ISOLABLE ATROPISOMERS OF 2-ARYL SUBSTITUTED INDOLINE DERIVATIVES. MO ANALYSIS OF RESTRICTED ROTATION

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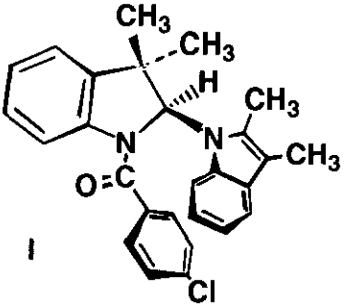
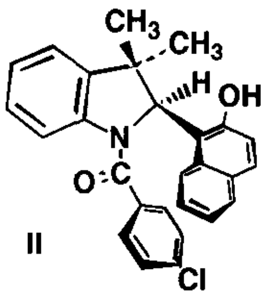
Abstract - The ground- and transition-state structures for restricted rotation of isolable atropisomers of 1-(4'-chlorobenzoyl)-2-(2"-hydroxynaphtyl)-3,3-dimethylindoline are calculated by AM1 method. The X-ray structural features of the atropisomers are approximately reproduced. Inspection of the transition-state structures indicates the presence of close nonbonded H/H contacts between the methyl hydrogens and the aromatic hydrogens. Based on the calculation data, the mechanism of the restricted rotation is discussed.

Isolation and structure elucidatiion of atropisomers have attracted much attention of organic chemists.[1] In particular, some drugs having conformational isomers due to hindered rotation have been explored from pharmacological view point.[2] Previously, we successfully isolated pairs of atropisomers of indoline type (I and II) arising from restricted rotation about Csp^3-Nsp^2 bond[3a] or Csp^3-Csp^2 bond[3b,c] and the conformations of both atropisomers were determined by single crystal X-ray analyses.



I

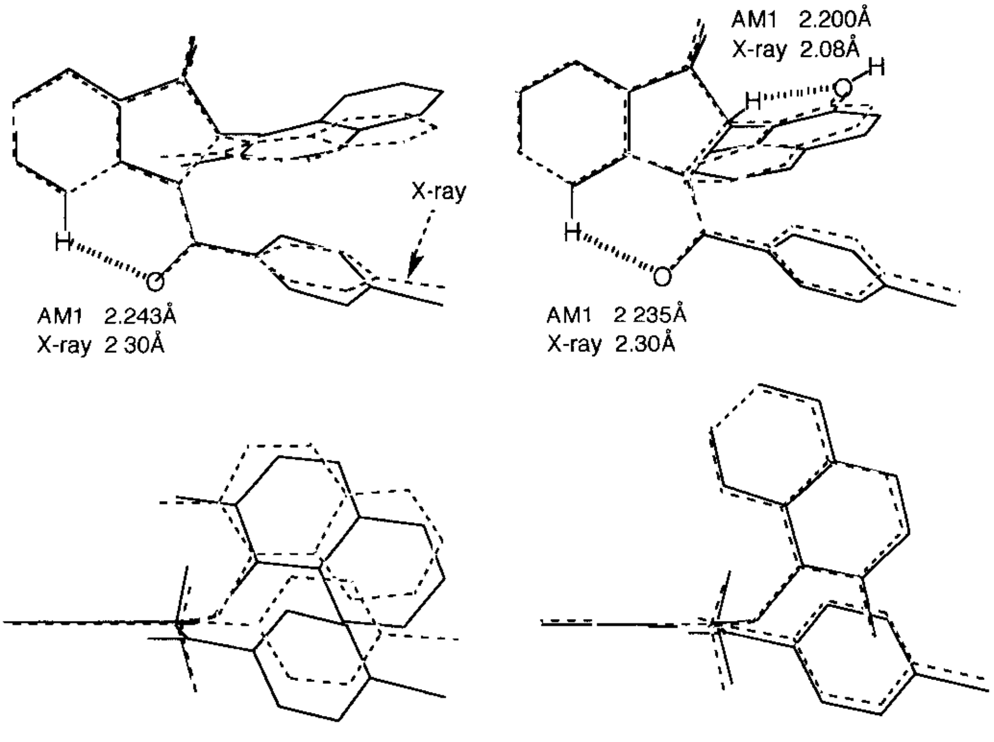


II

In this paper, we wish to report the MO simulation for atropisomerism of 1-(4'-chlorobenzoyl)-2-(2"-hydroxynaphtyl)-3,3-dimethylindoline (II).

First, we carried out AM1 calculations[4] on the diastereomeric atropisomers (IIa and IIb) of II using the crystal coordinates. The fully optimized ground-state structures (GSa and GSb) of IIa and IIb are depicted in Figure 1, in which the indoline moieties are graphically superimposed with those of the X-ray structures. The heat of formation

(Δ*Hf*) of GSb is about 1.88 kcal/mol smaller than that of GSa,[5] in accordance with the observed relative stability that the equilibrium experiment gave a 60:40 mixture of IIb and IIa.[3c] As can be seen in Figure 1, the X-ray structures are approximately reproduced. The amide nitrogens (N1) have sp^2 character [6] (see Figure 3 for atom numbering). The sums of the bond angles at N1 of GSa and GSb are 359.1° and 358.2°, respectively.



