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Epimerization of Tilivalline

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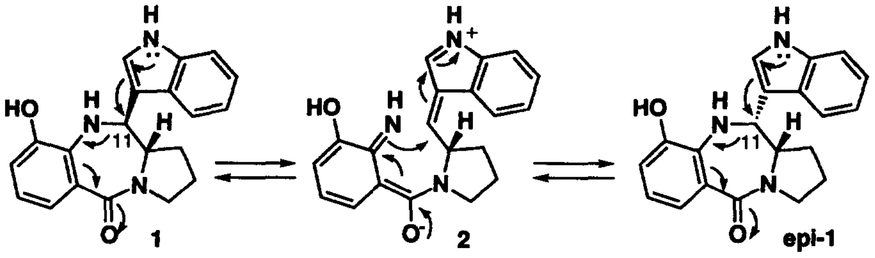
Abstract : Epimerization of tilivalline (**1**) at the C_{11}-position occurred by treatment with zinc chloride to give a mixture of **1** and its 11-epimer (**epi-1**) in a ratio of 83 : 17. The computational chemical analysis of the thermodynamic stability of **1** and **epi-1** through MM3(92) also revealed the energetic preference of **1** and the calculated equilibrium ratio of **1** and **epi-1** was consistent with the experimental results. The torsional and bending angle parameters around the amide bond were determined.

We have already accomplished a completely stereoselective synthesis of tilivalline, a pyrrolo[2,1-c][1,4]benzodiazepine derivative isolated from *Klebsiella pneumoniae* var. *oxytoca*,[1] utilizing a new Mannich type cyclization.[2] The high stereoselectivity due to the effect of zinc chloride as a catalyst has been discussed in the preceding paper by use of the semi-empirical molecular orbital method.[3] We now wish to report the epimerization of tilivalline and its computational chemical analysis.

When tilivalline (**1**) was treated successively with chlorotrimethylsilane - sodium iodide followed by zinc chloride, i.e. the reaction conditions of the Mannich type cyclization without the addition of indole,[2] the products were found to be a mixture of tilivalline (**1**) and its 11-epimer (**epi-1**) in a ratio of 94 : 6. Further investigation revealed that treatment of **1** with zinc chloride in warm acetonitrile gave a mixture of **1** and **epi-1** in a ratio of 83 : 17. Heating of **1** in acetonitrile without zinc chloride did not cause any epimerization at all, as summarized in Table 1. The isomerization is likely to occur via the intermediate **2**.

Next we estimated the stability of tilivalline (**1**) and its epimer (**epi-1**) by calculation using MM3(92).[4] We first evaluated and compared the calculation methods with the experimental data utilizing cyclopropane as a model since the thermodynamic properties of cyclopropane have been well investigated. Performance of various force fields for cyclopropane is shown in Table 2, which revealed that MM3(92) would be the most reliable of the calculation methods, as expected.

Table 1. Isomerization of Tilivalline



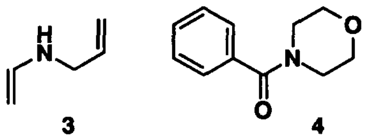
Run	Method	Reaction Conditions		Ratio of **1** : **epi-1**
1	A	(i) TMSCl, NaI pyridine, MeCN	-15°C, 30 min	94 : 6
		(ii) $ZnCl_2$	-15°C, 30 min 52°C, 6 h	
2	B	$ZnCl_2$, MeCN	50~55°C, 24 h	83 : 17
3	C	MeCN	50~55°C, 24 h	100 : 0

Table 2. Perfomance of Various Force Fields for Cyclopropane

Method	$(H_{298}° - H_0°)/298$ cal/mol•deg	$-(G_{298}° - H_0°)/298$ cal/mol•deg	$Cp_{298}°$ cal/mol•deg	$S_{298}°$ cal/mol•deg
Experiment[a]	9.15	47.59	13.28	56.74
MM3(92)	9.10	47.56	13.06	56.66
Bigstron 3 (MM2)	10.23	47.96	——	58.21
MNDO	8.89	47.58	12.40	56.47
AM1	8.90	45.81	12.45	56.42
PM3	8.94	47.51	12.61	56.45

a) Ref. 5

However, three parameters were found to be missing when using MM3(92). These were two torsional parameters O-Csp^2-Csp^2-Nsp^3 -(1) and Csp^2-Nsp^3-Csp^3-Csp^2 -(2), and a bending angle parameter Csp^2-Ccarbonyl-Namide -(3). The torsional parameter (1) has been already reported[6] to be $V_1 = -2.74$, $V_2 = 43.01$, and $V_3 = 2.60$, which we employed. MM3(92) and MOPAC Ver. 6.0 - AM1 for MO were used to determine the parameters (2) and (3). The parameter (2) was determined to be $V_1 = -2.375$, $V_2 = 0.045$, and $V_3 = -1.731$ by the aid of the non-linear least squares method so that the relative energies of allylvinylamine **3**[6,7] with MM3(92) could reproduce the relative energies with AM1. Since the bending angle of N-benzoylmorpholine **4** with AM1 could not reproduce the bending angle from X-ray analysis, this parameter (3) was determined to be $K_b = 1.000$, Tzero = 118.000 so that the bending angle of **4** with MM3(92) could reproduce the bending angle of X-ray analysis.[8]



