Rotational Isomerism in Fluorene Derivatives XIV[1] Conformational Equilibria of 9-Substituted 9-(2-Cyanomethylphenyl) fluorene Derivatives

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Abstract

A series of 9-substituted 9-(2-cyanomethylphenyl)fluorene derivatives such as 9-hydro-(**4**), 9-bromo-(**5**), 9-methoxy-(**6**) and 9-hydroxy-9-(2-cyanomethylphenyl)fluorene (**7**) were prepared, and their conformational equilibria (*ap*⇄*sp*) were investigated on the bases of their ^{1}H NMR spectra.

It was confirmed that **4** existed as equilibrium mixture (*ap*/*sp* = 1.5/1) at room temperature, and **7** existed predominantly as the *ap*-conformer (*ap*/*sp* = 4.4/1) at -50℃, furthermore, both **5** and **6** existed overwhelmingly as the *ap*-forms at room temperature and at low temperature, respectively.

Introduction

We have recently investigated the conformational equilibria (*ap*⇄*sp*) of 9-(2-substituted phenyl)fluorene derivatives, in which such substrates are methy-[2], methoxy-[3], methylthio-[4], methylsulfinyl-[4], dimethylamino-[5], methoxymethyl-[6] and methyl amino group[1], on the bases of their DNMR spectra. In the present paper, we wish to report on the preparation of 9-substituted 9-(2-cyanomethylphenyl)fluorene derivatives and to discuss the conformational equilibria of these compounds by their ^{1}H NMR spectra.

Results and Discussion

Preparation of 9-Substituted 9-(2-Cyanomethylphenyl)fluorene Derivatives.

Starting material 9-(2-methylphenyl)-9-fluorenol (**1**)[7] was easily obtained by the reaction of fluorenone with 2-meththylphenylmagnesium bromide in absoluted ether. The reaction of 1 with NBS in carbon tetrachloride in the presence of small amount of BPO gave 9-(2-bromomethylphenyl)-9-fluorenol (**2**)[6]. Compound **2** was converted to 9-(2-iodomethylphenyl)fluorene (**3**) by treatment with hydroiodic acid in acetic acid[6]. The reaction of 3 with sodium cyanide in acetonitrile - water gave 9 -(2

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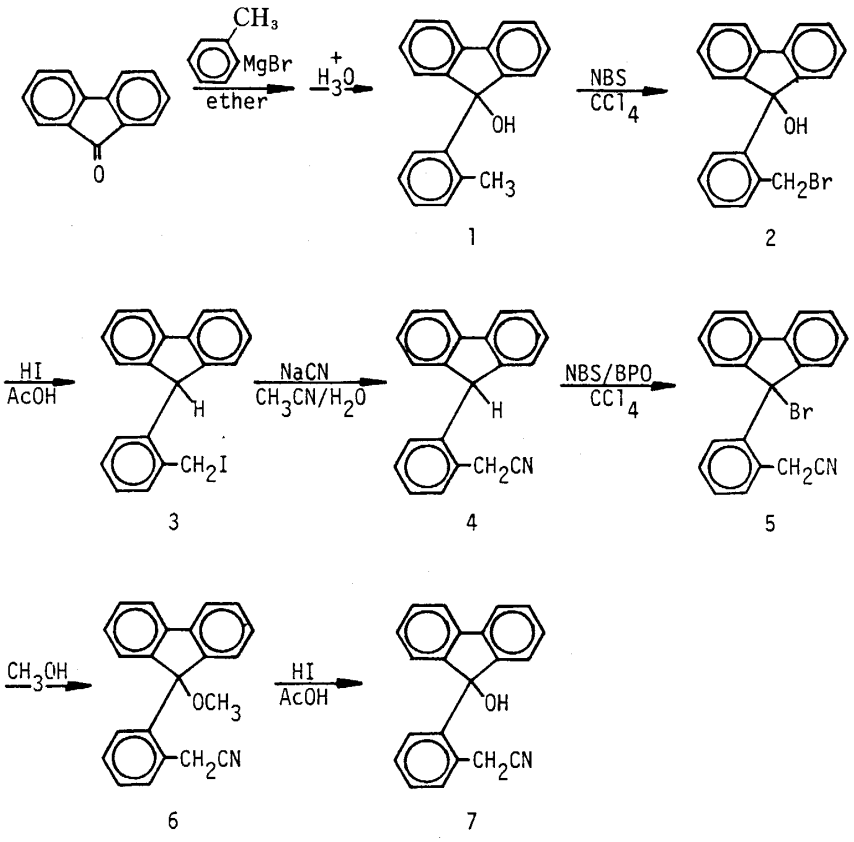


Scheme 1

Table 1 Syntheses of 9−substituted 9−(2−cyanomethylphenyl)−fluorene derivatives.

