X-RAY STRUCTURES OF A PAIR OF ATROPISOMERS OF 1-(3'-SUBSTITUTED BENZOYL)-2-NAPHTHYLINDOLINES AND SOME COMMENTS

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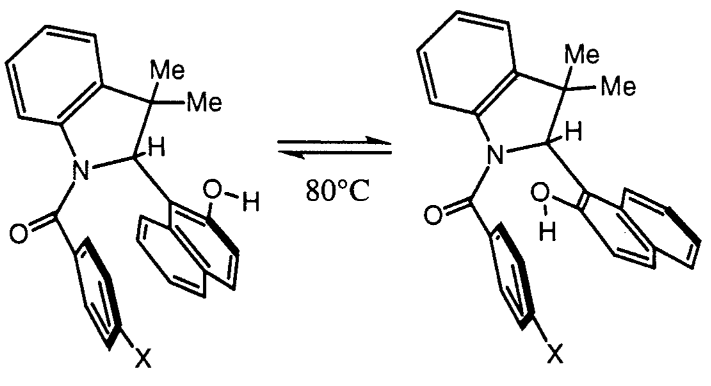
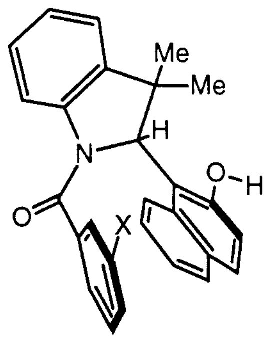
Abstract - A pair of atropisomers due to restricted rotation about C_{sp^3}—C_{sp^2} bond for 1-(3'-nitrobenzoyl)-2-(2''-hydroxynaphthyl)-3,3-dimethylindoline was isolated. The conformational analysis of both isomers was performed based on the crystallographic and ^{1}H-NMR spectral data.

Atropisomers have attracted continuous attention from both theoretical[1] and biological[2] points of view, although there are few examples of isolation of a pair of atropisomers. Recently, it has been proposed that atropisomers can be used as a probe for detection of intramolecular weak interactions.[1c] In the system having parallel-stacked aryl groups, it has been suggested that charge-transfer[1b] or through-space polar/π interaction[3] is operative between the two aryl units. In this connection, we reported the isolation and crystal structure elucidation of two pairs of atropisomers [**1a, b, 2a,b** (Csp^3—Csp^2)] of 1-(4'-substituted benzoyl)-2-aryl-3,3-dimethylindoline and found the strong through-space interaction between the aryl moieties.[4e]



X=Cl **1a** ↔ **1b**
X=NO_2 **2a** ↔ **2b**



X=NO_2 **3a,b**

This communication describes the conformational feature of the aromatic ring of the acyl moiety based on the ^{1}H-NMR and crystallographic data of a pair of diastereomeric atropisomers of the 3-nitrobenzoyl derivative (**3a,b**). Coupling of 1-(3'-nitrobenzoyl)-2-hydroxy-3,3-dimethylindolines with ß-naphthol in the presence of $BF_3 \bullet Et_2O$ in dioxane at room temperature gave 1-(3'-nitrobenzoyl)-2-(2"-hydroxynaphthyl)-3,3-dimethylindolines (**3**), which were separated into a pair of atropisomers (**3a**: 23%, **3b**: 34%) by chromatography on silica gel ($CHCl_3$:AcOEt =10:1).[4e]

