Tetrahedron 66 (2010) 898–903

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Conformation of aromatic rings in isolable atropisomers of 2-arylindoline derivatives and kinetic evidences for π–π interaction

Masashi Eto [a], Koki Yamaguchi [b], Itaru Shinohara [b], Fumikazu Ito [b], Yasuyuki Yoshitake [b], Kazunobu Harano [b,*]

[a] Liberal Arts Education Center, Aso Campus, Tokai University, 5435 Kawayo, Minami-Aso, Kumamoto 869-1404, Japan
[b] Faculty of Pharmaceutical Sciences, Sojo University, 4-22-1 Ikeda, Kumamoto 860-0082, Japan

ARTICLE INFO

Article history:
Received 7 October 2009
Received in revised form 20 November 2009
Accepted 24 November 2009
Available online 27 November 2009

Keywords:
1-Aroyl-2-aryl-3,3-dimethylindoline
Diastereomeric atropisomer
π–π Interaction
Equilibrium constant
Substituent effect

ABSTRACT

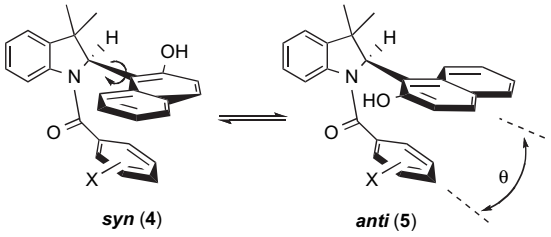
The equilibrium constants [K=***anti***/***syn***] of a pair of atropisomers due to restricted rotation about Csp^3–Csp^2 bond for [2-(2-hydroxynaphthalen-1-yl)-3,3-dimethylindolin-1-yl](4-substituted phenyl)methanone were determined in some solvents. The presence of the effective π–π interaction was demonstrated by the correlation between the equilibrium constants (K) and the substituent effect of the phenyl groups (σ_p), suggesting that the 'neutral–type' interaction is operative.

1. Introduction

Atropisomers are stereoisomers resulting from hindered rotation about single bonds where the barrier to rotation is high enough to allow the isolation of the conformational isomers.[1] Recently, Oki proposed that atropisomers can be used as a probe for detection of intramolecular weak yet attractive interactions.[2] Among the noncovalent weak interactions, π–π interactions between aromatic rings have attracted much attention due to their importance in such area as molecular recognition and structures of biological molecules.[3] Cozzi et al. showed that coulombic or electrostatic attraction is operative in the parallel-stacked aryl units based on a population ratio of the rotamers of π-cofacial 1,8-diarylnaphthalenes.[4]

In the previous papers, we reported a facile synthetic method of 2-aryl substituted indoline derivatives by condensation of (2-hydroxy-3,3-dimethylindolin-1-yl)(substituted phenyl)methanone (**1**) with various electron-rich aromatic compounds (**2** or **3**) and successfully isolated 16 pairs of the atropisomers of indoline type arising from restricted rotation around Csp^3–Csp^2 bond.[5] These compounds are useful as models for quantitatively studying substituent effects on π–π interactions because the structure has a parallel-stacked aryl units. In the X-ray crystal structures of the 4-nitrophenyl derivatives (**4a** and **5a**), we found strong through-space interaction between the 4-nitrophenyl and 2-hydroxynaphthyl rings (Fig. 1).[5e] The two aryl rings take a face-to-face disposition and the degree of overlap for the ***anti*** isomer is larger than the ***syn*** isomer.

The conformational features of the aryl groups are similar to those observed in 4-chrloro or 3-nitrophenyl derivatives. The



X	θ (°)	
	syn (**4**)	*anti* (**5**)
4-NO_2	28.6 (**4a**)	12.8 (**5a**)
4-Cl	35.2 (**4b**)	17.3 (**5b**)
3-NO_2	32.1	27.3
3-Cl	-	21.8

Figure 1. Interplanar angle between phenyl and naphthyl rings found in X-ray structures of atropisomers (**4**, **5**)[5e].

* Corresponding author.
E-mail address: harano@ph.sojo-u.ac.jp (K. Harano).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.11.102

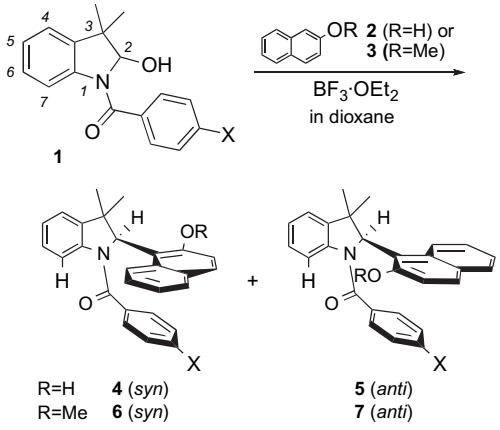
interplanar angles between the phenyl and the naphthyl rings for ***anti*** and ***syn*** are 12.8 and 28.6°, respectively. The angle for ***anti*** of 4-nitrophenyl derivative (**5a**) is much smaller than that for 4-chloro or 3-substituted phenyl derivatives. The discrepancy between ***syn*** and ***anti*** isomers seems to be due to donor–acceptor interaction and steric effect of substituents on the phenyl ring.

