Molecular Mechanics Study on the Folded Conformation of Semotiadil, a Ca^{2+} Antagonist Having a Benzothiazine Skeleton

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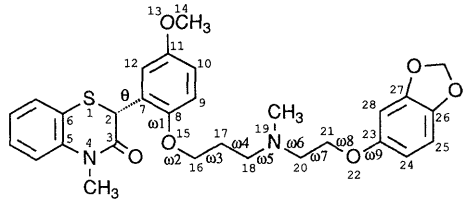
The conformation of semotiadil (1) was investigated by the molecular mechanics method. The analysis of energy components of the stable conformations suggested that stabilities are principally under the control of van der Waals and torsional energy terms. Two major van der Waals interactions were found between the 2-phenyl and the methylenedioxyphenyl rings, and between the alkylamine side chain and the benzothiazine ring. The torsional energy term was caused mainly by the alkylamino side chain conformation. Stable conformations would be useful when considering possible solution conformations of 1.

Keywords conformational analysis; molecular mechanics; semotiadil; SD-3211; calcium ion antagonist

Since the first report on the synthesis and the Ca^{2+} antagonistic activity of Semotiadil (semotiadil (**1**) fumarate; SD-3211),[1] detailed pharmacological profiles of **1** such as its greater selectivity for vascular smooth muscle than two other non-dihydropyridine type Ca^{2+} antagonists, diltiazem and verapamil, have been elucidated so far (Fig. 1).[2]

However, the stereochemistry of **1** in protic solution has also been studied regarding the structure–activity relationship by circular dichroism (CD)[3] and nuclear magnetic resonance (NMR)[4] spectrometries. Although the NMR spectrometry is generally a very effective method for analyzing the molecular conformation, it gave only limited information concerning the stereochemistry of **1**: unequivalent proton signals for the methylenedioxy group and signal shifts of aromatic protons of the 2-phenyl and the methylenedioxyphenyl (MDP) groups to lower magnetic field with increasing temperature were observed, suggesting the adjacency of the two aromatic rings (folded conformation).

This time, then, the stereochemistry of **1** was studied using molecular mechanics (MM) methods. Involvement of a small number of extended conformations of **1** in the folded form could be possible, but in this study the predominant folded conformations of **1** were examined. Solvent molecules were not considered explicitly because intramolecular interactions would work principally in the folded conformations.



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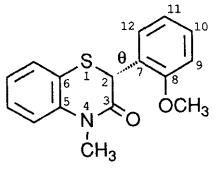

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Fig. 1. Structural Formulae of **1** and **2** Showing Atomic Numbering and Torsional Notations

θ [C(3)–C(2)–C(7)–C(8)], $\omega1$ [C(7)–C(8)–O(15)–C(16)], $\omega2$ [C(8)–O(15)–C(16)–C(17)], $\omega3$ [O(15)–C(16)–C(17)–C(18)], $\omega4$ [C(16)–C(17)–C(18)–N(19)], $\omega5$ [C(17)–C(18)–N(19)–C(20)], $\omega6$ [C(18)–N(19)–C(20)–C(21)], $\omega7$ [N(19)–C(20)–C(21)–O(22)], $\omega8$ [C(20)–C(21)–O(22)–C(23)], $\omega9$ [C(21)–O(22)–C(23)–C(24)].

Calculations

MM calculations were performed by MM2[5] in MM2-PRIME (Japan Chemistry Program Exchange, P009). PM3[6] in MOPAC ver. 5.00 (Quantum Chemistry Program Exchange, No. 455) was used for molecular orbital calculations. The program LOCALMIN for searching local minimum structures and other necessary programs were made by us. All the calculations were done on a VAX station 3100 or 3200 (Digital Equipment). Extended conformations of **1** were eliminated in such a way that the conformations having a longer distance between midpoints of the 2-phenyl and the MDP rings than between the 2-phenyl ring and the amine nitrogen were discarded. LOCALMIN compared the energy of a conformation with those of the nearest neighboring conformations in the space defined with $\omega2$–$\omega8$ to give local minimum conformations. The initial structure for the conformation analysis of **1** was that of the X-ray crystallography of **1** as mandelic acid salt,[7] in which the torsions $\omega2$–$\omega8$ were all *anti*.

Results and Discussion

Conformation Analysis of Model Compounds (2) Four conformations (**2a—d**, Fig. 2) could be possible for a 2-phenylbenzothiazine partial structure of **1**; an axial or equatorial 2-phenyl group with respect to the benzothiazine skeleton, and a rotation about the torsional angle θ(C(8)–C(7)–C(2)–C(3)). The conformational analysis of model compound (**2**) by the molecular orbital method (PM3) suggested that the conformation **2a** was the most unstable while **2d** was the most stable (Table I). The energy difference between conformation **2b** or **2c** from **2d** did not appear sufficient to eliminate their participation in the conformations of **2**.

