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DENSITY FUNCTIONAL THEORY STUDY OF THE PREFERRED CONFORMATION OF GEISSOSCHIZINE

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Abstract - Density functional theory (DFT) study of the hitherto proposed structures of geissoschizine (**1**) has proved that the structure (**1a**) having hydrogen bond between the enol hydroxyl and Nb functions with a *trans*-quinolizidine-type C/D ring and twistboat D ring (proposed by van Tamelen and Wright) is the most stable one. A strong contribution of the zwitterionic species (**1a’**) to **1a** is suggested together with the reasons why **1a’** was not found as a local minimum. Calculations of ^{1}H- and ^{13}C- NMR chemical shifts based on this structure also support its structure.

INTRODUCTION

Geissoschizine (**1**) is one of the key biosynthetic intermediates of monoterpenoid indole alkaloids.[1] The structural elucidation of **1** was carried out independently by Rapoport *et al.*[2] and Janot.[3] The relative and absolute stereochemistries of **1** have been confirmed by a number of racemic and chiral total syntheses.[4] Despite the apparent simplicity of the chemical structure, however, the determination of the conformation was never easy. Confusion arose from the presence of a highly deshielded ^{1}H-NMR signal at δ 4.51 (dd, *J*=11.3, 1.5 Hz) and the absence of Bohlmann bands in the IR spectrum, while these observations were not encountered in the corresponding methyl ether (**2**).[5,6] After structure (**1a**) having a *trans*-quinolizidine-type C/D ring system with a twistboat D ring (cf. stereostructure (**1a**) shown in Chart 1) was suggested by van Tamelen and Wright,[7] two structures having a *cis*-quinolizidine-type C/D ring system with a boat or twistboat D ring were proposed independently by three groups.[5,8,9] Although we have reported detailed ^{1}H-NMR assignments[10] later in support of van Tamelen’s hydrogen bonded and/or zwitterionic *trans*-quinolizidine structure, no other direct proof such as X-Ray crystal structure analysis or definite NOE results has been published until now. In the present study, we, in an attempt to find the most stable conformer, performed density functional theory (DFT) calculations of the hitherto proposed structures including the zwitterionic structure (**1a'**) and other possible ones to find which one is most stable. As a result, structure (**1a)** was obtained as the global minimum.[11] Lounasmaa and Hanhinen[12] published a review of the conformations of geissoschizine and related synthetic molecules based on ^{13}C-NMR spectral data focusing on the shift positions of C6. The diagnostic value of the C6 carbon shifts in the study of indole alkaloids having quinolizidine ring was first pointed out by Wenkert *et al*.[13] We calculated the ^{1}H- and ^{13}C-NMR shifts of the structure (**1a**) and compared them with the observed data.

RESULTS AND DISCUSSION

DFT calculations were carried out using Gaussian 98[14] at the B3LYP level of theory with 6-31G(d) basis set. Free energy difference (ΔG°) was calculated between geometrically optimized structures. ^{1}H- and ^{13}C-NMR shifts were calculated using the optimized structure under the key word "nmr" of the Gaussian 98 program.[14]

Geometrical optimization using the structure that possesses *trans*-quinolizidin*e*-type C/D ring system as the initial structure has led to the optimized structure (**1a**). This structure was first suggested by van Tamelen and Wright[7] and later supported by us on the ground of detailed ^{1}H-NMR spectral assignments**.**[10] The optimized structure showed the hydrogen of enol function is not equidistant between O and N: the O17-H distance is 1.02 Å [15] while the N4···H distance is 1.67 Å. This structure fits well with the criterion for "hydrogen bonding".[#]

Using other possible conformers as the initial structures, three other C/D-*trans* conformers (**3**-**5**) were obtained as the local minima.[11] Conformers (**3** and **4)** are molecules with a C/D-*trans*-D-chair conformation. The difference lies in the conformation of the side chain moiety: the carbomethoxyl group orients to the β-side in **3** and the α-side in **4**, and in either case, the enol OH forms a hydrogen bond

