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Reactivities of Stable Rotamers. XXV. Deprotonation at the 9-Position of 9-(2-Substituted 1-naphthyl)fluorene Rotamers with Butyllithium[1,2]

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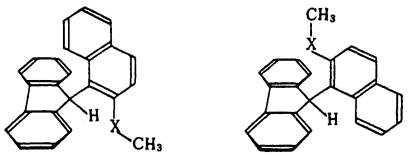
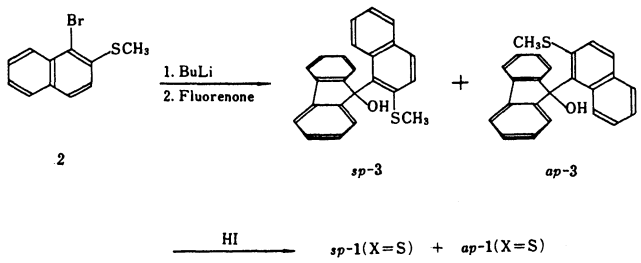
Deprotonation of 9-(2-substituted 1-naphthyl)fluorene rotamers, where the substituent is a dimethylamino, a methoxy, or a methylthio, has been carried out with butyllithium in hexane-benzene. While the reactions of the *ap*-isomers were generally slower than those of the *sp*-isomers, the difference in the methoxy compounds was the greatest among the compounds examined. The results are discussed on the basis of the ease of ligation of the substituent and the steric effects that prevail in the *ap*-isomers, together with the distance between 9-position and the ligation site in the subsituent.

Since the successful isolation of stable rotamers at room temperature,[3] we have been interested in reactivities of rotamers and have been able to show some interesting differences in their reactivities.[4] Among those examined so far, the difference in the rates of deprotonation of 9-(2-methoxy-1-naphthyl)fluorene rotamers (**1**: X=O) was one of the greatest.[2] We have thus been interested to explore further to understand the reactivity differences of these rotamers and have carried out the similar reactions of 9-(2-substituted 1-naphthyl)fluorene (**1**) rotamers where X is NCH_3, O, or S. This paper is to report the results and to discuss the interesting differences observed in the investigation.



sp-1 *ap*-1

The syntheses of the dimethylamino compound (**1**: X=CH_3N) and the methoxy compound (**1**: X=O) were already reported.[5,6] The methylthio compound (**1**: X=S) was synthesized in the following way. 1-Bromo-2-methylthionaphthalene (**2**) was lithiated with butyllithium and was treated with 9-fluorenone to afford a mixture of *ap*- and *sp*-9-(2-methylthio-1-naphthyl)-9-fluorenol (**3**) which was reduced with hydriodic acid to give the desired compound (**1**: X=S). The rotamers were separated by chromatography on silica gel.



2 *sp*-3 *ap*-3

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The barriers to isomerization of the dimethylamino and the methoxy compounds have been reported.[5,6] The barrier to rotation of the methylthio compound was determined. It was 29.6 kcal mol^{-1} (1 cal=4.184 J) for the *ap*→*sp* process and 31.0 kcal mol^{-1} for the reverse process at 101 °C. The equilibrium constant, *sp*/*ap*, was 7.31 at the same temperature. Calculation of the rate constants of isomerization was carried out by assuming that the entropy of activation was zero[6,7] to find that the rates of deprotonation described below were larger than the rates of isomerization by a factor of more than 100 if the deprotonation was carried out at 34 °C in the cases of the dimethylamino and the methylthio compounds. However, the rates of deprotonation of the methoxy compound were only 5 times faster than those of isomerization from the *ap*-form to the *sp* at the same temperature.

We had to compromise, between the isomerization and the deprotonation, and decided to run the reaction with butyllithium in hexane-benzene at low temperatures where the contamination by the other rotamer, that might be formed by rotation under the reaction conditions, was minimal and the reaction rates were large enough for the conventional measurements. Because of the technical reasons, the reactions of the *ap*-forms were generally carried out only at 34 °C and the rates of the reactions were followed by the NMR integration, whereas those of the *sp*-forms below 40 °C and followed by mass spectra after decomposition of the lithiated product with trifluoroacetic acid-*d*. Therefore the rates of the reaction were compared by calculation of those of the *sp*-isomers with the use of kinetic parameters obtained from the results at low temperatures. The kinetics apparently followed the pseudo-first-order rate law in the substrate for both rotamers of **1**. The results are shown in Table 1, in which the second-order rate constants were compared with those of 9-(2-methyl-1-naphthyl)fluorene rotamers[8] that do not carry heteroatoms in the substituent.