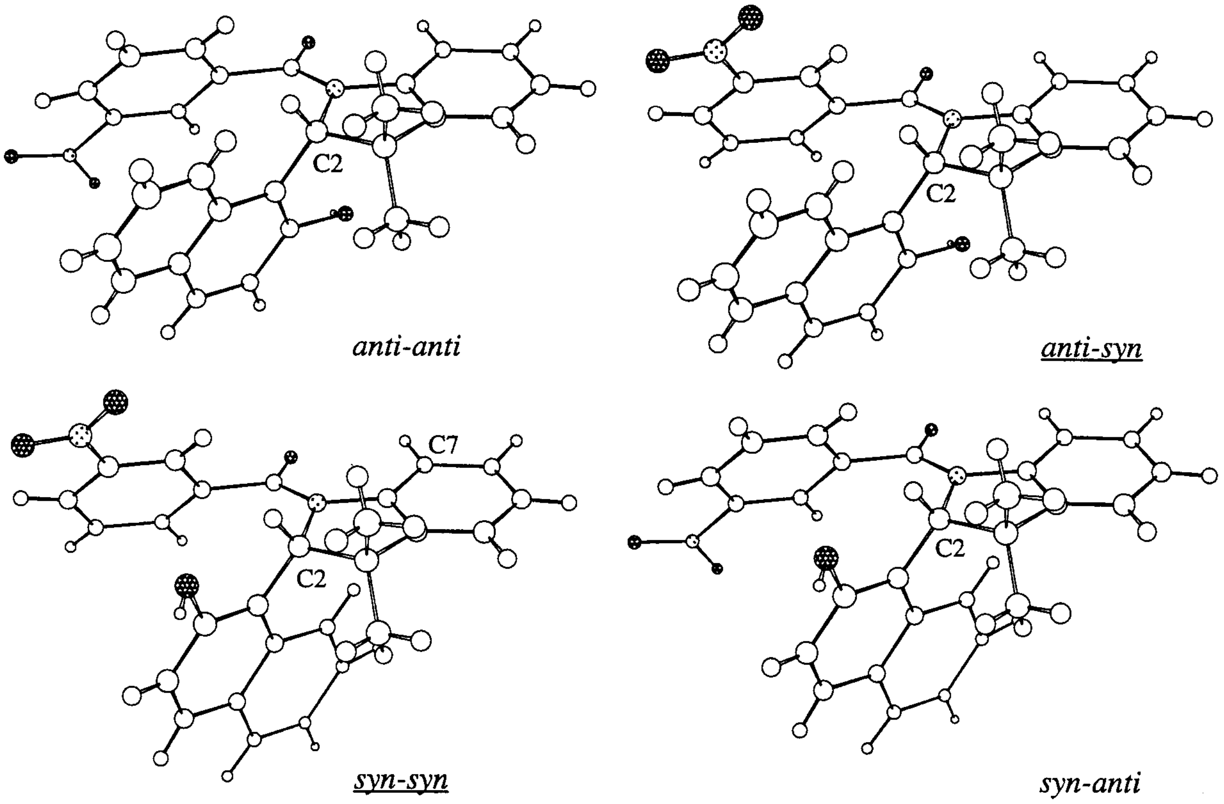
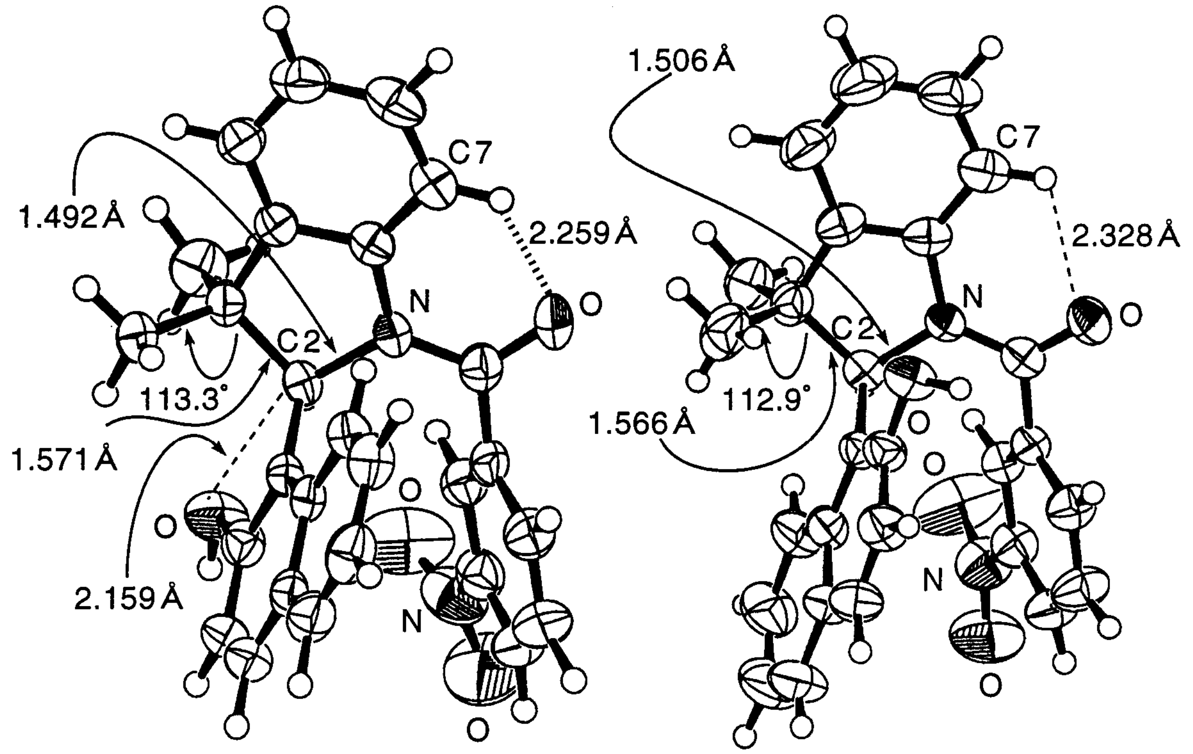


