Pergamon

Tetrahedron Vol. 50, No. 32, pp. 9775-9780, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4020/94 $7.00+0.00

0040-4020(94)00562-1

Effect of Zinc Halides on the High Stereoselectivity of a New Mannich Type Cyclization in the Tilivalline Synthesis
A Computational Chemical Analysis

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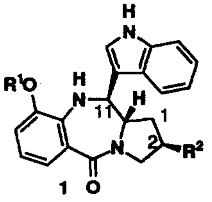
Abstract : The calculation by the semi-empirical molecular orbital method concerning the effect of zinc halides on the high stereoselectivity of a new Mannich type cyclization in our tilivalline synthesis has revealed that (1) zinc chloride coordinates with the N_{10} atom during the reaction and (2) the steric hindrance on the α side and the extension of LUMO to the β side in the intermediate **7** govern the high steroselectivity.

Tilivalline (**1a**), a metabolite isolated from *Klebsiella pneumoniae* var. *oxytoca*,[1] belongs to a group of pyrrolo[2,1-c][1,4]benzodiazepines, a characteristic skeleton of anthramycin-type antibiotics. We have already accomplished stereoselective syntheses of **1a**,[2] its analogs **1b~1e**,[3] and 11-substituted pyrrolo[2,1-c][1,4]benzodiazepin-5-ones (**2**)[4] utilizing a novel intramolecular Mannich type cyclization as a key step. Furthermore, we have already found that this Mannich type cyclization is also efficiently applicable to construct 2-indolyl-1,4-benzodiazepin-5-ones **3**.[4] We have been interested in the reason for the high stereoselective synthesis of **1a** and its derivatives. In our tilivalline synthesis, we considered and explained that the attack of indole occurred only from the less hindered face of the intermediate imine **4**, in which zinc chloride coordinated to both the N_{10} atom and the silylated phenol-oxygen,[2] as depicted in Scheme 1.

In order to prove this hypothesis by the computer chemistry, we calculated the state of the intermediate **4** using the semi-empirical molecular orbital method. AM1 [5] and PM3 [6] of MOPAC Ver. 6.0 were employed for the calculation. Since the attempted direct optimization of the intermediate imine **4** failed for the divergence of the self-consistent field calculation,[7] the stepwise optimization was carried out. After the optimization of the structure **5** (R = H, Me, Et, i-Pr, and t-Bu) and then the O-silylated **5** (R = H, H_3Si, MeH_2Si, Me_2HSi, and Me_3Si), the structures of the



	R^1	R^2
1a	H	H
1b	CH_3	H
1c	$PhCH_2$	H
1d	H	OH
1e	H	$PhCH_2O$

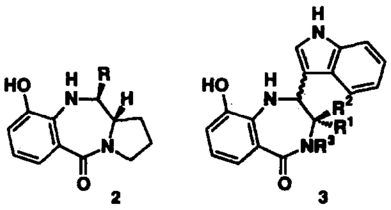
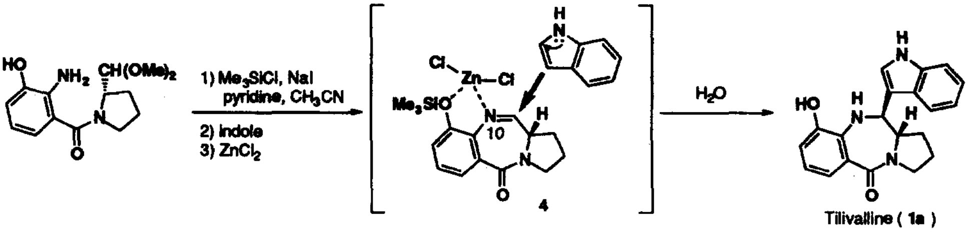
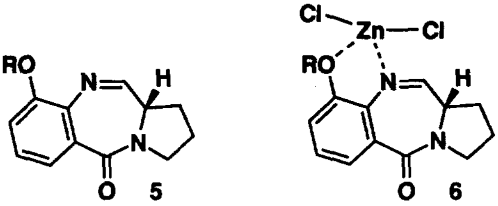


Fig. 1



Scheme 1

Table 1. ΔH_f [kcal/mol] of the Intermediates **5** and **6**



	R	H	Me	Et	i-Pr	t-Bu
5	AM1	-19.832	-13.306	-18.932	-23.119	-24.482
	PM3	-38.074	-30.894	-35.809	-41.895	-46.937
6	AM1	-77.275	-69.276	-74.484	-77.790	-80.401
	PM3	-99.019	-88.687	-93.375	-98.860	-108.882

