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Dynamic NMR study on the *trans*-fused eight-membered ether ring model representing G ring of brevetoxin A

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Abstract—Conformational analysis of the *trans*-fused eight-membered ether ring model (**2**) representing G ring of brevetoxin A (**1**) was carried out by dynamic NMR study in combination with molecular mechanics calculations.

Marine polycyclic ethers, represented by brevetoxins and ciguatoxins, have attracted intense attention of natural products chemists due to their unique ladder-shaped structures and potent biological activities.[1] One of common structural features among these polycyclic ethers is *trans*-fused medium-sized ether rings, which are mostly in the middle parts of the molecules and speculated to play important roles upon interaction with their target proteins based on their conformational flexibility. In fact, structure–activity relationship of brevetoxin B indicated that reduction of the double bonds decreases its binding affinity to the voltage-sensitive sodium channel, its target protein.[2] This experimental result was explained by notable change of the whole molecular shape especially at the eight-membered H ring by this chemical derivatization. Therefore, it is significant to survey detailed conformational properties of such medium-sized ether rings. Previously, our and Isobe's groups reported dynamic NMR studies on the exchangeable conformations of the nine-membered F ring models of ciguatoxins.[3] Additionally, in 2000 Isobe's group reported synthesis and dynamic NMR study on ciguatoxin HIJ ring model possessing the *trans*-fused eight-membered I ring.[4]

Brevetoxin A (**1**),[5] (Fig. 1) isolated from the red tide dinoflagellate *Gymnodinium breve* Davis, shows signal broadening in its ^{1}H and ^{13}C NMR spectra along the DEFG ring system, which has been thought to be due to a slow conformational change of the nine-membered E ring since such a phenomenon is seen around the corresponding structure of ciguatoxins. Herein, we report that ^{13}C NMR signal broadening occurs in an eight-membered ring model representing G ring of brevetoxin A, indicating that this ring also contributes to the slow conformational change.

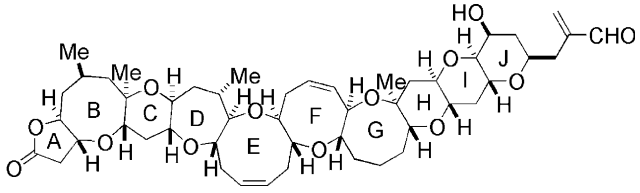

Figure 1. Structure of brevetoxin A (**1**).

Synthesis of the brevetoxin A (F′)GH ring model (**2**) commenced with known mixed thioketal **3**[6] (Scheme 1). At first, **3** was oxidized to a mixture of the corresponding sulfoxide and sulfone by *m*-chloroperbenzoic acid (*m*CPBA). A methyl group on C32 carbon[7] was introduced by the action of trimethylaluminum (Me_3Al) to the mixture according to Nicolaou's report[8] to afford compound **4**. Hydrogenation of the double bond and hydrogenolysis of benzylidene acetal moiety of **4** proceeded under standard hydrogenation condition to give diol. The (F′)-ring was recovered as a benzylidene acetal to furnish the targeted model **2**. Configuration at the C32 position of **2** was confirmed from a NOESY spectrum showing a strong NOE between H26 and 32-Me.

^{1}H and ^{13}C NMR signals of **2** were completely assigned from COSY, HMQC, and HMBC spectra.[9] Inspection

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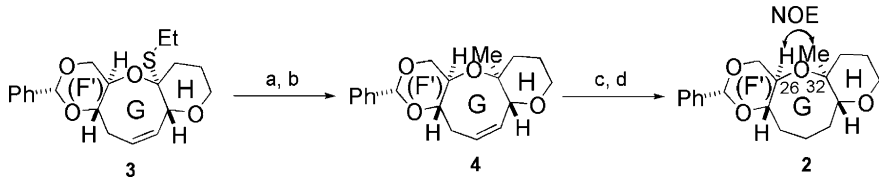

Scheme 1. Reagents and conditions: (a) *m*CPBA, CH_2Cl_2, 0 °C; (b) Me_3Al, CH_2Cl_2, 0 °C; (c) H_2, Pd/C, MeOH, rt; (d) $PhCH(OMe)_2$, CSA, CH_2Cl_2, rt, 60% (4 steps).

on NMR spectra of **2** found ^{13}C NMR signals involved in the eight-membered G ring were broadened at 20 °C (Fig. 2a), indicating a slow conformational change in an NMR time scale. On the other hand, broadening of ^{1}H NMR signals was not observed at that temperature, based on higher sensitivity of ^{13}C NMR to conformational change due to its wider range of resonance frequency. ^{13}C NMR spectrum at −90 °C was measured and two sets of signals derived from two conformers were appeared (Fig. 2c). ^{13}C NMR signals at −90 °C are assigned properly to satisfy a ratio of two conformers. The ratio is calculated to be ca. 83:17 at 20 °C from two sets of chemical shifts at −90 °C and the weight-averaged ones at 20 °C. Thus, energy difference (ΔG) between the two conformers is revealed to be ca. 3.9 kJ/mol from Boltzmann equation (Fig. 3). In addition, dynamic NMR study exhibited that activation energy of the conformational change of **2** is ca. 45 kJ/mol at the coalescence temperature of C28 signal (−20 °C).