Figure 1. Possible Isomers due to Rotation about the C2—Naphthyl and CO—3'-Nitrophenyl Bonds. The *syn/anti* Orientation of the Nitro or Hydroxy Group is Defined with Respect to the C2 Hydrogen

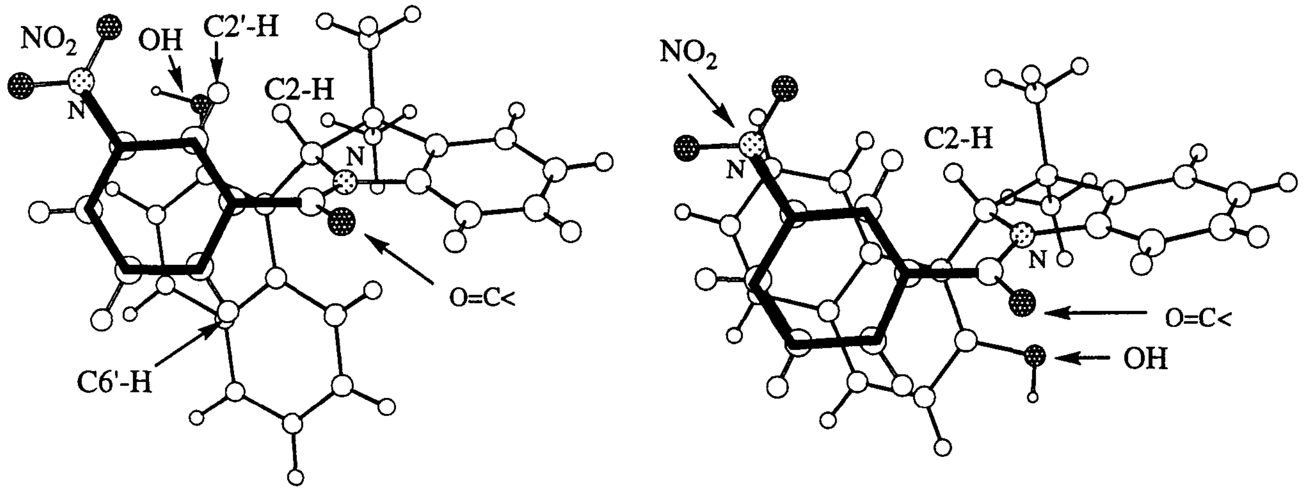
Both isomers are stable at room temperature and gave an equilibrium mixture[4f] on heating at 80° in dioxane. The ^{1}H-NMR spectra of 3a and 3b showed a characteristic spectral feature[4c] of the atropisomers of this type: the ^{1}H-NMR spectra indicated the presence of the C-H••O= type hydrogen bond[5] between the C7 hydrogen and the amide carbonyl, excluding the possibility of atropisomerism due to restricted rotation about the >N—CO bond.[1b] The C2 methine proton of 3a resonated at lower field than 3b, this being attributable to the proximity effect[4c] of the oxygen atom on the naphthalene ring. Taking these facts into consideration, there are four possible rotational isomers due to restricted rotation about the C2—naphthyl and CO—(3'-nitrophenyl) bonds (see Figure 1). In order to obtain further information about the molecular conformation, we performed the single-crystal X-Ray analyses[6] of **3a** and **3b**. As can be seen in Figure 2, **3a** is the *syn-syn* isomer and **3b** is the *anti-syn* isomer.