Compd.	9−Substituent	mp(℃)	Yield (%)	^{1}H−NMR ($CDCl_3$) : δ(ppm)at rt		
				2'−CH_2CN	9−Substituent	6'−H
4	H	oil	96	2.40s(1.5)[a] 3.96s(1)	4.82s(1.5) 5.08s(1)	6.36d
5	Br	151−153 (dec.)	74	2.50s	−	
6	OCH_3	133−135	42	2.98br.s	2.80s	
7	OH	182−184 (dec.)	55	2.72br.s	−	

a) Ratios of signal intensities are shown in parenthese.

-cyanomethylphenyl)fluorene (**4**). The reaction of **4** with NBS and BPO in carbon tetrachloride gave 9-bromo-9-(2-cyanomethylphenyl)fluorene (**5**). 9-(2-Cyanomethylphenyl)-9-methoxyfluorene (**6**) was obtained by reflux of methanol solution of **5**. The cleavage of an ether bond in **6** with hydrogen iodide gave 9-(2-cyanomethylphenyl)-9-fluorenol (**4**).

The melting points, yields and a part of ^{1}H NMR data of obtained 9-(2-cyanomethyl-

phenyl)fluorene derivatives are shown in Table 1.

Conformational Equilibria of 9-Substituted 9-(2-cyanomethylphenyl)fluorene Derivatives.

In general, two rotamers *ap* and *sp* of 9-(2-substituted phenyl)fluorene derivatives were observed on their NMR spectra at room temperature or at low temperature owing to their high barriers to rotation about the C(9)-C(Ar) bond. In fact, as shown in Table 1, two signals(*ap* and *sp*) of cyanomethyl group of 4 were observed at 2.40 and 3.96 ppm as singlets (K (*ap*/*sp*)=1.5/1) at room temperature, respectively. The ^{1}H NMR spectrum of 4 in $CDCl_3$ is illustrated in Fig.1, and the isomerization process of 4 by the rotation about C(9)-C(Ar) bond is shown in Fig.2.

In compound **5**, since the chemical shift of cyanomethyl group appeared at 2.50 ppm, which was almost near to that of the *ap*-form of **4**, as sharp singlet even at low temperature, we recognized that **5** should exist only as the *ap*-form.

In compound **6** and **7**, it was difficult to estimate their predominant conformers on ^{1}H NMR spectra at room temperature. thus, their DNMR spectra at low temperature (-62℃) were measured in the usual way. The signals of cyanomethyl group at low

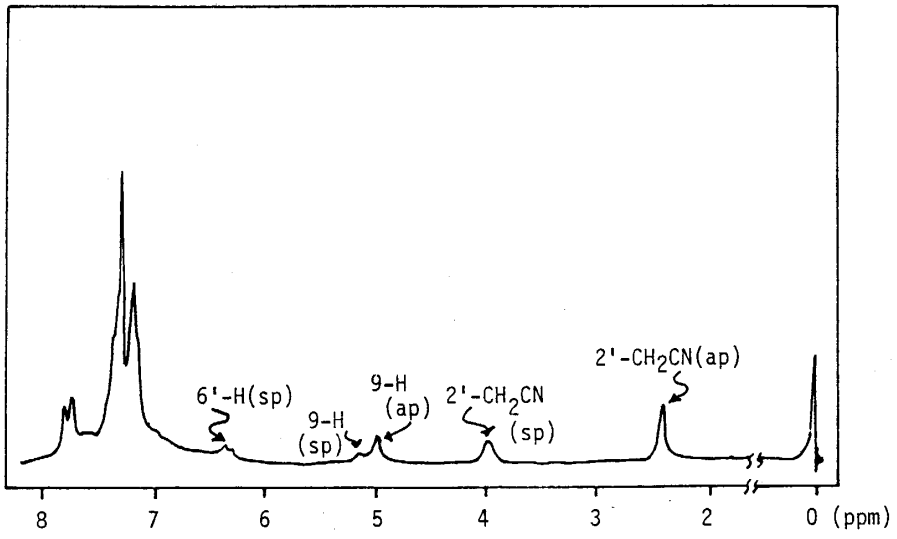
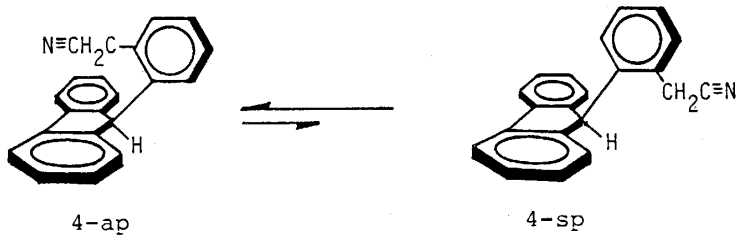


Fig. 1 ^{1}H NMR spectrum of **4** in $CDCl_3$ at room temperature.



