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Rotational Isomerism in Fluorene Derivatives. XV.[1] Conformational Equilibria of 2-Substituted and 2,7-Disubstituted 9-(2′-Dimethylaminophenyl)-fluorene Derivatives and the Effects of Acid on Them

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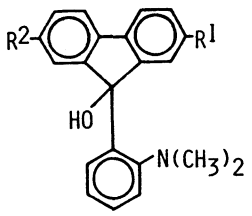
Several 9-(2′-dimethylaminophenyl)-9-fluorenols (**2**) and 9-(2′-dimethylaminophenyl)fluorenes (**3**), which had electron-attracting or electron-releasing groups at 2- or 2,7-positions of the fluorene ring, were synthesized. The conformational equilibria (anti⇄syn) of **2** and **3** in $CDCl_3$ lay near to their syn sides. However, the equilibria of **2** in DMSO-d_6 inclined to the anti side. By the addition of trifluoroacetic acid to the solution of **3** in $CDCl_3$, *anti*-**3** salts were formed and stabilized by the N-H···π interaction between the dimethylammonio group and the fluorene ring. In this case, the intensities of the N-H···π interaction were affected by the magnitudes of the π-electron density of the fluorene ring.

During the course of an investigation on the conformational equilibria (anti⇄syn)[2] in 9-(2′-substituted phenyl)fluorenes, we recently recognized the presence of the N-H···π interaction between the dimethylammonio group and the fluorene ring in the anti-form of ammonium trifluoroacetate of 9-(2′-dimethylaminophenyl)fluorene (**3a**).[3] In the present paper, we wish to report on the syntheses of several 2-substituted and 2,7-disubstituted 9-(2′-dimethylaminophenyl)fluorene derivatives having electron-attracting or releasing groups as substituents, and on the investigation of the effects of these substituents on their conformational equilibria in $CDCl_3$, DMSO-d_6, and trifluoroacetic acid.



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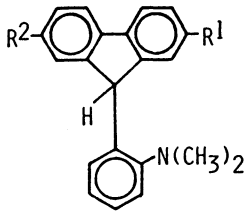

3

		R^1	R^2
2a,	**3a**	H	H
2b,	**3b**	Br	H
2c,	**3c**	Br	Br
2d,	**3d**	CH_3	H
2e,	**3e**	CH_3O	H
2f,	**3f**	CH_3O	CH_3O
	3g	OH	H
	3h	OH	OH

Scheme 1.

Results and Discussion

Preparation of 2-Substituted and 2,7-Disubstituted 9-(2′-Dimethylaminophenyl)fluorenes (3). The reaction of 2-substituted or 2,7-disubstituted fluorenones (**1**) with 2-dimethylaminophenylmagnesium bromide in ether gave the corresponding fluorenols (**2**) (**2b—2f** in Scheme 1). The reduction of **2b—2d** with hydrogen iodide in acetic acid in the presence of red phosphorus gave the desired fluorenes **3b—3d**. The same treatment of **2e** and **2f** with hydrogen iodide and red phosphorus

Table 1. Syntheses of 2-Substituted and 2,7-Disubstituted 9-(2′-Dimethylaminophenyl-9-fluorenols (**2**) and 2-Substituted and 2,7-Disubstituted 9-(2′-Dimethylaminophenyl)fluorenes (**3**)

Compd	R^1	R^2	Y	Mp	Yield	^{1}H NMR: δ/ppm					
						In $CDCl_3$					In DMSO-d_6
				θ_m/°C	%	$N(CH_3)_2$	R^1, R^2	Y	6′-H	Aromatics	$N(CH_3)_2$
2a[2]	H	H	OH	174—176	85	2.84s	—		6.36br.d	6.74—7.52m	1.96s
2b	Br	H	OH	160—161	50	2.94s	—		6.52br.d	6.80—7.90m	1.80s
2c	Br	Br	OH	262—263	51	2.94s	—		6.50br.d	6.80—7.70m	1.71s
2d	CH_3	H	OH	153—155	41	2.98s	2.36s		6.56br.d	6.90—7.80m	1.98s
2e	CH_3O	H	OH	195—196	59	2.84s	3.70s		6.28br.d	6.40—7.50m	2.03s
2f	CH_3O	CH_3O	OH	191—192	80	3.03s	3.81s		6.55br.d	6.70—7.60m	2.10s
3a[2]	H	H	H	122	69	2.86br.s	—	5.86br.s	6.34br.d	6.74—7.72m	
3b	Br	H	H	133—135	55	2.92br.s	—	5.96br.s	6.40br.d	6.80—7.90m	
3c	Br	Br	H	191—193	62	2.93br.s	—	5.98br.s	6.40br.d	6.80—8.00m	
3d	CH_3	H	H	—[a]	56	2.92br.s	2.36s	5.90br.s	6.44br.d	6.70—7.90m	
3e	CH_3O	H	H	86—87	27	2.92br.s	2.76s	5.84br.s	6.38br.d	6.60—7.80m	
3f	CH_3O	CH_3O	H	90—91	52	2.96br.s	3.79s	5.90br.s	6.49br.d	6.70—7.80m	

