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THE CIRCULAR DICHROISM AND ABSOLUTE CONFIGURATION OF ARGEMONINE

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Abstract– The CD and isotropic electronic absorption spectra of ( )-argemonine are reported. The spectra are analysed by means of an exciton model in which the transition moments of the two veratrole chromophores interact to give the helical charge displacements responsible for the optical activity of the corresponding absorption bands. The relative frequencies and signs of the rotational strengths calculated for the (1S,5S) configuration of argemonine correspond to the positions and signs of the circular dichroism bands observed in the spectrum of the naturally-occuring ( )-isomer. The empirical comparison of Cotton-effect curves is found to be of limited validity for relating stereochemical configurations.

THE ALKALOID argemonine, $C_{21}H_{25}NO_4$, $[\alpha]_D^{24}$ $-187{\cdot}93^\circ$ ($CHCl_3$), has been shown, by chemical and spectroscopic[1,2] studies, to be the N-methyl derivative of pavine[3] with the annellated bicyclo [3.3.1] azanonadiene structure (I). Recent preliminary communications report, from chemical degradations of the alkaloid[4,5] and from an analysis of its CD spectrum,[6,7] that (−)-argemonine has the 1S,5S stereochemical configuration I. In the present work the measurement and the non-empirical analysis of the isotropic absorption and CD spectrum of (−)-argemonine (Fig. 1, Table) is described.

Argemonine contains two non-coplanar veratrole chromophores, and the optical activity of the alkaloid derives largely from interactions between the transition dipoles of the two veratrole groups. As in other dissymmetric multiple-chromophore systems, such as calycanthine[8] and Tröger's base[9] (II), which each contain two non-coplanar aniline chromophores, the interactions have the same magnitude but opposite sign for the two enantiomers. The absolute configuration of such double-chromophore systems is thus given by comparing the observed optical activity, measured as the

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[1] M. J. Martell, T. O. Soine and L. B. Ker, *J. Am. Chem. Soc.* **85**, 1022 (1963).

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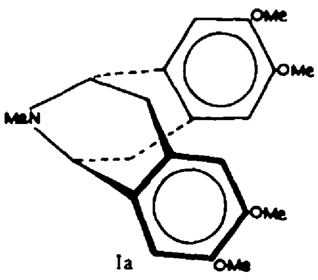
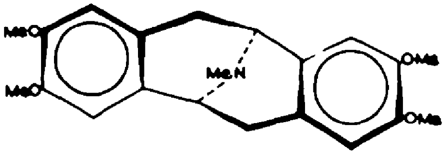
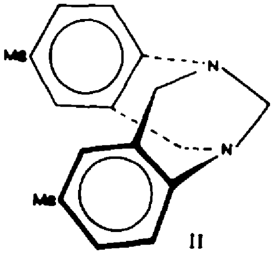


Ia

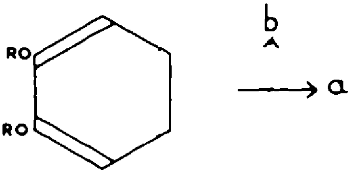


Ib

CD, with the theoretical rotational strengths of the two optical isomers. The experimental rotational strengths are estimated from the observed CD band areas, and the corresponding theoretical quantities are obtained from the absorption spectrum of the monomer chromophore and the calculated transition dipole interactions between the two chromophores of the dimeric system (Fig. 1, Table).



II



III

In argemonine, as in calycanthine[8] and Tröger's base,[9] the two chromophores are related by a two-fold axis of rotation, these molecules belonging to the point group C_2. A given electronic transition of the veratrole chromophore is doubly degenerate in argemonine, to a zero-order approximation, but the degeneracy is split by Coulombic interactions between the transition charge densities of the two chromophores. If the excitation dipoles of the two chromophores are not coplanar, the two resultant transitions, one with A and the other with B symmetry in the group C_2, have in general different energies, and each involves a helical charge displacement which is right-handed for one interaction mode and left-handed for the other. The helical motion of an electron generates an electric (p) and a magnetic (μ) dipole moment, which are parallel for the right-handed and anti-parallel for the left-handed charge displacement (Fig. 2). The electric and the magnetic moment are vectors, and their scalar product represents the rotational strength of the transition. Thus the A and the B interaction modes of the excitation dipoles of the two veratrole chromophores in argemonine are expected to give a pair of adjacent CD bands with opposed signs in the wavelength region of each isotropic absorption band. In the enantiomeric molecule the two circular dichroism bands have the same frequencies and magnitudes but the signs are interchanged.

