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Molecular Mechanics Calculations of the Geometry and Racemization Energies of Sterically Hindered *N*-Aryl- and *N*-Heteroarylpyrroles

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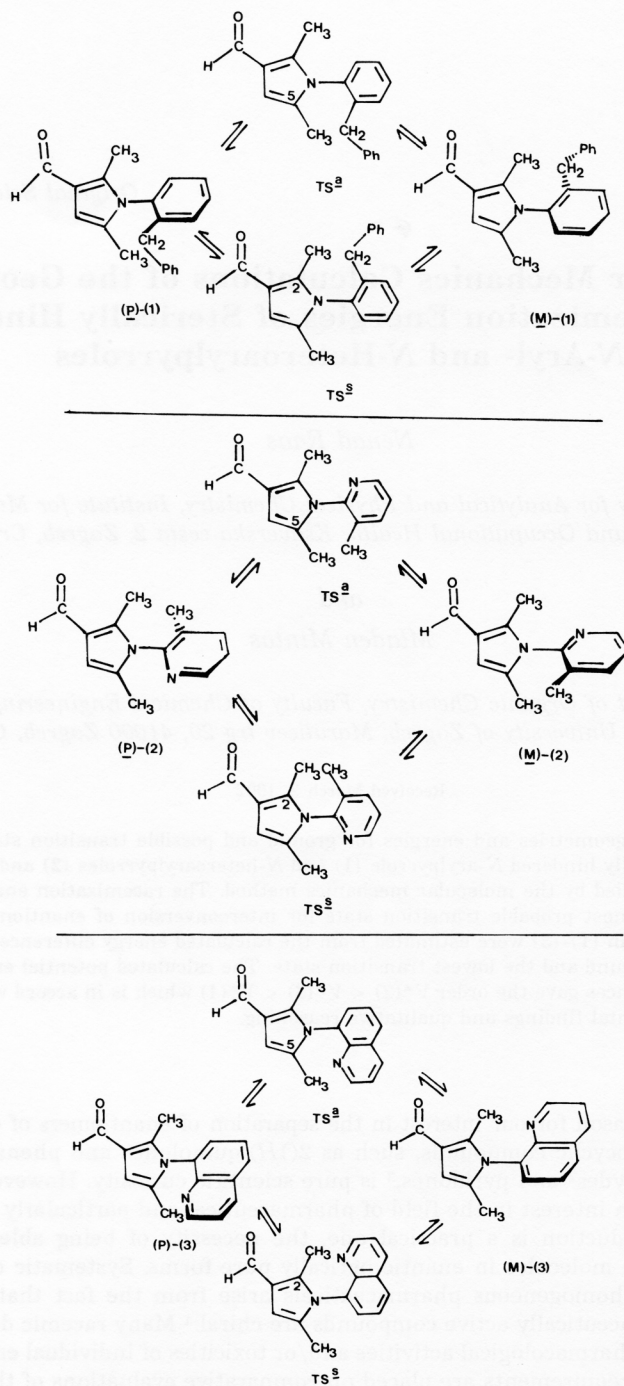
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The geometries and energies for ground and possible transition states of sterically hindered *N*-arylpyrrole (1) and *N*-heteroarylpyrroles (2) and (3) were studied by the molecular mechanics method. The racemization energy and the most probable transition state for interconversion of enantiomers (P) \rightleftharpoons (M) in (1)–(3) were estimated from the calculated energy difference between ground and the lowest transition state. The calculated potential energy differences gave the order $V^*(2) < V^*(3) < V^*(1)$ which is in accord with experimental findings and qualitative reasoning.

Part of the reason for our interest in the separation of enantiomers of chiral *N*-aryl substituted heterocyclic compounds, such as 2(1*H*)-quinolones and phenatridinones,¹ pyrrole carbaldehydes² and pyridones,³ is pure scientific curiosity. However, the main reason for such an interest in the field of pharmaceutical and particularly biochemical research and production is a practical one, the necessity of being able to produce biologically active molecules in enantiomerically pure forms. Systematic demands for enantiomerically homogeneous pharmaceuticals arise from the fact that more than half of all pharmaceutically active compounds are chiral.⁴ Many racemic drugs possess totally different pharmacological activities and/or toxicities of individual enantiomers.⁵ Therefore, strict requirements are placed on comparative evaluations of the activities, toxicities and pharmacokinetics of the separated enantiomers of racemic drugs.



