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Molecular Modeling of 3,8-dihydroxy-3-(hydroxymethyl)-6-methoxy-4,5-dimethylisochroman-1-one tautomersusing MOPAC Software

Wilanfranco C. Tayone[a*], Janeth C. Tayone[b]

[a,b]*Davao Oriental State College of Science and Technology, Mathematics and Natural Sciences Department, Mati City 8200, Davao Oriental, Philippines*

[a]*wilanfrancotayone@yahoo.com*

[b]*njtayone2005@yahoo.com*

Abstract

An isocoumarin type of compound known as 3,8-dihydroxy-3-(hydroxymethyl)-6-methoxy-4,5-dimethylisochroman-1-one (**2**) was studied for the molecular modeling using MOPAC. This compound that was originally isolated from the culture broth of *Leptosphaeria* sp. KTC 727 existed in anomeric tautomerization that could not be purified by chromatographic technique. Previous investigations revealed that the (3*R**,4*S**)-**2** major tautomer is more stable and thus the principal component of the tautomeric pair. This study however, provided new evidence and confirmed the aforementioned claim via theoretical calculation approach. Moreover, a plausible biogenic reaction pathway for the interconversion between major and minor tautomers is likewise proposed.

Keywords: isocoumarin; molecular modeling; Molecular Orbital Package (MOPAC); tautomers; z-matrix

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* Corresponding author. Mobile (+63)-917-244-0955;
E-mail address: wilanfrancotayone@yahoo.com

1. Introduction

Isocoumarins are secondary metabolites that are structurally related to the coumarins. They are phenolic substances made of fused benzene and an α-pyrone rings (1 in Figure 1). Isocoumarin moieties are important components in several natural products that exhibit a broad range of biological activities including antitumor, [1] antifungal, [2] antimicrobial, [3,4] antiviral, [5]cytotoxic, [6] anti-inflammatory, [7] and antiangiogenic [8]. The author together with other Japanese researchers recently isolated and published[9] an isocoumarin compound 3,8-dihydroxy-3-(hydroxymethyl)-6-methoxy-4,5-dimethylisochroman-1-one (**2** in Figure 1) from *Leptosphaeria sp*. KTC 727 fungus. This study is part of the author's continuing search for active metabolites from fungi [10-12].

Although the ESIMS data provided only a nominal protonated molecular ion, the ^{1}H-NMR spectrum in $CDCl_3$ disclosed the sampleto consist of a pair of tautomers with approximately 7:1 ratio (Figure 2) which could not be purified by chromatography.The ^{13}C-NMR spectra also corroborated the presence of (3*R**,4*S**)-**2** (major) and (3*S**,4*S**)-**2** (minor) tautomers. Taking their chemical shifts and molecular formulae into account, the minor component was expected to be a stereomeric tautomer around the C_3hemiacetal moiety.This study is focus on the molecular modeling of 3,8-dihydroxy-3-(hydroxymethyl)-6-methoxy-4,5-dimethylisochroman-1-one (**2**) tautomers using Molecular Orbital Package (MOPAC) software. It aims to understand the co-existence of two tautomers and provide an explanation why one tautomer is present in greater amount.

2. Materials and methods

The WinMopac7.21 version written by Dr. Roman Shchepin and Dmitriy Litvinov was used in this study. This program is an improved version of MOPAC7 with convenient windows interface and an integrated external molecular viewer called RasWin for easy viewing of the three dimensional structures. MOPAC is a semi-empirical computer program for the study of structures of compounds. It is a software use for *in-silico* studies especially for molecules that are too difficult to investigate experimentally [13-17]. This program is compatible with Windows XP, Vista and Windows 7 (both 32 and 64 bit) [18]. The semi-empirical method used in these calculations was Modified Neglect of Diatomic Overlap (MNDO).