In the present work, as in previous studies[8, 10], the Coulombic interaction is approximated by the assumption that an excitation moment of the veratrole chromophore generated by the absorption of radiation is a point electric dipole located at

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[10] J. Mason (Banus) and S. F. Mason, *Tetrahedron* 23, 1919 (1967).

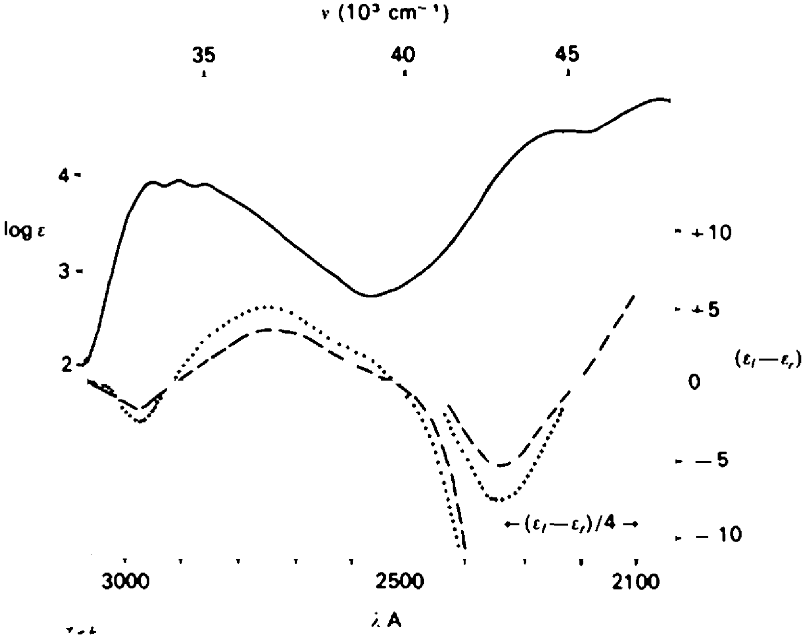

FIG. 1. The absorption spectrum ——, and the circular dichroism - -- at 295°, and ········ at 80°K of argemonine in ethanol isopentane ether (2:5:5).

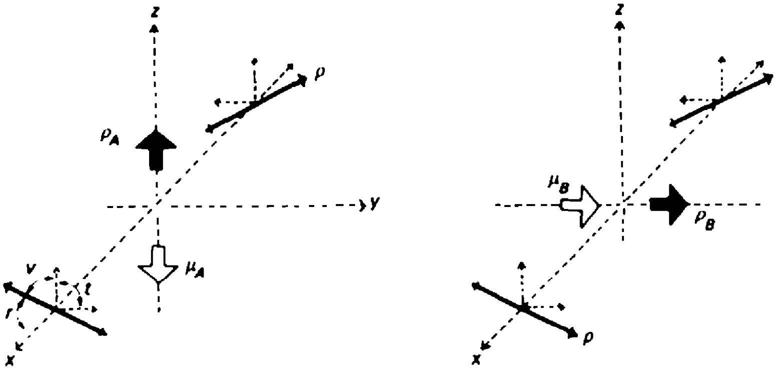

FIG. 2. The Cartesian coordinates of a double-chromophore system with a two-fold rotation axis of symmetry, and the coupling modes of two excitation dipole ρ separated by a distance d giving a resultant transition (a) with A symmetry and (b) with B symmetry in the group C_2. The resultant electric-dipole and magnetic-dipole transition moments are ρ_A and μ_A, respectively, for the A coupling mode, and ρ_B and μ_B, respectively, for the B coupling mode. The x-axis is defined by the joining the centres of the dipoles and z is the symmetry axis. The radial, tangential, and vertical angles between each dipole and its local Cartesian axes, x, y, and z, are r, t, and v, respectively.

the centre of the benzene ring. On this basis the rotational strengths R of the two transitions resulting from the dipole–dipole interaction of the excitation moments of the two veratrole chromophores are given by,

$$R_A = -R_B = \pi \bar{\nu} d \rho^2 \cos v \cos t \tag{1}$$

and the separation $\Delta\bar{\nu}$ between the two resultant transition frequencies is

$$\Delta\bar{\nu} = \bar{\nu}_A - \bar{\nu}_B = 2\rho^2 (\cos^2 v - \cos^2 t + 2\cos^2 r)\, hcd^3 \tag{2}$$

