ORGANIC AND BIOLOGICAL CHEMISTRY

Electrophilic Substitution at Saturated Carbon. XX. Stereochemical Fates of Ammonium Carbanide and Related Ion Pairs[1,2]

BY DONALD J. CRAM AND LAWRENCE GOSSER[3]

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Optically pure 2-(N,N-dimethylcarboxamido)-9-methylfluorene deuterated ((−)-II-d) and nondeuterated ((−)-II-h) in the 9-position have been prepared. The rate constants for base-catalyzed hydrogen–deuterium exchange between II and the medium (k_e) have been roughly compared with those for racemization (k_α). Values of k_e/k_α varied from extremes of about 150 to 0.2 depending on solvent, base, and the presence of added salt. With potassium phenoxide–phenol in benzene exchange occurred with high retention ($k_e/k_\alpha \gg 1$). A similar result was observed with ammonia in tetrahydrofuran or in *tert*-butyl alcohol, or with tripropylamine in benzene–phenol or *tert*-butyl alcohol. Ammonia in dimethyl sulfoxide or potassium bicarbonate in ethylene glycol gave exchange which went with complete racemization ($k_e/k_\alpha = 1$). With tripropylamine as base in methanol, exchange gave moderately high inversion of configuration ($k_e/k_\alpha = 0.65$). In tetrahydrofuran with triethylamine as base, net racemization without exchange was observed ($k_e/k_\alpha = 0.2$). These data demonstrate that in solvents of low dielectric constant, the ammonium cation of an ammonium carbanide ion pair rotates and donates a proton back to carbon (where deuterium was originally) faster than dissociation occurs. In tetrahydrofuran with triethylamine as base (no obvious proton donors), racemization without exchange is the dominating process. In solvents of high dielectric constant, ion-pair dissociation is faster than ion rotation and ion-pair collapse. In proton-donating solvents of high dielectric constant with a nonproton-donating base (a *tert*-amine), the carbanion of the ion pair is inverted by proton capture from the face of the carbanion remote from the cation. The rates of ammonia-catalyzed exchange were found to increase by an estimated 10^6 to 10^8 in passing from benzene to *tert*-butyl alcohol to tetrahydrofuran to methanol to dimethyl sulfoxide. With *n*-propylamine as base in tetrahydrofuran, addition of either lithium bromide or propylammonium acetate (0.5 N) increased the rate by 10^2 to 10^3 in tetrahydrofuran. The added salt decreased the stereospecificity of both the retention and inversion reactions.

Earlier work demonstrated that alkoxide-catalyzed hydrogen isotope exchange between hydroxylic solvents and the benzyl positions of 2-phenylbutane and of 1-methoxyphenylethane could be made to occur with high retention, total racemization, or net inversion, depending on the solvent used.[4] The relatively low acidity of these systems coupled with steric constraints to planarity of the derived carbanions placed both experimental and theoretical limitations on the investigation.

2-phenylbutane-2-d 1-methoxyphenyl-ethane-1-d I-d, A = OH   II-d, A = N(CH$_3$)$_2$
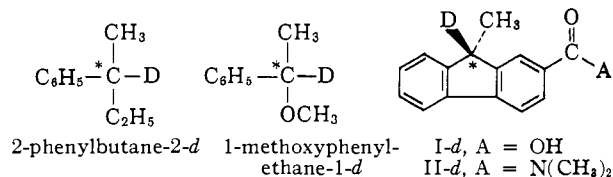
In the present study optically pure 2-carboxy-9-methylfluorene-9-d (I-d) and 2-(N,N-dimethylcarboxyamido)-9-methylfluorene-9-d (II-d) have been prepared, and their relative rates of base-catalyzed isotopic exchange and racemization were crudely measured. Compounds I and II have pK_a's estimated[5] at 25 (proton of 9-position) and 21, respectively. They

give anions which are isoelectric with anthracene, and which should favor a planar configuration. These systems, particularly II, provide a vehicle for the study of the fate of ammonium carbanide and related ion pairs under a variety of conditions. This investigation is a survey of the mechanisms available for the formation, disposition, and collapse of carbanions in the presence of proton or deuteron donors.

Preparation, Deuteration, and Resolution of I and II.—Acetylation of 9-methylfluorene provided 2-acetyl-9-methylfluorene which was oxidized with sodium hypobromite to I. The hydrogen in the 9-position exchanged its hydrogen for deuterium at room temperature in a solution of potassium hydroxide in deuterium oxide. Successive treatments of I with fresh batches of deuterium oxide provided I which contained from 0.97–0.99 atom of deuterium per molecule.[6] The nuclear magnetic resonance spectra of the deuterated samples indicated that from 95–100% of the deuterium was in the 9-position. No deuteration of the benzene rings could be detected. In many of the base-catalyzed exchange reactions of deuterated I and II, deuterium was completely removed from the molecule under mild conditions. These facts indicated that little if any deuteration of the benzene rings accompanied the preparation of I-d.

Acids I-h and I-d were resolved through their quinine and cinchonidine salts, the former giving (−)-I-(h and d) and the latter (+)-I-h. The enantiomers approached the same magnitude of rotation, a fact that suggests that near optical purity was reached. Deuterated and nondeuterated samples possessed the same rotations within experimental error. These acids were converted to their respective acid chlorides

(1) This research was sponsored in part by the U. S. Army Research Office (Durham).

(2) Some of the results of this paper were published in preliminary form: D. J. Cram and L. Gosser, *J. Am. Chem. Soc.*, **85**, 3890 (1963).

(3) U. S. Rubber Predoctoral Fellow at U.C.L.A., 1963–1964.

(4) D. J. Cram, C. A. Kingsbury, and B. Rickborn, *J. Am. Chem. Soc.*, **83**, 3688 (1961).

(5) The pK_a of fluorene is listed as 23 (A. Streitwieser, Jr., J. I. Brauman, and J. H. Hammons, *ibid.*, in press). The data of Pearson and Dillon [R. G. Pearson and R. L. Dillon, *ibid.*, **75**, 2439 (1953)] indicate that replacement of one of the hydrogens of a methylene by an alkyl group reduces the acidity of the remaining hydrogen by about 2 pK_a units. Thus the pK_a of 9-methylfluorene should be about 25. The anion of I is expected to be only slightly more acidic than the hydrocarbon. The dimethylamide II racemizes under much more mild conditions than I, and is estimated to be about 4 pK_a units lower (p$K_a \sim$ 21).

(6) Combustions and analyses of the water produced (falling drop method) were carried out by J. Nemeth, Urbana, Ill.

TABLE I

ISOTOPIC EXCHANGE EXPERIMENTS WITH $(-)$-I-h, $(-)$-I-d,[a] AND $(-)$-II-d[b] WHICH OCCURRED WITH TOTAL RACEMIZATION

	Substrate		Base					%	%	
Run	Nature	Concn., M	Nature	Concn., M	Solvent	T, °C.	Time, hr.	exch.[c]	racem.[d]	k_e/k_α[e]
1	I-h	0.3	$DOCH_2CH_2OK$	0.1	$DOCH_2CH_2OD$[f]	25	3	84	83	1
2	I-h	.3	$DOCH_2CH_2OK$	.1	$DOCH_2CH_2OD$[f]	26	0.5	18	20	1
3	I-h	.3	DOK	.2	D_2O[g]	24	3.8	22	22	1
4	I-d	.2	$CH_3CO_2K\cdot3H_2O$	.6	CH_3CO_2H	200	53	65	66	1
5	II-h	.1	$KHCO_3$[h]	.06	$DOCH_2CH_2OD$[f]	53	1.5	23	23	1
6	II-h	.1	$KHCO_3$[h]	.06	$DOCH_2CH_2OD$[f]	53	6	67	65	1
7	II-h	.1	$KHCO_3$[h]	.06	$DOCH_2CH_2OD$[f]	50	4.7	48	46	1
8	II-h	.2	KOC_5H_5	.026	$(CH_3)_3COD$[i,j]	27	7	63	62	1
9	II-h	.2	KOC_6H_5	.024	$(CH_3)_3COD$[i,j]	25	7	50	54	0.9
10	II-d	.1	KOC_6H_5	.8	C_6H_5OH[k]	102	2	40	38	1
11	II-d	.02	NH_3	.2	$(CH_3)_2SO$	25	1.5	8	9	1
12	II-d	.03	NH_3	.8	CH_3OH	75	4	31	31	1

[a] 0.99 atom of deuterium per molecule. [b] 0.97–0.99 atom of deuterium per molecule. [c] Deuterium content determined by infrared analysis based on standards of known deuterium content. [d] α_{obsd} varied between 2.00 and 0.25°. [e] See text for method of calculation. [f] 1.98 atoms of deuterium per molecule. [g] 1.99 atoms of deuterium per molecule. [h] Dried over P_2O_5. [i] 0.97 atom of deuterium per molecule. [j] Solution was 0.025 M in phenol. [k] Contained 10% by weight of *tert*-butyl alcohol.

and thence to their N,N-dimethylamides. Again enantiomers possessed rotations of essentially equal magnitude, and the deuterated and nondeuterated compounds exhibited rotations identical with one another within experimental error. These stereoisomers all possessed sharp melting points which were different from their corresponding racemates.

Isotopic Exchange Experiments.—Optically active protonated and deuterated I and II were submitted to exchange experiments with catalytic amounts of base. In most experiments, the starting materials were recovered before complete exchange had occurred. The amount of deuterium in the recovered material was measured through use of infrared spectral techniques to an absolute error of ±2%. The rotations of the starting materials and products were compared under the same conditions, and the loss in optical activity measured. The ratio of the one-point pseudo-first-order rate constants for exchange and racemization were then calculated through use of eq. 1. This

$$k_e/k_\alpha = \frac{\ln(1 - \text{fraction of material that underwent exchange})}{\ln(1 - \text{fraction of material that underwent racemization})} \quad (1)$$

number is independent of the extent of reaction only if the accumulation of deuterium in the proton reservoir is negligible and $k_\alpha^H/k_\alpha^D = 1$.

In all but three runs (35, 42, and 43) out of a total of 49, the exchange reactions were carried out in the presence of a sufficiently large isotopic pool to avoid any significant reincorporation of isotope in the starting material once initial exchange had taken place.

Hydrogen-deuterium isotope effects on the exchange and racemization of carbon acids in some of the solvents used in the present investigation gave values of k_e^H/k_e^D and k_α^H/k_α^D that ranged between 0.3 and 3.0 with most of the values being close to unity.[4,7] Calculations based on models of $k_e/k_\alpha > 1$ (retention competing with racemization) or $k_e/k_\alpha = 0.5$ (inversion) indicate that the values of k_e/k_α would be significantly modified if k_α^H/k_α^D were as small as 0.3 or as large as 3.0. However, when isotopically homogeneous starting material is employed, values of $k_\alpha^H/k_\alpha^D \neq 1$ cannot

(7) (a) D. J. Cram, D. H. Scott, and W. D. Nielsen, *J. Am. Chem. Soc.*, **83**, 3696 (1961); (b) D. J. Cram and S. H. Pine, *ibid.*, **85**, 1096 (1963).

cause $(k_e/k_\alpha)_{obsd} > 1$ to be anything other than $(k_e/k_\alpha)_{actual} > 1$, or $(k_e/k_\alpha)_{obsd} < 1$ to be anything other than $(k_e/k_\alpha)_{actual} < 1$. Furthermore, $k_\alpha^H/k_\alpha^D \neq 1$ cannot cause $(k_e/k_\alpha)_{obsd} = 1$ to be anything other than $(k_e/k_\alpha)_{actual} = 1$. Thus, although isotope effects would in some cases change the values of k_e/k_α, the qualitative picture would remain unaltered.[8]

A large number of bases and solvents were surveyed for their effects on the ratio k_e/k_α, which in turn relates to the stereochemical course of the exchange reactions (see Discussion). Table I records the results of exchange experiments of I-(h and d) and II-(h and d). Runs 1-10 involved all four substrates, a number of hydroxylic solvents, and several charged oxygen bases such as potassium alkoxides, hydroxide, acetate, and phenoxide. Amide $(-)$-II-d served as substrate and ammonia as base in runs 11 and 12, and dimethyl sulfoxide and methanol were the solvents. In these twelve runs, k_e/k_α varied between 0.9 and 1.0. The fact that k_e and k_α were essentially equal attests to the general validity of the methods employed.

