Molecular Structure and Electronic Spectrum of Taspine: Semiempirical Calculations

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AM1 calculations show that taspine has the three energy-minima along the rotation-like nuclear displacement of the dimethylaminoethyl group. They correspond to two enantiomeric structures and a *Cs* structure, which have nearly equal energies. The energy barrier between the enantiomeric structures and the *Cs* structure is calculated to be about 1 kcal/mol. The small barrier readily causes an intramolecular interconversion of the two enantiomers through the *Cs* structure and thus results in the optical inactivity of taspine. CNDO/S calculations show that the electronic spectra of the enantiomer and the *Cs* structure are quite similar. These calculated spectra are in good agreement with the observed electronic spectra.

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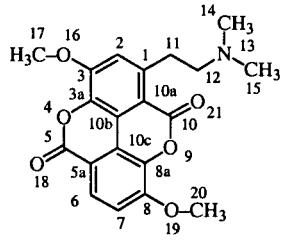
Introduction.

Taspine ($C_{20}H_{19}NO_6$) [1-6] is a novel alkaloid that has the dilactonic, tertiary amine structure **1** [7-9] with no close structural relative among other alkaloids. This alkaloid exhibits pronounced biological activities [10-13]. Recently, Kelly and Xie have succeeded in the synthesis of taspine [14]. However, no X-ray structural analysis of taspine has been reported. This has aroused our interest in an examination of the molecular structure of taspine, because this molecule has a dimethylaminoethyl side-chain. The purpose of this paper is to obtain the molecular structure of taspine by use of AM1 method [15]. Further, we calculate the electronic spectrum of taspine using CNDO/S method [16-18] and compare it with the observed electronic spectrum.

Calculation Method.

Calculations reported were carried out with the MOPAC 93 Program [19]. Full geometry optimizations were performed by using AM1 method [15]. All structural parameters were optimized. The ground-state structure was minimized until a gradient norm of less than 0.01 kcal mol^{-1} $Å^{-1}$ was achieved. The optimized structures were also checked by frequency calculations to confirm that they are minima. To calculate the electronic spectrum, CNDO/S method [16-18] was used. One hundred single excitations were considered. All calculations in this work were carried out with the use of the Silicon graphics(SGI), IRIS INDIGO/ELAN and IBM, RS/6000 model 590.



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Results and Discussion.

Molecular Structure.

Since taspine has the dimethylaminoethyl side-chain, we begin by obtaining the most stable side-chain conformation. The side-chain part has three dihedral angles to be examined: C2-C1-C11-C12 (θ_1), C1-C11-C12-N13 (θ_2), and C11-C12-N13-C14 (θ_3).

Starting with the conformation with $\theta_1 = 0.0°$, which is unrestricted through the calculations, we calculated the most favorable set of θ_2 and θ_3; $\theta_2 = 180.0°$ and $\theta_3 = 65.9°$. This structure **1a**, shown in Figure 1, has *Cs* symmetry. The skeletal bond lengths are summarized in Table 1.

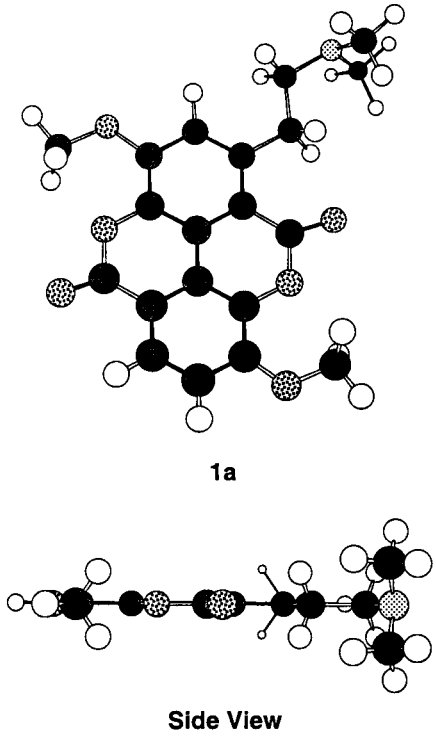

Figure 1. Symmetrical *Cs* structure of taspine **1a**.

