X-RAY STRUCTURES OF A PAIR OF ATROPISOMERS OF 1-ACYL-2-ARYLINDOLINES. REMARKABLE THROUGH-SPACE ARYL-ARYL INTERACTION

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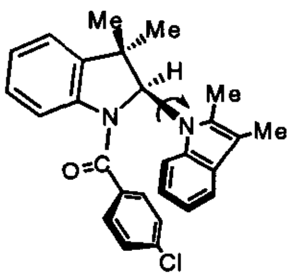
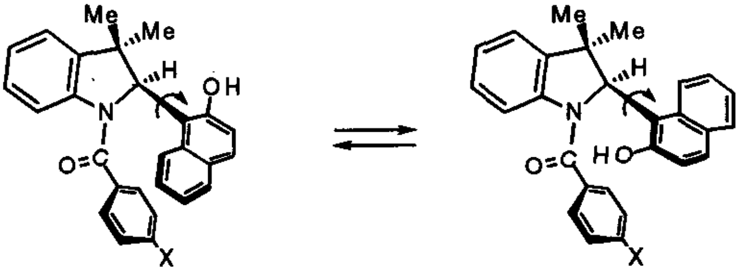
Abstract - A pair of atropisomers due to restricted rotation about C_{sp^3}-C_{sp^2} bond for 1-(4'-nitrobenzoyl)-2-(2"-hydroxynaphthyl)-3,3-dimethylindoline was isolated. The crystal structures of a pairs of the atropisomers indicate the presence of a significant through-space interaction between the aryl moieties.

Rotamers about single bonds have been found in a wide variety of organic compounds as a result of the application of nmr spectroscopy to organic compounds.[1a] However, there are few examples of isolation of a pair of atropisomers, althrough they have attracted considerable attention from both theoretical[1] and biological[2] points of view. 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 gorups, it has been suggested that charge-transfer[1d] or through-space polar/π interaction[3] is operative between the two aryl units. For an insight into the real nature of such interactions, the three-dimentional informations about a pair of atropisomers seem to be essential.

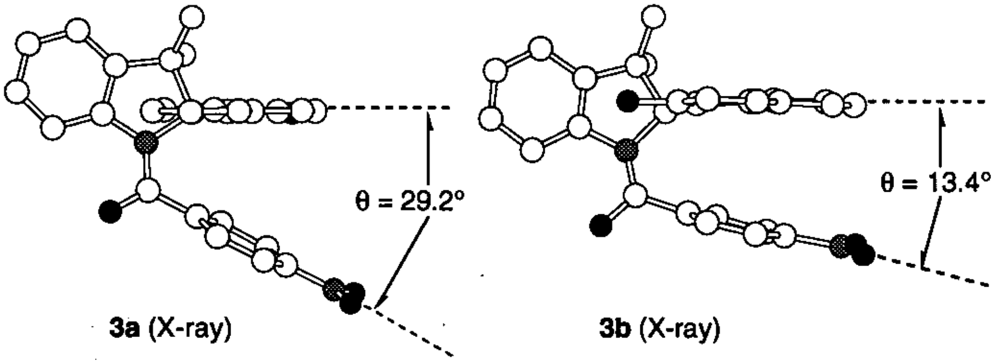


1a,b



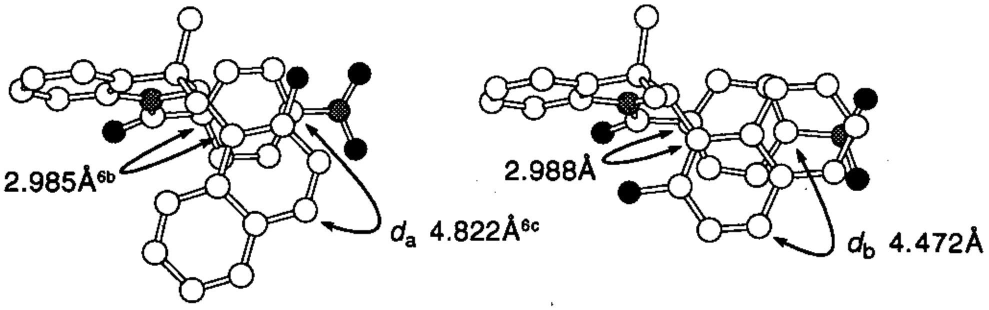
X=Cl **2a** ⟷ **2b**
X=NO_2 **3a** ⟷ **3b**