Calorimetric studies on 2-phenyl-1,3-dioxanes, which has a similar structure to **2**, have shown that the equatorial 2-phenyl ring is more favorable than the axial one.[8] MM studies also supported these results.[9] MM calculations on

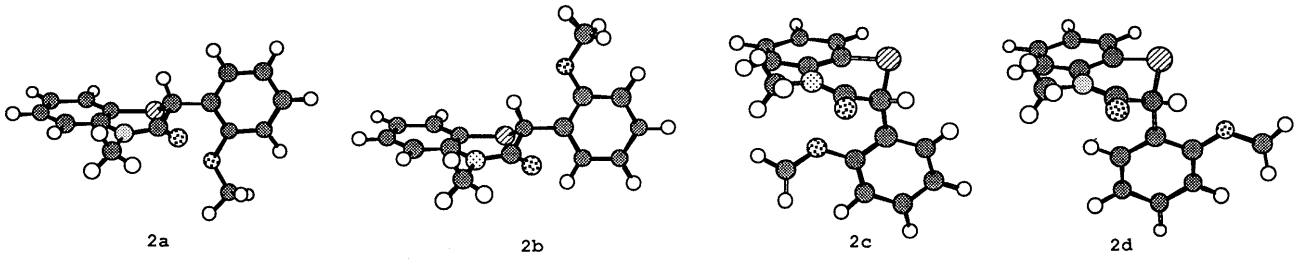

Fig. 2. Four Possible Conformations of **2**

2a, equatorial, $\theta = 90$ deg.; **2b**, equatorial, $\theta = 240$ deg.; **2c**, axial, $\theta = 30$ deg.; **2d**, axial, $\theta = 210$ deg.

TABLE I. Conformational Energies (kcal·mol^{-1}) of **2a—d**

Conformation	PM3	MM2
2a	4.05	0.24
2b	1.80	0.00
2c	2.03	0.73
2d	0.00	0.32

2a—d (deficient parameters were obtained by the method shown in the following section), however, suggested that none of the four conformations had prominent stability (Table I).

Recently, an equatorial orientation of the 2-phenyl group in 2-phenylbenzothiazines[3] or **1**[7] in ethanol solution was suggested by analysis of their CD spectra. In addition, an X-ray crystallographic analysis of **1** mandelic acid salt revealed the equatorial orientation of the 2-phenyl ring.[7] Hence, an equatorial conformation would be the most plausible for the 2-phenyl ring of **2**.

Analysis of 2-Phenyl Group Rotation in 2 Although the MM method is known to be effective for the study of molecular structures, insufficient parameter sets, particularly for torsional terms involving heteroatoms, make its practical application difficult in many cases. Since the molecule **1** case exhibited those exact limitations, an attempt to complement those MM parameters was made.

The energy profiles were surveyed for rigid rotators on the equatorial 2-phenyl ring rotation of **2** by MM2 including only a van der Waals interaction. Van der Waals parameters are often available, even though other parameters such as torsional ones are deficient. The results showed two energy barriers at about $\theta = 0$ and 180 deg., and similar results were also obtained in the estimation using van der Waals parameters of ECEPP/2[10] or the Tripos Force Field 5.2 (TFF)[11] method. The energy curve calculated on the same molecule by the molecular orbital method (PM3) showed a similar pattern to that of the MM results (Fig. 3). The addition of torsional terms, which were involved in the 2-phenyl ring rotation in TFF, caused no significant change in energy (*ca.* 0.1 kcal·mol^{-1}). Accordingly, it would be concluded that the energy profile of the 2-phenyl rotation is controlled mainly by van der Waals interactions in MM.

Parameter Estimation for MM Calculations Most deficient parameters for MM2 to calculate **1** were torsional terms of the 2-phenylbenzothiazine structure. The effect of torsional energy on the 2-phenyl ring rotation for the benzothiazine was found to be very small, as mentioned above. Thus, the corresponding TFF torsional parameters

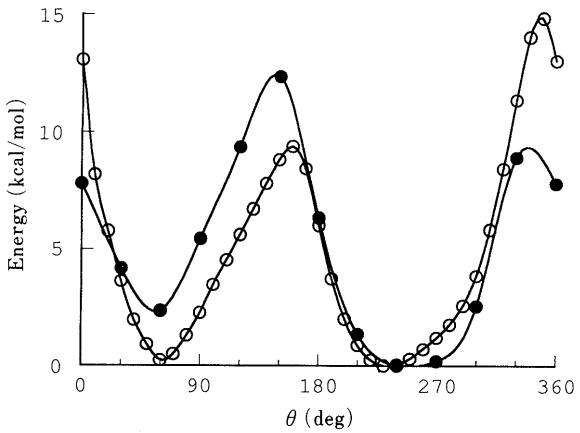

Fig. 3. Energy Potential Curves of 2-Phenyl Ring Rotation in Equatorial Conformation of **2**

●, PM3; ○, MM2.