On the other hands, in the crystal packing structure, the intermolecular hydrogen-bonded dimeric structures were found in the ***anti*** isomers, whereas the ***syn*** isomers were linked by intermolecular hydrogen bonds.[5b,g] The intermolecular edge-to-face interaction[6] is also found between the naphthyl hydrogens and the 4-nitrophenyl ring of the adjacent molecule.[5g] Therefore, it is necessary to know the degree of effect of π–π interaction on the conformational change. This prompted us to prove the presence of the π–π interaction in solution. In this paper we demonstrate the evidence based on the substituent effect on equilibrium constants of the interconversion between ***syn*** and ***anti*** isomers of 4-substituted phenyl derivatives.

2. Results

2.1. Preparation and isolation of the atropisomers

According to the established procedure,[5c] coupling reaction of (2-hydroxy-3,3-dimethylindolin-1-yl)(4-substituted phenyl)metha none (**1**) with 2-naphthol (**2**) was performed in the presence of $BF_3{\cdot}Et_2O$ in dioxane. Each reaction gave a mixture of atropisomers ([2-(2-hydroxynaphthalen-1-yl)-3,3-dimethylindolin-1-yl] (4-sub stituted phenyl) methanone), which were separated into a pair of atropisomers [***syn*** (**4**) and ***anti*** (**5**)] by fractional recrystallization or chromatography on silica gel (Scheme 1). The methoxy derivatives **6** and **7** were obtained by using **3** instead of **2**.[5i]



Scheme 1.

2.2. Single crystal X-ray analysis

In order to know the substituent effect of the phenyl group on the conformation of the aryl rings, the X-ray structure analyses were performed on important compounds for discussion. A pair of ***syn*** and ***anti*** isomers (**4c**, **5c**) of the 4-phenyl derivative and ***anti*** isomers of 4-methylphenyl (**5d**) and 4-dimethylaminophenyl (**5f**) derivative could be analyzed successfully. The ORTEP drawings of the atropisomers are depicted in Figure 2.

As can be seen in Figure 2, each isomer of same type has the common structural features in agreement with the previously reported X-ray structures[5g], in which the amide carbonyl oxygen turns to the C7-H of the indoline moiety and the aryl ring is not coplanar with the >NCO- plane. The interatomic distances between

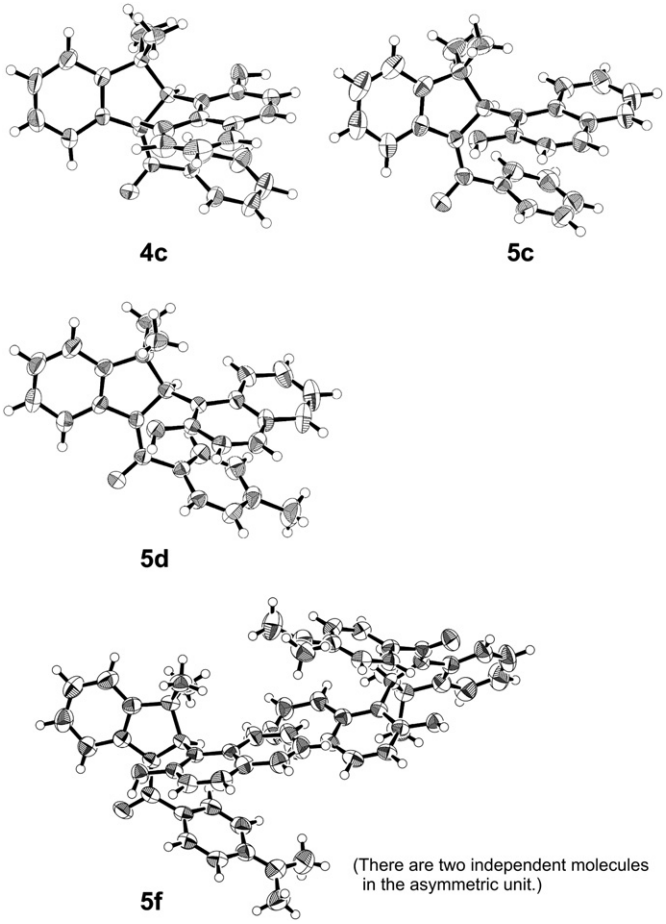


Figure 2. ORTEP drawing of **4c**, **5c**, **5d**, and **5f**.

the amide carbonyl oxygen and C7-H are 2.273 Å (**4c**), 2.295 Å (**5c**), 2.259 Å (**5d**), and 2.275 Å (2.305 Å) (**5f**), indicating the presence of CH···O= type hydrogen bonding.[7] The phenyl and the naphthyl rings take a face-to-face disposition. The degree of overlap between the aromatic rings for ***anti*** isomer (**5c**) is larger than the ***syn*** isomer (**4c**). The interplanar angles between the napththyl and the phenyl rings for ***anti*** isomers **5c**, **5d**, and **5f** are 21.0°, 18.3°, and 33.6 (36.2)°, respectively.

2.3. Crystal packing structure

The crystal packing diagrams are illustrated in Figure 3. The ***syn*** isomer (**4c**) is linked by intermolecular hydrogen bonds between >NC=O and napththyl OH group. In the ***anti*** isomers (**5c**, **5d**, **5f**), the two molecules forms a dimer linked by strong hydrogen bonds between the amide carbonyl and the napththyl OH group making the 16-membered cyclic hydrogen-bonded structure (Fig. 3a). In the **5f** isomer, the CH···π interaction is found between the methyl hydrogen of 4-dimethylaminophenyl group and the phenyl ring of the neighboring molecule (Fig. 3b). The distance is 2.961 Å.

