

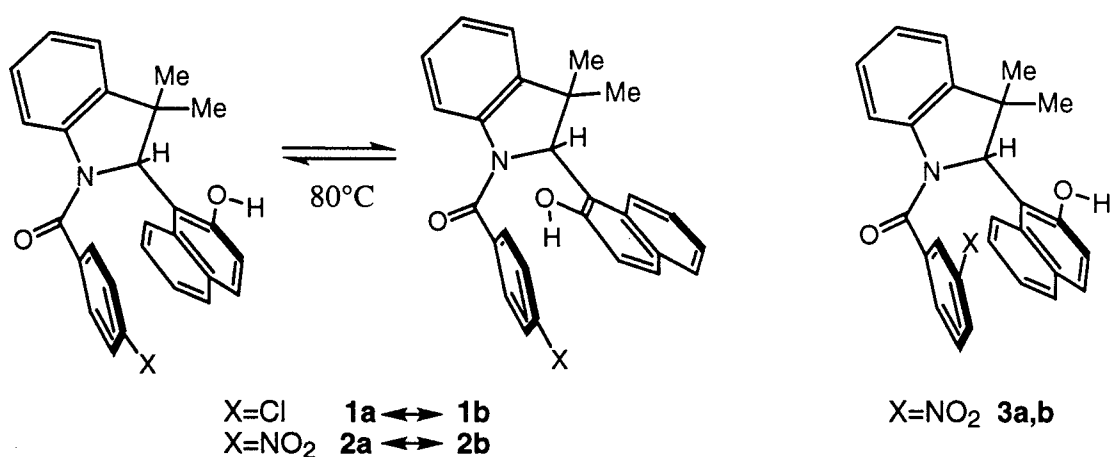
X-RAY STRUCTURES OF A PAIR OF ATROPISOMERS OF 1-(3'-SUBSTITUTED BENZOYL)-2-NAPHTHYLINDOLINES AND SOME COMMENTS

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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 1H -NMR spectral data.

Atropisomers have attracted continuous attention from both theoretical¹ and biological² 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 interaction³ 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** ($C_{sp^3}-C_{sp^2}$)] of 1-(4'-substituted benzoyl)-2-aryl-3,3-dimethylindoline and found the strong through-space interaction between the aryl moieties.^{4e}



This communication describes the conformational feature of the aromatic ring of the acyl moiety based on the ^1H -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 β -naphthol in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ 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 ($\text{CHCl}_3:\text{AcOEt}=10:1$).^{4e}

