POTASSIUM DERIVATIVES OF FLUORENE AS INTERMEDIATES IN THE PREPARATION OF C_9-SUBSTITUTED FLUORENES

III. THE INFLUENCE OF SOLVENT AND METAL IN THE FORMATION OF C_9-SUBSTITUTED FLUORENES FROM 9-FLUORENYL METALS[1]

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ABSTRACT

Equimolar quantities of 9-fluorenyl-potassium, -sodium, or -lithium and alkyl or aralkyl halides at room temperature in ether solvents yielded a mixture of unchanged fluorene, C_9-monosubstituted fluorene, and C_9-disubstituted fluorene. The amount of disubstitution never exceeded that of unchanged fluorene, and was found to be maximum ($\sim 35\%$) for the potassium compound in 1,2-dimethoxyethane, somewhat less for the sodium analogue, and small ($\sim 5\%$) for the lithium compound. In hydrocarbon solvents such as hexane, 9-fluorenylpotassium gave only 7% of C_9-disubstituted fluorene. The lithium compound, upon reaction with methyl iodide or ethyl iodide gave, along with unreacted fluorene, only C_9-monosubstituted fluorene. But reaction of 9-fluorenyllithium with benzyl chloride in hexane gave a small quantity ($\sim 5\%$) of disubstituted fluorene as well as the monosubstituted product.

The results are explained in terms of (*a*) the solubilities of the organometallic compounds in ether and hydrocarbon solvents, (*b*) the polarity of the metal carbon bond, and (*c*) the acidity of the hydrogen on C_9 of fluorene.

INTRODUCTION

A recent publication described the infrared spectra of a number of C_9-mono- and -di-substituted fluorenes (1). For the infrared work the 9,9-disubstituted fluorenes were prepared by treating one mole of fluorene in dioxane with two gram equivalents of potassium metal. The metalated product was then brought into reaction with two moles of the appropriate halide. Contaminating monosubstituted and unsubstituted fluorene was then removed either by crystallization, or by chromatography.

Attempts to prepare C_9-monosubstituted fluorene from the reaction between equimolar proportions of fluorene and potassium in dioxane, followed by the addition of an equivalent amount of alkyl or aralkyl halide led to a mixture of C_9-monosubstituted, C_9-disubstituted, and unsubstituted fluorene whose separations were frequently somewhat tedious for routine synthesis. Accordingly, the C_9-monosubstituted compounds required for the absorption studies were prepared more conveniently by the procedure developed by Greenhow, White, and McNeil (2).

This paper describes the results of a study of mono- versus di-substitution at carbon 9 of fluorene when 9-fluorenyl-lithium, -sodium, or -potassium was allowed to react with an equimolar quantity of an alkyl or aralkyl halide in the solvents hexane (or heptane), dioxane, 1,2-dimethoxyethane (DME), 1,2-diethoxyethane (DEE), and tetrahydrofuran (THF).

RESULTS

The Reaction of 9-Fluorenylpotassium with Alkyl and Aralkyl Halides in Ether andHydrocarbon Solvents

The 9-fluorenylpotassium required for this work was prepared from equimolar amounts of potassium and fluorene (1). This could be readily isolated and transferred to the solvent chosen for study.

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Two outstanding differences were observed between the reactions at room temperature of 9-fluorenylpotassium with organic halides in *ether* solvents and its reaction with these halides in hydrocarbon solvents. *Firstly*, when dioxane, diethyl ether, diisopropyl ether, or di-*n*-butyl ether was the solvent, reaction of the organometallic compound with the organic halide was relatively fast. Within 5 minutes nearly all of the solid suspension of 9-fluorenylpotassium had disappeared. On the other hand, when *n*-heptane was the suspending solvent, much of the 9-fluorenylpotassium was still unchanged after an interval of 30 minutes. The marked difference in the rate of reaction was no doubt due to the partial solution of the 9-fluorenylpotassium which occurred in the ethers but not in heptane. This was borne out by the observation that the depth of the reddish color of the ether solution could be correlated, if only roughly, with the rate of reaction when, for the experiments concerned, equivalent quantities of reagents were used. No color was observed in the solvent for the heptane suspension, hence, in this medium, the reaction with the halide is considered to occur heterogeneously on the surface of the suspended solid, resulting in a much slower reaction dependent in part upon diffusion rate and efficiency of stirring. *Secondly*, reaction of 9-fluorenylpotassium with an organic halide in molar ratio 1:1 in *ethers* gave considerable quantities of 9,9-disubstituted fluorene along with C_9-monosubstituted and also unchanged fluorene while the same reaction in *heptane* gave essentially monosubstitution with relatively little 9,9-disubstituted fluorene. The amount of disubstituted material obtained from the reaction in dioxane was about 25% of the fluorene originally used to form the potassium compound and fell somewhat short of equivalence to the amount of unchanged fluorene. This extra quantity of fluorene most likely was that which had originally failed to react with the metal. From an examination of the results of alkylation in dioxane solvent with methyl iodide, ethyl bromide, allyl bromide, and benzyl chloride, the ratio of disubstitution to monosubstitution appears to be independent of the size of the alkyl or aralkyl group (Table I).

