recorder, the voltage applied across the cell being measured on the X axis and the resulting current being determined by observing the voltage drop across a standard resistor connected between the Y input terminals of the recorder.

The capillary constant for the dropping mercury electrode ($m^{2/3}t^{1/6}$) was 1.41 mg$^{2/3}$ sec$^{-1/2}$ at -0.5 V *vs.* Ag|AgBr in dimethylformamide containing 2×10^{-2} M tetraethylammonium bromide. The anode was a 10-cm length of 1-mm diameter silver wire, coiled in a spiral about the lower end of the dropping mercury capillary. All polarograms were determined at 25.0 ± 0.2° with thoroughly deaerated solutions which were between 4×10^{-4} and 5×10^{-4} M in substrate and 2×10^{-2} M in tetraethylammonium bromide. Cell resistance, measured with a Serfass Model RC M15 conductivity bridge and a tiny platinized platinum electrode sealed through the end of a glass tube which replaced the dropping mercury capillary, was approximately 1300 ohms for the dimethylformamide system and 800 ohms for the acetonitrile system.

3-Iodobiphenyl was synthesized from 3-aminobiphenyl[19] and *p*-iododimethylaniline from dimethylaniline.[20] The *p*-iodo, *p*-bromo, and *m*-chloro derivatives of trimethylanilinium bromide were prepared by methylation of the corresponding dimethylaniline derivative.[20] A sample of *p*-iodobenzophenone was furnished by Professor Albert J. Fry. All other halogen compounds were obtained from Eastman Organic Chemicals or K & K Laboratories, Inc.

Fisher reagent grade dimethylformamide was purified by refluxing over calcium hydride (5 g/1.5 l.) for 1 hr at a pressure of approximately 1 mm, and then distilling under vacuum through a 24-in. column packed with glass helices. The first 10% of the distillate was discarded as well as any other 10% fraction which showed appreciable decomposition before a cathode potential of -2.3 V *vs.* Ag|AgBr was reached. Acetonitrile (Matheson Coleman and Bell), refluxed for 10 min over sodium hydride (1 g/l.) and distilled rapidly,[21] was found to contain considerable reducible impurity. Satisfactorily pure solvent could be obtained, however, by repeating the reflux with a fresh portion of sodium hydride and then distilling at atmospheric pressure through a 24-in., helix-packed column; the resulting solvent was usable to about -2.3 V *vs.* Ag|AgBr.

Eastman reagent grade tetraethylammonium bromide was recrystallized by adding 27 ml of anhydrous ether to a solution of 3 g of tetraethylammonium bromide in 9 ml of 95% ethanol. The precipitate was dried *in vacuo* for 36–48 hr before use and stored in a vacuum desiccator over silica gel for a maximum of 2 weeks.

Acknowledgment. We thank Professor Peter A. Leermakers, Professor Dwight Smith, and Dr. Ted Evans for helpful and stimulating discussions.

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Electrophilic Substitution at Saturated Carbon. XXXVIII. Survey of Substituent Effects on Stereochemical Fate of Fluorenyl Carbanions[1]

Donald J. Cram, Warren T. Ford, and Lawrence Gosser

Contribution No. 2147 from the Department of Chemistry, University of California at Los Angeles, Los Angeles, California 90024. *Received November 1, 1967*

Abstract: A survey has been made of the values of k_e/k_α (one-point rate constant for base-catalyzed isotopic exchange over that for racemization) for five deuterated, optically active, 9-methylfluorenyl systems substituted with amido, nitro, and cyano groups. The syntheses of optically active 9-deuterio-9-methylfluorenyl systems with the following substituents are described: 2-cyano (II), 2-nitro (III), 3-N,N-dimethylcarboxamido (IV), and 2-N,N-dimethylcarboxamido-7-nitro (V). The k_e/k_α values of these compounds and those of 2-(N,N-dimethylcarboxamido)-9-methylfluorene (I) were found to vary markedly with changes in substituent character, substituent position, media, and pK_a relationship between carbon acid and the conjugate acid of the base employed. In tetrahydrofuran-*t*-butyl alcohol with tri-*n*-propylamine as base, the 2-amido system I undergoes isotopic exchange with retention of configuration under conditions that the other four systems (II–V) give isoracemization (intramolecular racemization). The 2-amido system I gives high retention with *n*-propylamine in tetrahydrofuran, whereas the 3-amide IV and 2-amido-7-nitro system V give low retention and total racemization, respectively, under the same conditions. The 2- and 3-amides in methanol-potassium methoxide gave predominantly racemization with exchange, and reaction rates separated only by a factor of 2. With nitro amide V, substitution of *p*-methylaniline in tetrahydrofuran for *n*-propylamine in tetrahydrofuran changed the stereochemical result from total racemization with exchange to high net retention. A rough comparison of the kinetic acidities of the hydrocarbons is made. These facts are interpreted in terms of the behavior of ammonium carbanide ion pairs, whose stereochemical fates depend on the relative rates of up to four fast processes: ion-pair dissociation, alkylammonium ion rotation, carbanion rotation, and proton capture. Particularly striking is the importance of charge distribution in the anion in making carbanion rotation competitive with the other processes.

A prior paper reported the preparation of and results of a survey of the stereochemical course of the base-catalyzed hydrogen isotopic exchange of carbon acid I with medium.[2] Values of k_e/k_α (rate constant for isotopic exchange over that for racemization) determined from single kinetic points were used as a qualitative probe. Thus, when $k_e/k_\alpha > 1$, isotopic exchange occurs with retention of configuration. When $k_e/k_\alpha = 1$, exchange goes with racemization. With $k_e/k_\alpha = 0.5$, exchange occurs with net inversion, and with $k_e/k_\alpha < 0.5$, racemization without exchange or *isoracemization* is observed. In this survey, values of k_e/k_α as high as >56 and as low as 0.69 were observed. Later detailed

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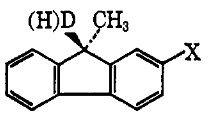
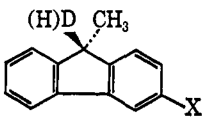
(1) This research was sponsored by the U. S. Army Research Office, Durham, N. C. The authors extend their thanks.

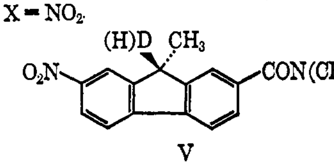
(2) D. J. Cram and L. Gosser, *J. Am. Chem. Soc.*, **86**, 5445 (1964).



I, X = CON(CH$_3$)$_2$
II, X = CN
III, X = NO$_2$



IV, X = CON(CH$_3$)$_2$
X, X = CO$_2$H



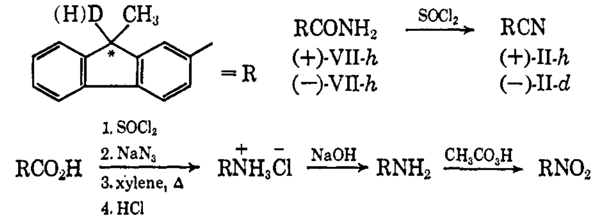
V

kinetic work demonstrated that the latter value obtained with potassium methoxide in methanol represented a blend of *isoinversion* (inversion without exchange) and racemization with exchange.[3] In a preliminary survey, V and 2-phenylbutyronitrile were found to give k_e/k_α values (one-point rate constants) that varied between <0.1 and 6.[4] The details of the survey as applied to 2-phenylbutyronitrile have appeared.[5]

This paper reports the results of a broader survey of one-point k_e/k_α values obtained for compounds II-V, whose syntheses in optically active deuterated form is also reported. In paper XXXIX,[6a] the results of a detailed kinetic study of nitro amide V is reported, and in paper XL,[6b] the detailed kinetic study is extended to isomeric amides I and II. Throughout this series of papers, the strategy of the inquiry has involved qualitative stereochemical surveys followed by detailed kinetic examination of those systems most amenable and interesting. In no case has the detailed kinetics set aside the results of the survey.

Methods and Results

Syntheses. Preparation of optically active and deuterated amide I has been reported previously,[1] as has optically active and deuterated acid and amide VI and VII. Conversions of these substances to II, III, and IV are formulated.



$$\mathrm{RCONH_2} \xrightarrow{\mathrm{SOCl_2}} \mathrm{RCN}$$

(+)-VII-*h* → (+)-II-*h*
(−)-VII-*h* → (−)-II-*d*

$$\mathrm{RCO_2H} \xrightarrow[\text{3. xylene, }\Delta\text{; 4. HCl}]{\text{1. SOCl}_2\text{; 2. NaN}_3} \mathrm{R\overset{+}{N}H_3\overset{-}{Cl}} \xrightarrow{\mathrm{NaOH}} \mathrm{RNH_2} \xrightarrow{\mathrm{CH_3CO_3H}} \mathrm{RNO_2}$$

(−)-VI-*d* (+)-VIII-*d* (−)-IX-*d* (−)-III-*d*

Acid X (9-methylfluorene-3-carboxylic acid) was produced by known procedures[7] in 9% over-all yield and was deuterated with sodium deuterioxide in a solution of 30 vol % dioxane in deuterium oxide (three treatments gave 98.3% of one atom of excess deuterium). Partial resolution of X-*d* was achieved by fractional crystallization of its salt with dehydroabietylamine[8] from 90% aqueous methanol, as was X-*h*. Conventional resolving agents failed. Acid (+)-X-*h* was converted to amide (+)-IV-*h* by the same method applied to its isomer.[2] In two conversions of (−)-X-*d* to (−)-IV-*d*, only 0.925 and 0.908 atom of deuterium per molecule were obtained in the product. Apparently, a small amount of dimethylamine-catalyzed isotopic exchange occurred during reaction.