Scheme 1

From versatile methods available for the preparation of enantiomerically pure compounds,⁶ liquid chromatography on triacetyl- or tribenzoylcellulose has proved to be efficient in separation of enantiomers of different, particularly lipophilic organic compounds, including substances of pharmaceutical interest.⁷ This class of compounds includes also pyrrole carbaldehydes which are found, according to patent literature,⁸ to be of »use in treating brain disorders.« This study is a continuation of our previous, molecular mechanics calculations of *N*-aryl-2(1*H*)-quinolone and *N*-aryl-4-pyridones.⁹ Also, we expect to explain our recent experimental results on the separation of enantiomers and measurements of barriers to racemization of *N*-aryl and *N*-heteroarylpyrroles.¹⁰ As the first step, we calculated the geometries and energies of the possible transition states (planar conformations) for the interconversion of enantiomers in *N*-(2-benzylphenyl)-2,5-dimethylpyrrole-3-carbaldehyde (**1**), *N*-(6-methyl-2-pyridyl)-2,5-dimethylpyrrole-3-carbaldehyde (**2**), and *N*-(8-quinolyl)-2,5-dimethylpyrrole-3-carbaldehyde (**3**) (see Scheme 1).

Due to restricted rotation about the C–N bond between the aryl and pyrrole rings, the ground state of compounds **1–3** is non-planar and, therefore, chiral. If the barrier to that process is sufficiently high, *i.e.* greater than *ca.* 100 kJ mol⁻¹ at room temperature,¹¹ then the separation of enantiomeric rotational isomers (M) and (P) should be possible.¹² Actually, in the case of compounds (MP)-(**1**) and (MP)-**3**, the separation of enantiomers was effected by liquid chromatography (LC) on optically active triacetylcellulose (TAC) as a chiral stationary phase.¹⁰ Hence, determination of the Gibbs free energy, ΔG^\ddagger , for partial rotation about the C–N bond in **3** and its lower limit in **1** was possible.¹⁰ On the contrary, (MP)-(**2**) showed no separation of enantiomers by LC on TAC and other chiral stationary phases, such as tribenzoylcellulose and silica coated with (+)-poly(tritylmethacrylate).¹⁰ ¹H NMR spectroscopy, in the presence of optically active auxiliaries, failed to give the rotational barrier in **2**. It has been stated that »the lone pair of pyridine nitrogen atom in **2** may be considered, in terms of steric requirements, as similar to the aromatic hydrogen atom in the *ortho*-position of the *N*-aryl group in **1**«. ¹⁰ The steric patterns of the C–N environment in **2** appears sufficient to give stable enantiomers and a barrier that »should be similar to the corresponding one obtained for **1**, *i.e.* greater than 128 kJ mol⁻¹«. ¹⁰ Therefore, the initial aim of the present study was to rationalize and express our experimental findings in a more quantitative way by using force-field calculations.

METHODS

Conformational potential was calculated from the basic formula:

$$\begin{aligned} \phi_T = & \frac{1}{2} \sum_i k_{d,i} (d_i - d_{o,i})^2 + \frac{1}{2} \sum_j k_{\theta,j} (\theta_j - \theta_{o,j})^2 + \\ & + \frac{1}{2} \sum_k \phi_k (1 \pm \cos n\gamma_k) + \sum_l (A_l \exp(-B_l r_l) - C_l r_l^6) \end{aligned} \quad (1)$$

where d , θ , γ and r stand for bond lengths, valence angles, torsional angles and non-bonded distance, respectively. K_d , d_o , k_θ , and θ_o are empirical parameters for bond stretching and angle bending, ϕ_k and n are torsional parameters (height and multi-

plicity of torsional barrier, respectively) and A , B and C are parameters for non-bonded Buckingham potential.