In runs 13-16 (see Table II) carried out with amide $(-)$-II-d in phenol and benzene with potassium phenoxide as catalyst, values of k_e/k_α ranged from 1.8-18. Acid I underwent exchange reactions at rates several powers of ten slower than amide II, and in all runs after the first four of Table I, amide II served as substrate. In all runs in tables other than I, $(-)$-II-d was employed. In run 17, the same media (benzene-phenol) was employed, but the base was changed from potassium phenoxide to tetramethylammonium phenoxide. The change reduced k_e/k_α to unity.

Table II also contains the results of exchange and racemization experiments catalyzed by ammonia, and by primary and secondary amines (runs 18-31). Five solvent systems were employed: pyridine, *tert*-butyl alcohol, tetrahydrofuran, tetrahydrofuran-water, and benzene. A control experiment in which ammonia

(8) If a reaction was allowed to go for one half-life of exchange and a value of $(k_e/k_\alpha)_{obsd} = 0.5$ obtained based on no isotope effect, then a value $k_\alpha^H k_\alpha^D = 0.3$ would reduce k_e/k_α to 0.3, whereas a value of $k_\alpha^H/k_\alpha^D = 3$ would increase k_e/k_α to 0.76. If a reaction was allowed to go four exchange half-lives and a value of $(k_e/k_\alpha)_{obsd} = 33$ obtained based on no isotope effect, then a value of $k_\alpha^H/k_\alpha^D = 3$ would reduce k_e/k_α to 15, whereas a value of $k_\alpha^H/k_\alpha^D = 0.3$ would increase k_e/k_α to 64. Similarly, if a reaction was allowed to go two exchange half-lives and a value of $(k_e/k_\alpha)_{obsd} = 5$ obtained based on no isotope effect, a value of $k_\alpha^H/k_\alpha^D = 3$ would reduce k_e/k_α to 2.9 and a value of $k_\alpha^H/k_\alpha^D = 0.3$ would increase k_e/k_α to 7.0.

TABLE II

ISOTOPIC EXCHANGE EXPERIMENTS WITH AMIDE $(-)$-II-d^a WHICH OCCURRED WITH NET RETENTION

| Run | Sub. concn., M | Base | | Solvent | T, °C. | Time, hr. | % exch. | % racem.[b] | k_e/k_α[c] |
		Nature	Concn., M						
13	0.1	KOC_6H_5	0.8	C_6H_5OH	100	3	38	35	1.1
14	.2	KOC_6H_5	.4	C_6H_5OH	100	6	28	17	1.8
15	.03	KOC_6H_5	.1	$C_6H_6-C_6H\ OH^d$	100	1.7	100	61	>4.9
16	.02	KOC_6H_5	.1	$C_6H_6-C_6H_5OH^d$	75	2	20	1	18
17	.02	$(CH_3)_4NOC_6H_5$	.05	$C_6H_6-C_6H_5OH^d$	75	10	18	18	1.0
18	.02	NH_3	.3	Pyridine	100	4	60	32	2.5
19	.02	NH_3	.3	Pyridine	100	4	77	47	2.3
20	.03	NH_3	.8	$(CH_3)_3COH$	200	3	100	8	>50
21	.03	NH_3	.8	$(CH_3)_3COH$	196	40	100	46	>7.5
22	.2	NH_3	4	$(CH_2)_4O$	25	9	31	12	2.9
23	.1	NH_3	4	$(CH_2)_4O$	27	7.7	43	33	1.4
24	.02	NH_3	0.3	$(CH_2)_4O$	145	5.7	95	2	148
25	.02	NH_3	.2	$(CH_2)_4O$	145	6	77	16	8.5
26	.02	NH_3	.3	$(CH_2)_4O \cdot H_2O^e$	160	30	100	22	>19
27	.02	NH_3	1.6	C_6H_6	227	21	93	70	2.2
28	.02	n-$C_3H_7NH_2$	0.5	$(CH_2)_4O$	145	1	100	7	>56
29	.02	n-$C_3H_7NH_2$	.6	$(CH_2)_4O$	145	12	100	68	>3.4
30	.02	$(n$-$C_3H_7)_2NH$	.6	$(CH_2)_4O$	145	15	100	37	>8.5
31	.02	$(CH_3)_2NH$	.6	$(CH_2)_4O$	138	12	96	72	2.4
32	.01	$(n$-$C_3H_7)_3N$	.5	$(CH_3)_3COH$	200	3.7	36	8	5.7
33	.1	$(n$-$C_3H_7)_3N$	.5	$(CH_3)_3COH$	200	37	100	49	>5.8
34	.02	$(n$-$C_3H_7)_3N$	1.0	$C_6H_6-C_6H_5OH^d$	145	24	96	88	1.5
35	.02	$(n$-$C_3H_7)_3N$	1.0	$C_6H_6-C_6H_5OH^d$	145	4.3	25	6	5
36	.1	$(n$-$C_3H_7)_3N$	0.4	C_6H_6	227	25	37	22	1.9
37	.4	$(n$-$C_3H_7)_3N$	.4	C_6H_5OH	100	13	35	30	1.2
38	.2	$(C_2H_5)_3N$	.4	$C_6H_6-CH_3OH^f$	227	21	99	47	>7.3
39	.02	$(CH_3)_3N$	.4	$C_6H_6-(C_2H_5)_3COH^g$	227	9.5	82	27	5.5

^{a} 0.97–0.99 atom of deuterium per molecule. ^{b} Observed rotations ranged from 2.00 to 0.25°. ^{c} See text for method of calculation. ^{d} 90% benzene–10% phenol by wt. ^{e} $(CH_2)_4O$, 0.2 M in H_2O. ^{f} 0.8 M methanol in benzene. ^{g} 0.8 M triethylcarbinol in benzene.

TABLE III

ISOTOPIC EXCHANGE EXPERIMENTS WITH AMIDE $(-)$-II-d^a WHICH OCCURRED WITH NET INVERSION, OR WITH NET RACEMIZATION WITHOUT EXCHANGE

| Run | Sub. concn., M | Base | | Solvent | T, °C. | Time, hr. | % exch. | % racem.[b] | k_e/k_α[c] |
		Nature	Concn., M						
40	0.1	$(n$-$C_3H_7)_3N$	0.7	CH_3OH	75	13	45	60	0.65
41	.1	$(n$-$C_3H_7)_3N$	.7	CH_3OH	75	13	46	59	.69
42	.07	$(n$-$C_3H_7)_3N$	.3	CH_3OH-H_2O^d	75	2	31	38	.78
43	.07	CH_3OK	.06	CH_3OH	25	2.5	15	21	.69
44	.06	$(C_2H_5)_3N$	.6	$HOCH_2CH_2OH$	50	5.5	51	53	.94
45	.1	$(n$-$C_3H_7)_3N$	.1	$(CH_3)_2SO$	75	6	26	34	.72
46	.1	$(C_2H_5)_3N$	.5	$(CH_2)_4O^e$	145	42	25	72	.23

^{a} 0.97–0.99 atom of deuterium per molecule. ^{b} Observed rotation varied between 2.00 and 0.25°. ^{c} See text for method of calculation. ^{d} 25% water by weight. ^{e} 0.5 M in lithium bromide.

was left out of the reaction carried out in pyridine (runs 18 and 19) established that pyridine alone did not catalyze the exchange. In this series, k_e/k_α varied from 1.4 (run 23) to 148 (run 24).

Tertiary amines were employed as catalysts in runs 32–39 of Table II. The solvents used were *tert*-butyl alcohol, phenol, benzene, and mixtures of benzene with phenol, methanol, or triethylcarbinol. Values of k_e/k_α varied from a high of greater than 7.3 (run 38) to a low of 1.2 (run 37).

Table III records the results of experiments in which k_e/k_α values were less than unity. All of these except run 43 involved *tert*-amine bases as catalysts, and the solvents included methanol, ethylene glycol, dimethyl sulfoxide, and tetrahydrofuran. Values of the ratio were all between 0.5 and unity except for that of run 46, which gave 0.2 and was conducted in tetrahydrofuran with no added proton source. Run 43 involved methanol–potassium methoxide, and k_e/k_α was 0.69, the same value obtained as when tripropylamine was employed in the same solvent (run 41).

Table IV reports the results of experiments designed to determine the effect of added salts on both the ratios of rates and the absolute rates themselves. Primary and tertiary amine bases were used as catalysts, tetrahydrofuran, *tert*-butyl alcohol, and methanol as solvents, and lithium bromide, n-propylammonium and tripropylammonium acetates were employed as salts. Added salts had an accelerating effect on the rates of exchange in nonpolar solvents (10^2–10^3), and tended to draw values of k_e/k_α toward unity.

Although the absolute values of k_e and k_α were not determined with accuracy, as solvent was changed the variation in their values are marked enough to require comment. With amines as catalysts, these constants increased in value by an estimated 10^6 to 10^8 as solvent was changed from benzene to *tert*-butyl alcohol to tetrahydrofuran to pyridine to methanol to dimethyl sulfoxide.

Attempts were made to carry out acid-catalyzed hydrogen–deuterium exchange reactions of I and II in formic acid, acetic acid–p-toluenesulfonic acid, and

TABLE IV

EFFECT OF ADDED SALTS ON RATES AND STEREOCHEMISTRY OF ISOTOPIC EXCHANGE OF AMIDE $(-)$-II-d^a

Run	Sub. concn., M	Base Nature	Concn., M	Solvent	Salt Nature	Concn., M	T, °C	Time, hr.	% exch.	% racem.[b]	k_e/k_α[c]
28	0.02	n-C$_3$H$_7$NH$_2$	0.5	(CH$_2$)$_4$O	...	..	145	1	100	7	>56
47	.02	n-C$_3$H$_7$NH$_2$	.5	(CH$_2$)$_4$O	LiBr	0.05	120	6	98	46	$\gtrsim$6.3
48	.02	n-C$_3$H$_7$NH$_2$	.5	(CH$_2$)$_4$O	n-C$_8$H$_7$NH$_8$OAc	.05	120	6	99	28	$\gtrsim$12
49	.04	n-C$_3$H$_7$NH$_2$	.5	(CH$_2$)$_4$O	LiBr	.5	75	2	93	60	2.9
50	.02	n-C$_3$H$_7$NH$_2$	.5	(CH$_2$)$_4$O	n-C$_3$H$_7$NH$_8$OAc	.5	75	1	94	40	5.6
32	.1	$(n$-C$_3$H$_7)_3$N	.5	(CH$_3$)$_3$COH	...	..	200	3.7	36	8	5.7
51	.1	$(n$-C$_3$H$_7)_3$N	.6	(CH$_3$)$_3$COH	$(n$-C$_3$H$_7)_3$NHOAc	0.4	145	10.7	59	25	3.1
41	.1	$(n$-C$_3$H$_7)_3$N	.7	CH$_3$OH	...	..	75	13	46	59	0.69
52	.1	$(n$-C$_3$H$_7)_3$N	.6	CH$_3$OH	$(n$-C$_3$H$_7)_3$NHOAc	0.4	50	24	43	37	0.82

^{a} 0.97–0.99 atom of deuterium per molecule. ^{b} Observed rotation varied between 2.00 and 0.25°. ^{c} See text for method of calculation.

trifluoroacetic acid at temperatures of 75–145°, but unchanged starting material was recovered.

Discussion

The relationships between values of k_e/k_α and the stereochemistry of the base-catalyzed exchange reaction are listed in Table V. Values higher than unity clearly
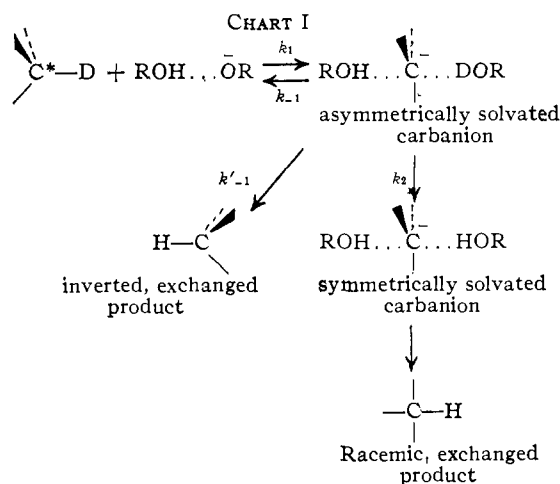
TABLE V

k_e/k_α	Stereochemical course
∞	100% retention
1	100% racemization
0.5	100% inversion
0	100% racemization without exchange

require a retention component in their mechanisms. Values lower than 0.5 also clearly require that some of the material has racemized without exchange. Values that lie between 0.5 and unity could reflect appropriate blends of mechanisms that give values greater than unity and less than 0.5. Therefore the inversion and racemization mechanisms are somewhat harder to identify by the ratios taken alone. However, the ratios themselves taken together with the way the ratios vary with the reaction conditions provide means of isolating the four general processes outlined. In the following sections, the relationships between these ratios, the conditions that produced them, and the mechanistic implications will be discussed. In some places reference will be made to the "front" and "back" faces of carbanions. The front face is that which originally carried the proton or deuteron, and the back the side remote from that proton or deuteron.