4-ap 4-sp

Fig. 2 Isomerization process (*ap*⇄*sp*) for **4**.

Table 2 ^{1}H NMR date of 2'-cyanomethyl groups (*ap*- and *sp*-form) and equilibrium constant of **4**, **6** and **7**.

Compd.	δ(ppm) of CH_2CN	K (*ap*/*sp*)	Temp.(℃)
4	2.40s(*ap*) 3.96s(*sp*)	1.5/1	rt
6	2.72s(*ap*) 4.62br.s(*sp*)	*ap* predominant[a)]	−62
7	2.46s(*ap*) 3.36s(*sp*)	4.4/1	−50

a) K value was not calculated because *sp*-form was obserbed only trace amount.

Table 3 Equilibrium constants and activation parameters for rotation in 9-(2-substituted phenyl) flourene derivatives.

Compd.	Y	K(*ap*/*sp*)	ΔG(kcal/mol) *ap*→*sp*	ΔG(kcal/mol) *sp*→*ap*
8[2)]	CH_3	1/1.6	16.3	16.5
9[3)]	OCH_3	1/17	11.3	13.1
10[4)]	SCH_3	*sp* overwhelming	—	—
11[4)]	$SOCH_3$	1/1.5	15.3	15.5
12[1)]	$NHCH_3$	2/1	15.9	15.5
13[5)]	$N(CH_3)_2$	1/12	13.8	15.5
14[6)]	CH_2OCH_3	1/4.1	16.1	16.9
4	CH_2CN	1.9/1	16.5	16.1

temperature and the equilibrium constants K (*ap*/*sp*) of these compounds are shown together with that of 4 in Table 2.

Intramolecular Interactions Affect the Conformational Equilibria of 9-(2-Substituted phenyl)fluorene Derivatives.

Equilibrium constants (K) between *ap*- and *sp*-conformers, and free energies of activation for the rotational barriers about the C(9)-C(Ar) bonds in several 9-(2-substituted phenyl)fluorene derivatives are shown in Table 3.

As shown the Table, conformational equilibria of these compounds expect 9-(2-methylaminophenyl) fluorene (**12**) and **4** lie so far to *sp* side. We have already reported that conformational equilibrium of **12** lie to the *ap* side owing to the presence of N-H$\cdots\pi$ interaction between methylamino group and fluorene ring in its *ap*-form to stabilize this from as shown in Fig.3. Compound **4** have also demonstrated that the *ap*-form is more predominant conformer than the *sp*-one. Thus, we presumed that an attractive interaction between cyanomethyl group and π-electron of fluorene ring acts to stabilize the *ap*-form as shown in Fig.3.

12-ap 4-ap

Fig. 3 NH···π interaction in **12**−*ap*, and N≡C···π interaction in **4**−*ap*.

Experimental

All melting points are uncorrected. The ^{1}H NMR spectra were recorded on a JEOL-MH-100 spectrometer with JEOL model JES-VT-3 variable temperature controller. The chemical shifts are expressed in ppm with tetramethylsilane as an internal standard. Dynamic NMR spectra were analyzed by using a modified version of the computer program DNMR 3. The IR spectra were measured on a IRA-1 spectrometer as potassium bromide pellets.

9-(2-Bromomethylphenyl)-9-fluorenol (2)[6] : To a solution of 9-(2-methylphenyl)-9-fluorenol (**1**)[7] (1.0 g,4 mmol) in CCl_4 (20ml) was added NBS (0.7 g,4mmol) and a small amount of BPO, and the mixture was reflixed for 30 min. After cooling the reaction mixture succinimide obtained was filtered off, and then the filtrate was concentrated. The crude product was washed with water, dried, and recrystallized from petroleum benzin to give 2 as colorless prisms ; yield 1.1g (85%) ; mp 146-147℃. ^{1}H NMR ($CDCl_3$) δ=2.38 (1H, br.s, OH), 4.02 (2H, br.s, CH_2Br), 7.0-8.0 (12H, m, $H_{arom.}$). Found : C, 68.73 ; H, 4.06%. Calcd for $C_{20}H_{18}OBr$: C, 68.39 ; H, 4.30%.