In order to estimate the three-dimensional structures of the two conformers, molecular mechanics calculations were performed using various force fields (MM2*, MM3*, AMBER*, OPLS*, and MMFF) on MacroModel® software.[10] As a result, only the two stable conformers for the eight-membered G ring flanked by two fused rings, 'crown' and 'boat–chair',[11] were found within 50 kJ/mol by all the force fields. The calculation result is consistent with the experimental result that two sets of NMR signals were observed. Comparison between predicted vicinal proton–proton coupling constants ($^{3}J_{HH}$)[12] and observed ones shows that the observed major conformer is 'crown' in all the solvents of CD_3OD, $CDCl_3$, and C_6D_6 (Table 1). The other conformer

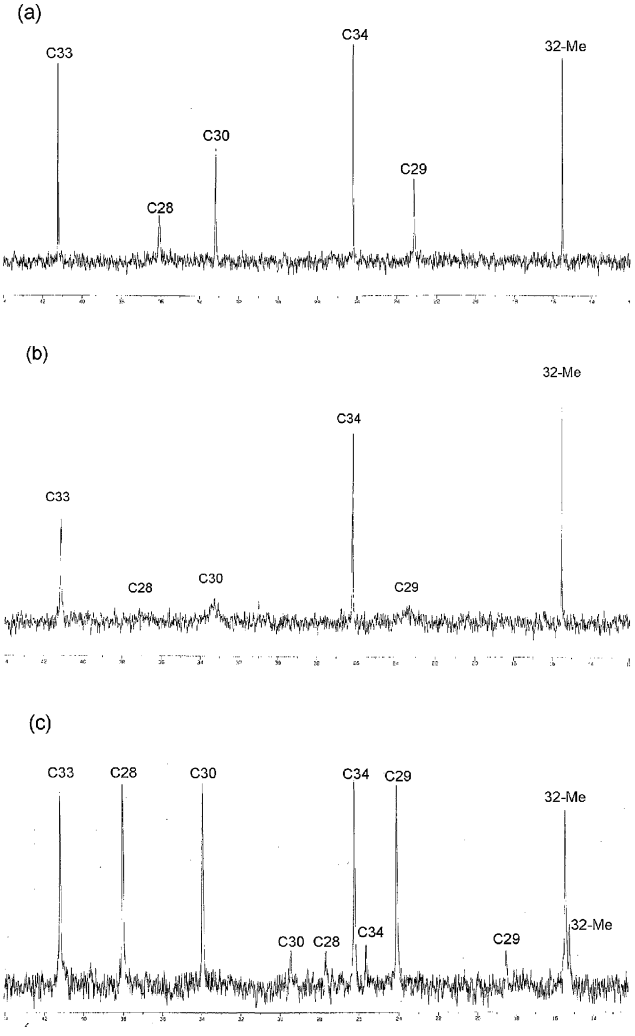

Figure 2. High field region (14–42 ppm) of ^{13}C NMR spectra of **2** at (a) 20 °C, (b) −20 °C, and (c) −90 °C in CD_3OD.

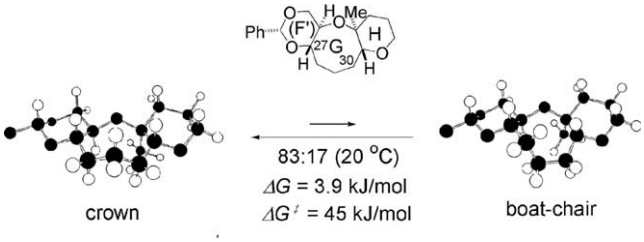

Figure 3. Conformational change of **2**.

Table 1. Observed and predicted $^{3}J_{HH}$ of **2** in Hz

$^{3}J_{HH}$		27–28α	27–28β	30α–31	30β–31
CD_3OD		9.1	3.2	—[a]	—[a]
$CDCl_3$		9.0	3.3	10.4	2.3
C_6D_6		8.9	3.3	10.3	1.8
'Crown'	MM2*	11.1	4.3	11.5	1.8
	MM3*	11.6	2.5	11.6	2.7
	AMBER*	11.6	2.6	11.5	3.6
	OPLS*	11.6	2.4	11.5	3.1
	MMFF	11.6	2.5	11.5	3.1
'Boat–chair'	MM2*	3.0	3.7	11.1	1.2
	MM3*	3.2	3.5	10.6	1.2
	AMBER*	3.3	3.1	11.0	1.4
	OPLS*	3.0	3.5	10.9	1.3
	MMFF	3.0	3.5	10.7	1.2

[a] First-order analysis was impossible.

Table 2. Calculated and observed energy difference (kJ/mol) between the two conformers of **2**

Force field	Solvent	'Crown'	'Boat–chair'
MM2*	—	+2.0	0.0
	H_2O	+2.0	0.0
	$CHCl_3$	+0.9	0.0
MM3*	—	+5.0	0.0
	H_2O	+2.5	0.0
	$CHCl_3$	+2.3	0.0
AMBER*	—	+8.7	0.0
	H_2O	+5.4	0.0
	$CHCl_3$	+4.6	0.0
OPLS*	—	+2.3	0.0
	H_2O	+0.1	0.0
	$CHCl_3$	0.0	+0.5
MMFF	—	+12.0	0.0
	H_2O	+6.3	0.0
	$CHCl_3$	+5.1	0.0
Observed	MeOH	0.0	+3.9

appears to be 'boat–chair' because $^3J_{HH}$ between H27 and H28α is slightly smaller than the predicted value for the 'crown' conformer. Contrary to the above observation in the NMR measurement, molecular mechanics calculations predict that 'boat–chair' conformer of **2** is more stable than 'crown' conformer, except for the case using OPLS* force field in $CHCl_3$ (Table 2). This shows limitation of conformational analysis by molecular mechanics calculation only.[13]

In summary, we demonstrated in this paper the activation energy of the conformational change of eight-membered ring model **2** is so low for the NMR time scale that its dynamic NMR study is possible in ^{13}C NMR and the G ring of brevetoxin A contributes to the conformational change of the whole molecule. Further investigations on conformational properties of medium-sized ether rings by model studies are under progress in our laboratory toward clarification of action mechanism of marine polycyclic ethers at the molecular level.

Acknowledgements

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