Rotational Isomerism in Fluorene Derivatives XIV
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-hydroxy-(4),
9-bromo-(5), 9-methoxy-(6) and 9-hydroxy-9-(2-cyanomethylphenyl)fluorene (7) were pre-
pared, and their conformational equilibria (ap zs sp) were investigated on the bases of their '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°C, 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 zs sp) of 9-(2-sub-
stituted phenyl)fluorene derivatives, in which such substrates are methy-2', methoxy-3',
methylthio-4', methylsulfanyl-6', dimethylamino-3', methoxymethyl-8' and methyl
amino group11, 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 deriv-
atives and to discuss the conformational equilibria of these compounds by their '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-methylphenylnagnesium 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)8. Compound 2 was converted
to 9-(2-iodomethylphenyl)fluorene (3) by treatment with hydroiodic acid in acetic
acid9. The reaction of 3 with sodium cyanide in acetonitrile-water gave 9-(2

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

<table>
<thead>
<tr>
<th>Compd.</th>
<th>9-Substituent</th>
<th>mp(°C)</th>
<th>Yield (%)</th>
<th>1H–NMR (CDCl₃): δ(ppm) at rt</th>
<th>6'-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>H</td>
<td>oil</td>
<td>96</td>
<td>2.40s(1.5) 4.82s(1.5) 3.96s(1) 5.08s(1)</td>
<td>6.36d</td>
</tr>
<tr>
<td>5</td>
<td>Br</td>
<td>151–153 (dec.)</td>
<td>74</td>
<td>2.50s</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>OCH₃</td>
<td>133–135 (dec.)</td>
<td>42</td>
<td>2.98br.s</td>
<td>2.80s</td>
</tr>
<tr>
<td>7</td>
<td>OH</td>
<td>182–184 (dec.)</td>
<td>55</td>
<td>2.72br.s</td>
<td>–</td>
</tr>
</tbody>
</table>

a) Ratios of signal intensities are shown in parentheses.

-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-fluorenom (4).

The melting points, yields and a part of '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 \( ^1H \) 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 \( ^1H \) NMR spectra at room temperature. thus, their DNMR spectra at low temperature \((-62^\circ C\) were measured in the usual way. The signals of cyanomethyl group at low

![Fig. 1 ^1H NMR spectrum of 4 in CDCl3 at room temperature.](image)

![Fig. 2 Isomerization process (ap \( \leftrightarrow \) sp) for 4.](image)
Table 2  
<table>
<thead>
<tr>
<th>Compd.</th>
<th>δ (ppm) of CH$_2$CN</th>
<th>K (ap/sp)</th>
<th>Temp. (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>2.40s (ap)</td>
<td>1.5/1</td>
<td>rt</td>
</tr>
<tr>
<td></td>
<td>3.96s (sp)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2.72s (ap)</td>
<td>ap predominant* a)</td>
<td>−62</td>
</tr>
<tr>
<td></td>
<td>4.62 br.s (sp)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>2.46s (ap)</td>
<td>4.4/1</td>
<td>−50</td>
</tr>
<tr>
<td></td>
<td>3.36s (sp)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Compd.</th>
<th>Y</th>
<th>K (ap/sp)</th>
<th>ΔG (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ap→sp</td>
<td>sp→ap</td>
</tr>
<tr>
<td>8</td>
<td>CH$_3$</td>
<td>1/1.6</td>
<td>16.3 16.5</td>
</tr>
<tr>
<td>9</td>
<td>OCH$_3$</td>
<td>1/17</td>
<td>11.3 13.1</td>
</tr>
<tr>
<td>10*</td>
<td>SCh$_3$</td>
<td>overwhelming</td>
<td>− −</td>
</tr>
<tr>
<td>11*</td>
<td>SOCH$_3$</td>
<td>1/1.5</td>
<td>15.3 15.5</td>
</tr>
<tr>
<td>12*</td>
<td>NHCH$_3$</td>
<td>2/1</td>
<td>15.9 15.5</td>
</tr>
<tr>
<td>13*</td>
<td>N(CH$_3$)$_2$</td>
<td>1/12</td>
<td>13.8 15.5</td>
</tr>
<tr>
<td>14*</td>
<td>CH$_2$OCH$_2$</td>
<td>1/4.1</td>
<td>16.1 16.9</td>
</tr>
<tr>
<td>4</td>
<td>CH$_3$CN</td>
<td>1.9/1</td>
<td>16.5 16.1</td>
</tr>
</tbody>
</table>

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 in 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⋯π 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.
Fig. 3 NH-π interaction in 12-αp, and N≡C-π interaction in 4-αp.