a) Light yellow liquid.

in acetic acid afforded a mixture of **3e** and 2-hydroxy compound (**3g**), and a mixture of **3f** and 2,7-dihydroxy compound (**3h**), respectively. Pure **3e** and **3f** were obtained by the treatment of each mixture with dimethyl sulfate in methanol. The mp's, yields, and NMR data of **2** and **3** are shown in Table 1.

Conformational Equilibria of 2 and 3 in $CDCl_3$. As shown in Table 1, dimethylamino protons and 6'-protons of **2b—2f** and **3b—3f** in $CDCl_3$ appeared at δ ca. 2.8—3.0 as singlets or broad singlets and at δ ca. 6.3—6.6 as broad doublets, respectively, as in the cases of **2a** and **3a**. For compound **2a** and **3a**, their conformational equilibria (anti⇄syn) have been investigated by the behavior of the chemical shifts of dimethylamino groups and 6'-protons, and these compounds have been confirmed to exist predominantly as the syn-form at room temperature.[3] From the similarity for the appearance of these chemical shifts as shown in the Table, it can be claimed that the equilibria of **2b—2f** and **3b—3f** are also inclined to the syn-form (Fig. 1).

DNMR spectra of **3b—3f** were observed in $CDCl_3$. However, the anti-signals were scarcely recognized at low temperature (−20 °C) because the equilibria lay close to the syn side. Furthermore, since **3b—3f** were almost insoluble in $CDCl_3$, the activation parameters of the internal rotation (anti⇄syn) of these compounds were not measured.

Conformational Equilibria of 2 in DMSO-d_6. We have already indicated the existence of intramolecular hydrogen bonding in **2a**[3] and 9-(2'-methoxyphenyl)-9-fluorenol[4] by the examination of their IR spectra in CCl_4 and their NMR spectra in $CDCl_3$ or DMSO-d_6. Accordingly, it was proved that the intramolecular hydrogen bonding between the hydrogen atom of the 9-hydroxyl group and the nitrogen atom of 2'-dimethylamino group stabilized the syn-form of **2** in $CDCl_3$ (Fig. 2).

In the compound **2a** in DMSO-d_6, particularly, the dimethylamino proton was observed at δ 1.96 as a singlet. That is, it could be noted that the equilibrium of the rotamer of **2a** lay near to the anti side.[3] The dimethylamino protons of **2b—2f** were similarly observed at δ 1.7—2.1 in DMSO-d_6. In these cases, intermolecular hydrogen bonding, which formed between the hydrogen atom of the 9-hydroxyl group and the oxygen atom of dimethyl sulfoxide, should stabilize the anti-form. Thus, the anti-form of **2** was exclusively predominant in DMSO-d_6 (Fig. 2).

As can be seen from Table 1, the chemical shifts of the dimethylamino protons in DMSO-d_6 were affected by the nature of the 2- or 2,7-substituents on the fluorene ring, and their increasing order of chemical shift was shown as follows; **2c<2b<2a<2d<2e<2f**. Each chemical shift was a specific values for compounds **2a—2f**, respectively. That is, these chemical shifts of **2** having stronger electron-attracting substituent appeared at higher magnetic field. In fact an electron-attracting substituent decreased the π-electron density of the fluorene ring. The repulsion between the fluorene ring and an unshared electron pair on the nitrogen atom in the dimethylamino group should be decreased. Thus, the magnitudes of the electron pair $\cdots$ π repulsive interaction in **2** can be given in the following order; **2c<2b<2a<2d<2e<2f**.

