Reactivities of Stable Rotamers. II. Lithiation of 9-(2-Methyl-1-naphthyl)-fluorene and Related Compounds[1]

Mikio NAKAMURA, Nobuo NAKAMURA, and Michinori ŌKI

Department of Chemistry, Faculty of Science, The University of Tokyo, Tokyo 113

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Studies were carried out on the rates of lithiation of 9-arylfluorenes, in which the aryls are hydrocarbons. The reactivities of these compounds are explained in terms of the effective blocking of the reaction site by the substituent. The steric effect of the substituent which is attached to the aryl group but is over the fluorene ring is found to play a role in the reactivities.

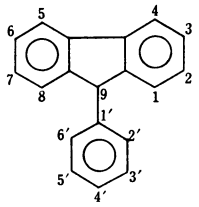
Abundant data on the reactivity of organic compounds have been obtained but they are usually weighted means of rotational isomers, except when the compound in question reacts at a site where no rotamer is possible. In the former case, the observed reaction rates may be expressed by the following equation if there are two possible rotamers:[2]

$$k_{obsd} = k_a N_a + k_b N_b, \quad (1)$$

where k and N denote the intrinsic reaction rates and molar fractions of each rotamer, respectively. When the reactivities of both rotamers are comparable, the reactivity of a less populated isomer can be neglected if the molar fraction is one-sided. However, it becomes significant if the reaction rate of a trace-populated rotamer is exceedingly high. Our recent finding on the difference in reactivities of rotamers[1] singles out the importance of this view.

In discussing the solvent effect on reactions, the consideration of rotamers becomes important because the solvation can stabilize the ground states of rotamers to a different degree, thus controlling the populations. The transition states derived from the different rotamers can also be affected by solvation in a different manner. Study of behavior of rotamer in various solvents thus is necessary for understanding the reactions which are affected by solvents.

We thought it would be worthwhile to launch a project on the reactivities of rotamers, since we could isolate various types of stable rotamers.[3] This is the first full paper of such a series giving a discussion on the lithiation of 9-arylfluorenes together with the origin of the difference in reactivities. The series of hydrocarbons was studied first, since it would not contain complexities such as ligation by oxygen atom in the case of 9-(2-methoxy-1-naphthyl)fluorene.[1] The numbering of arylfluorenes used throughout this text is given below.



Experimental

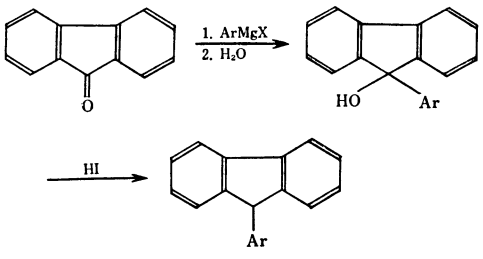
NMR Measurement. ^{1}H NMR spectra were determined on a Hitachi R-20B spectrometer obtained at 60 MHz. The temperature was calibrated by the peak separation of ethylene glycol. The error in temperature reading was estimated to be ±1.0 °C. ^{13}C NMR spectra were measured on a JNM-FX 60 spectrometer operating at 15.04 MHz, ^{13}C–^{1}H coupling constants being obtained from all proton undecoupled spectra. The estimated error in the coupling constants was ±0.5 Hz.

Kinetic Measurement. A solution of 0.098 mmol of a 9-arylfluorene in 0.08 ml of benzene was mixed with 0.2 ml of butyllithium in hexane. The quantity of butyllithium was calculated to be *ca.* 1.0 mmol from the integration of methylene signals α to lithium. The rates of reaction were followed by integrating the proton signals due to 4-H and 5-H of the fluorene ring. The protons give signals at δ *ca.* 7.8 in the mother compounds whereas the lithio dervatives give signals at δ 8.0 or below.

9-(*p*-Tolyl)fluorene gave signals at δ *ca.* 8.0 due to 4 protons, two of which are unknown, on lithiation. Integration and calculation were carried out with this fact being taken into consideration. In the case of 9-(2-methyl-1-naphthyl)fluorene, the lithio derivative was hardly soluble in the solvent system and the integrated area of a signal due to 9-H of the mother compound had to be compared with that of a signal due to 9-H of 9-(2,6-xylyl)fluorene which did not react to a measurable extent.