Racemization Mechanisms.—The 12 runs of Table I gave values of $k_e/k_\alpha = 1.0 \pm 0.1$. Eight different bases and solvents and four substrates were involved, and the values of k_e varied by as much as an estimated 10^6. The discrete character of these results in the face of the wide variation in conditions, substrates, and rates points to the operation of a distinct racemization mechanism for the exchange reaction. Intervention of a planar fluorenyl carbanion in a symmetrical solvent shell as a discrete intermediate provides a highly likely explanation of these results. Such an intermediate possesses a plane of symmetry, and proton capture at the two faces of the carbanion should occur with equal probability to give racemic product. The transition states for the initial proton abstraction from the optically active material must have been asymmetric. The initially produced carbanion also must have been asymmetric in the sense that it remained hydrogen bonded to the leaving group for a

finite length of time before passing into a symmetrical solvent shell.

Runs 1–3 and 5–7 (Table I) were carried out in solvents of high dielectric constant in which dissociated anions probably were the catalytic species, and in which the carbanion was hydrogen bonded both front and back (see Chart I). Such a mechanism would require that $k_2 \gg k_{-1}$. If $k_{-1} \gtrsim k_2$, net inversion would have been observed, since $k'_{-1} \sim k_{-1}$ (no isotope effect in proton capture), but this result was not found in these runs.

CHART I

In run 11 of Table I ammonia (0.2 M) served as both proton donor and base, and dimethyl sulfoxide as solvent. Since substrate (amide $(-)$-II-d) was only 0.02 M, the proton greatly exceeded the deuterium pool in the reaction mixture. Under the reaction conditions (25°), dimethyl sulfoxide would not be expected to be part of the proton pool. Hydrogen-deuterium exchange between methanol and 2-octyl phenyl sulfoxide was found to occur at a convenient rate in dimethyl sulfoxide 1.2 M in methanol and 0.18 M in potassium methoxide only when heated to 60°.[7b] On the other hand, the interesting question arises as to whether the dissociated monodeuterated ammonium ion formed reacted directly with the carbanion, or first exchanged its protons with the dissolved ammonia to form nondeuterated ammonium ions. The rate constant for exchange of protons between ammonia and ammonium ions has been measured at 25° in water[9] and has a value of about 10^9 sec.$^{-1}M^{-1}$. The reaction between ammonium ions and carbanion should also

(9) (a) M. T. Emerson, E. Grunwald, and R. A. Kromhout, *J. Chem. Phys.*, **33**, 547 (1960); (b) E. Grunwald, P. J. Karabatsos, R. A. Kromhout, and E. L. Purlee, *ibid.*, **33**, 556 (1960).

be extremely fast, but the concentration of carbanions should be many powers of ten lower than that of ammonia. A high precision measurement of k_e/k_α would provide an answer to this question, since k_e/k_α would be exactly unity if the abstracted deuterium were completely drowned in the ammonia pool, but less than unity if some deuterium was donated to the rear side of a planar carbanion. If no isotope effect was operative in the capture of protium or deuterium by the carbanion, and if no ammonium ion–ammonia exchange occurred, k_e/k_α would approach 0.75. These alternatives are formulated. The present data are not precise enough to answer this question.

no ammonium–ammonia exchange

racemic   racemic

complete ammonium–ammonia exchange

racemic
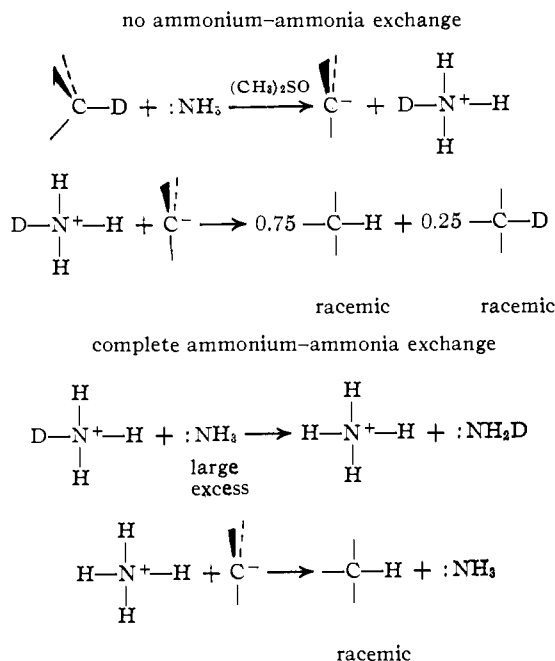
Retention Mechanisms.—In the runs of Table II, $k_e/k_\alpha > 1$. In all of these experiments, amide (−)-II-d (p$K_a \sim 21$) served as substrate, solvents of fairly low dielectric constant were employed, and proton donors of relatively high acidity (p$K_a \sim 10$) were available to the carbanion. Although values of k_e/k_α as high as 148 were obtained (run 24), a retention mechanism was always blended with others which reduced the ratio from the limiting value of infinity to some finite value.

In runs 13 and 14 of Table II, amide (−)-II-d underwent exchange catalyzed by potassium phenoxide in phenol to give k_e/k_α values of 1.1 to 1.8, and in runs 15 and 16 in 90% benzene–10% phenol to give values as high as 18. The higher retention correlates with the lower concentrations of potassium phenoxide and of proton donors, and with the medium of lower dielectric constant. These solvent and salt effects suggest that the retention and racemization mechanisms merge, and that one or the other can be made to predominate by controlling the dissociating power of the medium. In the mechanism outlined in Chart II, solvated potassium phenoxide ion-pairs are pictured as the active base that abstracts deuterium from (−)-II-d. The potassium ion of the new ion pair has the mole of deuterated phenol just formed and one or more phenol molecules of the medium as ligands. Simple rotation of the potassium ion with its ligands results in an ion-pair in which the carbanion is hydrogen

bonded to a phenol molecule originally from the medium. Collapse of this species produces exchanged product of retained configuration. Dissociation of the potassium carbanide ion-pair competes with potassium ion ligand rotation; the free planar carbanion passes into a symmetrical solvent shell and gives racemic product.
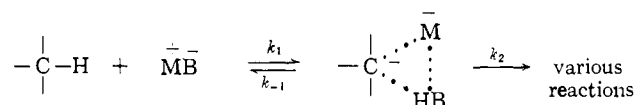
In this scheme, $k_2 > k_3$ and k'_{-1} in phenol with 0.8 M potassium phenoxide present, whereas in 90% benzene–10% phenol 0.1 M in potassium phenoxide, k_3 and $k'_{-1} > k_2$. The isotope effect for hydrogen $vs.$ deuterium capture should be small ($k_{-1} \sim k'_{-1}$), and therefore in nondissociating solvents, $k_{-1} > k_2$. In other words, potassium carbanide ion-pairs are formed many times for each time that any detectable change occurs.

CHART II

exchanged product
of retained configuration (−)-II-h
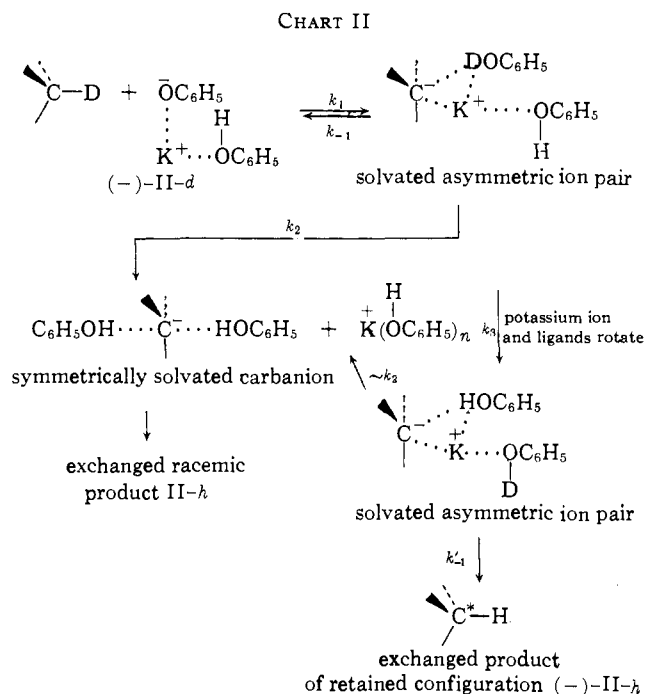
More insight can be gained about the factors which affect the relative rates of ion-pair dissociation and proton transfers within ion pairs by comparing the results obtained in benzene–phenol ($k_e/k_\alpha = 18$) with those obtained in $tert$-butyl alcohol 0.025 M in phenol ($k_e/k_\alpha = 1$, runs 8 and 9 of Table I). Potassium phenoxide at 0.1 M or less served as base in both sets of experiments, and the dissociating powers of the media were probably comparable. Since $tert$-butyl alcohol is a stronger base and was present in concentrations about 400 times that of phenol, it is safe to assume that the potassium ion of the potassium phenoxide ion-pair had $tert$-butyl alcohol molecules as ligands in runs 8 and 9. If the rates of ion-pair dissociation (k_2) and of potassium ligand rotation (k_3) were comparable in the two sets of experiments, then the difference in stereochemical results must reflect differences in k'_{-1}. This conclusion is very reasonable, since the rate of proton transfer should be fastest when the difference in pK_a between the acid being destroyed and that being made is the greatest. The pK_a of II-d is probably about 21, that of $tert$-butyl alcohol about 19, and that of phenol about 10. Clearly k'_{-1} for proton transfer from phenol to carbanion should be much greater than

k'_{-1} for proton transfer from *tert*-butyl alcohol to carbanion.[10]

These conclusions have wide implications with regard to the mechanism of any reaction which involves the abstraction of a proton from carbon by a base. Values of k_{-1}/k_2 probably can be made to vary over a large

$$-\overset{|}{\underset{|}{C}}-H + \overset{-}{M}\overset{-}{B} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} -\overset{|}{\underset{|}{C}}\overset{\cdots\overset{-}{M}}{\underset{\cdots HB}{:}} \overset{k_2}{\longrightarrow} \text{various reactions}$$

range by appropriate control of variables. Values of k_{-1} should increase the greater the difference in pK_a between CH and BH. Values of k_{-1}/k_2 should decrease with increasing solvent polarity if k_2 involves ion-pair dissociation.

The hypothesis developed here provides a simple explanation for the widely different isotope effects observed for base-catalyzed hydrogen-deuterium exchange and racemization experiments at saturated carbon. With weak carbon acids such as 2-phenyl-sulfonyloctane or 2-phenylbutane and alcohols which were much stronger acids, k_e^H/k_e^D and k_α^H/k_α^D gave values less than or near unity.[4,7] In contrast, Steitwieser, *et al.*,[11] obtained a k_e^H/k_e^D value of 10 or more in the lithium cyclohexylamide catalyzed isotopic exchange of toluene in cyclohexylamine. This large isotope effect reflects the breaking of covalent bonds in the rate-determining transition state, which means that $k_2 > k_{-1}$, and correlates with the fact that the pK_a's of toluene and cyclohexylamine are rather close together. In the cases where low or negative isotope effects are observed, $k_{-1} > k_2$. The rate-determining transition states for k_e and k_α then involve only the making and breaking of hydrogen bonds (as, for example, in the process controlled by k_3 in Chart II) for which low and possibly negative isotope effects are expected.
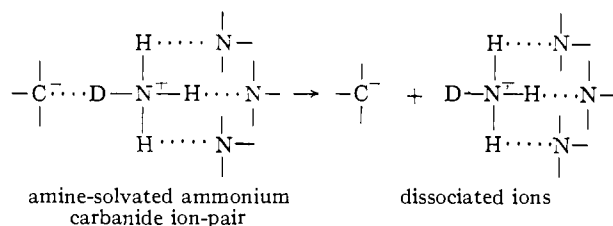
Run 17 was conducted in 90% benzene–10% phenol with tetramethylammonium phenoxide as base, and k_e/k_α was unity. This result is in striking contrast to the value of 18 obtained in the same medium with potassium phenoxide as catalyst (run 16). Clearly, the presence of the potassium ion is required for the retention mechanism, a fact consistent with the interpretations of Chart II. Loss of the coordinating ability of the cation of the ion-pair by substitution of tetramethylammonium ion for potassium ion results in total cancellation of the retention mechanism.