Nitro amide (−)-V-*d* was prepared by nitration of (+)-I-*d* in acetic acid with 90% nitric acid with loss of neither deuterium nor optical activity.

Determination of k_e/k_α Values. The general procedure for determination of k_e/k_α values involved placing substrate and medium in a tube sealed under nitrogen at −78°. After reaction, the tubes were opened at −78°, the product was acidified and extracted into dichloromethane, and the recovered material was chromatographed on silica gel. The final dry product was analyzed polarimetrically for its degree of racemization. The extent of isotopic exchange was determined by infrared methods for each compound with materials of known deuterium content as standards. When incompletely deuterated amide IV was employed, the extent of racemization was corrected for isotope effects, which are reported elsewhere,[6b] except in those runs involving (+)-IV-*h* and (−)-IV-*d* in methanol–potassium methoxide (12 and 13). The kinetic isotope effects for racemization were determined for these carbon acids and medium by following the rates of racemization in a polarimeter tube (eight or more points taken; see Experimental Section). The isotope effects observed were $(k_H/k_D)_\alpha^{CH_3OD} = 6.3$ and $(k_D^{CH_3OH}/k_D^{CH_3OD})_\alpha = 2.20$. These values are within experimental error of values obtained under the same conditions for amide I.[3]

Table I reports the k_e/k_α values calculated by means of eq 1 for compounds I–V. In each run except 15, the proton reservoir of the medium was less than ~2% consumed by isotopic exchange when the reaction was interrupted.

$$k_e/k_\alpha = \frac{\log(1 - \text{fraction exchanged})}{\log(1 - \text{fraction racemized})} \qquad (1)$$

In all runs except those made with tri-*n*-propylamine as base (or no base, runs 15 and 16), the medium contained isotopic donors of approximately the same pK_a as the conjugate acid of the base used. In the next paper[6a] it is demonstrated that addition of low concentrations of tri-*n*-propylammonium iodide of the isotopic variety opposite that of the carbon acid used has no affect on k_e/k_α values when nitro amide V is run under the conditions of runs 17 and 18. When there are primary kinetic isotope effects on racemization, and exchange occurs with net retention or net inversion, values of k_e/k_α obtained from eq 1 are dependent on the extent of racemization at time of quenching. Because of isotope effects and experimental errors, the k_e/k_α values in Table I are only approximate, and small differences between them are not meaningful.

Kinetic Acidities. It was desirable to have some measure of the relative rates of exchange or racemization of the five carbon acids employed in this study and that of fluorene and 9-methylfluorene. Values have been collected from several sources, and a crude

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[3] W. T. Ford, E. W. Graham, and D. J. Cram, *J. Am. Chem. Soc.*, **89**, 4661 (1967).

[4] D. J. Cram and L. Gosser, *ibid.*, **86**, 2950 (1964).

[5] D. J. Cram and L. Gosser, *ibid.*, **86**, 5457 (1964).

[6] (a) W. T. Ford and D. J. Cram, *ibid.*, **90**, 2606 (1968); (b) W. T. Ford and D. J. Cram, *ibid.*, **90**, 2612 (1968).

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Table I. Values of k_e/k_α Obtained for 9-Methylfluorene Derivatives

Run	Carbon acid		Solvent	Base		T, °C	Time, hr	% exch	% rac	k_e/k_α[a]
	Nature	Concn, M		Nature	Concn, M					
1[b]	(−)-I-d	0.02	$(CH_2)_4O$	n-$PrNH_2$	0.5	145	1	100	7	>56
2[c]	(−)-I-d	0.01	t-BuOH	$(n\text{-}Pr)_3N$	0.5	200	3.7	36	8	5.7
3	(−)-II-d	0.13	t-BuOH	$(n\text{-}Pr)_3N$	1.1	100	3.5	10	49	0.1
4	(−)-III-d	0.06	t-BuOH	$(n\text{-}Pr)_3N$	1.1	50	24	≤20	92	≤0.1
5	(−)-IV-d	0.046	t-BuOH	$(n\text{-}Pr)_3N$	0.6	130	8	8	45	0.14
6[d]	(−)-IV-d	0.032	$(CH_2)_4O$	n-$PrNH_2$	0.4–1.2	25–75	...	...	...	1.4–2.5
7	(+)-IV-h	0.032	$(CH_2)_4O$	n-$PrND_2$[e]	0.95	25	1.0	62	65	0.9
8	(−)-IV-d	0.031	Pyridine	n-$PrNH_2$	0.69	25	2.0	68	67	1.0
9	(−)-IV-d	0.032	C_6H_6	n-$PrNH_2$	0.69	75	10.5	78	29	4.4
10	(−)-IV-d	0.032	$(CH_2)_4O$	RNH_2[f]	0.60	75	12	29	20	1.6
11	(−)-IV-d	0.046	$(CH_2)_4O$	p-$NO_2C_6H_4NH_2$[i]	0.70	190	26.5	39	16	≥2.8
12	(+)-IV-h	0.054	CH_3OD[g]	CH_3OK	0.03	25	0.5	53	56	0.9
13	(−)-IV-d	0.054	CH_3OH	CH_3OK	0.03	25	3.5	49	42	1.2
14[h]	(−)-V-d	0.035	$(CH_2)_4O$–t-BuOH[j]	$(n\text{-}Pr)_3N$	1.06	25	...	...	...	0.1
15	(+)-V-d	0.092	$(CH_2)_4O$	None	...	140	18	61	96	0.3
16	(+)-V-d	0.083	$(CH_2)_4O$–t-BuOH[k]	None	...	140	3	11	10	1.0
17[l]	(+)-V-h	0.07	$(CH_2)_4O$–t-BuOD[m]	$(n\text{-}Pr)_3N$	0.60	75	2	48	99	0.1
18[n]	(+)-V-d	0.07	$(CH_2)_4O$–t-BuOH	$(n\text{-}Pr)_3N$	0.60	75	2	35	100	<0.1
19[o]	(+)-V-d	0.01	$(CH_2)_4O$	n-$PrNH_2$	0.10	−22	0.5	10	11	1
20[p]	(+)-V-d	0.05	$(CH_2)_4O$	p-$CH_3C_6H_4NH_2$	0.50	131	1.0	50	10	6

[a] Estimated accuracy ±25% except in runs 6 and 14 where accurately determined rate constants were used. [b] Run 28, Table II, ref 2. [c] Run 32, Table II, ref 2. [d] Runs 22 and 25, Table III, and runs 44 and 46, Table V, ref 6b. [e] Reference 17. [f] 1-Phenylcyclohexylamine. [g] Deuterium, 0.99 atom per molecule, ref 3. [h] Runs 7 and 15, Table I, ref 6a. [i] A kinetic isotope effect of 2 was assumed to correct for the ~9% (−)-IV-h in the starting material. [j] $(CH_2)_4O$–t-BuOH, 80:20 by volume. [k] 1.8 M t-BuOH in $(CH_2)_4O$. [l] Run 12, Table I, ref 4. [m] Deuterium, 0.99 atom per molecule [D. J. Cram and B. Rickborn, *J. Am. Chem. Soc.*, **83**, 2178 (1961)]. [n] Run 13, Table I, ref 4. [o] Run 11, Table I, ref 4. [p] Run 10, Table I, ref 4.

scale has been developed in Table II. The relative values for 9-methylfluorene and fluorene are for detritiation in methanol–sodium methoxide[9] at 45°. The relative values for fluorene and amide I are potassium methoxide catalyzed hydrogen–deuterium exchange rates at 25° in methanol-O-d containing 25% (volume) dimethyl sulfoxide.[10] The relative values for amides I and IV are for racemization of protonated carbon acid in methanol-O-d catalyzed by potassium methoxide at 25°. The k_e/k_α values under these conditions are within experimental error of one another, and are close to unity.[3]

Table II. Relative Rates of Isotopic Exchange of Carbon Acids

Compound	k_{rel}[a]	k_{rel}[b]
9-Methylfluorene (MF)	0.26	
Fluorene	1.00	
2-Amido-MF (I)	6.22	
3-Amido-MF (IV)	13.2	13.2
2-Cyano-MF (II)		375
2-Nitro-MF (III)		905
2-Amido-7-nitro-MF (V)		5500

[a] CH_3OH-CH_3O^-. [b] $(CH_2)_4O$-$PrNH_2$.