The results indicate that the reaction rates are enhanced when a heteroatom is introduced to the 1-substituent of the naphthalene nucleus. It is well known that butyllithium forms a hexamer in hydro-

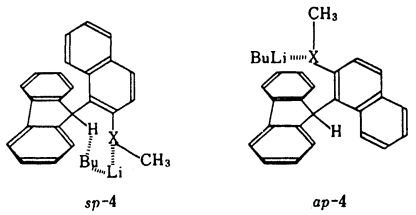
Table 1. Second-Order Rate Consants ($\times 10^5/s^{-1}$ mol^{-1} L) of Lithiation of **1** at 34.0 °C

2-Substituent	$N(CH_3)_2$	OCH_3	SCH_3	CH_3[a]
sp	34.2	1090	13.1	0.14
ap	27.8	2.73	4.68	1.0

a) At 42 °C.[8] Due to the change in precedence of the substituent in the sequence rule, that shown in the line of *sp* is actually the *ap* form and vice versa. This arrangement is taken for the convenience of the comparison.

carbon solvents.[9] Therefore, butyllithium is a very bulky reagent under the reaction conditions unless some assistance for deaggregation by the substrate is not available. We conclude therefore that the heteroatom in the substituent acts to deaggregate butyllithium in this instance as in the cases of solvents with heteroatoms.[10]

The enhancement is larger in the *sp* forms than in the *ap* forms. This might be attributed to the fact that in the ligated form of the *ap* (oversimplified as *ap*-**4**) the distance between the butyllithium and the 9-H is too far for the deprotonation to occur directly, whereas the direct deprotonation from the ligated form of *sp*, which is also shown by an oversimplified form (*sp*-**4**), is possible.



sp-4 *ap*-4

However, the enhancement is not very remarkable for both *ap* and *sp* forms of the compounds examined here, an only exception being *sp*-**1** (X=O). When one compares the rates of the reactions of *ap*-forms, the largest enhancement is seen in the nitrogen compound (*ap*-**1**: X=NCH_3) but the enhancement in the oxygen and the sulfur compounds is only a factor of ca. 5 relative to the compound which carries no heteroatoms, *sp*-9-(2-methyl-1-naphthyl)fluorene. This will mean that the deaggregation due to ligation of the heteroatom in the substituent in the *ap*-form is not efficient in the enhancement of the reaction rates.

To make a sharp contrast, the enhancement of the rates was distinct in the *sp*-isomers, the smallest case, sulfur, giving the enhancement of a factor of ca. 100, when one compares the rates with that of the methyl compound. Especially large is the enhancement by the oxygen-substituent, the factor being ca. 10^4.

We should like to attribute the results both to the steric effects that become operative on ligation of the heteroatom to the lithium cation and the ability of the heteroatom to ligate to the lithium. Although the amino-nitrogen is known to be the best ligating heteroatom to the lithium cation,[11] if the ligation takes place to the amino-nitrogen in compound **1** (X=NCH_3) the steric effects will be great even in the *sp*-form (*sp*-**4**): since alkyllithium is known to be largely covalent,[12] the butyl group will accompany the lithium atom in every case and the situation will not change to a large extent even when the ligation of the heteroatom takes place.[13] We believe that the stable conformation of the dimethylamino group in *sp*-**1** (X=NCH_3) is such that the lone-pair electrons of the nitrogen atom directs to the 9-H to minimize the steric effects and probably due to the presence of a weak hydrogen bond between the 9-CH of the fluorene and the heteroatom in the 2-substituent of the naphthalene.[15] However this conformation is no longer stable if the amino-nitrogen ligates to the lithium cation because of the accompanying steric effects.

By contrast, the oxygen and the sulfur atom have two pairs of unshared electrons, one of which can be used to ligate to the lithium cation without causing too much steric hindrance in these cases. The largest enhancement by the oxygen-substituent in the *sp* must be attributed to this effect. The sulfur atom is known to be a weakly ligating atom to the lithium cation.[16] The results observed here are derived by this nature together with the factor that the sulfur atom has two pairs of the unshared electrons.