In runs 18–27 of Table II, $(-)$-II-d was allowed to undergo exchange with ammonia in a variety of solvents of low dielectric constant. The ammonia concentration in all of these runs exceeded that of substrate by a factor of at least 10, so the proton greatly exceeded the deuteron reservoir (factor of at least 30) in each run, and thereby in effect made exchange irreversible. Values of k_e/k_α ranged from 1.4 to 148, which indicates a blend of a retention with some other mechanism of $k_e/k_\alpha \leqq 1$. Of the three available, the inversion mechanism seems the least likely since this

(10) These conclusions are further supported by the fact that with $(-)$-2-phenylbutane-2-d as substrate, *tert*-butyl alcohol as solvent, and potassium *tert*-butoxide as base, $k_e/k_\alpha \sim 10$ (ref. 4). The difference in pK_a between substrate and solvent must have been at least 17 units, and therefore proton capture by carbanion was faster than ion-pair dissociation.
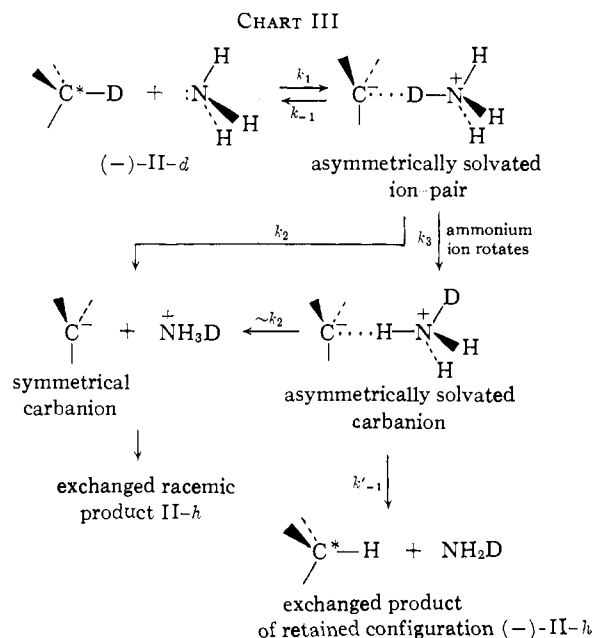
(11) A. Streitwieser, Jr., W. C. Langworthy, and D. E. Van Sickle. *J. Am. Chem. Soc.*, **84**, 251 (1962).

can be made to predominate only in dissociating solvents (see later section). Some support for the racemization being the competing mechanism is found in the fact that k_e/k_α decreases drastically with increasing concentrations of ammonia. Thus in run 23 in tetrahydrofuran 0.3 M in ammonia, $k_e/k_\alpha = 148$, but decreased to 1.4 when the same solvent was 4 M in ammonia. Similarly, pyridine as solvent gave low values ($k_e/k_\alpha \sim 2.4$, runs 17 and 18). Both ammonia and pyridine by their strong hydrogen-bonding abilities should increase the rate of dissociation of ammonium carbanide ion pairs.

$$-\overset{H\cdots\overset{|}{N}-}{\underset{H\cdots\overset{|}{N}-}{\overset{|}{C}{\cdots}D-\overset{|}{N}\overset{-}{-}H{\cdots}\overset{|}{N}-}} \rightarrow -\overset{|}{C}^- + D-\overset{|}{N}\overset{-}{-}H{\cdots}\overset{H\cdots\overset{|}{N}-}{\underset{H\cdots\overset{|}{N}-}{\overset{|}{N}-}}$$

amine-solvated ammonium   dissociated ions
carbanide ion-pair

The existence of a retention mechanism indicates that the ammonium ion of the ammonium carbanide ion-pair rotates and collapses to exchanged product of the same configuration at comparable or greater rates than the ion-pair dissociates and loses configuration. In terms of the scheme outlined in Chart III, k_3 and $k'_{-1} \gtrsim k_2$. In the high retention runs, $k'_{-1} \gg k_2$, and since $k'_{-1} \sim k_{-1}$ (only a small isotope effect is likely), $k_{-1} \gg k_2$. If $k_{-1} \gg k_3$, as is probable, ion-pairs are formed many times for each time any detectable change occurs.

Striking similarities exist between runs 13–16 with potassium phenoxide-phenol as base-acid and runs 18–27 with ammonia-ammonium as base-acid. Both sets of results are interpretable on the basis of a competition between ion-pair dissociation, and cation rotation within the ion-pair (compare Charts II and III). The stereospecificity in both types of experi-

CHART III

$(-)$-II-d asymmetrically solvated
ion pair

symmetrical   asymmetrically solvated
carbanion   carbanion

exchanged racemic
product II-h

exchanged product
of retained configuration $(-)$-II-h

ments is reduced by an increase in base concentration. The pK_a's of the proton donors (phenol and ammonium ion) which capture carbanion are both close to 10.

Equally interesting is the difference between the runs made with potassium phenoxide and with ammonia in *tert*-butyl alcohol as solvent (compare run 8 of Table I with run 20 of Table II). Unlike potassium phenoxide which depends on its ligands of *tert*-butyl alcohol for proton donors, the ammonium ion has four "built-in" protons which make its behavior more independent of the acidity of the medium.

Rearrangements of cations (NH_3D^+ and $C_6H_5OHK^+$-DOC_6H_5) within ion pairs have how been demonstrated for two systems that involve carbanions. In other work[12] it was found that an anion underwent an allylic rearrangement within an ion-pair. Phenomena of this type are now common in carbonium ion chemistry. One of the earliest examples of cationic rearrangement within an ion-pair involved a phenyl migration occurring faster than the ion-pair collapsed to an alkyl tosylate.[13]

In tetrahydrofuran, the uses of primary and secondary amines as catalysts and proton sources for the racemization and exchange of $(-)$-II-d provide results qualitatively similar to those obtained with ammonia (see runs 28–31). These amines were present in concentrations at least 25 times greater than substrate, so deuterated amine never became an effective catalyst for possible exchange in the reverse direction. The values of k_e/k_α varied between 2.4 and >56. Thus a diminution in the number of protons available on the cation of the ion-pair may lower the stereospecificity somewhat, but not drastically.

In runs 32–39 (Table II), *tert*-amines were used as bases and hydroxyl-containing compounds as proton donors for exchange reactions of $(-)$-II-d in media of low dielectric constant. Values of k_e/k_α ranged from 1.2 to >7.3, which again indicate that the reactions occur with predominant retention.

Although potassium phenoxide in *tert*-butyl alcohol gave $k_e/k_\alpha = 1$ (run 8, Table I), tripropylamine in *tert*-butyl alcohol gave a value of 5.7 (run 32). This contrast in results suggests that the proton donors which capture the carbanion are different in the two runs, consisting of *tert*-butyl alcohol in run 8, and tripropylammonium ion in run 32. This explanation requires that the active base that gives retention in run 32 is a tripropylammonium *tert*-butoxide ion-pair formed in small equilibrium concentration in *tert*-butyl alcohol. Such a scheme provides a proton donor of sufficient acidity to promote the required fast reaction with the carbanion, but also makes provision for this proton donor to be oriented at the front face of the carbanion. The mechanism is outlined in Chart IV.

The processes that reduce k_e/k_α from infinity to a finite value in these runs are: (1) Either *tert*-amines or oxides could act as bases, and the carbanide ion-pairs produced could dissociate to produce symmetrical carbanions which give racemic-exchanged amide. (2) Either base could give ion-pairs, carbanions could rotate within the ion-pairs, and racemized but non-exchanged amide could be produced. (3) Either base could give ion-pairs, the carbanion of which was solvated at the front by the leaving group (deuteron donor) and at the back by proton donors of the medium. Capture at the back would lead to inverted-exchanged

(12) D. J. Cram and R. T. Uyeda, *J. Am. Chem. Soc.*, **84**, 4358 (1962).
(13) D. J. Cram, *ibid.*, **74**, 2129 (1952).

CHART IV

exchanged product of
retained configuration , $(-)$-II-h
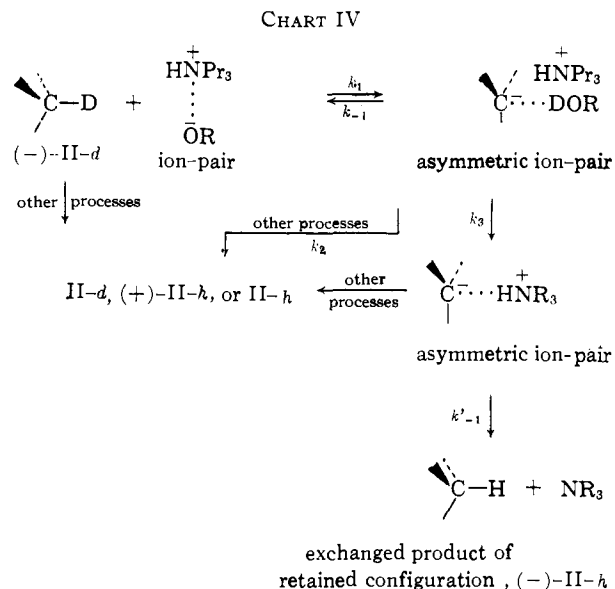
material. These three possibilities are listed because with *tert*-amine and the proper medium (dielectric constant–acidity combination), some of these processes can be made to dominate (see next sections).

Run 36 was conducted with pure tripropylamine as base in dry benzene, and $k_e/k_\alpha = 1.9$. The question arises as to where the protons came from. Conceivably, the *tert*-amine could serve as proton source by entering into elimination reactions in the form of its conjugate acid and with carbanion acting as base (see formulas).
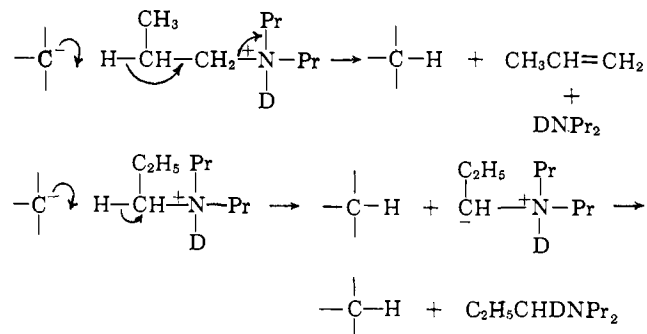

These possibilities were eliminated by recovering the amine from the run, and examining it for deuterium[6] and dipropylamine (v.p.c.). Neither were present, and the conclusion was reached that the proton donor was adventitious moisture.

Inversion Mechanism.—In runs 40–44 of Table III, values of k_e/k_α ranged between 0.65 and 0.94. These runs involved methanol, methanol–water, and ethylene glycol as solvents, all of which have relatively high dielectric constants. The base in two of the runs in methanol was tripropylamine and in the third was potassium methoxide. The catalyst in ethylene glycol was triethylamine. Aside from run 45 (Table III), which was carried out in dimethyl sulfoxide and will be discussed in the next section, only these combinations of solvent and base gave k_e/k_α values between 0.5 and 1. In principle, such values could reflect blends of the following mechanisms: (1) inversion and racemization, (2) inversion and retention, (3) racemization without isotopic exchange and ordinary racemi-
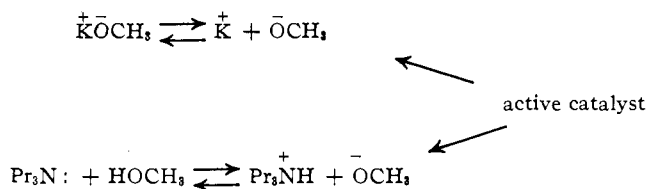
zation and exchange, (4) racemization without isotopic exchange and retention.