In Eqs (1) and (2), $\bar{\nu}$ is the wave number and ρ the dipole moment of the transition in the isolated veratrole chromophore, and d is the distance between the excitation dipoles of the two chromophores in the dimeric system. The dipole strength, ρ^2, of a given veratrole transition is obtained from the area of the corresponding absorption band of the molecule. Each of the two excitation dipoles ρ has components directed parallel to the Cartesian axes of the dimeric system, and the magnitudes of the components are determined by the cosines of the vertical, tangential, and radial angles, v, t, and r, respectively, between the excitation dipole and the local Cartesian axes (Fig. 2).

The angles, v, t, and r, required for the calculation of the rotational strengths and the relative frequencies depend upon the orientation of the excitation dipole within the veratrole chromophore as well as the mutual stereochemical disposition of the two chromophores in argemonine. In the quartz UV region veratrole gives absorption bands at 2800 and 2250 Å, which are termed the α- and the p-band, respectively, in the classification of Clar,[11] or the ^1L_b and the ^1L_a bands, respectively, according to the nomenclature of Platt.[12]. The corresponding bands of benzene are forbidden, as the component transition dipoles mutually cancel. However, in substituted benzenes the component transition dipole at the position of substitution is changed in magnitude, giving a non-zero resultant moment.[13] For disubstituted benzenes the resultant moment is the vector sum of the two component transition dipoles induced by the substituents, and absorption intensities predicted by this method show good agreement with experiment.[13] Vector addition of the component dipoles induced by the two methoxy groups gives a resultant moment orientated along the two-fold rotation axis of veratrole a (III, R = Me) for the longer wavelength α-band and along the in-plane direction perpendicular to that axis b (III, R = Me) for the shorter wavelength p-band. The circularly polarized absorption spectrum of the tris-catechyl-arsenate (V) ion shows[10] that the transitions responsible for the α- and the p-band of the closely-related catechol chromophore are directed along the a and b axes, respectively, of (III, R = H).

Values of the stereochemical parameters, d, v, t, and r (Eqs 1 and 2) are determined not only by the transition moment directions in the veratrole chromophore but also by the spatial relations between the two chromophores in argemonine. The stereochemical parameters have unique values in a rigid dimeric systems, such as calycanthine,[8] but they have a range of values in the case of argemonine, owing to the conformational lability of the molecule. Models indicate that the extreme forms of

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[11] E. Clar, *Chem. Ber.* **69**, 607 (1936); *Polycyclic Hydrocarbons*. Springer, Berlin, Academic Press, London (1964).

[12] J. R. Platt, *J. Chem. Phys.* **17**, 484 (1949).

[13] J. R. Platt, *J. Chem. Phys.* **19**, 263 (1951).

TABLE 1. THE CD AND ABSORPTION SPECTRUM OF ARGEMONINE, AND THE THEORETICAL ROTATIONAL STRENGTHS R_A AND R_B (EQ. 1) AND FREQUENCY INTERVALS $\Delta\bar{\nu} = \bar{\nu}_A - \bar{\nu}_B$ (EQ. 2) FOR THE FOLDED (Ia) AND OPEN CONFORMATION (Ib) OF THE (1S:5S) CONFIGURATION. THE FREQUENCY $\bar{\nu}_{CD}$, MAXIMUM DIFFERENTIAL EXTINCTION COEFFICIENT $(\varepsilon_l - \varepsilon_r)$, AND THE ROTATIONAL STRENGTH R, OF THE CD IN ETHANOL ISOPENTANE-ETHER (2:5:5) at 80°K, AND THE FREQUENCY ν_{abs}, MAXIMUM EXTINCTION COEFFICIENT ε_{max}, AND THE DIPOLE STRENGTH D, OF THE ISOTROPIC ABSORPTION.