The four most reactive compounds in Table II (II–V) were compared by rates of racemization of the deuterated compounds in tetrahydrofuran with n-propylamine. The k_e/k_α values for IV and V were 1.8 (run 6) and 1.0 (run 19) in this medium. The rates of racemization of optically active deuterated II–V were followed in tetrahydrofuran–propylamine (see Experimental Section), and third-order rate constants[6b] were calculated from a minimum of eight points. It is likely that cyano compound II and nitro compound III have k_e/k_α values between 1.0 and 1.8 in this medium, and a value of 1.4 was assumed to allow estimation of isotopic exchange rate constants from the racemization rates. From these data, the relative values of isotopic exchange for compounds II–V were calculated and are recorded in Table II. No direct measurement of the pK_a's of these carbon acids are available, but they probably range from about 15 to 20.

Discussion

Charge Distribution Effects on Stereochemistry of Isotopic Exchange. A comparison of k_e/k_α values for systems I–V is found in Table III. In tripropylamine–t-butyl alcohol, the 2-amide I gives fairly high retention ($k_e/k_\alpha = 5.7$), whereas the other four systems give high isoinversion ($k_e/k_\alpha \sim 0.1$). Particularly striking is the difference between isomeric amides I and IV. When the amide group is *meta* to the site of proton removal, the exchange gives retention; when *para*, inversion, the k_e/k_α values differing by a factor of about 40. The kinetic acidities of the two amides in methanol–potassium methoxide differ by only a factor of 2,[3] and thus this large factor of 50 cannot be correlated with acidity differences of the two systems. Apparently, the stereochemical course of exchange in this example is more sensitive to substituent effects than is the ionization process. Differences in charge distribution in the 2- and 3-amide anion appear as the most likely explanation for the marked change in stereochemical course for the exchange reaction. In the anion of the 2-amide, charge distribution on oxygen involves dearomatization of both aryl groups, whereas only one is involved with the anion of the 3-amide (compare resonance structures A and B). The anion from I is expected to carry less negative charge than that of IV, and this structural effect seriously affects the relative rates of the isoinversion component of the mechanism. In other words, the anion from amide IV provides a

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(9) A. Streitwieser, Jr., A. P. Marchand, and A. H. Pudjaatmaka, *J. Am. Chem. Soc.*, **89**, 693 (1967).

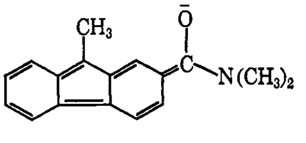
(10) D. J. Cram and W. D. Kollmeyer, *ibid.*, **90**, 1791 (1968).

Table III. Comparison of k_e/k_α Values for Substituted 9-Methylfluorenyl (MF) Carbon Acids

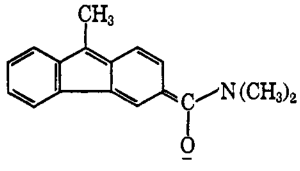
	Medium					
	$(n\text{-Pr})_3N$-t-BuOH		n-$PrNH_2$-$(CH_2)_4O$		CH_3OK-CH_3OH	
Compounds	k_e/k_α	Run	k_e/k_α	Run	k_e/k_α	Run
2-Amido-MF (I)	5.7	2	>56	1	0.82	*a*
3-Amido-MF (IV)	0.14	5	1.4–2.5	6	1.2	13
2-Cyano-MF (II)	0.1	3	...	..	...	..
2-Nitro-MF (III)	≤0.1	4	...	..	...	..
2-Amido-7-nitro-MF (V)	0.1^b	14	1.0	19	...	..

[a] Reference 3. [b] Solvent 4:1 (volume) $(CH_2)_4O$-t-BuOH.

path for the proton abstracted from its front face to be transported by base to its back face without being drowned in the isotopic pool. The anion from amide I



A, oxyanion from I



B, oxyanion from IV

provides a poorer road for such a journey. These data strongly support the *conducted tour mechanism for isoinversion*.[3,4,11] In this scheme, tri-n-propylamine abstracts a proton from the front face of amide IV, and through a series of hydrogen-bonded intermediates (each with its own charge distribution) *conducts* the proton from C-9 out to oxygen, around the (in effect) spherical array of hydrogen-bonding sites on oxygen, and back to C-9 on the opposite face of the anion. Collapse of the final ammonium carbanide ion pair to the covalent state gives isoinverted product.

The fact that nitro and cyano compounds II, III, and V also give $k_e/k_\alpha \sim 0.1$ suggests that the cyano and nitro groups carry more negative charge than does the amido group. Extensive kinetic analysis of the reaction of V with this medium is reported elsewhere.[6a]

The results obtained in propylamine–tetrahydrofuran also support this view. Here the scale is shifted since the amine catalyst is also the isotopic pool, and exchange can occur simply by rotation of the *propylammonium ion* within the ammonium carbanide ion pair. This process competes with the conducted-tour mechanism, in which in effect the carbanion rotates within the ammonium carbanide ion pair. Thus, although both amides I and IV give net retention, k_e/k_α of I exceeds that of IV by factors of <50 to >8, and IV has an isoinversion component buried in the over-all result.[6b] The two amides have been studied extensively in this medium, and detailed discussion is postponed.[6b] With nitro amide V the k_e/k_α value decreased to unity, a fact that suggests that with this more stable carbanion, the ion pair lasted long enough for randomizing reactions (*e.g.*, dissociation) to prevail.

Medium and Basic Catalyst Effects on Stereochemical Course of Isotopic Exchange. As has been noted throughout these studies,[11] medium effects play an important role in determining the stereochemical fate of carbanions. Comparison of the results obtained for the 3-amide IV in methanol–potassium methoxide and tripropylamine in t-butyl alcohol indicate that stereospecificity was lower in the more ionizing and dissociating medium, as has been noted before[2] for the 2-amide I. The stereospecificity depends on ion-pair reorganization reactions occurring faster than ion-pair dissociation which leads to racemic product. Thus, the solvents of high dielectric constant tend to give racemization and the nondissociating solvents either retention or isoinversion, depending on the relative rates of rotation of anion and cation in the ion pair.

Less gross effects are visible in the data of Table I. With the 3-amide IV and propylamine as base, k_e/k_α values changed from 4.4 in benzene to 1.8 in tetrahydrofuran to 1.0 in pyridine (runs 9, 6, and 8). Apparently, the less polar, less hydrogen-bonding solvent benzene favors propylammonium ion rotation over competing processes that symmetrize the system. The dielectric constants of the three solvents are 2.27 for benzene, 7.39 for tetrahydrofuran, and 12.3 for pyridine at 25°.[12]

In runs 6 and 11 carried out with tetrahydrofuran as solvent and amide IV as carbon acid, the less basic catalyst, p-nitroaniline, gave higher retention ($k_e/k_\alpha \geq 2.8$) than did propylamine (at 0.70 M amine, $k_e/k_\alpha \cong 1.8$), although the effect is small. A bigger difference is found in runs 19 and 20 in which nitro amide V served as carbon acid and tetrahydrofuran as medium. With propylamine as base, $k_e/k_\alpha = 1$, and with p-methylaniline, $k_e/k_\alpha = 6$. In both comparisons, but particularly in the latter, the less basic catalyst provided the higher retention. The retention mechanisms depend on ion-pair collapse to the covalent state proceeding faster than ion-pair dissociation and carbanion rotation processes. Collapse to the covalent state is expected to be faster the larger the pK_a difference between the carbon acid and the conjugate acid of the base employed. The pK_a of n-propylammonium ion is 10.58,[13] whereas that of the p-nitroanilinium ion is 1.9.[14]

In run 10 with 3-amide IV in tetrahydrofuran, 1-phenylcyclohexylamine was substituted for the usual propylamine. Although the rate of reaction was markedly decreased (factor ~60) with the more hindered amine, little change in k_e/k_α was observed. Further comparison of the two primary amines is not justified because of the large effect of steric inhibition of solvation on basicity and reactivity of amines.[15]

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(12) "Landolt-Börnstein Tabellen," Vol. 6, Springer-Verlag, Berlin, 1959, pp 619, 635, 651.

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(14) N. F. Hall, *ibid.*, 52, 5112 (1930).

(15) (a) S. T. McDowell and C. J. M. Stirling, *J. Chem. Soc., B*, 343 (1967); (b) R. G. Pearson and D. A. Vogelsong, *J. Am. Chem. Soc.*, 80, 1038, 1048 (1958).

In runs 15 and 16 in tetrahydrofuran and tetrahydrofuran–*t*-butyl alcohol without basic catalyst at 140°, nitro amide V underwent isotopic exchange and racemization. Exchange must have occurred with adventitious moisture in the run in tetrahydrofuran, which gave $k_e/k_\alpha = 0.3$ (run 15). The result does not reflect a true isoinversion, since this term defines a process that occurs intramolecularly in the presence of an appropriate isotopic reservoir, where a distinction can be made. This value went to 1.0 when *t*-butyl alcohol was present (run 16). The base in these reactions could either have been the solvent or the amide group of a second molecule of carbon acid. The pK_a's of the conjugate acids of benzamide and tetrahydrofuran are about the same.[16] The much greater concentration of tetrahydrofuran makes it likely that it served as base. The pK_a's of the conjugate acids of amides are about 10 units higher than those of nitro compounds.[16] In any case, no stereospecificity is visible in these results. These experiments point to the necessity of control runs when relatively strong carbon acids and weak bases are employed. An example is run 11 in which 3-amide IV was heated to 190° for 26.5 hr in tetrahydrofuran with *p*-nitroaniline as base (0.70 *M*). In a control run, a 0.094 *M* solution of (−)-IV-*d* was heated at 200° in tetrahydrofuran for 24 hr. The recovered material was 10% racemized. Hence, over half of the observed racemization in run 11 was not catalyzed by the added amine base.