TABLE I

Conversion of fluorene into the mono- and di-substituted derivatives by reaction of 9-fluorenylpotassium with various alkyl halides in dioxane solvent

Alkyl halide	% disubstitution	% monosubstitution	% fluorene
Methyl iodide	26	43	31
Ethyl bromide	27	43	30
Allyl bromide	27	40	33
Benzyl chloride	23	(*)	(*)

*Accurate amounts unknown since quantitative separation of the monobenzylfluorene from fluorene was not achieved either by crystallization or chromatography.

With heptane as solvent, only about 5% of the original fluorene was converted to 9,9-disubstituted fluorene while the quantity of C_9-monosubstituted product actually isolated was 75 to 85%. The remainder of the product was unchanged fluorene.

The characteristic absorption bands used to identify the presence of C_9-mono- and C_9-di-substitution (1) and to follow the extent of separation are given in Table II. The absorption spectra of 9-ethylfluorene and 9,9-diethylfluorene, previously unreported (1) are shown in Figs. 1 and 2. The small region from 1050 to 1110 cm^{-1} is quite helpful for the determination of mono- versus di-methylfluorene. The absorption is not intense but quite sharp and distinct. Dimethyl fluorene shows a band at 1078 cm^{-1} (with a smaller one at 1085 cm^{-1}). Monomethylfluorene shows no absorption at these positions

TABLE II

Characteristic absorption bands in the infrared for C_9-substituted fluorenes (cm^{-1})

Methyl		Ethyl†		Benzyl		Allyl	
mono-	di-	mono-	di-	mono-	di-	mono-	di-
		658 m	Nil				
						681 mw*	681 mw*
				700 s*	700 s*		
719 m	Nil	Nil	Nil				
				Nil	720 ms		
						727 ms	Nil
		735–40 (broad)	735–40 (narrow)				
				746–48	746–48		
				754 s	Nil	754 s	—
758 s*	758 s*						
				Nil	761–64 s	—	761–64 s
793 s	Nil	Nil	Nil				
Nil	Nil	820 w	Nil				
Nil	Nil	838 w	Nil				
		869 mw*	869 mw*				
				905–9 m*	905–9 w		
						913 s*	913 s*
			925 m*				
932 m	932 m						

m = medium; s = strong; w = weak

*The disubstituted compounds absorb approximately twice as much as do the monosubstituted fluorenes and have broader bands.

†In addition, the monoethyl compound shows two strong bands at 748 cm^{-1} and 760 cm^{-1}, the former more intense than the latter. The diethyl compound shows strong adsorption at 754 cm^{-1} and 760 cm^{-1} the latter stronger than the former.

but in turn exhibits sharp though weak absorption at 1098 cm^{-1}. Fluorene absorbs only at 1089 cm^{-1} in this region (Fig. 3).

Influence of Solvent and Metal in C_9-Mono- and -Di-substitution

Table III shows the results of the reaction of methyl iodide and 9-fluorenylpotassium in cyclic- and poly-ethers, in hydrocarbons, and in mixtures of ethers and hydrocarbons. In Tables IV and V are listed the results of similar reactions of the sodium and lithium analogues with methyl iodide.

