lization energy is a result of the small values of the stabilization energies in the radicals. However, in comparison with Koopmans' IP estimates it is seen that hyperconjugative and inductive effects are still operative in the radicals, but that they destabilize the singly occupied HOMO of the radical to a larger extent than they stabilize the lower lying orbitals.

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Conformational Analysis of the Pyrrolizidine Alkaloid Senecionine Using Molecular Mechanics

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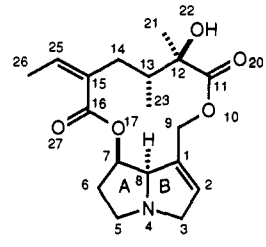
Abstract: A molecular mechanics (MM) program is used to identify low-energy conformations of the pyrrolizidine alkaloid (PA) senecionine. Ab initio calculations on hydroxyacetic acid were carried out in order to develop new MM parameters for α-hydroxy esters. Potential conformations of the macrocyclic ring of senecionine were systematically generated and minimized. Analysis of the resulting data indicates that several conformations should be readily accessible in solution at room temperature. This is in contrast to the solid state, where a number of related PA's show nearly identical conformations. The influence of MM parameter choice and the role of hydrogen bonding are also discussed.

The pyrrolizidine alkaloids (PA's) are a diverse family of plant metabolites containing the 4-azabicyclo[3.3.0]octane or closely related ring system.[1] Many of these alkaloids are potent hepatotoxins,[2] carcinogens, and mutagens[3] and have been shown to represent a serious environmental threat to human and animal health.[4] The problem is particularly acute in geographical regions where livestock ingest significant quantities of PA's from plant sources such as *Senecio* species, since these alkaloids can pass through the food chain.[5]

As a result of our synthetic investigation of the PA's[6] we became interested in conformational aspects of members of the group that contain a dicarboxylic (necic) ester spanning the pyrrolizidine nucleus. In particular, we were intrigued by reports that a number of macrolactone PA's related to senecionine (**1**) exhibited nearly



1, Senecionine

identical conformations in the solid phase.[7] The structures of these PA's are shown in Figure 1. This fact was especially surprising in light of the variety of functional groups present in the 12-membered macrocyclic diester portion of these molecules. In order to gain insight into this remarkable conformational homogeneity we undertook a molecular mechanics study of senecionine. We report herein the results of this investigation which suggest that, in solution, senecionine should exist in several conformations of nearly equal energy.

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Results and Discussion

Computational Methods. Early investigations into conformational aspects of this family of alkaloids recognized that the pyrrolizidine nucleus could exist in either an exo-buckled or endo-buckled conformation.[8] In most cases, including the systems of interest to us, the exo-buckled geometry was predominant due to diminished steric interactions present in this conformer (Figure

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(7) (a) Senecionine: Mackay, M. F.; Culvenor, C. C. J. *Acta Crystallogr., Sect. B* **1982**, *38*, 2754-2758. (b) Jacobine: Perez-Salazar, D.; Cano, F. H.; Garcia-Blanco, S. *Cryst. Struct. Commun.* **1978**, *7*, 105-109. (c) Jacobine methanol solvate: Rohrer, D. C.; Karchesy, J.; Deinzer, M. *Acta Crystallogr., Sect. C* **1984**, *40*, 1449-1452. (d) Retrorsine: Coleman, P. C.; Coucourakis, E. D.; Pretorius, J. A. *S. Afr. J. Chem.* **1980**, *33*, 116-119. (e) Swazine: Liang, M.; Sommerville, P. *Tetrahedron Lett.* **1972**, *13*, 5183-5186. (f) Yamataimine: Hikichi, M.; Furuya, M. *Tetrahedron Lett.* **1978**, *19*, 767-770. (g) Senecicannabine: Asada, Y.; Furuya, T.; Shiro, M.; Nakai, H. *Tetrahedron Lett.* **1982**, *23*, 189-192. (h) Anacrotine ethanol water solvate: Mackay, M. F.; Sadek, M.; Culvenor, C. C. J. *Acta Crystallogr., Sect. C* **1984**, *40*, 1073-1077. (i) Senkirkine: Birnbau, G. I. *J. Am. Chem. Soc.* **1974**, *96*, 6165-6168. (j) Otosenine: Perez-Salazar, A.; Cano, F. H.; Fayos, J.; Martinez-Carrera, S.; Garcia-Blanco, S. *Acta Crystallogr., Sect. B* **1977**, *33*, 3525-3527.