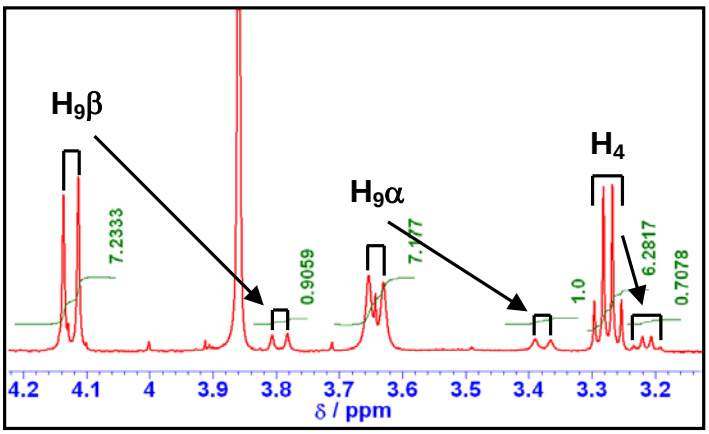
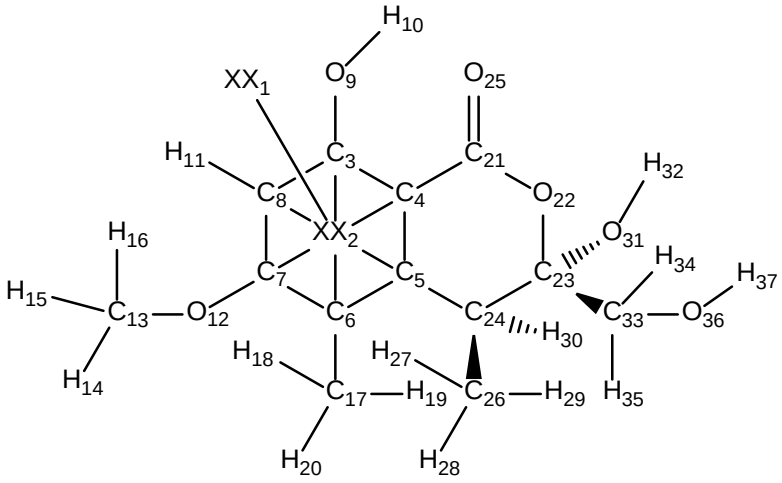


Fig. 2.^{1}H-NMR spectrum of 2 showing the presence of two tautomers

The first task was to specify the type of calculation and is controlled by keywords. The initial molecular geometry (in the form of a z-matrix) was then read by the program and performed iterative computations as starting point of the optimization process until the program finds the most stable geometry. The geometric positions of the atoms in a molecule were defined using a z-matrix. The column of 1's that follow after the bond lengths, bond angles and dihedral angles are parameters that need to be optimized. The descriptions of the atoms for the major(figure 3) and minor (figure 4) tautomers are most easily achieved by using a dummy atom XX. This is an imaginary point in space that is treated as an atom for the purpose of defining its geometric position. The dummy atom was then removed so that only the real molecule remains.



XX									
XX	1.00	1					1	0	0
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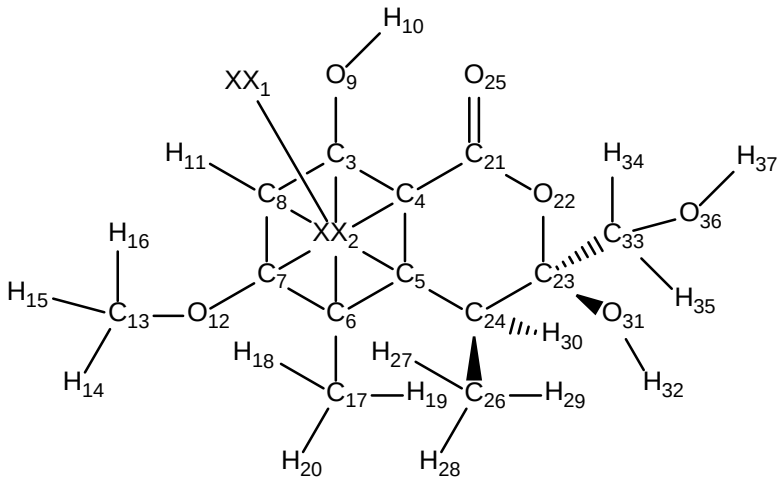
C	1.00	1	90	1	60	1	2	1	3
C	1.00	1	90	1	60	1	2	1	4
C	1.00	1	90	1	60	1	2	1	5
C	1.00	1	90	1	60	1	2	1	6
C	1.00	1	90	1	60	1	2	1	7
O	1.40	1	130	1	180	1	3	8	2
H	1.10	1	130	1	360	1	9	3	4
H	1.20	1	130	1	180	1	8	3	7
O	1.40	1	130	1	180	1	7	6	8
C	1.30	1	130	1	369	1	12	7	8
H	1.10	1	130	1	180	1	13	12	7
H	1.10	1	110	1	110	1	13	14	12
H	1.10	1	110	1	110	1	13	14	15
C	1.50	1	130	1	180	1	6	5	7
H	1.10	1	110	1	180	1	17	6	5
H	1.10	1	110	1	110	1	17	18	6

