

MOLECULAR-MECHANICS CALCULATIONS OF THE GEOMETRY AND RACEMIZATION ENERGIES OF AN N-ARYL-2(1H)-QUINOLONE AND N-ARYL-4-PYRIDONES

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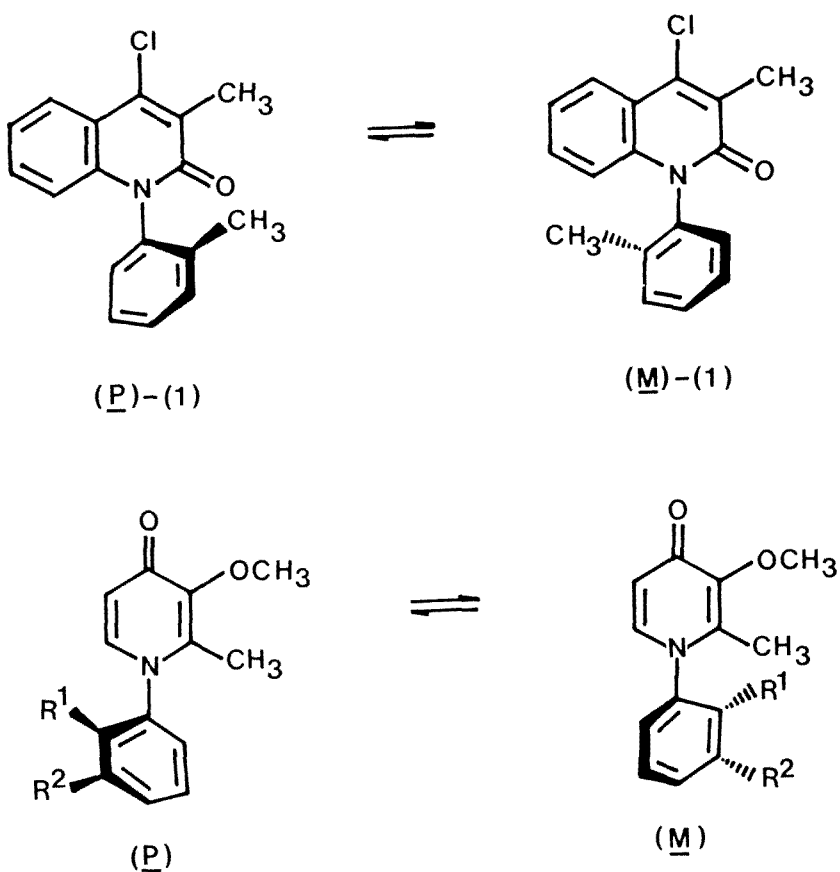
Abstract

The geometries and energies for ground and possible transition states of the quinolone (1) and pyridones (2)–(4) were calculated by the molecular-mechanics method. The calculated energy differences between ground and the lowest transition state are in good correlation ($r = 0.994$) with the corresponding experimental racemization energies for interconversion of enantiomers (P) \rightleftharpoons (M) in (1)–(4). However, the calculated potential energy differences do not correspond to measured differences in Gibbs energies. The fact was tentatively attributed to neglect of the entropy contribution to Gibbs energies.

The preparation of enantiomers is of increasing interest in the field of chemical, pharmaceutical and, particularly, biochemical research and production [1]. Part of the reason for such an interest undoubtedly lies in pure scientific curiosity [2]. However, the main reason for that interest is an applied one: the necessity of being able to produce physiologically active compounds in enantiomerically pure forms. Two operationally different methods can be distinguished for that purpose: enantioselective (or: asymmetric) synthesis [3,4] and physical separation of racemic mixtures. It has been shown that liquid chromatography on triacetylcellulose ("chiral column") is a versatile method which has been successfully applied to the separation of enantiomers of different classes of organic compounds [1], including compounds of pharmaceutical interest, e.g. anaesthetic ketamine [1] and methaqualone [5], an anticonvulsive and hypnotic agent.