The possibility that racemization without isotopic exchange contributed to the over-all result (3 and 4 above) can be discounted. The only authentic example of this mechanism available was carried out in tetrahydrofuran dried with Molecular Sieves (run 46 of Table III) and with tripropylamine as base. The source of protons needed to account for the 25% exchange observed is not known, but enough were available to raise k_e/k_α from a theoretical value of 0 to 0.2. Solvents such as methanol and ethylene glycol are not only rich in acidic proton donors ($pK_a \sim 16$), but are also good dissociating solvents for ion-pairs. Racemization without isotopic exchange *via* rearrangement within an ion-pair in a dissociating solvent is highly improbable. Just as unlikely is a mechanism in which the tripropylammonium carbanide ion-pair dissociated and came back together without either ion undergoing proton transfer reactions with methanol or ethylene glycol.

The two remaining possibilities involve blends of inversion with racemization (1 above) or inversion with retention (2 above). The only clue as to which applies derives from run 52, which was conducted under conditions the same as run 41 (methanol, tripropylamine) except that propylammonium acetate was added (Table IV). The value of k_e/k_α was raised from 0.69 to 0.82 by addition of the salt (see below for discussion). The effect of added salts on runs which gave net retention was to reduce values of k_e/k_α (see below). These facts indicate that added salts tend to enhance ion-pair dissociation, which promotes the racemization mechanism. Thus runs 40–44 probably involve competitive inversion and racemization. The most likely mechanisms are outlined in Chart V.

CHART V
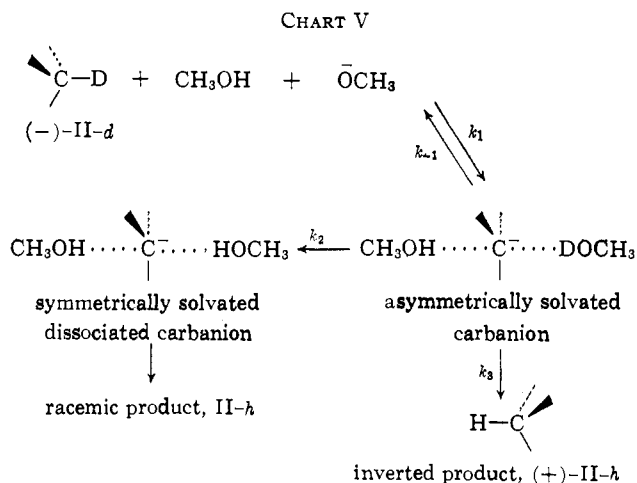
Runs 41 and 43 both gave k_e/k_α values of 0.69 in spite of the fact that tripropylamine was the added

$$\overset{+}{\text{K}}\overset{-}{\text{OCH}}_3 \rightleftharpoons \overset{+}{\text{K}} + \overset{-}{\text{OCH}}_3$$

active catalyst

$$\text{Pr}_3\text{N}: + \text{HOCH}_3 \rightleftharpoons \text{Pr}_3\overset{+}{\text{NH}} + \overset{-}{\text{OCH}}_3$$

base in the former and potassium methoxide was the added base in the latter experiment. This coincidence

of values suggests that dissociated methoxide anion was the active catalytic species in both runs. The carbanion formulated in Chart V is hydrogen bonded at the back by a molecule of protonated methanol from the solvent, whereas the carbanion is hydrogen bonded at the front by the deuterated methanol molecule just formed. Front side capture regenerates starting material, whereas back side capture gives inverted-exchanged product. The rates of k_{-1} and k_3 should be identical except for the isotope effect. The observed net inversion indicates that $k_3 \gtrsim k_2$, and therefore $k_{-1} \gtrsim k_2$. Thus even in the dissociating solvent, methanol, proton capture by hydrogen-bonded carbanion occurs at rates comparable to rates of exhange between hydrogen-bonded methanol and solvent methanol.

The results are not inconsistent with tripropylamine as the active base. In the mechanism visualized (see Chart VI), solvent would hydrogen bond at the back, and deuterated tripropylammonium ion at the front of the carbanion generated. Proton capture from the back would produce a *product* separated ion-pair, and could only happen in a dissociating solvent such as methanol. In such a scheme, k_{-1} should be much higher valued than k_2 since tripropylammonium ion is more acidic by about six powers of ten than methanol.
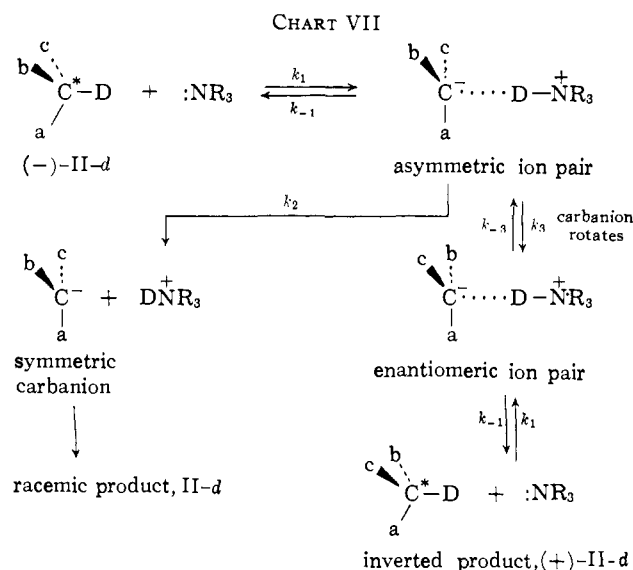
CHART VI
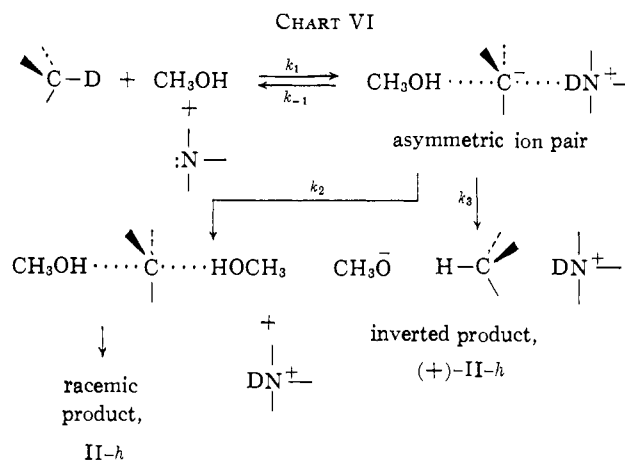
Run 12 of Table I was conducted under identical conditions with run 40 of Table III (in methanol) except that ammonia was substituted for tripropylamine. As a result, k_e/k_α changed from 0.65 to 1.0. These data indicated that ammonia and not methoxide anion was the active base in 12. The presence on the ammonium ion of four acidic hydrogens, each capable of hydrogen bonding, is probably responsible for the difference in stereochemistry. In terms of Chart VI, $k_2 \gg k_3$ for the ammonium ion, but for tripropylammonium ion $k_3 \gtrsim k_2$. The bulk of the three propyl groups of the latter ion would undoubtedly inhibit solvation, and reduce k_2 relative to k_3.

In run 42, 25% water–75% methanol served as medium and tripropylamine as base. The presence of the water increased k_e/k_α from 0.69 to 0.78, probably by slightly altering the delicate balance between k_2 and k_3.

Mechanism of Racemization without Exchange.—In run 46 of Table III, (−)-II-d was submitted to racemization with triethylamine in tetrahydrofuran under conditions where considerable precautions had been

made to exclude moisture. A value for k_e/k_α of 0.2 was obtained. The source of protons responsible for this exchange was not determined. In run 45, $(-)$-II-d with tripropylamine in dimethyl sulfoxide gave $k_e/k_\alpha = 0.72$. Possibly dimethyl sulfoxide served as the proton source.

Two mechanisms can be envisioned for these racemizations, the first involving rotation of the carbanion within the ion-pair much the same as rotation of the ammonium ion occurred in the retention mechanism (see previous section). The second involves dissociation of the ion-pair to give symmetrical carbanion which is then attacked front and back with equal probability by the $tert$-ammonium deuteron donor to give racemic product (see Chart VII).

CHART VII

(−)-II-d　　　　　　　　　　asymmetric ion pair

symmetric carbanion

enantiomeric ion pair

racemic product, II-d

inverted product, (+)-II-d

In tetrahydrofuran, ion-pair dissociation (k_2) is expected to be slow compared to carbanion rotation within the ion-pair (k_3). Ion-pair collapse is undoubtedly faster than either one ($k_{-1} >> k_2$ or k_3), and so the ion-pair is formed many times for each time some discernible change has occurred. Since dimethyl sulfoxide is a dissociating solvent ($\epsilon = 48$), racemization without exchange probably occurs by the ion-pair dissociative scheme. Tripropylamine used as base in this experiment is not strong enough to pull protons from dimethyl sulfoxide and thus form protonated tripropylammonium ions.[14] On the other hand, the fluorenyl anion derived from II might have taken protons from the solvent. The pK_a of II is probably about 21, whereas that of dimethyl sulfoxide is about 31.[15]

Effect of Solvent and Added Salts on Rates of Exchange and Racemization of Amide II.—Table IV records the results of addition of lithium bromide and alkylammonium acetate salts to racemization–exchange runs involving $(+)$-II-d as substrate and amines as catalysts. In tetrahydrofuran with n-propylamine as base, addition of enough lithium bromide to make the solution 0.05 M and then 0.5 M reduced k_e/k_α from >56 to $\gtrsim 6.3$ to 2.9 (runs 28, 47, and 49). Addition of enough propylammonium acetate to give 0.05 M and then 0.5 M solutions reduced k_e/k_α from >56 to $\gtrsim 12$ to 5.6 (runs 28, 48, and 50). In $tert$-butyl

alcohol as solvent and tripropylamine as base, addition of enough tripropylamine acetate to give a 0.4 M solution reduced k_e/k_α from 5.7 to 3.1 (runs 32 and 51). In methanol with tripropylamine as base, addition of sufficient tripropylammonium acetate to provide a 0.4 M solution increased k_e/k_α from 0.69 to 0.82 (runs 41 and 52).

Clearly, added salt has the net effect of reducing the stereospecificity of the reactions in question, whether the salt is proton-donating or not, or whether the stereospecific part of the reaction is one of retention or of inversion. This result strengthens the interpretations given earlier that in these three solvent systems the stereospecific reactions occur within ion-pairs, and are in competition with ion-pair dissociative processes, which provide nonstereospecific reactions. The added salts have the effect of promoting ion-pair dissociation through a great increase in effective dielectric constant in the vicinity of the ion-pair.

In the poor ionizing solvent tetrahydrofuran, the added salts also had the effect of increasing the rate of isotope exchange by an estimated two to three powers of ten. These striking salt effects probably reflect an increase in the values of the ionization rates (k_1 of Chart III) as well as the dissociative and ion-pair reorganization rates (k_2 and k_3 of Chart III). Neutral bases and substrates generate charged species in the ionization process, and the presence of salt clusters with their high electrostatic fields should certainly lower the energy of the transition states for ionization, dissociation, and the making and breaking of hydrogen bonds to the carbanion. On the other hand, the rates of return of the charged species to the covalent state should be lowered by the added salts. In other words, k_{-1} and k'_{-1} of Chart III should be depressed by the added salts. The salt effect (rate increases) observed in $tert$-butyl alcohol–tripropyl amine probably reflects an increase in concentration of the active base tripropylammonium $tert$-butoxide. These salt effects are similar to those observed in carbonium ion formation from uncharged starting materials (alkyl tosylates) in nonpolar solvents.[16]

Dramatic solvent effects on rates of isotopic exchange and racemization are apparent in those runs which involve neutral bases and substrates. With ammonia as base (Table II), k_e and k_α increased by an estimated total of 10^6 to 10^8 in passing from benzene ($\epsilon = 3$) to $tert$-butyl alcohol ($\epsilon = 11$) to tetrahydrofuran ($\epsilon = 7.4$) to pyridine ($\epsilon = 12.5$) to methanol ($\epsilon = 34$) to dimethyl sulfoxide ($\epsilon = 49$). Although the correlation of rate with dielectric constant is rough, it nevertheless is visible (only $tert$-butyl alcohol is out of place). Clearly the large solvent effect with uncharged base and substrate points to the development of considerable charge in the transition state for proton abstraction. How much of the large rate increase associated with polar solvents is associated with rates of ionization and how much is caused by depression of return of the ion-pair to the covalent condition remains to be demonstrated.

Experimental

2-Acetyl-9-methylfluorene.—Methylation of fluorene[17] in 100-g. batches in a 1-l. stainless steel bomb at 210° for 15 hr. gave 97%

(14) D. J. Cram and S. H. Pine, *J. Am. Chem. Soc.*, **85**, 1096 (1963).

(15) E. C. Steiner and J. M. Gilbert, *ibid.*, in press.

