	H	Me

the plane, either above (**1A**) or below (**1B**). Recently, Allinger[16] stated, according to MM calculations, that "γ-butyrolactone prefers the conformation with four planar ring atoms, and the β carbon out of the plane of the remainder of the five-membered ring".

The importance of two-parametric torsional energy surface calculation in conformational analysis and dynamics has been demonstrated.[17] In the present work an extensive coverage of the torsional energy surface of **1** was carried out using a highly automated routine[18] implemented into the MM2 program. Endocyclic dihedral angles C_1–C_5–C_4–C_3 and C_1–C_2–C_3–C_4 were driven from ±60° to ∓60° with a 10° step size. Results are shown in Figure 1, and the existence of only two equivalent conformers, **1A** and **1B**, can be easily deduced.

In view of the known pitfalls of the two-parametric torsional energy coverage,[17i] Ōsawa's procedure[19] was followed for the analysis of the surface obtained, i.e., the characterization of all the stationary points was carried out with BIGSTRN-3 program[20] modified as to be able to calculate molecules containing heteroatoms. Starting from the transition state for interconversion of **1A** into **1B**, the eigenvector distorsion option allows one to find the two interconnected minima. The obtained barrier is very low (1.16 kcal/mol); thus an absolutely free interconversion between the two conformers exists. The transition state for this interconversion is conformation **1P** with all endocyclic dihedral angles exactly equal to 0°, while the minima have the C_2–CO–O_5–C_4 fragment nearly planar (dihedral angle equal to ±2.9°) (Table I).

2,3-Disubstituted-γ-butyrolactones. Computational results on *cis*- and *trans*-2,3-dimethyl-γ-butyrolactone (**5c** and **5t**, respectively) are shown in Table II. In **5c**, conformer A is revealed as the most stable (66.83%). This indicates that an "axial" methyl on C_3 is preferred over an "axial" methyl on C_2 as a consequence of the absence of 1,3-diaxial interactions between methyl and protons on O_5 and C_1 in conformer A. However, conformer B does dis-

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Table II. MM2 Calculated Conformer Distribution (%), 3JHH Calculated Coupling Constants (Hz) for Each Conformer, and "Average" Coupling Constants and Experimental Coupling Constants (Hz) for the Ring Protons of Compounds 5 to 12