9-(2-Iodomethylphenyl) fluorene (3)[6] : To a solution of **2** (1g, 3mmol) in acetic acid (15ml) was added hydroiodic acid (57%, 2.1g, 9mmol), and the mixture was refluxed for 2 hr. Upon cooling to room temperature, the reation mixture was poured into water, extracted with benzene. The benzene solution was washed with $NaHSO_3$ solution, dried with $MgSO_4$, and concentrated in vacuo. The crude product was recrystallized from petroleum benzin to give 3 as light yellow crystals ; yield 0.52g (47%) ; mp 117-119℃. ^{1}H NMR ($CDCl_3$) δ=3.26, 4.75 (0.4H and 1.6H, two s, CH_2I), 4.84, 5.29 (0.8H and 0.2H, two s, 9-H), 6.12-7.78 (12H, m, $H_{arom.}$). Found : C, 62.64 ; H, 3.76%. Calcd for $C_{20}H_{15}I$: C, 62.84 ; H, 3.95%.

9-(2-Cyanomethylphenyl) fluorene (4) : A mixture of compound 3 (1.50g, 3.9mmol) and sodium cyanide (0.23g, 4.7mmol) in acetonitrile (30 ml)-water (2ml) was refluxed for 45 min. Upon cooling to room temperature, the reaction mixture was poured into water, extracted with benzene. The benzene solution was washed with $NaHSO_3$ solution to remove iodine isolated, washed with water, dried over $MgSO_4$, and concentrated in vacuo. The crude product was dissolved in benzene and chromatographed over Al_2O_3 to give **4** as yellow oil ; yield 1.06g (96%). ^{1}H NMR ($CDCl_3$) δ=2.40, 3.96 (1.2H and 0.8H, two s, CH_2CN), 4.92, 5.08 (0.6H and 0.4H, two s,9-H), 6.36 (0.4H, d, J=

8Hz, 6′-H), 7.78 (2H, d, J=8Hz, 4- and 5-H), 6.7-7.7 (9.6H, m, $H_{arom.}$). IR (KBr) ; 2240 cm^{-1} (C≡N).

9-Bromo-9-(2-cyanomethylphenyl) fluorene (5) : To a solution of **4** (2.03g, 5.6mmol) in CCl_4 (100ml) was added NBS (1.20g, 6.8mmol) and a small amount of BPO, and the mixture was refluxed for 4 hr. After cooling the reaction mixture succinimide obtained was filtered off ; the filtrate was concentrated in vacuo. The crude product was dissolved in benzene, and the solution was washed with water, dried over $MgSO_4$, and distilled off. The residue was recrystallized from *n*-hexane to give **5** as yellow prisms : yield 1.92g (74%) ; mp 151-153℃ (dec.). ^1H NMR ($CDCl_3$) δ=2.50 (2, s, CH_2 CN), 7.76 (2H, d, J=7.5Hz, 4-and 5-H), 8.70 (1H, d, J=8Hz, 6-H), 7.1-7.7 (9H, m, $H_{arom.}$). IR (KBr) ; 2240cm^{-1} (C≡N).

9-(2-Cyanomethylpheny1)-9-methoxyfluorene (6) : A solution of 5 (1.90g, 5.3mmol) in methanol (80ml) was refluxed 20hr. After cooling to room temperature, the reaction mixture was poured into water, and extracted with benzene. The benzene solution was washed with water, dride over $MgSO_4$,and concentrated in vacuo. The crude product was dissolved in CCl_4 and chromatographed over silica gel, and was recrystallized from n-hexane to give **6** as colorless prisms ; yield 1.10g (67%) ; mp 133-135 ℃. ^1H NMR ($CDCl_3$) δ=2.80 (3H, s, OCH_3), 2.98 (2H, br.s, CH_2CN), 7.76 (2H, d, J=8Hz, 4-and 5-H), 7.1-7.7 (10H, m, $H_{arom.}$). IR (KBr) ; 2240cm^{-1} (C≡N).

9-(2-Cyanomethylpheny1)-9-fluorenol (7) : To a solution of **6** (0.62g, 2.0mmol) in acetic acid (30ml) was added hydroiodic acid (57%, 0.45g, 2.0mmol), and the mixture was heated at 60-70 ℃ for 8 hr. After cooling to room temperature, the reaction mixture was poured into water, extracted with benzene. The benzene solution was washed with $NaHSO_3$ solution to remove iodine isolated, washed with water, dried over $MgSO_4$, and distilled off in vacuo. The crude product was dissolved in CCl_4 and chromatographed over silica gel. The eluate was recrystallized from *n*-hexane -benzene to give 7 as colorless needles ; yield 0.33g (55%) ; mp182-183℃ (dec.). ^1H NMR ($CDCl_3$) δ=2.70 (2H, br.s, CH_2CN), 7.72 (2H, d, J=8Hz, 4-and 5-H), 6.9-7.6 (10H, m, $H_{arom.}$). IR (KBr) ; 3400cm^{-1} (OH), 2230cm^{-1} (C≡N).

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