The present study has its precedent in our previous studies on the separation of enantiomers and barriers to the racemization of atropisomeric N-aryl-2(1H)-quinolones

and N-aryl-6(5H)-phenanthridinones [6], N-arylpyrroles [7] and N-aryl-4-pyridones [8]. Our recent results on the Gibbs energy of activation ΔG^\ddagger for the restricted rotation around the C-N bond in quinolone (1) [6] (see scheme 1) led to the suggestion



	R ¹	R ²
(2)	Cl	H
(3)	CH ₃	H
(4)	Benzo	

Scheme 1.

that the preferred pathway for interconversion of enantiomers (P) \rightleftharpoons (M) is "one in which the bulky ortho-substituent passes the carbonyl rather than the benzo ring" [6] (cf. scheme 1). In the present paper, we tried to express our experimental findings in a more quantitative way; therefore we calculated, using the molecular-mechanics

Table 1
Parameters for molecular-mechanics calculations^a

Bond	Bonding potential		
	k_0 [kcal mol ⁻¹ Å ⁻²]	b_0	
C-C	399.0	1.50	
C-H	590.3	1.04	
C-O	399.0	1.41	
K-K	757.6	1.365	
K-C	779.2	1.50	
K-H	654.9	1.046	
K-O	339.0	1.41	
K-Q	1745.0	1.196	
K-X	654.9	1.72	
K-N (in ring)	757.6	1.365	
K-N (ring-ring)	757.6	1.45	
Angle	Angle-bending and out-of-plane deformation potential		
	k_θ, k_χ [kcal mol ⁻¹ rad ⁻²]	θ_0 [rad]	
H-C-Y	44.9	1.911	
C-C-Y, C-O-K, K-C-K	50.0	1.911	
K-K-K, K-K-N, K-N-K	89.4	2.094	
K-K-O(Q), N-K-O(Q)	70.0	2.094	
K(N)-K-H(C, X)	41.1	2.094	
(all angles)	50.0		
Angle	Torsion potential		
	V_n [kcal mol ⁻¹ rad ⁻²]	n	
Y-C-C(O)-Y	0.33	3	
K-K(N)-K-Y	6.66	-2	
Y-K-K-Y	3.36	-2	
K-K-K-Q	1.12	-2	
Distance	Non-bonding (Buckingham) potential		
	$A \times 10^{-4}$ [kcal mol ⁻¹]	B [Å ⁻¹]	C [kcal mol ⁻¹]
H—H	2.86	5.2	40.1
H—C	3.28	4.13	155.0
C—C(K, N)	3.77	3.513	476.0
K—K(N) (FF1)	3.77	3.513	476.0
(FF2)	4.14	3.094	1120.0
O(Q)—C(A, K)	6.37	3.881	441.0
Q(O)—H	5.75	4.727	122.0
H—K(N)	3.28	4.13	155.0

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Table 1 (continued)

Distance	Non-bonding (Buckingham) potential		
	$A \times 10^{-4}$ [kcal mol ⁻¹]	B [Å ⁻¹]	C [kcal mol ⁻¹]
X—O(Q)	3.79	4.13	181.4
X—C(K)	3.79	3.56	439.1
X—H	3.79	4.41	122.4
X—N	3.79	4.06	199.41

^aUnusual symbols: K, sp² carbon atom; Q, carbonyl oxygen atom; X, halogen atom (chlorine); Y, any atom.

Conformational potential:

$$V = \frac{1}{2} \sum_i k_{b,i} (b_i - b_{0,i})^2 + \frac{1}{2} \sum_j k_{\theta,j} (\theta_j - \theta_{0,j})^2 + \frac{1}{2} \sum_k V_n (1 \pm \cos n\phi_k) \\ + \sum_l (A_l \exp(-B_l r_l) - C_l r_l^{-6}) + \frac{1}{2} \sum_m k_{\chi,m} \chi_m^2,$$

where b , θ , ϕ , and χ denote the bond lengths, valence, torsional and out-of-plane angles, respectively; r is non-bonded distance [9]. Parameters are based on modified Dashevsky force field [10]; differences are mostly the parameters for out-of-plane deformation potential and for K–N bond. The FF2 was previously derived from FF1 by adjusting the parameters for K–K non-bonding potential to obtain agreement with experimental difference between gauche and trans conformers of 1, 2-diphenylethanes [10]. The geometry and energy of possible transition states were computed by minimizing the energy of strictly plane-symmetrical initial conformations only with the steepest-descent method. The procedure [11] forbids, due to zero gradient vector in the direction perpendicular to the plane of symmetry, any asymmetrical change of molecular conformation. The minimization was performed until the gradient norm of the potential energy dropped below 1 kJ mol⁻¹ Å⁻¹, making the results reliable within 1 kJ mol⁻¹. To obtain the geometry of possible transition states which lack the plane of symmetry (cf. (3c), table 3), the procedure was followed by rotation around the K–OCH₄ bond until the lowest value of strain energy was obtained.