TABLE III

Products of the reaction of equimolar amounts of 9-fluorenylpotassium and methyl iodide in various solvents

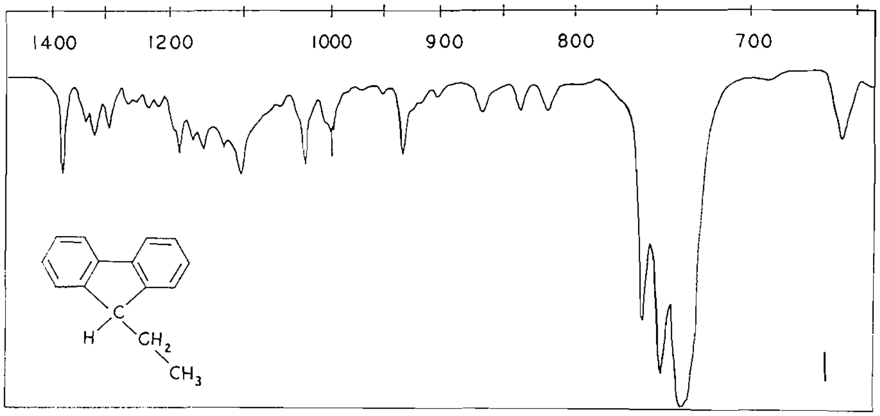
Solvent	Time§ (hr)	Apparent extent of metalation	Dimethylfluorene, %	Monomethylfluorene, %	Fluorene, %
DME	1	Complete	35	30	35
DEE	1–2	Complete	25	22	53
THF	4	Complete	20	20	60
Dioxane	4	Complete	25	40	35
Toluene–DME*	4	Complete	20	20	60
Toluene–DEE*	4	Complete	—	—	—
Toluene–THF*	4	Complete	10	25	65
Toluene–dioxane*	4	Incomplete	5	40	55
Heptane–DME*†	3	Complete	33	30	37
Hexane or heptane‡	4	—	7	40	53

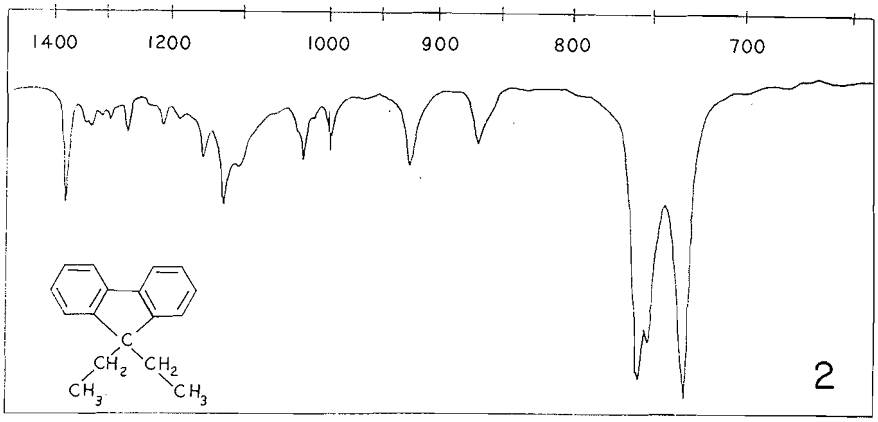
*The ratio of ether to toluene was 1:4 by volume.

†Two layers were formed during the reaction, the lower one containing the ether and the metal organic compound (ref. 3).

‡The potassium fluorenyl was prepared in dioxane, isolated by filtration, and suspended in the hydrocarbon for the reaction with CH_3I.

§The time allowed for the formation of the organometallic compound at reflux temperature of the solution.





Figs. 1 and 2.

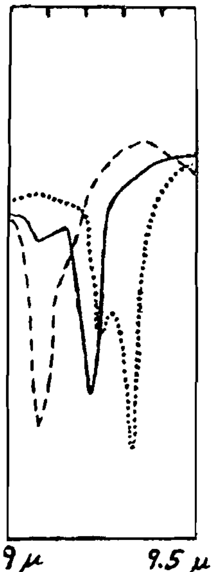


Fig. 3. The 9μ to 9.5μ region (1110 cm^{-1} to 1050 cm^{-1}) of the infrared spectrum of fluorene ———, 9-methylfluorene - - - - -, and 9,9-dimethylfluorene . . . . , taken in CS$_2$ solution.

TABLE IV

Products of the reaction of equimolar amounts of 9-fluorenylsodium and methyl iodide in various solvents

Reagent	Solvent	Time* (hr)	Apparent extent of metalation	Dimethyl-fluorene, %	Mono-methyl-fluorene, %	Fluorene, %
Na	DME	36	Complete	35	30	35
Na	DEE	40–50	Incomplete	20	40	40
Na	THF	48	†			
Na	Dioxane	36	‡			
$NaNH_2$	DME	3	Incomplete	15	40	45
$NaNH_2$	Dioxane	3	See experimental	10	35	55
	n-Heptane	§		None found	65	35

*Time allowed for the reaction between the metal or amide and fluorene in the refluxing solvents.
†The metalation with sodium metal was incomplete in all cases (ref. 3).
‡The extent of metalation was too small for separation of products.
§The sodamide was allowed to react with fluorene in refluxing dioxane for 3 hours. The precipitate was removed from the cooled solution, washed free of dioxane with hexane, and suspended in heptane.

