Conformational Behavior on 2,2,3-Trisubstituted 1,2,3,4-Tetrahydroquinoline Alkaloids, Virantmycin, Benzastatins, and their Congeners, Evaluated by Semi-empirical Molecular Orbital Calculations

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The conformational behaviors on ring inversion between two half-chair conformers **a** and **b** in physiologically active 2,2,3-trisubstituted 1,2,3,4-tetrahydroquinoline alkaloids, virantmycin (**1**), benzastatin C (**6**), benzastatin D (**7**), and their congeners **2-5**, which were revealed by their nmr studies have been quantitatively evaluated by semi-empirical molecular orbital calculations (PM3). The geometries of respective half-chair conformers **a** and **b** in compounds **1-7** were optimized and it was found that their thermodynamic distributions are approximately valid in comparison with the coupling constants observed in their nmr experiments. Furthermore, these calculations estimated the energy barriers for ring inversion in compounds **1-7** in the range of *ca.* 4.86-11.13 kcal/mol, which were compatible with rapid interconversions between **a** and **b** at room temperature.

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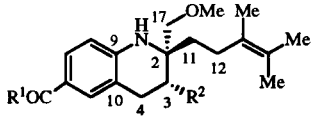
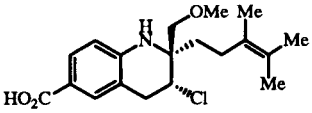
Introduction.

The antibiotic virantmycin (**1**), the unique tetrahydroquinoline alkaloid isolated from the fermentation broth of *Streptomyces nitrosporeus* by Omura *et al.* in 1981, has been found to exhibit antifungal and prominent inhibitory activity against various RNA and DNA viruses [1]. Although its gross structure was elucidated mainly by nmr studies, the relative and absolute stereochemistry at the two chiral centers (C2 and C3) have remained unknown [2]. For the purpose of determining the stereochemistry of virantmycin (**1**), we have embarked on its synthetic studies and accomplished total synthesis of **1** in both racemic and optically active forms to establish eventually the absolute configuration as 2*R*, 3*R* [3, 4]. In the course of the assignment of the relative stereochemistry in our synthetic 2,2,3-trisubstituted 1,2,3,4-tetrahydroquinoline ring compounds **1-5**, we have encountered an occurrence of very rapid ring inversion at room temperature between half-chair conformers **A** and **B**, which was invoked by coupling constants and NOE experiments in their ^{1}H nmr spectra and chemical capture of both half-chair conformers (Figure 1). On the other hand although Sanders' group has earlier reported the relative stereochemistry of **2** than our group still based on nmr experiments [5], they have not at all described the phenomenon of ring inversion in contrast to our observation.

Recently, benzastatins C (**6**) and D (**7**) whose structures are closely related to **1** have been isolated from the same *Streptomyces sp.* as the producing organism of **1** by Yoo *et al.* and disclosed an inhibitory activity against glutamate toxicity and lipid peroxidation [6]. In determining the relative stereochemistry of benzastatins C (**6**) and D (**7**) they have also reported the phenomenon of ring inversion between the half-chair conformers **A** and **B** in consistency with our observation. Thus, these conformational behaviors function as a decisive factor in elucidation of the relative configuration and each assignment of C4 methylene protons in these compounds **1-7** and might play an important role for a broad spectrum of their biological activities mentioned above as well. In this article I would like to evaluate thermodynamic stabilities of conformers corresponding to the half-chair conformers **A** and **B** and energy barriers [7] for ring inversion between both conformers in 2,2,3-trisubstituted 1,2,3,4-tetrahydroquinoline ring systems **1-7** by semi-empirical molecular orbital calculations, as compared with the results obtained by their nmr studies.



1 R^1 = OH, R^2 = Cl
2 R^1 = OMe, R^2 = OH



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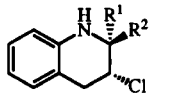
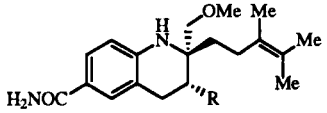


4 R^1 = CH_2OMe, R^2 = Et
5 R^1 = Et, R^2 = CH_2OMe



6 R = Cl
7 R = OH

Results and Discussion.

