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Reactivities of Stable Rotamers. XII. Reactions of 9-(2-Bromomethyl-6-methylphenyl)fluorene Rotamers with Nucleophiles[1,2]

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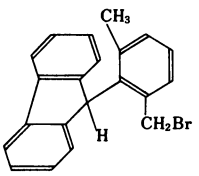
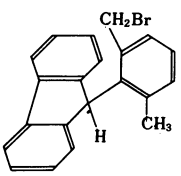
Rates of some substitution reactions of 9-(2-bromomethyl-6-methylphenyl)fluorene rotamers with nucleophiles are compared. Methanolysis of the rotamers proceeded smoothly in the *sp* form but was sluggish in the *ap*. Reactions of the *sp* form with sodium methoxide afforded 6-methylspiro[benzocyclobutene-1(2*H*), 9'-[9*H*]fluorene] and *sp*-9-(2-methoxymethyl-6-methylphenyl)fluorene, the former being a minor product. In addition to these, isomerization to the *ap* was detected. In contrast, the *ap* form afforded the spiro compound as a major product and the *ap* form of the methoxy compound as a minor product. Menschutkin reactions with pyridine bases were much faster in the *sp* form than in the *ap*. These results are attributed to the steric effect in the transition states of the reactions: the *sp* form reacts much faster than the *ap* because of the presence of the fluorene moiety in proximity of the reaction site in the latter.

Understanding of reactivities of rotational isomers is essential, if we wish to improve the selectivity of a reaction which is carried out at a low temperature, where conformations are frozen. To achieve this end, we have been studying the reactivities of stable rotamers since the success in isolating atropisomers at room temperature.[3,4] In a previous paper,[5] we gave a full account of the research on ionization reactions of 9-(2-bromomethyl-6-methylphenyl)fluorene (**1**) rotamers and a general conclusion is that, if the transition state for a reaction is space-demanding, the reaction is very slow in the *ap* form relative to that in the *sp* form. Similar conclusions were reached in related compounds.[1,6]



sp-1



ap-1

This paper reports the results of investigations on the reactivities of *sp*-**1** and *ap*-**1** with some nucleophiles. Since S_N2 type reactions are space-demanding in their transition states, the relative reactivities (k_{sp}/k_{ap}) are expected to be large in these reactions and the expectation is proved to be true.

Results and Discussion

Main reactions investigated in this work are summarized in the following chart, together with a related reaction.

Methanolysis of alkyl halides is known to be autocatalytic. Therefore, only the initial reaction rates are valid, if we wish to discuss the results quantitatively.[7] Alternatively, a base which shows proton affinity but no affinity to other acids may be added to obtain reliable data. Furthermore, it was pointed out that benzyl halides react in both S_N1 and S_N2 fashions in solvolytic reactions.[8]

Heating a rotamer of **1** in methanol containing *ca.* 2 (v/v)% of chloroform, which was necessary for facile