TABLE V

Products from the reaction of equimolar amounts of 9-fluorenyllithium and methyl iodide in various solvents

Solvent	Time*	Apparent extent of metalation	Dimethyl-fluorene, %	Mono-methyl-fluorene, %	Fluorene, %
DME	4–5	Complete	5	80–85	15–10
DEE	5–6	Complete	5	60	35
THF	8	Complete	1–2	~85	14–13
Hexane†	—		0	80	20

*Time allotted for the formation of the organometallic compound in the refluxing solvent.
†9-Fluorenyllithium was prepared in DEE, then isolated, suspended in hexane, and treated with methyl iodide.

In general, it can be seen that in dimethoxyethane (DME), diethoxyethane (DEE), and tetrahydrofuran (THF), 9-fluorenylpotassium and 9-fluorenylsodium, treated with equimolar amounts of methyl iodide, gave from 20 to 35% disubstitution. In addition, at *least* the same amount of unreacted fluorene was formed along with 20 to 40% of monosubstitution. The efficiency of the solvent in promoting conversion to the dimethylated product is, in decreasing order, DME > DEE > THF. This is the same solvent order which was found previously in the study of the influence of solvent on the extent of reaction of potassium with fluorene (3). Hydrocarbon solvents, or ethers mixed with hydrocarbon solvents, generally gave less dimethylation but somewhat more monomethylation than was found when the pure ethers were used.

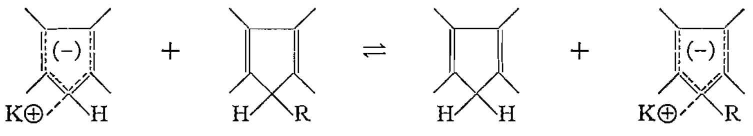
The exception was the reaction of 9-fluorenylpotassium with methyl iodide in a mixture of heptane and DME (Table III). However, that one obtained results similar to those found when pure DME was employed, can be explained. When the metal had reacted with the fluorene in this mixed solvent, two liquid layers appeared—the lower being essentially that due to the ether containing 9-fluorenylpotassium, while the upper was primarily heptane contaminated with some DME but containing no 9-fluorenylpotassium. Hence, the lower layer, where further reactions with methyl iodide occurred, approximated the conditions which held in the case where the solvent was DME only.

The 9-fluorenyllithium (prepared by precipitation from cold DEE (3)) treated with an equimolar amount of methyl iodide, gave little or no dimethylation in ether or hydrocarbon solvents. In all cases a high yield of monosubstituted fluorene was obtained.

DISCUSSION

The results of the reaction of 9-fluorenyl-lithium, -sodium, or -potassium can be rationalized on the basis of (*a*) the insolubility of the organometallic compound in hydrocarbons such as hexane, but solubility, though limited in some cases, in ethers, (*b*) the relative electropositive nature of the three metals thus giving rise to both the ionic character and reactivity of the carbon–metal bond in fluorene in the order K—C > Na—C > Li—C, (*c*) the acidic properties of fluorene and C_9-monosubstituted fluorenes.

In non-polar and non-ionizing solvents such as hexane, all three alkali metal salts possess closely associated cations and anions having a considerable amount of covalent character in the metal–carbon bond. The degree of covalency is expected to be in the order Li > Na > K. The reaction of the organic halide (RX) in hexane occurs by attack at the surface of the insoluble and suspended solid. The more polar C—K bond should react with the organic halide more quickly than does the C—Li bond. The monosubstituted fluorene, as soon as it is formed, can escape from the surface of the solid into solution. However, if the newly formed 9-monosubstituted fluorene possesses an acidic hydrogen, there will occur on the surface of the solid a reaction such as shown in A between this product and more of the salt, the extent of which depends upon the acidity of the monosubstituted fluorene. This would lead to disubstitution after further reaction with the alkyl halide. Since little or no disubstitution occurred in the reaction of 9-fluorenyl-lithium, and very little 9,9-disubstituted fluorene was formed when the potassium and sodium analogues reacted with alkyl or aralkyl halides in hexane or heptane, it is apparent that the polar halide was absorbed from the solution and reacted with the organometallic compound much more readily than did the 9-monoalkylated fluorene which escaped into solution before it reacted further. The small amount of disubstituted fluorene actually observed in the case of the potassium salt in hexane arose no doubt from a scheme such as that suggested in reaction A due to the greater ionic character of the K—C bond.