		Model (Ia)[a]		Model (Ib)[b]		Experimental					
Band	Component	R (10^{-40} cgs)	$\bar{\nu}_A - \bar{\nu}_B$ (cm^{-1})	R (10^{-40} cgs)	$\bar{\nu}_A - \bar{\nu}_B$ (cm^{-1})	$\bar{\nu}_{CD}$ (cm^{-1})	$(\varepsilon_l - \varepsilon_r)_{max}$ (M^{-1} cm^{-1})	R (10^{-40} cgs)	ν_{abs} (cm^{-1})	ε_{max} (M^{-1} cm^{-1})	D (10^{-36} cgs)
α	B	−19		−5·6		33,700	−1·3	−1·4	34,600	8200	6·0
			+370		+290						
	A	+19		+5·6		36,400	+5·1	+10			
p	A	−92		−178		42,800	−29	−46	44,200	14,000	11·6
			−420		−180						
	B	+92		+178		48,000	+ve	+ve			

[a] Calculated from $d = 4{\cdot}90$ Å, and cos v, cos t, and cos r values of +0·672, +0·174, and +0·720, respectively, for the α-band system; and −0·241, +0·966, and +0·089 respectively, for the p-band system.

[b] Calculated from $d = 5{\cdot}90$ Å, and cos v, cos t, and cos r values of +0·191, +0·174, and +0·966, respectively, for the α-band system; and −0·414, +0·906, and +0·089, respectively, for the p-band system.

argemonine are the folded (Ia) and open conformation (Ib), in which the two central rings have a twist and a half-boat stereochemistry, respectively. The folded conformation (Ia) is probably the more stable, as the angles of the two central rings are strained and two pairs of C—H bonds are eclipsed in the open conformation (Ib). A closely analogous conformational lability obtains in Tröger's base (II), and here the absorption spectrum shows[9, 14] that the folded conformation, in which there is the greater conjugation between the benzene ring and the lone-pair of the attached nitrogen atom, is the more stable of the two. The theoretical CD of Tröger's base is sensitive to the conformational form of the molecule, and the rotational strengths change sign on passing from the folded to the open structure.[9]

However, in the case of argemonine the qualitative form of the theoretical CD spectrum depends only upon the configuration and is independent of the conformation. For the particular absolute configuration (1S:5S) considered (I), the set of stereochemical parameters, *d*, *v*, *t*, and *r*, for each of the two conformations, measured from models of (Ia) and (Ib), indicates that the signs of the two CD bands associated with either the α- or the p-absorption band system should run, from longer to shorter wavelengths, negative and then positive (Table). For the enantiomeric (1R:5R) configuration the sequence of signs would be reversed. As the observed CD bands lie in the order negative and then positive to higher frequencies in the region of both the α- and the p-band system (Fig. 1, Table), it is concluded that argemonine has the (1S:5S) stereochemical configuration (I).

Quantitatively the two CD bands of opposite sign associated with a given absorption band system do not have equal areas (Fig. 1), and in general the experimental rotational strengths are smaller in magnitude than the corresponding theoretical value (Table). The calculated and the observed succession of rotational strengths shows that a given CD band is flanked on either side by dichroism bands of opposite sign, and where the bands overlap there is a mutual cancellation of band area. Accordingly the observed rotational strengths are appreciably smaller than the theoretical values if the frequency interval between the transitions with rotational strengths of opposed sign is less than twice the band width ($\sim 2500 \text{ cm}^{-1}$).

Additional factors responsible for the poor quantitative agreement between the observed and the calculated rotational strengths are the use of the point dipole approximation and the neglect of configurational interaction between transitions of the same symmetry. The dimensions of the veratrole chromophores are of the same order as the distance between them in argemonine, and the excitation moments do not approximate at all closely to point dipoles in relation to the distance *d* (Fig. 2). However, the qualitative stereochemical conclusions are not altered by taking the excitation moments to be dipoles with the length or the breadth of the veratrole chromophore.

The dipole moments of the transitions responsible for the α- and p-bands of veratrole are orthogonal (III) and they do not mix, but in argemonine the resultant transitions of the same symmetry deriving from different veratrole excitations interact, and rotational and dipole strength is redistributed between the different band systems to some extent. In particular the argemone transitions with A symmetry resulting from the α- and the p-excitations of veratrole are closer together in energy than the corresponding B transitions and they should mix to the greater degree. The

[14] B. M. Wepster, *Rec. Trav. Chim.* 72, 661 (1953).

isotropic absorption intensity of the p-band system of argemonine is twice that of the p-band of veratrole, as expected if configurational interaction is unimportant, but the corresponding ratio for the α-bands is 3·2, indicating that the resultant transitions of the α-band system of argemonine acquire additional dipole strength by mixing with the transitions of higher-energy band systems. In order to allow empirically for the anomalous ratio in the calculation of rotational strengths R (Eq. 1) and the frequency interval $\Delta\bar{\nu}$ (Eq. 2), the effective dipole strength ρ^2 of the veratrole chromophore was taken to be one-half of the observed dipole strength of the corresponding band system of argemonine, estimated from the isotropic absorption band area.