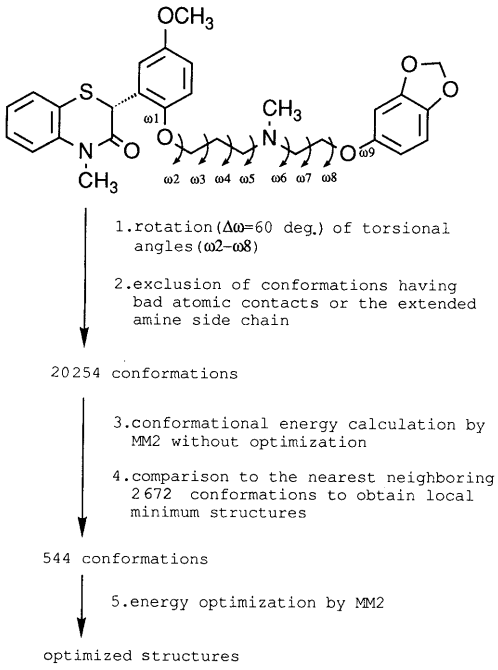

Fig. 4. Procedure for the Conformational Analysis of **1**

were used in the present study. The torsional constants for S(1)–C(2)–C(3)–N(4) were set as zeros because the expansion of the TFF torsional energy curve with the MM2 torsional function was unsuccessful. Bond stretching force constants were also obtained from TFF. Others were from the report of Hopfinger.[12]

Most of these parameters are similar in their magnitude to those of the similar atom sets in MM2, but a little larger. The energy profile for the 2-phenyl ring rotation on **2** by MM2 with these parameters reproduced that of PM3 (Fig. 3), showing that these parameters could be acceptable. In addition, the result of PM3 suggested that the conformation **2b** (θ, *ca.* 240 deg.) was preferable to **2a** (θ, *ca.* 60 deg.), and that was also shown in the crystal state of **1**.[7]

Conformational Analysis of 1 It is quite reasonable to consider that the long aminoalkyl chain which connects the 2-phenyl ring and the MDP ring would govern the conformation of **1**. Each torsional angle ($\omega 2$–$\omega 8$) of the side chain was rotated stepwisely (60 deg.) to give 6^7 conformations. Figure 4 shows the procedure. The carbons (C(14), C(16)) were placed onto the 2-phenyl ring plane and C(21) was placed onto the MDP, according to an NMR study on anisole.[13] These were also observed in the results of X-ray analysis.[7]

The conformations having bad atomic contacts or obviously extended structures were excluded to reduce the number of candidate structures for calculation. The remaining 20254 conformations were subjected to energy calculations without structure optimization.

The potential energy of each conformation of **1** could be represented as a point in a 7-dimensional space consisting of $\omega 2$–$\omega 8$ axes. A local minimum conformation has lower energy than any other neighboring conformations. In order to obtain local minimum conformations, energy comparison for each conformation was made with the nearest neighbors (2186 conformers) in the space by the program LOCALMIN. A similar technique can be seen in the systematic search for the conformation analysis of diphenylalkylamines.[14] This would show propriety of LOCALMIN for searching local minimum conformations. Forty-one local minimum conformations and an additional 503 conformations having close proximities to local minima were, then, optimized within MM2.

The ten most stable conformations (I—X) are given in Table II. The energy components of I—X suggested that the torsional terms and the van der Waals terms except for 1,4-interactions would control the stabilities of these conformations. This is because the sums of the above two energy terms showed good correlation with the steric energies of I—X. The principal factor which affects the torsional energies was found to be the conformational difference among the alkylamino side chains. The energy difference about the torsional angles with respect to the estimated parameters was not significant among those conformations. The analysis on the van der Waals energy term indicated that two major attractive interactions were effective for the stable conformations, *i.e.*, one was the interaction between the 2-phenyl group and the MDP group (-0.86——-3.45 kcal·mol^{-1}), and the other was

Table II. Conformational Energy (kcal·mol^{-1}) of I—X

Conformation	Steric energy	Torsion	vdW[a]		
			Total	2-Ph···MDP[b]	BT[c]···chain[d]
I	38.72	0.27	−13.79	−3.15	−4.19
II	38.87	−4.47	−8.91	−2.47	−1.46
III	38.90	−3.74	−8.80	−2.33	−2.17
IV	38.91	−3.26	−11.39	−2.57	−2.81
V	39.39	−3.87	−8.78	−2.23	−1.72
VI	39.42	−0.11	−11.24	−0.86	−2.61
VII	39.95	−2.83	−10.13	−1.67	−2.07
VIII	40.10	−0.95	−10.69	−3.45	−1.71
IX	40.20	−2.19	−10.44	−2.38	−3.70
X	40.34	−2.75	−9.39	−1.92	−2.03

a) Van der Waals interaction energy excluding 1,4-interaction. *b*) MDP; methylenedioxyphenyl part of **1**. *c*) BT; benzothiazine part of **1**. *d*) Chain; aminoalkyl side chain of **1**.