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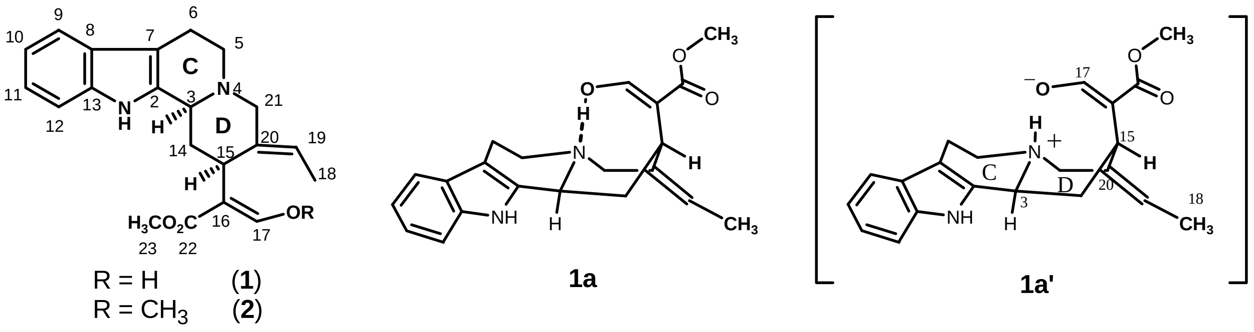
[#] Definition of hydrogen bonding: a hydrogen atom serves as a bridge between two electronegative atoms (X, Y), holding one by a covalent bond (X-H) and the other by purely electrostatic forces (Y---H: the bond is indicated by a dotted line). Its stabilization energy is about 5 kcal/mol. Hence, the former distance (X-H) is short and the latter one (Y---H) is long. The four local minima (**3**-**6**) have all hydrogen bond between H(O$\underline{\text{H}}$) and O(C$\underline{\text{O}}$). The O-H as well as O(CO)---H distances are almost the same for all of them, respectively. For **3**, the O-H distance is 0.96Å and O(CO)---H distance is 1.97Å



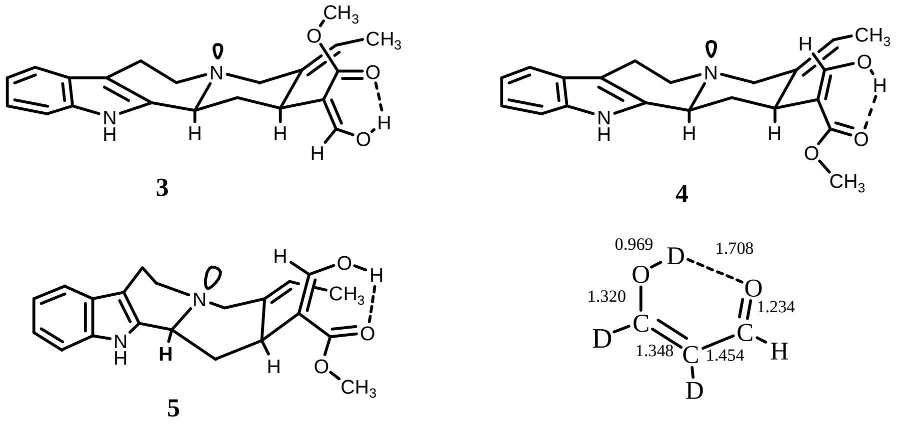
R = H (**1**)
R = CH$_3$ (**2**)

1a

1a'

Chart 1

with the ester carbonyl oxygen. Conformer (**5**) also has a *trans*-quinolizidine moiety and the D ring takes another type of boat conformation. Just as **3** and **4**, the enol OH group in **5** forms a hydrogen bond with the ester carbonyl oxygen. Calculated conformational energies and free energy differences are shown in Table 1.



3

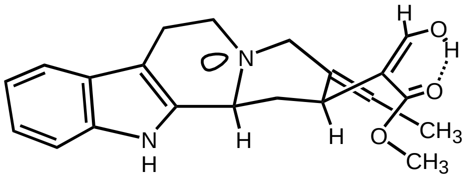
4

5

7

Chart 2

Contrary to the *trans*-fused C/D ring systems, single conformer with *cis*-fused C/D ring systems was obtained as the local minimum, irrespective of the initial structures.[16] This conformer (**6)** turned out to be identical to the structure proposed by Rackur and Winterfeldt[8] and by Goutarel *et al.*[9] (Figure 1). The energy value for **6** is also included in Table 1.