Table 1
Skeletal Bond Lengths (Å) of **1a**

bond	length	bond	length
C(1)-C(2)	1.396	C(2)-C(3)	1.408
C(3)-C(3a)	1.412	C(3a)-O(4)	1.384
O(4)-C(5)	1.393	C(5)-C(5a)	1.459
C(5a)-C(6)	1.398	C(6)-C(7)	1.390
C(7)-C(8)	1.411	C(8)-C(8a)	1.414
C(8a)-O(9)	1.382	O(9)-C(10)	1.395
C(10)-C(10a)	1.461	C(1)-C(10a)	1.409
C(3a)-C(10b)	1.401	C(5a)-C(10c)	1.405
C(8a)-C(10c)	1.401	C(10a)-C(10b)	1.407
C(10b)-C(10c)	1.442	C(1)-C(11)	1.486
C(11)-C(12)	1.530	C(12)-N(13)	1.450
N(13)-C(14)	1.445	N(13)-C(15)	1.445
C(3)-O(16)	1.370	O(16)-C(17)	1.428
C(5)-O(18)	1.230	C(8)-O(19)	1.370
O(19)-C(20)	1.428	C(10)-O(21)	1.232

Table 2
Skeletal Bond Lengths (Å) of **1b**

bond	length	bond	length
C(1)-C(2)	1.399	C(2)-C(3)	1.406
C(3)-C(3a)	1.413	C(3a)-O(4)	1.384
O(4)-C(5)	1.393	C(5)-C(5a)	1.459
C(5a)-C(6)	1.398	C(6)-C(7)	1.390
C(7)-C(8)	1.411	C(8)-C(8a)	1.414
C(8a)-O(9)	1.382	O(9)-C(10)	1.396
C(10)-C(10a)	1.462	C(1)-C(10a)	1.406
C(3a)-C(10b)	1.401	C(5a)-C(10c)	1.405
C(8a)-C(10c)	1.401	C(10a)-C(10b)	1.409
C(10b)-C(10c)	1.443	C(1)-C(11)	1.488
C(11)-C(12)	1.537	C(12)-N(13)	1.447
N(13)-C(14)	1.444	N(13)-C(15)	1.446
C(3)-O(16)	1.370	O(16)-C(17)	1.428
C(5)-O(18)	1.230	C(8)-O(19)	1.370
O(19)-C(20)	1.428	C(10)-O(21)	1.232

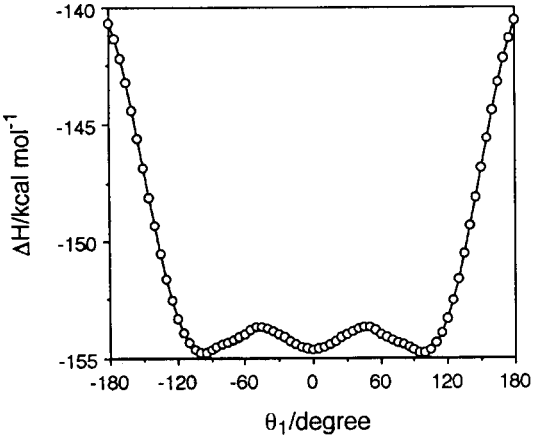

Figure 2. Potential-energy curve around θ_1: ΔH denotes heat of formation.

Table 3
Calculated Singlet Transition Energies (ΔE) and Intensities (f) of **1a** and **1b**

molecular structure	ΔE/eV	theoretical f	experimental ΔE/eV(log ε)
1a	3.64	0.149	3.55 (4.07) [a]
			3.72 (3.99) [a]
	3.87	0.000	
	3.89	0.000	
	3.95	0.001	
	4.03	0.059	4.16 (4.0) [b]
	4.49	0.005	
	4.82	1.488	4.35 (4.1) [a]
	4.87	0.030	
	5.19	0.876	5.02 (4.85) [a]
1b	3.63	0.159	3.55 (4.07) [a]
			3.72 (3.99) [a]
	3.87	0.000	
	3.93	0.000	
	3.96	0.001	
	4.03	0.052	4.16 (4.0) [b]
	4.50	0.006	
	4.82	1.446	4.35 (4.1) [a]
	4.85	0.064	
	5.18	0.923	5.02 (4.85) [a]

[a] Reference Talapatra, *et al.* (1982). [b] Reference Platonova, *et al.* (1956).