In each case, plot of $\log(1-x/a)$ *vs.* time gave a straight line and the pseudo-first order rate constants were obtained in the usual way. The errors are given in Table 3. The rates of reaction of 9-(2,6-xylyl)- and 9-(2-*t*-butylphenyl)-fluorene were too small to measure in hexane–benzene solution whereas those of other compounds were too large to measure in ether.

Syntheses. Syntheses were carried out by the Grignard reaction of fluorenone with the corresponding arylmagnesium halide followed by reduction with hydriodic acid.[4]



Some 9-aryl-9-fluorenols were not isolated but reduced directly. The overall yields were 50—70%.

9-Aryl-9-fluorenol. To a vigorously stirred solution of arylmagnesium halide prepared from 0.02 mol of aryl halide, 0.02 mol of magnesium and 40 ml of tetrahydrofuran, 0.02 mol of fluorenone was added at 0 °C. The mixture was stirred for 3 h at room temperature and then heated under reflux for 1 h. The cooled mixture was decomposed with dilute hydrochloric acid. The organic layer was separated and the aqueous layer was extracted with ether. The

combined organic layer was washed with aqueous sodium bicarbonate and dried over sodium sulfate. The following compounds were isolated by chromatography on silica gel.

9-(2-Isopropylphenyl)-9-fluorenol. Mp 147—148 °C. Yield 65%. ^{1}H NMR ($CDCl_3$, δ): 0.48 [$(CH_3)_2CH$], 2.18 [$(CH_3)_2CH$], 2.3(OH), 8.3(6'-H). Found: C, 88.11; H, 6.77%. Calcd for $C_{22}H_{20}O$: C, 87.96; H, 6.71%.

The compound exists in an ap form solely. The high chemical shift of the $(CH_3)_2CH$ signals and appearance of a signal due to 6'-H at a low field support the assignment.

9-(2-t-Butylphenyl)-9-fluorenol. Mp 156.5—158.0 °C. Yield 66%. ^{1}H NMR ($CDCl_3$, δ): 1.79 (*t*-Bu), 2.3 (OH), 6.42 (6'-H). Found: C, 88.16; H, 7.08%. Calcd for $C_{23}H_{22}O$: C, 87.86; H, 7.05%.

The compound is judged to exist in an sp form from the low field *t*-butyl signal and a high field 6'-H signal.

9-Arylfluorene. 9-Aryl-9-fluorenol (*ca.* 0.01 mol) was dissolved in 30—60 ml of acetic acid and heated with 10 ml of 57% hydriodic acid for 1 h at 80 °C. The mixture was washed with aqueous sodium bisulfite and then with sodium bicarbonate, and dried over sodium sulfate. After evaporation of the solvent the product was purified by either chromatography on alumina or thin layer chromatography on silica gel. The yield was 75—80%. Pertinent data are given in Tables 1 and 2.

Table 1. 9-Arylfluorenes

Aryl	Mp (°C)	Calcd %		Found %	
		C	H	C	H
p-$CH_3C_6H_4$	127.0—127.5[a]				
2,6-$(CH_3)_2C_6H_3$	84.5—85.0	93.29	6.71	93.08	6.69
o-$CH_3C_6H_4$	90.5—91.5[b]	93.71	6.29	93.99	6.27
o-$(CH_3)_2CHC_6H_4$	88.0—89.0	92.91	7.09	92.78	7.13
o-$(CH_3)_3CC_6H_4$	179.5—180.5	92.57	7.43	92.61	7.40
2-Methyl-1-naphthyl					
sp	118.0—119.0	94.08	5.92	93.81	5.74
ap	125.0—126.0	94.08	5.92	93.85	5.75

a) Reported melting point was 125 °C.[12]
b) Reported melting point was 129—130.5 °C.[13]

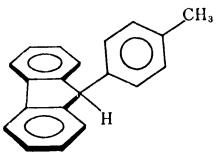
Results and Discussion

Assignment of the Conformation of 9-Arylfluorenes. Features of the conformation of the ap and sp forms of 9-arylfluorenes are characterized by the fact that the alkyl group is located over the fluorene ring in ap (sp in the case of 2-methyl-1-naphthyl derivative (**8**)) form, whereas it is almost within the plane of the fluorene ring in sp (ap in the case of **8**) form. The opposite situation exists for 6'-protons of the aryl group.