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Table I. Optimized Geometry for Hydroxyacetic Acid[a]

bond lengths		bond angles		dihedral angles	
unit	length, Å	unit	angle, deg	unit	angle, deg
C=O	1.1971	O=C—O[b]	120.00	H—O—C=O[b]	0.00
C(sp²)—O	1.3584	C(sp²)—O—H[b]	120.00	O—C(sp²)—C—O[b]	180.00
O—H (acid)	0.9636	O—C(sp²)—C	108.70	C—(sp²)—C—O[b]	180.00
C—C	1.4965	C—C—H	107.44	H—O—C(sp²)—C[b]	180.00
C—H	1.0837	C(sp²)—C—O	107.27	O—C(sp²)—C—H	57.92
C—O	1.4250	C—O—H	111.03		
O—H	0.9650				

[a] STO 3-21G calculation with C_s symmetry maintained during optimization. [b] Fixed during optimization.

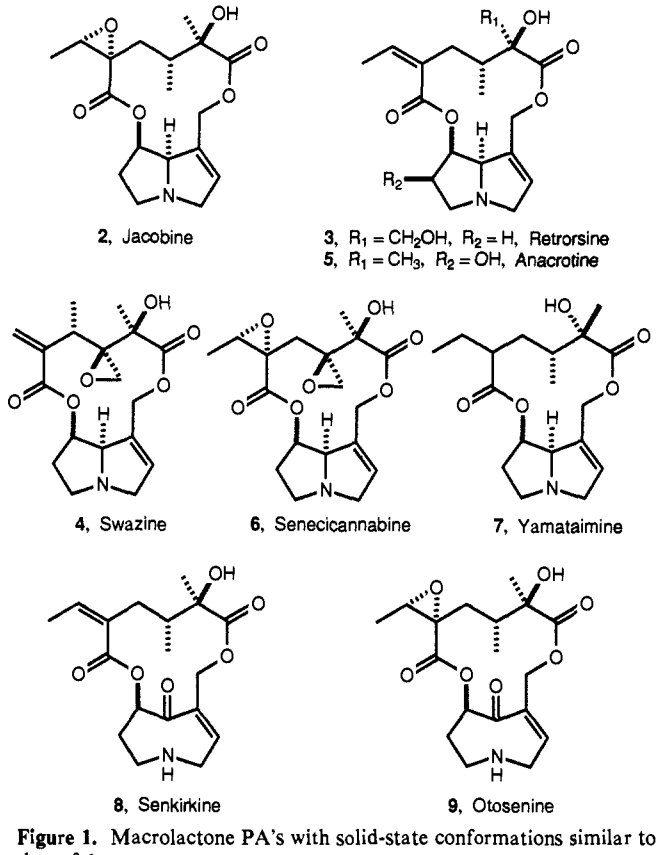

Figure 1. Macrolactone PA's with solid-state conformations similar to that of **1**.

Table II. Rotational Energy Profile for Hydroxyacetic Acid[a]

HO-C-C-OH angle, deg	relative energy: STO 3-21G, kcal/mol	relative energy: MM2,[b] kcal/mol
0	5.31	5.27
10	5.11	5.10
30	3.85	4.06
45	2.99	3.22
58	2.74	2.85
75	3.06	2.98
90	3.54	3.45
105	3.74	3.79
122	3.31	3.47
150	1.37	1.42
170	0.17	0.16
180	0.00	0.00

[a] Rigid rotor approximation using optimized ab initio geometry. [b] Using parameters developed as described in text.