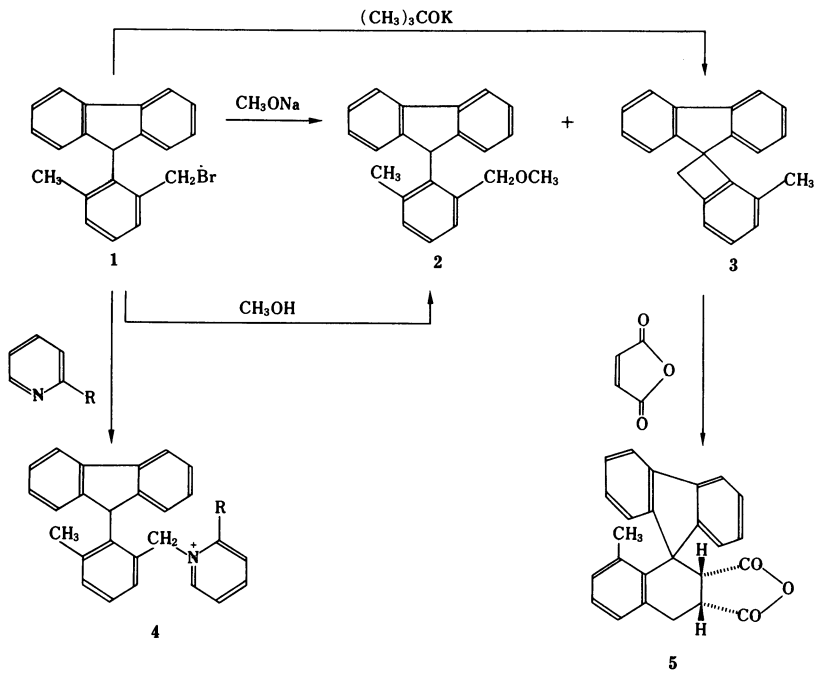


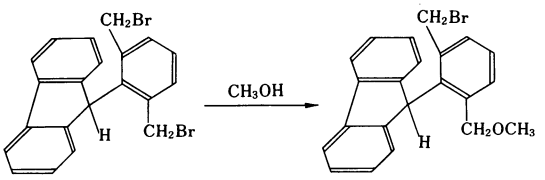
TABLE 1. CONDITIONS AND PRODUCTS OF REACTIONS OF **1** WITH SODIUM METHOXIDE IN METHANOL

Temp/°C	Time/min	Substrate	Conversion	Products (%)[a]			
				Isomerization	*sp*-**2**	*ap*-**2**	**3**
25	500	*sp*-**1**	72	4	78	Trace	19
		ap-**1**	58	8	6	Trace	86
50	80	*sp*-**1**	94	0	72	7	20
		ap-**1**	88	0	5	Trace	95

a) Normalized to 100%.

dissolution, at 52 °C afforded methanolysis products, *sp*- and *ap*-9-(2-methoxymethyl-6-methylphenyl)fluorene (**2**). The reaction obeyed the pseudo-first order rate law until 20—30% completion. The rate constants were obtained as follows: $k_{sp}=5.5\times10^{-3}\,min^{-1}$, $k_{ap}=1.9\times10^{-4}\,min^{-1}$. *Under competitive conditions,* k_{sp}/k_{ap} was *ca.* 29 which is in good agreement with the data of the individual constants.[9]

The data allured us to investigate the methanolysis of 9-[2,6-bis(bromomethyl)phenyl]fluorene (**6**).[5] This compound possesses a diastereotopic pair of bromomethyl groups but thier reactivities should be different to a great extent. Indeed, methanolysis of **6** afforded *ap*-9-(2-bromomethyl-6-methoxymethylphenyl)-fluorene (**7**) as a sole product.



6 **7**

Using a strong base as a nucleophile should erase the effect of proton which is produced by the reaction but may cause deprotonation at the 9-position of fluorene. We have experiences of base-catalyzed isomerization of rotamers of 9-arylfluorenes.[6] Thus the use of a strong base should materialize the competitive reactions between deprotonation from the 9-position of fluorene and nucleophilic substitution at the CH_2Br group in **1**. As such a base, we examined the case of methoxide. This reaction afforded a mixture of 9-(2-methoxymethyl-6-methylphenyl)fluorene (**2**) and a spiro compound, 6-methylspiro[benzocyclobutene-1(2*H*),9′-[9*H*]fluorene] (**3**), which was also prepared by treating either *sp*-**1** or *ap*-**1** with sodium hydride. The reaction conditions and product distributions are summarized in Table 1.

Isomerization of *sp*-**1** to the *ap* form and the reverse are observed at 25 °C to a small extent. Since the formation of **3** must proceed *via* deprotonation at the 9-position followed by an intramolecular S_N2 reaction, the observation of the isomerization suggests that the intramolecular S_N2 reaction is slower than the deprotonation. Nonexistence of the isomerization of **1** in the reactions at 50 °C may mean that the rate of the cyclization is comparable with that of the deprotonation at this temperature. The mechanism of the formation of the isomerized methoxycompound (**2**) is not clear, since **2** can be formed either by isomerization of **1** or that of **2**. Probably the both mechanisms are involved. The most interesting point here is that, in *sp*-**1**, the substitution to produce *sp*-**2** is a main reaction, whereas, in *ap*-**1**, the deprotonation is main. Apparently the S_N2 type substitution is faster than the deprotonation in *sp*-**1**, but the S_N2 type reaction is so slow in the *ap* that the deprotonation becomes the main reaction.