H	1.10	1	110	1	110	1	17	18	19
C	1.50	1	110	1	180	1	4	5	3
O	1.30	1	120	1	180	1	21	4	3
C	1.30	1	120	1	360	1	22	21	4
C	1.50	1	130	1	180	1	5	4	6
O	1.40	1	130	1	180	1	21	4	5
C	1.40	1	110	1	250	1	24	23	5
H	1.20	1	110	1	120	1	26	24	23
H	1.20	1	110	1	110	1	26	27	24
H	1.20	1	110	1	110	1	26	27	28
H	1.30	1	120	1	110	1	24	26	23
O	1.50	1	120	1	360	1	23	24	30
H	1.30	1	100	1	150	1	31	23	24
C	1.90	1	80	1	100	1	23	22	31
H	1.30	1	90	1	60	1	33	23	22
H	1.30	1	-160	1	60	1	33	34	23
O	1.30	1	-100	1	110	1	33	34	35
H	1.30	1	110	1	-110	1	36	33	34

Fig. 3.Z-matrix of major tautomer, (3*R**,4*S**)-2

The first atom (XX_1) is always placed at the origin of coordinate system and on top of the z-matrix. Its position and connectivity could not be defined yet since there is no atom that precedes it. The second atom, the second dummy atom (XX_2) in Figure 3, must now be defined. Only the distance from atom 1 need be defined because the second atom is always placed on a predetermined axis. The second line means that XX_2 is bound to atom 1 (XX_1) at a distance of 1.00 Angstrom. The third atom, C_3 in figure 3, is defined using the distance from the XX_2 dummy atom and the XX_1-XX_2-C_3 angle. The third line in figure 3 implies that the carbon atom, C, is bound to the second dummy atom (XX_2), at a distance of 1.00 angstrom and makes an angle with the first dummy atom (XX_1) of 90°. The fourth atom (C_4) is defined exactly as the third except that an extra parameter is needed to specify its position uniquely.

The exact position is defined using a dihedral angle to C_3. Thus, the fourth line in figure 3 defines a carbon atom that is bonded to atom number 2 (XX_2) at a distance of 1.00 angstrom, making an angle with the first atom (XX_1) of 90° and a dihedral angle with atom number 3 (C_3) of 60°. The exact positions of the remaining atoms are distinctly defined by the bond lengths, bond angles and dihedral angles in similar fashion described above.The relative positions of the atoms for both tautomers are similar except at C_{23} where the hydroxymethyl group is up and down respectively, for major and minor tautomers.



XX									
XX	1.00	1					1	0	0
C	1.00	1	90	1			2	1	0
C	1.00	1	90	1	60	1	2	1	3
C	1.00	1	90	1	60	1	2	1	4
C	1.00	1	90	1	60	1	2	1	5
C	1.00	1	90	1	60	1	2	1	6
C	1.00	1	90	1	60	1	2	1	7
O	1.40	1	130	1	180	1	3	8	2
H	1.10	1	130	1	360	1	9	3	4
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H	1.10	1	110	1	110	1	13	14	15
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H	1.10	1	110	1	180	1	17	6	5
H	1.10	1	110	1	110	1	17	18	6
H	1.10	1	110	1	110	1	17	18	19
C	1.50	1	110	1	180	1	4	5	3
O	1.30	1	120	1	180	1	21	4	3
C	1.30	1	120	1	360	1	22	21	4
C	1.50	1	130	1	180	1	5	4	6
O	1.40	1	130	1	180	1	21	4	5
C	1.40	1	110	1	250	1	24	23	5
H	1.20	1	110	1	120	1	26	24	23
H	1.20	1	110	1	110	1	26	27	24