Table III. MM2 Parameters Employed[a]

atom types				V_1	V_2	V_3
6	1	3	6[b]	3.55	−0.02	2.09
6	1	3	7[b]	−0.42	2.33	0.64
2	2	3	7	0.91	2.38	0.50
1	2	3	7	0.00	2.38	0.00
2	2	3	6	1.00	1.00	0.00
1	2	3	6	0.00	1.00	0.00

[a] Standard MM2 atom types given. For atom types 2-3 the stretching constant was 9.0 and the natural bond length was 1.480 Å. [b] Parameters developed in this study. Since data from only one structure were used to develop these parameters, their use in other systems requires caution.

2). This conclusion was based on analysis of NMR data as well as crystallographic studies. In the conformational analysis reported here the pyrrolizidine nucleus was placed in the exo-buckled conformation and the geometry optimized with molecular mechanics (MM).[9] This parent nucleus was then used as a template to construct an ensemble of macrocyclic structures for further processing (vide infra). While the pyrrolizidine nucleus was not held fixed during minimization of the molecule, it showed no tendency to move from the exo-buckled shape. In addition, preliminary studies revealed the exo/endo energy difference to be greater than 5 kcal/mol.

It is important in conformational analysis of large rings by molecular mechanics to systematically examine the potential energy surface. Still's RINGMAKER program[10] is well suited for this purpose, although other methods have been developed.[11] Using RINGMAKER, an ensemble of potential conformations for the PA was constructed by generating all possible combinations of dihedral angles for the macrocycle backbone fused to the pyrrolizidine nucleus. This ensemble was then examined for unfavorable transannular contacts and the feasibility of ring closure. Substituents were added to the basic skeleton and the entire ensemble minimized with respect to energy using the MODEL program of Still which incorporates Allinger's MM2 program.[9]

Our conformational studies were initially directed toward jacobine.[12] Beginning with the exo-buckled pyrrolizidine nucleus and using the programs described above, a number of low-energy conformations were identified. Analysis of these structures and comparison with the crystallographic data[7b,c] indicated substantial divergence. Since a probable cause of this discrepancy appeared to be the lack of complete MM parameters for the α-hydroxy ester and α,β-epoxide moieties of jacobine, we undertook an ab initio investigation to develop more accurate parameters for these functional groups.

Hydroxyacetic acid was chosen as a model system for the α-hydroxy ester moiety of jacobine, and Gaussian 82[13] was used to find and optimize the global minimum. The STO 3-21G basis set was employed, and the carboxylic acid group was held in an s-cis orientation. The hydroxyl group was fixed in an s-trans position which minimized interactions with the carbonyl group. The rigid rotor approximation (ω) was then used to generate a torsional energy profile. While this approximation slightly ov-

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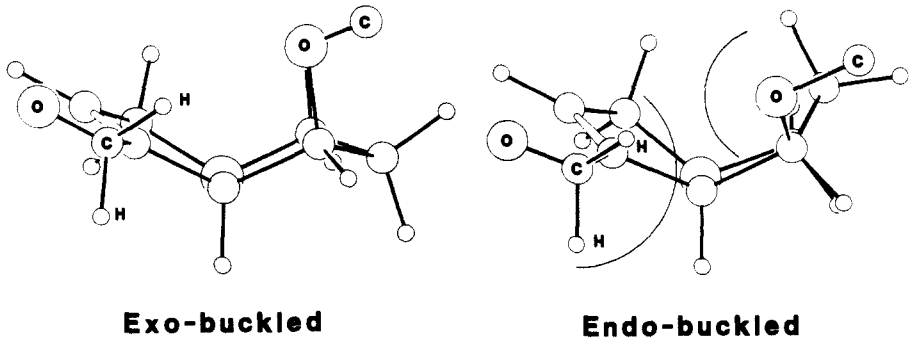

Figure 2. Exo- and endo-buckled conformations of the pyrrolizidine nucleus.

