Electrophilic Substitution at Saturated Carbon. XL. Charge Distribution Effects on Kinetic Components of Racemization and Isotopic Exchange of Isomeric Fluorenyl Carbon Acids[1]

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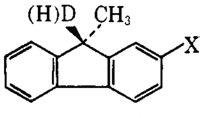
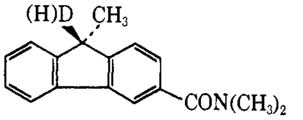
Abstract: The kinetics of hydrogen isotope exchange and racemization of optically active and 9-deuterated 2-(N,N-dimethylcarboxamido)-9-methylfluorene (I) and 3-(N,N-dimethylcarboxamido)-9-methylfluorene (IV) with *n*-propylamine were studied in tetrahydrofuran. Over most of the range of base concentration studied, (+)-I-*h*, (+)-IV-*h*, and (−)-IV-*d* racemized by third-order kinetics and underwent isotopic exchange by a mixture of second- and third-order kinetics. Second-order isotopic exchange occurred with very high retention of configuration for (+)-I-*d*, k_e/k_α values (ratio of rate constants for exchange and racemization) being greater than 93. This value dropped to $k_e/k_\alpha > 2.5$ for (−)-IV-*d*. Third-order isotopic exchange occurred with high retention (k_e/k_α = 14–54) for (+)-I-*d* but with net inversion (k_e/k_α = 0.45–0.89) for (−)-IV-*d*. Third-order racemization of (−)-IV-*d* included a sizable isoinversion (inversion without exchange) component. Isomer IV (3-amide) exchanged 1.1–1.4 times faster and racemized 75–86 times faster than isomer I (2-amide). The entire racemization rate factor was due to a more negative entropy of activation for (+)-I-*h*. The isotope effects for racemization of (+)-IV-*h* and (−)-IV-*d* decreased dramatically with temperature, and racemization of (+)-IV-*h* proceeded with significantly lower enthalpy and entropy of activation than did the racemization of (−)-IV-*d*. The second-order kinetics are interpreted as reflecting reaction between amine monomer and carbon acid, and the third-order reaction between amine dimer and carbon acid. The isotopic exchange with retention is interpreted as occurring through ammonium carbanide contact ion pair. Rotation of the ammonium ion within the ion pair and collapse to the covalent state provide exchange with retention. The isoinversion and inversion with exchange components are interpreted in terms of a conducted-tour mechanism. Here the amine-complexed ammonium ion migrates along the negatively charged π cloud to the oxygen of the 3-amide group, into the plane of the fluorene system, back to the 9 position on the side remote from the origin, all without hydrogen-bond dissociation. Collapse to the covalent state before amine rotation occurs provides isoinversion, and after, inversion with exchange. The difference in results between the 2- and 3-amide is attributed to charge distribution effects, charge being better distributed on the oxygen of the 3- than of the 2-amide. The kinetic isotope effects are interpreted in terms of a combination of normal and proton tunneling effects.

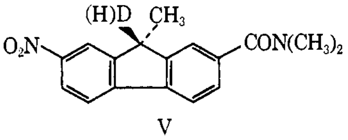
Results of a survey of k_e/k_α values (ratio of rate constant of isotopic exchange to that of racemization) for the base-catalyzed hydrogen isotope reactions of compounds I–V have been reported.[2] In the survey, the ratios were determined from single points. In nondissociating solvents with amine bases, carbon acid I exchanged with high retention of configuration ($k_e/k_\alpha >> 1$). The other four substances under similar conditions provided k_e/k_α values in the range of $\lesssim 0.1$ to 4. A detailed kinetic examination was made of isotopic exchange of compound V in in tetrahydrofuran–*t*-butyl alcohol–tri-*n*-propylamine,[3] and the degree of isoracemization was found to decrease when the polarity of the medium increased or when salts were added to the medium.



I, X = $CON(CH_3)_2$
II, X = CN
III, X = NO_2



IV



V

In the survey the difference in behavior of isomeric amides I and IV, which differ only in the position of the amido group, was particularly striking. This paper reports a detailed kinetic comparison of the characteristics of the racemization and isotopic exchange reactions with *n*-propylamine of these two isomers in tetrahydrofuran.