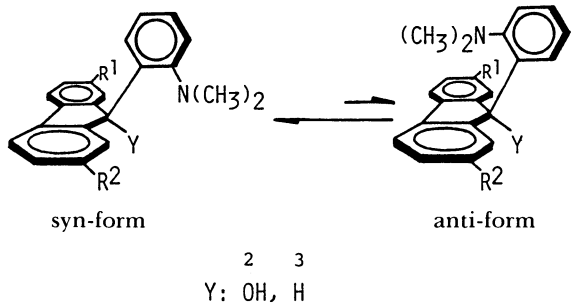

Fig. 1. Conformational equilibria between syn and anti forms of **2** and **3** in $CDCl_3$.

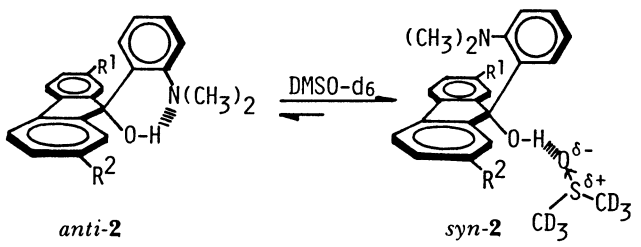

Fig. 2. Interconversion between syn and anti conformers of **2** in DMSO-d_6.

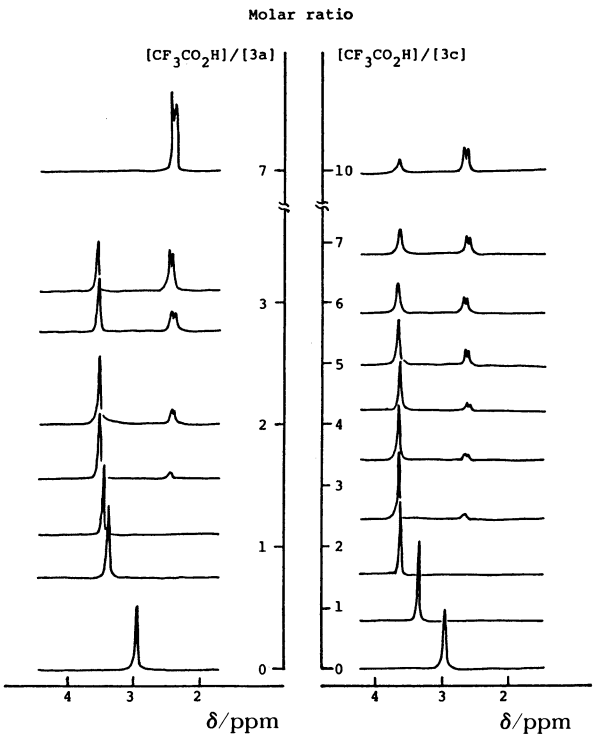

Fig. 3. Isomerization of **3a** and **3c** by addition of trifluoroacetic acid at 0 °C.

N-H···π Interaction of Ammonium Trifluoroacetates of 3. As shown in the previous paper,[3] we recognized that an N-H···π interaction between the dimethylammonio group and the fluorene ring stabilized the anti-form of **3a**-trifluoroacetate. Accordingly, it is interesting to investigate the influence of the π-density of the fluorene ring for the N-H···π interaction in **3**. In 2-substituted and 2,7-disubstituted 9-arylfluorene derivatives, the substituents should not affect the rotation about C(9)-C(Ar) bonds and the stabilization of the syn form. The electronic properties of these substituents change the π-density of the fluorene ring.

The variation of the ^{1}H NMR signals of the dimethylamino groups was followed upon addition of trifluoroacetic acid in $CDCl_3$ solution of **3b—3f**. For an example, the examination for **3c** was illustrated as compared with that of **3a** in Fig. 3.

The methyl signal (singlet) of *syn*-**3c** moved to a lower field on increasing the amount of acid added. When excess equivalent of acid was added ($[CF_3CO_2H]/[\mathbf{3c}]\approx3$), the methyl signal (doublet) of the anti-salt appeared. Further added acid ($[CF_3CO_2H]/[\mathbf{3c}]>10$) reversed the intensities of the anti- and syn-signals, and the syn-signal then almost disappeared. The methyl signal of **3a** in $CDCl_3$ also behaved in the similar manner on adding acid.[3] However, the anti-signal of the **3a**-salt has already appeared when $[CF_3CO_2H]/[\mathbf{3a}]\approx1.5$ (see Fig. 3).

Thus, the intensities of the two methyl signals (syn and anti) of the **3c**-salt changed more slowly compared with those of **3a**-salt. These experimental results should be attributed to the weaker N-H···π interaction in the **3c**-salt than in the **3a**-salt. Accordingly, the π-electron density of the fluorene ring of the **3c**-salt should be smaller than that of the **3a**-salt. This phenomenon can be understood from the fact that the electron-attracting property of bromine decreases the π-electron density of the fluorene ring in **3c**.