2.4. Molecular orbital calculations

In order to know the nature of electronic interaction between the naphthyl and the phenyl ring, the molecular structure optimizations of **5a**, **5c**, and **5f** were examined using molecular orbital calculation. First, we tried to use *ab initio* and density functional theory (DFT) calculations.[8] However the B3LYP/6-31G(d) or HF/6-311++G(d,p) level of calculations could not reproduced both the sp^2 nature of the amide group. On the other hand, semi-empirical

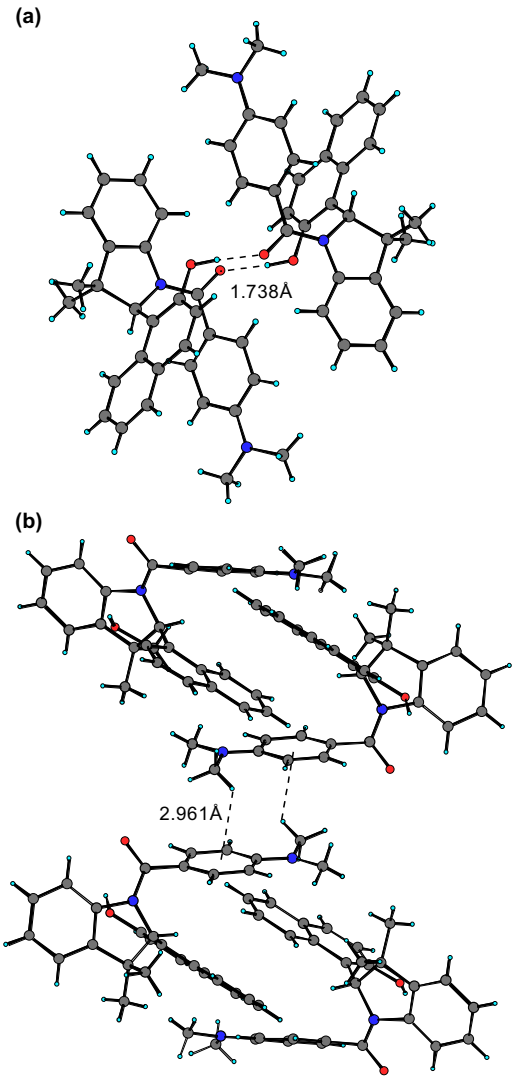


Figure 3. Crystal packing of **5f**. (a) Hydrogen-bonded Dimer. (b) CH···π Interaction.

PM6[9] structure optimization approximately reproduced both the coplanarity of the amide group and the conformational feature of the aryl rings observed in the crystal structure of **5a** (Fig. 4).[10]

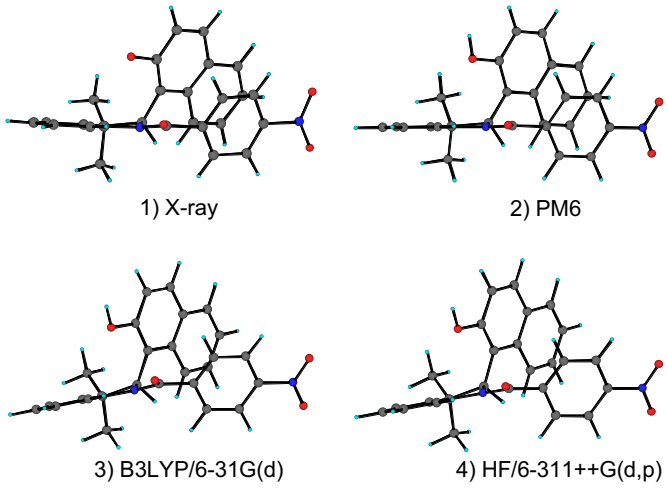


Figure 4. Planarity of the amide moiety for X-ray and calculated structures of **5a** (***anti***). Dihedral angle of C8a-N-CO-Ar: (1) 180.0°; (2) 179.7°; (3) 170.4°; (4) 169.4°.

The calculated interplanar angles between the napththyl and the phenyl rings for ***anti*** isomers **5a**, **5c**, and **5f** are 14.9°, 20.6°, and 19.2°, respectively (Fig. 5). The unsubstituted phenyl derivative (**5c**) showed a maximum value. The interatomic distances

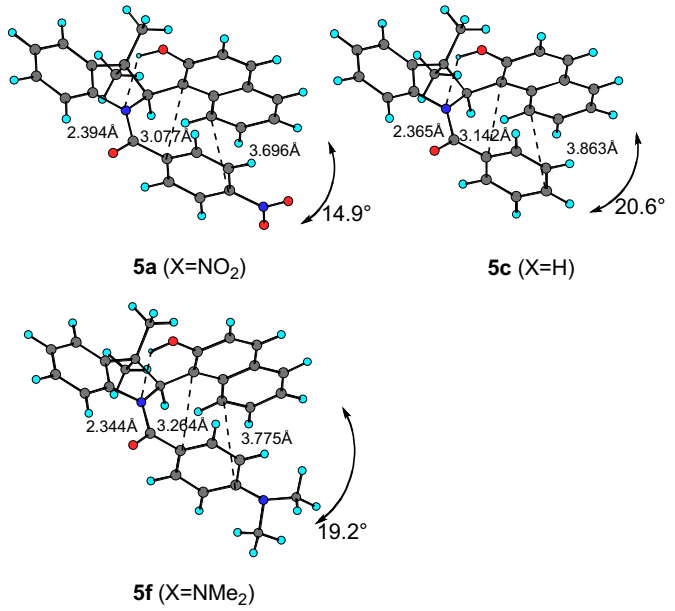


Figure 5. Comparison of the interatomic distances and interplanar angles for assessment of aromatic interaction between the substituted phenyl and naphthyl rings for the PM6-calculated structures of **5a**, **5c**, and **5f**.