Results

Preparations of 2-amide I[4] and 3-amide IV[2] optically active and deuterated have been reported elsewhere. The same samples were used in the three investigations.

Kinetics of Isotopic Exchange of 2-(N,N-Dimethylcarboxamido)-9-methylfluorene-9-*d* (I-*d*). Data for exchange kinetics of I-*d* in tetrahydrofuran with *n*-propylamine appear in Table I. All runs were carried out in ampoules. Pseudo-first-order rates were followed by measuring the appearance of a sharp peak at 1146 cm^{-1} in the infrared spectrum of I-*h*. The substrate concentration of 0.032 *M* was chosen as the lowest possible one which would allow direct comparison of these exchange rates to racemization rates of (+)-I-*h* and exchange and racemization rates of isomeric amides (+)-IV-*h* and (−)-IV-*d*. High base concentrations were chosen to provide an excess of exchangeable pro-

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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).

[3] W. T. Ford and D. J. Cram, *ibid.*, 90, 2606 (1968).

[4] D. J. Cram and L. Gosser, *ibid.*, 86, 5445 (1964).

Table I. Rates of Isotopic Exchange[a] of 0.032 *M* 2-Amide (I-*d*)[b] in Tetrahydrofuran with *n*-Propylamine

Run	Amine concn, *M*[c]	*T*, °C[d]	% reacn followed	$10^4 k_{obsd}$,[e] sec^{-1}	$10^4 k_2$,[f] l. mol^{-1} sec^{-1}	$10^4 k_3$,[f] $l.^2$ mol^{-2} sec^{-1}
1	1.162	75.07	76	7.37 ± 0.15	6.34 ± 0.19	5.46 ± 0.22
2	0.921	75.04	80	5.02 ± 0.11	5.45 ± 0.17	5.92 ± 0.25
3	0.783	75.05	77	3.64 ± 0.15	4.65 ± 0.24	5.93 ± 0.36
4	0.783	75.05	80	3.53 ± 0.13	4.51 ± 0.21	5.76 ± 0.33
5	0.602	75.06	83	2.82 ± 0.06	4.68 ± 0.15	7.78 ± 0.32
6	0.397	75.08	72	1.715 ± 0.024	4.32 ± 0.10	10.89 ± 0.37
7	0.789	49.85	70	1.116 ± 0.044	1.414 ± 0.071	1.79 ± 1.0
8	0.776	49.85	70	1.171 ± 0.024	1.509 ± 0.036	1.94 ± 0.8
9	0.776	24.91	68	0.252 ± 0.003	0.325 ± 0.007	0.419 ± 0.013
10	0.789	24.89	66	0.247 ± 0.005	0.313 ± 0.010	0.397 ± 0.016

[a] Six to eight data points taken per run. [b] 97% of one excess atom of deuterium per molecule. [c] Concentrations were determined at room temperature. No corrections were made for expansion at higher temperatures. [d] ±0.05°. [e] Pseudo-first-order rate constants with standard deviations were calculated by a least-squares computer program. [f] Second- and third-order rate constants with standard deviations were calculated from k_{obsd} and [amine] assuming a ±1% error in the latter.

Table II. Rates of Racemization[a] of 0.032 *M* 2-Amide ((+)-I-*h*) in Tetrahydrofuran-*n*-Propylamine