IIa

IIb

Figure 1. X-Ray and AM1-calculated structures of IIa and IIb

In each case, the oxygen atom of the amide group forms hydrogen bond with the 7-position of the indoline moiety (-H••••O=: *ca.* 2.24Å). The C2-H proton also forms hydrogen bond with the oxygen atom of the OH group of the naphthalene ring. These observations are in accordance with the X-ray structural feature.

In the course of structure optimization with one complete rotation about the C2-C36 bond, there are two maximum points of potential energy near the dihedral angle (N1-C2-C36-C37) of 30° and 210°. The crude transition states were obtained from the maximum-point structures and refined by TS routine[4] to give the two transition structures (TS1 and TS2). The Δ*Hf*'s of TS1 and TS2 are 71.89 and 61.83 kcal/mol, respectively. The Δ*Hf* of TS1 is *ca.* 10 kcal/mol higher than that of TS2. The energy profile is depicted in Figure 2.

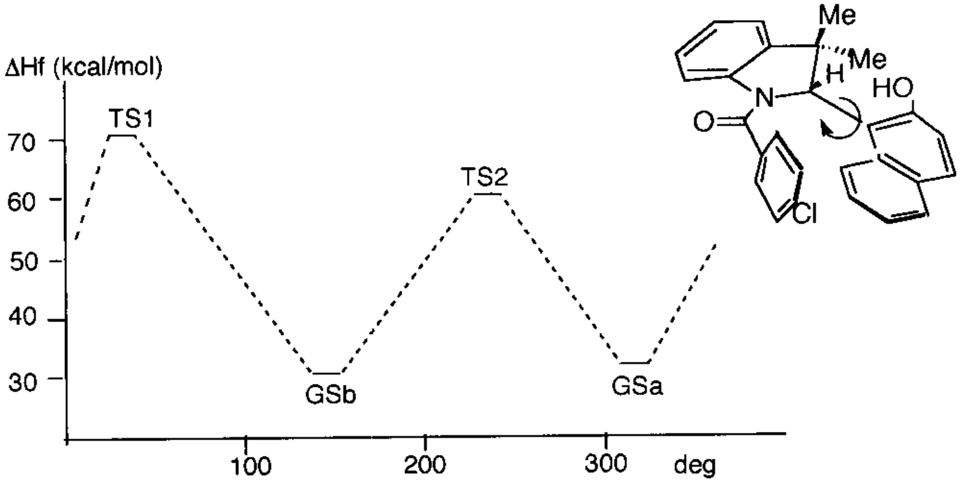
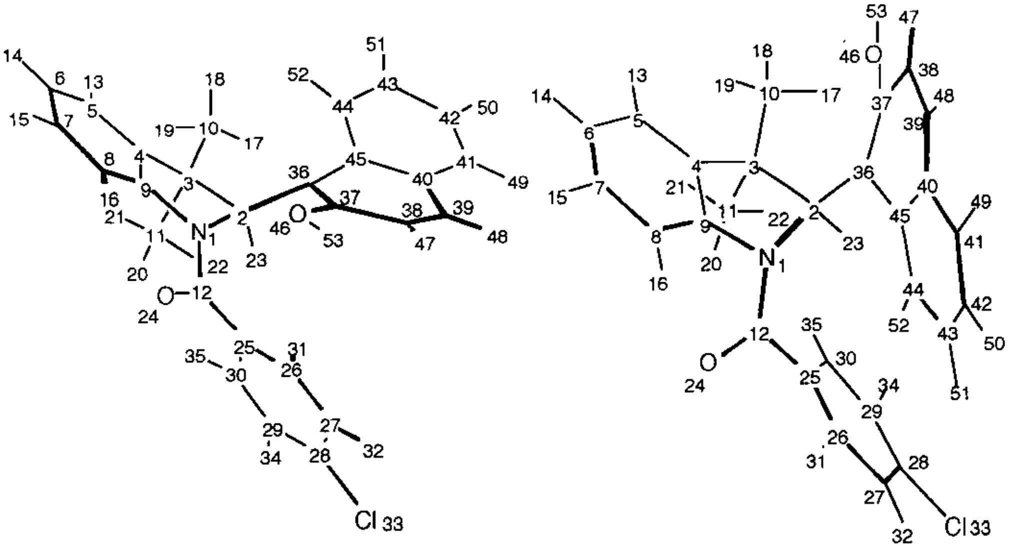