(16) S. Winstein, S. Smith, and D. Darwish, *ibid.*, **81**, 5511 (1959).

(17) C. L. Schoen and E. I. Becker, *ibid.*, **77**, 6030 (1955).

yields of 9-methylfluorene, m.p. 44°, lit. 45–46°. This material was acetylated by a procedure patterned after that applied to fluorene itself.[18] To a well-stirred solution of 320 g. of 9-methylfluorene in 1400 ml. of carbon disulfide was added 454 g. of aluminum chloride, and the mixture was heated to reflux. Heat was removed, and 165 ml. of freshly distilled acetic anhydride was added at such a rate as to maintain gentle reflux at the same time that the mixture was well stirred. The dark green precipitate was collected, washed with carbon disulfide, and air dried for 24 hr. The resulting tan solid was added slowly to a stirred solution of 130 ml. of concentrated hydrochloric acid in 3 l. of water. The product was collected, air dried, and dissolved in chloroform. The chloroform solution was dried over sodium sulfate and the chloroform was evaporated. The residue was distilled at 0.2 mm. (b.p. 145°) under nitrogen to give a solid, m.p. 113–115°, recrystallization of which from acetone gave 275 g. (70%) of white crystals, m.p. 117–117.5°.

Anal. Calcd. for $C_{16}H_{14}O$: C, 86.46; H, 6.35. Found: C, 86.29; H, 6.45.

9-Methylfluorene-2-carboxylic Acid (I).—In a typical run, 285 g. of sodium hydroxide was dissolved in 1200 ml. of water and cooled to 10°. Technical bromine (460 g.) was added dropwise with stirring to the solution maintained at 10°. A solution of 200 g. of 2-acetyl-9-methylfluorene in 650 ml. of purified dioxane[19] was added slowly and at such a rate as to keep the temperature below 15°. After about an hour of stirring, the temperature rose rapidly to 25° and then fell back to 10°. After 2.5 hr. the ketone had gone completely into solution, and starch–iodine paper was not discolored by a drop from the reaction mixture. The reaction mixture was shaken with a liter of water and a liter of ether. The basic aqueous layer was acidified with 6 N hydrochloric acid. The precipitate was collected and air dried to give 200 g. of a slightly yellow powder, m.p. 211–216°. Recrystallization of this material from acetone (ethanol or methanol were also suitable) gave white crystals, m.p. 211–222°, wt. 100 g. (50%).

Anal. Calcd. for $C_{15}H_{12}O_2$: C, 80.33; H, 5.40. Found: C, 80.24; H, 5.32.

Another 63 g., m.p. 219.5–221.5°, was obtained from the mother liquors.

Resolution of 9-Methylfluorene-2-carboxylic Acid ((+)- and (−)-I).—A hot solution of 14.6 g. of I in 360 ml. of acetone was combined with a hot solution of 21.2 g. of quinine in 72 ml. of chloroform. The resulting solution was filtered, seeded, and allowed to cool to 25°. After 48 hr., 19 g. of salt was collected and recrystallized 9 times from chloroform to give 1.4 g. of salt. The progress of the resolution was followed by converting small amounts of salt to the free acid as follows. The salt was shaken with 6 N hydrochloric acid and ether. The ether solution was washed with 2 N hydrochloric acid and with water, dried, and evaporated to give a white powder. The amounts of salt recovered at different stages of the resolution and the rotations of the corresponding acids were: 1st crystallization, 19 g., $[\alpha]^{25}_{546}$ −7.5°; 2nd, 14 g., $[\alpha]^{25}_{546}$ −17.3°; 4th, 8.8 g., $[\alpha]^{25}_{546}$ −33.6°; 6th, 6.7 g., $[\alpha]^{25}_{546}$ −36.4°; 7th, 5.5 g., $[\alpha]^{25}_{546}$ −39.6°; 8th, 3.8 g., $[\alpha]^{25}_{546}$ −40.1°; 9th, 1.4 g., $[\alpha]^{25}_{546}$ −39.4°; *c* 1.0 to 6.2 in dioxane for all rotation (see below). This acid was crystallized from acetone to give fine white needles of (−)-I, m.p. 215–216°.

Partially active acid ($[\alpha]^{25}_{546}$ +8°), 14.9 g., obtained from quinine mother liquors was dissolved in 136 ml. of acetone, and the solution was combined with a solution of 19.5 g. of cinchonidine in 246 ml. of chloroform. The resulting solution was seeded and left at 25° for 20 hr. The salt (14.4 g.) was collected and recrystallized 8 times from chloroform–acetone. The amounts of salt recovered at different stages and the rotations of the corresponding acids were: 1st recrystallization, 10 g., $[\alpha]^{25}_{546}$ +23.0°; 3rd recrystallization, 7 g., $[\alpha]^{25}_{546}$ +37.0°; 5th recrystallization, 5.1 g., $[\alpha]^{25}_{546}$ + 40.0°; 8th recrystallization, 2.9 g., $[\alpha]^{25}_{546}$ +39.6°; *c* 1.0 to 6.2 in dioxane for all rotations (see below). Recrystallization of this acid from acetone gave (+)-I as white needles, m.p. 215–216°.

In a subsequent large-scale resolution, 82 g. of a much recrystallized cinchonidine salt was converted to 31.5 g. of acid, $[\alpha]^{25}_{546}$ + 40.2°, *c* 2.84 in dioxane, m.p. 210.5–212.5°. Three recrystallizations of this material from acetone gave material, m.p. 216–216.5°, $[\alpha]^{25}_{546}$ + 43.1°, *c* 6.65 in dioxane, whose properties did not change with further purification.

Anal. Calcd. for $C_{15}H_{12}O_2$: C, 80.33; H, 5.40. Found: C, 80.15; H, 5.39.

The rotation of a sample of partially optically active acid was measured at different concentrations in dioxane; *c* 1.00, $[\alpha]^{25}_{546}$ −33.8°; *c* 3.2, $[\alpha]^{25}_{546}$ −33.4°; *c* 6.19, $[\alpha]^{25}_{546}$ −34.2°.

2-(N,N-Dimethylcarboxamido)-9-methylfluorene (II).—Racemic acid I (5.0 g.) was refluxed with 10 ml. of thionyl chloride for about 30 min. The excess thionyl chloride was evaporated at reduced pressure; 25 ml. of benzene was added and similarly evaporated. The acid chloride was dissolved in 250 ml. of ether, chilled to 0°, and 3 ml. of dimethylamine dissolved in 13 ml. of dry ether was added. The mixture was allowed to stand for 1.5 min., and shaken with dilute hydrochloric acid. The ether layer was washed with dilute hydrochloric acid, once with water, was dried, and evaporated to give 5 g. of yellow crystals, m.p. 131–133°. Two recrystallizations of this material from methanol–water gave 4.0 g. of light yellow crystals (II), m.p. 133–134°.

Anal. Calcd. for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.07; H, 6.64; N, 5.61.

(−)-2-(N,N-Dimethylcarboxamido)-9-methylfluorene ((−)-II).—The (−)-amide was prepared (see above) from 27 g. of (−)-I, $[\alpha]^{25}_{546}$ −39.5°, *c* 2.0 in dioxane. The crude amide was recrystallized twice from ether to give 22 g. of (−)-II, m.p. 126–127°, $[\alpha]^{24}_{546}$ −33.1°, *c* 4.9 dioxane; $[\alpha]^{25}_{546}$ −33.5°, *c* 5.52 benzene. A sample of (−)-amide when passed through neutral activity I alumina with 25% ether–chloroform gave material 65% racemized. Another sample of the above material was passed through unactivated silicic acid with benzene to give material which when recrystallized from acetone gave m.p. 126–127°, $[\alpha]^{25}_{546}$ −33.2°, *c* 6.02 in dioxane. A mixture of 8 mg. of (−)-amide and 12 mg. of racemic amide gave m.p. 120–122°.

(+)-2-(N,N-Dimethylcarboxamido)-9-methylfluorene ((+)-II).—From 20.0 g. of (+)-I, $[\alpha]^{25}_{546}$ + 43.1°, *c* 6.6 dioxane, was obtained 17.0 g. of acetone-recrystallized (+)-II, m.p. 126–127°, $[\alpha]^{25}_{546}$ +34.0°, *c* 6.10 dioxane.

Anal. Calcd. for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.45; H, 6.90; N, 5.85.

9-Methylfluorene-2-carboxylic Acid-9-d (I-d).—Racemic acid I (10 g., m.p. 220–221°), was dissolved in a solution of 30 ml. of 50% deuterium oxide and 4 g. of potassium hydroxide. The flask was stoppered and stirred at 25° for 40 hr. (10 racemization half-lives). The solution was frozen and the water removed by lyophilization. The procedure was repeated with 27.5 ml. of 90% deuterium oxide and with 29 ml. of 98% deuterium oxide and 25 ml. of 99.5% deuterium oxide. The solid remaining after the last exchange was ground in a mortar, and shaken with 550 ml. of ether and 20 ml. of concentrated hydrochloric acid dissolved in 500 ml. of water. The aqueous layer was extracted with an additional 100 ml. of ether; the combined ether layers were washed with water, dried, and evaporated to give 9.5 g. of yellowish solid, m.p. 215–219°. Two recrystallizations of this material from acetone gave 6 g. of I-d, m.p. 220–221°, 0.994 atom of deuterium per molecule by combustion and falling drop method.[6] A similar procedure was applied to batches as large as 300 g. of acid.

(−)-9-Methylfluorene-2-carboxylic Acid-9-d ((−)-I-d).—Deuterated acid, 0.99 atom of deuterium per molecule (80 g.), was resolved through the quinine salt (seven recrystallizations) to give after recycling of the filtrates and recrystallization of the acid 9.1 g. of (−)-I-d, m.p. 216–216.5°, $[\alpha]^{25}_{546}$ −42.8°, *c* 3.53 in dioxane, 0.99 atom of deuterium per molecule.[6] In another run, 300 g. of deuterated I gave 18.7 g. of (−)-I, $[\alpha]^{25}_{546}$ −43.1°, *c* 6.26 in dioxane.

(−)-2-(N,N-Dimethylcarboxamido)-9-methylfluorene-9-d ((−)-II-d).—From 7.0 g. of acid, m.p. 216–216.5°, $[\alpha]^{25}_D$ −42.8°, 0.99 atom of deuterium per molecule, was obtained 5.3 g. of (−)-II-d, m.p. 126–127°, $[\alpha]^{25}_{546}$ −34.0°, *c* 6.09 in dioxane, 0.99 atom of deuterium per molecule.[6] From acid, m.p. 216–216.5°, $[\alpha]^{25}_{546}$ −43.1°, *c* 6.26 in dioxane, was obtained amide, m.p. 126–127°, $[\alpha]^{25}_{546}$ −34.3°, *c* 6.15 in dioxane, 0.97 atom of deuterium per molecule.[6]

2-Carboxamido-9-methylfluorene.—The procedure used resembled that employed for the N,N-dimethyl analog. From 3.0 g. of acid I was obtained 2.0 g. of amide, m.p. 188.5–189.5° (two recrystallizations from acetone).

Anal. Calcd. for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.77; H, 6.05; N, 6.57.

Purification of Solvents and Amines.—Methanol, *tert*-butyl alcohol, dimethyl sulfoxide, aand ethylene glycol were distilled from Molecular Sieves and stored over Molecular Sieves. Prep-

(18) F. E. Ray and G. Rieveschl, Jr., *J. Am. Chem. Soc.*, **65**, 836 (1943).
(19) L. F. Fieser, "Experiments in Organic Chemistry." D.C. Heath and Co., Boston, Mass., 1957, p. 284.

arations of O-deuterated *tert*-butyl alcohol and ethylene glycol have been described earlier.[20] Reagent grade benzene was dried over Molecular Sieves before use, and tetrahydrofuran was distilled from lithium aluminum hydride immediately before use.

Tri-*n*-propylamine was mixed with molecular sieves and *p*-toluenesulfonyl chloride and allowed to stand at 25° for 12 hr. The amine was distilled from the mixture and fractionally distilled, a center cut with a constant boiling point of 156° (n^{25}D 1.4145) being collected.[21] The infrared spectrum of the material indicated less than 0.5% of propylamine or dipropylamine was present. After storage, the amine was always redistilled from Molecular Sieves before use.