To obtain the most favorable value of the dihedral angle θ_1, we then calculated the potential-energy curve for θ_1 in steps of 5° from 0° to 180° and from 0° to -180°, starting with θ_2 = 180.0° and θ_3 = 65.9°, which are unconstrained through the calculations. Figure 2 shows the calculated potential-energy curve, which is symmetric around θ_1 = 0°. The potential-energy curve has three energy minima. One corresponds to the structure **1a** that has θ_1 = 0.0°, θ_2 = 180.0°, and θ_3 = 65.9°. The other two minima correspond to the enantiomeric forms **1b** and **1b'** (θ_1 = -97.9° and 97.9°) shown in Figure 3: θ_2 = -176.3° and θ_3 = 61.9° for **1b** and θ_2 = 176.3°, and θ_3 = 70.1° for **1b'**. The skeletal bond lengths of **1b** are summarized in Table 2. Although the three structures have nearly equal energies, the two enantiomers **1b** and **1b'** are the most stable; heat of formation is calculated to be -154.63 kcal/mol for **1a** and -154.77 kcal/mol for **1b** and **1b'**. The two minima (the corresponding structures **1a** and **1b** or **1a** and **1b'**) are separated by a relatively small -46.3° or 46.3° barrier of about 1 kcal/mol.

Owing to the small barriers between **1a** and **1b** (or **1b'**), the rotation-like nuclear displacement of the dimethylaminoethyl group readily occurs at room temperature. This pseudo-rotation about the C1-C13 bond in taspine serves to interconvert the two enantiomers **1b** and **1b'** *via* the symmetrical *Cs* structure **1a**. The facile process gives rise to an 'intramolecular' racemization and thus leads to the optical inactivity. Although inspection of the structure of taspine indicates that this molecule shows the optical

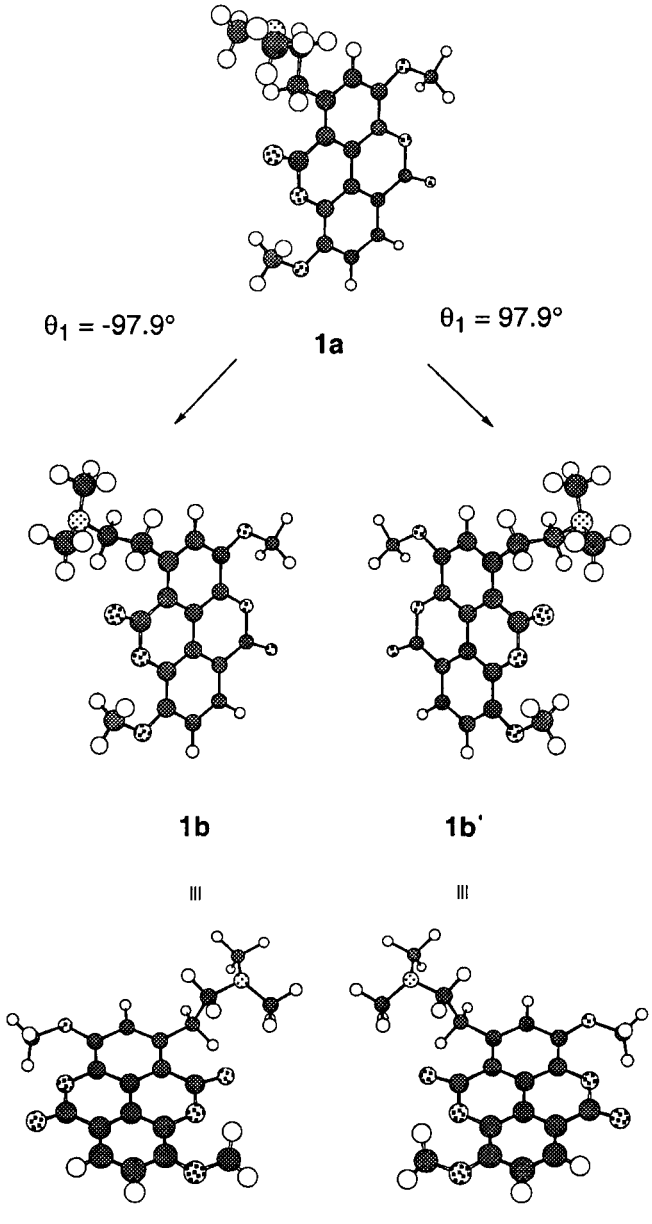

Figure 3. Enantiomers of taspine **1b** and **1b'**.

inactivity [2,7,14], our calculations reveal the mechanism of the optical inactivity: the optical inactivity originates from the facile interconversion of the enantiomers **1b** and **1b'** and not from the adoption of the optically inactive *Cs* structure.