The reason why we have believed in an existence of equilibrium at room temperature between the half-chair conformers **A** and **B** is as follows. The ^{1}H nmr data of piperidine ring protons in **1-7** is listed in Table 1. In all of the compounds diagnostic coupling constants to distinguish the half-chair conformers **A** and **B** were $J_{3\text{-}4L}$ = 5.8-6.7 Hz and $J_{3\text{-}4S}$ = 4.3-5 Hz. These values seemingly appear to support the half-chair conformer **A**. When NOE experiments were performed in compounds **4-7**, however, the concurrent NOEs proving an existence of both half-chair conformers **a** and **b**

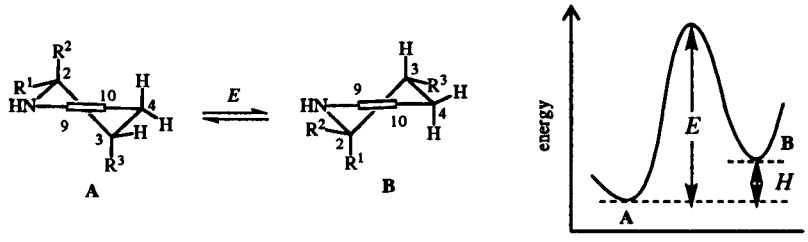


Figure 1. Ring inversion between half-chair conformers **A** and **B**.

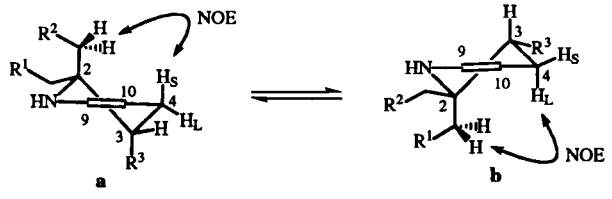
were observed by us [3d] and Yoo *et al.* [6b] (Figure 2). As a result, it has been found that the conformation of this piperidine ring is very flexible to exist as a mixture equilibrated between two conformers **a** and **b** at room temperature and the coupling constants between H3 and H_24 have been observed as average values of those of the conformers.

4-7 (Table 1). Capturing of these mobile compounds **1**, **3**, **4**, and **5** as rigid cyclic carbamates **8**, **9**, **10**, and **11**, respectively, which adopt only one conformation corresponding to the either half-chair conformer **A** or **B** (Figure 4), moreover confirmed the phenomenon of ring inversion in these tetrahydroquinoline ring systems [3d].

Table 1
^{1}H NMR Data in $CDCl_3$ of Piperidine Ring Protons at C3 and C4 in **1-7**[a]

	1	**2** ours	**2** Sanders [5]	**3**	**4**	**5**	**6** [6b]	**7** [6b]
H3	4.36 (dd, 6.1, 4.7)	3.97 (dd, 6, 5)	3.95 (m)	4.42 (dd, 6.6, 4.9)	4.35 (dd, 6.7, 4.9)	4.45 (dd, 6.7, 4.9)	4.36 (dd, 6.0, 4.8)	3.97 (m)
H_S4	3.37 (dd, 17.1, 4.7)	3.10 (dd, 17, 5)	3.08 (dd, 16.6, 4.3)	3.28 (dd, 17.1, 4.9)	3.31 (dd, 17.1, 4.9)	3.25 (dd, 17.1, 4.9)	3.36 (dd, 17.1, 4.8)	3.10 (dd, 16.8, 4.4)
H_L4	3.11 (dd, 17.1, 6.1)	2.84 (dd, 17, 6)	2.82 (dd, 16.6, 5.8)	3.13 (dd, 17.1, 6.6)	3.06 (dd, 17.1, 6.7)	3.08 (dd, 17.1, 6.7)	3.10 (dd, 17.1, 6.0)	2.84 (dd, 16.8, 5.9)

[a] Chemical shifts in ppm, multiplicities, and coupling constants in Hz are described.



4 R^1 = OMe, R^2 = Me, R^3 = Cl; **5** R^1 = Me, R^2 = OMe, R^3 = Cl
6 R^1 = OMe, R^2 = $CH_2CMe{=}CMe_2$, R^3 = Cl
7 R^1 = OMe, R^2 = $CH_2CMe{=}CMe_2$, R^3 = OH

Figure 2. Concurrent NOEs observed by us (**4** and **5**)[3d)] and Yoo *et al.* (**6** and **7**) [6b].

