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INVESTIGATION OF THE DYNAMICS OF THE CONFORMATIONAL TRANSITIONS OF DIMERIC ISOQUINOLINE ALKALOIDS BY NMR SPECTROSCOPY AND MOLECULAR MECHANICS

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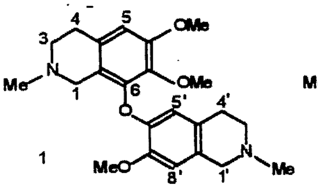
The conformational dynamics of the dimeric isoquinoline alkaloid turconidine has been investigated by the methods of NMR spectroscopy and molecular mechanics. The main conformational states and the trajectories of their mutual transitions have been established. A high lability of the molecule and the predominant state of the dimer in three of the eight possible conformations with respect to the ether bond have been shown.

Many important properties of alkaloids and other classes of natural compounds are exhibited in the liquid phase (in an aqueous medium) and here an important role may be played by the dynamic processes that are involved in establishing an equilibrium between different conformations of the compounds. Since these properties are frequently averaged, an investigation of the dynamics of the possible conformational transitions acquires great value for their explanation and for finding structure–property relationships.



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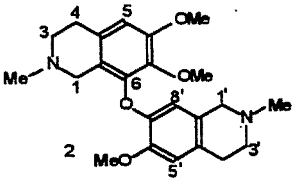

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In an investigation by NMR spectroscopic methods of the dimeric isoquinoline alkaloids turcberidine (**1**) and turconidine (**2**) [1, 2], which differ by the mutual positions of the ether oxygen bridge, the question arose of the possible orientations of the two halves of the ether with respect to one another in order to explain the upfield shift of the signal of the H-8′ proton of compound (**2**) by 0.3-0.4 ppm and H-5′ of compound (**1**) by 0.2-0.3 ppm relative to the signals of the same protons in N-substituted 6,7-dimethoxytetrahydroisoquinolines [3, 4]. Although the dihedral barriers to rotation at the ether oxygen atom are small, nevertheless the steric hindrance due to Van der Waals repulsion in such molecules may be considerable. In view of this, we have used the methods of NMR spectroscopy and calculations by molecular mechanics (MM) to make a detailed study of the possibilities of conformational transitions connected with rotation about the ether bonds of dimeric ethers of the isoquinoline alkaloids (**1**) and (**2**) and some of their model compounds.

Figure 1 shows the turconidine molecule in one of the hypothetical conformations — a "bent" structure. If the axes of rotation O—C8—C5 (axis of rotation α) and O—C7′—C4′ (axis of rotation β) pass through the ether bonds, the "bent" structure can be represented as having the values of the angles $\alpha = 90°$ and $\beta = 90°$. At the values $\alpha = 0°$ and $\beta = 0°$ ("planar" structure) the aromatic rings lie in a common plane with the two C—O bonds of the ether bridge. The oxygens of

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TABLE 1. Numerical Characteristics of Singular Points of the Potential Surface (energy of M5 taken as 0 kcal/mole)

Singular points	α°	β°	*E*, kcal/mole	Singular points	α°	β°	*E*, kcal/mole
P1*	15	15	33.91	T1*	80	95	6.18
P2	180	0	35.11	T2	175	95	10.92
P3	0	180	26.29	T3	85	−165	3.15
P4	180	180	30.52	T4	5	80	7.03
M1*	105	140	2.26	T5	100	−10	6.13
M2	65	55	0.40	T6	−75	155	3.56
M3	−70	120	0.65	T7	−95	80	7.66
M4	−115	45	4.46	T8	−100	15	6.00
M5	−100	−125	0.00	T9	−80	−95	1.95
M6	−50	−70	0.98	T10	−180	−85	8.95
M7	65	−120	1.04	T11	10	−90	5.04
M8	115	−50	3.65	T12	95	−85	5.76

***P*) maxima; *M*) maxima; *T*) transition points.

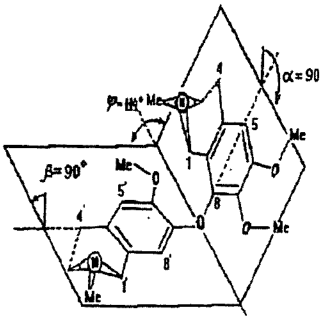

Fig. 1. Spatial structure of turconidine at $\alpha = 90°$ and $\beta = 90°$ ("bent" structure).

the methoxy groups in the C7 and C6′ positions must then experience very strong Van der Waals repulsion since they practically coincide with one another in a common plane.