3 **4**

Fig. 1

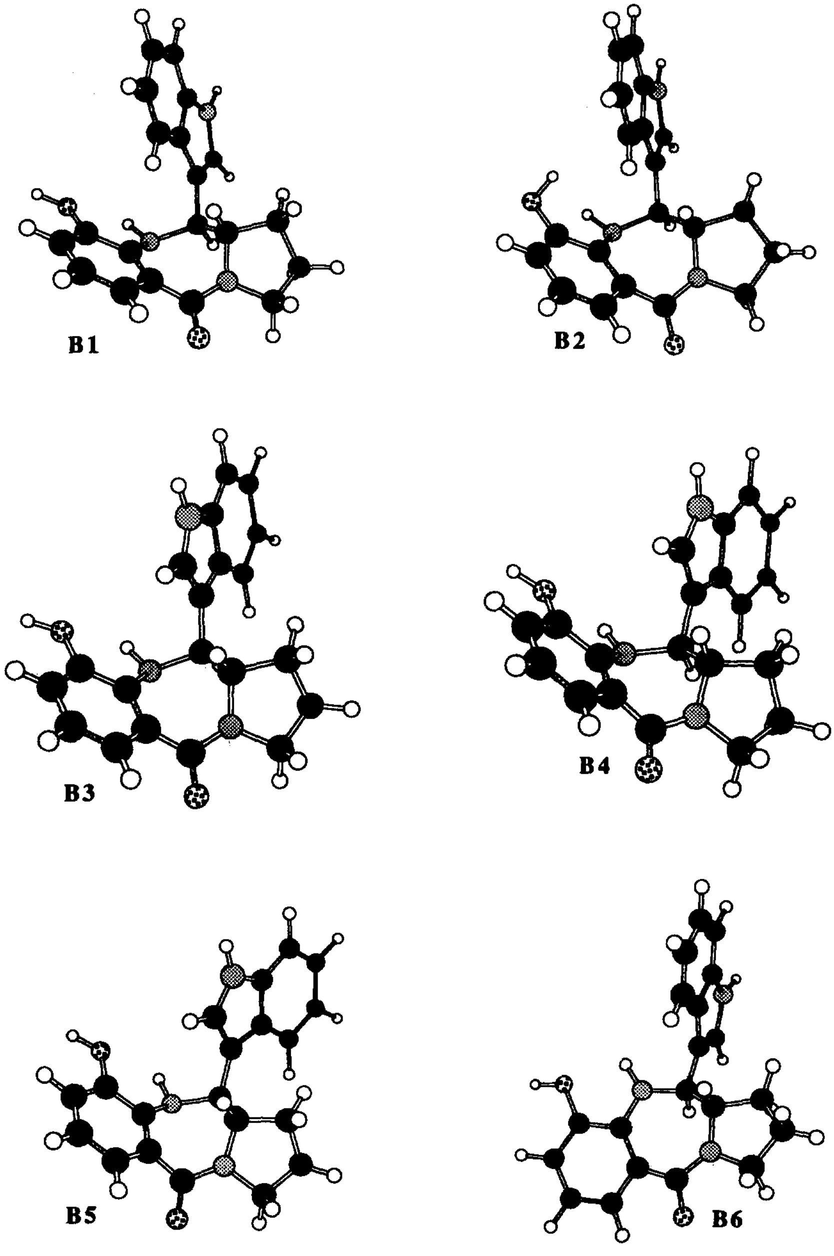
The computational chemical analysis utilizing the above parameters revealed that the mean free energy of tilivalline (1) was 241.868 kcal/mol while that of **epi-1** was 242.796 kcal/mol. The difference was -0.928 kcal/mol and hence the equilibrium ratio of **1** and **epi-1** was calculated to be 82.7 : 17.3, which was consistent with the experimental value (see run 2 in Table 1). Thus tilivalline (1) proved to be thermodynamically more stable than **epi-1** and to have the preferred configuration. In terms of conformations, **B1~B5** in tilivalline (1) occupied about 90% of all possible conformations, and especially **B1** occupied about 50% independently. The conformations of **A1~A3** in **epi-1** occupied about 90% of all possible conformations, as shown in Table 3.

