Conformational Analyses of Hydrobenzo[*c*]phenanthridine Alkaloids based on ^{1}H Relaxation Times and Nuclear Overhauser Effects

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Conformational analyses based on ^{1}H relaxation times (T_1) and nuclear Overhauser effects (n.O.e.s) have been carried out for several hydrobenzo[*c*]phenanthridine alkaloids. Calculated and observed values of T_1 and n.O.e.s have been compared for several possible conformations, and optimum conformations are proposed. These are in reasonable agreement with previous data with the exception of ring *B* and the *N*-methyl group. The correlation times for molecular motion have also been evaluated, and are discussed in connection with molecular structures and conformations.

Many conformational analyses in solution have been carried out on bioactive compounds and natural products by means of ^{1}H and ^{13}C n.m.r. spectroscopy. In addition to chemical shift and coupling constant studies nuclear Overhauser effects (n.O.e.s) and spin–lattice relaxation times (T_1) have been applied extensively.[1] In this paper, we report a computer-assisted method for conformational analysis using ^{1}H T_1 and n.O.e., and investigate its utility in the study of some alkaloids as compared with the conventional method of chemical shifts and coupling constants. Four hydrobenzo[*c*]phenanthridine-type alkaloids, chelidonine (**1**), corynoline (**3**), and their acetates (**2**) and (**4**), have been studied in this manner.

Many experiments[2] have been carried out on the preferred conformations of these alkaloids using i.r. and ^{1}H and ^{13}C n.m.r. Since they have *cis*-fused rings (*B*/*C*), two main conformational types may be discerned in which the aromatic ring *A* is either equatorial (*anti*-type) or axial (*syn*-type) with respect to ring *C*. The conformations of rings *B* and *C* must also be considered: half-chair or half-boat as well as twist-half-chair or twist-half-boat. In addition, the orientation of the *N*-methyl group may be in question. Some possible conformations are shown in Figure 1, and the Newman projection of ring conformations are presented in Figures 2 and 3.

For proton–proton intramolecular dipolar relaxation, non-selective (T_1^{ns}) and selective (T_1^{s}) relaxation times of nucleus *i* can be written as equations (1) and (2),[3] respectively, where A and B are the correlation terms given in equations (3) and (4), N_j

$$T_{1i}^{ns} = A/\left[\sum_{j\neq i} N_j\left(r_{ij}^{-6}\right) + (N_i - 1)r_{ii}^{-6}\right] \quad (1)$$

$$T_{1i}^{s} = B/\left[\sum_{j\neq i} N_j\langle r_{ij}^{-6}\rangle\right] \quad (2)$$

$$A = 10/\{\hbar^2\gamma_H^4[3\tau_c/(1 + \omega_0^2\tau_c^2) + 12\tau_c/(1 + 4\omega_0^2\tau_c^2)]\} \quad (3)$$

$$B = 10/\{\hbar^2\gamma_H^4[3\tau_c/(1 + \omega_0^2\tau_c^2) + 6\tau_c/(1 + 4\omega_0^2\tau_c^2) + \tau_c]\} \quad (4)$$

is the number of magnetically equivalent nuclei *j*, r_{ij} is the distance between protons *i* and *j*, and the brackets in $\langle r_{ij}^{-6}\rangle$ indicate conformational averages,[1a] where appropriate.

The fractional enhancement $f_d(s)$ at nucleus *d* on saturating signal *s* (n.O.e. value) is given by equation (5),[3] where $g_d(i)$ (the geometric term) is given by equation (6), and C (the correlation term) by equation (7). As can be seen from equations (1), (2), and (5), T_1^{ns}, T_1^{s}, and the n.O.e.s are functions of the geometric factors ($\langle r_{ij}\rangle$) and the correlation time (τ_c); by optimizing the fit for a given conformation τ_c is derived. By

