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 Csp3—Csp2 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 interactions1e In the system having parallel-stacked aryl groups, it has been suggested that charge-transfer1b 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 (Csp3—Csp2)] 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=NO2  2a ⇌ 2b

80°C
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 \(\beta\)-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 (\(\text{CHCl}_3\cdot\text{AcOEt} = 10:1\)).

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\(\cdots\)O= type hydrogen bond\(^5\) between the C7 hydrogen and the amide carbonyl, excluding the possibility of atropisomerism due to restricted rotation about the \(\text{N}\cdots\text{CO}\) 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 analyses\(^6\) of 3a and 3b. As can be seen in Figure 2, 3a is the \(\text{syn-syn}\) isomer and 3b is the \(\text{anti-syn}\) 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-
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).

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 calculation9a,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)9d 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.
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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_{2}O_{4}, M = 438.5, monoclinic, space group P2_1/c, a = 14.167(2), c = 15.906(9) Å, β = 102.15(7)°, V = 2256.6(4) Å³, Dm = 1.288 g cm⁻³ (by flotation in aq. KI), Dc = 1.291 g cm⁻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_{2}O_{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) Å³, Dm = 1.281 g cm⁻³ (by flotation in aq. KI), Dc = 1.289 g cm⁻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.


8. The 3,5-dimethylbenzoyl derivatives: mp 196-197°C and mp 190-191°C.

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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