	conformer A[a]			conformer B[a]			calculated J's		experimental J's	
compd	%[b]	$J_{2,3}$	$J_{3,41}$, $J_{3,42}$	%[b]	$J_{2,3}$	$J_{3,41}$, $J_{3,4}$	$J_{2,3}$	$J_{3,41}$, $J_{3,42}$	$J_{2,3}$	$J_{3,4}$
5c	66.83	7.29	1.12, 8.65	31.37	7.76	8.91, 5.52	7.44	3.57, 7.67		2.5, 5.5[c]
5t	93.46	11.14	3.58, 8.85	6.54	0.75	8.79, 1.13	10.46	3.92, 8.35		
6c	96.16[d]	5.25[e]	1.28, 6.92[e]	3.83[d]	8.03[e]	6.78, 6.52[e]	5.39	1.48, 6.92	5.5[f]	
6t	66.17[d]	9.01[e]	4.44, 6.83[e]	33.82[d]	0.51[e]	7.16, 1.16[e]	6.14	5.36, 4.91		
		$J_{2,31}$, $J_{2,32}$	$J_{31,4}$, $J_{32,4}$		$J_{2,31}$, $J_{2,32}$	$J_{31,4}$, $J_{32,4}$	$J_{2,31}$, $J_{2,32}$	$J_{31,4}$, $J_{32,4}$	$J_{2,31}$, $J_{2,32}$	$J_{31,4}$, $J_{32,4}$
7c	96.30	10.66, 7.05	10.40, 6.05	3.70	2.11, 9.81	2.74, 9.56	10.35, 7.16	10.12, 6.17	12.8, 8.5[g]	10.8, 6.0[g]
7t	75.97	10.32, 7.40	8.80, 1.61	24.03	1.20, 8.60	6.41, 10.08	8.13, 7.69	8.23, 3.64	9.0, 8.0[h]	7.5, 7.0[h]
		$J_{21,3}$, $J_{22,3}$	$J_{3,4}$		$J_{21,3}$, $J_{22,3}$	$J_{3,4}$	$J_{21,3}$, $J_{22,3}$	$J_{3,4}$	$J_{21,3}$, $J_{22,3}$	$J_{3,4}$
8c	36.16	8.04, 1.11	5.42	63.84	7.34, 10.75	6.85	7.59, 7.26	6.33		6.0[i]
8t	81.91	10.09, 7.46	9.27	18.09	1.53, 8.42	1.41	8.54, 7.63	7.85		7.8[i]
9c	87.03[d]	6.21, 1.16[e]	3.58[e]	12.97[d]	8.42, 8.55[e]	7.00[e]	6.48, 2.12	3.99	5.3, 1.5[j]	3.6[j]
9t	37.09[d]	8.08, 8.38[e]	7.16[e]	62.91[d]	1.46, 6.50[e]	1.15[e]	3.93, 7.21	3.39	3.6, 6.5[k]	2.8[k]
		$J_{2,3}$	$J_{3,4}$		$J_{2,3}$	$J_{3,4}$	$J_{2,3}$	$J_{3,4}$	$J_{2,3}$	$J_{3,4}$
10cc	86.89	7.26	5.38	13.11	8.83	7.54	7.47	5.66	7[l]	4.5[l]
10tt	97.28	11.15	9.34	2.72	1.74	2.37	10.90	9.15	11.5[l]	9[l]
10ct	56.26	7.65	1.30	43.74	7.86	9.44	7.74	4.86	7.5[l]	6[l]
10tc	89.78	11.33	6.93	10.22	0.66	5.69	10.54	6.80	10.8[l]	6.7[l]
11cc	98.83[d]	5.24[e]	3.48[e]	1.18[d]	9.07[e]	7.44[e]	5.30	3.50	4.7[m]	3.3[m]
11tt	88.31[d]	9.12[e]	7.35[e]	11.69[d]	0.86[e]	1.59[e]	8.16	6.68	9.2[n]	7.4[n]
11ct	91.98[d]	5.56[e]	1.09[e]	8.02[d]	8.20[e]	7.29[e]	5.81	1.59	5.6[m]	1.1[m]
11tc	50.13[d]	9.03[e]	7.09[e]	49.87[d]	0.47[e]	3.80[e]	4.77	5.44	5.0[o]	5.0[o]
12cc	95.46	5.22	3.46	4.54	8.92	7.41	5.39	3.64	6.0[p,q]	4.5[p,q]
12tt	82.97	9.40	7.60	17.03	1.18	1.84	8.00	6.62	5.9[r]	4.9[r]
12ct	85.50	5.59	1.10	14.50	8.09	7.50	5.95	2.03	6.0[s]	3.0[s]
12tc	36.30	9.31	7.02	63.70	0.54	4.10	3.73	5.16	3.0[p,q]	5.0[p,q]

[a] See structure 1 for explanation. [b] Population according to Boltzman's distribution. Energy values were obtained from MM2 results. [c] Reference 21. [d] Values obtained considering the three rotamers around C–OH bond. [e] Coupling constants corresponding to the most stable rotamer. [f] Reference 22. [g] Values relative to *cis*-3,5-di-*tert*-butyl-1. Other reported J values for $J_{2,31}$, $J_{2,32}$ and $J_{31,4}$, $J_{32,4}$ are as follows: *cis*-3,5-diphenyl-1, 12.9, 8.1 and 10.8, 5.7 Hz; *cis*-5-methyl-3-phenyl-1, 12.8, 8.5 and 10.8, 5.7 Hz; *cis*-3-methyl-5-phenyl-1, 12.9, 8.1 and 10.8, 5.8 Hz. Reference 24. [h] Values relative to *trans*-3,5-di-*tert*-butyl-1. Other reported J values for $J_{2,31}$, $J_{2,32}$ and $J_{31,4}$, $J_{32,4}$ are as follows: *trans*-3,5-diphenyl-1, 9.7, 8.1 and 7.8, 5.8 Hz; *trans*-5-methyl-3-phenyl-1, 9.0, 7.0 and 6.8, 6.2 Hz; *trans*-3-methyl-5-phenyl-1, 9.0, 7.0 and 7.5, 5.5 Hz. Reference 24. [i] Reference 26. [j] Reference 27. Other reported J values for $J_{21,3}$, $J_{22,3}$, and $J_{3,4}$ are 5.6, 1.2 and 3.8 Hz (ref 28). [k] Reference 29. [l] Reference 30. [m] Values relative to the 2-butyl derivative. Reference 33. [n] Reference 29. Other reported J values for $J_{2,3}$ and $J_{3,4}$ are 8.0 and 7.0 Hz (ref 34), 8.5 and 7.0 (ref 35), and 8.2 and 7.5 Hz (footnote m). [o] Reference 34. Other reported J values for $J_{2,3}$ and $J_{3,4}$ are 3.4 and 5.0 Hz (footnote m). [p] Reference 37. [q] Values relative to the 3-C_{16} derivatives. Reference 36. [r] Values relative to the 3-butyl-4-iso-butoxycarbonyl derivatives. Reference 5. [s] Reference 40. Other reported J values for $J_{2,3}$ and $J_{3,4}$ are 6.0 and 0 Hz (footnotes q and r).