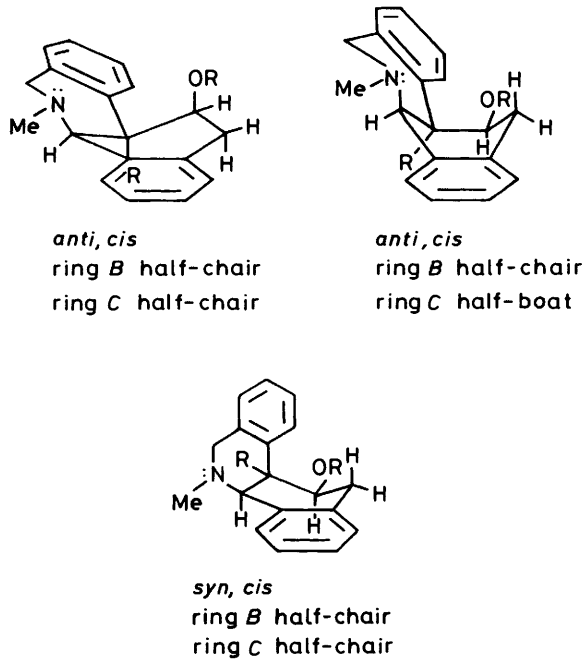


Figure 1. Several possible conformations for the alkaloids

$$f_d(s) = C\left[\sum_s g_d(s) - \sum_{i\neq d,s} f_i(s)g_d(i)\right] = -C\sum_{i\neq d} f_i(s)g_d(i);\ f_s(s) = -1 \quad (5)$$

$$g_d(i) = N_i\langle r_{di}^{-6}\rangle \Big/ \sum_j N_j\langle r_{dj}^{-6}\rangle \quad (6)$$

$$C = [6\tau_c/(1 + 4\omega_0^2\tau_c^2) - \tau_c]/[3\tau_c/(1 + \omega_0^2\tau_c^2) + 6\tau_c/(1 + 4\omega_0^2\tau_c^2) + \tau_c] \quad (7)$$

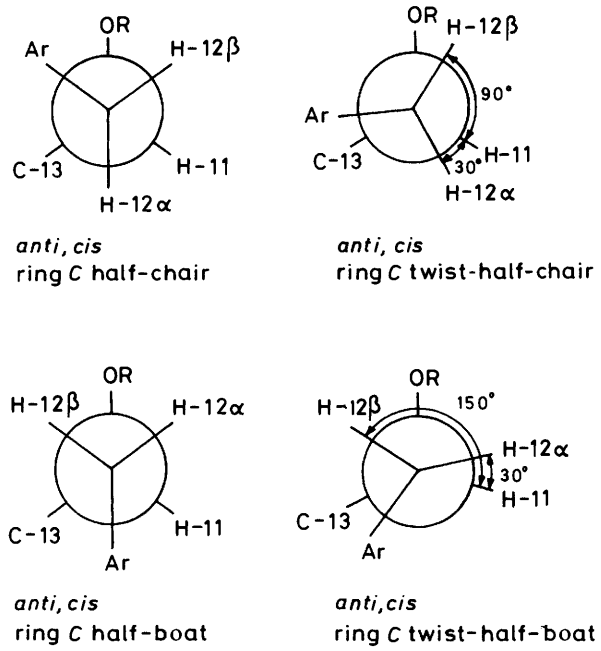


Figure 2. Newman projections for the possible conformations of ring *C*

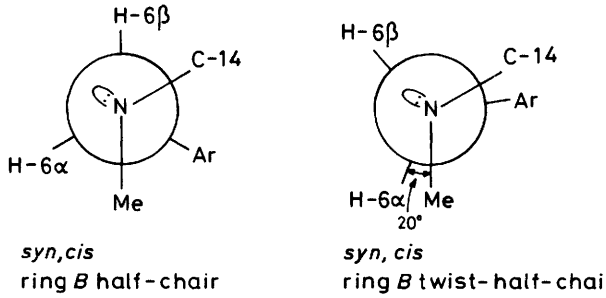


Figure 3. Newman projections for the possible conformations of ring *B*

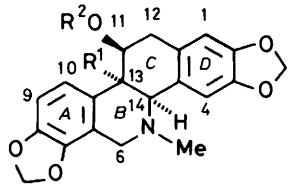
comparing the calculated values with the observed values of T_1 and n.O.e., the optimum conformation can be determined.

In the extreme narrowing limit where $\omega_0\tau_c \ll 1$, B/A becomes 1.5 and so T_1^s/T_1^{ns} should be constant (1.5) regardless of the values of τ_c or $\langle r_{ij} \rangle$. This is the condition in the present study (see later section). It is therefore meaningless to calculate T_1^{ns} and T_1^s separately, and the observed T_1^s values are not used in the calculations.