Coming back to the data of *ap*-isomers, we still see the effect of the ligating atom: the amino compound gives the largest rate constant for the lithiation. It is also interesting to note that, while the *ap*-rotamers of 9-(2-dimethylaminomethyl-, methoxymethyl-, or methylthiomethyl-1-naphthyl)fluorene, which has one extra methylene group inserted between the 1-naphthyl-carbon and the heteroatom of **1**, exhibit reaction rates that obey second-order rate law,[14] the *ap*-forms of **1** all exhibit practically pseudo-first-order rates. The difference in the reaction conditions between the present case and that reported is the concentrations of the substrates: in the earlier paper, concentrations were higher than those used in this work by ca. 10. These suggest that the rates of the reactions we observe might involve both the second-order and the first-order ones. Thus we carried out the study on the effects of concentration of the substrate on the methoxy compound (*ap*-**1**: X=O).

The results shown in Table 2 indicate that there is indeed the effects of concentration observed: the higher concentration enhances the lithiation rates. However,

Table 2. The Effect of Concentration on the Apparent Pseudo-First-Order Rate Constants of Lithiation of *ap*-**1** (X=O) at 34 °C

Concentration/10^{-3} mol L^{-1}	Rate const/10^{-5} s^{-1}
6.34	2.48
12.7	2.62
31.3	3.11

there is one thing we have to take into account before discussing the data in Table 2. That is, the rates of rotation of the methoxy compound (**1**: X=O) are large enough, so that we cannot neglect the contribution of isomerization by rotation, especially at 40 °C.

We assumed that the rates of rotation under the reaction conditions were equal to those without the added butyllithium. Then the rates of isomerization can be calculated by the activation parameters reported previously.[6] Fortunately the rates of reaction of the *sp*-form, which was formed by isomerization, was large enough to assume that it reacted instantaneously to form the lithiated compound under the conditions. Then we can write the following equation for the decrease in the amount of the *ap*-form.

$$k_{obs} = k_{ap} + k_{iso} \quad (1)$$

where k_{ap} is the rate constant of lithiation of *ap*-**1** (X=O) and k_{iso} the rate of isomerization. Using these assumptions, we obtain the rates of lithiation of *ap*-**1** (X=O) as shown in Table 3. This kind of consideration will not be necessary for the compounds, in which X=N(CH$_3$)$_2$ or S, because their barrier to rotation is higher than the oxygen compound.

$$k_{obs} = k_1 + k_{iso} + k_2[ap\text{-}\mathbf{1}] \quad (2)$$

Then using the data in Tables 2 and 3 together with Eq. 2, we obtain k_2 as 2.55×10^{-4} s^{-1} L mol^{-1}. Thus, whereas the contribution of the second-order reaction at the concentration of 6.34×10^{-3} mol L^{-1} is only 6.5%, that at the concentration of 31.3×10^{-3} mol L^{-1} is 26%. It is clear that at the concentration reported previously (0.31 mol L^{-1}) the contribution of the first-order reaction is very minor.

Although detailed discussion of the reaction rates of the *ap* forms is precluded because of various unknown factors, we believe the first-order rate constant of the methoxy compound is significantly larger than that of the hydrocarbon. Probably this is caused by the fact that the methoxyl group is smaller than the methyl group to make the access of the deprotonation reagent to the 9-H easier by rotation of the naphthyl group.

The largest rates of the reaction of the dimethylamino compound in the *ap* series may involve factors of the most favorable ligation of the amino-nitrogen, the steric effects on ligation, and unassisted deprotonation. The detailed discussion of the factors is not possible at present.

Table 3. Observed Rate Constants, Calculated Isomerization Rate Constants, and True Rates of Lithiation of Compound **1** (X=O) at 34 °C

Temp/°C	k_{obs}/s^{-1}($\times10^5$)	k_{iso}/s^{-1} ($\times10^5$)	k_1/s^{-1}($\times10^5$)
20	0.607	0.192	0.415
26	1.14	0.429	0.710
34	2.48	1.19	1.29
40	4.40	2.48	1.92

a) For the definition of k_1 and k_{iso}, see text.

Table 4. Apparent Pseudo-First-Order Rate Constants ($\times10^5$/s^{-1}) of Lithiation of **1**

Form	Substituent	Rate constants(Temp/°C)
sp	N(CH$_3$)$_2$	3.07 (0.0), 6.88 (10.0), 9.22 (15.0), 12.7 (20.0)
sp	OCH$_3$	5.67 (−18.0), 9.04 (−14.0), 13.7 (−10.0), 25.1 (−5.0)
ap	OCH$_3$	0.607 (20.0), 1.14 (26.0), 2.48 (34.0), 4.40 (40.0)
sp	SCH$_3$	1.85 (10.0), 4.36 (20.0), 9.18 (30.0), 17.7 (40.0)