Table IV. Structural Data for the α,β-Unsaturated Ester Group of Selected Pyrrolizidine Alkaloids[a]

compd	C15–C16 bond length, Å	C14–C15–C16–O17 dihedral angle, deg
1	1.49	46.4
2	1.51	50.7
3	1.50	45.0
4	*b*	54.0
5	1.48	58.5
6	1.50	50.4
7	1.52	51.6
8	1.50	39.3
9	1.47	53.8

[a] Data taken from ref 7. [b] Not available.

erestimates rotational barriers,[14] it represents a reasonable compromise between the accuracy required and computing time. Analysis of the ab initio data indicated that the global minimum occurs when the carbonyl double bond eclipses the α C–O bond and that a local minimum occurs when the α C–H bond is eclipsed by the carbonyl group. These results are fully consistent with similar studies of rotation about sp^2–sp^3 bonds.[15] The results of this calculation are summarized in Tables I and II.

The results of this ab initio study verified the source of the inconsistencies and indicated that parameter development would be necessary. The program TORFIT[16] was used to adjust torsional parameters for the central C–C bond so that the relative ab initio energies were reproduced. The new parameters are listed in Table III.

Similar ab initio studies were carried out on glycidic acid as a model for the α,β-epoxide of jacobine. However, our efforts at developing new parameters for this system were thwarted by a lack of literature data needed to supplement our calculations and therefore we decided to pursue a detailed study of senecionine instead. The latter is a close relative of jacobine having an α,β-unsaturated ester in place of the epoxide.

Senecionine. In order to faithfully model senecionine a careful choice of MM parameters for the α,β-unsaturated ester group was necessary. Although this functionality generally exhibits conjugation and therefore remains more or less planar, this is not true for the macrocyclic PA's shown in Figure 1. In these molecules the α,β-unsaturated system is only slightly conjugated, as determined from the lengthening of the central C–C bond and twisting of the normally planar system in the solid state (Table IV).[17]

The parameters chosen for the senecionine calculation reflect this phenomenon. The parameter for the C–C bond length was

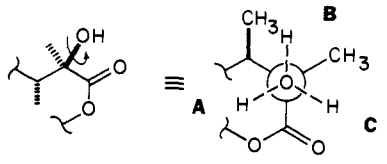

Figure 3. Staggered conformations of the C12–O22 hydroxyl substituent of senecionine. Location of the hydroxyl hydrogen atom in regions A and C permits hydrogen bonding with the O20 carbonyl whereas region B does not.

taken from the work of Watson.[18] For the α,β-unsaturated ester, the parameters should give a relatively low torsional barrier with minima at both the s-cis and s-trans conformations, since a large barrier reflects a high degree of conjugation and would be unsatisfactory for the molecules at hand.[19] The 1977 MM2 parameters for this sytem provide a soft potential which reflects the greater flexibility of the unsaturated group in the PA's. The parameters for the unsaturated ester used in this study are listed in Table III.

Having developed or chosen appropriate parameters, we proceeded to generate and analyze conformations of senecionine. RINGMAKER was used to produce 583 potential conformations of the macrocyclic ring fused to the exo-buckled pyrrolizidine nucleus. Each framework structure then had the substituents and hydrogens added and was optimized with respect to energy and geometry. In the final stage of the computation, the hydroxyl H atom and lone pairs were added in each of the three possible staggered locations (Figure 3).[20] These structures were further minimized to give a final set of conformations for analysis.

As mentioned above, one of the most striking features of the group of PA's shown in Figure 1 is the similarity of their solid-state conformations. This is reflected in the macrocyclic dihedral angles that have relatively small standard deviations. Data for the nine compounds are collected in Table V. Another common feature that is often used to describe the molecular shape of PA's is the angle between the two ester carbonyls. In the 12-membered macrocyclic PA's they are nearly antiparallel. These data are also included in Table V.