Experimental

Compounds (**1**), (**3**), and (**4**) are natural products; (**2**) was obtained by acetylation of (**1**). The alkaloids were dissolved in $CDCl_3$ (0.03 mol l^{-1}) and the solutions were degassed and sealed under vacuum.

The ^1H n.m.r. spectra were observed with a Varian XL-200 spectrometer operating at 200.06 MHz and 24 °C. The non-selective ^1H spin–lattice relaxation times (T_1^{ns}) were obtained by using the inversion-recovery (180° − τ − 90° − *t*) method, in which 10—15 τ values were usually included in the analysis of the data, based on the initial slope of a plot of $\ln(M_\infty - M_\tau)$ *vs.* τ. These *M* values were obtained from measurements of the sum of the peak heights of a multiplet corresponding to a given proton. The selective spin–lattice relaxation times (T_1^s) were measured by applying a selective 180° pulse to a given multiplet



	R^1	R^2
(**1**)	H	H
(**2**)	H	Ac
(**3**)	Me	H
(**4**)	Me	Ac

through the decoupler channel, at the specified frequency, and then detecting the magnetization after a time τ, using a non-selective 90° pulse.

The n.O.e. values were obtained from the n.O.e. difference spectra in which the control spectrum with the decoupler off-resonance was subtracted from the spectrum after signal saturation.

The reported values of T_1^{ns}, T_1^s, and n.O.e. are the averages for two or three experiments.

Calculations were carried out on an NEC ACOS-1000 computer at the Computation Center, Osaka University. On the basis of equations (1), (2), and (5), a computer program was written;[1j,k] that is T_1^{ns} values were calculated by an interative least-squares fit of equation (1) to the observed values, treating A as variable, and the $f_d(s)$ values were derived by an iterative least-squares fit of equation (5) to the observed n.O.e. values, treating C as an adjustable parameter. The optimum value of τ_c was thus obtained. Several possible conformations were used as input, and internuclear distances were estimated from Dreiding models.

Since it was difficult to obtain large absolute observed values of the n.O.e.s under the experimental conditions, the calculations were carried out in the following manner. First, the optimum value of τ_c was derived from T_1^{ns}, and then the obtained τ_c was used as input for the calculation of the n.O.e. Agreement factors (*R*-factors) obtained from the calculation of T_1^{ns} and n.O.e. for each conformation were used as a guide to determine the optimum conformation.

Results and Discussion

Spin–Lattice Relaxation Times and N.O.e. Values.—^1H Non-selective and selective spin–lattice relaxation times (T_1^{ns} and T_1^s) are listed in Table 1 for each proton of compounds (**1**)—(**4**). Except for the methyl and some methylene protons, the T_1^s values are about 1.5 times larger than the T_1^{ns} values, within experimental error. This result indicates that we are in the extreme narrowing limit and that these observed T_1 values are modulated mainly by intramolecular dipolar relaxation, because equations (1) and (2) are satisfied. For methyl and methylenedioxy groups, the observed T_1^{ns} values should be the same as T_1^s because of the equivalence of spins. Other methylene protons, for example H-12 (α or β) have a T_1^s/T_1^{ns} value smaller than 1.5, since it is difficult to invert one proton resonance independently of the other. The value for H-11 of (**1**) and (**3**) is also smaller, possibly owing to the effect of the hydroxy group.

T_1 Values of methylenedioxy protons are relatively larger than those of the other methylene protons. This suggests that the internal molecular motion is anisotropic; therefore these data are omitted in the conformational calculations.

In Tables 2—5, the observed n.O.e. values are listed for each

Table 1. Non-selective (T_1^{ns}) and selective (T_1^{s}) ^{1}H spin–lattice relaxation times[a] for compounds (**1**)—(**4**)