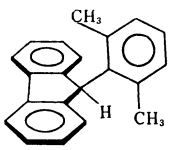
The spacial arrangement of the alkyl group is reflected in the chemical shift of the alkyl protons. 9-(2,6-Xylyl)fluorene (**2**) gives signals due to methyls at δ 1.12 and δ 2.70. The former should be due to a methyl over the ring and the latter to a methyl within the plane of the ring. Thus, if we can observe two forms in ^{1}H NMR spectra, the assignment is straightforward by comparison of the chemical shift.

The conformation of the *t*-butyl compound can also be assigned by taking advantage of the above facts, although it exists as a single form. The *t*-butyl signal is located in a lower field than that of *t*-butylbenzene (δ 1.32),[5] the chemical shift of the 6'-H signal being located at a high field close to the other known sp forms. Thus the conformation of 9-(2-*t*-butylphenyl)fluorene (**3**) should be sp, this being in line with the consideration of the steric effect.

Rates of Lithiation. The pseudo-first order rate constants of lithiation of 9-arylfluorenes are given in Table 3. For the sake of convenience we will start the discussion from the symmetric compounds.



(**1**)



(**2**)

The internal rotation about the C_9–C_{ar} bond in 9-(*p*-tolyl)fluorene (**1**) should be fast at room temperature since analogous 9-(*m*-tolyl)fluorene is known to rotate fast even at −85 °C, whereas that in **2** is frozen.[6] The very low reactivity of **2** can be attributed to the steric blocking of the approach of the deprotonating reagent by the methyl group. Room for the approach of the reagent is made by rotation about the C_9–C_{ar} bond, the rotation itself requiring a fair amount of energy in com-

Table 2. NMR spectral data of rotameric 9-arylfluorenes in $CDCl_3$ at room temperature (δ from TMS)

Aryl		^{1}H NMR			^{13}C NMR			$J_{^{13}C-^1H}$ of 9-C
		CH_3	9-H	6'-H	CH_3	9-C	Other aliphatic C	
p-$CH_3C_6H_4$		2.27	4.99		22.73	53.93		128.8
2,6-$(CH_3)_2C_6H_3$		2.70 1.12	5.50		21.67 18.67	49.88		124.4
o-$CH_3C_6H_4$[a]	sp	2.63	5.30	6.38	20.33	49.79		127.6
	ap	1.13	4.90	>7.5	18.28	55.96		125.1
o-$(CH_3)_2CHC_6H_4$	sp	1.46	5.42	6.33	24.93	48.90	29.42	127.6
	ap	0.47	4.87	>7.5	23.13	56.33	28.04	122.7
o-$(CH_3)_3CC_6H_4$	sp	1.72	5.86	6.22	32.55	50.97	35.55	127.2
2-Methyl-1-naphthyl	sp	1.33	6.16	8.50[b]	19.48	48.50		122.7
	ap	2.83	5.78	6.43[b]	21.51	50.04		123.3

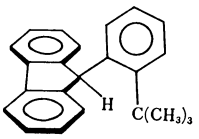
a) The ^{1}H NMR data were obtained at 0 °C.
b) These signals are due to 8'-H's of the naphthalene ring.