In the other compounds variable results have been reported (Figure 3). In compound **1** the NOE attributed to the half-chair conformer **b** could only be observed and in compound **3** there was no observing NOE corresponding to either half-chair conformer [3d]. In the case of **2** the NOEs attributed to both half-chair conformers **a** and **b** have been practically observed by our [3e] and Sanders' groups [5], independently, but it has been unclear why the two groups observed only the distinct NOEs respectively. Anyway, it seemed that the equilibria between the half-chair conformers **a** and **b** still exist because of the coupling constants between H3 and H_24 similar to the compounds

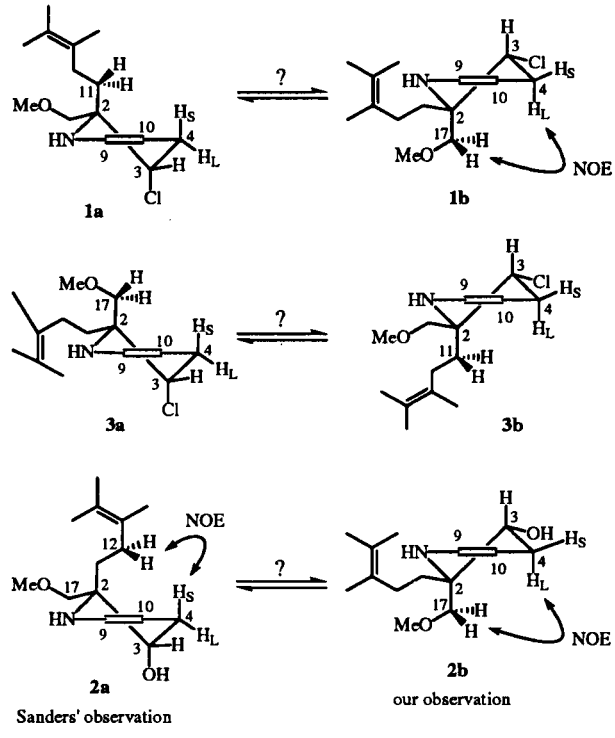


Figure 3. Some NOEs observed by us (**1b** and **2b**) [3d,e] and Sanders *et al.* (**2a**) [5].

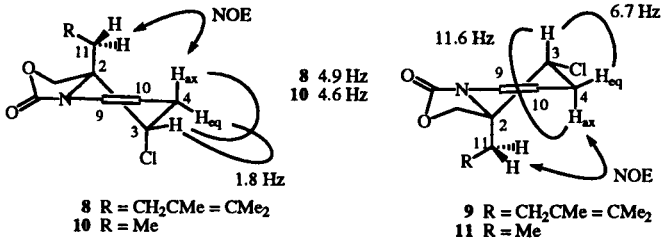


Figure 4. NOEs and J values observed in cyclic carbamates **8-11**.

Table 2
Heats of Formation for Optimized Conformers **a** and **b** and Energy Barriers between Them Computed by PM3

	H_a [a]	H_b [a]	H [b]	~ **a** : **b** [c]	E [d]
5	-40.33567	-40.57500	0.23933	40.1 : 59.9	6.95348
4	-39.75167	-41.48358	1.73191	5.20 : 94.8	4.86064
3	-139.95674	-139.63890	0.31784	63.0 : 37.0	9.90876
1	-139.73836	-140.53682	0.79846	20.8 : 79.2	7.89839
2	-169.10863	-168.01459	1.09404	86.2 : 13.8	11.13166
6	-89.35456	-90.13138	0.77682	21.4 : 78.6	7.88980
7	-126.97243	-125.87642	1.09601	86.3 : 13.7	9.25356

[a] H (kcal/mol): heat of formation. [b] H: | Ha–Hb |. [c] Approximate population (%) at 300 K of half-chair conformers corresponding to the types of **a** and **b** based on H. [d] E (kcal/mol): energy barrier for ring inversion between the optimized half-chair conformers **a** and **b**.