Table 5. Activation Parameters for the Lithiation of **1**

Form	Substituent	ΔH^*/kcal mol^{-1}	ΔS^*/cal mol^{-1} K^{-1}
sp	N(CH$_3$)$_2$	10.8±0.5	−39.3±1.8
sp	OCH$_3$	14.9±1.7	−18.9±6.4
ap	OCH$_3$	13.3±1.9	−37.7±6.2
sp	SCH$_3$	12.7±1.2	−35.2±3.9

The products obtained after protonation of the lithiated compounds were *sp*-**1** in all the cases examined. We believe this is caused by the fact that the lithium compound obtained from the *sp* form is stabilized by ligation of the heteroatom in the substituent. The protonation of organolithium compounds is known to proceed with retention of stereochemistry,[17] there must be reasons for the isomerization of *ap*-**1** to *sp*-**1**. We believe that, in the *ap*-form, the initially formed lithium compound may be *ap* as well but, due to the fact that a larger substituent in the 9-position of the 9-arylfluorenes reduces the barrier height,[18] the rotation about the C$_9$(fluorene)-to-C$_1$(naphthalene) bond becomes easier and thermodynamically stable form is taken.

Experimental

Materials. 9-(2-Methoxy-1-naphthyl)fluorene rotamers were prepared according to the method described previously[6] with a minor modification. Since the method described earlier gives *ap*-isomer as a minor product which isomerizes easily at room temperature, the purification of this form is rather tedious. We thus prepared *ap*-**1** (X=O) by treating the corresponding phenol as described below. 9-(2-Dimethylamino-1-naphthyl)fluorene rotamers (**1**: X=NCH$_3$) were prepared by the method described in the literature.[5]

***ap*-9-(2-Methoxy-1-naphthyl)fluorene [*ap*-1 (X=O)].** To a solution of 2.0 g (6.5 mmol) of *ap*-1-(9-fluorenyl)-2-naphthol[6] in 100 mL of ether was added 4.3 mL (6.5 mmol) of a ca. 15% solution of butyllithium in hexane at −78 °C under a nitrogen atmosphere. After addition of 1.0 mL (8.8 mmol) of methyl trifluoromethanesulfonate, the mixture was warmed up to room temperature, and was stirred for 30 min. The mixture was poured into water. The ether layer was separated and the aqueous layer was extracted with ether. The combined ether solution was dried over magnesium sulfate. Evaporation of the solvent gave a crude product of which recrystallization from hexane–dichloromethane afforded 1.5

g (72%) of the desired product.[6] ^{1}H NMR ($CDCl_3$) δ=3.00 (3H, s), 5.81 (1H, s), 6.9—7.9 (13H, m), 8.3—8.5 (1H, m).

9-(2-Methylthio-1-naphthyl)fluoren-9-ol (3). To a solution of 10 g (40 mmol) of 1-bromo-2-methylthionaphthalene[19] in 300 mL of dry benzene was added 27 mL (41 mmol) of a ca. 15% hexane solution of butyllithium at ca. 0 °C under a nitrogen atmosphere. After stirring for 4 h at room temperature, 7.2 g (40 mmol) of 9-fluorenone was added rapidly. The mixture was refluxed for 4 h, cooled to room temperature, and treated with ca. 5% hydrochloric acid. The ether layer was separated and the aqueous layer was extracted with ether. The combined ether solution was dried over magnesium sulfate and filtered. After evaporation of the solvent from the filtrate, the residue was chromatographed on silica gel with 4 : 1 hexane-dichloromethane eluent to give 13 g (93%) of the desired product which consisted of the *sp* and the *ap* rotamers in 10 : 1 ratio. This product was used directly for the next reaction. The following ^{1}H NMR data ($CDCl_3$, δ) were collected: *sp* 2.72 (3H, s), 6.7—8.8 (14H, m); *ap* 1.89 (3H, s), 9.5—9.7 (1H, m).