Table 3. Rates of lithiation of 9-arylfluorenes in hexane–benzene-d_6 at 42 °C

Aryl	Conformation	Pseudo-first order rate constant (k s^{-1})	k_{rel}
p-$CH_3C_6H_4$		$(1.2\pm0.1)\times10^{-4}$	23
2,6-$(CH_3)_2C_6H_3$[a]		0	0
o-$CH_3C_6H_4$	ap	$(4.1\pm0.2)\times10^{-5}$	8
o-$(CH_3)_2CHC_6H_4$	ap	$(1.9\pm0.4)\times10^{-5}$	4
o-$(CH_3)_3CC_6H_4$[a]	sp	0	0
2-Methyl-1-naphthyl	sp	$(3.6\pm0.6)\times10^{-5}$	7
	ap	$(5.2\pm0.6)\times10^{-6}$	1

a) These compounds were successfully lithiated in diethyl-ether. The rate constants at 34 °C were $(5.4\pm0.4)\times10^{-4}$ s^{-1} and $(4.3\pm0.3)\times10^{-6}$ s^{-1} for the dimethyl and the t-butyl compounds, respectively.

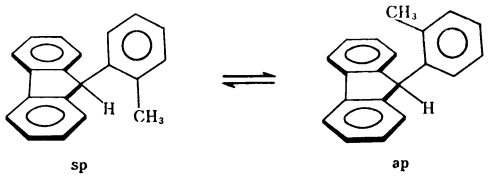
pound **2**. The steric hindrance toward the reaction seems to be of major importance in this case.



(**3**)

The importance of the steric hindrance is also demonstrated in **3**. Although the barrier to internal rotation about the C_9–C_{ar} bond is unknown, the compound exists as one form exclusively even at 180 °C, probably because the steric interference between the t-butyl group and the fluorene ring in an ap form is very severe. Compound $\mathbf{3}_{sp}$ failed to react with butyllithium in hexane–benzene-d_6 as did compound **2**. This should be attributed to the steric effect of the t-butyl group. Importance of the steric effect on lithiation of thiophene derivatives has been pointed out by Wiersema and Gronovitz.[7]

Both compounds **2** and **3** can be lithiated in ether, though they cannot be lithiated in hexane–C_6D_6. Ether would stabilize the transition state of proton abstraction where the polar nature of the C–H bond is developed to some extent. The pseudo-first order rate constants of **2** and **3** at 34 °C were 5.4×10^{-4} s^{-1} and 4.3×10^{-6} s^{-1}, respectively. The rates reflect the steric effect, compound **3** reacting much more slowly than compound **2**. The occurrence of the reaction of compound **3** in spite of the presence of the bulky substituent might be ascribed to rotation about the C_9–C_{ar} bond to some degree to open a path for the reagent approach.



(**4**)

Rates of rotation about the C_9–C_{ar} bond of 9-(o-tolyl)-fluorene (**4**) are estimated to be 10^1-10^2 s^{-1} at ambient temperature from the reported barrier.[6] Thus the rates of rotation are much greater than those of lithiation by butyllithium, the factor being 10^5-10^6. Equilibration between the sp and ap forms is quick. The observed reaction rates can be expressed by the following equation, where the suffixes sp and ap stand for the respective rates and moleculr fractions of the rotamers:

$$k_{obsd} = k_{sp}N_{sp} + k_{ap}N_{ap}. \quad (2)$$

The circumstances of the reaction site of the sp and ap forms can be taken to be similar to those of compounds **2** and **1**, respectively, since o-tolyl, p-tolyl, and 2,6-xylyl groups should not differ much in giving the electronic effect. It is reasonable to assume that $\mathbf{4}_{sp}$ does not react with butyllithium, when the k_{sp} value is practically zero. Equation 2 can be rewritten as follows and k_{ap} can be obtained from the observed rates and the equilibrium constant K:

$$k_{ap} = \left(1+\frac{1}{K}\right)k_{obsd}. \quad (3)$$

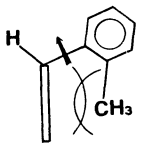
The equilibrium constant was obtained in toluene-d_8 as 1/1.3* by integrating the two methyl signals. It was found to be independent of temperature. Putting the equilibrium constant and the observed rate constant, $k_{obsd}=(1.8\pm0.2)\times10^{-5}$ s^{-1}, into Eq. 3, we find k_{ap} at 42 °C to be $(4.1\pm0.2)\times10^{-5}$ s^{-1}.