In order to energetically evaluate these conformational behaviors, semi-empirical molecular orbital calculations have been performed. First of all, thermodynamic stabilities between both half-chair conformers **a** and **b** in these compounds were compared in the conformers optimized by PM3 calculations [8,9]. The results are shown in Table 2 and Figure 5. The thermodynamic differences (ΔH in kcal/mol) between the energy minimum conformers of half-chair conformers **a** and **b** in respective compounds **1-7** are not so large (at most 1.73191 kcal/mol). Therefore, if the energy barriers for ring inversion between the half-chair conformers **a** and **b** are low (*vide infra*), it is energetically possible for both conformers **a** and **b** to concurrently exist at room temperature. At that time, the approximate populations (%) of half-chair conformers **a**:**b** at 300 K might be estimated based on ΔH only between the energy minimum conformers **a** and **b** (Table 2).

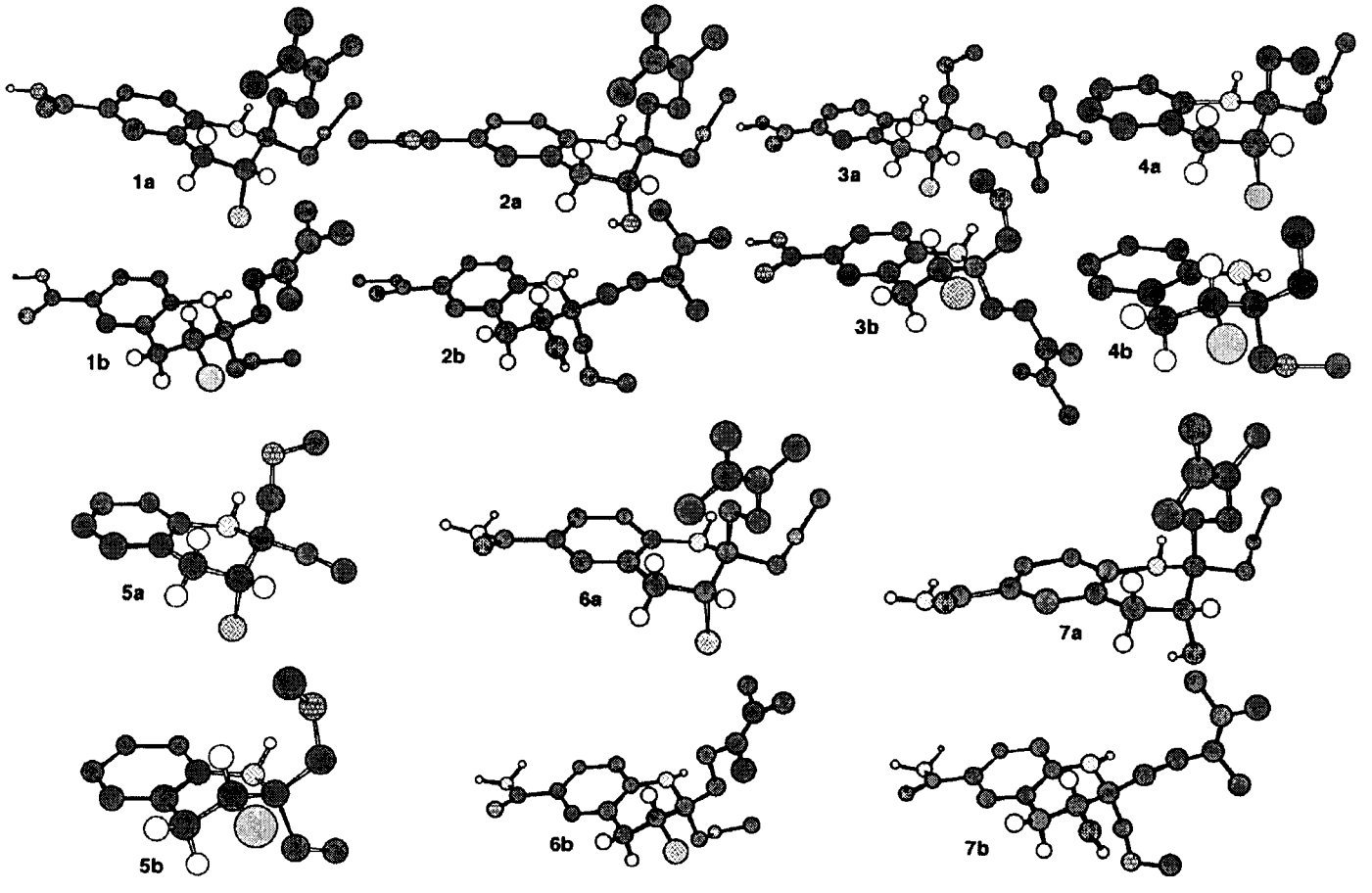


Figure 5. The optimized structures of half-chair conformers **a** and **b** in **1-7** by PM3. Hydrogens on the carbons except for C3 and C4 have been omitted for clarity.

The validity of the above population approximately estimated may be inspected to a certain extent by comparing the coupling constants weighted on the basis of the population for **a**:**b** with the experimental values. This evaluation has been carried out by means of the modified Karplus equation (Eq. 1) proposed by Altona *et al.* [10] for an ethane fragment with three substituens. Equation 1 relates the vicinal coupling constants J to the empirical parameters P, the dihedral angles ϕ, the Huggins electronegativities [11] χ of the substituents attached to the rotational system, and their relative orientations ξ with respect to the considered protons [12].

$$^3J_{ij} = P_1\cos^2\phi + P_2\cos\phi + P_3 + \Sigma\Delta\chi_i\{P_4 + P_5\cos^2(\xi_i\cdot\phi + P_6\cdot|\Delta\chi_i|)\} \quad (1)$$

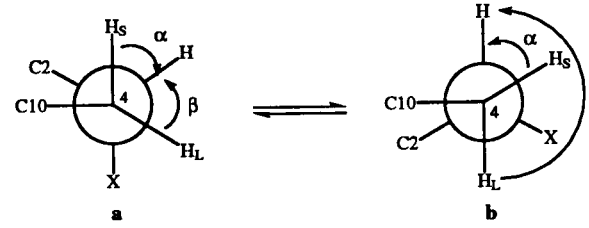