H	1.20	1	110	1	110	1	26	27	28
H	1.30	1	110	1	110	1	24	26	23
O	1.50	1	120	1	-150	1	23	22	24
H	1.30	1	110	1	300	1	31	23	22
C	1.50	1	100	1	-110	1	23	31	24
H	1.30	1	110	1	150	1	33	23	31
H	1.30	1	110	1	120	1	33	34	23
O	1.30	1	-110	1	60	1	33	34	23
H	1.30	1	110	1	150	1	36	33	35

Fig. 4.Z-matrix of minor tautomer, (3*S**,4*S**)-2

The molecules are now completely defined and the z-matrices are then converted to its corresponding MOPAC input independently for iterative calculation. The calculations were done using Acer Aspire personal computer in Windows 7 Ultimate with Intel® Processor Core™ i3-2367M CPU @ 1.40 GHz and 4.00 GB Random Access Memory (RAM).

3. Results and discussion

The summary of results in MOPAC calculation is shown in Table 1. These numbers were obtained from the brief results tab output.

Table 1. Summary of results in MOPAC computations

Tautomer	ΔH_f (Kcal/mol)	Ionization Potential (ev)	Electronic Energy (ev)	Core-core Repulsion (ev)
Major, (3*R**,4*S**)-**2**	-238.14737	9.13924	-24147.43616	20324.91042
Minor, (3*S**,4*S**)-**2**	-237.07736	9.31690	-24201.80140	20379.32209

The major tautomer (3*R**,4*S**)-**2** has lower theoretically computedheat of formation and thus more stable than the minor component. This finding was further confirmed by the final geometry obtained after optimization of both tautomers as shown in figure 5. The equatorial position of the C_{23}-hydroxymethyl substituent of the major tautomer tends to reduce the steric effect in the pyrone ring.

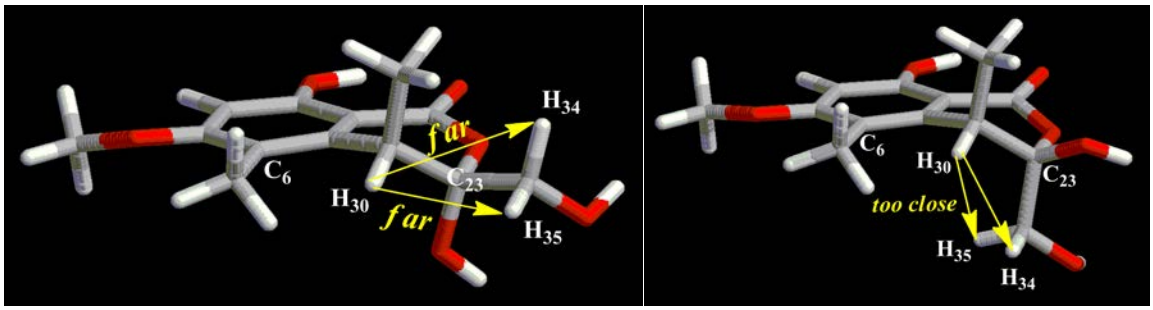

Fig. 5.Final geometry obtained after optimization of major (left) and minor (right) tautomers

Substituents that are in the equatorial position are less crowded, because the groups would be farther, which results in less steric interference, thus making the compound more stable. Therefore, the substituent extends into space and away from the rest of the molecule. However, if it is in axial position, it's always going to be nearer from other groups thus creating more steric strain. The hydroxymethyl substituent at C_{23} for the major tautomer is in equatorial position and is the more stable conformer because it has more room and fewer steric interactions. In contrast, the hydroxymethyl group for the minor tautomer is in axial position. This generates unfavorable steric interactions between the axial hydroxymethyl group at C_{23} to the methyl group at C_6 and H_{30}. Notice that the pyran ring is not planar but puckered towards the benzene ring making it relatively closer to the aromatic methyl substituent. These were confirmed by the computed interatomic distances provided by MOPAC. The methylene protons (H_{34} and H_{35}) of the major tautomer are relatively farther to H_{30}(3.94 Å and 3.69 Å respectively). Both methylene protons of the major tautomer are also far from the methyl group (C_6CH_3) attached in the benzene ring than those of the minor tautomer making it the more stable conformer. The calculated (MOPAC) semi-empirical interatomic distances of the major and minor tautomers are shown in table 2.