So far discussion has been given on the rates of lithiation from the viewpoint of steric effect given by the group located closely to the hydrogen to be abstracted. Close examination of the data reveals, however, that the above treatment is only a first approximation; the rate of lithiation of $\mathbf{4}_{ap}$ is about 1/3 of that of **1**. We wish to attribute the fact to the steric effect of the methyl group anti to the 9-hydrogen for the following reasons.

Two possibilities can be considered. One is the bond-angle enlargement due to the substituent-fluorene interaction (see **5**). This will necessarily give additional steric hindrance to the approach of the reagent toward the 9-H and simultaneously cause the change in hybridization. From an examination of the NMR C–H coupling constants (Table 2), the larger substituent in 2′-position of the aryl group in the ap form causes a decrease in magnitude of the coupling constant: $^1J_{CH}$'s decrease from 128.8 to 125.1 Hz by going from **1** to $\mathbf{4}_{sp}$ and from 125.1 to 122.7 Hz by going from $\mathbf{4}_{ap}$ to $\mathbf{7}_{ap}$. The s-character and C–H coupling constants are correlated,[8] although the correlation is questionable in highly strained molecules.[9] The difference in the chemical shifts of 9-C's in ^{13}C NMR spectra increases as the size of the alkyl group increases, the results supporting the bond-angle deformation at 9-C. Thus the decrease in $^1J_{CH}$ and the change in chemical shifts are interpreted as an increase in p-character of the C–H bond orbital. However, this should result in easier deprotonation of $\mathbf{4}_{ap}$ relative to **1** from a kinetic viewpoint and is contrary to the observed trend. Thus the change in hybridization is of minor importance. The steric effect resulting from deformation may also be a minor one since the equilibrium constant is 1/1.3 for $\mathbf{4}_{sp}\rightleftharpoons\mathbf{4}_{ap}$. If it were a major effect, the population ratio should have been affected to a greater extent.

The other possibility is the steric effect caused by the substituent on rotation about the C_9–C_{ar} bond. The access of the deprotonating reagent to the 9-H would

* The equilibrium constant in $CDCl_3$ at 0 °C was reported to be 1/1.6.[6]



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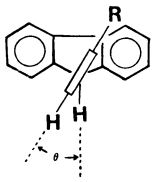
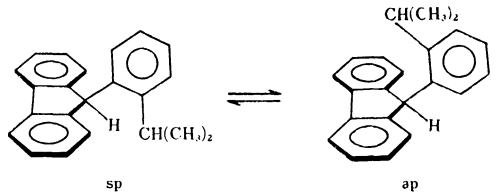


(6)

be facilitated by the rotation (see **6**) which forms room for the access at the expense of increasing steric interaction between the substituent and the fluorene ring. Thus higher energy is required for rotation about the bond to a same degree (θ) in compound $\mathbf{4}_{ap}$ than in compound **1**.

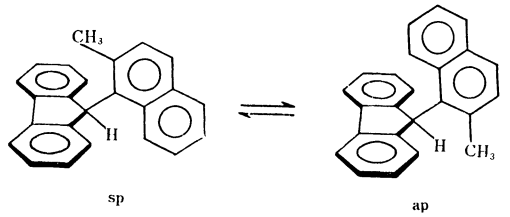
Although the second possibility can be tested in the case of 9-(2-*t*-butylphenyl)fluorene (**2**), the ap form is not detected because of its relative instability to the sp form. Thus 9-(2-isopropylphenyl)fluorene (**7**) was prepared and its reactivity was examined. The compound shows a barrier to rotation (ΔG_c^*) of 19 kcal/mol at 92 °C as determined from the coalescence temperature of the 9-H signals. The rate of rotation at 42 °C is of the order of 10^{-1} s^{-1}. The equilibrium constants for rotamers at 42 °C were 1/2.4 in $CDCl_3$, and 1/1.8 in hexane–C_6D_6.