3a (*syn-syn*) **3b** (*anti-syn*)

Figure 2. ORTEP Drawing of the Atropisomers (**3a**, *syn-syn*) and (**3b**, *anti-syn*). The C2 Hydrogen is Hidden behind the C2 Atom in Each Isomer

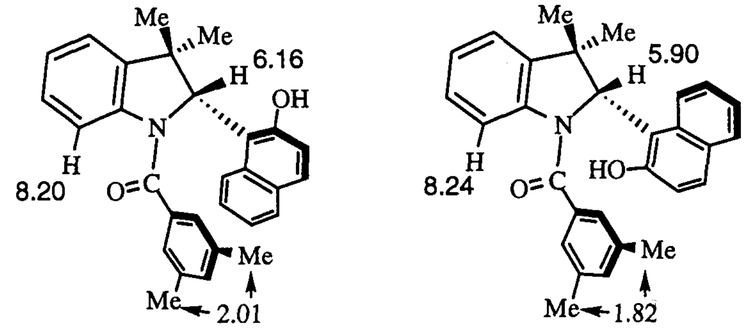
The conformations are nearly identical except for the disposition of the naphthyl ring, in which the 3'-nitro group is *syn* with respect to the C2 hydrogen in both cases. The C2-H••OH distance of **3a** is 2.159Å, indicating the presence of C-H••O type hydrogen bonding.[5] The C2-C3 bond lengths (1.571Å for **3a** and 1.566Å for **3b**) and N-C2 bond lengths (1.492Å for **3a** and 1.506Å for **3b**) are longer than the normal values.[7] These bond elongations might be due to steric repulsion between the naphthyl ring and the 3,3-dimethyl groups and the 3'-nitrophenyl group respectively. The interplanar angles between the 3'-nitrophenyl ring and the amide plane are 66.5° and 54.0° for **3a** and **3b** respectively. The interatomic distances between the amide carbonyl oxygen and C7 hydrogen (>C=O••H-C7) are 2.259 and 2.328Å for **3a** and **3b** respectively. This conformational feature was found in solution. The ^{1}H-NMR spectrum showed that the C7 aromatic proton resonated at 8.3-8.4 ppm as a characteristic low-field shifted signal[4c] in both cases. Figure 3 shows the overlapping of the 3'-nitrophenyl and naphthyl rings of both isomers looking perpendicular to the 3'-nitrophenyl ring. Inspection of the X-Ray structure of **3a** suggests that C6'-H of the 3'-nitrophenyl moiety resonates at a higher field than C2'-H because of the ring current effect of the naphthyl ring. Contrary to the expectation, however, both aromatic protons at 7.14-7.31 ppm have suffered upfield shift relative to those at 7.6-8.8 ppm of 3-nitrobenzoic acid, indicating that the 3'-nitrophenyl moiety rotates freely about the CO—Ar bond at room temperature. In order to get additional information about the mobility of the aryl ring of the acyl moiety, we prepared a pair of atropisomers of the 3,5-dimethyl-



3a (*syn-syn*) **3b** (*anti-syn*)