Triethylamine was also purified by the above procedure, b.p. 88°. Triethylcarbinol (Eastman) was fractionally distilled, and a center constant-boiling cut was collected, b.p. 142°, n^{25}D 1.4276. Commercial 98–100% formic acid was cooled to 0° and phosphorus pentoxide added.[22] The formic acid was distilled under vacuum at 25°, and the distillate was shown to contain less than 0.2% of water by Karl Fischer titration. Commercial trifluoroacetic acid was allowed to stand at 25° for 12 hr., and then refluxed for 1.5 hr. over phosphorus pentoxide.[23] Fractional distillation of the material gave constant-boiling material, b.p. 71°.

Eastman *n*-propylamine was allowed to stand for 24 hr. over Molecular Sieves, and was then fractionally distilled to give a center constant-boiling cut, b.p. 47.3°, n^{25}D 1.3850. Eastman dipropylamine was similarly purified, b.p. 108.5°, n^{25}D 1.4016. The infrared spectrum of this secondary amine indicated that less than 0.5% of monopropylamine was present.

Attempts to Racemize Optically Active Acid I and Amide II under Acidic Conditions.—Treatment of optically pure amide ((−)-II) with 90% formic acid at 75° for 7 days gave optically pure acid ((−)-I). When submitted to the action of 90% formic acid (1.2 M in sodium formate) for 21 hr. at 75°, optically pure amide (−)-II was recovered unchanged. Treatment of optically pure amide ((−)-II) with dry formic acid (0.9 M in sodium formate) for 33 hr. at 100–115° gave optically pure (−)-I. A solution of optically pure (+)-I in dry trifluoroacetic acid 0.6 M in pyridine was heated at 105–110° for 40 hr. and was found to decrease in rotation by 10%. Treatment of optically pure (+)-I with dry glacial acetic acid 0.1 M in *p*-toluenesulfonic acid for 12 hr. at 145° gave back impure (+)-I with a rotation 5% lower than starting material.

Purification of Amide II.—Under the higher temperature conditions used for some of the racemization and isotopic exchange reactions (*e.g.*, runs involving *tert*-butyl alcohol and ammonia), recovered substrate was contaminated with foreign materials such as 2-carboxamido-9-methylfluorene. These impurities were removed from the products through chromatography on silicic acid[24] and sublimation.

As a control on the procedures, the following experiments were conducted. Amide (−)-II-*h* (135 mg., $[\alpha]^{25}_{546}$ −33.2°, *c* 6 dioxane) was homogenized with racemic II-*d* (0.995 atom of deuterium per molecule).[6] Part of this mixture was retained for reference. The remainder was mixed with 25 mg. of 2-carboxamido-9-methylfluorene, and chromatographed on a column of dry silicic acid (heated at 200° for 2 hr.) with first benzene and then benzene–ether as developer. The desired amide II was eluted with benzene–ether; 117 mg. This material was sublimed at 100–110° (0.1 mm.) to give 108 mg. of white crystals which exhibited a rotation of $[\alpha]^{25}_{546}$ −17.2°, *c* 6.29 dioxane. The reference sample gave $[\alpha]^{25}_{546}$ −17.4°, *c* 5.92 dioxane. The recovered sample was analyzed for deuterium by the infrared method (see below) and found to contain the same amount as the reference sample (within the 0.5% limits of experimental error).

Further controls demonstrated that if mixtures of crystalline racemic and optically active II were *incompletely* sublimed, the sublimate was enriched 5–17% in the optically active material. However, when vaporized from a melt at 130–135° at 0.05 to 0.1 mm. pressure, no fractionation was encountered. To avoid fractionation of the product from the runs themselves, vaporization from the melt and complete sublimation were the procedures employed. The chromatograph–melt distillation procedure was again tested by subjecting a crude sample of (−)-II-*d* to two crys-

tallizations from acetone to give material, $[\alpha]^{25}_{546}$ −34.3°, *c* 6.15 in dioxane, 5.68 atom % excess deuterium.[6] Purification of the crude sample by the chromatograph–melt distillation procedure gave material, $[\alpha]^{25}_{546}$ −34.3°, *c* 6.31 in dioxane, 5.69 atom % excess deuterium.[6]

Ammonolysis of Amide II as a Side Reaction to Racemization and Exchange.—Racemic II-*h*, 300 mg., 25 ml. of dry distilled *tert*-butyl alcohol, and 1 ml. of anhydrous liquid ammonia were sealed in a heavy walled tube under a stream of nitrogen and heated in a 190° Wood metal bath for 86 hr. The tube was opened, the solvent evaporated, and the remaining glass gave an infrared spectrum (KBr pellet) characteristic of primary amide and ammonium salts (2.95 and 3.15 μ). The glass was dissolved in benzene, washed with dilute sodium hydroxide, and the organic layer was dried and evaporated. When acidified, 8 mg. of acid I separated, m.p. 205°. Chromatography of the residue from the benzene layer on silicic acid with benzene–ether as developer gave 150 mg. of amide II, m.p. 125–128°, and 16 mg. of primary amide, m.p. 177°.

A similar experiment was carried out to simulate the experiments with ammonia in tetrahydrofuran. A heavy-walled tube containing 30 ml. of purified tetrahydrofuran, 1 ml. of anhydrous liquid ammonia, and 300 mg. of racemic amide II was sealed under nitrogen and heated at 145° for 246 hr. The tube was opened and the products isolated as in the above experiment: 6 mg. of acid I, 206 mg. of amide II, and 22 mg. of 2-carboxamido-9-methylfluorene.

Deuterium Analysis of Amides (II-*h*–II-*d* Mixtures.)—The infrared spectrum of II-*h* possesses a strong peak at 1150 cm.$^{-1}$ which is absent in the spectrum of II-*d*. The spectrum of II-*d* contains a fairly strong peak at 1180 cm.$^{-1}$ which is more intense than in II-*h*. Analyses were performed with a Perkin-Elmer 421 with dual grating interchange, slits manually controlled at 400 μ, attenuator speed 7.00, gain 4, suppression 0, source current 0.33 amp., 4/1 abcissa expansion, and with a scan speed of about 7 cm.$^{-1}$/min. Under these conditions the noise level at an optical density of 0.8 was about 0.002 optical density unit. A set of 5 standards varying from 0 to 99.5% II-*d*[6] was prepared by weighing protio compound and/or deuterio compound into screw cap vials, adding solvent from a syringe, and reweighing to obtain the weight of solvent. The carbon tetrachloride solutions (g. II/g. CCl₄ values ranged from 0.0215 to 0.0222) were placed in 0.4-mm. cells, and the region from 1175 to 1125 cm.$^{-1}$ was scanned. After scanning the region, the top of the 1150 cm.$^{-1}$ peak was rescanned, and the two values were always within 0.002–0.003 optical density unit of one another. The peak heights were determined by the base line method. A plot of optical density/concentration against the percentage II-*h* in the mixture was found to be linear from 16% II-*h* to 100% II-*h* (lower protio content standards were not tried). The maximum deviation of the points from the line was 1% II-*h*. Unknown samples were similarly prepared and run using the same cells in the same session as the knowns. In analysis of subsequent batches of unknowns three fresh standards at about 100% II-*h*, 60% II-*h*, and 20% II-*h* were prepared and run with the batch of unknowns (amide concentrations were close to those specified above). With one batch of 9 unknowns and 3 knowns the region from 1200 to 1125 cm.$^{-1}$ was scanned for each sample, and a calibration curve (linear) for the 1180 cm.$^{-1}$ deuterium-sensitive peak was prepared as well as the usual one for the 1150 cm.$^{-1}$ peak. For these 9 samples the % II-*h* was determined from both peaks. In one case the two values differed by 2.5%, in a second by 1.5%, and in the other seven by 1% or less.

Deuterium Analyses of Acids (I-*h* and I-*d* Mixtures).—The infrared spectra of I-*h* and I-*d* in tetrahydrofuran differed in the 13–14μ region, I-*d* absorbing more strongly at 13.2 μ and I-*h* at 13.8 μ. The peak at 13.2 μ was mainly used, and the peak at 13.8 μ used only for confirmatory purposes. As in analyses of the amides II, five knowns were prepared ranging from 100% I-*h* to 95% I-*d* at concentrations which varied between 0.052 and 0.061 g. of substrate per g. of tetrahydrofuran. A plot of optical density against % II-*d* gave a good straight line. Cells of 0.1 mm. path length were used, and a fresh calibration curve was prepared each time analyses were performed.

General Procedure for Runs.—Reactions were carried out in sealed glass tubes. At temperatures under 100° ordinary Pyrex test tubes were used. At temperatures over 100° special heavy-walled Pyrex tubes were employed. The substrate, solvent, and base were placed in a clean, dry tube, which was closed with a drying tube and frozen in a Dry Ice–acetone bath. The drying

(20) D. J. Cram and B. Rickborn, *J. Am. Chem. Soc.*, **83**, 2182 (1961).

(21) A. 1. Vogel [*J. Chem. Soc.*, 1825 (1948)] report b.p. 156.5°, n^{20}D 1.4171, for tri-*n*-propylamine.

(22) G. Rienacker, *Z. anorg. allgem. Chem.*, **227**, 358 (1936).

(23) W. Dannhauser and R. H. Cole, *J. Am. Chem. Soc.*, **74**, 6105 (1952).

(24) K. N. Trueblood and E. W. Malmberg, *Anal. Chem.*, **21**, 1055 (1949).

tube was removed and the reaction tube flushed with nitrogen as it was sealed with a torch. After the tube had been heated for the required time, it was cooled in Dry Ice–acetone and opened. In no case had a noticeable amount of pressure developed during the run. The tube contents were shaken with a mixture of dilute hydrochloric acid and ether. In runs 10, 11, 13–16, 34, 35, and 37, carbon tetrachloride was used instead of ether. The organic layer was washed with water, dried, and evaporated. The residue was then either purified by silicic acid chromatography and/or distillation, or was submitted directly to polarimetric and infrared analysis. Details of sample procedures are outlined in the following section. The rotations of the recovered substrate and the starting material were measured in solutions of the same concentration in dioxane at similar temperatures. Concentrations were chosen so that starting material gave α_{obsd} of 2° or more. Normally 10 readings for both the free path and the sample were made and the average deviation was about 0.01°. In runs 7, 9, 12, 13, 16, 19, 21, 22, 24, 29, 30, 33, 35, 36, 37, 41, and 45, the infrared spectrum of the recovered substrate used for analysis was taken and found to contain no spurious peaks. In runs 15, 21, 38, and 39 the nitrogen content of the recovered substrate used for analysis was submitted to a miro-Dumas determination of nitrogen. The largest deviation from theory calculated for II-h was 0.36%.

Details Concerning Various Runs.—Runs 1–6 were conducted without either chromatography or sublimation of the product. Run 1 is typical of the six. Clean potassium (48 mg.) was dissolved in 3.0 ml. of deuterated ethylene glycol under nitrogen (temperature, 0–10°). Acid I-h (79% optically pure) was added to the basic solution and the resulting solution was allowed to stand at 26° for 3 hr. Product was recovered by the standard procedure and analyzed directly. In run 7, the recovered product was chromatographed (68% recovery) and then sublimed (13% loss on sublimation).

Run 8.—Clean potassium (10.4 mg.) was dissolved in a solution of 2 ml. of deuterated *tert*-butyl alcohol and 49.4 mg. of phenol under dry nitrogen. A solution of 150 mg. of (–)-II-h (98% optically pure) in 3 ml. of deuterated *tert*-butyl alcohol was prepared, 0.7 ml. of the basic solution was added, and the resulting solution was allowed to stand for 7 hr. at 27° in a sealed tube. The amide was recovered by the standard procedure, dried under vacuum, and submitted to polarimetric and isotopic analysis. In run 9, the recovered amide was chromatographed (90% recovery) and sublimed (23% loss). In run 10, a mixture of 3.55 g. of reagent grade phenol and 0.325 g. of potassium *tert*-butoxide was warmed in a nitrogen atmosphere to produce a solution of potassium phenoxide in phenol. The solution was frozen, 100 mg. of (–)-II-d (~ 100% optically pure) was added, and the tube was sealed under nitrogen. It was heated at 102° for 2 hr., and the amide recovered in the usual way. After drying, the product was analyzed directly. In run 13, phenol was dried over Molecular Sieves under nitrogen at 80° for 6 hr., and to 4.70 g. in a tube was added 148 mg. of clean potassium (tube was at 42° and was under nitrogen). After standing at 100° for 3 hr., the product was recovered and analyzed directly. Run 14 was similarly conducted, but the product was chromatographed (81% recovery) and sublimed (12% loss) before analysis.