Dihedral angles (α = $\angle H_S$-C4-C3-H3, β = $\angle H_L$-C4-C3-H3) between $H_2$4 and H3 in the optimized half-chair conformers **a** and **b** (Figure 6) and vicinal coupling constants (J_α, J_β) estimated by the Equation 1 based on the dihedral angles are listed in Table 3. The theoretical J_α and J_β values are rather consistent with those observed in cyclic carbamates **8-11** adopting a rigid half-chair conformation (*cf.* Fig. 4). Coupling constants ($J_{3\text{-}4S}$, $J_{3\text{-}4L}$) weighted on the basis of the approximate populations in Table 2 are also shown in Table 3. Although the estimated $J_{3\text{-}4S}$ values in all compounds **1-7** are well corresponding to their ^{1}H nmr data in Table 1, concerning the $J_{3\text{-}4L}$ subtle perturbations between estimation and observation have been encountered except for **5** and **3**. On the one hand compounds **4**, **1**, and **6** have little larger $J_{3\text{-}4L}$, and on the other hand compounds **2** and **7** smaller. Therefore, these results may precisely imply the more population of **a** in the former incorporating chlorine at C3 position and **b** in the latter incorporating hydroxy group. Anyway, the ratios **a**:**b** in respective compounds estimated by ΔH only between the energy minimum half-chair conformers **a** and **b** are not so much incompatible with the nmr experiments.

Table 3

Dihedral Angles and Theoretical Coupling Constants in the Optimized Half-chair Conformers **a** and **b** and the Weighted Coupling Constants

		α [a]	β [a]	J_α [b]	J_β [b]	$J_{3\text{-}4S}$ [c]	$J_{3\text{-}4L}$ [c]
5	**a**	+51.852	–64.788	3.54	2.86	3.49	8.16
	b	–61.788	–179.157	3.45	11.7		
4	**a**	+38.741	–76.657	5.54	1.69	4.81	10.7
	b	–53.171	–169.943	4.77	11.2		
3	**a**	+52.522	–64.299	3.46	2.98	3.46	6.21
	b	–61.641	–179.008	3.45	11.7		
1	**a**	+40.175	–75.276	5.30	1.84	4.88	9.25
	b	–53.533	–170.287	4.77	11.2		
2	**a**	+39.573	–75.613	4.73	1.95	4.90	3.07
	b	–47.714	–163.317	5.95	10.1		
6	**a**	+40.053	–75.433	5.33	1.84	4.89	9.19
	b	–53.402	–170.212	4.77	11.2		
7	**a**	+39.620	–75.550	4.73	1.95	4.92	3.06
	b	–47.171	–162.749	6.11	10.1		