A

The electron-donor properties of ethers, however, causes some of the salt to be soluble in some cases (e.g. dioxane) while most or all of the alkali metal compound is dissolved in others (e.g. DME). In solution, because of this association of the ether and the organometallic compound (3), the ionic character of the metal–carbon bond is increased—more so for the more electropositive metals potassium and sodium than for the lithium. Reaction in solution between the salt and the organic halide therefore is expected to, and actually did, occur more rapidly. The newly formed 9-monosubstituted compound, which is also in solution, is thus able to set up an equilibrium similar to that shown in A but involving the solvated organometallic compound and that portion of the 9-fluorenyl metal as yet unreacted. The 9-alkyl-9-fluorenyl-potassium (-sodium or -lithium) can then react with a second molecule of the organic halide to give the disubstituted fluorene. Thus, there is produced one molecule of unchanged fluorene for every molecule of disubstituted fluorene. In all our experiments, there has been no case where more disubstituted than unsubstituted product has been produced, in agreement with the reaction shown in A. The position of equilibrium will then depend upon the relative acidities of the fluorene and monosubstituted fluorene and upon the rapidity with which the organic halide reacts with the monometalated fluorene. The assumption that disubstitution is obtained via the above equilibrium occurring primarily *in solution* is supported by the greater extent of disubstitution actually found in solvents wherein almost all, if not all, the organometal was dissolved (Tables III and IV). Since the lithium derivative gave very little disubstitution in any solvent (Table V), even in those wherein it is quite soluble, it is obvious that the extent of ionic character of the carbon–metal bond is an important factor which establishes the degree to which such an equilibrium as portrayed by A can be established in competition with the direct reaction of the monometalated compound with the alkyl halide. Usually alkylation at a carbon atom reduces the acidity while arylation increases the acidity of the remaining hydrogen(s) at the same carbon atom. The greater acidity of 9-phenylfluorene over that of fluorene has been recorded (4, 5), but to our knowledge no report compares the acidity of 9-alkylated fluorenes with that of the parent substance. Since disubstitution was actually observed in this work, especially in the case of the more effective ethers, the acidity of 9-alkylfluorenes should be at least of the same order as, but is more likely greater than, that of the unsubstituted fluorene. The tendency of the C_9-substituent to become coplanar with the planar fluorene molecule would lend stability to the 9-substituted fluorenyl anion. A substituent on C_9 may prefer this coplanar arrangement due to steric factors and thus enhance the acidity of the C_9—H. Furthermore, the acidity of the 9-monoalkylated fluorene must be greater than that of fluorene to compete as successfully as it does with the polar bond in the organic halide for the organometallic compound. That the 9-monoalkylated compound should be more acidic than is fluorene due to steric considerations, is not clearly shown from the results of the reaction of 9-fluorenylpotassium with the halides, methyl iodide, ethyl bromide, allyl bromide, and benzyl chloride in dioxane (Table I) since approximately the same extent of disubstitution occurred in each regardless of the size of the group. This lack of differentiation might be due to the highly reactive and therefore less discriminating, K—C bond. But the results of reaction of the 9-fluorenyllithium and 9-fluorenylsodium with methyl iodide and benzyl chloride do support this point of view. Equimolar mixtures of 9-fluorenylsodium and benzyl chloride gave 16% of the 9,9-disubstituted fluorene while only 10% of the dimethylated fluorene was obtained when the halide was methyl iodide. In the case of 9-fluorenyllithium, although reaction with methyl iodide in hexane gave no detectable disubstituted fluorene, nearly 5% of dibenzylfluorene was obtained from the reaction of the lithium salt with benzyl chloride in hexane. The question of the relationship of the size of the C_9-substituent and the ratio of di- to mono-substituted product obviously requires further study.