between C4 of phenyl and C8 of naphthyl ring are 3.696, 3.863, and 3.775 Å, which are parallel to the order of the interplanar angle. These indicate that the aryl rings are attracted by intramolecular forces, which may be rationalized by the frontier molecular orbital energy separation between the substituted benzenes and 2-naphthol.[5g] The B3LYP/6-31G(d) calculated interplanar angle of **5c** is 36.2°, considerably larger than that of the crystal structure.

In the PM6-calculated structure of **5** (***anti***), the intramolecular ArOH···N short contact is found. The phenolic hydrogen atom is situated just above the N–C7a bond connecting the amide carbonyl and the benzene ring of indoline moiety. The interatomic distances between the amide nitrogen atom and the phenolic hydrogen atom in **5a**, **5c**, and **5f** are 2.394, 2.365, and 2.344 Å, respectively. In the ^{1}H NMR spectra, the hydroxy protons of **5a**, **5c**, and **5f** resonate at 9.80, 9.59, and 9.49 ppm as sharp singlet signals, respectively.[5g] These protons resonated at ca. 0.4–0.7 ppm higher field than the 4-OH proton signal (10.19 ppm, br s) of the coupling product of **1c** and 1-naphthol ([2-(4-hydroxynaphthalen-1-yl)-3,3-dimethylindolin-1-yl] phenyl methanone).[11] The chemical shift of a hydroxy proton signal is a balance between two opposite contributions: a downfield shift due to the ArOH···N hydrogen bonding and an upfield shift due to the anisotropic effect of the conjugated system.

The stabilization energy of **5c** due to OH···N interaction was calculated to be 4.2 kcal/mol in comparison with the local minimum ***anti*** structure without the interaction. The more elaborate DFT calculation at B3LYP/6-31G(d) level for 2-(2-hydroxyphenyl)-3,3-dimethylindoline-1-carbaldehyde indicated that the stabilization energy due to the interaction is 1.5 kcal/mol, in which the OH···N distance is 2.126 Å. In the local minimum ***anti*** structure without OH···N interaction, the hydrogen atom is far distant from the N atom (Fig. 6). These observations suggest that both the effective π–π interaction and the ArOH···N interaction affect the stabilization of the ground-state structures of the ***anti*** atropisomers. Similar interaction is found in the ***syn*** isomer due to intramolecular CH···O type hydrogen bond[7d] between the C2-H and the ArOH, supported

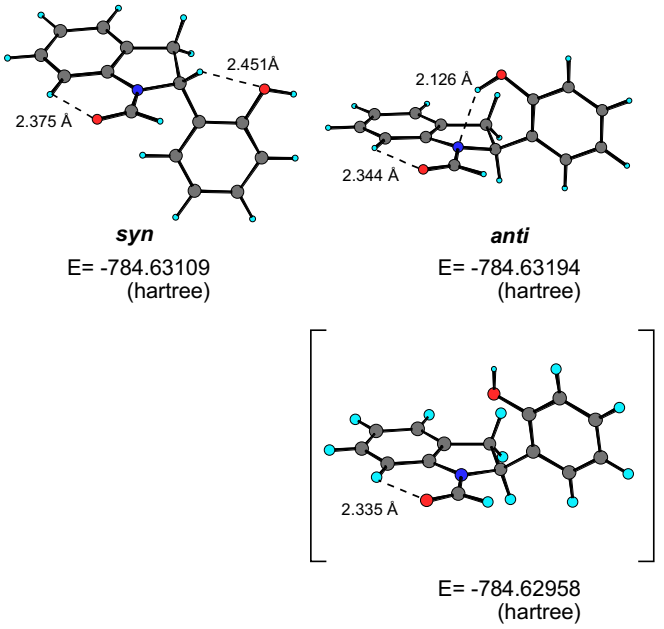


Figure 6. Estimation of ArOH···N and CH···O interactions for the structure of 2-(2-hydroxyphenyl)-3,3-dimethylindoline-1-carbaldehyde by DFT calculation.

by the similar ^{1}H NMR spectral behavior due to the ring current effect of the benzoyl ring.

2.5. Equilibrium reactions

Heating of **4a**–**f** in some solvents at 80° for 48 h caused transformation into equilibrium mixtures of **4a**–**f** and **5a**–**f**. The equilibrium constants [*K*=***anti*** (**5**)/***syn*** (**4**)], which were evaluated by the ^{1}H NMR spectral integration of the C2-H, are shown in Table 1. The substituent effect for the interconversion (**4**⇆**5**) on the equilibrium constant was examined by plotting *K* against Hammett's σ_p values[12] (Fig. 7).