method, the geometries and energies of the possible transition states (planar conformations) for the interconversion of enantiomers in quinolone (1) and pyridones (2)–(4) (cf. scheme 1).

Setting the most critical parameter $b_{0,N-C}$ to 1.45 Å (table 1), a fair reproduction of X-ray bond distances [13,14] between two aromatic rings was obtained. The N–C distance in compound (2) was reproduced (with FF1, table 1) nearly within the experimental error; in the other compounds, it was reproduced within 0.1 Å (table 2). The torsional angles were not so well reproduced. The differences

Table 2
Results of molecular-mechanics calculations*

N-(2-methylphenyl)-4-chloro-3-methyl-2(1H)-quinolone (1) [6, 12]			
Property	Experimental	Theoretical	
		FF1	FF2
V [kJ mol ⁻¹]	–	24.554	202.166
N–C [Å]	1.445	1.460	1.476
K–N–K–K [°]	83.3	91.2	90.5
V^* [kJ mol ⁻¹]		158.3	156.4
ΔG^* [kJ mol ⁻¹]	127.5(7)		
N-(2-chlorophenyl)-3-methoxy-2-methyl-4-pyridone (2) [8, 13]			
Property	Experimental	Theoretical	
		FF1	FF2
V [kJ mol ⁻¹]	–	11.415	126.584
N–C [Å]	1.451	1.455	1.467
K–N–K–K [°]	– 89.4	– 92.8	– 90.4
C–O–K–K [°]	– 104.8	– 91.1	– 92.7
V^* [kJ mol ⁻¹]		73.8	78.0
ΔG^* [kJ mol ⁻¹]	109.6(2)		
N-(2-methylphenyl)-3-methoxy-2-methyl-4-pyridone (3) [8]			
Property	Experimental	Theoretical	
		FF1	FF2
V [kJ mol ⁻¹]	–	8.709(3a)	123.850(3a)
	–	9.556(3b)	124.243(3b)
N–C [Å]	–	1.457	1.468
K–N–K–K [°]	–	– 78.7(3a)	– 85.6(3a)
	–	– 91.2(3b)	– 89.5(3b)
C–O–K–K [°]	–	86.1(3a)	90.2(3a)
	–	– 91.7(3b)	– 93.1(3b)
V^* [kJ mol ⁻¹]	–	90.6	92.6
ΔG^* [kJ mol ⁻¹]	111.2(2)		

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Table 2 (continued)

N-(1-naphthyl)-3-methoxy-2-methyl-4-pyridone (4) [13, 14]			
Property	Experimental	Theoretical	
		FF1	FF2
V [kJ mol ⁻¹]	–	23.781	201.090
N–C [Å]	1.446	1.458	1.474
K–N–K–K [°]	–94.9	–88.8	–88.3
C–O–K–K [°]	–102.9	–92.1	–92.8
V [‡] [kJ mol ⁻¹]	–	126.9	126.4
ΔG [‡] [kJ mol ⁻¹]	121.0(4)		

^aV represents conformational potential of ground state, and V[‡] energy difference between the conformers corresponding to ground and transition state (cf. table 3); transition state was taken to be equal to the lowest planar conformation. Standard deviations of measured ΔG[‡] are given in parentheses.