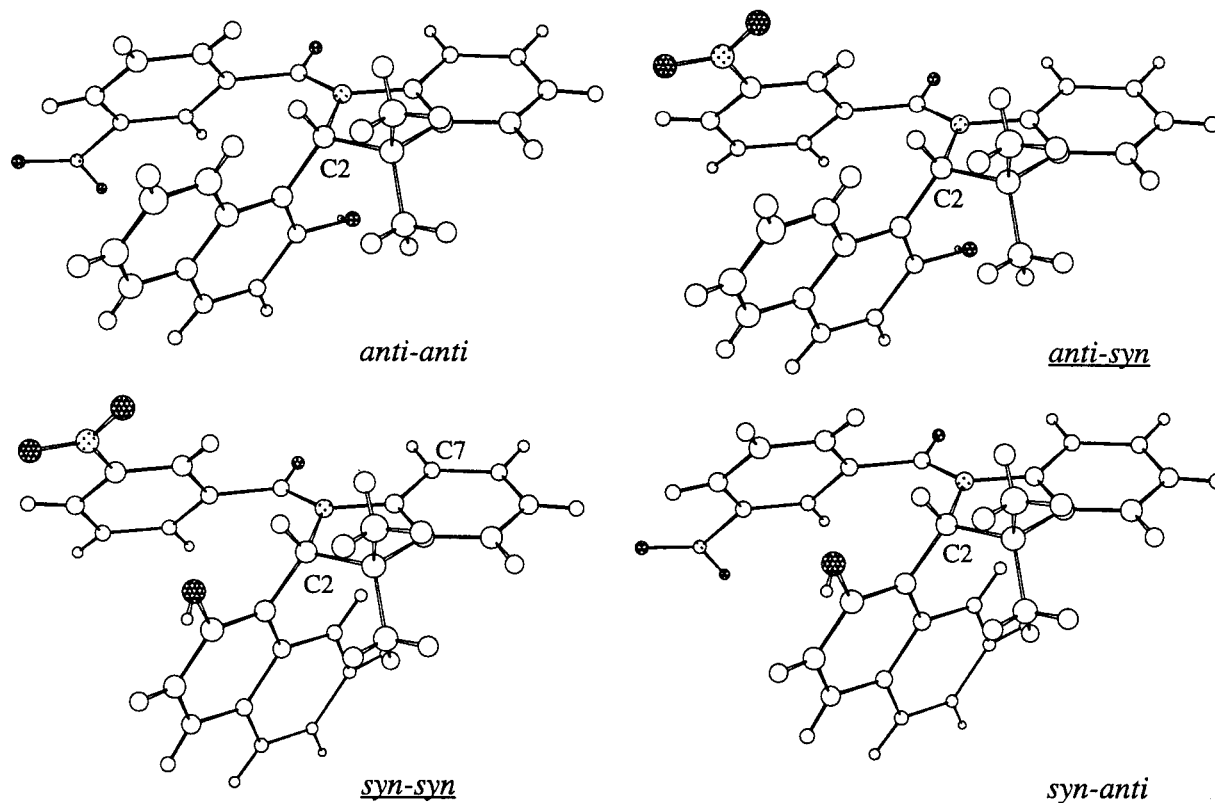


Figure 1. Possible Isomers due to Rotation about the C2—Naphthyl and CO—3'-Nitrophenyl Bonds. The *syn/anti* Orientation of the Nitro or Hydroxy Group is Defined with Respect to the C2 Hydrogen

Both isomers are stable at room temperature and gave an equilibrium mixture^{4f} on heating at 80° in dioxane. The ^1H -NMR spectra of **3a** and **3b** showed a characteristic spectral feature^{4c} of the atropisomers of this type: the ^1H -NMR spectra indicated the presence of the $\text{C-H}\cdots\text{O}=\text{}$ type hydrogen bond⁵ between the C7 hydrogen and the amide carbonyl, excluding the possibility of atropisomerism due to restricted rotation about the $>\text{N}-\text{CO}$ 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 analyses⁶ of **3a** and **3b**. As can be seen in Figure 2, **3a** is the *syn-syn* isomer and **3b** is the *anti-syn* isomer.