The geometry and energy of possible transition states were computed by minimizing the energy of strictly plane-symmetrical initial conformation with only the steepest-descent method. The procedure forbids,¹³ due to zero gradient vector in the direction perpendicular to the plane of symmetry, all asymmetrical change of molecular conformation. The minimization was performed until the gradient norm of potential energy dropped below $0.1 \text{ kJ mol}^{-1} \text{ \AA}$, making the results (according to our experience) reliable within $0.5\text{--}1 \text{ kJ}^{-1}$.

The force field FF1 is essentially Dashevsky's force field,¹⁴ which was modified to cope with the pyrrole ring (new parameters are presented in Table I). The field was checked on the crystal structure of *N*-(4-fluorophenyl)-2,5-dimethylpyrrole-3-carbaldehyde,¹⁵ yielding with reproduction of bond lengths $\pm 0.2 \text{ \AA}$, and angles within 2° . Force field FF2 has, in addition, parameters for electron lone pair placed on nitrogen, which were taken to be equal to parameters for sulphur lone pair.¹⁶ All computations were done using Rasmussen's program for molecular mechanics.¹⁷

TABLE I
*Parameters for molecular-mechanics calculations**

Bond	Bonding potential	
	$k_d / \text{kcal mol}^{-1} \text{ \AA}^{-2}$	$d_0 / \text{\AA}$
K-K	757.6	1.387
K-H	654.9	1.046
K-C	779.2	1.500
K-N (in pyrrole ring)	757.6	1.387
(ring-ring)	757.6	1.430
N-X (FF2)	600.0	0.679
Angle	Angle-bending potential	
	$k_\theta / \text{kcal mol}^{-1} \text{ rad}^{-2}$	θ_0 / rad
K-K-K (in ring)	89.4	1.883
(out of ring)	89.4	2.200
K-K-N	89.4	1.883
K-N-K	89.4	1.883
K-K-H	41.1	2.200
K-K-O	70.0	2.094
K-N-X (FF2)	600.	2.094

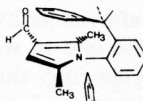
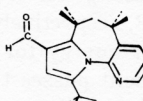
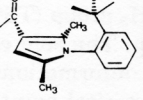
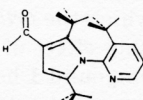
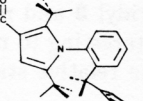
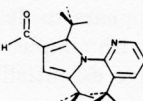
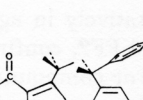
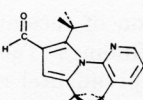
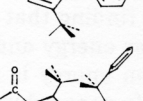
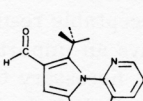
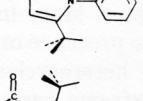
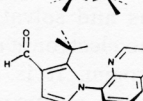
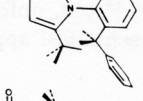
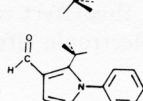
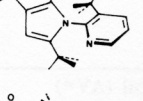
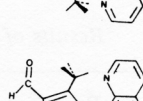
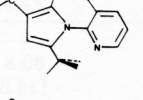
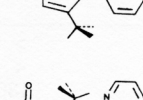
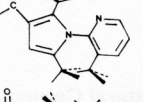
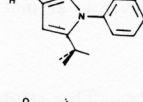
* K denotes sp^2 carbon atom, X is a lone pair situated on nitrogen atom (having the same non-bonded parameters as hydrogen). Only the parameters for pyrrole ring were presented here. Other parameters were the same as used previously [9.14]

RESULTS AND DISCUSSION

It is probable that most of the influence on the Gibbs energy of activation, ΔG^\ddagger , for interconversion of enantiomers (P) \rightleftharpoons (M) arises from interactions in the transition states. Therefore, ΔG^\ddagger values refer, in the first approximation, to partial rotation about the C-N bond *via* the energetically more favourable transition state. There are two possible general transition states for this rotation: the bulky *ortho*-aryl substituent