According to the idea discussed above, the reaction of **1** with *t*-butoxide should produce **3** as a sole product, since S_N2 reactions of *t*-butoxide is known to be unimportant.[10] Indeed, treatment of either *sp*-**1** or *ap*-**1** with potassium *t*-butoxide in *t*-butyl alcohol produced the spiro compound (**3**) as a sole product. The relative reactivity (k_{sp}/k_{ap}) was 1.4. The cause for this difference in the reactivities of the rotamers is probably ligation between the cation and the bromine atom in the 2-substituent, which is close to the reaction site in the *sp* form. Since potassium *t*-butoxide exists most probably as ion pairs in *t*-butyl alcohol which has a low dielectric constant,[11] ligation of the bromine to potassium ion should reduce the effective size of the alkoxide to some extent. Such an example of assistance in deprotonation has been reported.[12]

The facile formation of the spiro compound (**3**) was a surprise for us because it contained a benzocyclobutene moiety; benzocyclobutenes are usually prepared by special techniques. In order to confirm the structure, we have carried out a reaction. Benzocyclobutenes are known to be pyrolyzed to produce *o*-quinone dimethides which can be trapped by a dienophile.[13] This reaction is used even for syntheses of natural products.[14] Heating a solution of **3** in toluene with maleic anhydride at 135 °C, we were able to isolate an adduct (**5**). Thus the structure of **3** is supported by a chemical means.

Pyridine bases are known to undergo pure S_N2 reactions with benzyl chloride.[15] Since their basicities are not high, their activity for deprotonation may not be very high as well. Thus it is hopeful that we examine pure S_N2 reactions of **1** without isomerization and formation of **3**, if we use a pyridine base. The results are summarized in Table 2. Compound *sp*-**1** reacts 35 times faster with 2-methylpyridine and 22 times faster with pyridine than *ap*-**1**.

Under the same conditions utilized for the reaction of **1** with 2-methylpyridine, benzyl bromide reacted with the

TABLE 2. RATES OF MENSCHUTKIN REACTIONS OF **1** WITH PYRIDINE BASES

		Pyridine	2-Methylpyridine
Temp/°C		35	34
k_2/L mol^{-1} s^{-1}	*sp*-**1**	8.5×10^{-4}	2.3×10^{-4}
	ap-**1**	3.9×10^{-5}	6.7×10^{-6}
k_{sp}/k_{ap}		22	35

base with a rate constant of 3.8×10^{-5} L mol^{-1} s^{-1}. The rate constant is in good agreement with that reported.[16] Thus benzyl bromide is about 6 times more reactive than *ap*-**1** but is less reactive than *sp*-**1** by a factor of *ca.* 6. The tendency of enhancement of the reaction rate by substitution of the ortho position of benzyl halides is known.[17] The explanation of the enhancement by the van der Waals interaction[18] may be valid in this case as well.

If we summarize the results presented above, the S_N2 type reactions are, without exception, slow in *ap*-**1** relative to *sp*-**1**. This is reasonable, from the experiences we have had before,[1,6] since S_N2 type reactions take space-demanding transition states which require high energy state in the *ap* because of the steric effect. The decrease in the difference in reactivities of the rotamers by going from 2-methylpyridine to pyridine is a reflection of the steric effect. It is also interesting to note that the relative reactivity of the bromomethyl group in the rotamers is not dependent on the nucleophilicity[19] of the nucleophiles: steric effects are the controlling factor in determining the relative reactivity because 2-methylpyridine which is rather a strong nucleophile exhibited the highest selectivity.

Experimental

9-(2-Methoxymethyl-6-methylphenyl)fluorene (2). A solution of 29 mg of *sp*-**1** in 3 mL of chloroform and 20 mL of methanol was heated at 50—60 °C for 24 h and then was poured into water. The mixture was extracted with ether and the extract was dried over magnesium sulfate. After evaporation of the solvent, the residue was submitted to silica-gel TLC (1:2 hexane–benzene) to afford *ca.* 95% *sp*-**2**, oil, which gave identical ^{1}H NMR spectrum with an authentic sample.[5]

Similar treatment of *ap*-**1** in methanol showed the presence of the starting material (35%) as well as *ap*-**2** (55%), of which ^{1}H NMR spectrum was identical with that of an authentic sample,[5] after 70 h heating.

ap-*9-(2-Bromomethyl-6-methoxymethylphenyl)fluorene (7).* A solution of 46 mg of **6**[5] in 0.5 mL of chloroform and 30 mL of methanol was heated at 50—60 °C for 7 h and the solvent was evaporaed. The residue was submitted to silica-gel TLC (3:1 hexane–benzene) to give 6 mg of the recovered material and 25 mg (58%) of the desired product. Recrystallization from hexane gave a pure sample, mp 91—92 °C Found: C, 69.43; H, 4.99; Br, 21.34%. Calcd for $C_{22}H_{19}BrO$: C, 69.67; H, 5.05; Br, 21.07%. ^{1}H NMR ($CDCl_3$, δ): 3.38 (2H, s), 3.44 (3H, s), 4.73 (2H, s), 5.57 (1H, s), 7.1—8.0 (11H, m).