Table 1
Equilibrium constant (*K*) from equilibrium reaction between several ***syn*** and ***anti*** isomers in solvent

Compd.	R	X	*K* (***anti***/***syn***)		
			Benzene	DMSO-d_6	EtOH
4a	OH	NO_2	1.14	1.02	0.58
4b	OH	Cl	0.96	0.63	0.43
4c	OH	H	0.94	0.54	0.34
4d	OH	Me	1.35	0.67	0.47
4e	OH	OMe	1.37	0.78	0.58
4f	OH	NMe_2	2.06	0.81	0.75
6a	OMe	NO_2	0.91	1.24	1.30
6c	OMe	H	0.54	0.63	0.83
6e	OMe	OMe	0.89	0.89	0.96

As can be seen in Figure 7a, the equilibrium constant in benzene was a minimum for the unsubstituted derivative (X=H) and larger when either electron-withdrawing (X=NO_2) or -donating (X=NMe_2) substituents were present. Both substituents cause ***anti*** (**5**) preference in the isomerization. In benzene solution, the plotting *K* against σ_p for **6** showed a similar U-shaped curve as observed in **4a**–**f** (Fig. 7b). However, the preference of ***anti*** isomer (**7**) decreased in comparison with the corresponding 2-hydroxynaphthyl derivatives (**5**).

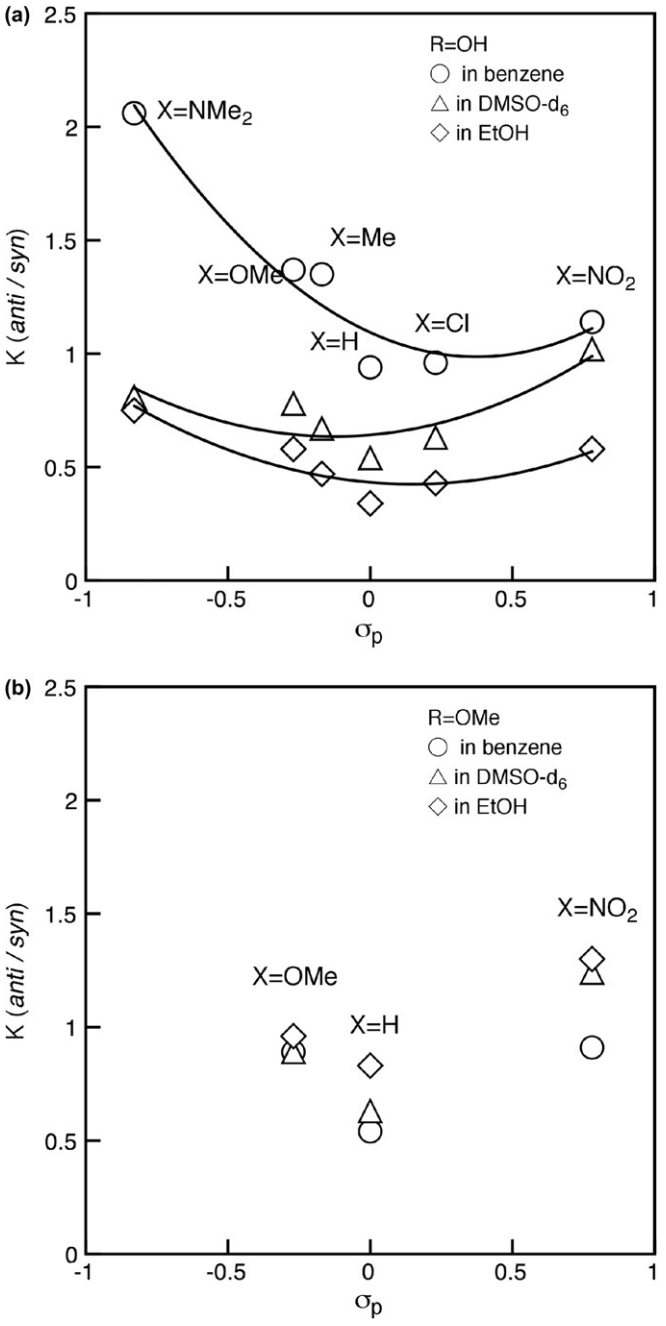


Figure 7. Plot of *K* for equilibrium reaction against Hammett's σ_p. (a) *K* (**4**⇆**5**) versus σ_p (b) *K* (**6**⇆**7**) versus σ_p.

3. Discussion

As mentioned above, the interplanar angle between the 4-substituted phenyl and naphthyl rings for the ***anti*** isomers (**5a**–**d**) in the crystal was largest for the unsubstituted derivative (**5c**). The value was smaller when nitro (**5a**) or methyl (**5d**) group was introduced on the phenyl ring. This suggests that the donor–acceptor attractive interaction between the aryl moieties is present in the crystal. However, contrary to our expectation, the angle of the 4-dimethylaminophenyl derivative (**5e**) is much larger than that of **5c**. The crystal structure indicates that the two molecules form a dimer linked by strong hydrogen bonds between the amide carbonyl and the naphthyl OH group. The intermolecular CH···π interaction exists between the 4-dimethylaminophenyl ring and the one of the neighboring molecule (Fig. 3). Therefore, the π–π interaction between the aryl rings should be assessed under consideration of the crystal packing features. The short contacts of the packing diagram indicated that the interplanar angle between the 4-

dimethylaminophenyl and naphthyl ring is expanded by the inclusion of the naphthyl ring of a neighboring molecule into the face-to-face space (Fig. 3b).