6

Figure 1

	Conformer	Potential energy, Hartree (ΔGÚ kcal/mol)
trans C/D ring	**1a**	-1149.8464 (0.00)
	3	-1149.8418 (2.83)
	4	-1149.8409 (3.45)
	5	-1149.8389 (4.70)
cis C/D ring	**6**	-1149.8403 (3.83)

Table 1

Table 1 clearly shows that the structure (**1a)** was most stable, the difference of free energy to next lowest one (**3**) being 2.83 kcal/mol. This value corresponds to the theoretical Boltzmann distribution ratio of 99.2: 0.8 favoring **1a** over **3**. Apparently geissoschizine exists in the structure (**1a)**. The reasons why structure (**1a)** was obtained as the global minimum are worthy to comment. Surely the short distance (2.68Å) between N4 and O17 brought about by the hydrogen bonding plays the most important role in determining the stereostructure of the framework. Due to this restriction, partial conformation around ring D and substituents on it are deformed so that D ring becomes (less favorable) twistboat having axial C15 substituent.

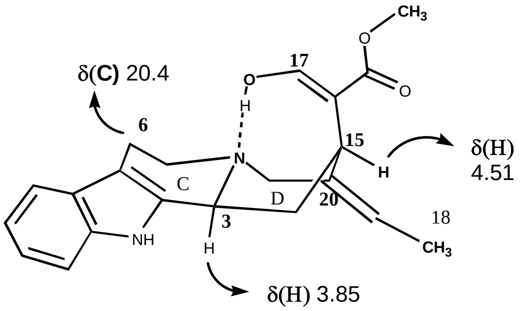
The zwitterionic structure (**1a'**) having essentially the same framework with **1a** was not found even as a local minimum and should be less stable than **1a**. Then how can we account for the absence of Bohlmann bands and a relatively stronger contribution of the enolate anion of the α-hydroxymethylene ester system in the UV spectrum (270 nm) in neutral solution, both being pointed out[7,10] as the supporting evidence for contribution of the zwitterionic structure for geissoschizine.

Baughcum *et al*. obtained the structural data (cf. **7** in Chart 2) for the enol form of malonaldehyde by microwave spectroscopy and determined that the barrier for shift (proton tunneling) of the enolic deuterium between the two oxygen atoms (in **7**) is about 4-5 kcal/mol.[17] Keeping this in mind, existence of **1a'** seems to be best explained as follows. Suppose that such proton tunneling occurs between **1a** and **1a'** with such a low barrier,[17] proportion of **1a** and **1a'** should be determined not under thermodynamic control but under kinetic control. Since acid-base reaction is the fastest one in chemistry, in an extreme case, we can expect 1 to 1 proportion for **1a** and **1a'**, irrespective of their stabilities.

Based on the optimized structure (**1a)**, ^{1}H- and ^{13}C-NMR chemical shifts were calculated by using Gaussian 98[14] program under the keyword "nmr" using 6-31G(d) basis set. The calculated values are shown in Table 2 together with the observed ones.[10] The calculated values are in agreement with the observed ones and this fact further supports structure (**1a)** to be the actual conformation of geissoschizine. It should be emphasized that the calculated C15-H chemical shift value, δ 4.45, is in good agreement with the observed values, δ 4.51 (500 MHz, $CDCl_3$),[10] and δ 4.48 (60 MHz, $CDCl_3$).[7] This extremely low shift position for the seemingly usual methine proton has caused, in addition to the lack of Bohlmann bands, quite big confusion in the chemistry of geissoschizine. The optimized structure (**1a**) demonstrates the proton to be located in the position susceptible to the combined downfield anisotropic effects from Δ19,20, Δ16,17, and ester carbonyl double bonds. Thus the observed downfield shift is fully explained by the partial conformation around ring D and the substituents on C15 and C20 in **1a**.