6-Methylspiro[benzocyclobutene-1(2H),9′-[9H]fluorene] (3). A solution of 140 mg (0.40 mmol) of a *ca.* 1:1 mixture of *sp*-**1** and *ap*-**1** in 3.5 mL of tetrahydrofuran was mixed with a suspension of 60 mg (2.5 mmol) of sodium hydride in 3.5 mL of tetrahydrofuran. To the mixture was added 0.7 mL of *N,N*-dimethylformamide and the whole was stirred for 3 h at 55—60 °C under a nitrogen atmosphere. After being cooled, the mixture was treated with 7 mL of ether containing 1.4 mL of methanol. Water was added and the organic layer was separated. The organic layer and ether extracts of the aqueous layer were combined, and washed successively with dilute hydrochloric acid and aqueous sodium hydrogencarbonate. The combined solution was dried and evaporated. The residue was purified by TLC (4:1 hexane–benzene) to give 80 mg (75%) of the desired product. Recrystallization of the product from ethanol–pentane gave a pure sample, mp 93 °C. Found: C, 94.28; H, 5.83%. Calcd for $C_{21}H_{16}$: C, 93.99; H, 6.01%. MS showed an M^+ peak at *m/z* 268 while the calculated value is 268. ^{1}H NMR ($CDCl_3$, δ): 1.49 (3H, s), 3.65 (2H, s), 6.9—7.9 (11H, m).

8′-Methyl-3′,4′-dihydrospiro[9H-fluorene-9,1′(2′H)-naphthalene]-cis-2′,3′-dicarboxylic Anhydride (5). A solution of 85 mg (0.32 mmol) of **3** and 40 mg (0.41 mmol) of maleic anhydride in 0.5 mL of toluene was sealed in a tube under a nitrogen atmosphre and heated in a boiling xylene bath for 2 d. The reaction mixture was cooled and the precipitate was collected. Washing the crystals with benzene afforded 45 mg of the desired product whereas the mother liquor afforded 25 mg of the starting material after evaporation followed by TLC on silica gel (3:1 hexane–benzene). The yield was 55%. A pure sample of **5**, mp 235—236 °C, was obtained by recrystallization of the crude product from benzene. Found: C, 82.04; H, 4.69%. Calcd for $C_{25}H_{18}O_3$: C, 81.95; H, 4.95%. MS (M^+): 366. ^{1}H NMR (DMSO-d_6, δ): 1.02 (3H, s), 3.4—4.4 (4H, m), 6.9—8.1 (11H, m). IR (KBr disk): 1860, 1780 cm^{-1}.

1-[2-(9-Fluorenyl)-3-methylbenzyl]-2-methylpyridinium Bromide (4: R=CH$_3$). A solution of 20 mg (57 μmol) of *sp*-**1** in 0.3 mL of acetone containing 50 μL (510 μmol) of 2-methylpyridine. The mixture was stirred for 2 h at 35 °C. The precipitate was collected and was washed with acetone to give 12 mg (48%) of the desired compound. Recrystallization of the product from methanol–ethanol–hexane afforded a pure sample, mp 227 °C (decomp). Found:, 73.30; H, 5.18; N, 3.33; Br, 18.21%. Calcd for $C_{27}H_{24}NBr$: C, 73.30; H, 5.47, N, 3.18; Br, 18.06%. ^{1}H NMR (DMSO-d_6, δ): 1.12 (3H, s), 2.96 (3H, s), 5.50 (1H, s), 6.39 (2H, s), 6.7—9.2 (15H, m).

Similar reaction of *ap*-**1** carried out for 3 d under a nitrogen atmosphere afforded colorless crystals, mp 210 °C (decomp), after recrystallization from acetone–hexane. Found: C, 71.59; H, 5.42; N, 3.11; Br, 17.87%. Calcd for $C_{27}H_{24}NBr\cdot1/2H_2O$: C, 71.84; H, 5.58; N, 3.10; Br, 17.70%. ^{1}H NMR (DMSO-d_6, δ): 1.81 (3H, s), 2.83 (3H, s), 4.40 (2H, s), 5.77 (1H, s), 6.6—8.5 (15H, m). ^{1}H NMR ($CDCl_3$, δ): 2.04 (3H, s), 2.79 (3H, s), 4.75 (2H, s), 5.62 (1H, s), 7.1—8.3 (15H, m). The *ap*-**4** (R=CH$_3$) was much more soluble in various solvents than *sp*-**4** (R=CH$_3$).