Run	Starting isotope[b]	Amine concn, *M*[c]	*T*, °C[d]	% reacn followed	$10^6 k_{obsd}$,[e] sec^{-1}	$10^6 k_3$,[f] $l.^2$ mol^{-2} sec^{-1}
11	*h*	1.183	75.06	89	14.29 ± 0.16	10.21 ± 0.32
12	*h*	1.000	75.15	75	10.00 ± 0.03	10.00 ± 0.23
13	*h*	0.779	75.09	78	6.17 ± 0.26	10.14 ± 0.63
14	*d*[g]	0.789	75.06	77	6.31 ± 0.03	10.14 ± 0.25
15	*h*	0.647	75.14	72	4.21 ± 0.02	10.06 ± 0.25
16	*h*	0.458	75.08	70	2.44 ± 0.02	11.64 ± 0.33
17[h]	*h*	0.781	75.08	72	9.74 ± 0.10	16.00 ± 0.48
18	*d*[g]	0.789	49.86	70	3.51 ± 0.02	5.64 ± 0.15
19	*d*[g]	0.788	49.85	63	3.33 ± 0.02	5.36 ± 0.15
20	*h*	0.731	24.88	50	1.528 ± 0.008	2.86 ± 0.06

[a] Seven to ten points per run. [b] Isotopic exchange of (+)-I-*d* was fast enough so that racemization of (+)-I-*h* was actually the measured rate constant even though (+)-I-*d* served in some runs as starting material. [c] Base concentrations were determined at room temperature. No corrections were made for concentration changes at elevated temperatures. [d] ±0.10°. [e] Pseudo-first-order rate constants with standard deviations were calculated by a least-squares computer program. [f] Third-order rate constants with standard deviations were calculated from [amine] and k_{obsd} assuming a ±1% error in the former. [g] 97% atom of excess deuterium per molecule. [h] Solution was 6×10^{-4} *M* in *n*-propylammonium iodide.

tons in the medium sufficient to ensure that effectively every deuterium which reached the solvent became lost in an excess of exchangeable protons. The largest fraction of deuterium in the total exchangeable hydrogens in any run was 3.9%. Since data were taken only to 70% exchange in that experiment (run 6), the highest fraction of deuterium present in the medium when any data point was taken was 2.7%. No deviations from first-order kinetics other than occasional random errors in data points were ever observed. The kinetic order of isotopic exchange of I-*d* changed with *n*-propylamine concentration. The nearly constant values of third-order rate constants (k_3 of Table I) in runs 1–4 imply that exchange was second order in amine from 0.8 to 1.2 *M* base. The nearly constant values of second-order rate constants (k_2) in runs 3–6 imply that exchange was first order in amine from 0.4 to 0.8 *M* base. A sharp discontinuity in base order is highly unlikely. Errors in the data of slightly more than the one standard deviation indicated in Table I would make the data compatible with a gradual transition from predominant second-order kinetics at low base concentration to predominant third-order kinetics at high base concentration. This interpretation is more plausible than one which would require very large errors at either high or low base concentration, masking second- or third-order kinetics over the entire range of amine concentrations. At the amine concentration for which the most data are available (0.8 *M*), both second- and third-order exchange reactions appear to occur.

Kinetics of Racemization of (+)-I-*h*. Data for racemization kinetics of (+)-I-*h* in tetrahydrofuran with *n*-propylamine appear in Table II. Runs at 50° and 75° were carried out in sealed ampoules. In run 20 at 25° the solution was held in a tightly stoppered polarimeter cell for 5 days. Hydrogen–deuterium exchange of (+)-I-*d* occurred with very high retention, making the rate of racemization of (+)-I-*d* with *n*-propylamine very difficult to measure. In runs 14, 18, and 19, (+)-I-*d* starting material was used to follow racemization rates of (+)-I-*h*. Because of the much faster exchange rate, the substrate in run 18 was only 6% deuterated at the time the first racemization point was taken and 2% deuterated at the time all succeeding points were taken. The total exchangeable hydrogens contained only 2% excess deuterium in runs 14, 18, and 19. Even a reasonably large substrate isotope effect for racemization would not affect the observed rate constants beyond the limits of error already assigned to them, as demonstrated by comparison of runs 13–14.

The constant value of third-order rate constants for runs 11–15 indicates that racemization of (+)-I-*h* was second order in *n*-propylamine at amine concentrations from 0.65 to 1.2 *M*. The higher value of k_3 in run 16 could be due to a large random error, but most likely reflects a trend toward second-order racemization at lower base concentrations, as observed with isotopic exchange of I-*d*. Racemization of (+)-I-*h* followed third-order kinetics at lower base concentration than exchange of I-*d*.