Electronic Spectrum.

We calculated the electronic spectra of **1a** and **1b** (or **1b'**) by using CNDO/S method. The results are summarized in Table 3 together with the experimental data. The calculated spectra of **1a** and **1b** (or **1b'**) are very similar to each other and are in good agreement with the observed electronic spectrum of taspine. This agreement and the negligibly small energy-difference between **1a** and **1b** (or **1b'**) suggest that the observed electronic spectrum is consist of the electronic spectra of **1a**, **1b**, and **1b'**.

Concluding Remarks.

We have revealed that taspine has a three energy-minimum structures: the *Cs* structure and the two enantiomeric structures. The calculated energies of the three structures are nearly degenerate, the energy barrier between the enantiomer and the *Cs* structure being very small. The interconversion of the two enantiomers through the *Cs* structure is predicted to occur readily at room temperatures. This facile interconversion is expected to provide taspine with the optical inactivity. The calculated electronic spectra of the three structures, similar to each other, agree well with the observed spectrum.

REFERENCES AND NOTES

[1] M. Shamma and J. L. Moniot, *J. Chem. Soc. D*, **18**, 1065 (1971).

[2] B. Talapatra, P. K. Chaudhuri, and S. K. Talapatra, *Phytochemistry*, **21**, 747 (1982).

[3] G. P. Perdue, R. N. Blomster, D. A. Blake, and N. R. Farnsworth, *J. Pharm. Sci.*, **68**, 124 (1979).

[4] A. J. Vaisberg, M. Milla, M. del Carmen Planas, J. L. Cordova, E. Rosas de Agusti, R. Ferreyra, M. del Carmen Mustiga, L. Carlin, and G. B. Hammond, *Planta Med.*, **55**, 140 (1989).

[5] Y. Cai, Z. P. Chen, and J. D. Phillipson, *Phytochemistry*, **32**, 755 (1993).

[6] L. Pieters, T. De Bruyne, B. van Poel, R. Vingerhoets, J. Totté, D. Vanden Berghe, and A. Vlietinck, *Phytomedicine*, **2**, 17 (1995).

[7] T. F. Platonova, A. D. Kuzuvkov, and P. S. Massagetov, *J. Gen. Chem. U.S.S.R.*, **23**, 921 (1953).

[8] T. F. Platonova, and A. D. Kuzuvkov, *J. Gen. Chem. U.S.S.R.*, **24**, 2215 (1954).

[9] T. F. Platonova, A. D. Kuzuvkov, and Yu. N. Sheinker, *J. Gen. Chem. U.S.S.R.*, **26**, 2957 (1956).

[10] B. H. Porras-Reyes, W. H. Lewis, J. Roman, L. Simchowitz, and T. A. Mustoe, *Proc. Soc. Exp. Biol. Med.*, **203**, 18 (1993).

[11] H. Itokawa, Y. Ichihara, M. Mochizuki, T. Enomori, H. Morita, O. Shirota, M. Inamatsu, and K. Takeya, *Chem. Pharm. Bull.*, **39**, 1041 (1991).

[12] L. Pieters, T. De Bruyne, M. Claeys, A. Vlietinck, M. Calomme, and D. Vanden Berghe, *J. Nat. Prod.*, **56**, 899 (1993).

[13] M. L. Sethi, *Can. J. Pharm. Sci.*, **12**, 7 (1977).

[14] T. R. Kelly and R. L. Xie, *J. Org. Chem.*, **63**, 8045 (1998).

[15] M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, and J. J. P. Stewart, *J. Am. Chem. Soc.*, **107**, 3902 (1985).

[16] H. Baumann, QCPE, **11**, 333 (1977).

[17] G. Buemi, QCMP #062.

[18] H. Kihara, JCPE Program No. 84 (1993).

[19] Mopac 93 release Fujitsu limited 1994.