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EVALUATION OF TWO POSSIBLE TRANSITION STATES IN INTRAMOLECULAR OXETANE / OXOLANE RING FORMATION BASED ON AM1 CALCULATIONS

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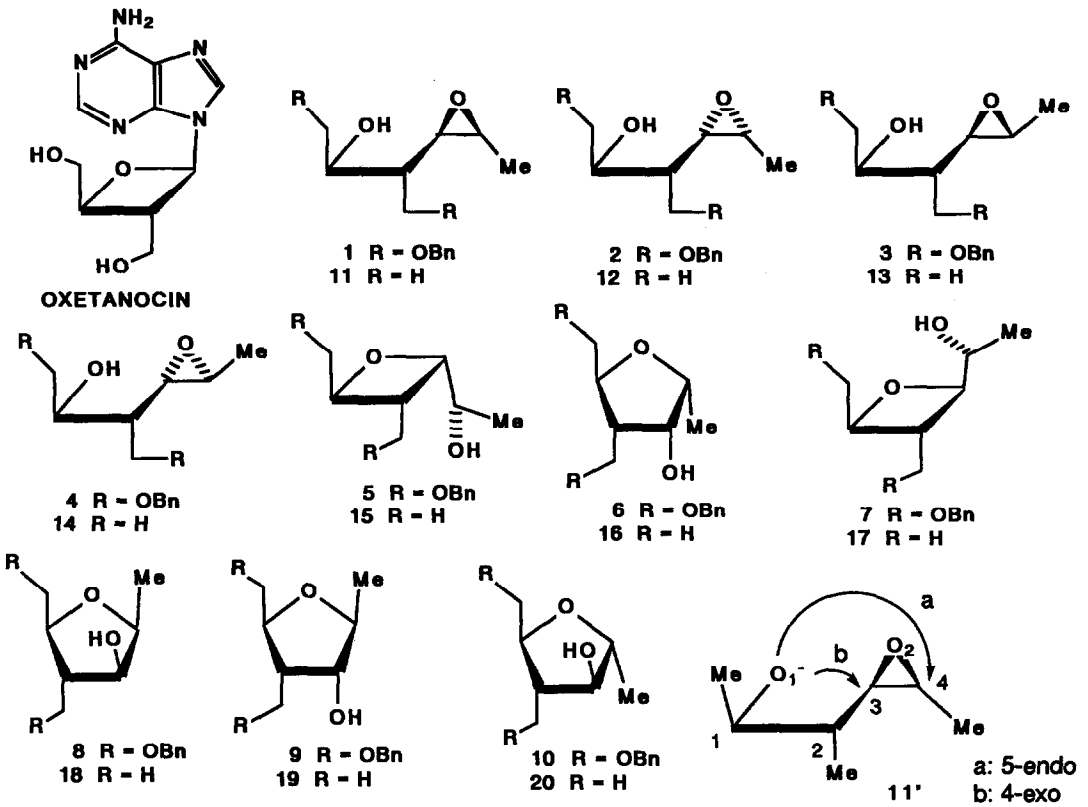
Summary AM1 calculations have been successfully carried out to evaluate relative stabilities of the two possible transition states (4-exo- and 5-endo-openings) in each intramolecular cyclization of four 3,4-epoxy alcohols, suggesting that two cis-epoxy alcohols give rise to the corresponding oxetanes while the tetrahydrofurans are only produced in the case of trans-epoxy alcohols.