Table III. Rates of Isotopic Exchange[a] of 0.032 *M* 3-Amide (IV-*d*)[b] with *n*-Propylamine in Tetrahydrofuran

Run	Amine concn, *M*[c]	T, °C[d]	% reacn followed	10^5k_{obsd},[e] sec^{-1}	10^5k_2,[f] l. mol^{-1} sec^{-1}	10^5k_3,[f] l.^2 mol^{-2} sec^{-1}
21	1.134	24.93	72	6.17 ± 0.72	5.4 ± 0.7	4.8 ± 0.7
22	1.109	24.94	67	5.39 ± 0.74	4.9 ± 0.7	4.4 ± 0.7
23	0.781	24.91	73	3.45 ± 0.40	4.4 ± 0.6	5.7 ± 0.8
24	0.770	24.90	65	3.47 ± 0.33	4.5 ± 0.5	5.9 ± 0.7
25	0.577	24.88	71	2.38 ± 0.20	4.1 ± 0.4	7.2 ± 0.7
26	0.782	49.89	84	14.1 ± 2.3	18 ± 3	23 ± 4
27	0.782	75.00	84	41.4 ± 5.2	53 ± 7	68 ± 10

[a] Six to eight data points were taken per run. [b] 90.8% of one atom of excess deuterium per molecule. [c] All base concentrations were determined at room temperature. No corrections were made for expansion at higher temperatures. [d] ±0.05°. [e] Pseudo-first-order rate constants with standard deviations were obtained by a least-squares method described in the Experimental Section. [f] Calculated from k_{obsd} and [amine] assuming a ±1% error in the latter.

Table IV. Rates of Racemization[a] of 3-Amide (+)-IV-*h* with *n*-Propylamine in Tetrahydrofuran

Run	(+)-IV-*h* concn, *M*	Amine concn, *M*[b]	T, °C[c]	% reacn followed	10^5k_{obsd},[d] sec^{-1}	10^5k_3,[e] l.^2 mol^{-2} sec^{-1}
28	0.032	1.390	24.91	77	37.5 ± 0.5	19.4 ± 0.6
29	0.032	0.976	24.91	75	19.7 ± 0.3	20.7 ± 0.7
30	0.0322	0.815	24.94	70	13.62 ± 0.19	20.5 ± 0.7
31	0.0318	0.780	24.90	70	13.65 ± 0.07	22.5 ± 0.6
32	0.032	0.569	24.90	55	6.22 ± 0.12	19.2 ± 0.8
33	0.032	0.340	24.90	55	2.96 ± 0.02	25.6 ± 0.7
34	0.159	0.779	24.92	76	17.28 ± 0.02	28.5 ± 0.6
35	0.100	0.793	24.90	69	15.89 ± 0.05	25.3 ± 0.6
36	0.0587	0.810	24.91	59	14.77 ± 0.04	22.5 ± 0.5
37	0.0159	0.796	24.93	54	13.83 ± 0.20	21.8 ± 0.8
38	0.1059	0.775	24.89	63	14.18 ± 0.11	23.6 ± 0.7
39	0.032	0.795	49.86	50	27.5 ± 0.6	43.5 ± 1.8
40	0.032	0.790	75.13	58	54.4 ± 0.9	87.2 ± 3.2
41[f]	0.032	0.795	24.90	72	23.1 ± 0.4	36.5 ± 1.4

[a] 7 to 18 data points per run. [b] Base concentrations were measured at room temperature. No corrections were made for changes in concentration at higher temperatures. [c] ±0.05°. [d] Pseudo-first-order rate constants with standard deviations were calculated by a least-squares computer program. [e] Obtained from k_{obsd} and [amine] assuming a ±1% error in the latter. [f] Base was *n*-$C_3H_7ND_2$, 1.97 atoms of excess deuterium per molecule.