1-[2-(9-Fluorenyl)-3-methylbenzyl]pyridinium Bromide (4: R=H). The reaction of **1** with pyridine was carried out similarly as described for the reaction of 2-methylpyridine.

sp-**4** (R=H), mp 216 °C (decomp). Found: C, 73.40; H, 5.25; N, 3.32; Br, 18.90%. Calcd for $C_{26}H_{22}NBr$: C, 72.90; H, 5.18; N, 3.27; Br, 18.65%. ^{1}H NMR (DMSO-d_6, δ): 1.04 (3H, s), 5.46 (1H, s), 6.38 (2H, s), 6.7—9.2 (16H, m).

ap-**4** (R=H), mp 189 °C (decomp). Found: C, 71.02; H, 4.92; N, 3.14; Br, 18.22%. Calcd for $C_{26}H_{22}NBr\cdot1/2H_2O$: C, 71.40; H, 5.30; N, 3.20; Br, 18.27%. ^{1}H NMR ($CDCl_3$, δ): 2.79 (3H s) 5.05 (2H, s), 5.60 (1H, s), 7.0—8.2 (16H, m).

Reaction of 1 with Sodium Methoxide. To a solution of 20 mg (57 μmol) of *sp*-**1** or *ap*-**1** and 15 mg of 2-methylnaphthalene, which served as an internal reference in the subsequent analysis, in 0.4 mL of chloroform and 28.6 mL of methanol, was added 1 mL of a methanolic solution of sodium methoxide, which was prepared by adding 0.13 g of sodium to 10.0 mL of methanol. After the solution was heated at appropriate temperatures for given times, the conversion ratio was checked by means of HPLC (a Waters M-6000 instrument) with a UV detecter. The reaction mixture was cooled and diluted with chilled water. The mixture was acidified with dilute hydrochloric acid and was extracted with dichloromethane. The organic layer was washed, dried, and evaporated. The residue in chloroform-*d* showed the presence of the spiro compound (**3**) and the methoxy compound (**2**) in addition to others. The results are summarized in Table 1.

Reaction of 1 with Potassium t-Butoxide. To a solution of 5 mg (14 μmol) each of *sp*-**1** and *ap*-**1** in 14 mL of *t*-butyl alcohol containing 3 mg of 2-methylnaphthalene, was added 1 mL of a solution of potassium *t*-butoxide (280 μmol) in

t-butyl alcohol, of which concentration was determined by titration. After 30 min, the reaction mixture was treated in a usual manner and the products were checked with ^{1}H NMR, HPLC, and/or TLC. No products other than the spiro compound (**3**) were detected.

Determinaion of Rates of Reactions. Methanolysis: A solution of 6.0 mg (17 μmol) each of *sp*-**1** and *ap*-**1** and 2.9 mg of fluorene in 0.4 mL of chloroform and 20 mL of methanol was heated at 52 °C. The aliquot was syringed out at appropriate intervals and the materials were analyzed with the use of HPLC, using the fluorene as an internal standard. The data satisfied the pseudo-first order rate law until 20—30% completion.

Menshutkin Reactions. To a solution of 12.5 mg (36 μmol) of *sp*-**1** or *ap*-**1** in 0.18 mL of dry acetone containing a small amount of dichloromethane or 1,2-dichloroethane in an NMR tube, was added 0.18 mL of a solution (0.190 mol/L) of pyridine and the tube was placed in an NMR probe at 35 °C. The decrease in the amount of the halide (**1**) was measured by taking the signal intensity of the added dichloromethane or 1,2-dichloroethane as an internal standard. The reaction obeyed the second-order rate law until 15—20% completion.

The reaction of **1** with 2-methylpyridine was monitored similarly except that the excess of an acetone solution (1.0 mol/L) of the base was used. Pseudo-first order rate constants thus obtained gave the second-order rate constants.

Competitive Reactions. Methanolysis was carried out as described in the section of rates of methanolysis except that 6.0 mg each of *sp*-**1** and *ap*-**1** were dissolved at the beginning. The relative reactivity was calculated by the following equation, where subscript 0 denotes the initial state.

$$k_{sp}/k_{ap} = \log \frac{[sp]}{[sp]_0} \Big/ \log \frac{[ap]}{[ap]_0}$$

Reaction with potassium *t*-butoxide was carried out similarly using 2-methylnaphthalene as an internal standard.

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