Effect of Direction of Isotope Transfer on Stereochemical Course of Exchange Reaction. In run 6 (−)-IV-*d* in tetrahydrofuran underwent isotopic exchange with $PrNH_2$, and at 0.95 *M* base, $k_e/k_\alpha \cong 1.7$.[6b] In run 7 (+)-IV-*h* in the same solvent underwent isotopic exchange with 0.95 *M* $PrND_2$, and $k_e/k_\alpha = 0.9$. This result indicates the presence of a small isotope effect on the stereochemical course of the exchange reaction. Apparently, in the propylammonium carbanide ion pair, the carbanion abstracts a proton from the propylammonium ion faster than a deuteron when both are available. This same trend was visible in the propylamine-catalyzed isomerization of indene systems.[17] This isotope effect is complex, and is small enough that it needs to be taken into consideration only when minor changes in k_e/k_α are interpreted.

Experimental Section

General Comments. All melting points were taken on a Mel-Temp apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter in a 1-dm cell, unless otherwise specified. Deuterium analysis by the combustion and falling drop method were performed by J. Németh, Urbana, Ill. Routine infrared spectra were taken on a Beckman IR-5 spectrophotometer, and routine nmr spectra on a Varian AR-60 machine.

(+)-2-(N,N-Dimethylcarboxamido)-9-methylfluorene ((+)-I-*h*). The reported[2] method was used to prepare (+)-I-*h* having mp 126.5–127°, $[\alpha]^{25}_{546}$ +31.2°, $[\alpha]^{25}_{436}$ +60.3° (*c* 1.5, methanol), and $[\alpha]^{25}_{546}$ +33.4° (*c* 1.2, dioxane). By the same method, (+)-I-*d* was prepared with mp 127–127.5°, $[\alpha]^{25}_{546}$ +32.0°, $[\alpha]^{25}_{436}$ +61.8° (*c* 1.5, methanol), $[\alpha]^{25}_{546}$ +33.7° (*c* 1.1, dioxane). It contained 0.97 atom of excess deuterium by combustion analysis. Rotations were accurate to ±1% under these conditions and were independent of concentration.

(−)-2-(N,N-Dimethylcarboxamido)-7-nitro-9-methylfluorene-9-*d* ((−)-V-*d*). With stirring, 50 ml of 90% nitric acid was added dropwise to a solution of 10.0 g of (+)-I-*d* in 50 ml of acetic acid. The temperature was held below 25° at all times. The orange solution was kept at 25° for 30 min after addition was completed, and poured into 1000 ml of water. The organic material was extracted with 500 ml of dichloromethane. The aqueous acid was washed twice with 250 ml of dichloromethane. The combined dichloromethane solutions were washed twice with 700 ml of water and dried. Evaporation of the solvent left an orange oil which was chromatographed over 400 g of silica gel. The desired yellow product was eluted with 1% methanol in dichloromethane. The chromatographed solid was recrystallized once from ethyl acetate and twice from 95% ethanol to give 4.7 g (40%) of (−)-V-*d* having mp 133–134° and $[\alpha]^{25}_{546}$ −39.3° (*c* 7.0, dioxane) (Zeiss polarimeter). Three more recrystallizations of the material from 95% ethanol removed an impurity, which was detectable by tlc. The final product gave mp 134–135°, 0.976 atom of excess deuterium per molecule by combustion analysis, and $[\alpha]^{25}_{546}$ −39.5° (*c* 6.8, dioxane). The latter material was used for all kinetic experiments. Infrared and nmr spectra were consistent with the assigned structure. Racemic V-*d* prepared similarly had mp 130–131°.

Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.90; H, 5.44; N, 9.45. Found: C, 68.85; H, 5.34; N, 9.58.

2-Cyano-9-methylfluorene (II). In a 5-ml, pear-shaped flask were placed 0.50 g of amide VII[2] (mp 186.5–188°, lit.[2] mp 189–189.5°) and 1.0 ml of thionyl chloride (Matheson reagent).[18] The mixture was refluxed 4 hr and cooled to 25°. Small chips of ice were added to hydrolyze excess thionyl chloride. The acidic slurry was neutralized to pH 6 (hydrion paper) with 6 *N* sodium hydroxide and extracted with 25 ml of dichloromethane in three protons. The combined organic solutions were washed twice with 5% potassium bicarbonate and twice with water, dried, and evaporated to give 0.35 g (75%) of crude II having mp 95–98°. Three recrystallizations from 95% ethanol gave material with a constant melting point of 102.5–103°. The assigned structure was consistent with its infrared spectrum.

Anal. Calcd for $C_{15}H_{11}N$: C, 87.78; H, 5.40; N, 6.82. Found: C, 87.77; H, 5.45; N, 7.01.

(+)-2-Carboxamido-9-methylfluorene ((+)-VII-*h*). The method previously described for preparation of racemic VII was used.[2] From 3.5 g of (+)-9-methylfluorene-2-carboxylic acid[2] ((+)-VI-*h*), mp 214.5–215.5°, $[\alpha]^{25}_{546}$ +43.6° (*c* 7.9, dioxane) (Zeiss polarimeter), was obtained 2.0 g (60%) of (+)-VII-*h* which had mp 221.5–222.5° and $[\alpha]^{25}_{546}$ +43.8° (*c* 3.6, dioxane) after one recrystallization from acetone. Its infrared spectrum was identical with that of racemic VII.

(+)-2-Cyano-9-methylfluorene ((+)-II-*h*). By the above procedure, 1.1 g of (+)-VII-*h* was converted to 0.50 g (50%) of (+)-II-*h* which had mp 104.5–105° and $[\alpha]^{25}_{546}$ +40.7° (*c* 3.6, dioxane) after two recrystallizations from methanol. The melting point was not changed by further recrystallization.

(−)-2-Carboxamido-9-methylfluorene-9-*d* ((−)-VII-*d*). The reported[2] method was used to prepare (−)-VI-*d* having mp 215–215.5°, $[\alpha]^{25}_{546}$ −38.7° (*c* 2.5, dioxane), and 0.966 atom of excess deuterium per molecule by combustion analysis. The reported procedure[2] provided conversion of 5.0 g of (−)-VI-*d* to 2.6 g of (−)-VII-*d* having mp 232–233°, $[\alpha]^{25}_{546}$ −48° (*c* 1.1, dioxane), and 0.93 atom of excess deuterium per molecule by combustion analysis. The loss of deuterium was probably due to a small amount of ammonia-catalyzed exchange during amide formation.

(−)-2-Cyano-9-methylfluorene-9-*d* ((−)-II-*d*). From the above sample of (−)-VII-*d*, (−)-II-*d* having mp 104.5–105°, $[\alpha]^{25}_{546}$ −41.8°, $[\alpha]^{25}_{436}$ −82.8° (*c* 4.3, dioxane), and 0.935 atom of excess deuterium per molecule by combustion analysis was prepared.

2-Amino-9-methylfluorene (IX). The procedures used for preparation of IX were based on those described by others.[7a,19] The acid chloride of acid VI was prepared by refluxing 16 ml of thionyl chloride over 8.0 g of VI (mp 218.5–220.5°) until the mixture was homogeneous. Excess thionyl chloride was removed by two rapid azeotropic distillations with benzene at reduced pressure. The acid chloride was dissolved in dry acetone and cooled to 0°. A solution of 3.0 g of sodium azide in 20 ml of water was added dropwise with stirring at 0°. That temperature was maintained for 1 hr before the solution was allowed to warm to 25°. The acetone solution was poured into 500 ml of water. A white solid was filtered, washed with water, and dried to give 8.3 g (93%) of 2-

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(16) E. M. Arnett, *Progr. Phys. Org. Chem.*, **1**, 324 (1963).

(17) J. Almy, R. T. Uyeda, and D. J. Cram, *J. Am. Chem. Soc.*, **89**, 6768 (1967).

(18) General procedure taken from J. N. Krynitsky and H. W. Carhart, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc.. New York, N. Y., 1963, p 436.

(19) P. A. S. Smith, *Org. Reactions*, **3**, 337, 449 (1946).

carboxazido-9-methylfluorene with mp 87–87.5°. The infrared spectrum of the material was consistent with the assigned structure. This compound, 8.2 g, was placed in 100 ml of acetic anhydride, and the solution was refluxed for 30 min.[7a] Water was added to hydrolyze the acetic anhydride, whereupon a yellow solid precipitated. The acidic mixture was extracted with dichloromethane. The dichloromethane solution was washed with water, dried, and evaporated to leave a solid which had mp 169–170° and weighed 4.8 g (58%) after one crystallization from benzene–hexane. The infrared and nmr spectra of this material indicated it to be N-acetyl-2-amino-9-methylfluorene. The compound, 3.1 g, and a mixture of 30 ml of concentrated hydrochloric acid and 30 ml of glacial acetic acid were refluxed together for 15 hr. The solution was neutralized with 6 *N* sodium hydroxide. The cooled mixture was extracted with ether. The ether solution was washed with water, dried, and evaporated to a brown oil. The oil was chromatographed over 175 g of silica gel with 70% ether in pentane as the eluent. The recovered oil solidified during storage at 0.1 mm for 24 hr. The yield was 2.0 g (68%) of 2-amino-9-methylfluorene (IX) with mp 67.5–69.0° after one recrystallization from chloroform–hexane. Overall yield from carboxylic acid VI was 39%. The infrared and nmr spectra of this material were consistent with the assigned structure.