	(1)		(2)		(3)		(4)	
	T_1^{ns}/s	T_1^{s}/s	T_1^{ns}/s	T_1^{s}/s	T_1^{ns}/s	T_1^{s}/s	T_1^{ns}/s	T_1^{s}/s
H-1	3.58	5.13	3.16	4.86	3.50	4.91	3.87	5.16
	(3.52)		(3.28)		(3.23)		(3.49)	
H-4	2.16	2.98	3.28	4.65	2.13	2.94	2.44	3.50
	(2.41)		(3.56)		(2.17)		(2.73)	
H-6α	0.62	1.01	0.57	0.79	0.61	0.86	0.60	0.94
	(0.56)		(0.57)		(0.50)		(0.53)	
H-6β	0.67	0.96	0.60	0.89	0.64	0.98	0.64	0.90
	(0.62)		(0.61)		(0.56)		(0.58)	
H-9	*b*	*b*	3.95	6.27	3.39	4.88	3.98	5.73
	(4.18)		(4.02)		(3.68)		(4.14)	
H-10	*b*	*b*	2.27	3.33	1.34	1.67	1.51	1.94
	(1.72)		(2.03)		(1.32)		(1.57)	
H-11	1.22	1.52	1.34	1.96	1.25	1.46	1.42	1.96
	(1.32)		(1.40)		(1.28)		(1.36)	
H-12α	0.62	0.65	0.53	0.62	0.64		0.57	0.57
	(0.52)		(0.52)		(0.55)	0.67	(0.50)	
H-12β	0.67	0.65	0.55	0.81			0.59	0.68
	(0.59)		(0.57)				(0.59)	
H-13	1.46	2.13	1.07	1.42				
	(1.39)		(1.14)					
H-14	1.45	1.95	1.00	1.46	1.26	1.75	1.21	1.60
	(1.23)		(1.08)		(1.20)		(1.19)	
NMe	0.43	0.46	0.53	0.55	0.43	0.45	0.72	0.76
13-Me					0.70	0.75	0.55	0.55
MeCO			1.47	1.40			1.46	1.44
OCH_2O	1.56	1.59	1.17	1.19	1.58	1.58	1.44	1.49

[a] Values in parentheses represent calculated values. [b] Undetectable because of an overlap of signals.

Table 2. N.O.e. values (%) for (**1**)[a]

	H-1	H-4	H-14	H-6α	H-6β	H-9	H-10	H-13	H-11	H-12α	H-12β
Satd.											
H-1, -4			14.8							2.3	4.5
			(15.8)							(2.7)	(2.5)
H-14		19.1		*b*				10.0			
		(30.3)		(6.3)				(15.9)			
NMe		17.9	4.2	5.3	8.5						
		(14.5)	(2.9)	(2.0)	(3.9)						
H-6α			*b*		27.9						
			(12.3)		(44.0)						
H-6β				28.7							
				(39.8)							
H-9, -10								10.8	3.5		
								(13.3)	(7.6)		
H-13			8.6				14.7		8.2		
			(14.2)				(15.6)		(11.5)		
H-11							8.3	9.1		7.4	3.1
							(9.9)	(12.4)		(7.2)	(0.3)
H-12α	16.1								17.2		*b*
	(15.5)								(15.9)		(40.9)
H-12β	22.6									*b*	
	(13.0)									(36.3)	

[a] Values in parentheses represent the calculated values. [b] The n.O.e. value is undetectable because the observed signal is close to the saturated signal.

compound. By using the difference spectra, small n.O.e.s of a few percent can be detected. Although it is difficult to obtain a large absolute value in these experiments, these n.O.e. values do reflect the molecular conformations, as can be seen from the comparison of observed and calculated values.

Conformational Calculations.—The calculations were carried out on T_1^{ns} to derive the optimum value for τ_c. In these calculations the T_1 values for the methyl and methylenedioxy groups were omitted. The calculated optimum value of τ_c was used in the calculations of the n.O.e. The results of the calculations (*R*-factors on T_1^{ns} and n.O.e., and τ_c values) for some possible conformations for each compound are presented in Tables 6—9, and the calculated values of T_1^{ns} and n.O.e. for the optimum conformation for each compound are also listed in Table 1 (T_1^{ns}) and Tables 2—5 (n.O.e.). The *R*-factors for the

Table 3. N.O.e. values (%) for (**2**)[a]

	H-1	H-4	H-14	H-6α	H-6β	H-9	H-10	H-13	H-11	H-12α	H-12β
Satd. H-1										4.7 (5.0)	2.8 (0.6)
H-4, -10			6.5 (3.9)		6.0 (5.5)	30.6 (44.5)		3.3 (4.3)			
H-14		11.1 (14.5)						14.6 (13.3)	12.2 (10.7)		
NMe		3.3 (2.0)	12.6 (18.3)	7.6 (9.6)				12.4 (14.7)			
H-6α					30.6 (43.3)						
H-6β		21.1 (26.9)		24.3 (39.8)							
H-13			11.6 (12.5)				7.4 (9.5)		12.3 (10.6)		
H-11			10.7 (8.7)				3.6 (2.1)	10.3 (8.7)		6.4 (7.0)	
H-12α	32.9 (26.3)								17.5 (16.2)		*b* (39.7)
H-12β							10.6 (12.7)			*b* (36.8)	

[a] Values in parentheses represent calculated values. [b] The n.O.e. value is undetectable because the observed signal is close to the saturated signal.