TABLE II

Calculated conformational energies, V, for ground and possible transition states

Compound	V / kJ mol ⁻¹		Compound	V / kJ mol ⁻¹	
	FF1	FF2		FF1	FF2
(1a) 	-12.2	-	(2e) 	101.1	128.4
(1b) 	-13.6	-	(2f) 	72.8	95.5
(1c) 	124.5	-	(2g) 	69.0	92.4
(1d) 	125.8	-	(2h) 	54.3	76.3
(1e) 	142.2	-	(2i) 	95.6	123.2
(1f) 	138.9	-	(3a) 	2.6	0.5
(2a) 	-11.8	-13.6	(3b) 	87.0	114.9
(2b) 	91.6	116.5	(3c) 	94.6	123.2
(2c) 	71.7	96.4	(3d) 	110.2	139.8
(2d) 	64.0	84.0	(3e) 	107.6	135.5

passing either the C(5)-CH₃, *i.e.* transition state *anti* (TS^a, see Scheme 1) or the C(2)-CH₃ group of the pyrrole ring, *i.e.* transition state *syn* (TS^s, see Scheme 1). It is apparent from Table II that CHO-substituted side of the pyrrole ring is energetically less favourable in comparison with the unsubstituted side by 3–8 kJ mol⁻¹ (*e.g.* **1e** and **1f**, **2f** and **2g**, **2e** and **2i**, **3b** and **3c**). From the energy data it can be proposed that the most probable geometry for transition state is **1c** (or possibly **1d**, **2h** and **3b** for molecules **1**, **2** and **3**, respectively). It follows (Table II) that the preferred pathway, corresponding to lower energy for all three compounds (**1–3**), is the one in which the bulky *ortho*-substituent passes the C(5)-CH₃ position of the pyrrole ring, that is TS^a (see Scheme 1). This may be explained by more severe steric interactions in the other transition state in which the *ortho*-substituent passes the C(2)-CH₃ group (TS^s), which is due to a buttressing effect of the adjacent carbaldehyde group. The sole exception could possibly be compound **1** because of very close energies for conformations **1c** and **1d**, where both pathways should be equally probable. From the sterical point of view, sterical influence appears to decrease in the order benzyl **1**, pyridyl **3** and methyl **2**, which is in accord with simple stereochemical reasoning. It is interesting to note that both force fields gave essentially the same result concerning the relative stability of the conformers.

The reproduction of racemization energies is at least qualitatively in agreement with experimental findings (Table III). Both force fields, FF1 and FF2, confirmed the semiquantitative experimental results for compounds **1** and **2**. For compound **3**, FF1 yielded a *ca.* 30% lower value than the measured racemization energy, but FF2 produced a quite acceptable result. This fact supports our earlier finding that the lone pair of nitrogen plays an important role in determining molecular energy and conformation.¹⁰ Also, it is necessary to keep in mind that racemization energy is not only influenced by steric factors (expressed as calculated ΔV^* in this paper) but also by molecular vibrations and solvation in ground and transition states. More important factors should be the electronic effects due to the position and the presence or absence of heterocyclic nitrogen. It is known that π -electron-deficient heterocycles exhibit higher barriers than π -electron-rich heterocycles.¹⁸ In some extreme cases (for *N*-arylazolinethiones), this effect can contribute even to 35 kJ mol⁻¹,¹⁹ but, unfortunately, calculations of electronic effects lies outside the molecular mechanical approach.

TABLE III
Results of molecular-mechanics calculations*

Compound	Experimental (ΔG^*)	Theoretical (ΔV^*)	
		FF1	FF2
(1)	> 128	138.1	–
(2)	< 100	66.1	89.8
(3)	130±2	84.4	114.5

* Energy values were given in kJ mol⁻¹

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SAŽETAK

Molekulsko-mehanički proračuni geometrije i racemizacijskih energija sterički ometanih *N*-aril- i *N*-heteroarilpirola

Nenad Raos i Mladen Mintas

Geometrije i energije osnovnih i mogućih prijelaznih stanja sterički ometanih *N*-arilpirola (1) i *N*-heteroarilpirola (2) i (3) istraživane su metodom molekulske mehanike. Racemizacijske energije i najvjerojatnija prijelazna stanja za interkonverziju enantiomera (P) \rightleftharpoons (M) spojeva (1)–(3) određeni su iz izračunanih razlika u energijama osnovnih i najnižih prijelaznih stanja. Računske razlike u potencijalnim energijama slijede niz $V^*(2) < V^*(3) < V^*(1)$ koji je u skladu s eksperimentalnim rezultatima i kvalitativnim razmatranjem.