Table VI contains data, including relative energies, for the 14 lowest energy conformations of senecionine identified in this study. In general, these conformations show considerable variation in the macrocycle. Certain conformations (**1a**, **1c**, **1e**, **1f**, **1g**, **1j**) are similar (but not identical) to the solid-state conformation, as judged by the standard deviation of the difference between the dihedral angles of the calculated conformation and that of the solid state. Representative ORTEP[21] drawings are given in Figure 4.

Examination of Table VI reveals several interesting trends. First, some macrocyclic angles show little variation through the

(14) (a) Pople, J. A. *Tetrahedron* **1974**, *30*, 1605–1615. (b) Wiberg has shown that large basis sets and/or inclusion of electron correlation effects are needed to obtain barrier heights close to known experimental values in related carbonyl systems. For the system under study the rigid rotor approximation appears to be sufficient. See: Wiberg, K. B.; Laidig, K. E. *J. Am. Chem. Soc.* **1987**, *109*, 5935–5943 and references therein.

(15) Oki, M. *Top. Stereochem.* **1983**, *14*, 1–81.

(16) TORFIT is a program for the development of MM2 torsional parameters (Hanson, B. A.; Ratliff, D. DePauw University, Greencastle, IN, 1987).

(17) The absence of conjugation is also evident in solution based on UV data. See ref 1b, pp 36–54.

(18) Watson, W. H.; Kashyap, R. P. *J. Org. Chem.* **1986**, *51*, 2521–2524.

(19) When the barrier between the s-cis and s-trans conformations is very high the unsaturated system is rigidly held in a planar form.

(20) Analysis of conformations derived from the same macrocycle with different hydroxyl orientations indicated that the location of the hydroxy group does not appreciably affect the conformation of the macrocycle.

(21) Johnson, C. K. *ORTEPII*, Report ORNL-5138. Oak Ridge National Laboratory, TN, 1976.

Table V. Macrocyclic Dihedral Angles of Selected Pyrrolizidine Alkaloids

compd	macrocyclic dihedral angle,[a] deg										C=O angle[b]
	1	2	3	4	5	6	7	8	9	10	
1	80.1	92.4	−179.0	54.0	60.5	−163.9	62.5	46.4	−172.6	169.8	163
2	85.6	88.4	179.2	51.8	63.3	−159.3	59.8	50.7	−175.8	167.2	161
3	81.0	91.4	−179.7	54.3	60.0	−164.1	64.0	45.0	−173.9	168.0	163
4	69.3	97.3	−177.6	63.3	60.3	−152.5	64.9	54.0	−173.0	175.5	160
5	80.7	92.6	179.3	53.7	62.6	−161.6	56.8	58.5	−176.0	157.9	166
6	89.2	89.0	177.8	50.9	60.5	−157.8	58.8	50.4	−178.4	172.0	*c*
7	89.8	89.4	177.6	50.9	59.0	−162.5	65.8	51.6	−175.6	167.6	160
8	78.0	89.8	178.5	61.6	58.4	−163.0	66.5	39.3	−174.1	156.0	152
9	74.5	93.8	176.9	62.9	58.4	−159.9	54.2	53.8	−178.1	153.0	167
mean	80.9	91.6	179.2	55.9	60.3	−160.5	61.5	50.0	−175.3	165.2	162
std dev	6.7	2.8	1.8	5.2	1.7	3.7	4.3	5.4	2.1	7.7	4

[a] Data from ref 7. Numbering system for dihedral angles: 1, C8–C1–C9–O10; 2, C1–C9–O10–C11; 3, C9–O10–C11–C12; 4, O10–C11–C12–C13; 5, C11–C12–C13–C14; 6, C12–C13–C14–C15; 7, C13–C14–C15–C16; 8, C14–C15–C16–O17; 9, C15–C16–O17–C7; 10, C16–O17–C7–C8. [b] Angle between ester carbonyl groups. [c] Not available.