In the course of our study on the synthesis of indolenines, we isolated two types of diastereomeric atropisomers [**1a,b** (Csp^3-Nsp^2) and **2a,b** (Csp^3-Csp^2)] of 1-(4'-chlorobenzoyl)-2-aryl-3,3-dimethylindoline and clarified the crystal structures of the four isomers.[4] This paper describes the conformational feature of the aromatic rings on the basis of the X-ray crystallographic data for a pair of the 4-nitrobenzoyl derivative (**3a,b**.). Coupling of 1-(4'-substituted benzoyl)-2-hydroxy-3,3-dimethylindolines with ß-naphthol in the presence of BF$_3$•Et$_2$O gave 1-(4'-substituted benzoyl)-2-(2"-hydroxynaphthyl)-3,3-dimethylindolines (**3**), which were separated into pairs of atropisomers by chromatography on silica gel.[4c] Of the compounds synthesized, we succeeded in determining crystal structures[5] of a pair of atropisomers for the 4-nitrobenzoyl derivative (**3a** and **3b**). As shown in Figures 1 and 2, both isomers have almost a same geometry except the naphthyl moiety, in which the 4-nitrophenyl group is nearly perpendicular to the amide plane conjugated with the benzene moiety of the indoline. The interplanar angles between the 4-nitrophenyl and naphthyl rings are of interest. The angles for **3a** and **3b** are 29.2° [6a] and 13.4°, respectively.



3a (X-ray) **3b** (X-ray)

Figure 1. Angles of Planes of Aromatic Rings for X-Ray Structures of a Pair of Atropisomers (**3a,b**).



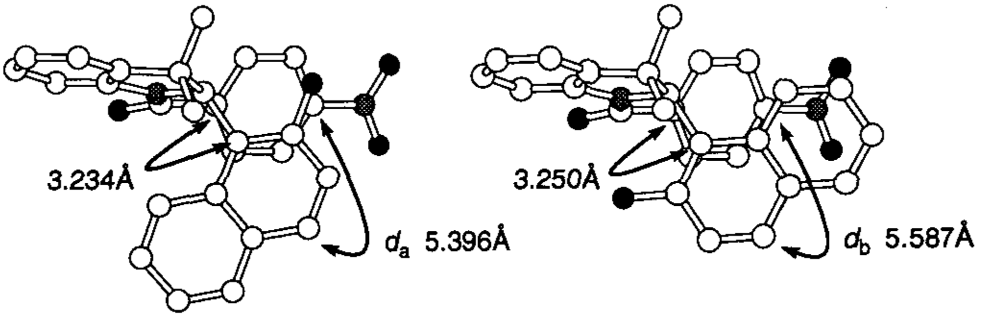
3a (X-ray) **3b** (X-ray)

Figure 2. Overlappings of Aomatic Rings Looking through Naphthalene Ring for X-Ray Structures of a Pair of Atropisomers (**3a,b**)

The views of overlapping of the aromatic rings through the naphthyl ring are shown in Figure 2, in which the important interatomic distances are shown for the estimation of degrees of the approach of the rings. The distance (d_b) between the atom of the 4-position of the 4-nitrophenyl ring and the one of the 4-position of the 2-naphthyl ring for **3b** are considerably shorter than that (d_a) of **3a**, suggesting that in **3b**, in spite of the presence of large steric repulsions between the aromatic rings, the two rings effectively overlap and approach one another.