play a 1,3-diaxial interaction between the C_2-methyl and the axial hydrogen on C_4. The calculated methyl conformational energy in this system already denotes such a phenomenon. An axial methyl group on C_2 is 1.16 kcal/mol less stable than an equatorial one, while on C_3 and on C_4 it is only 0.64 kcal/mol and 0.46 kcal/mol less stable, respectively.

The situation is similar, but not equal, in **5t**. In this compound both methyl groups are in equatorial positions in conformer A while they are axial in conformer B. Consequently, it is not surprising that A is almost exclusively preferred over B.

Since a wide range of natural products having γ-butyrolactone rings containing one hydroxyl group in the β-position (or C_3), the corresponding hydroxy derivatives were also studied. Thus, *cis*- and *trans*-3-hydroxy-2-methyl-γ-butyrolactone (**6c** and **6t**, respectively) were examined. Considering relative configuration, these compounds should behave similarly to **5**. However, compound **6c** presents a conformer distribution very similar to that of **5t**. This fact should be attributed to the stability of the O–C–C–O unit in a gauche conformation. The program MM2 treats the O–C–C–O unit as to make gauche more stable than anti conformers to reproduce the conformational preference on ethylene glycol.[23] In turn, compound **6t** presents a conformer distribution similar to **5c**, since conformer **6t-B** is more stable than conformer **6c-B** as a consequence of the gauche effect. Finally, it is worth noting that for all compounds studied so far $J_{\text{trans}} > J_{\text{cis}}$ (Table II) (10.46 Hz for **5t** vs. 7.44 Hz for **5c**, and 6.14 Hz for **6t** vs. 5.39 Hz for **6c**).

2,4-Disubstituted-γ-butyrolactones. Only methyl-substituted derivatives were considered. The *cis*-2,4-dimethyl-γ-butyrolactone (**7c**) is calculated to have a great preference for conformer A (96.30%) over B; see Table II. Obviously the presence of two axial methyl groups in conformer B produces this unstability. In the trans stereoisomer, **7t**, conformer B is slightly more stable than in **7c**. The agreement between calculated and experimental coupling constants is qualitatively good[25] for these lactones.

3,4-Disubstituted-γ-butyrolactones. According to calculations the *cis*-3,4-dimethyl-γ-butyrolactone (**8c**) exists to an extent of 63.84% in conformer B, having C_3-methyl in axial and C_4-methyl in equatorial positions (Table II).

The small preference of **8c** for conformer B rather than A is difficultly attributable to one single factor. However, a careful study of MM2 results indicates that the torsional and van der Waals' contributions to the total steric energy are the two main reasons to account for this fact. On the other hand, compound **8t** shows a clear preference for conformer A (81.91%) as a consequence of the stability conferred by two equatorial methyl groups.

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The 3-hydroxy derivatives, **9c** and **9t**, show a behavior opposite to that of **8**. While MM2 results indicate that **8c** and **8t** prefer conformer B and A, respectively, **9c** and **9t** prefer A and B, respectively. Consequently, the change of the methyl group for a hydroxyl produces such a different trend. "Gauche" effect is the main factor for this behavior because it stabilizes any conformer having a O–C–C–O unit in gauche conformation (A in **9c** and B in **9t**). Conformer B in **9t** possesses a destabilization produced by the presence of the axial C_4-methyl.

Again the calculated $J_{3,4}$ indicates that the contribution of the two conformers should be taken into account in order to match the experimental values. On the other hand, it is noteworthy that the influence of the electronegativity of the substituent in the averaged J value, a difference of 2–4 Hz, exists when a methyl is changed for a hydroxyl group.