If the energy of steric strain is calculated as a function of the angles of rotation α and β, this energy can be represented in the form of the potential surface of Fig. 2. This potential surface exhibits four maxima, eight minima, and twelve transitional saddle points of the energy of steric stress. The following topological details of the surface are characteristic: each vertex is surrounded by six minima and six saddle points; each minimum is located between three maxima and is adjacent through one saddle point to three other minima. The depth of the minima varies within a range of 4.5 kcal/mole, and the level of the transition points within a range of 9 kcal/mole. The maxima represent four variants of "planar" structures with stress energies of 26-35 kcal/mole. The "bent" conformation of Fig. 1 is also unstable and coincides with transition point T1, which has an energy 5.8 kcal/mole higher than the neighboring minimum M2. Other numerical characteristics of the potential surface are given in Table 1.

Of the molecules, 83% are present only at the three main minima with the most probable conformations: these are the minima M5, M2, and M3. Also informative is the representation of only the lower part of the potential surface, with $E < 6.5$ kcal/mole (Fig. 3). Within the "gully" formed in Fig. 3 are concentrated 99.999% of all the molecules. The free migration of the conformation of the dimer along the vertical "gully" at an angle $\alpha = 90°$ is obvious. This corresponds to the rotation of the lower part of the dimer about the β axis with a rotation barrier ≤ 7.2 kcal/mole.

The rotation of the upper half of the dimer about the α axis (movement in a horizontal direction in Fig. 3) is associated with far greater steric hindrance: the departure of the main conformational states from the "gully" is determined by a rotational barrier of 9.4-12.6 kcal/mole. Also possible is the synchronous rotation of both halves of the dimer: inclined trajectory in Fig. 3 with the condition $\alpha + \beta = 90°$ (rotation barrier 9.2-10.8 kcal/mole).

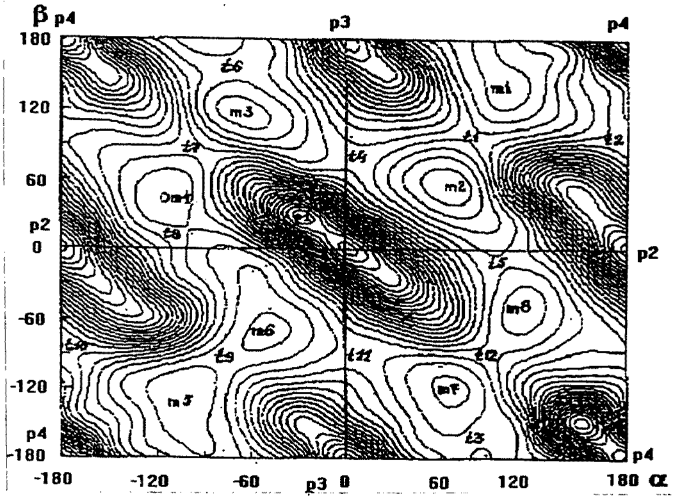

Fig. 2. Potential surface of a diisoquinoline ether as a function of the angles α and β: *P*) maxima; *M*) maxima; *T*) transition points.

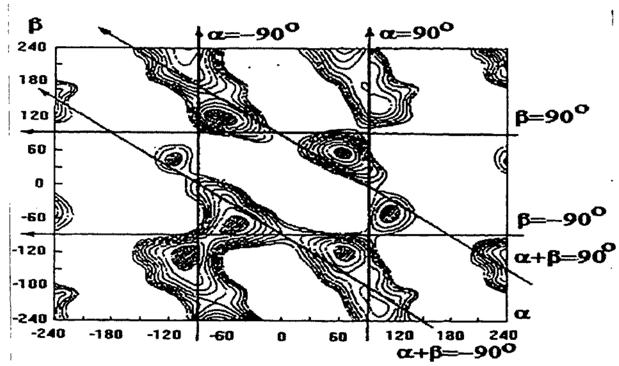

Fig. 3. Lower part of the potential surface and trajectories of rotational motion of a diisoquinoline ether: $\alpha = \pm 90°$ — rotation of the lower part of the dimer; $\beta = \pm 90°$ — rotation of the upper part of the dimer; $\alpha + \beta = \pm 90°$ — combined rotation of both halves of the dimer.

The sequence of single transitions from minimum to minimum is associated with energy barriers of from 0.9 to 9.0 kcal/mole. It is striking that in all eight conformations with minimum energies, M1-M8, the planes of the benzene rings *B* and *B'* are practically perpendicular to one another. The mechanism of the single conformational transitions in this representation can be regarded as a kind of flip-flop (jumplike) transition between states with an orthogonal arrangement of the aromatic systems.