[a] Dihedral angles (degrees) between $H_2$4 and H3 in the optimized conformers **a** and **b** (*cf.* Figure 6).[b] Theoretical coupling constants (Hz) estimated by the Equation 1 based on the dihedral angles α and β. [c] Coupling constants (Hz) weighted on the basis of the approximate populations in Table 2.



X = Cl or OH
α = ∠Hs-C4-C3-H3
β = ∠HL-C4-C3-H3

Figure 6. Newman projection around C4-C3 bond in the optimized conformers **a** and **b**.

For the purpose of spectroscopically capturing the two conformers **a** and **b**, we have previously carried out measurement of ^{1}H nmr spectra of **1** at low temperature (0 °C, –20 °C, and –40 °C), but chemical shifts and coupling constants in these spectra were essentially the same as those at room temperature. Therefore, the energy barrier for ring inversion between the half-chair conformers **1a** and **1b** must be estimated to be rather low. I would like to evaluate energy barriers ΔE for ring inversion between **a** and **b** in these compounds **1-7** by semi-empirical molecular orbital calculations.

The energy barrier ΔE for interconversion of **a** and **b** was estimated by the following method. Untill the half-chair conformer **a** has reached the half-chair conformer **b**, an arbitrary dihedral angle was rotated with a few degrees increment, where geometries were fully optimized under the single torsional constraint employed. The example of compound **5** is shown in Figure 7. Four times rotations of dihedral angles (Cl-C3-C2-C17 in **5a** to **5a-1**, C12-C11-C2-N in **5a-1** to **5a-2**, O-C17-C2-C3 in **5a-2** to **5a-3**, and OMe-O-C17-C2 in **5a-3** to **5b**) were required for the conversion of **5a** to **5b**. In this energy diagram the difference ΔE = 6.95348 kcal/mol between the highest and lowest energies could be estimated as an energy barrier for ring inversion in compound **5**. However, this ΔE must be considered as an upper limit of the energy barrier, because this energy diagram only shows one possible path from **5a** to **5b**.

The energy barriers ΔE in kcal/mol for ring inversion similarly estimated in other compounds have been described in Table 2. The values of ΔE are in the range of *ca.* 4.86-11.13 kcal/mol. Even the largest ΔE is at most 11.13166 kcal/mol, which is much the same as the energy barrier (10.8 kcal/mol) for ring inversion in cyclohexane [13]. Thus, these results of calculations quantitatively demonstrate that rapid interconversions between half-chair conformers **a** and **b** in these all compounds **1-7** occur at