2-Nitro-9-methylfluorene (III). A mixture of 498 mg (2.55 mmol) of IX, 10 ml of glacial acetic acid, 3.1 ml (30 mmol) of 30% hydrogen peroxide, and 0.2 ml of concentrated sulfuric acid was held at 100° for 4 hr.[20] After cooling, the acidic solution was poured into 100 ml of water. A heavy solid precipitated. The mixture was extracted with three portions of dichloromethane. The resulting red organic solution was washed four times with saturated sodium bicarbonate solution and twice with water, dried, and evaporated to a red oil. The oil was chromatographed over 60 g of silica gel. A yellow solid whose infrared and nmr spectra corresponded to III was eluted with 10% ether in pentane. One recrystallization of the material from methanol gave crystals with mp 81–82°, which did not change upon further recrystallization, weight ~200 mg.

Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92. Found: C, 74.91; H, 4.85.

2-Amino-9-methylfluorene Hydrochloride (VIII). The procedure described above was used to convert 5.43 g of VI (mp 218.5–220.5°) to its acid chloride. When treated with sodium azide activated by the method of Smith,[19] it gave 5.79 g (96%) of solid with mp 88° dec (*vs.* 87–87.5° using unactivated sodium azide). The carbonyl azide was heated in 50 ml of refluxing xylene for 30 min. The progress of rearrangement was followed by observing the disappearance of azide absorption and the appearance of isocyanate absorption at 4.7 and 4.4 μ, respectively, in the infrared spectrum of the reaction mixture. After a brief cooling period, 25 ml of concentrated hydrochloric acid was added. The heterogeneous mixture was refluxed 2.5 hr. After cooling to 25°, a yellow solid was filtered and washed with water. A second crop of solid appeared in the filtrate and was collected. The combined yield was 4.42 g (79% from VI) of VIII with mp 227–233° dec. Its infrared spectrum (KBr) was consistent with the assigned structure.

A 2.22-g sample of this salt was converted to IX by extraction with 92 ml of 0.104 *N* sodium hydroxide (0.96 equiv) and ether–pentane. The organic solution was dried and evaporated to leave 1.66 g (89%) of crude IX having mp 60–64°.

(+)-2-Amino-9-methylfluorene-9-*d* Hydrochloride ((+)-VIII-*d*). By the procedure described above 2.01 g of (−)-VI-*d* was converted to 2.11 g of carbonyl azide which had mp 84–85° dec, $[\alpha]^{25}_{546}$ −64°, $[\alpha]^{25}_{436}$ −139° (*c* 0.6, dioxane). The carbonyl azide was converted to 1.80 g (87% from the acid) of (+)-IX-*d* with mp 236–238° dec, $[\alpha]^{25}_{546}$ +8.5° (*c* 0.5, acetone).

(−)-2-Amino-9-methylfluorene-9-*d* ((−)-IX-*d*). Free amine was prepared by dropping 70 ml (7.3 mmol) of 0.104 *N* sodium hydroxide into a heterogeneous mixture of 1.80 g (7.76 mmol) of (+)-VIII-*d* in 50 ml of water and 50 ml of ether. The ether layer turned yellow as (−)-IX-*d* was extracted into it. The product was isolated to give 1.34 g (77%) of solid with mp 61–63°, $[\alpha]^{25}_{546}$ −47.9°, $[\alpha]^{25}_{436}$ −101° (*c* 0.9, dioxane).

(−)-2-Nitro-9-methylfluorene-9-*d* ((−)-III-*d*). By the above procedure, 1.33 g of (−)-IX-*d* was converted to (−)-III-*d*. Two major components were isolated after silica gel chromatography. The first, (−)-III-*d*, was eluted with 3% ether in pentane. After one recrystallization from methanol, 487 mg (31%) of yellow solid with mp 68.5–70°, $[\alpha]^{25}_{546}$ −88° (*c* 1.1, dioxane), was obtained. Two more recrystallizations from pentane gave material with $[\alpha]^{25}_{546}$ −92° (*c* 1.0, dioxane), 0.988 atom of excess deuterium by combustion analysis and mp 71.2–71.8°, which did not change with further recrystallization. The second component, 80 mg, had $[\alpha]^{25}_{546}$ −194° (*c* 0.2, dioxane) and mp 188–190°. Its infrared spectrum showed a strong ester carbonyl absorption at 5.78 μ and nitro group absorption at 6.53 and 7.43 μ. The substance was probably an acetyl derivative of a hydroxy-2-nitro-9-methylfluorene-9-*d*.

9-Methylfluorene-3-carboxylic Acid (X). Fluorene-3-carboxylic acid was prepared[7a] in six steps from 1,4-dimethylbenzene in the following yields: *p*-xylene to 2-bromo-1,4-dimethylbenzene (86%) to 1-(2,5-xylyl)cyclohexene (45%) to 1,4-dimethyl-2-phenylbenzene (50%) to 2-phenyl-1,4-benzenedicarboxylic acid (75%) to fluorenone-3-carboxylic acid (95%) to fluorene-3-carboxylic acid (88%), mp 230–231°. This material was methylated by a procedure[7b] patterned after that used for methylation of fluorene. In a 180-ml capacity Monel steel bomb were placed 2.0 g of the above acid, 1.8 g of sodium methoxide, and 9 ml of methanol. The bomb was closed and heated to 170° for 14 hr. After cooling, the bomb was opened, emptied, and rinsed with water. Acidification with 6 *N* hydrochloric acid produced a light gray solid which was extracted into two 60-ml portions of ether. The combined ether solutions were washed with 2 *N* hydrochloric acid and with water and dried. Evaporation of the ether left a light yellow solid with mp 182–185°. This solid was sublimed at 140° (0.1 mm) to give 1.74 g (82%) of X with mp 191–193°. A second sublimation raised the melting point to 194.5–195°.

Anal. Calcd for $C_{15}H_{12}O_2$: C, 80.34; H, 5.39. Found: C, 80.47; H, 5.56.

The structure of 9-methylfluorene-3-carboxylic acid was confirmed by its infrared and nmr spectra.

The procedure worked equally well on crude brown fluorene-3-carboxylic acid having mp 223–226°. The crude XII was easily sublimed to give white solid. On large-scale runs starting with up to 50 g of crude acid, methylation was performed in a 1000-ml capacity stainless steel bomb. Care must be taken to keep the bomb temperature below 200°. After 200° decarboxylation as well as methylation occurred to give 9-methylfluorene in high yield. Yields of 60% of sublimed X were obtained. After one sublimation of X to remove dark colored impurities, recrystallization from methanol gave pure product.

Dehydroabietylamine. Isolation of dehydroabietylamine from Hercules Powder Co. Amine D and purification by recrystallization of its acetate salt from toluene were carried out as reported,[8] melting point of its acetate 137–139°. The acetate salt was converted to a light yellow amorphous solid (free amine).

Resolution of 9-Methylfluorene-3-carboxylic Acid (X). Hot solutions of 2.87 g (10.0 mmol) of dehydroabietylamine in 20 ml of methanol and 2.26 g (10.1 mmol) of X in 15 ml of methanol were combined and reduced to 20 ml. The solution was cooled to 25°. After 5 days, 1.30 g (25%) of salts was collected, washed with water, and dried. The progress of the resolution was followed by converting 50-mg portions of the salt back to the free acid using the following procedure. The salt was shaken with 10 ml of 1 *N* formic acid and 5 ml of ether. The acidic solution was washed with another 5 ml of ether. The combined ether solutions were washed twice with 10 ml of 1 *N* formic acid and twice with 10 ml of water, dried, and evaporated. Attempts to perform this conversion with mineral acids resulted in troublesome emulsions of the corresponding dehydroabietylammonium salts. Optical rotation of the recovered acid was measured at *c* 0.91–1.3, dioxane. Acid recovered in this manner from once-crystallized salt had $[\alpha]^{25}_{546}$ −6.0°, $[\alpha]^{25}_{436}$ −13.6°.

Subsequent recrystallizations of the salt were carried out as follows. The salt was dissolved in 10–15 ml of methanol per gram of salt. Enough hot water to make the solution 10% water by volume was added and thoroughly mixed. The salt crystallized at 25° and its solubility decreased as its optical purity increased. Second crystallization gave 825 mg (66%), $[\alpha]^{25}_{546}$ −7.7°, $[\alpha]^{25}_{436}$ −16.7°; third crystallization gave 546 mg (70%), $[\alpha]^{25}_{546}$ −9.9°, −22.1°; fourth crystallization gave 390 mg (71%), $[\alpha]^{25}_{546}$ −9.8°, $[\alpha]^{25}_{436}$ −21.4°, mp 184–185°. After four crystallizations the salt was converted to free carboxylic acid X which was recrystallized from methanol to give white needles having $[\alpha]^{25}_{546}$ −13.5°, $[\alpha]^{25}_{436}$ −27.0°, mp 186.5–187.5°.