To know the effect of the formation of the hydrogen-bonded dimer on the conformational change in crystal structure, PM6 calculation was examined for the dimer of **5a**. The method predicted that the interplanar angle is 24.0°, which is significantly larger than the observed one (12.8°) or the calculated value of the monomer (14.9°). The structural feature of the hydrogen-bonded dimer could not be reproduced by PM6 method. This suggests that the deformation of the 4-nitrophenyl and naphthyl rings is not arisen from the dimer formation but from other intramolecular interactions.

In order to obtain the experimental evidence of the effective π–π interaction and the intramolecular weak interactions, we explored the correlation between the equilibrium constants (*K*) for the interconversion (***syn*⇆*anti***) in some solvents and the substituent effect of the phenyl groups. The plotting *K* against σ_p gave U-shaped curve (Fig. 7). A plot of the *K* values against the PM6 HOMO energies of 4-substituted benzene also gave a U-shaped curve (Fig. 8).

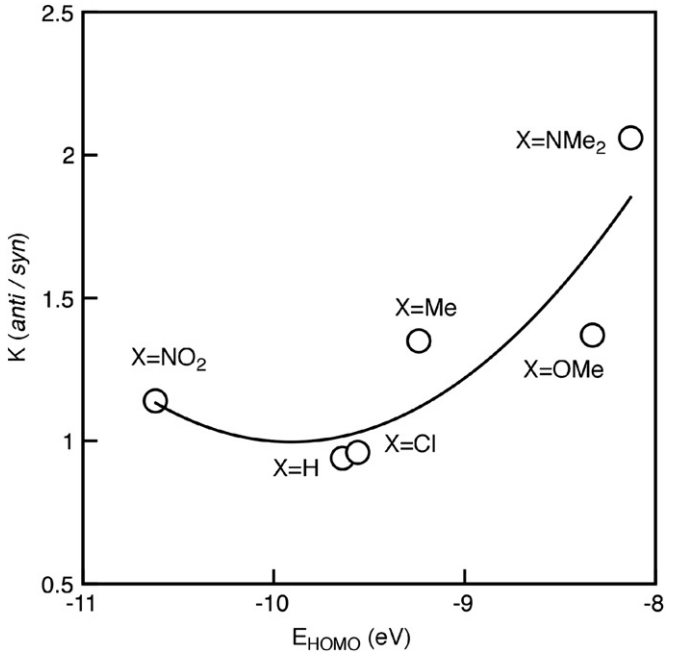


Figure 8. Plot of *K* for equilibrium reaction in benzene against the E_{HOMO} of 4-substituted benzene.

These facts can be attributed to the change of the frontier orbital interaction with introduction of the substituents on phenyl ring.[13] Inspection of the orbital phase interaction indicates that the degree of orbital overlap for the ***anti*** (**5**) isomer is more effective than the ***syn*** (**4**) isomer.[5g] Therefore, the plot of U-shaped curve between *K* and σ_p clearly indicates that the 'neutral-type' donor–acceptor interaction[14] between the naphthyl and the phenyl group is operative in solution. The fact that 1-[2-(2-hydroxynaphthalen-1-yl)-3,3-dimethylindolin-1-yl]ethanone (so-called *N*-acetyl derivative) shows ***syn*** preference on the equilibrium reaction[5i] supports the presence of the attractive π–π interaction between the aromatic rings.

The preference of ***anti*** isomer (**5**) decreased in polar solvent, such as DMSO-d_6 regardless of the substituents on the phenyl ring. To know the solvent effect on the relative stability of the isomers, the ground-state structures of **4a** and **5a** were calculated in some solvents using Conductor-like Screening Model (COSMO)[15] approach. The calculation indicates that the ***anti*** (**5a**) preference decrease with an increase of solvent polarity Table 2. For example, the difference (ΔΔHf) on changing the solvent from benzene to DMSO are 1.3 and 0.7 kcal/mol, respectively. Taking the overestimation of ArOH···N type stabilization into consideration, there might be little difference for the relative stability of the isomers in polar solvents.

Table 2
Heats of formation (ΔHf)[a] of ***syn*** and ***anti*** isomers in several solvents calcuated by PM6-COSMO method

Solvent	R=OH		R=OMe	
	4a (***syn***)	**5a** (***anti***)	**6a** (***syn***)	**7a** (***anti***)
Gas	−5.9	−8.0 (−4.3[b])	−1.7	−0.0
Benzene	−13.7	−15.0 (−12.4[b])	−8.5	−7.3
DMSO	−23.9	−24.6 (-23.1[b])	—	—
H_2O	−24.2	−24.5 (−23.4[b])	—	—

[a] kcal/mol.
[b] ΔHf without N···HOAr interaction.

To know the role of 2-hydroxyl group on the naphthalene ring in the relative stability of the isomers, the equilibrium constants of 2-methoxynaphthyl derivatives (**6a**, **6c**, and **6e**) were evaluated. In benzene solution, the plotting *K* against σ_p for **6** showed a similar U-shaped curve as observed in **4a**–**f** (Table 1 and Fig. 7). However, the preference of ***anti*** isomer (**7**) decreased in comparison with the corresponding 2-hydroxynaphtyl derivatives (**5**). The lack of the ArOH···N interaction due to the methylation of the 2-hydroxy group reduces the energetic preference for ***anti*** (**7**), resulting in decrease of the *K* value.[16] The COSMO method predicts that the ΔHf of the ***syn*** isomer is 1.2 kcal/mol lower than that of ***anti*** isomer. This corresponds to the observed relative stability showing that the *K* value is 0.91. In addition to this, the solvent change from benzene to ethanol causes the mode of hydrogen bond from intramolecular weak >CH···O(Me)– bond to intermolecular EtOH···O(Me)– bond resulting in the decrease of ***syn*** isomer (**6**).