2,3,4-Trisubstituted-γ-butyrolactones. Four different relative configurations are possible for this class of compounds, i.e., cis,cis, trans,trans, cis,trans, and trans,cis. Both 2,3,4-trimethyl- and 3-hydroxy-2,4-dimethyl-γ-butyrolactones are considered in this section.

2,3,4-Trimethyl-γ-butyrolactones (**10cc**, **10tt**, and **10tc**) show almost exclusive preference for conformer A, while in **10ct** both conformers, A and B, show almost the same population (Table II).

In **10cc** and **10tt**, conformer B has a 1,3-diaxial Me/Me interaction. Consequently, A will be the most stable conformer in both cases. Compound **10tc** lacks any 1,3-diaxial Me/Me interaction in its conformer B, but it does have two axial methyl groups (on C_2 and C_3) while conformer A presents one axial (on C_4) and two equatorial (on C_2 and C_3) methyl groups. However, compound **10ct** presents almost equally stable conformers A and B. This fact may be surprising because it indicates that an envelope conformer having two axial and one equatorial methyl groups (A) is as stable as another envelope conformer having two equatorial and one axial methyl groups (B). The difference is due to which methyl group is equatorial and which one is axial. A detailed study of MM2 results on **10ct** indicates that the main reason is based on the torsional contribution to the total steric energy. Conformer A has an O–CO–C–Me unit forming a dihedral angle of 30.1°, while the same unit in conformer B possesses a dihedral angle of 76.5°. Translated into energy units it means A is more stabilized than B by 1.039 kcal/mol.[31] This fact has been previously realized in some calculations on 2,4,6-trimethylcyclohexanones[32] where the conformers having an axial methyl group in either C_2 or C_6 were less stable.

The MM2 calculated conformer distribution in all these compounds, **10cc**, **10tt**, **10ct**, and **10tc**, should be quantitatively correct on the basis of the good agreement between experimental and calculated coupling constants (Table II).

It is noteworthy to say here again that in these compounds some of the J_{trans} are larger than the corresponding J_{cis} (compare **10tt** and **10cc**). Therefore, configurational assignments based on the rule $J_{\text{cis}} > J_{\text{trans}}$ in five-membered rings[4] could lead to wrong conclusions. Thus, looking at the experimental J's, **10cc** could easily be misassigned configuration **10ct**. Similarly, **10tt** could be misassigned as **10cc**.

All the 3-hydroxy-2,4-dimethyl-γ-butyrolactones, except the trans,cis configuration **11tc**, show a clear preference for conformer A (percentage larger than 88% in all cases; Table II). In **11cc**, conformer A has two equatorial methyl groups and one axial hydroxyl group. This, in turn, allows unit O–C–C–O to exist in gauche conformation, producing a larger proportion of A over B (98.8% over 1.2%). The trans,trans configuration, **11tt**, clearly prefers A because in this conformation all the substituents occupy equatorial positions. In **11ct** the combination of gauche effect and the torsional contribution of the MeCC=O unit produces the almost exclusive existence of conformer A. However, conformers A and B of **11tc** are almost equally stable, the stabilization of conformer B seems to be due to the gauche effect on the O–C–C–O unit and to the presence of one equatorial C_5-methyl despite the presence of two equatorial groups (hydroxyl and C_2-methyl) in conformer A.

The agreement between calculated and experimental coupling constants in these compounds is good. This point reinforces the importance of gauche effects since a higher contribution of conformers B in **11cc**, **11tt**, and **11ct** and conformer A in **11tc** would produce very different calculated J values, which therefore would show a much poorer agreement. We can find here new examples of $J_{\text{trans}} > J_{\text{cis}}$ in five-membered rings (consider **11cc** and **11tt**).