Table 4. N.O.e. values (%) for (**3**)[a]

	H-1	H-4	H-14	H-6α	H-6β	H-9	H-10	H-11	H-12
Satd. H-1, -4			15.1 (16.8)						3.4 (2.6)
H-14		19.9 (30.1)		2.1 (6.3)					
NMe		22.0 (14.3)	4.1 (3.2)	5.1 (2.0)	10.7 (3.9)				
H-6α			*b* (13.0)		24.6 (43.9)				
H-6β				20.2 (39.6)					
H-10								0 (10.0)	
13-Me			10.7 (11.0)				21.0 (21.1)	0 (7.8)	3.0 (3.1)
H-11							8.8 (10.1)		6.4 (7.0)
H-12	39.0 (46.8)							20.5 (28.3)	

[a] Values in parentheses represent calculated values. [b] The n.O.e. value is undetectable because the observed signal is close to the saturated signal.

n.O.e.s are relatively large for all compounds. This must be due to the experimental limitation that large values of the n.O.e. cannot be observed under the experimental conditions.

For compounds (**1**) and (**3**), the *anti,cis*-type conformation with half- or twist-half-chair forms of rings *B* and *C* has been proposed,[2] because the hydrogen bond between the hydroxy group and the nitrogen lone-pair stabilizes this conformation. Thus, four different *anti,cis*-conformations were considered in the calculation for (**1**) (Table 6). Possible conformations of ring *C* (half-chair and twist-half-chair) are defined as shown in Figure 2. The axial hydroxy group substituted at C-11 is expected to deform ring *C*. The smaller *R*-factor for the n.O.e.s of conformation II or IV (ring *C* twist-half-chair) as compared with I (ring *C* half-chair) suggests the deforming of ring *C*, although there is not much difference in T_1^{ns} between I and II. Conformation I cannot reproduce the medium n.O.e. value of H-1 on saturating H-12α (the calculated values are 0.6% for conformation I and 15.5% for II or IV while the observed value is 16.1%). In considering the *N*-methyl group conformation, three possibilities were investigated, namely equatorial (II), an equilibrium between equatorial and axial (*eq*:*ax ca.* 50:50) (III), and an equilibrium slightly shifted to the equatorial orientation (*eq*:*ax ca.* 75:25) (IV). Conformation IV shows the smallest *R*-factor for T_1^{ns}, although that for the n.O.e. is slightly larger than that for II. The larger difference in the *R*-factor for the T_1^{ns} between IV and II is mainly attributed to the difference in the calculated T_1^{ns} for H-4 ($T_1^{calc.}$ 1.63 s for II and 2.41 s for IV; T_1^{obs} 2.16 s). From these calculations, the conformation IV is concluded to be the optimum conformation for (**1**), namely the *anti,cis*-type in which rings *B* and *C* are present in the half-chair and twist-half-chair conformations, respectively, and the *N*-methyl group is in an equilibrium slightly shifted towards the equatorial (*eq*:*ax ca.* 75:25). This is consistent with the results from the 470 MHz ^{1}H n.m.r. and ^{13}C n.m.r. studies,[2g] except for the equatorial conformation of the *N*-methyl group.

Since actetylation of the hydroxy group in (**1**) eliminates the

Table 5. N.O.e. values (%) for (**4**)[a]

	H-1	H-4	H-14	H-6α	H-6β	H-9	H-10	H-11	H-12α	H-12β
Satd. H-1									4.4 (6.5)	
H-4			10.1 (13.7)							
H-14,-6α		19.7 (32.4)			*b* (43.0)					
N-Me		12.7 (10.0)	4.8 (6.4)	3.7 (3.3)	4.8 (4.5)					
H-6β				*b* (38.5)						
H-10)								7.4 (5.7)		
13-Me			12.7 (11.9)				17.4 (22.9)	13.8 (19.8)		
H-11							6.5 (6.6)		6.0 (7.1)	
H-12α	33.5 (37.4)						17.3 (15.9)			*b* (42.5)
H-12β									*b* (37.5)	

[a] Values in parentheses represent calculated values. [b] The n.O.e. value is undetectable because the observed signal is close to the saturated signal.