In summary, the presence of the effective π–π interaction between the parallel-stacked aryl units and the intramoleculer interactions (ArOH···N and CH···O interactions) in **4** and **5** affects the stabilization of the rotamers and the conformational change of the aryl groups (Fig. 9).

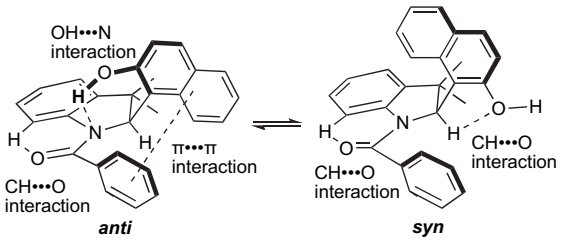


Figure 9. Plausible intramolecular weak interactions.

4. Experimental

4.1. Materials

[2-(2-hydroxynaphthalen-1-yl)-3,3-dimethylindolin-1-yl](4-substituted phenyl)methanone (**4**, **5**) were prepared by the previously reported method.[5c]

4.2. Crystal structure analysis

The single crystals of **4c**, **5c**, **5d**, and **5f** were prepared by slow evaporation of its ethanol solution at room temperature. All measurements were performed on a Rigaku RAXIS RAPID imaging plate area detector with graphite-monochromated Mo-Kα radiation (λ=0.7107 Å). The data were collected at a temperature of

23±1 °C to a maximum 2θ value of 55°. The structure was solved by direct method (SIR-92[17a]), and hydrogen atoms were placed at the calculation. The structure was refined by a full-matrix least-squares technique using anisotropic thermal parameters for non-hydrogen atoms and a riding model for hydrogen atoms. All calculations were performed using the crystallographic software package Crystal Structure.[17b,c] These X-ray crystallographic data have been deposited at the Cambridge Crystallographic Data Centre (CCDC).

4.2.1. Crystal data of ***4c****.* $C_{27}H_{23}NO_2$, M=393.48, orthorhombic, space group *Pbca* (#61), a=16.789(3), b=17.503(3), c=14.234(4) Å, V=4182(1) Å^3, Z=8, Dc=1.250 g/cm^3, R=0.120, R_w=0.154, CCDC ref. No. 749425; **5c**: $C_{27}H_{23}NO_2$, M=393.48, trigonal, space group *R-3* (#148), a=26.210(1), c=16.1455(6) Å, V=9605.4(7) Å^3, Z=18, Dc=1.224 g/cm^3, R=0.057, R_w=0.104, CCDC ref. No. 749426; **5d**: $C_{28}H_{25}NO_2$, M=407.51, monoclinic, space group $P2_1/n$ (#14), a=14.408(1), b=10.814(1), c=15.833(1) Å, β=116.596(5)°, V=2205.9(2) Å^3, Z=4, Dc=1.227 g/cm^3, R=0.057, R_w=0.098, CCDC ref. No. 749427; **5f**: $C_{58}H_{56}N_4O_4$, M=873.10, triclinic, space group *P*-1 (#2), a=9.7381(5), b=11.0881(6), c=22.018(1) Å, α=80.275(2), β=89.114(1), γ=85.609(1)°, V=2336.4(2) Å^3, Z=2, Dc=1.241 g/cm^3, R=0.068, R_w=0.098, CCDC ref. No. 749428.

4.3. Equilibrium reaction between *syn* (4) and *anti* (5) isomers (general procedure)

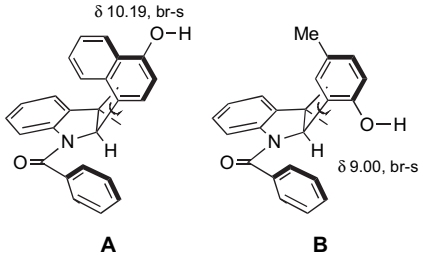
A benzene solution of **4** (10 mg) in a sealed tube was heated in a thermostated oil bath at 80 °C for 48 h. After evaporation of the solvent under reduced pressure, the residue was analyzed by ^{1}H NMR. The equilibrium constant (K=***anti*** (**5**)/***syn*** (**4**)) was evaluated by the spectral integration of the C2-H.