Table 3. $\Delta G_{298.16}$, $\Delta\Delta G_{298.16}$ [kcal/mol], and Distribution [%] of **1** and **epi-1**

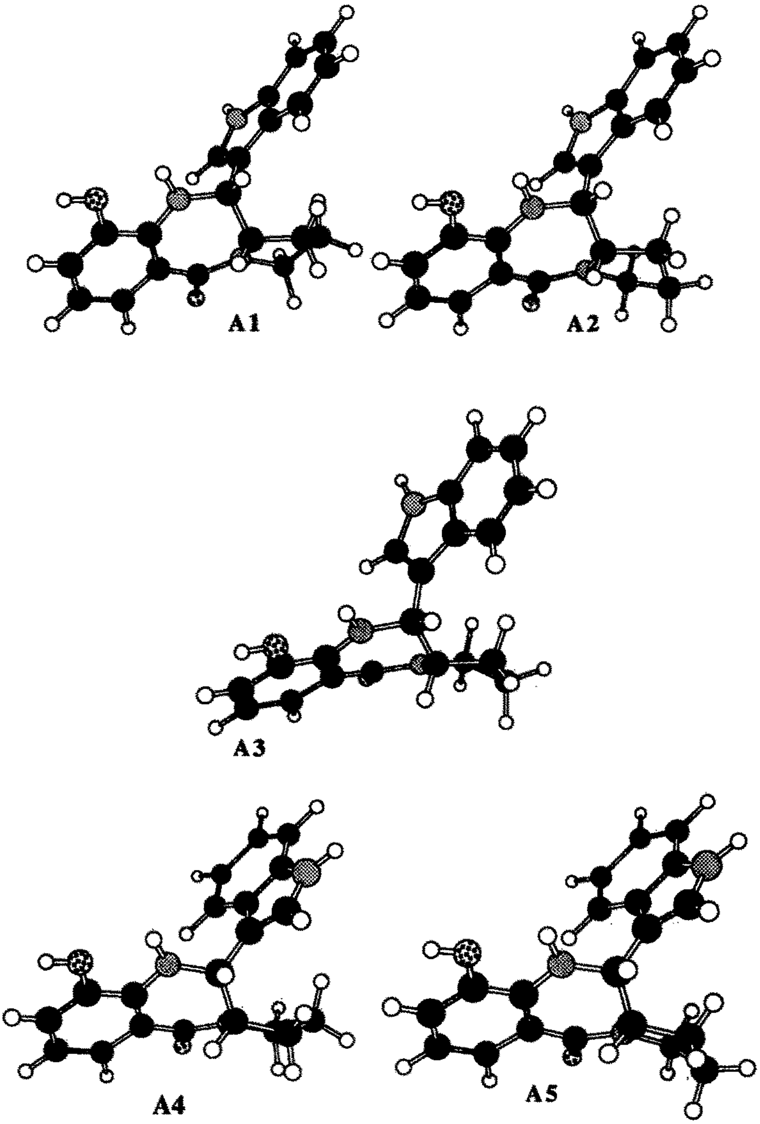
Conformer of 1	ΔG	ΔΔG	Distribution[a]	Conformer of **epi-1**	ΔG	ΔΔG	Distribution[a]
B1	241.848	0.000	51.840	**A1**	242.780	0.000	39.928
B2	242.416	0.568	19.874	**A2**	243.053	0.273	25.186
B3	242.946	1.098	8.124	**A3**	243.057	0.277	25.016
B4	242.948	1.100	8.097	**A4**	243.915	1.135	5.878
B5	242.952	1.104	8.042	**A5**	244.360	1.580	2.774
B6	243.527	1.679	3.047				

a) Boltzmann distribution at 298.16 K

The Optimized Structures of Tilivalline (**1**)



The Optimized Structures of Epi - Tilivalline (**epi-1**)



Further we performed the energy calculation on 1 and **epi-1** by use of AM1[9] and PM3[10] for comparison. Tilivalline (1) was again revealed to be more stable than **epi-1** in terms of the heat of formation, as shown in Table 4. According to the optimized structures, the shape of 1 was approximately spherical, while that of **epi-1** was warped to the β side.

Table 4. Δ Hf [kcal/mol] and Isomerization of Tilivalline

	$H_{f(1)} - H_{f(epi-1)}$	1 : epi-1
AM1	-1.601	93.7 : 6.3
PM3	-0.317	63.1 : 36.9

Finally, the intramolecular hydrogen bonds were investigated to calculate the energy of the hydrogen bonds in **1** and **epi-1**. The data in Table 5 revealed that most conformers had the intramolecular hydrogen bond between the phenolic oxygen and anilinic hydrogen but not between the phenolic hydrogen and anilinic nitrogen. This intramolecular hydrogen bond would be important factor influencing the thermodynamic stability of **1** and **epi-1**.