	R	H	H_3Si	MeH_2Si	Me_2HSi	Me_3Si
5	AM1	-19.832	-26.109	-42.482	-57.942	-72.414
	PM3	-38.074	-48.602	-66.411	-83.438	-101.497
6	AM1	-77.275	-80.378	-96.308	-111.687	-130.505
	PM3	-99.019	-108.582	-125.242	-142.767	-170.477

Table 2. Distance [Å] between Zn and N, and Zn and O of **6**

	R	H	Me	Et	i-Pr	t-Bu
Zn - N	AM1	2.334	2.327	2.300	2.297	2.365
	PM3	2.148	2.151	2.153	2.157	2.156
Zn - O	AM1	3.963	3.718	3.741	3.728	2.981
	PM3	3.776	3.783	3.849	3.858	3.811

	R	H	H_3Si	MeH_2Si	Me_2HSi	Me_3Si
Zn - N	AM1	2.334	2.305	2.300	2.297	2.381
	PM3	2.148	2.136	2.138	2.133	2.381
Zn - O	AM1	3.963	3.678	3.741	3.728	4.011
	PM3	3.776	3.732	3.802	3.796	3.817

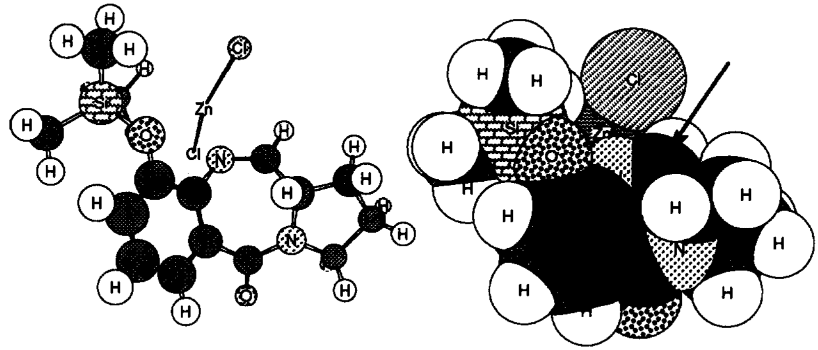
Table 3. Bond Orders between Zn and N, and Zn and O of **6** (R = Me_3Si)

	Zn - - - N	Zn - - - O
AM1	0.2311	0.0011
PM3	0.5675	0.0019

imine-zinc chloride complex **6** were optimized to calculate ΔH_f value, shown in Table 1. Both the distances and the bond orders of **6** were calculated between Zn and N_{10} bonds, then between Zn and O bonds, as shown in Tables 2 and 3. Based on the calculation results using AM1, the optimized structure of **4** was shown from both the α and β sides in Fig. 2. These optimized structures have revealed that the α side of the molecule is sterically more hindered than the β side owing to the presence of the pyrrolidine ring, as expected.[2,3] Interestingly, zinc chloride coordinates to the N_{10} atom at the α side, which also regulates the attack of indole from the α side. The reason why zinc chloride would not bind at the β side is that the high repulsion between H_{11a} and a chloride atom of zinc chloride would not make the coordinate bond between the N_{10} and Zn atoms. We have already observed[3] that the replacement of indole with sodium cyanide in the Mannich type cyclization causes the low selectivity (α : β = 40 : 60) of the reaction. This suggests that there is a small space allowing a less bulky nucleophile such as a cyanide ion to attack from the α side.

We have already proposed[2,3] that zinc chloride will coordinate to both the phenolic oxygen and anilinic nitrogen during the Mannich type cyclization, as shown in the structure **4**. Surprisingly, however, the calculated data have revealed that zinc chloride coordinates only to the anilinic nitrogen, but not the phenolic oxygen atom. As shown in Tables 2 and 3, the distance and the bond order of Zn - N_{10} are 2.381 Å and 0.2311, respectively, while those of Zn - O are 4.011 Å and 0.0011, respectively. Thus the structure of the intermediate complex will be depicted as **7** (Fig. 3), but not **4** (Scheme 1). The steric hindrance between a chloride of zinc chloride and a methyl group in the Otrimethylsilyl function will preclude the access of zinc chloride to the phenolic oxygen atom. Incidentally, ΔG value of **5** (R = Me_3Si)and **7** were calculated by the vibrational analysis, as summarized in Table 4. Since ΔG value of **7** (-38.0 kcal/mol) is much higher than that (-121.4 kcal/mol) of **5** and zinc chloride, the coordination of zinc chloride to **5** will occur only by heating.

