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Reaction Pathway for Epimerization of Tilivalline

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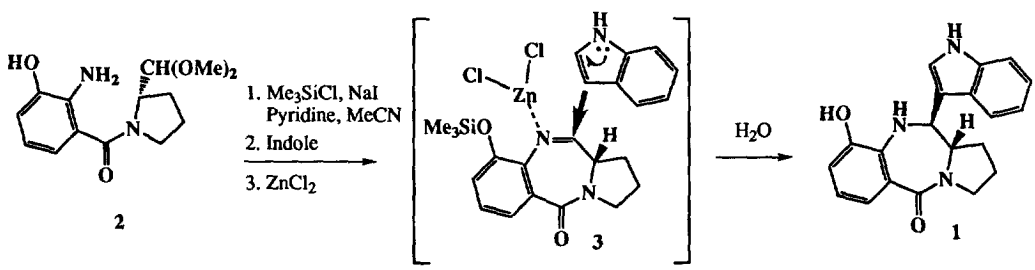
Abstract : A series of the reaction pathway for the epimerization of tilivalline has been revealed in detail at the AM1 semi-empirical level.

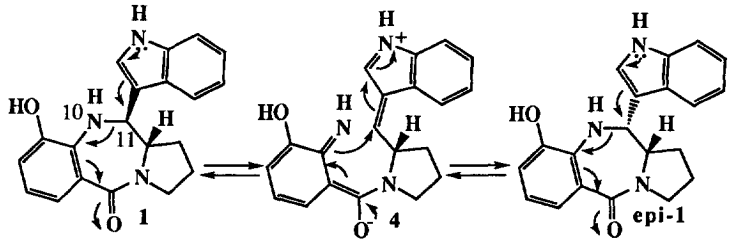
We have already accomplished a completely stereoselective synthesis of tilivalline (**1**), a pyrrolo[2,1-c][1,4]benzodiazepine derivative isolated from *Klebsiella pneumonia* var. *oxytoca*,[1] utilizing a new Mannich type cyclization,[2-5] as shown in Scheme 1. The high stereoselectivity due to the effect of zinc chloride as a catalyst has been discussed by use of the semi-empirical molecular orbital method.[6] Furthermore, the thermodynamic stability for the epimerization of **1** has been reported by use of the molecular mechanics method.[7] We now wish to report the detailed reaction pathway for the epimerization of **1**.



Scheme 1 The stereoselective synthetic route for tilivalline (**1**)

When **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, the products were found to be a mixture of **1** and 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 84 : 16. Heating of **1** in acetonitrile without zinc chloride did not cause any epimerization at all, as summarized in Table 1.[3] This isomerization is likely to occur via an intermediate **4**.

Table 1 Experimental results for epimerization of tilivalline (**1**)



Run	Method	Reaction Conditions		Ratio of **1** : **epi-1**
1	A	(1) Me_3SiCl, NaI, pyridine, MeCN	-15°C, 30 min	94 : 6
		(2) $ZnCl_2$	-15°C, 30 min 52°C, 6 h	
2	B	$ZnCl_2$, MeCN	50~55°C, 24 h	84 : 16
3	C	MeCN	50~55°C, 24 h	100 : 0

AM1 semi-empirical molecular orbital calculation was performed by MOPAC93[8] on a Titan 2-800 and a DEC AlphaServer 2100 5/250 workstation. Input coordinates were built with the CSC Chem 3D plus Ver. 3.1 on a Power Macintosh 8100/80 personal computer. Geometry was optimized by using the PRECISE option in order to decrease the gradient norm. Respective transition states for respective reaction steps were located using the TS method[9] and the SADDLE routine[10] implemented in MOPAC93 and characterized by establishing that the force constant matrix had the only one negative frequency. To verify that calculated transition states connect reactants and products, AM1 level intrinsic reaction coordinate following (IRC) calculations[11] were done with respect to each transition state.

First of all, we investigated how much energy the first step of the epimerization required in order to break the bond between N_{10} and C_{11}. As a result of survey, the first transition state **5** and the first intermediate **6** were obtained (Figures 1 and 2).[11,12] The obtained transition state structure **5** had the only one negative frequency (123.9*i* cm^{-1}). Structures of the obtained transition state **5** or the intermediate **6** were similar to **1**.