Figure 3. Overlapping of Aromatic Rings Looking Perpendicular to the 3'-Nitrophenyl Ring, Found in X-Ray Structures of the Atropisomers (**3a,b**)

benzoyl (**4**) derivative.[8] A pair of diastereomeric atropisomers (*syn*-**4** and *anti*-**4**) was successfully isolated as crystals. The ^{1}H-NMR analysis of the C2 and C7 methine protons of both atropisomers indicated that the rotations around the >N—CO and C2 —naphthyl bonds are restricted at room temperature (see Figure 4). Heating *syn*-**4** or *anti*-**4** in dioxane at 80° C for several hours caused transformation into an equilibrium mixture of the atropisomers (*anti/syn* =1.27). As for the conformation of the 3',5'-dimethylphenyl ring, the ring is considered to rotate freely about the CO—Ar bond, which may be judged from the fact that the two methyl proton signals of the 3',5'-dimethylphenyl ring appeared as a singlet in both isomers, indicating that the two methyl groups of the 3',5'-dimethylphenyl ring are magnetically equivalent at room temperature. The AM1 calculation[9a,b] of **3** supports this assumption. The optimized geometries and rotational barriers for the *anti-syn* -> *anti-anti* process are shown in Figure 5. The barriers to rotation about the CO—Ar bond corresponding to two transition states (TS3 and TS4)[4d] were calculated to be 6.67 and 7.84 kcal/mol, respectively. These barriers are remarkably lower than the barriers to rotation of the naphthyl ring [TS1 (39.6 kcal/mol) and TS2 (29.6 kcal/mol)] (see *anti-syn* -> *syn-syn* process).[9c]



syn-**4** *anti*-**4**

Figure 4. The ^{1}H-NMR Spectral Data (δ) of *syn*-**4** and *anti*-**4**

In solution, the free rotation about the CO—Ar bond is considered to play an important role to enhance the rotational barrier of the naphthyl ring.