Table 2. Selected interatomic distances of the major and minor tautomers

Compound	Interatomic Distance (Angstrom)			
	H_{34} - H_{30}	H_{35} - H_{30}	H_{34}-C_6CH_3	H_{35}- C_6CH_3
(3*R**,4*S**)-**2** major	3.94	3.69	5.03	5.51
(3*S**,4*S**)-**2** minor	1.89	2.01	4.13	4.69

The proposed biogenic reaction mechanism for the interconversion of major and minor tautomers is shown in figure 6. The chemical equilibrium that exists between both tautomers may somehow explain its co-existence. This equilibrium is established when the carbonyl oxygen of the major tautomer attacks the proton of water (**i**) prompting a series of electron delocalization towards the positive center in (**ii**). As the hemiacetal bond between

C_3 (carbon bound to two oxygen atoms) and carbonyl carbon C_1 is cleaved, it forms the open-chain compound (**iii**). The unrestricted sp^3 - sp^2 (carbon bearing the hydroxymethoxy group) bond can freely rotate to change its position. The electron rich carbonyl oxygen at C_1 then attacks the electron deficient sp^2 carbon as shown in **iv** forming **v**. It then eventually reformed the cyclic moiety of the compound to afford the minor tautomer **vi**. When the hemiacetal bond is reformed, the C=O group on C_1 may attack either of the two stereochemically distinct sides of the ketone group on C_3. Which side it actually does attack on, determines whether the major or minor tautomer is formed.

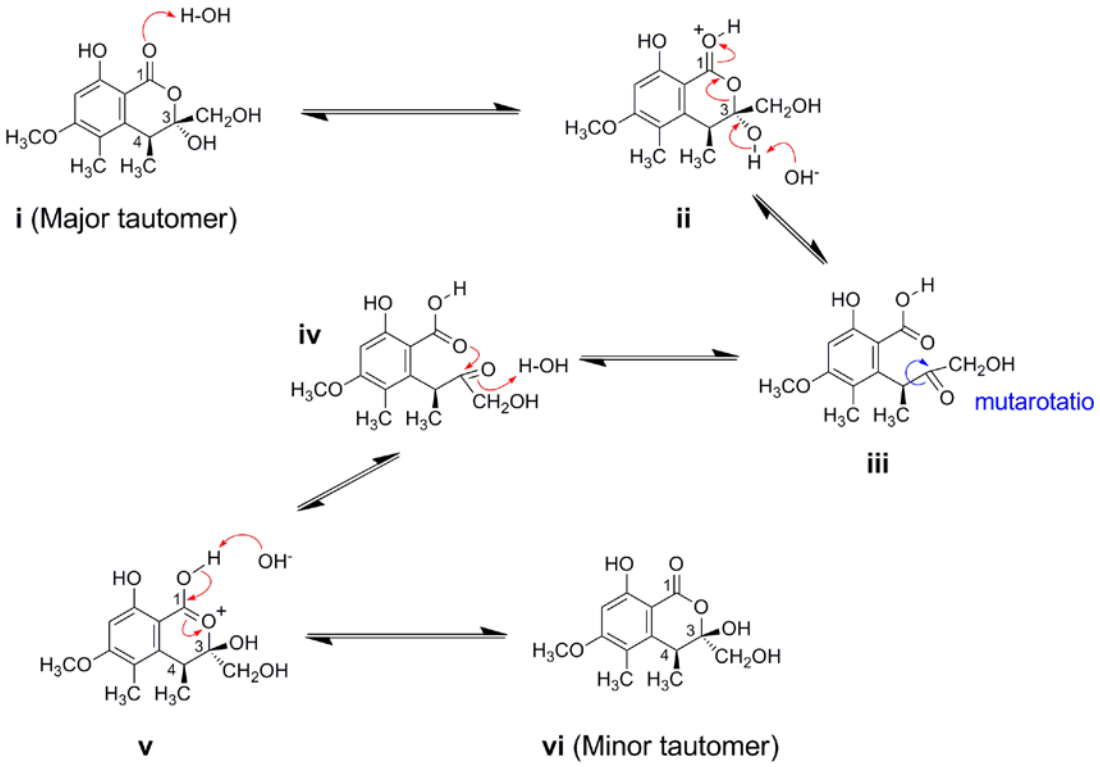

Fig. 6. Proposed reaction pathway for the interconversion of major-2 and minor-2

4. Conclusion

This study demonstrated the potential of computer assisted approach as a powerful tool in structural analyses of compounds that are inaccessible via conventional experimental way.

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