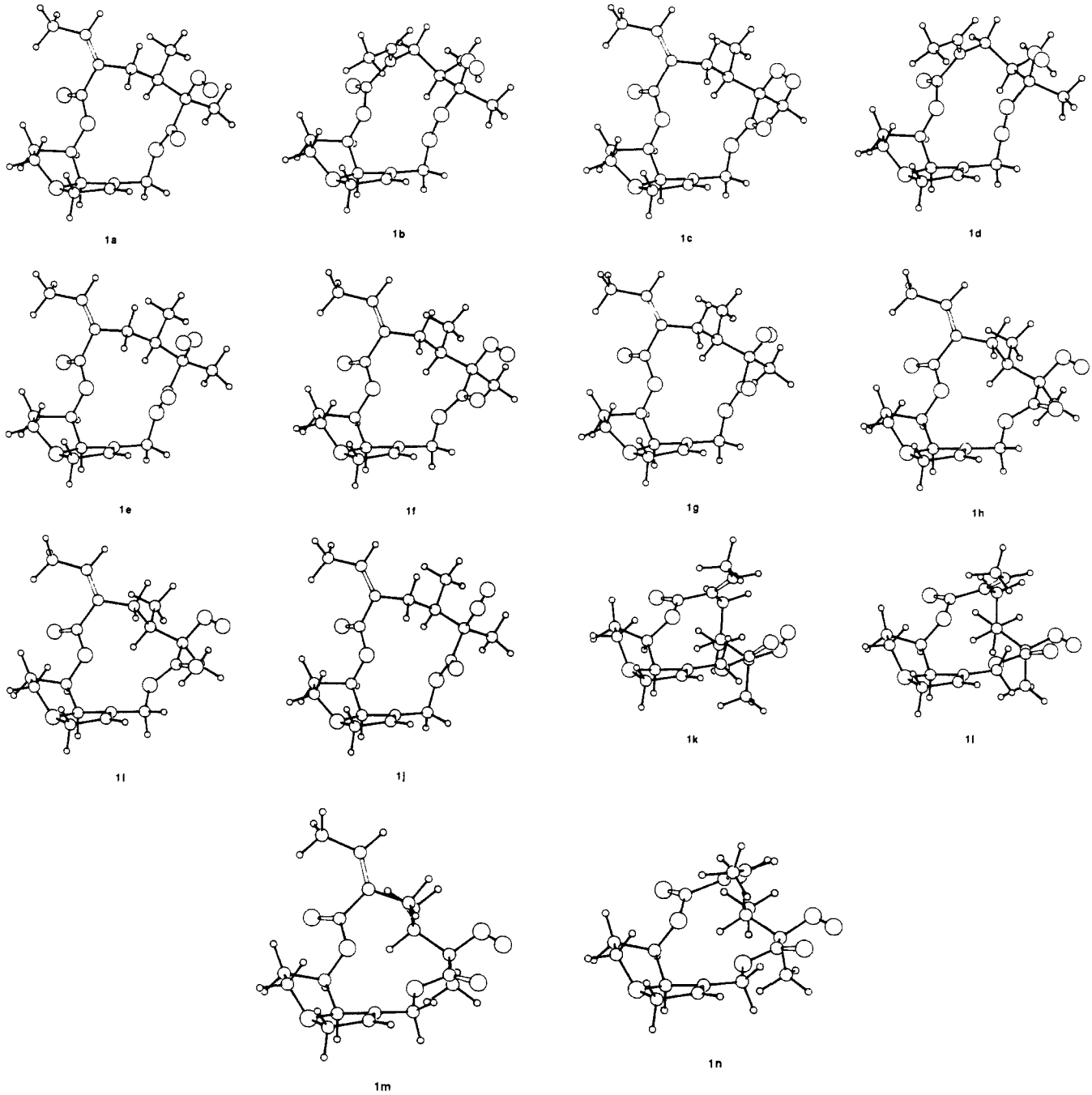

Figure 4. ORTEP plots of the 14 lowest energy conformers (**1a–n**) of senecionine.