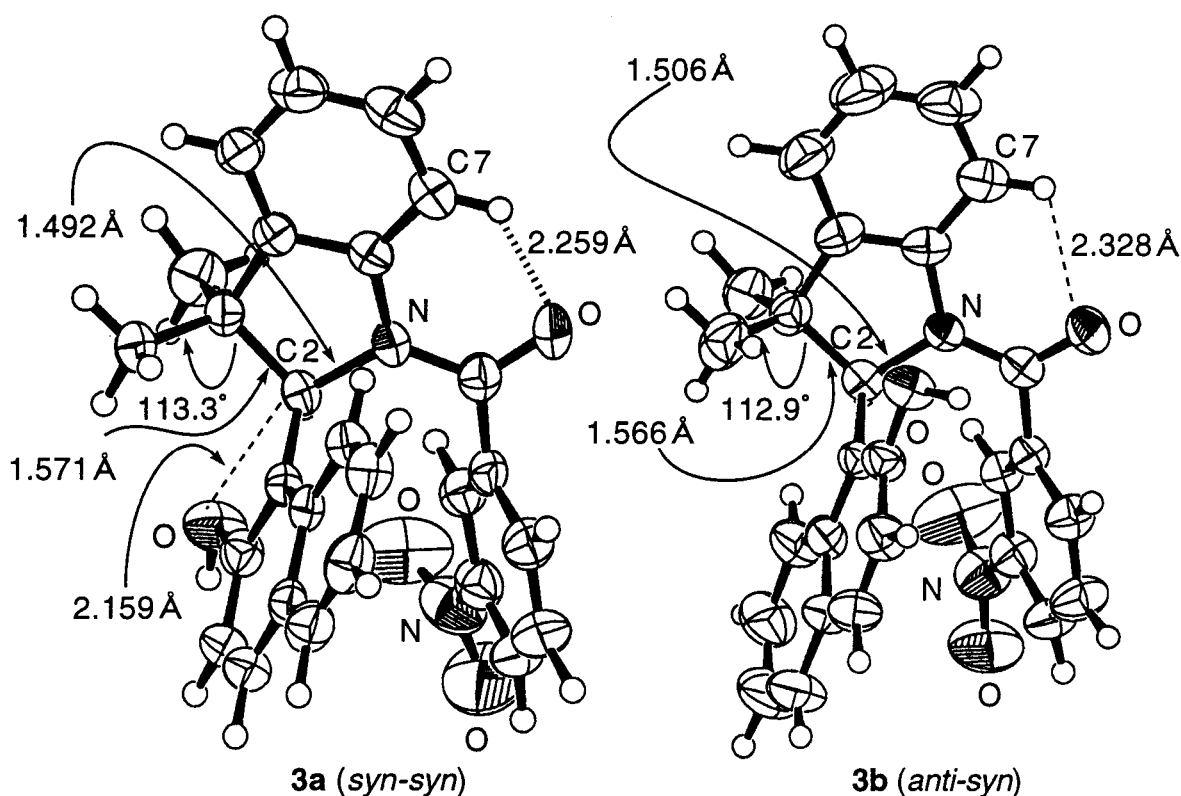


Figure 2. ORTEP Drawing of the Atropisomers (**3a**, *syn-syn*) and (**3b**, *anti-syn*). The C2 Hydrogen is Hidden behind the C2 Atom in Each Isomer

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 2.159 Å, indicating the presence of C-H...O type hydrogen bonding.⁵ The C2-C3 bond lengths (1.571 Å for **3a** and 1.566 Å for **3b**) and N-C2 bond lengths (1.492 Å for **3a** and 1.506 Å 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 2.328 Å for **3a** and **3b** respectively. This conformational feature was found in solution. The ¹H-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-