The resolution was also performed on a larger scale starting with 34.7 g of X and 44.1 g of dehydroabietylamine. The procedure was the same as above except that 90% aqueous methanol was used for the first crystallization as well as all succeeding ones. However,

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[20] Procedure was patterned after that of R. R. Holmes and R. P. Bayer, *J. Am. Chem. Soc.*, **82**, 3454 (1960).

once the free acid reached an optical rotation in the range $[\alpha]^{25}_{546}$ −9 to −12°, it did not fractionate further. All attempts at fractional crystallization of this material from methanol, acetone, toluene, and chloroform resulted in recovery of material in the same range of rotations, even when white needles of (−)-X-*h* with $[\alpha]^{25}_{546}$ −13.5° were used as seed crystals.

The salt recovered from the mother liquors of the first three crystallizations of the large-scale resolution was converted to free acid and recrystallized from methanol to obtain material with mp 175–178°, $[\alpha]^{25}_{546}$ +10.8°, $[\alpha]^{25}_{436}$ +23.1°.

9-Methylfluorene-3-carboxylic Acid-9-*d* (X-*d*). The exchange procedure used was patterned after the exchange of 9-methylfluorene-2-carboxylic acid reported previously.[2] A solution of 38.3 g of 9-methylfluorene-3-carboxylic acid (0.171 mol) and 7.5 g of sodium hydroxide reagent (0.187 mol) in 119 g of 94% deuterium oxide and 41 g of dioxane (purified by the method of Fieser[21]) was stirred at room temperature for 13 hr in a flask protected from atmospheric moisture. The racemization of (−)-X-*h* had a half-life of about 3 hr under these conditions. The solvent was removed by lyophilization. The recovered solid was dissolved in 103 g of 99% deuterium oxide and 37 g of dioxane and stirred for 12 hr before the solvent was again removed by lyophilization. The progress of deuteration was followed by comparing the nmr signals of hydroxyl protons in the lyophilate with the protons of acetone as an internal standard. By this method the mixture contained 0.97 atom of deuterium at each exchangeable position after two exchanges. The solid recovered from the second exchange was dissolved in 119 g of 97.75% deuterium oxide and 57 g of dioxane and stirred for 24 hr. The solvent was again removed by lyophilization. The lyophilate contained more than 0.99 atom of deuterium in each hydroxyl position. The dry solid residue was extracted with 500 ml of 2 *N* hydrochloric acid and two portions of ether totalling 1200 ml. The ether solution was washed twice with 2 *N* hydrochloric acid, washed twice with water, dried, and evaporated. The recovered solid was recrystallized twice from methanol to give 28.8 g (75%) of X-*d* with mp 194–195°.

The deuterium content of X-*d* at the 9 position was determined by comparing the relative areas of its residual proton quartet at τ 6.0 and the methine proton singlet of *p*-biphenylylmethoxyphenylmethane[22] as internal standard at τ 4.8. A solution containing 16 mole % X-*d* and an amount of standard equivalent to 1.0% of the X-*d* in dimethyl sulfoxide-d_6 (97% deuterated)[22] was scanned with a Varian computer of average transients on a Varian A-60 spectrometer to obtain the time-averaged spectrum used for deuterium analysis. By this method X-*d* contained 0.983 atom of excess deuterium per molecule at the 9 position.

(−)-9-Methylfluorene-3-carboxylic Acid-9-*d* ((−)-X-*d*). The procedure described for resolution of X-*h* was used. All rotations reported are *c* 0.9–1.2, dioxane. From 28.8 g of X-*d* (0.128 mol) and 32.8 g of dehydroabietylamine (0.115 mol) were obtained the following crops: first crystallization, 30.0 g (49%), $[\alpha]^{25}_{546}$ −4.0°, $[\alpha]^{25}_{436}$ −8.3°; second crystallization, 23.0 g (77%), $[\alpha]^{25}_{546}$ −8.3°, $[\alpha]^{25}_{436}$ −17.5°; third crystallization, 16.4 g (71%), $[\alpha]^{25}_{546}$ −9.1°, $[\alpha]^{25}_{436}$ −183°.

After three crystallizations the salt was converted to free acid (−)-X-*d* which was recrystallized twice from methanol to give 2.4 g of fine needles with mp 175–179°, $[\alpha]^{25}_{546}$ −10.5°, $[\alpha]^{25}_{436}$ −22.2°. The salts recovered from the mother liquors were converted to free acid. Recrystallization from methanol gave 2.4 g of (−)-X-*d* having $[\alpha]^{25}_{546}$ −8.2°, $[\alpha]^{25}_{436}$ −17.4°; 2.2 g of (+)-X-*d* having $[\alpha]^{25}_{546}$ +9.2°, $[\alpha]^{25}_{436}$ +19.2°; and 9.5 g of (+)-X-*d* having $[\alpha]^{25}_{546}$ +1.8°, $[\alpha]^{25}_{436}$ +3.7°. The latter contained 0.981 atom of excess deuterium per molecule when analyzed by nmr (see above method).

3-(N,N-Dimethylcarboxamido)-9-methylfluorene (IV). The procedure reported[2] for isomer I was used. A mixture of 500 mg of X and 1.0 ml of thionyl chloride was refluxed 45 min. Excess thionyl chloride was removed by azeotropic distillation with three 5-ml portions of benzene at 25 mm. The remaining oil was dissolved in 10 ml of ether and chilled to 0°. From a cylinder, 0.5 ml of dimethylamine was condensed at −78°, diluted to 2 ml with ether, and added to the acid chloride solution with stirring. After warming to 25°, the resulting mixture was extracted with ether and 2 *N* hydrochloric acid. The ether solution was washed twice with 2 *N* hydrochloric acid and twice with water, dried, and evaporated to give a white solid. The solid was chromatographed over silica gel using 80% ether in pentane as the eluent. Two recrystallizations from ether–pentane gave 375 mg (67%) of white plates of IV with mp 93–93.5° which did not change with further recrystallization. The infrared spectrum of IV was very similar to that of its isomer, 2-(N,N-dimethylcarboxamido)-9-methylfluorene (I).

Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.23; H, 6.81; N, 5.45.

(+)-3-(N,N-Dimethylcarboxamido)-9-methylfluorene ((+)-IV-*h*). By the procedure described above, 875 mg of (+)-X-*h*, $[\alpha]^{25}_{546}$ +10.8° (*c* 1.0, dioxane), was converted to 575 mg (66%) of (+)-IV-*h* having mp 84–88°, $[\alpha]^{25}_{546}$ +7.7°, $[\alpha]^{25}_{436}$ +14.7° (*c* 1.0, dioxane). On a larger scale, 5.0 g of (+)-X-*h* ($[\alpha]^{25}_{546}$ +10.8°) was converted to 3.2 g (57%) of (+)-IV-*h* with mp 78–84°, $[\alpha]^{25}_{546}$ +5.8°, $[\alpha]^{25}_{436}$ +11.3° (*c* 1.0, dioxane).

Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.04; H, 6.62; N, 5.29.

3-(N,N-Dimethylcarboxamido)-9-methylfluorene-9-*d* (IV-*d*). The above procedure was employed with 304 mg of X-*d* to give 196 mg (57%) of IV-*d* having mp 91.5–92.5° after two recrystallizations from ether–pentane. The deuterium content of IV-*d* was determined by an nmr method similar to that used for X-*d*. The ^{13}C satellite at τ 5.8 of the N,N-dimethyl singlet was used as an internal standard and compared to the residual proton quartet centered at τ 6.0. By this method IV-*d* contained 0.988 atom of deuterium per molecule compared to 0.983 atom of deuterium in the starting acid. This analytical method is most likely accurate to ±0.005 atom of deuterium.

(−)-3-(N,N-Dimethylcarboxamido)-9-methylfluorene-9-*d* ((−)-IV-*d*). The procedure described above was used with one modification. The ether solution was quenched in 2 *N* hydrochloric acid at 0° instead of 25°. By this method 1.75 g of (−)-X-*d* ($[\alpha]^{25}_{336}$ −10.5°) was converted to 1.19 g (61%) of partially optically active (−)-IV-*d* having mp 83–86°, $[\alpha]^{25}_{546}$ −6.1°, $[\alpha]^{25}_{436}$ −11.8° (*c* 1.0, dioxane), and 0.925 atom of deuterium per molecule by nmr. On a larger scale, 4.3 g of (−)-X-*d* was converted to 3.4 g (62%) of (−)-IV-*d* with $[\alpha]^{25}_{546}$ −6.0°, $[\alpha]^{25}_{436}$ −11.7° (*c* 1.0, dioxane), and 0.908 atom of deuterium per molecule.

Anal. Calcd: C, 80.95; H and D, 7.16; N, 5.55. Found: C, 80.95; H, 7.02; N, 5.71 for the 92.5% deuterated material.