The areas of the CD bands of argemonine in a mixed ethanol-isopentane-ether solvent increase by ~30% on lowering the temperature from 295° to 80°K (Fig. 1). This observation suggests that the conformation with the larger rotational strength in the lower frequency region is the more stable, although changes in solvation or in the population of vibrational energy levels with temperature may contribute to the increase in band area. Solvation changes are probably not important as the CD and absorption spectra of argemonine in ethanol and in hexane at room temperature are virtually identical. However, a reduction in temperature decreases the population of excited vibrational levels occupied in the electronic ground state of the molecule, resulting in a reduction of the isotropic absorption and circular dichroism bandwidth. The overlap of adjacent circular dichroism bands with opposed signs is diminished by the decrease in band width, and in consequence the dichroism band areas are enhanced.

The observed increase in band area is too large to be ascribed solely to the vibronic effect, and it is probable that a shift in the equilibrium between the conformations (Ia) and (Ib), and possibly intermediate conformations, contributes to the increase. The folded form (Ia) is the more stable conformation not only from steric considerations but also from the CD evidence. The theoretical rotational strength of the open conformation (Ib) is smaller than that observed from the A component of the α-band system (Table), whereas a larger value is to be expected from considerations of dichroism band-overlap. For the α-band system the folded conformation (Ia) has the larger theoretical rotational strengths. These are compatible with the corresponding experimental values, which increase as the temperature is lowered, so that (Ia) is the more stable conformation and is predominant at room temperature.

In a recent communication[4] reporting the absolute configuration of (−)-argemonine from degradative studies, it is suggested, from an empirical comparison of the respective ORD curves, that the (+)-isomer of Tröger's base has the same configuration (1S,3S) as (−)-argemonine. This particular comparison illustrates the shortcomings inherent in the empirical comparison of Cotton-effect curves, for the non-empirical analysis of the CD spectrum of Tröger's base at 80°K shows[9] that the (+)-isomer has the (1R,3R) configuration (II). Although argemonine (I) and Tröger's base (II) are structurally similar dimeric systems, the transition dipoles of the respective monomer chromophores have different orientations. The transition moment of lowest frequency in aniline is directed in the molecular plane perpendicular to the two-fold symmetry axis of the chromophore,[9, 13] whereas the corresponding moment is orientated along the two-fold axis a of veratrole (III, R = Me). The resultant CD band due to the A coupling mode is positive and that due to the B mode is negative for the (1S,5S)-configuration of argemonine and the analogous (1S,3S)-configuration of Tröger's base. However, the A coupling mode has a lower absorption frequency than the B mode in Tröger's base, but it lies at a higher frequency in argemonine, so that the CD spectra of (1S,5S)-argemonine and of (1S,3S)-Tröger's base in the wavelength region of the lowest-energy absorption band are enantiomeric in form.

EXPERIMENTAL

A sample of (−)-argemonine was kindly provided by Professor T. O. Soine.[1]

Absorption spectra were measured with an Optica CF 4 grating spectrophotometer and CD with a Jouan Dichrograph. CD spectra were obtained in EtOH and hexane at room temp and in an EtOH isopentane-ether mixture (2:5:5) at 295°, 195°, and 80°K. The low-temp spectra were corrected for solvent contraction, and the 195°K spectrum was found to be intermediate in form between those recorded (Fig. 1). No other environmental effects were noted.

The experimental rotational R and dipole strengths D (Table 1) were obtained in c.g.s. units from the appropriate band areas through the expressions,[8]

$$R = 22{\cdot}9 \times 10^{\;40} \int [\varepsilon_l - \varepsilon_r)\, \bar{\nu}]\, d\bar{\nu}$$

and

$$D = \rho^2 = 91{\cdot}8 \times 10^{-40} \int (\varepsilon \bar{\nu})\, d\, \bar{\nu}$$

where the frequency $\bar{\nu}$ is in cm^{-1} and the decadic molar extinction coefficient ε is in M^{-1} cm^{-1}.

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