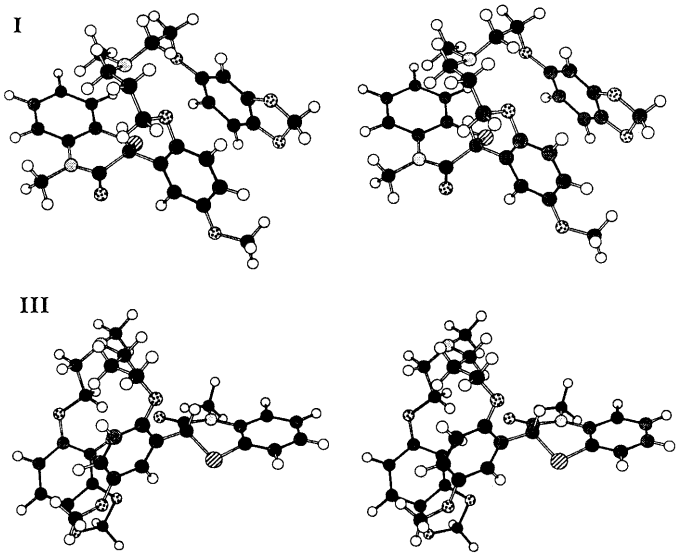

Fig. 5. Stereo Views of Conformations I and III

Table III. Stereochemistry of I—X

Conformation	Dist (Å)[a]	Ang (deg.)[b]	Torsional angle (deg.)								
	2-Ph···MDP[c]	2-Ph//MDP[c]	$\omega 1$	$\omega 2$	$\omega 3$	$\omega 4$	$\omega 5$	$\omega 6$	$\omega 7$	$\omega 8$	$\omega 9$
I	3.782	15	91	−173	65	−63	−60	−177	−44	−78	2
II	4.496	24	−164	65	53	−177	57	54	177	175	12
III	4.640	25	150	−57	−54	−178	−57	−59	176	−177	−12
IV	4.152	33	−176	175	−78	55	−169	59	33	69	10
V	4.712	23	−157	61	50	179	55	57	179	178	13
VI	6.576	49	−158	175	−59	174	−172	68	63	−75	−71
VII	5.068	63	165	−176	59	52	−174	67	114	−71	−11
VIII	3.657	13	165	−164	67	68	−152	77	53	172	−2
IX	4.538	27	−142	174	−44	−48	−65	175	−50	−68	−18
X	4.941	43	173	−164	57	47	−165	61	143	−82	5

a) Dist; distance between the middle points of the 2 aromatic rings. *b*) Ang; angle between the 2 aromatic ring planes. *c*) MDP; methylenedioxyphenyl part of **1**.

between the alkylamino side chain and the benzothiazine ring (-1.46——-4.19 kcal·mol^{-1}). Both the interactions were indicated to be equally important for stable conformations.

The conformations (I—X) could be classified into 3 types according to the locations of the MDP to the 2-phenyl ring or the benzothiazine. The MDP ring was found near the 2-phenyl ring on the sulfur side of the benzothiazine in type A (I, II, IV, V, IX), and on the opposite side of the 2-phenyl ring plane in type B (III, VII, VIII, X). The stable conformations (I, III) in each type are shown in Fig. 5. In the remainder (VI), the MDP ring was found near the benzothiazine.

In many conformations in types A and B, the MDP rings located near the 2-phenyl rings and both aromatic planes were almost parallel to each other (Table III). The aminoalkyl chain was attached to the front of the benzothiazine ring. These could explain the involvement of the van der Waals interactions in the stable conformations.

The conformations obtained in this study suggested that the proximities between the protons C(2)H and C(24)H, and/or C(2)H and C(28)H observed with their NOEs,[4] would agree with the results mentioned here.

Conclusion

The conformation of **1** was estimated by the MM method. MM calculations were effective for the study of stereochemistry of a molecule such as **1** which does not have enough protons to be examined by NMR. The energy components of conformations (I—X) suggested that the van der Waals interactions between the alkylamino side chain and the benzothiazine ring and between the 2-phenyl and the MDP rings were important for their conformational stabilities. The stable conformations obtained, which could explain the above interactions structurally, would be useful for considering possible solution conformations of **1**.

Information is still insufficient for estimating the contribution of each conformer to whole conformations of **1** in aqueous solution, and study of the structure–activity relationship is now under investigation.

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