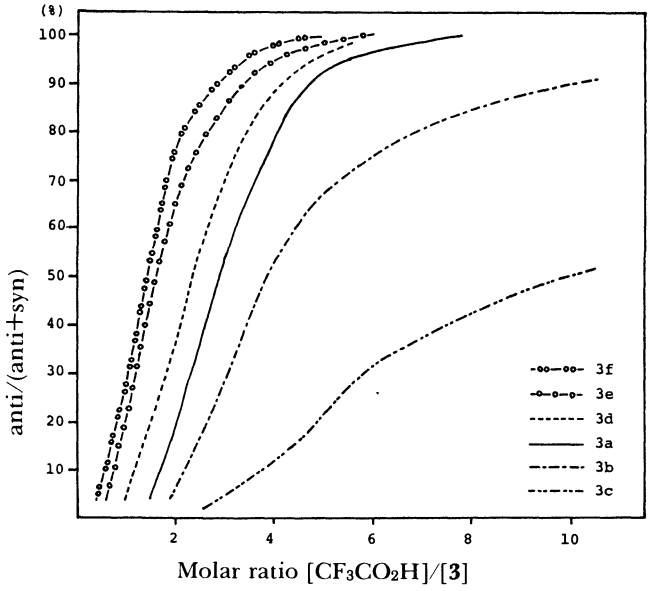

Fig. 4. Proportion of *anti*-**3** salt depend on the molar ratio of CF_3CO_2H vs. **3** ($[\mathbf{3}]/[CDCl_3]$=ca. 5×10^{-5} mol/0.4 ml).

On the other hand, in compound **3f**, the rate of variation of the conformational equilibria following the addition of trifluoroacetic acid was much faster than that of **3a**. The relationship between the variation of the conformational equilibria and the concentration of the acid in **3b—3f** are shown together with that in **3a** in Fig. 4.

It is apparent that the larger is the π-electron densities of the fluorene ring, the stronger is the N-H···π interaction; the magnitudes of the N-H···π interactions in *anti*-**3**-salts are given in the following order; **3f>3e>3d>3a>3b>3c**.

Experimental

^{1}H NMR spectra were recorded on a JEOL-MH-100 spectrometer with a JEOL model JES-VT-3 variable temperature controller. The chemical shifts are expressed in ppm, with tetramethylsilane as an internal standard. Mass spectra were recorded on a JEOL JMS-D spectrometer. The IR spectra were measured on a JASO IRA-1 spectrometer. All melting points are uncorrected.

2,7-Dibromo-9-(2′-dimethylaminophenyl)-9-fluorenol (2c). Typical Procedure. A solution of 2,7-dibromofluorenone (4.0 g, 12 mmol) in dry benzene was added to the Grignard reagent which was prepared from magnesium turnings (0.5 g, 12.5 mmol) and *o*-bromo-*N*,*N*-dimethylaniline (2.5 g, 12.5 mmol). The mixture was refluxed for 1 h. After cooling, the solution was poured into dil. hydrochloric acid. The solid precipitate was alkalized with sodium hydroxide solution and extracted with chloroform. The organic layer was dried with magnesium sulfate and distilled off in vacuo, leaving a residue which was recrystallized from chloroform to give **2c** as colorless prisms; yield 2.9 g (51%), mp 262—263 °C. Found: C, 54.90; H, 3.60; N, 3.05%. Calcd for $C_{21}H_{17}NOBr_2$: C, 54.93; H, 3.73; N, 3.05%.

2-Bromo-9-(2′-dimethylaminophenyl)-9-fluorenol (2b). Yield 50%; colorless crystals; mp 160—161 °C (from chloroform). Found: C, 66.21; H, 4.74; N, 3.52%. Calcd for $C_{21}H_{18}NOBr$: C, 66.33; H, 4.77; N, 3.68%.

2-Methyl-9-(2′-dimethylaminophenyl)-9-fluorenol (2d). Yield 41%; colorless needles; mp 153—155 °C (from chloroform). Found: C, 83.54; H, 6.75; N, 4.43%. Calcd for $C_{22}H_{21}NO$: C, 83.78; H, 6.71; N, 4.44%.