Oxetanocin is the first natural nucleoside bearing an oxetanose as a sugar moiety.[1] In addition, oxetanocin and its derivatives show potent antiviral activities against herpes simplex virus I and II, humancytomegalo virus and HIV.[2] From the biological and structural points of view, oxetanocin is quite attractive to synthetic organic chemists. Thus, we and other two groups have succeeded in total synthesis of oxetanocin.[3,4] Recently, we further carried out an efficient synthesis of the oxetanosyl acetates as synthetic intermediates of oxetanocin,[3,5] wherein the key feature of our methodology was the oxetane ring formation by intramolecular cyclization of 3,4-epoxy alcohols using KOH - aq.DMSO. Interestingly, base-catalyzed reaction of the two cis-epoxy alcohols (**1**, **2**) afforded the desired oxetanes (**5**, **7**) and the tetrahydrofurans (**6**, **8**) in the following yields: 66% (**5**/**6** = 3.5) in **1**; 61% (**7**/**8** = 14.5) in **2**. On the other hand, the corresponding tetrahydrofurans (**9**, **10**) were only produced in 79% yields from a 1 : 1 mixture of the two trans-epoxy alcohols (**3**, **4**).[5,6] From these data, 4-exo-opening in both **1** and **2** is more favorable than the corresponding 5-endo-opening, while only the latter takes place in the cases of **3** and **4**. In order to examine the 4-exo and 5-endo selectivities in these systems, two possible transition states in each intramolecular cyclization of four simple 3,4-epoxy alcohols (**11** - **14**) were evaluated by means of AM1 calculations,[7] as follows. Initially, starting from the most stable conformer (ΔHf = -69.62 Kcal/mol) of the reactant (**11'**) the oxygen atom (O_1) at C_1-position was gradually brought close to the reaction center C_3 or C_4, and the energy minimization was carried out at each fixed distance ($O_1...C_3$ or $O_1...C_4$) to get the heat of formation (ΔHf), as shown in Table 1, wherein the largest ΔHf values (-36.93 and -37.16 Kcal/mol) refer to the transition states ([**A**], [**B**]) leading to an oxetane (**15**) and a tetrahydrofuran (**16**), respectively. As seen in Table 1, the activation energies in each reaction are 32.69 and 32.46 Kcal/mol respectively, indicating that formation of **16** was slightly favorable rather than that of **15** in contrast to the experimental results in **1**. According to the same procedure as described above, AM1 calculations of the remaining cis-epoxy alcohol (**12**) were also carried out, as shown in Table 2, indicating that the oxetane (**17**) is mainly formed from the transition state [**C**] (activation energy: 31.94 Kcal/mol) rather than the tetrahydrofuran (**18**) from [**D**] (activation energy: 33.19 Kcal/mol). On the other hand, Tables 3 and 4 indicates

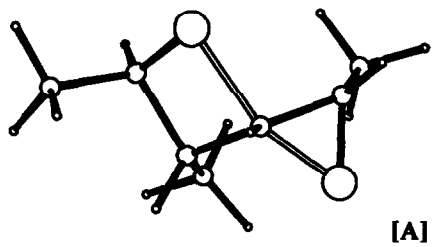


that both trans-epoxy alcohols (13, 14) are only converted into the corresponding tetrahydrofurans (19, 20) through [E] (activation energy: 29.91 Kcal/mol) and [F] (activation energy: 28.77 Kcal/mol), respectively. The AM1 calculated data are roughly compatible with the observed ones,[5,6] if substituent effect is taken into consideration. In the case of the cis-3,4-epoxy alcohol (12), 4-exo selectivity is more favorable than 5-endo selectivity, because of steric hindrance due to the methyl group at C_4-position.

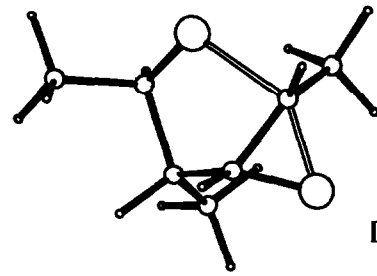
Table 1. Two possible transition states starting from an alcoxide of cis-3,4-epoxy alcohol (11).

	4-exo-opening			5-endo-opening		
	C_3-O_1 dist.*	ΔHf**	C_3-O_2 dist.*	C_4-O_1 dist.*	ΔHf**	C_4-O_2 dist.*
reactant	2.692	-69.62	1.452	3.930	-69.62	1.436
	2.500	-66.63	1.452	2.900	-67.45	1.443
	2.100	-51.61	1.480	2.500	-62.25	1.459
	1.920	-38.28	1.536	2.100	-46.27	1.502
	1.910	-37.62	1.554			
T. S.	1.900	-36.93	1.580	1.950	-37.16	1.585
	1.890	-54.05	2.336	1.940	-69.10	2.371
product	1.476	-78.30	2.393	1.435	-108.49	2.447
activation energy		32.69 Kcal/mol			32.46 Kcal/mol	

* Å, ** Kcal/mol



[A]

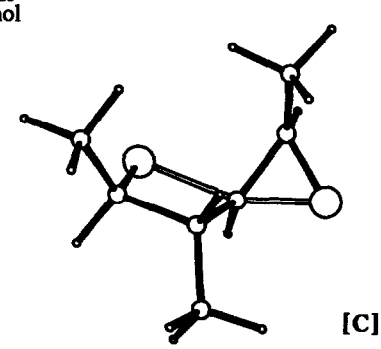


[B]

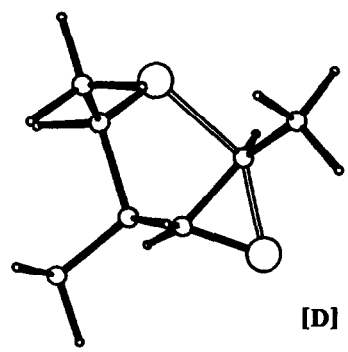
Table 2. Two possible transition states starting from an alcoxide of cis-3,4-epoxy alcohol (12).