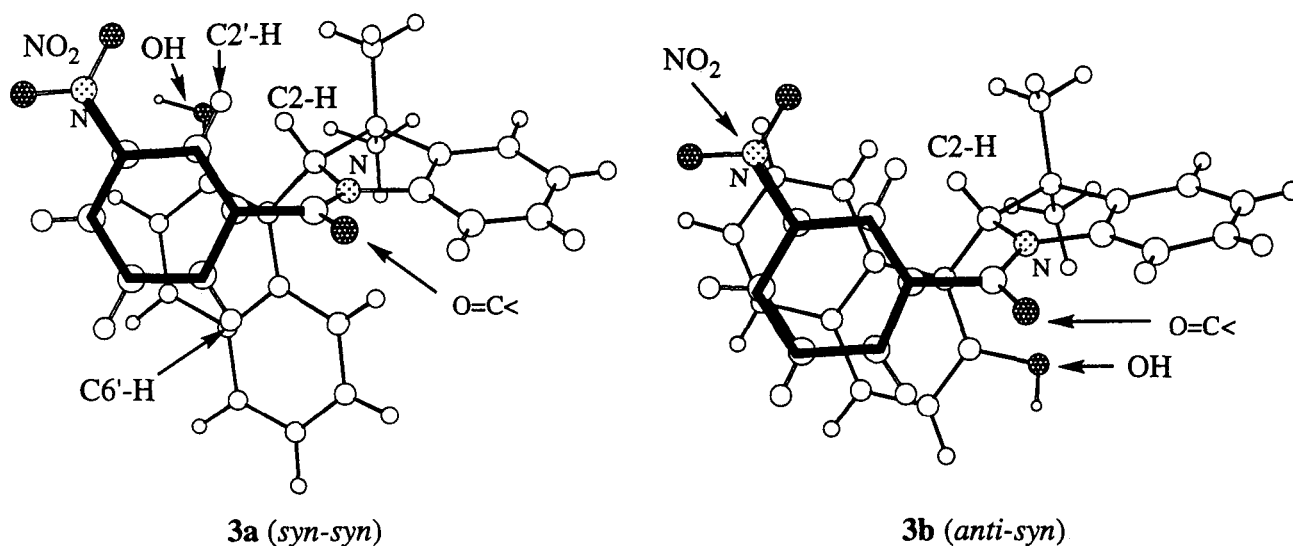


Figure 3. Overlapping of Aromatic Rings Looking Perpendicular to the 3'-Nitrophenyl Ring, Found in X-Ray Structures of the Atropisomers (**3a,b**)

benzoyl (**4**) derivative.⁸ A pair of diastereomeric atropisomers (*syn-4* and *anti-4*) was successfully isolated as crystals. The ¹H-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).

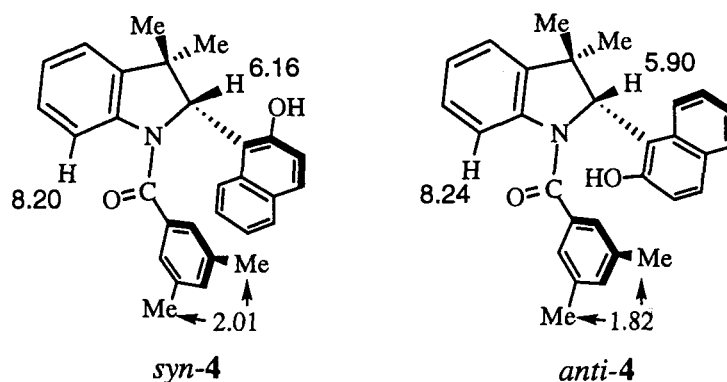


Figure 4. The ¹H-NMR Spectral Data (δ) of *syn-4* and *anti-4*

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}

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.