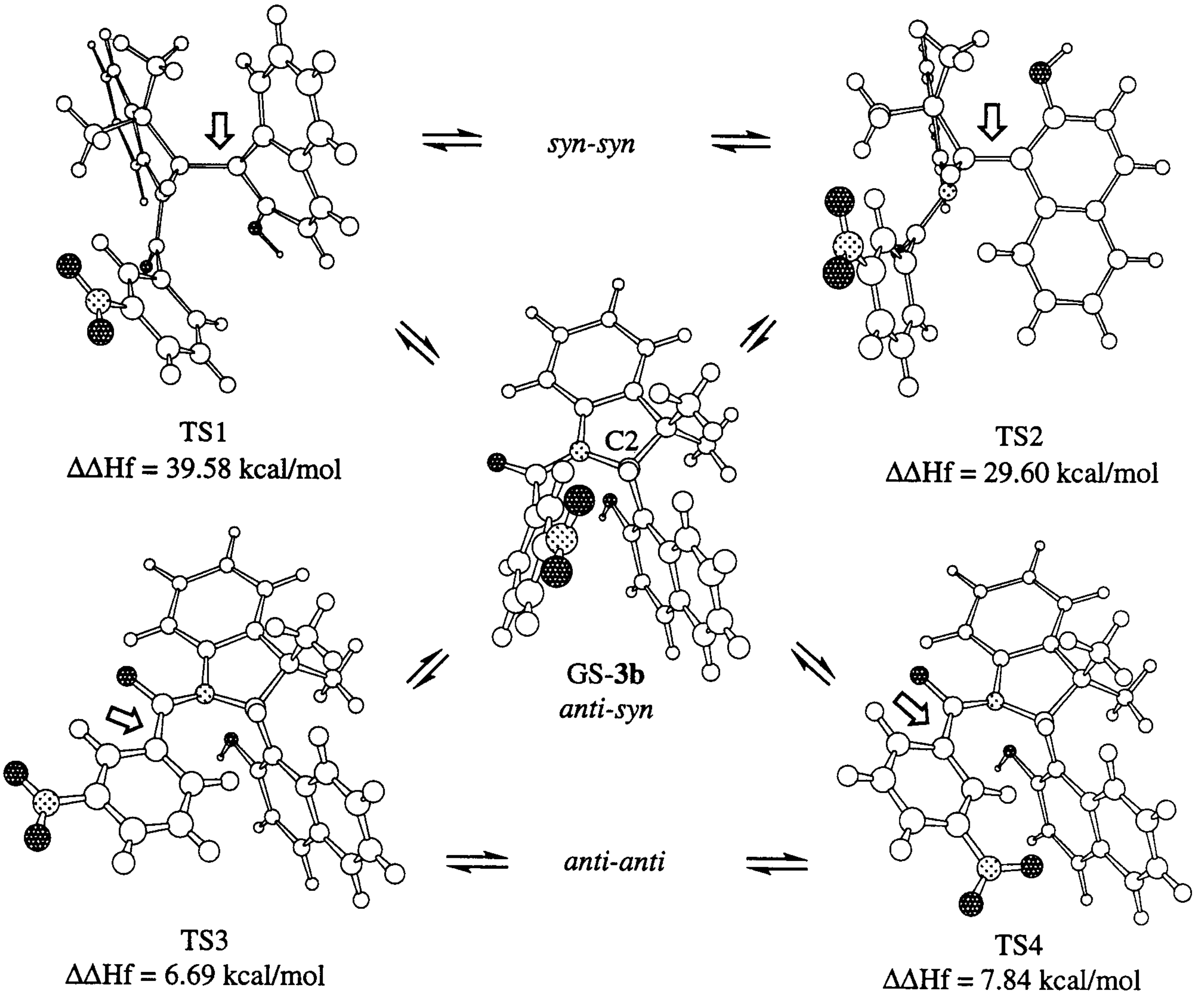


Figure 5. Ground-state (GS) and Transition-state (TS) Structures for Rotation about the 2”-Hydroxynaphthyl—C2 and 3’-Nitrophenyl—C=O Bonds and Rotational Barriers Calculated by AM1

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6. Single crystals of **3a** or **3b** were prepared by slow evaporation of an ethanol solution at room temperature. X-Ray measurements were performed on a RIGAKU AFC7R four-circle autodiffractometer with graphite monochromated Mo Kα radiation (λ=0.7107 Å) and a rotating anode generator. The structures are solved by the direct method. All calculations were performed on a Silicon Graphics IRIS Indigo WS with teXan Crystal Structure Analysis Package.

   Crystal Data; **3a**: $C_{27}H_{22}N_2O_4$, M = 438.5, monoclinic, space group $P2_1/c$, a = 10.243(1), b = 14.167(2), c = 15.906(9) Å, β = 102.15(7)°, V = 2256.6(4) Å^3, Dm = 1.288 gcm^{-3} (by flotation in aq. KI), Dc = 1.291 gcm^{-3}, Z = 4, Number of reflections measured = 5689, Number of observed reflections [I>3σ(I)] = 5397, R = 0.050, Rw = 0.038. **3b**: $C_{27}H_{22}N_2O_4$ M = 438.5, triclinic, Space group $P2_1/c$, a = 7.826(2), b = 24.570(2), c = 11.845(4) Å, β = 98.30(3)°, V = 2253.6(10) Å^3, Dm = 1.281 gcm^{-3} (by flotation in aq. KI), Dc = 1.289 gcm^{-3}, Z = 4, Number of reflections measured = 3639, Number of observed reflections [I>3σ(I)] = 3332, R = 0.047, Rw = 0.038. The atomic coordinates at the present stage are available by E-mail.
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9. a) J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902. b) AM1 calculations were run through the CS Chem3D Pro interface using MOPAC93 on a Power Macintosh G3 computer. The rotational barriers were estimated from [ΔHf(TS)-ΔHf(GS)], in which the heat of formation (ΔHf) of GS-**3b** is 43.30 kcal/mol. c) AM1 method is suitable for the structure optimization of atropisomers involving amide groups. The TS calculation of the atropisomers of *p*-chlorobenzoyl derivative gave a similar result.[4d]

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