(7)

The results expected from the steric effect are as follows. The population of the sp form is greater than that of **4**, but the ap form is still detectable. The deformation of the bond angle for the ap form is detected by a decrease in C–H coupling constant from the sp form. If the angle deformation is a main factor which retards the reaction, the isopropyl compound ($\mathbf{7}_{ap}$) should react still more sluggishly than the methyl compound ($\mathbf{4}_{ap}$). On the other hand, if the steric effect on rotation to open room for access of the reagent is the main factor, $\mathbf{7}_{ap}$ is expected to show a little less reactivity than $\mathbf{4}_{ap}$, since the isopropyl group is known to be a little bulkier than the methyl group.[10]

The observed pseudo-first order rate constant was 6.9×10^{-6} s^{-1} for compound **7** at 42 °C. The value was treated in the same way as in the case of compound **4**, the value obtained for k_{ap} being 1.9×10^{-5} s^{-1}. The



(8)

result is in line with the expectation, as in the change in $^1J_{CH}$ values. We conclude that the steric effect on the rotation is a main factor controlling the reactivities of these compounds of similar steric environment at the reaction site.

We thought it would be worthwhile to compare the reactivities of stable rotamers of 9-(2-methyl-1-naphthyl)-fluorene (**8**) as an extension of the above discussion. The compound was prepared by Siddall and Stewart, although the rotamers were concentrated but not completely isolated.[6] The equilibrium constant of the two forms was 1.0 and was not affected by temperature. The barrier (ΔG^*) to rotation about the C_9–C_{ar} bond was reported to be 29.2 kcal/mol at 116 °C. The rate of isomerization was 6.2×10^{-7} s^{-1} at 67 °C.

We were able to isolate these stable rotamers by repeated thin layer chromatography: sp, mp 121—122 °C; ap, mp 125—126 °C. The pseudo-first order rate constants for deprotonation obtained were 5.2×10^{-6} s^{-1} and 3.6×10^{-5} s^{-1} for $\mathbf{8}_{ap}$ and $\mathbf{8}_{sp}$, respectively, at 42 °C. Since the rotation about the C_9–C_{ar} bond is negligible at 42 °C, we observed the net reaction rates for the respective isomers. There is a difference in reactivities by a factor of **7**.

The results indicate that a methyl group is more effective than a benzo group in blocking the reaction. This is an unusual indication since the benzo is usually a larger group than the methyl in stereochemistry and 9-(1-naphthyl)fluorene is known to give a higher barrier to rotation than 9-(*o*-tolyl)fluorene by *ca.* 1 kcal/mol.[6] The apparent discrepancy can be understood by considering the geometry of the transition state for the proton abstraction. The main factor which rules the reaction rate is the easiness of rotation to open up room for access for the reagent. The methyl group is considered to be a rotating top and its van der Waals radius is 2.0 Å, whereas the benzo ring extends within a plane but has van der Waals thickness of only 1.85 Å. Thus room for the reagent would be made by a smaller displacement for the sp form than for the ap form. The higher reactivity of $\mathbf{8}_{ap}$ than **2** might be attributed to a similar cause. The methyl group over the fluorene ring would give larger steric hindrance than the benzo group when the same degree of rotation is required. It is also interesting to note that $\mathbf{8}_{sp}$ shows about the same reactivity as $\mathbf{4}_{ap}$. The same degree of rotation would be sufficient for the reaction to occur in these compounds.

Although both $\mathbf{8}_{ap}$ and $\mathbf{8}_{sp}$ give identical ^{1}H NMR spectra on lithiation, stereochemistry of the lithio derivatives is hard to study because of its poor solubility and the difficulty in detecting the difference in spectral characteristics. It might be a mixture of two forms which give resembling NMR peaks, or a single form, or a mixture which shows no signals of a minor constituent. Quenching an extremely dilute solution of the lithio derivative of **8** in hexane–benzene with water afforded the sp and the ap forms in an 8 : 1 ratio. If we can assume that quenching of the lithio derivative with a highly covalent C–Li bond proceeds with the retention of configuration, as is observed in other cases,[11] the stability of the lithio derivatives could be discussed.

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