In order to know the nature of electronic interaction between the aryl groups of **3a** and **3b**, the molecular orbital (MO) structure optimizations were performed using semiempirical AM1 and PM3 SCF-MO methods ,[6] starting from the X-ray data and allowing full geometry optimization. The PM3 method could not reproduce the sp^2 nature of the amide group, whereas the AM1 structure optimization[7] approximately reproduced the planarity of the amide group. However, both MO methods could not reproduce the conformational feature of the aryl rings observed in the crystal structure of **3b** (see Figure 3). The interatomic distances (d_a and d_b) are considerably longer than those of **3a** and **3b**. In contrast to the X-ray structural data, d_b was calculated to be ca. 0.2 Å longer than d_a.

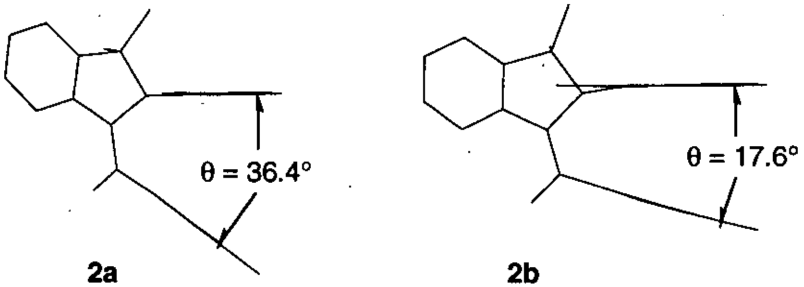
These indicate that the aromatic rings are attracted by intramolecular forces which can not be assessed by present-stage semiempirical SCF-MO methods.



3a (AM1) **3b** (AM1)

Figure 3. Overlappings of Aromatic Rings Looking through Naphthalene Ring for AM1-Calculated Geometries of a Pair of Atropisomers (**3a,b**)

In the light of these informations, we reexamined the previouly reported X-ray structures of a pair of atropisomers (**2a,b**) for the 4-chlorobenzoyl derivative.[4b,c] The conformational features of the aryl moieties are essentially same to those observed in **3a,b** (Figure 4). The interplanar angles between the two aryl groups for **2a** and **2b** are 36.4° and 17.6°, respectively. In comparison of **2b** with **3b**, the angle for the 4-chlorobenzoyl derivative (**2b**) is larger than that for the 4-nitrobenzoyl derivative (**3b**). This discrepancy may be attributable to the degree of acceptability of the 4-substituted benzoyl group.



2a **2b**

Figure 4. Line Drawing of Crystal Structures of a Pair of Atropisomers for the 4-Chlorobenzoyl derivative (**2a,b**)[4b]

The absence of a charge-transfer absorption band in solution but deep coloration of the crystal of **3b** compared with **3a** could not rule out that intramolecular charge-transfer interaction is a contributor of the aryl/aryl interactions, wherein the naphtyl group behaves as a donor and the 4-nitrobenzoyl group as an acceptor.[8] These findings and observations suggest that aryl/aryl interactions affect the stabilization of the ground-state structure and conformational change of the aryl units.

The conformational study on the present and related systems is currently under investigation.

ACKNOWLEDGMENT

We thank Miss T. Kitaoka and Mr T. Moriguchi for experimental assistance.