4.4. Molecular orbital (MO) calculations

Semi-empirical MO (PM6) calculations were run through Winmostar[18] interface using MOPAC2009[9] on a DELL Dimension9200 computer. Solvent effects were considered at the PM6 level using the COSMO algorithm[15] incorporated in MOPAC2009. The ab initio and DFT computations were performed with GAUSSIAN03[8] on a HIT Linux cluster server made up of dual 1.6 GHz Itanium 2 processors. Zero-point energy (ZPE) corrections were scaled by 0.9804.[19]

References and notes

1. (a) Oki, M. *Angew. Chem.*, **1976**, *88*, 67–74; (b) Oki, M. In *Topics in Stereochemistry*; Allinger, N. L., Eliel, E. L., Wilen, S. H., Eds.; John Wiley & Sons: New York, NY, 1983; Vol. 14, pp 47–79.
2. Oki, M. *Acc. Chem. Res.* **1990**, *23*, 351–356.
3. (a) Hunter, C. A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1584–1586; (b) Hunter, C. A. *Chem. Soc. Rev.* **1994**, *23*, 101–109.
4. (a) Cozzi, F.; Cinquini, M.; Annunziata, R.; Dwyer, T.; Siegel, J. S. *J. Am. Chem. Soc.* **1992**, *114*, 5729–5733; (b) Cozzi, F.; Cinquini, M.; Annunziata, R.; Siegel, J. S. *J. Am. Chem. Soc.*, **1993**, *115*, 5330–5331.
5. (a) Harano, K.; Yasuda, M.; Ida, Y.; Komori, T.; Taguchi, T. *Cryst. Struct. Commun.* **1981**, *10*, 165–171; (b) Eto, M.; Harano, K.; Hisano, T.; Kitamura, T. *J. Heterocycl. Chem.*, **1992**, *29*, 311–315; (c) Kitamura, T.; Harano, K.; Hisano, T. *Chem. Pharm. Bull.* **1992**, *40*, 2255–2261; (d) Eto, M.; Ito, F.; Kitamura, T.; Harano, K. *Heterocycles* **1994**, *38*, 2159–2163; (e) Eto, M.; Ito, F.; Kitamura, T.; Harano, K. *Heterocycles* **1996**, *43*, 1159–1163; (f) Watanabe, A.; Moriguchi, M.; Ito, Ito; Yoshitake, Y.; Eto, M.; Harano, K. *Heterocycles* **2000**, *53*, 1–6; (g) Ito, F.; Moriguchi, T.; Yoshitake, Y.; Eto, M.; Yahara, S.; Harano, K. *Chem. Pharm. Bull.* **2003**, *51*, 688–696; (h) Watanabe, A.; Yamaguchi, K.; Ito, F.; Yoshitake, Y.; Harano, K. *Heterocycles* **2007**, *71*, 343–359; (i) Eto, M.; Ito, F.; Sato, H.; Shinohara, I.; Yamaguchi, K.; Yoshitake, Y.; Harano, K. *Heterocycles* **2009**, *78*, 1485–1496.
6. Nishio, M.; Hirota, M.; Umezawa, Y. *The CH···π interaction; Evidence Nature and Consequences*; Wiley: New York, NY, 1998.
7. (a) Taylor, R.; Kennard, O. *J. Am. Chem. Soc.*, **1982**, *104*, 5063–5070; (b) Desiraju, G. R. *Acc. Chem. Res.* **1991**, *24*, 290–296; (c) Steiner, T.; Kanters, J. A.; Kroon, J. A. *Chem. Commun.* **1996**, 1277–1278; (d) Steiner, T. *Crystallogr. Rev.* **1996**, *6*, 1–57.
8. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Revision C.02*; Gaussian,: Wallingford CT, 2004.
9. MOPAC2009: Stewart, J. J. P. Stewart computational chemistry, version 9.062M web Http://OpenMOPAC.net.
10. The PM6 calculation reproduced the relative stability of the isomers. The heat of formations of ground-state structures for ***syn*** (**4a**) and ***anti*** (**5a**) are −5.9 and −8.0 kcal/mol, respectively (see Table 2).
11. The hydroxy proton signals of the non-atropisomeric indoline derivatives, such as compounds A and B, appeared as broad singlets in DMSO-d_6. On the other hand, the protons of the ***anti*** isomers (**5a**–**f**) appeared characteristically as sharp singlets at 9.5–9.8 ppm under the same conditions of measurement. The difference in the signal shape suggests that the decrease of conformational mobility of the hydroxyaryl group due to the intramolecular ArOH···N interaction.



12. Hammet, L. P. *Physical Organic Chemistry*, 2nd ed.; McGraw-Hill: New York, NY, 1970.
13. Henri-Rousseau, O.; Texier, F. *J. Chem. Educ.* **1978**, *55*, 437–440.
14. Sustmann, R.; Trill, H. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 838–840.
15. (a) Klamt, A.; Schurmann, G. *J. Chem. Soc., Perkin Trans. 2* **1993**, 799–805; (b) Klamt, A. *J. Phys. Chem.* **1996**, *100*, 3349–3353.
16. The rate constants for the isomerization between ***syn*** and ***anti*** isomers are measured according to the established method.[5c] The activation energies of **4b** and the 2-methoxynaphthyl derivative (**6b**) in diphenylether are 24.2 and 20.3 kcal/mol, respectively. The barrier to rotation of **6b** is lower than that of **4b**. This fact suggests that the intramolecular ArOH···N interaction partially affects the stabilization of the rotamers.
17. (a) SIR92: Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M.; Polidori, G.; Camalli, M. *J. Appl. Crystallogr.* **1994**, *27*, 435–436; (b) CrystalStructure 3.6.0: *Crystal Structure Analysis Package*; Rigaku and Rigaku/MSC: USA, 2000–2004; (c) CRYSTALS Issue 10: Watkin, D. J.; Prout, C. K.; Carruthers, J. R.; Betteridge, P. W. *Chemical Crystallography Laboratory*; Oxford: UK, 1996.
18. Senda, N. *Idemitsu Technical Report* **2006**, *49*, 106–111.
19. Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 10502–10513.