9-(2-Methylthio-1-naphthyl)fluorene (1: X=S). A mixture of 10 g (28 mmol) of the product obtained above in 1 L of acetic acid and 100 mL of ca. 57% hydriodic acid was stirred for 30 min at room temperature and then poured into water. The mixture was extracted with ether and the combined ether solution was washed with aqueous sodium hydrogensulfite and then with aqueous sodium hydrogencarbonate. After drying over magnesium sulfate, the solvent was evaporated and the residue was submitted to chromatography on silica gel. Elution with hexane afforded 2.7 g (28%) of the *sp* rotamer which was purified by recrystallization from acetonitrile and then that with 10 : 1 hexane-dichloromethane did 4.0 g (42%) of the *ap* rotamer which was also purified by recrystallization from acetonitrile.

ap-**1** (X=S), mp 158.5—159.5 °C. Found: C, 85.47; H, 5.43; S, 9.60%. Calcd for $C_{24}H_{18}S$: C, 85.17; H, 5.36; S, 9.47%. ^{1}H NMR ($CDCl_3$) δ=1.91 (3H, s), 6.06 (1H, s), 7.0—7.9 (13H, m), 8.3—8.5 (1H, m).

sp-**1** (X=S), mp 145.5—146.0 °C. Found: 84.99; H, 5.36; S, 9.54%. Calcd for $C_{24}H_{18}S$: C, 85.17; H, 5.36; S, 9.47%. ^{1}H NMR ($CDCl_3$) δ=2.70 (3H, s), 6.52 (1H, s), 6.3—8.0 (14H, m).

Determination of Barriers to Rotation. *ap*-**1** (X=S) which was the unfavorable rotamer at equilibrium was dissolved in toluene-d_8 (30 mg of the sample in 0.4 mL of the solvent) and the solution was placed in an NMR sample tube. The tube was heated in a boiling water bath and the decrease in the starting material and the increase in *sp*-**1** (X=S) were determined by integration of the respective NMR signals with a Varian EM 390 spectrometer. The equilibrium constant was obtained after 96 h heating. The rate constant was obtained by assuming reversible unimolecular reactions.

Kinetic Study of Lithiation. A solution of ca. 0.03 mmol of an *sp*-rotamer in 2.0 mL of benzene was prepared as a stock solution. Eight portions of 0.2 mL each of the stock solution were placed in small tubes and frozen at −78 °C under a nitrogen atmosphere. To the sample solutions, 0.3 mL each of ca. 15% hexane solution of butyllithium was added. The mixture was immersed in a thermostatted bath and the rates of the reaction were determined by quenching the sample solution at an appropriate time interval with 0.1 mL of trifluoroacetic acid-*d* in 1 mL of toluene at −78 °C. The ratios of the 9-deuterio compound to the 9-protio compound were determined by the intensities of the molecular ion peaks in the mass spectra. Correction for the natural abundance of isotopes that give [M^+ +1] peaks was made according to the literature.[20] The results are shown in Table 4. *ap*-**1** (X=O) was treated similarly.

Table 4 shows the calculated activation parameters from the second-order rate constants. Entropies of activation are very large negative in every case to indicate that the reaction has the nature that the freedom of the substrates is restricted in the transition state.

For the determination of the rates of lithiation of the *ap* isomers, intensities of the proton signals in NMR spectra were used. A solution of 44 mmol (0.13 mmol) of the sample in 0.2 mL of benzene-d_6 was placed in an NMR sample tube and frozen at −78 °C under a nitrogen atmosphere. After addition of 0.3 mL of ca. 15% solution of butyllithium in hexane, the mixture was warmed with stirring to make a homogeneous solution and kept at 34 °C. It is known that, when lithiation takes place, the proton signals due to 4-H and 5-H of the fluorene ring appears at δ 8.0—8.3 and that at δ 8.2—8.5 due to 8-H of the naphthalene ring in the *ap* series disappears.[14] The intensities of these signals as well as those due to the 9-H of the fluorene ring could be directly used for the determination of the rates in the cases of the *sp*-isomers. For the *ap*-isomers, initial concentration of the substrate was calculated by dividing the sum of intensities of signals at δ 8.0—8.5 and at δ ca. 6 by 2. The amount of the lithiated compound was calculated by subtracting the intensity of the signal at δ ca. 6 from that at δ 8.0—8.5 and dividing the difference by 2. The results are shown in Table 1.

The quantity of the butyllithium in the solution was calculated from the signal intensity due to the α-protons of butyllithium. It was ca. 0.9 mol L^{-1}. This confirms that the pseudo-first-order conditions are satisfied.

The ^{1}H NMR spectra were obtained with a Varian EM 390 spectrophotometer and the mass spectra on a JEOL D300.

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13) We have discussed that on ligation of a Lewis base to organolithiums the C-Li bond may be lengthened and the ionic character of the bond may increase.[14] At the extreme case of the ligation, the bond will be ionic. However, the discussion presented here holds in those cases as well, because the carbanion will form an intimate ion pair which is as bulky as the covalent species.

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