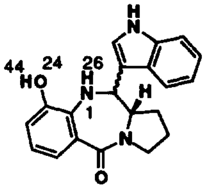


Table 5. Hydrogen Bond Energy [kcal/mol] of 1 and epi-1

	B1	**B2**	**B3**	**B4**	**B5**	**B6**
N(1), H(44)	0.1344	-0.1857	0.1318	0.1318	0.1310	0.1391
O(24), H(26)	-0.2428	-0.1434	-0.2247	-0.2252	-0.2233	-0.2558

	A1	**A2**	**A3**	**A4**	**A5**
N(1), H(44)	0.1438	0.1454	0.1445	0.1401	0.1431
O(24), H(26)	-0.2219	-0.2232	-0.2213	-0.2184	-0.2211

In conclusion, it is clear that tilivalline (**1**) is more stable than **epi-1** in terms of the free energy. Furthermore, equilibrium ratio of **1** and **epi-1** in experiment proved to be consistent with that with MM3(92) and the isomerization arrived at the equilibrium point.

Acknowledgement: We thank Professor Chikara Kaneko of Tohoku University for his pointing out the possible epimerization of tilivalline.

EXPERIMENTAL SECTION

Input coordinates were built with the Chem3D Plus Ver. 2.0.1 and Ver. 3.1 from CSC on a Macintosh SE and LC520 personal computers. The non-linear least square's analysis was performed with the Solver implemented in the MicroSoft Excel Ver. 4.0 on a personal computer. All calculations with MOPAC Ver. 6.0 were carried out on a HP Apollo DN10000 and a HP 9000/750 workstations.

Epimerization of Tilivalline

(1) With zinc chloride : A mixture of tilivalline (**1**) (67 mg, 0.2 mmol) and zinc chloride (110 mg, 0.8 mmol) (dried for 2 h at 150 °C in vacuo before use) in acetonitrile (3 ml) was stirred at 50~55 °C for 24 h under argon. After ice-cooling, sat. aq. sodium bicarbonate (10 ml) and then water (50 ml) were added and the mixture was extracted with ethyl acetate (150 ml). The extracts were washed with sat. aq. sodium chloride (50 ml) and dried over sodium sulfate. After concentration, a mixture of tilivalline (**1**) and 11-epi-tilivalline (**epi-1**) was obtained as a yellow brown amorphous solid, a part of which was subjected to HPLC as shown below for the determination of the ratio of **1/epi-1**. A pure sample of **epi-1** was obtained by silica gel column chromatography (BW 200, hexane/ethyl acetate = 1/3) ; mp 256~258 °C, (hot plate method) (lit.,[1]) mp 252 °C) ^{1}H-NMR (DMSO-d_6/$CDCl_3$) δ ; 0.80~0.96 (m, 1H), 1.23~1.39 (m, 1H), 1.90~2.13 (m, 2H), 3.18~3.23 (m, 1H), 3.58~3.68 (m, 1H), 4.23~4.39 (m, 1H), 5.19 (d, 1H, J=2.7Hz), 6.64~7.67 (m, 8H), 9.03 (brs, 1H, disappeared with D_2O), 9.76 (brs, 1H).

HPLC analysis of the mixture of **1** and **epi-1** : A mixture (0.33 mg) of **1** and **epi-1** was dissolved in methanol (0.2 ml and 0.2 μl of the solution was subjected to HPLC using DEVELOSIL 60-5 (i.d. 4.6 × 150 mm, purchased from Chemco Co., Ltd.) (flow rate : 1.0 ml/min ; eluate, hexane/isopropanol = 3/1; detection, UV 281 nm). The mixture showed two peaks (R.T. = 4.01 min (**epi-1**) and 10.59 min (**1**)) in a ratio of **1/epi-1** = 83/17.

(2) With chlorotrimethylsilane, sodium iodide, pyridine and zinc chloride (under a new Mannich type cyclization conditions) :[2] Chlorotrimethylsilane (61 μl, 0.48 mmol) was added dropwise to a suspension of tilivalline (**1**) (40 mg, 0.48 mmol), sodium iodide (72 mg, 0.48 mmol), and pyridine (48 μl, 0.6 mmol) in acetonitrile (1.2 ml) at -15 °C under argon. After the mixture was stirred at -15 °C for 30 min, zinc chloride (66 mg, 0.48 mmol) was added and the whole was stirred at -15 °C for 30 min and then at 52 °C for 6 h. Saturated aq. sodium bicarbonate (1.2 ml), then AcOEt (25 ml) were added to the mixture, and insoluble materials were filtered off. The filtrate was separated and the organic layer was washed with sat. aq. NaCl then dried over sodium sulfate. After concentration in vacuo, the residue was purified by silica gel column chromatography (BW 200, hexane/AcOEt = 1/3) to give tilivalline (**1**) (29 mg, 73 %) and 11-epi-tilivalline (**epi-1**) (2 mg, 5 %) (**1/epi-1** = 94/6).

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