View from the β side



View from the α side

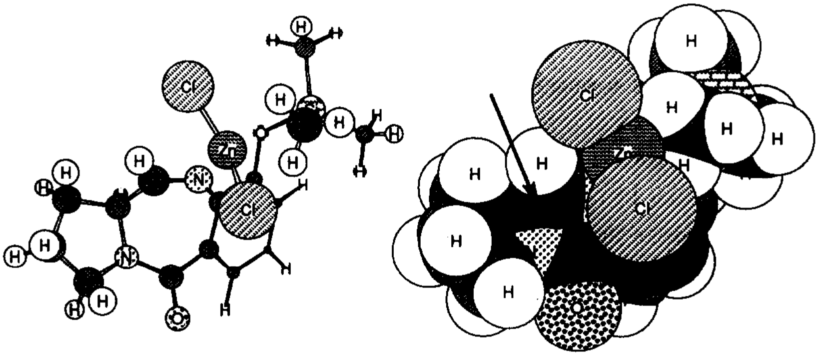


Fig.2

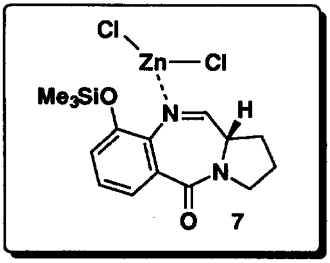


Fig. 3

Table 4. ΔH_f and ΔG [kcal/mol] of $ZnCl_2$, the Intermediate **5** and **7**

		$ZnCl_2$ [a]	**5**	**7**
ΔH_f	AM1	-99.2	-72.4	-130.5
	PM3		-101.5	-170.5
ΔG	AM1	-88.3	-33.1	-38.0
	PM3		-32.4	-36.9

a) Ref. 8.

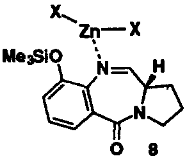
We also investigated the frontier orbitals (HOMO -LUMO) for the intermediate **5** (R = Me_3Si), complex intermediate **7** and indole, as shown in Table 5. The complex intermediate **7** strikingly decreases both the HOMO and LUMO energies, compared with **5**. As the gap between LUMO's energy of **7** and HOMO's of indole decreases relatively, it will be easy for each orbital to interact : LUMO of **7** extends to the β side while LUMO of the α side in **7** little extends because of the coordination of zinc chloride to N_{10} of **5**. Thus, zinc chloride has been revealed to be an effective catalyst in this new Mannich type cyclization which is consistent with the well-known nucleophlic addition of indole.

Table 5. HOMO and LUMO [eV] of each Intermadiate **5**,**7** and Indole

		5	**7**	Indole
LUMO	AM1	-0.3303	-0.9180	0.3000
	PM3	-0.2663	-1.2717	0.0993
HOMO	AM1	-8.8447	-9.5074	-8.4680
	PM3	-8.7117	-9.6376	-8.4681

Furthermore, the effect of the halogen atom of the zinc catalyst was investigated. As shown in Table 6 the order of the effective stability to **8** in zinc halides is Br>Cl>F>I in AM1 and Cl>F>Br>I in PM3. The discrepancy may be derived from used parameters in MOPAC Ver. 6.0. However, the data in Table 6 have revealed that zinc iodide is not suitable as a catalyst and the coordination occurs only between Zn and the N_{10} atom, but not the oxygen.

Table 6. ΔH_f [kcal/mol] and Distance [Å] of Zn - N and Zn - O in Complexes **8**



	X	F	Cl	Br	I
ΔHf	AM1	-130.269	-130.505	-133.221	-66.893
	PM3	-165.862	-170.477	-151.749	-110.849
Zn - N	AM1	2.365	2.381	2.496	2.475
	PM3	2.146	2.156	2.104	2.112
Zn - O	AM1	4.025	4.011	4.060	4.057
	PM3	3.776	3.817	3.695	3.712

In conclusion, the semi-empirical molecular orbital method has revealed that (1) zinc chloride is the effective catalyst in the new Mannich type cyclization, (2) the coordinate bond proposed previously [2,3] lays only between Zn and the N_{10} atom, (3) the coordination of zinc chloride will occur only by heating, and (4) the high stereoselectivity is due to the steric hindrance on the α side and the extension of LUMO in the intermediate **7**.

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. All calculations with MOPAC Ver. 6.0 were carried out on a HP Apollo DN10000 and a HP 9000/750 workstations.

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(*Received in UK* 9 *May* 1994; *revised* 22 *June* 1994; *accepted* 24 *June* 1994)