2-Methoxy-9-(2′-dimethylaminophenyl)-9-fluorenol (2e). Yield 59%; colorless crystals; mp 195—196 °C (from benzene). Found: C, 79.47; H, 6.18; N, 4.06%. Calcd for $C_{22}H_{21}NO_2$: C, 79.78; H, 6.39; N, 4.23%.

2,7-Dimethoxy-9-(2′-dimethylaminophenyl)-9-fluorenol (2f). Yield 80%; colorless crystals; mp 191—192 °C (from benzene). Found: C, 76.66; H, 6.53; N, 3.65%. Calcd for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88%.

2,7-Dibromo-9-(2′-dimethylaminophenyl)fluorene (3c). Typical Procedure. To a solution of **2c** (1.4 g, 3mmol) in acetic acid (10 ml) was added red phosphorus (0.3 g, 10 mmol) and hydriodic acid (57%, 6.0 g, 50 mmol), and the mixture was refluxed for 4 h. After cooling, red phosphorus was filtered off and the solvent distilled off in vacuo. The

residue was alkalized by sodium hydroxide solution, extracted with benzene and the extract dried with magnesium sulfate. The solution was evaporated in vacuo, leaving a residue which was recrystallized from chloroform to give **3c** as colorless crystals; yield 0.8 g (62%), mp 191—193 °C. Found: C, 56.68; H, 3.78; N, 3.31%. Calcd for $C_{21}H_{17}NBr_2$: C, 56.91; H, 3.87; N, 3.16%.

2-Bromo-9-(2′-dimethylaminophenyl)fluorene (3b). Yield 55%; colorless crystals; mp 133—135 °C (from chloroform). Found: C, 69.11; H, 4.88; N, 3.94%. Calcd for $C_{21}H_{18}NBr$: C, 69.24; H, 4.98; N, 3.84%.

2-Methyl-9-(2′-dimethylaminophenyl)fluorene (3d). Yield 56%; oil; MS *m/z*: 219 (M^+).

2-Methoxy-9-(2′-dimethylaminophenyl)fluorene (3e). Hydriodic acid (57%, 6 g, 50 mmol) and red phosphrous (0.3 g, 10 mmol) were added to a solution of **2e** (1 g, 3 mmol) in acetic acid (20 ml) and refluxed for 3 h. The reaction mixture was concentrated in vacuo and the residue was treated with sodium hydrogensulfite. The solid precipitate was collected by filtration and dissolved in methanol. To the solution was added dimethyl sulfate (0.76 g, 6 mmol) and sodium hydroxide (0.36 g, 9 mmol), and the mixture was refluxed for 1 h. After cooling, the precipitate was washed with water and recrystallized from methanol to give **3e** as colorless crystals; yield 0.26 g (27%), mp 86—87 °C. Found: C, 83.89; H, 6.46; N, 4.37%. Calcd for $C_{22}H_{21}NO$: C, 83.78; H, 6.71; N, 4.44%.

2,7-Dimethoxy-9-(2′-dimethylaminophenyl)fluorene (3f). To a solution of **2f** (0.44 g, 1.2 mmol) in acetic acid (10 ml) was added hydriodic acid (57%,3 g, 25 mmol) and the mixture was refluxed for 2 h. The reaction mixture was worked up as described for the preparation of **3e**, to give **3f** as colorless crystals; yield 0.22 g (52%), mp 90—91 °C. Found: C, 80.17; H, 6.68; N, 4.12%. Calcd for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.05%.

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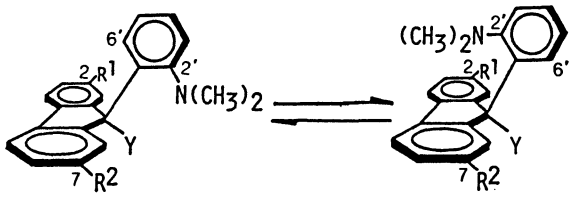
References

1) Part XIV of this series: A. Nishida, S. Shirakawa, S. Fujisaki, and S. Kajigaeshi, *Tec. Rep. Yamaguchi Univ.*, **4**, 145 (1988).

2) The conformations of 2-substituted and 2,7-disubstituted 9-(2′-dimethylaminophenyl)fluorenes were specified by the anti and syn nomenclature. The present IUPAC nomenclature of *ap* and *sp* for our systems is valid only when the fluorene ring is unsubstituted or symmetrically substituted. When unsymmetrically substituted a chiral center is created; the conformation must be specified in addition to the ±*sc*, ±*ac* nomenclature.



syn anti

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