Experimental

All melting points are uncorrected. The 1H 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-fluorenone (2): To a solution of 9-(2-methylphenyl)-9-fluorenone (1) (1.0 g, 4 mmol) in CCl₄ (20 ml) was added NBS (0.7 g, 4 mmol) and a small amount of BPO, and the mixture was refluxed 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 benzine to give 2 as colorless prisms; yield 1.1 g (85%); mp 146-147°C. 1H NMR (CDCl₃) δ = 2.38 (1H, br.s, OH), 4.02 (2H, br.s, CH₂Br), 7.0-8.0 (12H, m, H₅a, m). Found: C, 68.73; H, 4.06%. Calcd for C₂₅H₁₈OBr: C, 68.39; H, 4.30%.

9-(2-Iodomethylphenyl) fluorene (3): To a solution of 2 (1g, 3 mmol) in acetic acid (15 ml) was added hydroiodic acid (57%, 2.1 g, 9 mmol), and the mixture was refluxed for 2 hr. Upon cooling to room temperature, the reaction mixture was poured into water, extracted with benzene. The benzene solution was washed with NaHSO₃ solution, dried with MgSO₄, and concentrated in vacuo. The crude product was recrystallized from petroleum benzine to give 3 as light yellow crystals; yield 0.52 g (47%); mp 117-119°C. 1H NMR (CDCl₃) δ = 3.26, 4.75 (0.4H and 1.6H, two s, CH₂I), 4.84, 5.29 (0.8H and 0.2H, two s, 9-H), 6.12-7.78 (12H, m, H₅a, m). Found: C, 62.64; H, 3.76%. Calcd for C₂₆H₁₅I: C, 62.84; H, 3.95%.

9-(2-Cyanomethylphenyl)fluorene (4): A mixture of compound 3 (1.50 g, 3.9 mmol) and sodium cyanide (0.23 g, 4.7 mmol) in acetonitrile (30 ml)-water (2 ml) 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 NaHSO₃ solution to remove iodine isolated, washed with water, dried over MgSO₄, and concentrated in vacuo. The crude product was dissolved in benzene and chromatographed over Al₂O₃ to give 4 as yellow oil; yield 1.06 g (96%). 1H NMR (CDCl₃) δ = 2.40, 3.96 (1.2H and 0.8H, two s, CH₂CN), 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\(^\circ\)C (dec.). \(^1\)H NMR (CDCl\(_3\)) \(\delta = 2.50\) (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); 2240 cm\(^{-1}\) (C≡N).  

9-(2-Cyanomethylphenyl)-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, dried 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 \(^\circ\)C. \(^1\)H NMR (CDCl\(_3\)) \(\delta = 2.80\) (3H, s, OCH\(_3\)), 2.98 (2H, br.s, CH\(_2\)CN), 7.76 (2H, d, J = 8Hz, 4-and 5-H), 7.1-7.7 (10H, m, H_{arom.-}). IR (KBr); 2240 cm\(^{-1}\) (C≡N).  

9-(2-Cyanomethylphenyl)-9-fluorenone (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 \(^\circ\)C 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\(_4\) 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\(^\circ\)C (dec.). \(^1\)H NMR (CDCl\(_3\)) \(\delta = 2.70\) (2H, br.s, CH\(_2\)CN), 7.72 (2H, d, J = 8Hz, 4-and 5-H), 6.9-7.6 (10H, m, H_{arom.-}). IR (KBr); 3400 cm\(^{-1}\) (OH), 2230 cm\(^{-1}\) (C≡N).  

References  
3) A. Nishida, S. Shiwaku, S. Fujisaki and S. Kajigaeshi, ibid., 1984, 574.  