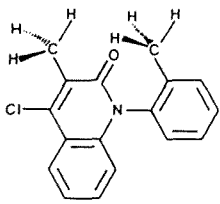
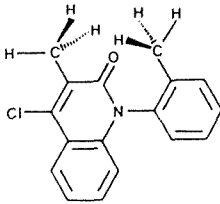
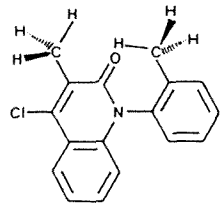
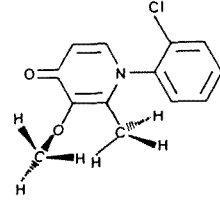
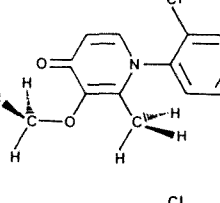
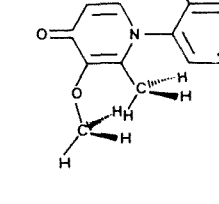
in the interangular torsion angle (K–N–K–K, table 2) vary from 1.0° (compound (2), FF2) to 7.9° (compound (1), FF1). The torsion angle C–O–K–K had a value up to 13.7° (compound (2), FF1) different from its experimental value. Close values obtained with different force fields (i.e. FF1 and FF2) suggest that the reason for such a disagreement can also be the packing interactions in the crystal lattice.

Contrary to a limited number of ground-state conformations (one for each compound, except compound (4)), it is possible to propose many conformations for a transition state (table 3). Altogether, we minimized two plane-symmetrical conformations of compounds (2) and (3), and three conformations of compounds (4) and (1). It is also possible to propose the same number of plane-symmetrical conformations of these compounds with interangular torsion angles differing by 180° from the presented ones, but their conformational energies were so high that they prevented any minimization.

The estimates of potential (conformational) energy difference ($V^{\ddagger} \approx \Delta H_{\text{calc}}^{\ddagger}$, cf. table 2) between the ground and transition states roughly agree with the measured ΔG[‡]. In one case (compound (4)), the agreement between experiment and theory is excellent (difference: 5.4 kJ mol⁻¹); the worst result was obtained with compound (2) (difference: 31.6 kJ mol⁻¹). In spite of the reproduction which cannot strictly satisfy quantitative criteria, it has to be noted that the increasing order of V[‡] for compounds (2), (3), (4), (1) follows the order of measured Gibbs energies of activation. Moreover, ΔG[‡] and V[‡] are highly correlated ($r = 0.994$ for FF1 and 0.995 for FF2), but the slope of the line V[‡] versus ΔG[‡] (4.51 for FF1, 4.14 for FF2) is higher than the "ideal" value (1.0). Obviously, this discrepancy between theoretical and experimental values should be attributed to the neglect of the TΔS term (e.g. the vibration contribution to Gibbs energy of activation) and to the possible imperfections of the

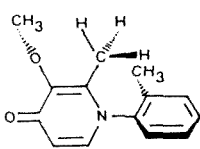
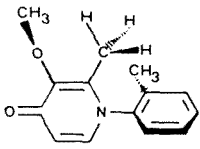
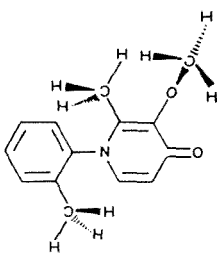
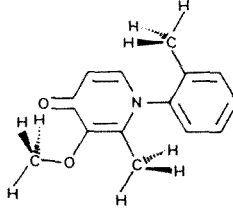
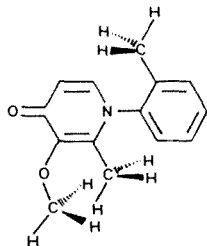
Table 3

Calculated conformational energies V for ground and possible transition states

Compound	V [kJ mol ⁻¹]		
	FF1	FF2	
(1a)		182.8	358.5
(1b)		183.3	358.9
(1c)		207.9	383.6
(2a)		85.2	204.5
(2b)		91.8	211.0
(2c)		124.1	242.4

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Table 3 (continued)

Compound	V [kJ mol ⁻¹]		
	FF1	FF2	
(3a)		8.7	123.9
(3b)		9.6	124.2
(3c)		99.3	216.5
(3d)		106.1	223.1
(3e)		139.7	255.7

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Table 3 (continued)

Compound	V [kJ mol ⁻¹]	
	FF1	FF2
(4a)	150.7	327.5
(4b)	158.2	333.9
(4c)	178.5	345.5
(4d)	194.1	369.2

force fields used. The quest for a more relativistic estimation of the activation energy for racemization reaction therefore calls for further studies.

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