Solvents, Bases, and Salts. Tetrahydrofuran was distilled in a nitrogen atmosphere from lithium aluminum hydride onto molecular sieves and used immediately afterward. Pure *t*-butyl alcohol was distilled from and stored over molecular sieves. Methanol was purified and distilled onto molecular sieves. Methanol-O-*d* was prepared by hydrolysis of dimethyl carbonate in deuterium oxide.[23] After purification and distillation it was stored in a dry nitrogen atmosphere. It contained 0.994 atom of excess deuterium per molecule by combustion analysis and more than 0.99 atom of excess deuterium per molecule by an nmr comparison of the hydroxyl protons and the ^{13}C satellite of the methyl group. Both methanol and methanol-O-*d* contained less than 0.03 wt % water by Karl Fischer titration. Pyridine was refluxed 10 hr over barium oxide and distilled through a 60-cm vacuum-jacketed column of glass helices onto molecular sieves. A center cut with bp 114.0° uncor and $n^{25}{}_{\mathrm{D}}$ 1.5075 was collected. Benzene (Baker reagent) was stored over molecular sieves and used without further purification. Tri-*n*-propylamine was purified as described previously,[2] bp 156° uncor and $n^{25}{}_{\mathrm{D}}$ 1.4145; *n*-propylamine was purified as described previously,[2] and had bp 47.5° uncor and $n^{25}{}_{\mathrm{D}}$ 1.3856. The *n*-propylamine-N-d_2 used contained 1.97 atoms of excess deuterium per molecule.[17] The 1-phenylcyclohexylamine (Aldrich) and *p*-nitroaniline were used without further purification.

Procedure for Runs with (−)-2-(N,N-Dimethylcarboxamido)-7-nitro-9-methylfluorene-9-*d* ((−)-V-*d*). The procedure described here was used in runs 14–20. All components of the reaction mixture, 150 mg of (−)-V-*d* and appropriate amounts of solvent and base, were placed in a clean, dry, constricted test tube. The tube was cooled to −78° and sealed at 20 mm in a nitrogen atmosphere. The tube was warmed until the solution became homogeneous and placed in a constant temperature bath. The reaction was quenched at −78°, the tube was opened, and its contents were poured into 2 *N* hydrochloric acid. The substrate was extracted with two portions of dichloromethane. The combined dichloromethane solution was washed twice with water, dried, and evaporated. The recovered V was chromatographed over silica gel using 1% methanol in dichloromethane as the eluent. Optical rotations were measured on a Zeiss polarimeter at *c* 5–8, dioxane.

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(21) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1957, p 284.

(22) W. D. Kollmeyer and D. J. Cram, *J. Am. Chem. Soc.*, 90, 1779 (1968).

(23) A. Streitwieser, Jr., L. Verbit, and P. Stang, *J. Org. Chem.*, **29**, 3706 (1964).

No dependence of rotation on concentration was apparent in this range. Observed rotations were accurate to ±0.02°, and values of per cent racemization were accurate to ±2% racemization.

Deuterium Analysis of V by Infrared Spectrophotometry. The deuterium content of recovered V was determined on a Perkin-Elmer Model 421 dual grating spectrophotometer having slits manually adjusted at 400 μ, attenuator speed 11.00, gain 4, suppression 0, and source current 0.30 A. Standard sodium chloride cells with a path length of 0.1 mm were used. A strong peak at 1103 cm^{-1} appeared in V-*d* but was absent in V-*h*, while a strong peak at 1156 cm^{-1} appeared in V-*h* but was absent in V-*d*. Under these conditions the noise level at an absorbance of 0.7 was about 0.003 absorbance unit. A set of six standards varying from 0 to 90.5% V-*d* was prepared by weighing amounts of V-*h* and V-*d* totalling 15–17 mg into screw-cap vials, adding chloroform from a syringe, and reweighing to obtain the weight of solvent. Aluminum foil lining in the vial caps was necessary to prevent evaporation of the chloroform. All weights of solvent were obtained within 30 min of the time of transfer of the solution to the infrared cell. The region 1175 to 1020 cm^{-1} was scanned twice at a speed of 22 cm^{-1} per minute. The peak tops were scanned three more times at a speed of 7 cm^{-1} per minute. Peak heights were determined using the base-line method.[2] Plots of absorbance per unit concentration *vs.* per cent V-*d* for the six standards gave straight lines for both peaks. Maximum deviation of the points from the lines was 3%. Some random scattering of points appeared at >80% V-*d* for the 1103-cm^{-1} peak and at <20% V-*d* for the 1156-cm^{-1} peak. Three standards were run for calibration before analysis of each batch of unknown samples. At high and low deuterium content, results from the more reliable peak were used. Deuterium content values from the two peaks agreed within 3% for analyses in the range of 25–60% deuterium.

Procedure for Run with (−)-2-Cyano-9-methylfluorene-9-*d* ((−)-II-*d*). Run 3 was performed in a sealed test tube as described for runs with (−)-V-*d* using 135 mg of (−)-II-*d* and appropriate amounts of *t*-butyl alcohol and tri-*n*-propylamine. Partially exchanged and racemized II was recovered also by the procedure described for V. Recovered II was chromatographed over silica gel using 2% ether in pentane as the eluent. It had mp 98–100.5° compared to 104.5–105° for starting material. Rotations were taken at *c* 1.4, dioxane. No stray peaks were noticed in the infrared spectrum of recovered II. A linear relationship between absorbance per unit concentration and deuterium content was assumed for a peak at 1159 cm^{-1} which appeared in II-*d* but not in II-*h*. The deuterium content was calculated from its absorbance per unit concentration at the 1159-cm^{-1} peak on a Beckman IR-5 spectrophotometer. All spectra were taken at a concentration of 180 mg/ml in chloroform with the same pair of 0.1-mm sodium chloride cells.

Procedure for Run with (−)-2-Nitro-9-methylfluorene-9-*d* ((−)-III-*d*). In run 4, a solution of 33 mg of (−)-III-*d* in 2.0 ml of *t*-butyl alcohol and 0.50 ml of tri-*n*-propylamine was prepared in a clean, dry test tube. The tube was closed with a septum cap and thermostated at 50° for 24 hr. After cooling, the solution was shaken with 5 ml of 2 *N* hydrochloric acid and 5 ml of ether. The ether solution was washed three times with water, dried, and evaporated. The optical rotation and infrared spectrum of the recovered yellow solid were recorded without further purification. No extraneous peaks were present in its infrared spectrum. The deuterium content of recovered material was estimated to be greater than 80% by comparison of its absorbance at 1170 cm^{-1} with those of III-*d* and III-*h*, assuming a linear relationship between deuterium content and absorbance per unit concentration. Spectra were taken on a Perkin-Elmer Model 421 dual-grating spectrophotometer under normal qualitative conditions with 100-mg/ml solutions of III in carbon tetrachloride in 0.1-mm sodium chloride cells. The optical rotation of recovered III was measured at *c* 1.3, dioxane at 546 mμ.

Procedures for Runs with 3-(N,N-Dimethylcarboxamido)-9-methylfluorene (IV). Runs 7, 8, 12, and 13 involved the following procedure. A solution of 40 mg of IV was prepared in 90% of the desired volume of solvent at 25°. The base, either *n*-propylamine or a 0.5 *M* solution of potassium methoxide in methanol or methanol-O-*d*, was added to the substrate solution at zero time. Additional solvent was quickly added to the capacity of the volumetric flask, the solution was mixed by drawing it in and out of a capillary dropper several times, and 1 ml was transferred to a thermostated polarimeter cell. The volumetric flask containing the remainder of the solution was placed in the same 25° bath used to thermostat the polarimeter cell. Change in rotation was followed at 436 mμ. From first-order rate data taken in the first 10% racemization, the initial rotation was determined by extrapolation to zero time. The solutions in both the polarimeter cell and the volumetric flask were quenched in 15 ml of 1 *M* hydrochloric acid. The time and rotation at quenching were recorded. The acidic mixture was shaken with two 10-ml portions of ether. The combined ether solution was washed with 1 *N* hydrochloric acid and with water, dried, and evaporated to leave the IV in the form of a gum.

The following procedure was used for runs 5, 9–11, and 14. A solution of (−)-IV-*d*, solvent, and base was prepared in a heavy-walled tube. After thorough mixing, 1 ml was transferred to a polarimeter cell. The initial rotation was measured at 25° and 436 mμ. The solution was returned to the tube from the polarimeter cell. The tube was sealed at −78° (1 mm) and placed in a constant temperature bath for the required time. The tube was cooled to −78° before opening. After the solution warmed to 25°, 1 ml was again used to measure its rotation under the same conditions. The partially exchanged material was recovered by the procedure described above.

In runs 5 and 13, the starting (−)-IV-*d* contained 0.908 atom of deuterium per molecule. In runs 8–11, starting (−)-IV-*d* contained 0.925 atom of deuterium per molecule. In each of these runs the reported per cent racemization in Table I has been corrected for (−)-IV-*h* contributions to the initial and final rotations. In all runs involving amine bases except run 11, the isotope effects for racemization in tetrahydrofuran with *n*-propylamine reported elsewhere[6b] for IV were assumed to hold. In run 11, $k_H/k_D = 2.0$ was assumed.