Inversion of the unshared pairs of the nitrogen atoms in the saturated rings will lead to mirror inversion of the potential surface through vertical ($\alpha = 0$) and horizontal ($\beta = 0$) sections of the surface. This will lead to an additional channel of transition between minima; for example, an effective intermixing of the most favorable minima M5, M2, and M3 will be possible.

For the three main conformations (M5, M2, and M3) the absolute most favorable configurations of the (**2**) molecule have been found and the interatomic distances for the most important groups of protons have been calculated. The Overhauser effects to be expected for these conformations have been calculated from these interatomic distances. The numerical value of the NOE was evaluated for the case of the maximum line narrowing ($\omega^2\tau^2 << 1$, where ω is the resonance frequency and τ the correlation time of the molecule) as $\eta = k/r^6$ [5]. The difference in the correlation times of different parts of the molecule (for example, methyl groups) was ignored. Table 2 gives both the calculated and the experimentally measured values of the

TABLE 2. NOE Values Calculated and Found Experimentally

Group observed	Group irradiated	M2		M3		M5		Exp. NOE, %
		distance, r (Å)	calc., η%	distance, r (Å)	calc., η%	distance, r (Å)	calc., η%	
5−H	4−CH_2	2.75	14.0	2.75	14.0	2.69	14.0	10
5−H	6−OCH_3	2.81	28.5	2.79	29.1	2.80	28.4	18
N−CH_3	1−CH_2	3.05	3.5	3.04	3.5	3.04	3.5	2
1−CH_2	6′−OCH_3	4.70	1.3	4.68	0.4	4.75	0.7	<1
8′−H	1−CH_2	5.12	0.3	3.26	0.7	4.44	0.7	3
8′−H	7−OCH_3	3.42	12.5	4.36	2.2	–	–	–
8′−H	1′−CH_2	2.72	13.2	2.76	13.2	2.71	13.6	14
5′−H	6′−OCH_3	3.66	5.3	3.66	5.3	3.60	6.0	16
5′−H	4′−CH_2	2.74	12.8	2.74	12.8	2.75	12.3	16.
N′−CH_2	1′−CH_2	3.05	3.4	3.06	3.4	3.05	3.4	2
Correl. coeff. R_k		77.0%		77.2%		78.4%		–

TABLE 3. Calculated Increments of the Effects of Ring Currents for Three Conformations of Turconidine

Conformation	Dihedral angle, deg.		φ	ρ	z	$\Delta\sigma$*
	α 7−8−O−7′	β 8−O−7′−6′				
M2	60	53	22	3.6	0.1	−0.09
M3	−62	127	16	1.6	1.8	+0.23
M5	−102	−130	30	1.7	1.7	+0.20

* $\Delta\sigma > 0$) screening; $\Delta\sigma < 0$) descreening.

Overhauser effect. Their comparison shows that the averaged conformation contains a large proportion of the M5 structure (this conformation is energetically more favorable than the others).

In order to evaluate the influence of the orientation in space of the aromatic ring of the other part of the dimer on the chemical shift of the H-8′ proton we used the method of Haigh and Mallion [6]. For the three conformations M2, M3, and M5 we calculated the increments of the effects of ring currents and also values of φ (degrees), ρ, and z in units of 0.139 nm for the H-8′ proton in a cylindrical system of coordinates, and determined values of $\Delta\sigma$ from tables [6]. The results are given in Table 3.

From Table 3 it may be concluded that screening by the aromatic ring makes the main contribution to the upfield shift of the signal of the H-8′ proton of compound (**2**). According to calculation the signal should shift upfeld by 0.2 ppm, which agrees well with experiment (0.3 ppm). This may also explain the upfield shift of the signal of the H-5′ proton in compound (**1**) by 0.2-0.3 ppm.

EXPERIMENTAL

NMR spectra were recorded as in [1, 2] and calculations were made by Allinger's method of molecular mechanics in the applied program MMX [7, 8].

Thus, a high lability of compounds (**1**) and (**2**) has been shown both by means of NMR and by calculation methods. Low conformational barriers do not permit the recording of individual conformations of a dimer by the methods of NMR spectroscopy. Nevertheless, the calculation of steric energy has revealed some restrictions on the conformational state of the dimer and the most probable transformations that agree satisfactorily with NMR results.

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