Due to the occurrence of several natural products or metabolites having γ-butyrolactone structures with an esterified hydroxyl group in C_3, the corresponding acetates of compounds **11**, **12cc**, **12tt**, **12ct**, and **12tc** were also studied (Table II). Again, their behavior is completely similar to that of **11**. While **12tc**, is calculated to prefer conformer B, the other configurations prefer conformer A. The explanation of such a preference is totally parallel to that found above for **11**'s. As far as coupling constants are concerned, the general agreement between experimental and calculated coupling constants for these compounds is very good.[37]

Conclusions

An extensive study of the correlation between conformational equilibrium and observed coupling constants in ^{1}H NMR has been carried out. The combination of MM2/3JHH programs is emerging as a new and powerful

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(38) The root-mean-square (rms) deviation for calculated J's of each individual bond are as follows: $J_{2,3}$ = 0.88 Hz and $J_{3,4}$ = 0.99 Hz. The rms's have been calculated by comparison of calculated J's and the nearest experimentally available J's. The use of the farthest J's produces a global rms of 1.27 Hz.

technique for conformational and configurational analysis as deduced from the agreement (rms = 0.93 Hz) between calculated and experimental coupling constants in γ-butyrolactone rings.[39] The importance of taking into account the contribution of even the less stable conformers can be hardly overemphasized, in order to accurately reproduce experimental J's. As an indirect consequence of this work, the rule $J_{cis} > J_{trans}$ should be applied cautiously in five-membered rings. In several of the products studied herein the order is just the opposite ($J_{trans} > J_{cis}$); a strict application of the former rule may lead to erroneous configurational assignments, unless the final conclusion is supported by some other evidences, such as chemical proof, two-dimensional NMR spectra, etc.

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Registry No. 1, 96-48-0; **5c**, 99341-90-9; **5t**, 99341-89-6; **6c**, 103776-34-7; **6t**, 103776-35-8; **7c**, 24405-07-0; **7t**, 24405-08-1; **8c**, 10150-95-5; **8t**, 10150-96-6; **9c**, 103834-19-1; **9t**, 103834-20-4; **10cc**, 53155-68-3; **10tt**, 53155-65-0; **10ct**, 53155-66-1; **10tc**, 53155-67-2; **11cc**, 103834-21-5; **11tt**, 103834-22-6; **11ct**, 103834-23-7; **11tc**, 103834-24-8; **12cc**, 103834-25-9; **12tt**, 103834-26-0; **12ct**, 103834-27-1; **12tc**, 103834-28-2.

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Molecular Mechanics Calculations on the C_{sp^3}–C_{sp^2} Rotation in the *N*,3,3-Trimethyl-2-phenyl-4-piperidone System

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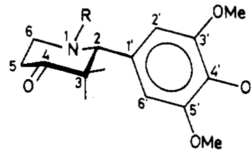
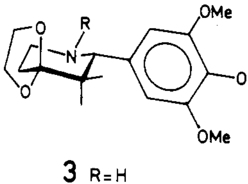
The rotational pathway of the phenyl ring in *N*,3,3-trimethyl-2-phenyl-4-piperidone has been determined by molecular mechanics calculations to be chair piperidone ⇌ twist-boat piperidone ⇌ phenyl rotation. The calculated barrier height for the process (ca. 63 kJ/mol) is in good agreement with the previously reported experimental value of 54 kJ/mol in a remotely substituted phenyl derivative determined by ^{1}H DNMR.

The restricted rotation around C_{sp^3}–C_{sp^2} bonds has been the subject of a number of studies.[1] However, not many examples can be found wherein the rotational barrier is high enough to be observed or measured by dynamic nuclear magnetic resonance spectroscopy techniques. Very recently we published[2] the synthesis and rotational barrier determination of one of the few examples: 1,3,3-trimethyl-2-(3,4,5-trimethoxyphenyl)-4-piperidone (1). The aryl group displays a rotational barrier of 54 kJ/mol as determined by ^{1}H NMR with $CDCl_3$ as solvent.[2] Rotational barriers of several other compounds (1.HCl, 2, 2·HCl, 3, 3·HCl, and 4) were also studied, showing a great influence of the N-methyl group on the barrier height.[2]

Molecular mechanics (MM) calculations have recently emerged as a powerful technique[3] with wide application to conformational analysis and molecular dynamics. One of the MM applications to the latter is the study of rotational barriers. In this respect, a very complete study has been published[4] recently on the rotational pathways of phenylcyclohexane and bicyclohexane systems in which the importance of the gauche-progauche[4] (gp) and gauche-progauche-ortho[4] (gpo) interactions on the barrier heights for phenyl rotation was stated. The compound of our study, 1, can present two gp interactions[4] in its rotational saddle point and, consequently, it can be expected



1 R=Me
2 R=H



3 R=H
4 R=Me

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