There exists the possibility that some, if not all, of the disubstitution might be due to unreacted metal, occluded in the organometallic compound, which would react with the monosubstituted fluorene during the process of the addition of the alkyl halide. A report is to be found in the literature that describes such a highly dispersed state of potassium metal in a solvent so as to render it indiscernible to the eye when the solution is cooled (6). Our rate of stirring certainly would not lead to such an ultrafine state of division of the metal—hence any substantial quantity of it which remained unreacted should be readily seen. In order to determine if the presence of unreacted metal actually does play a part in producing disubstituted fluorene, an experiment was performed in which the reaction between equimolar quantities (0.05 mole) of fluorene and potassium in 50 ml of DME was allowed to proceed for just 15 minutes. To the mixture, containing definitely some unreacted potassium, was added 0.05 mole of methyl iodide. By chromatography of the isolated solid on alumina using hexane as eluant, there was obtained 30% dimethylfluorene, 18% monomethylfluorene, and the remainder as unchanged fluorene. Since the experiments in which all the metal had apparently reacted to form 9-fluorenylpotassium gave 35% di- and 30% mono-methylfluorene, the conclusion must therefore be made that in those cases where unreacted metal does remain, the metal does cause dialkylation, somewhat more readily than in those reactions where only 9-fluorenylpotassium is present. This requires that the monomethylfluorene be more acidic than is fluorene. However, in those solutions where complete reaction of the metal with fluorene has occurred, dialkylation would proceed via an exchange such as shown in equation A.

In this connection, attempts to increase above 65% the yields of dialkylated fluorene, from the reaction with alkyl halides of the "9,9-fluorenyldipotassium" reported in the first of this series of articles (1), have met with consistent failure. Further experimentation has shown that the first atom of potassium reacted with fluorene to produce 9-fluorenylpotassium and an equivalent amount of hydrogen. However, treatment of the 9-fluorenylpotassium with a second equivalent of potassium in dioxane evolved *no hydrogen*. The metal, finely dispersed in the precipitated 9-fluorenylpotassium could not be readily perceived as unreacted metal. However, the reaction of two equivalents of potassium metal with one of fluorene in *DME* gave a clear solution of 9-fluorenylpotassium. Under these conditions the second equivalent of potassium remained unreacted and could be clearly seen suspended in the solvent if less vigorous stirring was employed. The existence of this second equivalent of potassium as unreacted metal, which would then react competitively with the alkyl halide and with the monoalkylated product, probably more rapidly with the former than with the latter, would thus account for the inability to produce more than 65% yield of 9,9-dialkylated fluorene (1). If this is so then at least some of the disubstituted fluorenes observed in the present work could arise from direct interaction of the monoalkylated fluorene and the residual metal in those cases of incomplete metalation.

EXPERIMENTAL

The various alkali metal salts of fluorene were prepared essentially according to published procedures (1, 3). For the present experiments a mixture of 0.05 mole of the metal, and 0.05 mole of fluorene in 50 ml of the appropriate refluxing solvent was used. The reaction times for preparation of the organometallic compound depended upon the particular experiment and are listed in the accompanying tables.

The alkyl halide (0.05 mole) was added to the cooled product (22°) slowly in order to avoid uncontrollable reaction. A 1-hour period of stirring at room temperature ensured complete reaction of the salt with the halide. The mixture was then poured into a separatory funnel containing water slightly acidified with dilute hydrochloric acid. The ether layer was separated and then dried over calcium chloride. After removal of the ether, a portion (1 g or less) of the product was passed through an 80 to 200 mesh alumina column, 60 cm × 1 cm, and eluted with pentane or hexane. Identification and estimation of the product in each small fraction (50 to 100 mg) was made by infrared spectroscopy using the absorption bands reported in Table II.

Crude benzylated fluorene was treated repeatedly with small portions of cold ethanol, thus effecting a separation of the soluble fluorene and monobenzylfluorene from the sparingly soluble dibenzylated fluorene. Complete separation of fluorene from the monobenzylfluorene was not achieved.

Experiments using the metal amides instead of metals were carried out similarly using the same quantities of reagents.

Greenhow's method (2) for the preparation of 9-fluorenylsodium was not successful in our hands (1). Since the solid material was required in experiments, the reaction of sodium metal and fluorene in DME, DEE, and THF, although quite facile was of no assistance because the salt failed to precipitate. The reaction of equimolar quantities of fluorene and powdered sodamide in refluxing dioxane gave satisfactory results. From deuteration experiments (1) approximately two thirds of the fluorene had metalated when a mixture of 8.3 g of fluorene, 1.95 g of sodamide, and 25 ml of dioxane was refluxed for 4 hours. Longer reaction time increased the extent of metalation. The 9-fluorenylsodium was readily separated from dioxane, but unreacted sodamide was also retained as a contaminant which could not be removed. Hence, the results of all reactions with 9-fluorenylsodium prepared by this method must be considered with this in mind.

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