Table 6. Results of the calculations for several conformations of (**1**)

	Conformation					*R*-Factor (%)	
No.	Type	Ring *B*	Ring *C*[a]	*N*-Me	$\tau_c/10^{-11}$	T_1^{ns}	N.O.e.
I	*anti,cis*	Half-chair	Half-chair	*eq*	6.3	13.5	46.0
II	*anti,cis*	Half-chair	Twist-half-chair	*eq*	5.4	13.0	40.1
III	*anti,cis*	Half-chair	Twist-half-chair	*eq*⇌*ax* (50:50)	6.8	15.5	49.8
IV	*anti,cis*	Half-chair	Twist-half-chair	*eq* ⇌ *ax* (75:25)	5.8	7.9	42.1

[a] The Newman projections are presented in Figure 2.

Table 7. Results of the calculations for several conformations of (**2**)

	Conformation					*R*-Factor (%)	
No.	Type	Ring *B*[a]	Ring *C*[a]	*N*-Me	$\tau_c/10^{-11}$	T_1^{ns}	N.O.e.
I	*anti,cis*	Half-chair	Twist-half-chair	*eq*	5.5	26.6	70.4
II	*syn,cis*	Half-chair	Half-chair	*ax*	5.6	8.9	40.4
III	*syn,cis*	Twist-half-chair	Half-chair	*ax*	5.8	7.3	35.9

[a] The Newman projections are presented in Figures 2 and 3.

hydrogen bond with the nitrogen lone-pair, which stabilizes the *anti,cis*-type conformation, the conformation of (**2**) is expected to be different from that of (**1**). An *X*-ray diffraction study has established the *syn,cis*-type conformation for chelidonine (**1**) *p*-bromobenzoate.[4] N.m.r. studies[2e,g] have also proposed the *syn,cis*-type conformation in which both rings (*B* and *C*) of compound (**2**) exist in half-chair form. Therefore, calculations were carried out for two *syn,cis*-type conformations and one *anti*-conformation for comparison with (**1**) (Table 7). Conformations of rings *B* and *C* are defined in Figures 3 and 2, respectively. The large values of the *R*-factor rule out the *anti,cis*-conformation. For the *syn,cis*-conformation, since the *N*-methyl group cannot exist in the equatorial form due to steric repulsion with H-4, the axial *N*-methyl group is presumed to twist ring *B*. The smaller *R*-factors for T_1^{ns} and the n.O.e. for conformation III support this assumption. Conformation III reproduces the T_1 value for H-14 ($T_1^{calc.}$ 1.48 s for conformation II and 1.08 s for III; T_1^{obs} 1.00 s). The calculated n.O.e. for H-14 on saturating the *N*-methyl signal is 5.6% for II and 18.3% for III; the observed n.O.e. is 12.6%. The calculated n.O.e. for H-13 is 22.0% for II and 14.7% for III; the observed value is 12.4% on saturating the *N*-methyl signal. Hence for (**2**), the *syn,cis*-conformation, with ring *B* in twist-half-chair form and ring *C* in half-chair form, and an axial *N*-methyl group (III), represents the optimum conformation. Ring *B* conformations for these alkaloids have never been analysed previously by n.m.r. experiments because a suitable chemical shift or coupling constant could not be measured.

The same four conformations were examined for (**3**), which also has a hydrogen bond between the hydroxy group and the nitrogen lone-pair (Table 8). The optimum conformation is the same as for (**1**), namely conformation IV. The relatively large *R*-factor for the n.O.e. is due to the observed values of zero for H-11 on saturating H-10 and the 13-methyl, whereas non-zero n.O.e.s are calculated. This may be the effect of the hydroxy group.

Compound (**4**) does not have a hydrogen bond because of the

Table 8. Results of the calculations for several conformations of (3)

No.	Conformation				$\tau_c/10^{-11}$	*R*-Factor (%)	
	Type	Ring *B*	Ring *C*[a]	*N*-Me		T_1^{ns}	N.O.e.
I	*anti,cis*	Half-chair	Half-chair	*eq*	6.2	16.2	45.7
II	*anti,cis*	Half-chair	Twist-half-chair	*eq*	6.2	15.1	44.3
III	*anti,cis*	Half-chair	Twist-half-chair	*eq*⇌*ax* (50:50)	6.7	11.3	54.9
IV	*anti,cis*	Half-chair	Twist-half-chair	*eq* ⇌ *ax* (75:25)	6.5	8.2	47.6

[a] The Newman projections are presented in Figure 2.