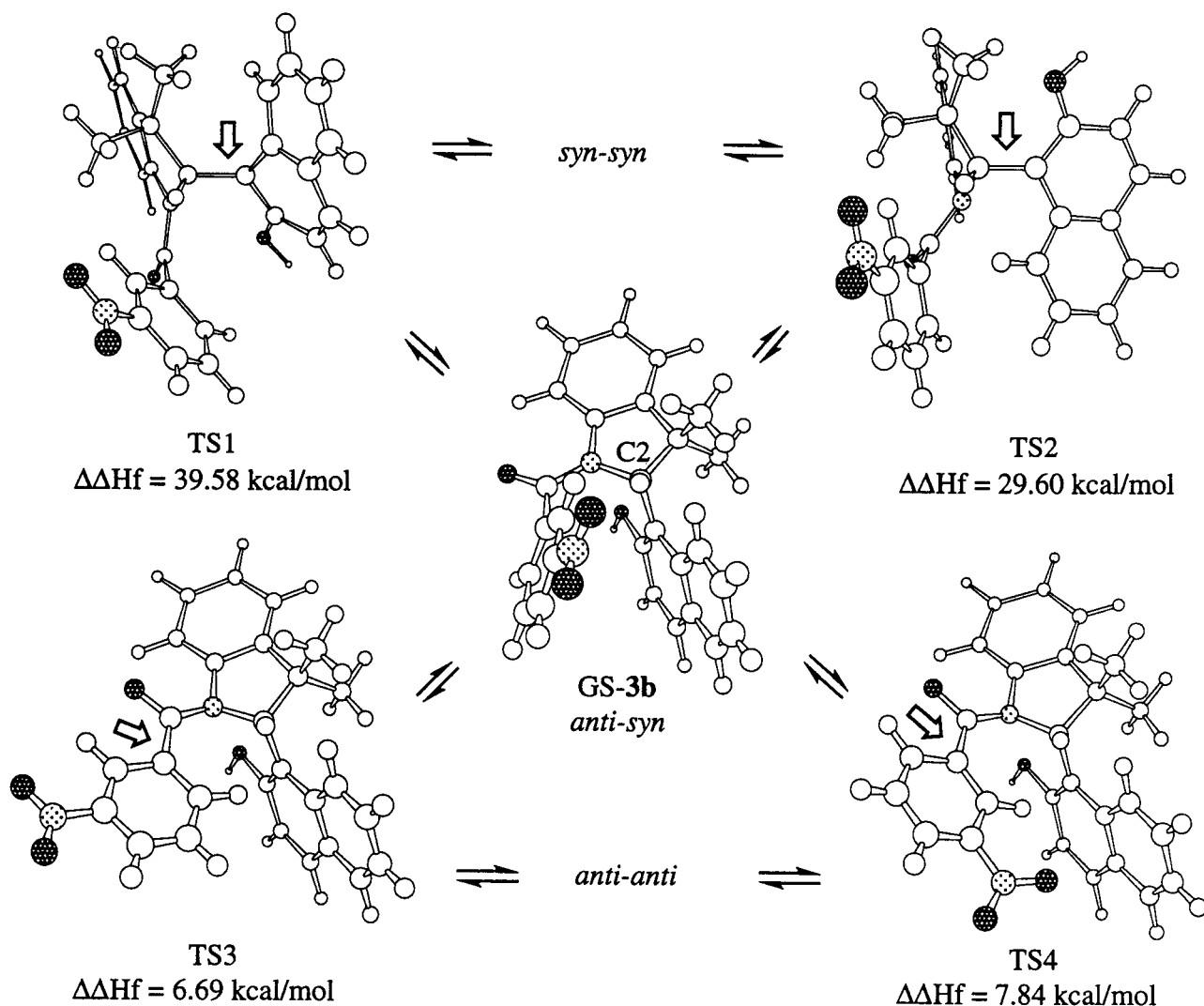


Figure 5. Ground-state (GS) and Transition-state (TS) Structures for Rotation about the 2''-Hydroxynaphthyl—C2 and 3'-Nitrophenyl—C=O Bonds and Rotational Barriers Calculated by AM1

ACKNOWLEDGMENT

The work was supported by the grants-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan. We thank Misses K. Meta, K. Hori, and N. Tashiro for experimental assistance.

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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 K α radiation ($\lambda=0.7107$ 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**: C₂₇H₂₂N₂O₄, $M = 438.5$, monoclinic, space group $P2_1/c$, $a = 10.243(1)$, $b = 14.167(2)$, $c = 15.906(9)$ Å, $\beta = 102.15(7)^\circ$, $V = 2256.6(4)$ Å³, $D_m = 1.288$ gcm⁻³ (by flotation in aq. KI), $D_c = 1.291$ gcm⁻³, $Z = 4$, Number of reflections measured = 5689, Number of observed reflections [$I > 3\sigma(I)$] = 5397, $R = 0.050$, $R_w = 0.038$. **3b**: C₂₇H₂₂N₂O₄, $M = 438.5$, triclinic, Space group $P2_1/c$, $a = 7.826(2)$, $b = 24.570(2)$, $c = 11.845(4)$ Å, $\beta = 98.30(3)^\circ$, $V = 2253.6(10)$ Å³, $D_m = 1.281$ gcm⁻³ (by flotation in aq. KI), $D_c = 1.289$ gcm⁻³, $Z = 4$, Number of reflections measured = 3639, Number of observed reflections [$I > 3\sigma(I)$] = 3332, $R = 0.047$, $R_w = 0.038$. 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 [$\Delta H_f(\text{TS}) - \Delta H_f(\text{GS})$], in which the heat of formation (ΔH_f) 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}

Received, 19th April, 1999