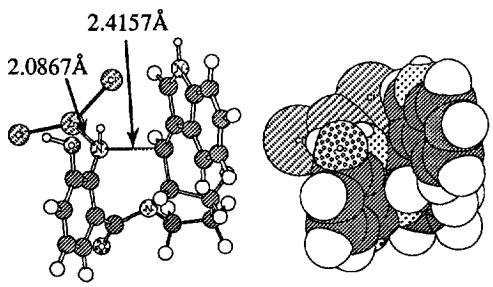


Figure 1 The structure of the first transition state **5**

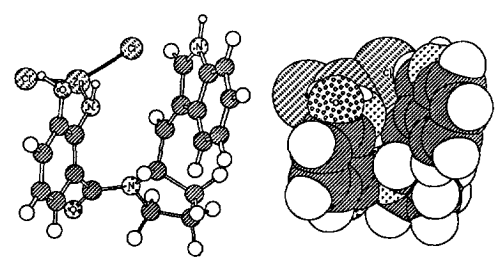


Figure 2 The structure of the first intermediate **6**

In the same way, we searched how much energy the final step of the epimerization required to break the bond between N_{10} and C_{11}. As a result, the final transition state **7** and the second intermediate **8** were obtained (Figures 3 and 4). The obtained transition state structure **7** had the only one negative frequency (371.5*i* cm^{-1}). The obtained transition state **7** or the intermediate **8** were similar to **epi-1**.

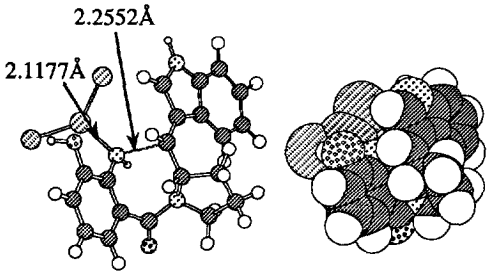


Figure 3 The structure of the final transition state **7**

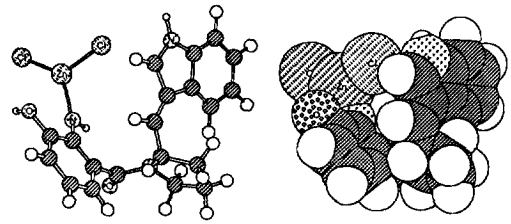


Figure 4 The structure of the second intermediate **8**

Finally, we explored the turning point in the epimerization. This turning point was very important to change a direction of the indolyl function. As a result, the second transition state **9** was found (Figure 5). The obtained transition state structure **9** had the only one negative frequency (265.1*i* cm^{-1}).

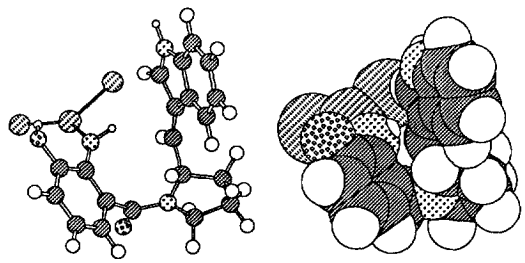


Figure 5 The structure of the second transition state **9**

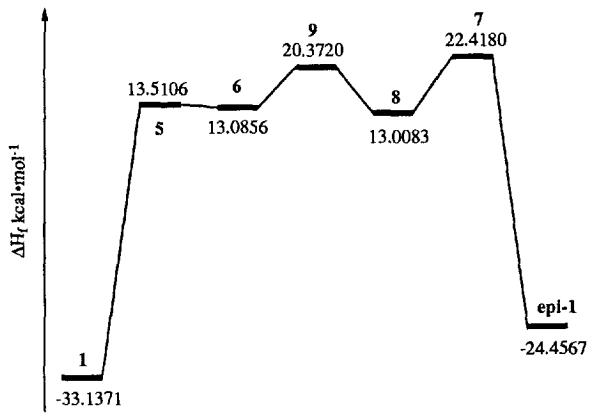


Figure 6 The energy diagram for the epimerization of **1**

Considering these results and the reported experiments,[2-5] it will be difficult for the epimerization to make progress because of some high energy barriers (Figure 6). When the reaction proceeds from **6** to **9**, it is more easily to return to **1** than to advance to **9** from the view point of the relative energy. However some high energy active species which obey a part of the Boltzmann's distribution overcome some high energy barriers. Therefore **1** changes into **epi-1** via the three transition states (**5**, **9**, **7**) and the two intermediates (**6**, **8**).

From the viewpoint of this reaction mechanism, the first step is to break the bond between N_{10} and C_{11}. The second step is the rotation of the indolyl function. When the rotation takes place, the amide bond also rotates in order to avoid the van der Waals' repulsion between the indolyl function and zinc chloride. The final step is the link between N_{10} and C_{11}.

In conclusion, the result at the AM1 semi-empirical level have revealed a series of the detailed reaction pathway for the epmimerization of tilivalline (**1**), which has made properties for transition states clear.

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