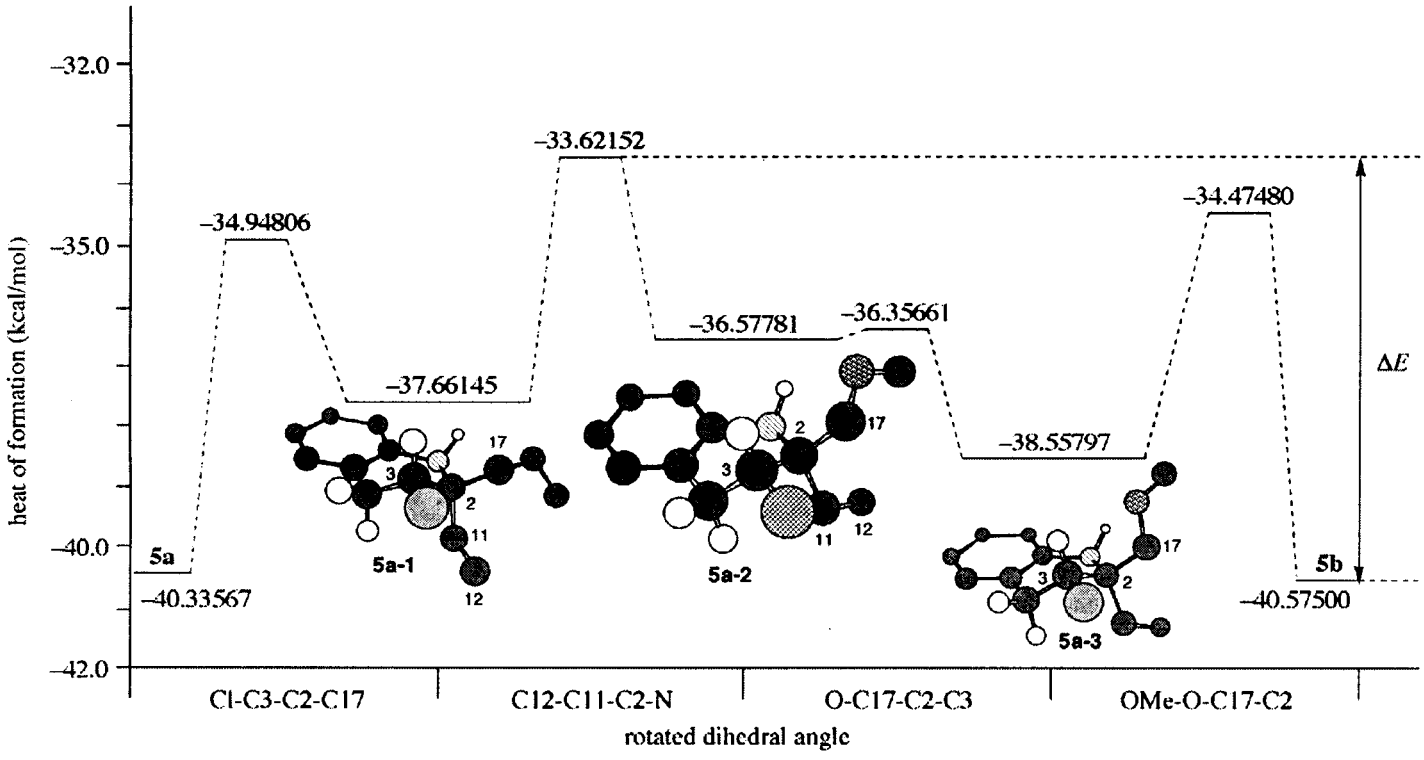


Figure 7. Energy diagram for one path from **5a** to **5b** attained by rotation of the indicated dihedral angles calculated by PM3.

room temperature in agreement with the nmr experiments by us and Yoo *et al.* (*vide supra*).

In conclusion conformational behaviors on biologically active alkaloids, virantmycin (**1**), benzastatin C (**6**), benzastatin D (**7**), and their congeners **2-5**, which are phenomena of ring inversion between half-chair conformers **a** and **b** revealed by their nmr studies, have been quantitatively explored by semi-empirical molecular orbital calculations. These calculations disclosed approximately valid populations for the energy minimum half-chair conformers **a** and **b** and estimated the energy barriers to the extent of at most *ca.* 11.13 kcal/mol, which were compatible with rapid interconversions between **a** and **b** at room temperature.

EXPERIMENTAL

All calculations were performed on Cache system {MOPAC (version 94.1)} employing the PM3 semi-empirical Hamiltonian developed by J. J. P. Stewart [9]. Pop-up menu "Minimize gradient by" in all geometry search options was NLLSQ which used a non-linear least squares gradient minimization method to locate the nearest geometry that has zero gradients. To optimize geometries shown in Figure 5, calculation type "Optimize geometry" was used. In that case pop-up menu "Optimize geometry by" in geometry search options was BFGS which used the Broyden-Fletcher-Goldfarb-Shanno method to locate the nearest minimum-energy geometry. To estimate energy barriers indicated in Table 2, calculation type "Optimize search" was used. In that case pop-up menu "Optimize geometry by" in geometry search options was EF, which used eigenvector following optimization to locate a minimum-energy geometry, and all other internal coordinates of the molecule were optimized at each geometry under the single torsional constraint employed.

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