Table VI. Macrocyclic Dihedral Angles of Final Senecionine Conformations

conformation	energy, kcal/mol	macrocyclic dihedral angles,[a] deg 1	2	3	4	5	6	7	8	9	10	C=O angle[b]	O—H region[c]	closest relative[d]
X-ray		80.1	92.4	−179.0	54.0	60.5	−163.9	62.5	46.4	−172.6	169.8	168		
1a	0.00	80.7	83.3	170.4	56.1	62.8	−154.1	69.6	30.2	179.5	175.6	151	C	**1e, 1j**
1b	0.67	66.7	80.2	155.9	54.9	78.5	−55.1	−69.5	129.4	−163.6	157.0	155	C	**1d**
1c	0.79	69.7	100.2	170.4	55.8	61.2	−157.1	64.1	35.2	−178.2	176.9	162	C	**1g**
1d	1.19	64.6	75.6	154.6	56.6	80.6	−54.1	−67.7	123.8	−168.0	160.2	149	A	**1b**
1e	1.29	79.9	77.8	170.4	60.9	63.3	−152.0	70.0	29.5	−178.7	173.2	144	A	**1a, 1j**
1f	1.44	68.0	108.3	168.7	50.4	59.9	−158.3	66.0	32.0	−177.6	176.0	163	C	
1g	1.63	66.7	92.3	175.1	65.8	60.1	−155.6	61.8	35.4	−173.9	179.1	150	A	**1c**
1h	2.48	55.4	134.4	166.3	42.6	57.5	−160.3	63.0	34.0	−172.7	175.5	168	C	**1i**
1i	2.57	56.4	126.1	165.8	48.3	57.7	−160.0	63.0	33.0	−174.5	175.8	169	A	**1h**
1j	2.60	79.6	83.1	171.3	58.5	62.6	−154.3	67.9	31.0	179.5	176.9	149	B	**1a, 1e**
1k	2.87	−18.1	164.5	−176.3	64.4	60.3	−75.8	−60.9	127.5	−141.0	147.6	145	A	**1l**
1l	2.90	2.0	167.7	174.8	53.1	60.9	−77.0	−62.0	131.9	−138.5	147.3	161	C	**1k**
1m	2.96	39.1	156.0	172.4	42.1	53.8	−159.3	57.7	39.1	−162.2	174.5	167	A	
1n	2.96	24.1	156.2	165.6	49.6	62.5	−74.5	−64.7	135.1	−140.5	150.0	165	C	

[a] Numbering system is given in footnote *a* of Table V. [b] Angle between ester carbonyl groups. [c] Region where the hydroxyl H is found (see Figure 2). [d] Conformation(s) in which the only significant difference is the hydroxyl H position.

series (angles O10–C11–C12–C13, C9–O10–C11–C12, C11–C12–C13–C14, and C16–O17–C7–C8). Second, some of the angles are linked in families.[22] Angle C14–C15–C16–O17 (the torsional angle of the unsaturated group) takes on one of the two values 33° or 128° (averages given). When the value is 33°, angle C12–C13–C14–C15 is approximately −157° and angle C13–C14–C15–C16 is roughly 65°. When the unsaturated torsional angle is 128°, the corresponding values are −68° and −65° respectively. These three angles are linked in this fashion in all conformers identified.

The conformation of the α-hydroxy ester group merits further comment. As mentioned above, the torsional angle O10–C11–C12–C13 is relatively constant and, for all the conformations, the average value for this angle is 55.1° (with a standard deviation of 7.7°). In the crystal structure of senecionine the angle is 54.0°. This excellent agreement lends support to the MM2 parameters developed for this study.