Isotope effects for racemization of IV in methanol with potassium methoxide were determined from the second-order rate constants reported in Table IV. Procedures used in measuring these rates were identical with those previously reported.[3] However, eight-point graphical, rather than least-squares, rate constants were obtained. All runs were pseudo first order in IV over about two half-lives. It was assumed that racemization was first order in potassium methoxide. The second-order rate constants give $(k_H^{CH_3OD}/k_D^{CH_3OD})_{rac} = 6.3$ for the substrate isotope effect and $(k_D^{CH_3OD}/k_D^{CH_3OH})_{rac} = 2.20$ for the solvent isotope effect, both of which are within experimental error of those reported for I elsewhere.[3]

Table IV. Racemization Rates in Methanol with Potassium Methoxide at 24.90 ± 0.05°

Substrate	Solvent	$KOCH_3$, *M*	10^5k_1, sec^{-1}	10^3k_2, l. mol^{-1} sec^{-1}
(−)-IV-*d*[a]	CH_3OH	0.0598	5.99	1.00
(−)-IV-*d*[a]	CH_3OD	0.0251	5.51	2.20
(+)-IV-*h*	CH_3OD	0.0251	35.0	13.9

[a] Substrate contained 0.925 atom of D per molecule. No correction was made for racemization due to protium in substrate.

Deuterium Analysis of IV by Infrared Spectrophotometry. Recovery of IV in the form of a gum caused some difficulty in deuterium analyses, because the gum included small amounts of residual solvent. Consequently, each recovered sample was rapidly chromatographed over a 1 × 15 cm column of silica gel before analysis. Chromatography columns were prepared with 30% pentane. Each sample was poured onto the column in a minimum amount of benzene. The 30% ether solution was passed through the column to remove benzene and other high-boiling solvents. The IV was eluted in three 10–15-ml fractions with pure ether. The ether from the combined fractions was evaporated to about 1 ml and transferred with a capillary dropper to a dry, preweighed vial. The remaining ether was evaporated from the vial. The vial was dried at least 4 hr in an evacuated desiccator over anhydrous calcium sulfate. This procedure afforded 85–95% recovery of IV. Small amounts of the dried gum were removed from the vial until between 14.6 and 15.4 mg of IV remained.

Standard mixtures of IV-*h* and IV-*d* were prepared by weighing amounts of the pure compounds totalling 15.0 ± 0.4 mg into vials. Two sets of standards were prepared. One set was chromatographed by the procedure above; the other was not. Each standard was dissolved in 0.100 ml of bromoform (Matheson reagent delivered by micropipet). Spectra were obtained in 0.1-mm sodium chloride cells. The difference in absorption (Δabs) between a peak at 1098 cm^{-1}, which appeared in IV-*h* but was absent in IV-*d*, and base line at 1028 cm^{-1} was measured on a Perkin-Elmer Model 421 dual-grating spectrophotometer with the following adjustments: slit program, 2 × 1000; amplifier gain, 5; attenuator speed, 700; scan speed, 30 cm^{-1}/min; suppression, 0; scale, IX; source current, 0.36 A. Under these conditions Δabs was reproducible to ±0.004 absorbance unit for 100% IV-*h* and ±0.001 unit for 90.8% IV-*d*.

The standards which had not been chromatographed gave a linear plot of 100 × abs/weight of sample in milligrams against per cent H in which no point was located more than 1% H from the line. The chromatographed standards gave a similar plot in which all points but one were located within 3% H of a straight line. The two plots had the same slope but different intercepts; the values of 100 × Δabs/mg for chromatographed material averaged about 0.11 unit higher than those for unchromatographed material. This shift in base line for chromatographed material was probably due to residue from evaporation of 30–50 ml of ether.

Unknown samples from runs 5–13 were analyzed by the procedure used for chromatographed standards. Deuterium contents were determined by interpolation from a calibration plot of chromatographed standards made immediately before unknown samples were analyzed. The per cent exchange results for runs 8, 9, and 11 were obtained from one analysis, while those for runs 5, 7, 10, 12, and 13 are average values for analysis of two independently chromatographed samples. Results of pairs of independent determinations differed by 1–4% except for run 12 where they differed by 10% H.

Table V. Racemization Rates of Fluorene Compounds in Tetrahydrofuran with *n*-Propylamine at 24.9°

Compound		Amine		k_3, l.^{2}
Nature	Concn, *M*	concn, *M*	k_1, sec^{-1}	mol^{-2} sec^{-1}
(−)-IV-*d*	0.032	0.801	2.09×10^{-5}	3.25×10^{-5}
(−)-II-*d*	0.033	0.780	7.44×10^{-4}	1.22×10^{-3}
(−)-III-*d*	0.034	0.819	1.97×10^{-3}	2.94×10^{-3}
(−)-V-*d*	0.036	0.797	1.14×10^{-2}	1.79×10^{-2}

Relative Reactivities of Fluorene Compounds. The relative racemization rates of (+)-I-*h* and (+)-IV-*h* in methanol-O-*d* with potassium methoxide were calculated from second-order rate constants in Table IV and from those reported previously.[3] Only the relative racemization rates of (−)-II-*d*, (−)-III-*d*, and (−)-V-*d* were determined specially for the comparisons in Table II. Data for these racemization rates are reported in Table V for *n*-propylamine catalysis in tetrahydrofuran. The procedure used was identical with that reported elsewhere[6b] for racemization of (+)-IV-*h*. Solutions were prepared at 25° and quickly transferred to a thermostated polarimeter cell. Because the half-life of racemization of (−)-V-*d* was about 1 min, for its rate the temperature was probably 25.0 ± 1.0°. Even an error of 5° in temperature would not qualitatively affect the relative rate of (−)-V-*d* because of the very low enthalpy of activation.[6b] At least eight points over one to three half-lives were taken in each run. If racemizations of V, II, and III were not third order, the results in Table II would not be greatly affected because of the narrow range of *n*-propylamine concentrations used.

Electrophilic Substitution at Saturated Carbon. XXXIX. Kinetics of Isoracemization of a Fluorenyl Carbon Acid[1]

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Abstract: The kinetics of tri-*n*-propylamine-catalyzed isotopic exchange and of racemization of (−)-2-(N,N-dimethylcarboxamido)-7-nitro-9-methylfluorene-9-*d* ((−)-V-*d*) in *t*-butyl alcohol–tetrahydrofuran 20:80 by volume were studied. The racemization reaction was first order in carbon acid over a concentration range of 0.0084 to 0.101 *M*. The changes in second-order rate constant for racemization as the amine concentration varied from 0.0168 to 1.08 *M* and from 0.0729 to 1.07 *M* for exchange were small enough that both reactions are properly considered first order in amine. The rate constant for exchange (k_e) decreased by a factor of 3 as the amine concentration was increased by a factor of 16. The rate constant for racemization decreased by 30% as the amine concentration was increased by a factor of 16. These trends are attributed to the change of dielectric constant of the medium as the amine concentration increased. The activation parameters for isotopic exchange were $\Delta H^{\ddagger} = 7.1 \pm 0.9$ kcal/mol and $\Delta S^{\ddagger} = -54 \pm 4$ eu, and for racemization were $\Delta H^{\ddagger} = 10.5 \pm 0.5$ kcal/mol and $\Delta S^{\ddagger} = -39 \pm 2$ eu. Values of k_e/k_α ranged from a low of 0.10 at 10 mol % amine to a high of 0.22 at 0.6 mol % amine concentration. Concentrations of tri-*n*-propylammonium iodide or tetra-*n*-butylammonium iodide of 0.0001 *M* had no effect on k_e/k_α values (∼0.1), but concentrations of 0.03 *M* of either salt produced values of unity. The observed isoracemization (intramolecular) is interpreted as occurring through a series of contact ion pairs by a conducted tour mechanism. The slower isotopic exchange is interpreted as involving reaction of solvent-separated ion pairs with solvent. The increase in the isotopic exchange rate relative to racemization when salts are added is interpreted in terms of salt catalyzing the formation of solvent separated from contact ion pairs.

The previous paper of this series reported the results of a survey of the stereochemistry of base-catalyzed hydrogen-deuterium exchange of five carbon acids derived from 9-methylfluorene (I–V). The technique involved determination of k_e/k_α values (ratios of one-point rate constants for isotopic exchange of carbon acids with medium to those for racemization).[2] In *t*-butyl alcohol–tri-*n*-propylamine, (−)-I-*d* gave $k_e/k_\alpha = 5.7$, whereas in the same medium II–IV gave k_e/k_α values of about 0.1. In 4:1 by volume *t*-butyl alcohol–tetrahydrofuran with tri-*n*-propylamine, (+)-V-*d* also gave $k_e/k_\alpha \sim 0.1$.[2] The difference in behavior of the systems was interpreted in terms of charge distribution effects of the substituent and its position on the carbanion. Greater localization of negative charge at C-9 led to exchange with retention of configuration ($k_e/k_\alpha > 1$) as was observed with I. Greater delocalization of nega-

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(1) This research was sponsored by the U. S. Army Research Office, Durham, N. C. The authors extend their thanks.

(2) D. J. Cram, W. T. Ford, and L. Gosser, *J. Am. Chem. Soc.*, **90**, 2598 (1968).