	4-exo-opening			5-endo-opening		
	C_3-O_1 dist.*	ΔHf**	C_3-O_2 dist.*	C_4-O_1 dist.*	ΔHf**	C_4-O_2 dist.*
reactant	2.783	-72.33	1.450	4.038	-72.33	1.437
	2.500	-69.86	1.456	2.900	-70.96	1.446
	2.300	-65.04	1.468	2.500	-65.14	1.460
	2.100	-54.56	1.485	2.100	-48.42	1.501
	1.920	-41.21	1.572			
T. S.	1.910	-40.39	1.590	1.950	-39.14	1.611
	1.900	-56.16	2.307	1.940	-70.37	2.380
	1.890	-56.82	2.309	1.930	-71.33	2.373
	1.880	-57.34	2.300			
product	1.477	-80.46	2.373	1.437	-109.83	2.447
activation energy		31.94 Kcal/mol			33.19 Kcal/mol	

* Å, ** Kcal/mol



[C]

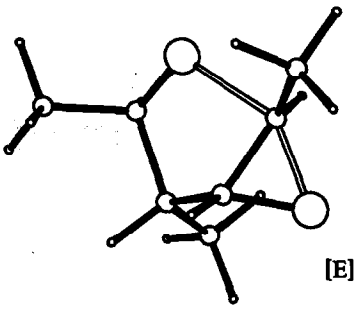


[D]

Table 3. Two possible transition states starting from an alcoxide of trans-3,4-epoxy alcohol (13).

	4-exo-opening			5-endo-opening		
	C_3-O_1 dist.*	ΔHf**	C_3-O_2 dist.*	C_4-O_1 dist.*	ΔHf**	C_4-O_2 dist.*
reactant	2.694	-72.42	1.450	3.938	-72.42	1.439
	2.500	-69.29	1.451	2.500	-66.48	1.450
	2.100	-54.08	1.481	2.100	-53.07	1.485
	1.920	-40.51	1.546	1.950	-43.74	1.537
T. S.	1.910	-39.73	1.546	1.930	-42.53	1.571
	1.900	-56.15	2.313	1.920	-71.99	2.370
product	1.478	-80.78	2.380	1.438	-109.27	2.436
activation energy		32.69 Kcal/mol			29.91 Kcal/mol	

* Å, ** Kcal/mol

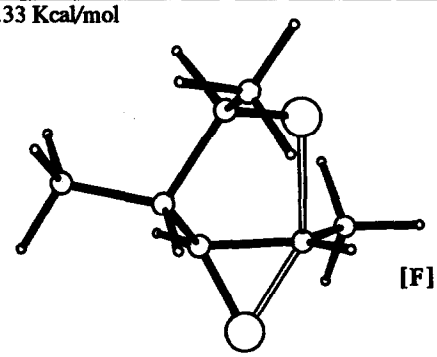


[E]

Table 4. Two possible transition states starting from an alcoxide of trans-3,4-epoxy alcohol (14).

	4-exo-opening			5-endo-opening		
	C_3-O_1 dist.*	ΔHf**	C_3-O_2 dist.*	C_4-O_1 dist.*	ΔHf**	C_4-O_2 dist.*
reactant	2.779	-72.81	1.449	4.026	-72.81	1.437
	2.500	-70.44	1.458	2.900	-70.98	1.444
	2.300	-65.67	1.467	2.500	-69.42	1.450
	2.100	-55.16	1.489	2.100	-54.94	1.485
	1.950	-43.93	1.533	1.960	-45.99	1.535
	1.940	-43.17	1.533	1.950	-45.34	1.542
	1.930	-42.63	1.556	1.940	-44.67	1.553
	1.910	-41.14	1.559			
T. S.	1.900	-40.48	1.584	1.930	-44.04	1.566
	1.890	-57.97	2.312	1.920	-73.12	2.364
				1.910	-73.99	2.366
product	1.479	-81.72	2.385	1.437	-110.46	2.431
activation energy		32.33 Kcal/mol			28.77 Kcal/mol	

* Å, ** Kcal/mol



[F]

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6. M. Nagai, K. Kato, T. Takita, S. Nishiyama, and S. Yamamura, submitted for publication.
7. AM1 calculations were performed using MOPAC program developed by James J. P. Stewart (University of Texas). We wish to thank Institute for Molecular Science for the use of MOPAC program in library of its computer center.

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