Table 9. Results of the calculations for several conformations of (4)

No.	Conformation				$\tau_c/10^{-11}$	*R*-Factor (%)	
	Type	Ring *B*[a]	Ring *C*[a]	*N*-Me		T_1^{ns}	N.O.e.
I	*anti,cis*	Half-chair	Half-boat	*eq*	6.0	7.9	30.4
II	*anti,cis*	Half-chair	Half-boat	*eq*⇌*ax* (50:50)	6.3	15.3	45.4
III	*anti,cis*	Half-chair	Twist-half-boat	*eq*	5.8	8.6	31.4
IV	*anti,cis*	Half-chair	Twist-half-boat	*eq*⇌*ax* (50:50)	6.0	13.5	48.3
V	*anti,cis*	Half-chair	Twist-half-chair	*eq*	5.5	14.1	59.3
VI	*syn,cis*	Twist-half-chair	Half-chair	*ax*	5.9	14.3	61.2

[a] The Newman projections are presented in Figures 2 and 3.

Table 10. Optimum conformations and correlation times for compounds (1)—(4)

Compound	Conformation				$\tau_c/10^{-11}$
	Type	Ring *B*	Ring *C*	*N*-Me	
(1)	*anti,cis*	Half-chair	Twist-half-chair	*eq* ⇌ *ax* (75:25)	5.8
(2)	*syn,cis*	Twist half-chair	Half-chair	*ax*	5.8
(3)	*anti,cis*	Half-chair	Twist-half-chair	*eq* ⇌ *ax* (75:25)	6.5
(4)	*anti,cis*	Half-chair	Half-boat	*eq*	6.0

acetylation of the hydroxy group, but it would not be able to exist in the *syn,cis*-type of conformation as does compound (2), because of steric hindrance between the *N*-methyl and 13-methyl groups. Thus, the boat form of ring *C* is expected; this has also been proposed on the basis of an *X*-ray diffraction study[5] and conventional n.m.r. studies.[2e,g] The calculations were carried out for (4) on four *anti,cis*-type conformations with ring *C* in the half-boat or twist-half-boat form, as well as for the *anti,cis*-type with ring *C* in the twist-half-chair form, and the *syn,cis*-type (Table 9). The latter two conformations were considered in comparison with those for other compounds, but show large *R*-factors for the n.O.e. The *N*-methyl conformation is equatorial rather than an equilibrium between equatorial and axial. The smaller *R*-factors are due to the better fit between the calculated and observed values of T_1 for H-4 and H-12β, and the n.O.e. values for H-4, H-6α, and H-6β on saturating the *N*-methyl signal for conformations I or III rather than for II or IV. Conformation I, the *anti,cis*-type with ring *B* in the half-chair form, ring *C* in the half-boat form, and an equatorial *N*-methyl group, is proposed as the optimum conformations, although the possibility of a twist-half-boat form for ring *C* cannot be ruled out because of the small *R*-factor differences between conformations I and III.

The optimum conformations for each alkaloid are summarized in Table 10. As already discussed, they are reasonable and fairly consistent with previous studies.[2]

Correlation Times and Molecular Motion.—The calculated correlation times (τ_c) for each optimum conformation are also listed in Table 10. These values confirm that the extreme narrowing conditions ($\omega_0\tau_c \ll 1$) holds. If we assume isotropic motion, the correlation time reflects the overall molecular motion. Acetylation will increase the molecular motion because of reduced interaction with solvent. The smaller τ_c values for (4) in comparison with (3) can be accounted for by this change. The *anti,cis*-type conformation leaves the molecule planar, whereas the *syn,cis*-type makes it bent. These conformational differences may change the molecular motion. Two different effects, the conformational change and the acetylation effect could compensate each other resulting in the same value of τ_c for (2) and (1). The larger value of τ_c for (3) in comparison with (1) may reflect the small change in the molecular size.