The role of hydrogen bonding in the conformations of senecionine was also investigated. In the solid state, the hydroxyl hydrogen of this molecule is hydrogen bonded to the nitrogen of an adjacent molecule.[7] In our study, the hydroxyl hydrogen was placed in each of the three possible staggered positions in order to assess the role of intramolecular hydrogen bonding. Several conclusions can be reached from our data. In all cases except one, the hydroxyl is hydrogen bonded to the adjacent carbonyl and is in staggered positions A or C (Figure 3).[23] The one conformer that does not exhibit hydrogen bonding is **1j**, in which the hydroxyl is in the B region. This exception supplied us with two important pieces of information. First, it provided a measure of the stabilization due to hydrogen bonding in the structure, since **1a** and **1j** are identical in all respects except for the location of the hydroxyl hydrogen (ΔE(**1j**/**1a**) = 2.6 kcal/mol). Second, it illustrated the role hydrogen bonding plays in determining the overall shape of the macrocycle. In all conformations studied, the position of the hydroxyl group (A, B, or C in Figure 3) had a negligible effect on the ring dihedral angles. This result validated our computational method in which the hydroxyl hydrogen was added in the final step.

Although it is more rigid than the macrocyclic portion of senecionine, the pyrrolizidine ring system nevertheless showed some interesting trends in the conformations identified. The symmetry elements of the fused five-membered rings were analyzed with the program PUCKER,[24] which utilizes the asymmetry parameters of Duax.[25] In general, ring A was always puckered to about the same extent and ring B remained flat. Ring A was also exo-buckled (ΔC_s(C6)). However, in higher energy conformations, ring A began to distort toward ΔC_2 (C5–C6) and ring B became significantly nonplanar, preferring a ΔC_s(N4) conformation. In fact, the distortion in ring A showed a linear relationship with the nonplanarity of ring B. Conformations **1k** and **1l** show even greater distortions of the pyrrolizidine substructure.

In summary, we have identified a number of energetically accessible conformations of the PA senecionine. In a molecule of this complexity energy differences must be interpreted with caution and differences of less than 1 kcal/mol are probably not significant. It is clear, however, that the solid-state conformation, revealed by the X-ray crystal structure, is by no means uniquely low in energy. In solution, several different conformations would be expected to be present. This has wide-ranging implications for structure–activity relationships among the PA's,[26] especially since the biological activity of these compounds has been related to the accessibility of the C1–C2 double bond.[27]

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Supplementary Material Available: Tables of complete ab initio data for hydroxyacetic acid and glycidic acid, summary of symmetry data for pyrrolizidine rings of the final conformations, and additional data on hydrogen bonding (19 pages). Ordering information is given on any current masthead page.

(22) The solid-state conformation of senecionine (and all the other PA's mentioned in this study) belongs to the first family. However, in the solid state, angle C14–C15–C16–O17 takes on a value of about 50° rather than 33° as observed in our work. This difference is due to the choice of torsional parameters for the α,β-unsaturated system. It is likely that an even softer torsional potential would bring these two values closer together.

(23) MM2 reproduces hydrogen bonding phenomena using dipolar interactions. See: Allinger, N. L.; Chang, S. H.-M.; Glaser, D. H.; Honig, H. *Isr. J. Chem.* **1980**, *20*, 51–56.

(24) PUCKER is a program for convenient identification of symmetry elements in 5- and 6-membered rings. (Hanson, B. A.; Dawson, S., DePauw University, Greencastle, IN, 1987.)

(25) Duax, W. L.; Weeks, C. M.; Rohrer, D. C. In *Topics in Sterochemistry*; Eliel, E. L., Allinger, N. L., Eds.; John Wiley: New York, 1976; Vol. 9, pp 271–283.

(26) A low-energy conformation may not necessarily be the physiologically active one. For a discussion of this point see: Davies, R. H.; Sheard, B.; Taylor, P. J. *J. Pharm. Sci.* **1979**, *68*, 396–397.

(27) (a) Wodak, S. J. *Acta Crystallogr., Sect. B* **1975**, *31*, 569–573. (b) Schoental, R. *Nature (London)* **1957**, *179*, 361–363 and references cited therein.