	Observed[7]			calculated		
Atom		^{1}H	^{13}C		^{1}H	^{13}C
1		7.97 (br s)			6.36	
2			132.8			126.6
3		3.85 (dd like, 11.6, 6.2)	53.5		3.77	52.3
5	α:	2.72 (ddd, 11.7, 11.7, 4.1)	50.5	α:	2.62	50.3
	β:	3.21 (dd, 11.7, 5.4)		β:	2.82	
6	α:	3.07 (dddd, 15.6, 11.7, 5.4, 2.2)	20.4	α:	2.56	22.6
	β:	2.82 (dd like, 15.6, 4.1)		β:	3.08	
7			107.7			103.0
8			126.5			120.0
9		7.48 (d, 8.0)	118.3		7.28	112.7
10		7.11 (td, 8.0, 1.1)	119.7		7.00	113.9
11		7.16 (td, 8.0, 1.1)	122.1		7.02	116.0
12		7.31 (d, 8.0)	110.9		6.87	103.6
13			136.5			127.6
14	α:	2.65 (ddd, 13.7, 11.3, 6.2)	33.8	α:	2.25	37.0
	β:	2.10 (ddd, 13.7, 11.6, 1.5)		β:	1.98	
15		4.51 (dd, 11.3, 1.5)	27.7		4.45	30.6
16			108.2			103.9
17		7.85 (s)	161.2		7.73	153.5
18		1.82 (dd, 6.9, 1.7)	13.1		1.84	14.5
19		5.41 (br q, 6.9)	121.8		5.37	119.6
20			133.2			130.1
21	α:	3.18 (d, 13.4)	59.1	α:	2.94	59.9
	β:	3.96 (dt, 13.4, 2.4)		β:	3.90	
CO			170.4			159.7
OCH_3		3.69 (s, 3H)	51.2		3.50	50.0

Table 2



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1a

Figure 2

Lambert *et al.*[18] have shown that simple protonation at nitrogen of *N*-methylpiperidine produces only a small effect on the chemical shifts of the carbon atoms in the ring: the signals of the α-, β- and γ-carbons of *N*-methylpiperidine are 56.7, 26.3 and 24.3 ppms, while those of its hydrogen iodide salts are 55.6, 23.9 and 21.8 ppms. This indicates that, even if the contribution of **1a'** is significant, the calculated values (correspond to those in neutral medium) do not differ from those obtained from **1a**. The diagnostic values (originally proposed by Wenkert[13] and later refined by Lounasmaa[12]) of the C6 shift positions for *cis*- and *trans*-quinolizidines are 21.6 ppm for the *trans* and 16.8 ppm for the *cis*-quinolizidines. As seen from Table 2, the calculated value (22.6 ppm) of C6 is quite close to 21.6 ppm.

CONCLUSION

Present study for geissoschizine has demonstrated that the hydrogen bonded structure (**1a**) (N···H-O) is the most stable one (global minimum) among all other conformers (local minima) in which conformer (**3**) being most stable.[19] The zwitterionic structure (**1a'**) ($N^{+}H$ O^{-}) having essentially the same framework with **1a** was not found even as a local minimum and should be less stable than **1a**. By assuming facile proton tunneling between **1a** and **1a'**, the contribution of **1a'** is explained by considering the ratio of them being determined under kinetic control. Due to restriction of shortening between the two atoms : N and O (**1a** by hydrogen bonding and **1a'** by electrostatic force), partial conformation around ring D and substituents on it are deformed so that D ring becomes (less favorable) twistboat having axial C15 substituent. On the contrary, there is no such restriction in **3** and hence, the corresponding partial conformation would be able to have more stable chair D ring with equatorial C15 substituent. Therefore, if above restriction is taken off, the framework essentially the same with **3** is expected to become the most stable conformation.[19] In accordance with this expectation, the methyl ether (**2**) shows Bohlmann bands and no UV maximum due to the enolate anion of the α-hydroxymethylene ester system. We believe that the work presented in this paper not only finalizes the long debate whether geissoschizine has *cis*- or *trans*-quinolizidine system but also provides for the first time the reason why significant contribution of the zwitterionic species (**1a'**) is possible in geissoschizine.

EXPERIMENTAL

DFT calculations DFT calculations were carried out for model structures using Gaussian 98 program[14] installed in a DEC Alpha Station 500/500 at the Graduate School of Pharmaceutical Sciences, Chiba University. Geometrical parameters were optimized at the B3LYP level of theory with 6-31G(d) basis set. Differences of free energy between the conformations were obtained from the self-consistent field (SCF) energies for the geometrically optimized structures.

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16. Geometrical optimization using the conformation proposed by Damak *et al.*[5] which has quasiaxial C15 substituent on twistboat ring D as the initial structure has again led to **6**. It is obvious that the conformation proposed by them is least probable for geissoschizine.
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