REFERENCES AND NOTES

1. a) M. Oki, "Topics in Stereochemistry," Vol. 14, ed by N. L. Allinger, E. L. Eliel, and S. H. Wilen, John Wiley and Sons, Inc., New York, 1983, pp. 47-79. b) M. Oki, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 87. c) M. Oki, *Acc. Chem. Res.*, 1990, **23**, 351. d) M. Nakamura and M. Oki, *Chem. Lett.*, **1976**, 651
2. W. C. Randall, P. S. Anderson, E. L. Cresson, C. A. Hunt, T. F. Lyon, K. E. Rittle, D. C. Remy, J. P. Springer, J. M. Hirshfield, K. Hoogsteen, M. Williams, E. A. Risley, and J. A. Tataro, *J. Med. Chem.*, 1979, **22**, 1222.
3. a) F. Cozzi, M. Cinquini, R. Annunziata, T. Dwyer, and J.S. Siegel, *J. Am. Chem. Soc.*, 1992, **114**, 5729. b) F. Cozzi, M. Cinquini, R. Annunziata, and J. S. Siegel, *J. Am. Chem. Soc.*, 1993, **115**, 5330.
4. a) The X-ray analyses of the 2-(2",3"-dimethylindolyl)-3,3-dimethylindoline derivatives: K. Harano, M. Yasuda, Y. Ida, T. Komori, and T. Taguchi, *Cryst. Struc. Commun.*, 1981, **10**, 165. b) The X-ray analyses of 2-(2"-hydroxynaphthyl)-3,3-dimethylindoline derivatives: M. Eto, K. Harano, T. Hisano, and T. Kitamura, *J. Heterocycl. Chem.*, 1992, **29**, 311. c) T. Kitamura, K. Harano, and T. Hisano, *Chem. Pharm. Bull.*, 1992, **40**, 2255
5. The single crystals of **3a** and **3b** suitable for X-ray analysis were obtained from slow evaporation of the

acetone-EtOH solution. The refraction data were measured on a RIGAKU AFC7R four-circle autodiffractometer with a graphite monochromated Mo Kα radiation and a rotating anode generator. The structures are solved by direct method and refined by block-diagonal least-square method. All calculations were performed on a Silicone Graphics IRIS Indigo WS with teXsan Crystal Structure Analysis Package. Crystal Data; **3a**: $C_{27}H_{22}N_2O_4$, M=438.5, monoclinic, Space group $P2_1/c$, a=15.809 (12), b=19.114 (21), c=16.965 (12)Å, ß=112.1 (1)°, V=4535 (7)Å^3, Dm=1.279 gcm^{-3} (by flotation in aq. KI), Dc=1.285 gcm^{-3}, Z=8, Mo Kα radiation (50 kV-150 mA), λ=0.7107 Å, Num of RD=7350, Num of F_{obs}=2648, R_f=0.078. The crystal structure contains two independent molecules in the asymmetric unit. Both molecules have almost the same geometry except for the nitro group.

3b: $C_{27}H_{22}N_2O_4$, M=438.5, trigonal, Space group $R\overline{3}$, a=26.153 (5), b=17.181 (11)Å, V=10177(4)Å^3, Dm=1.265 gcm^{-3} (by flotation in aq. KI), Dc=1.288 gcm^{-3}, Z=18, Mo Kα radiation (50 kV-150 mA), λ=0.7107 Å, Num of RD=3417, Num of F_{obs}=1200, R_f=0.083.

The details of the X-ray and MO calculation data will be appeared in a separate paper. The atomic coordinates at the present stage are available by E-mail.

6. a) An average of the values of independent molecules (**A**, θ=28.7°; **B**, θ=29.7°). b) An average: Molecule **A**, 2.970Å; molecul **B**, 3.000Å. c) An average: Molecule **A**, 4.692Å; molecule **B**, 4.952Å.
7. J. J. P. Stewart, *QCPE Bull.*, 1989, **9**, 10, *idem, J. Comp. Chem.*, 1989, **10**, 209, 221. The MO calculations were performed on a Fujitsu S-4/2 EWS using MOPAC V6.01.
8. The AM1 MO calculation on **3b** indicated that the HOMO and LUMO are almost entirely localized on the anilino and the nitrobenzoyl moieties, respectively, whereas the NHOMO is localized on the naphtyl moiety. The observed conformation is considered to be very favorble for the HOMO-LUMO interaction of both aryl rings.

Received, 13th February, 1996