Conclusions

This systematic method of conformational analysis based on ^{1}H T_1 and n.O.e. values gives good results for some hydrobenzo[*c*]phenanthridine alkaloids, consistent with previous results[2] except for the conformations of ring *B* for (2) and the *N*-methyl groups of (1), (3), and (4). The twist-half-chair conformation is proposed for ring *B* of (2), which has never been elucidated by studies of ^{1}H chemical shifts, coupling constants, nor ^{13}C chemical shifts. Furthermore, by this method, the conform-

ational equilibrium can be discussed in terms of the weighted-average of internuclear distances $\langle r_{ij} \rangle$, as shown for the *N*-methyl groups of (**1**) and (**3**).

As can be seen in Tables 6—9, the *R*-factors for T_1^{ns} are much smaller than those for the n.O.e.s, *i.e.* a better fit can be obtained between the observed and calculated values for T_1^{ns} than for the n.O.e.s. In previous conformational analyses, the n.O.e. has been used more than T_1 data. It should be emphasized, however, that useful results can also be obtained from T_1 by careful experimentation. In addition, one of the advantages of this method is that the correlation time is also measured, which reflects the molecular motion.

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References

1 (*a*) R. E. Schirmer, J. P. Davis, J. H. Noggle, and P. A. Hart, *J. Am. Chem. Soc.*, 1972, **94**, 2561; (*b*) M.-C. Kuo, T. Drankenberg, and W. A. Gibbons, *J. Am. Chem. Soc.*, 1980, **102**, 520; (*c*) F. Heatley, L. Akhter, and R. T. Brown, *J. Chem. Soc., Perkin Trans. 2*, 1980, 919; (*d*) D. Kaplan and G. Navon, *J. Chem. Soc., Perkin Trans. 2*, 1981, 1374; (*e*) M. P. Williamson and D. H. Williams, *J. Am. Chem. Soc.*, 1981, **103**, 6580; (*f*) K. Bock, S. Josephson, and D. R. Bundle, *J. Chem. Soc., Perkin Trans. 2*, 1982, 59; (*g*) P. Dais, T. K. M. Shing, and A. S. Perlin, *J. Am. Chem. Soc.*, 1984, **106**, 3082; (*h*) B. K. Hunter, L. D. Hall, and J. K. M. Sanders, *J. Chem. Soc., Perkin Trans. 1*, 1983, 657; (*i*) D. Nuehaus, R. N. Sheppard, and I. R. C. Bick, *J. Am. Chem. Soc.*, 1983, **105**, 5996; (*j*) M. Sugiura, H. Beierbeck, P. C. Bélanger, and G. Kotovych, *J. Am. Chem. Soc.*, 1984, **106**, 4021; (*k*) M. Sugiura, H. Beierbeck, G. Kotovych, and P. C. Bélanger, *Can. J. Chem.*, 1984, **62**, 1640; (*l*) H. Haruyama, H. Kurihara, and M. Kondo, *Chem. Pharm. Bull.*, 1985, **33**, 905; (*m*) M. D. Bruch, J. H. Noggle, and L. M. Gierash, *J. Am. Chem. Soc.*, 1985, **107**, 1400, and references therein.

2 (*a*) E. Seoane, *An. Real. Soc. Espan. Fis. Quim. Madrid, Ser. B*, 1965, **61**, 755; (*b*) H.-W. Bersh, *Arch. Pharm. (Weinheim)*, 1958, **291**, 491; (*c*) C. Y. Chen and D. B. MacLean, *Can. J. Chem.*, 1967, **45**, 3001; (*d*) S. Naruto, S. Arakawa, and H. Kaneko, *Tetrahedron Lett.*, 1968, 1705; (*e*) N. Takao, K. Iwasa, M. Kamigauchi, and M. Sugiura, *Chem. Pharm. Bull.*, 1978, **26**, 1880; (*f*) M. Cushman and T. C. Choong, *Heterocycles*, 1980, **14**, 1935; (*g*) M. Cushman, A. Abbaspour, K. Iwasa, and N. Takao, *J. Nat. Prod.*, 1984, **47**, 630.

3 J. H. Noggle and R. E. Schirmer, 'The Nuclear Overhauser Effect,' Academic Press, New York, 1971.

4 N. Takao, N. Morita, M. Kamigauchi, K. Iwasa, K. Tomita, T. Fujiwara, and S. Fujii, *Acta Crystallogr., Ser. B*, 1981, **37**, 2043.

5 T. Kametani, T. Honda, M. Ihara, H. Shimanouchi, and Y. Sasada, *J. Chem. Soc., Perkin Trans. 2*, 1978, 1605.

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