Run 15.—Reagent phenol (1.80 g.) which had been dried over Molecular Sieves under nitrogen as a liquid was transferred under nitrogen to a 4.5-in. test tube and then frozen. Clean potassium (79 mg.) was added and the tube was placed in an 8-in. test tube which was flushed with dry oxygen-free nitrogen. The tube was then warmed to melt the phenol and dissolve the potassium. The solution was then frozen and 20 ml. of benzene was pipetted into the space around the small inner test tube. Amide (–)-II-d was added, and the tube was sealed under a stream of nitrogen. The tube was then warmed to 100°, the contents of each tube mixed by shaking, and the material was allowed to stand at 100° for 1.7 hr. Product was isolated in the usual way, chromatographed (80% recovery), and sublimed (10% loss). Run 16 was similarly conducted (75° for 2.3 hr.). Chromatography of the product gave 83% recovery, and sublimation 6% loss.

Run 17.—A 10% solution of tetramethylammonium hydroxide in water (Eastman) was decolorized with Norit and filtered under nitrogen. The water was removed under reduced pressure at temperatures no higher than room temperature. The resulting white solid was dried to constant weight at room temperature and 0.01 mm. A solution of 0.896 g. of this material in 10.0 ml. of methanol was prepared. A 2.0-ml. aliquot of this solution was titrated to the phenolphthalein end point with 18.22 ml. of 0.0511

N H$_2$SO$_4$ and to the brom cresol green end point with 18.95 ml. About 4% of the total base then consists of trimethylamine and/or carbonate. Titration of the methanol solution with Karl Fischer reagent indicated that the solid contained about 60% water by weight. This tetramethylammonium hydroxide (0.475 g.) was mixed with 50 ml. of a dry benzene–10% phenol solution, and the resulting mixture was dried over Molecular Sieves under nitrogen for several hours. Titration with Karl Fischer reagent indicated that the solution contained less than 0.7 mg. of water/ml. of solution. This solution (40 ml.) was sealed in a tube under a stream of nitrogen with 200 mg. of (–)-II-d. The tube was heated at 75° for 10 hr. The contents of the tube were washed twice with dilute hydrochloric acid and once with water. The benzene was evaporated from the benzene solution at ~50° and 100 mm. on a rotary evaporator. Carbon tetrachloride (50 ml.) was added to the residue and the resulting solution was extracted with four 150-ml. portions of ~60° water, and then dried. The solvent was removed on the rotary evaporator and the residue was chromatographed through 3 g. of activated silicic acid with benzene and benzene–ether to give 140 mg. of a yellowish solid which was then distilled at 130–135° (pot temperature) and 0.01 mm. to give 116 mg. of white crystals. The crystals were crushed and thoroughly mixed in an agate mortar and pestle, and the resulting powder was analyzed for rotation and deuterium content as described above.

Runs 11, 15, and 18–27.—Anhydrous ammonia was introduced into the tubes as follows. One end of a piece of glass tubing was sealed, a volume of acetone equal to that of the desired liquid ammonia was added, and the position of the meniscus was marked. The tube was then dried and chilled to –80°, and anhydrous ammonia was collected until the liquid reached the mark. The tube was drawn out to leave a long fragile seal, warmed to room temperature, and dried. If not enough free space was left below the seal the ampoule exploded violently when warmed to room temperature. The ampoule was then placed in the reaction tube with the solvent and substrate. The reaction tube was chilled, the fragile seal on the enclosed ampoule was broken, and the reaction tube was sealed under nitrogen. In several runs, at the end of the reaction period, the tube was chilled and opened under standard acid which was back titrated to check the amount of ammonia in the reaction mixture. In other runs, solvent and base were evaporated under reduced pressure at the end of the heating period. In all cases tubes being chilled were closed with drying tubes as much as possible. In runs 18, 23, and 25, the recovered amide was analyzed directly. In the other runs of this group, recovered amide was chromatographed (65–100% recovery) and either totally sublimed or distilled (8–26% loss). Greatest losses in chromatography and distillation or sublimation were observed in those runs involving the highest temperatures.

Controls for those runs conducted in pyridine (runs 18 and 19) were conducted as follows. A sample of (–)-II-h (~98% optically pure) was heated at 102° for 22 hr. and recovered by the standard method without chromatography or distillation. Loss in optical activity was less than 2%.

Runs 28–31 were conducted with use of appropriate combinations of procedures listed above. The amide recovered in runs 28–30 were chromatographed (77–95% recovery) and either totally sublimed or distilled (10–22% loss). In run 31, the product was analyzed directly.

Runs 32–46.—Appropriate combinations of procedures illustrated previously were employed. Amide recovered from all runs was chromatographed (65–95% recovery) and totally distilled or sublimed before analysis. In run 34, a 10% solution of pure phenol in benzene was allowed to stand over Molecular Sieves for 48 hr., and this material was used as solvent. In run 35, the benzene–phenol solution was dried for 10 days over Molecular Sieves.

Run 36 was in principle carried out in the absence of any ordinary proton donor aside from adventitious moisture. Since 37% isotopic exchange occurred, the question arose whether the protons came from the tripropylamine. At the end of the run, the tube contents were shaken with 30 ml. of dilute hydrochloric acid and 30 ml. of ether. The ether layer was washed with 40 ml. of water, dried, the ether evaporated, and the amide recovered in the customary way. The acid layer was washed with ether, neutralized with aqueous sodium hydroxide, and extracted twice with pentane. The pentane solution was dried, evaporated, and the residual oil distilled at atmospheric pressure to give recovered

tripropylamine, n^{25}D 1.4116, 0.00 atom % excess deuterium.[6] Vapor phase chromatography of this material demonstrated that less than 1% of dipropylamine was present.

Runs 46–56 involved procedures similar to those employed previously except for the added salts. Those involving lithium bromide were carried out as follows. A flask was weighed and commercial lithium bromide was added. The flask was evacuated and heated with a flame. The solid melted, the melt bubbled, and finally a white powder was produced. The flask was re-

weighed (8.28 g. of salt) and 190 ml. of purified tetrahydrofuran was added. After the salt dissolved, Molecular Sieves were added. The 0.05 M solutions were obtained by appropriate dilution of aliquots of this stock solution. The amine–amine salt mixtures (runs 48, 50, 51, and 52) were obtained by measuring the appropriate amounts of amine and glacial acetic acid into the reaction tube with a syringe. In all of these runs, the recovered amide was chromatographed (83–95% recovery) and totally distilled (5–22% loss).

[CONTRIBUTION NO. 1641 FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES, LOS ANGELES, CALIFORNIA]

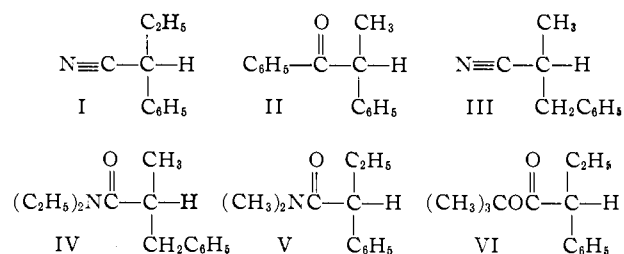# Electrophilic Substitution at Saturated Carbon. XXI. Isoracemization Reactions Involving Ion-Pair Intermediates[1]

BY DONALD J. CRAM AND LAWRENCE GOSSER[2]

The stereochemical course of the base-catalyzed deuterium–hydrogen exchange reaction at carbon has been studied with (+)-2-phenylbutyronitile-2-d ((+)-I-d) and (+)-1,2-diphenyl-1-propanone ((+)-II) in a variety of solvent–base systems. The relative rates of the exchange reaction (rate constant k_e) and of racemization (rate constant k_α) were measured, and the ratios of k_e/k_α were used as a criterion of steric course. Values of k_e/k_α greater than unity point to substitution with retention of configuration; values of unity require substitution with racemization; values of less than unity but greater than 0.5 can indicate substitution with net inversion; values of less than 0.5 require racemization without substitution (isoracemization). With ammonia as base in tert-butyl alcohol, or tetrahydrofuran as solvent, substitution proceeded with low net retention (k_e/k_α = 1.5 to 1.2). This result is interpreted in terms of rotation of the ammonium ion within an ammonium carbanide ion-pair intermediate. With ammonia as base in methanol or dimethyl sulfoxide, with tetramethylammonium phenoxide in 90% benzene–10% phenol, or with n-propylamine in tetrahydrofuran, exchange proceeded with racemization (k_e/k_α = 1). In these runs, the ion-pair intermediates appear to dissociate faster than they rotate. With potassium bicarbonate in ethylene glycol or tripropylamine in methanol, exchange proceeded with net inversion ($k_e/k_\alpha \sim$ 0.85). With tripropylamine as base in a variety of nondissociating solvents, values of k_e/k_α ranging from 0.72 (tetrahydrofuran 1.5 M in methanol and 1.5 M in dimethyl sulfoxide) to 0.05 (tetrahydrofuran 1.5 M in tert-butyl alcohol) were observed. Addition of tetrabutylammonium iodide (0.1 M) to the last reaction mixture gave k_e/k_α = 0.09, whereas tripropylammonium iodide gave 0.19. In these experiments, isoracemization occurs, probably by carbanion rotation within tripropylammonium carbanide ion-pairs. Treatment of ketone (+)-II with tripropylamine in either tert-butyl alcohol-O-d or tetrahydrofuran 1.5 M in tert-butyl alcohol-O-d gave k_e/k_α = 1. This result is interpreted in terms of ion-pair dissociation occurring faster than carbanion rotation within the ion-pair.

In a preceding paper of this series,[3] the rates of base-catalyzed hydrogen–deuterium exchange and racemization of optically active nitrile III, amides IV and V, and ester VI with tert-butyl alcohol-O-d were compared and found to be equal to one another. Similarly, nitrile III and amide V underwent exchange and racemization at equal rates in ethylene glycol-O-d-potassium ethylene glycoxide. In a much earlier study, Wilson, et al.,[4] found that the rates of hydrogen–deuterium exchange and racemization of optically active 1-phenyl-2-methyl-1-butanone were equal in a basic solution of dioxane–deuterium oxide. In all of these investigations, the results were interpreted as involving a symmetrical ambient carbanion as an intermediate, which protonated largely on the more electronegative element to form a tautomer incapable of optical activity. Subsequently, this tautomer reverted to its more stable form with hydrogen attached to carbon.

In investigations of the stereochemical course of the base-catalyzed decarboxylation reaction,[5] nitriles I

$$N\equiv C-\underset{\underset{\text{I}}{C_6H_5}}{\overset{\overset{C_2H_5}{|}}{C}}-H \qquad C_6H_5-\underset{\underset{\text{II}}{C_6H_5}}{\overset{\overset{O}{\|}}{C}}-\underset{}{\overset{\overset{CH_3}{|}}{C}}-H \qquad N\equiv C-\underset{\underset{\text{III}}{CH_2C_6H_5}}{\overset{\overset{CH_3}{|}}{C}}-H$$

$$(C_2H_5)_2N\underset{\underset{\text{IV}}{CH_2C_6H_5}}{\overset{\overset{O}{\|}\overset{CH_3}{|}}{C}-C}-H \qquad (CH_3)_2N\underset{\underset{\text{V}}{C_6H_5}}{\overset{\overset{O}{\|}\overset{C_2H_5}{|}}{C}-C}-H \qquad (CH_3)_3CO\underset{\underset{\text{VI}}{C_6H_5}}{\overset{\overset{O}{\|}\overset{C_2H_5}{|}}{C}-C}-H$$

and III were produced with a maximum of 16% net retention and 12% net inversion, depending on the nature of the solvent and the cation of the basic catalyst. This low order of specificity was interpreted as reflecting asymmetric solvation of carbanions or asymmetric ion-pairs as intermediates. The competing racemization process was considered to reflect at least partial protonation on nitrogen of the nitrile anions.

Subsequently, the base-catalyzed deuterium–hydrogen exchange reactions of 2-(N,N-dimethylcarboxamido)-9-methylfluorene-9-d-(VII-d) with a variety of alcohols and amines were studied.[6] The 9-fluorenyl anion is undoubtedly an intermediate in these exchange reactions. Charge is highly delocalized in this ion and, although itself symmetric, it was found capable of maintaining an asymmetric environment long enough

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(2) U. S. Rubber Fellow at the University of California at Los Angeles, 1963–1964.

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