Figure 2. Potential energy diagram for II

The transition structures are depicted in Figure 3. The dihedral angles of the N1-C2-C36-C37 for TS1 and TS2 are 27.2° and 227.7°, respectively. In TS2, there are serious repulsive van der Waals (VDW) interactions between atoms. The distance of the methyl hydrogens (H17, H18) and the oxygen atom (O46) of the hydroxy group on the naphtyl group is 2.13-2.16Å. The VDW energy calculation[7] of these interactions showed 2.12-2.34 kcal/mol destabilization, which may be partially canceled by the hydrogen-bonding stabilization.[1b]



TS1 TS2

Figure 3. AM1-Calculated transition structures (TS1 and TS2)

The interaction between the C25 atom of the 4-chlorobenzoyl moiety and the hydrogen atom (H52) on the naphtyl ring is also repulsive (2.273Å). The calculation indicates the presence of serious H/H short contacts. The shortest distance is *ca.* 2.067Å which is found between the methyl hydrogen (H20) and the ortho hydrogen atom (H35) of the 4-chlorobenzoyl moiety. This VDW repulsive enegy runs to about 1.0 kcal/mol. Inspection of TS1 also indicates the presence of H/H short contacts. The shortest distance is *ca.* 1.80Å between the methyl hydrogen atom (H18) and the hydrogen atom (H52) on the naphthyl group (3.57 kcal/mol destabilization). The VDW interaction between H17 and H52 is also repulsive (*ca.* 0.8 kcal/mol). The important VDW interactions are listed in Table.

Table Van der Waals Interaction Energy (kcal/mol)[a] in TS1 and TS2

TS1				TS2			
atom	pair	r(Å)	energy	atom	pair	r(Å)	energy
C10	C44	2.848	0.61	C10	O46	2.478	1.68
C10	H52	2.325	1.15				
C12	O46	2.674	0.83[b]				
H16	O24	2.334	0.92[b]				
H17	H52	2.203	0.81	H17	O46	2.155	2.12[b]
H18	H52	1.798	3.57	H18	O46	2.131	2.34[b]
H20	H35	2.131	0.53	H20	H35	2.067	1.01
				H22	H35	2.143	0.59
H23	C30	2.467	0.71	H23	C30	2.493	0.62
				H23	H35	2.136	0.73
				C25	H52	2.273	1.64

a) The energies greater than 0.5 kcal/mol are listed.
b) The coulombic interactions calculated by ENPART option showed -0.1~-0.4 eV stabilization.

The AM1-calculated TS structures (TS1 and TS2) are strained considerably. The planarity of the naphthalene ring is significantly distorted as shown in Figure 3: the dihedral angles of C37-C36-C45-C40 for TS1 and TS2 are 26.0 and 39.5°, respectively. The five-membered rings are strongly puckered in comparison with the ground-state structures: the C9-C4-C3-C2 dihedral angles of TS1 and TS2 are 19.3 and 22.6°, respectively. The N1-C2, C2-C3 and C2-C36 bonds suffered significant elongation in light of the overcrowding. The C2-C3 bond lengths exceed 1.6Å. Even in such the strained structures, the amide carbonyls (O24) still make hydrogen bond with the indoline hydrogen (H16) at the 7 position: the O24-H16 distance is 2.334Å for TS1 and 2.526Å for TS2. In the TS2, the amide nitrogen has a moderate sp^3 character showing that the sum of the bond angles at N1 is 348.3°.

The AM1-calculated activation energy (ΔE) for the GSa to GSb conversion is 28.7 kcal/mol [ΔE=ΔHf(TS2)-ΔHf(GSa)], approximately reproducing the observed value (ΔE =26.0 kcal/mol).[8]

In summary, analysis of the TS structures indicates that the restricted rotation is mainly brought about by the steric interactions between the C3-methyl hydrogens and aromatic ring protons. Development of engineering work station (EWS) allows us to carry out the SCF-MO simulation on time-consuming molecules like the present case. The semiempirical AM1 method seems to be a useful tool for estimation of rotational barrier and analysis of restricted rotation in the molecules which are hard to be subjected to molecular mechanics (MM) calculations.

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5. The MNDO-PM3 calculation did not reproduce the relative stability: GSa is 1.2 kcal/mol more stable than GSb.
6. The MNDO and PM3 calculations gave significant sp^3 character. These methods seem to underestimate the rotation barrior of >N-CO bonds.
7. The VDW energy calculation was performed using the formula adopted in the MM2 program.
8. The rate constants are followed by hplc. The activation energies are as follows: the 1-(4'-chlorobenzoyl)-3,3-dimethyl derivative, ΔE =26.0 kcal/mol; 1-(4'-nitrobenzoyl)-3,3-dimethyl derivative, ΔE =26.1 kcal/mol; 1-acetyl-3,3-dimethyl derivative, ΔE =24.3 kcal/mol; spiro[cyclohexane-3,1'-1-(4'-chlorobenzoyl)indoline] derivative, ΔE =28.3 kcal/mol.

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