Kinetics of Exchange of 3-(N,N-Dimethylcarboxamido)-9-methylfluorene-9-*d* (IV-*d*). Kinetic data for isotopic exchange of IV-*d* with *n*-propylamine in tetrahydrofuran are reported in Table III. Rates were followed by appearance of a sharp peak at 1098 cm^{-1} in the infrared spectrum of IV-*h*. The rather large standard deviations for observed rate constants were due to difficulties encountered in the isolation and purification of recovered mixtures of IV-*h* and IV-*d*. All runs were carried out in ampoules. Recovered IV for each kinetic point, usually a gum rather than a solid, was chromatographed over silica gel before the infrared analysis. Large random errors were found in one or more points of each run, but there was no discernible deviation from pseudo-first-order kinetics. Inspection of the second- and third-order rate constants in Table III indicates that isotopic exchange of IV-*d* was neither second nor third order in the range of base concentrations used. The data are consistent with a sum of second- and third-order processes, as observed for exchange of isomeric I-*d*.

Kinetics of Racemization of (+)-IV-*h*. Data for racemization of (+)-IV-*h* with *n*-propylamine in tetrahydrofuran are reported in Table IV. All runs at 25° were performed in a thermostated polarimeter cell. At elevated temperatures sealed ampoules were used. Larger limits of error are reported for racemization rates of (+)-IV-*h* than for isomeric (+)-I-*h* because in most runs with the former compound the initial rotation was about 0.1°, and individual rotation measurements were accurate to ±0.002°. The low rotations of (+)-IV-*h* and (−)-IV-*d* dictated the substrate concentration and the *n*-propylamine concentrations used in kinetics of 2-amide I as well as 3-amide IV. Any lower substrate concentration would have greatly magnified errors in racemization rates of (+)-IV-*h* and (−)-IV-*d*.

Inspection of the third-order rate constants for runs 28–32 shows a nearly constant value with no apparent trends in the data. Hence, in the base concentration range of 0.57 to 1.39 *M*, racemization was first order in substrate and second order in amine. The scatter of third-order constants beyond their standard deviations was probably due to random variation in polarimeter response from one period of operation to the next. The higher value of k_3 in run 33 probably means that second-order racemization was important at amine concentrations below 0.57 *M*.

Runs 30–31 and 34–38 show the effect of variation of substrate concentration on observed rates. The rates were unaffected by changes in substrate concentration from 0.0159 to 0.0587 *M*. At higher concentrations some process bimolecular in substrate may be important, but at the concentration used in all kinetics with I and IV except runs 34–38, 0.032 *M*, racemization of (+)-IV-*h* was simply first order in substrate.

Kinetics of Racemization of (−)-IV-*d*. Data for racemization of (+)-IV-*d* with *n*-propylamine in tetrahydrofuran are recorded in Table V. Two complications made the data less accurate than that for (+)-IV-*h*. First, the material used was contaminated with 7.5 or

9.2% of (−)-IV-*h* and had to be corrected for its contribution to the racemization. Second and more important, exchange of (−)-IV-*d* proceeded with net retention. As a result, observed rates of racemization increased with time because of formation of faster racemizing (−)-IV-*d* *via* exchange with retention. Only the observed rate at zero time was a true measure of the racemization of (−)-IV-*d*. All of the rate constants except that in run 44 were obtained by extrapolation to zero time from three or four data points in the first 30% racemization. The constant for run 44 was determined from eight data points in the first 6% racemization.

Table V. Rates of Racemization[a] of 0.032 *M* 3-Amide ((−)-IV-*d*) with *n*-Propylamine in Tetrahydrofuran

Run	Amine concn, *M*[b]	*T*, °C[c]	$10^6 k_{obsd}$,[d] sec^{-1}	$10^6 k_3$,[e] l.^{2} mol^{-2} sec^{-1}
42[f]	1.355	24.90	48	26
43[f]	0.942	24.93	28	32
44[g]	0.801	24.93	20.9 ± 0.5	32.5
45[f]	0.788	24.90	24	38
46[f]	0.596	24.90	9.4	26
47[f]	0.281	24.91	4.4	56
48[f]	0.780	49.90	109	180
49[g]	0.785	49.87	92	150
50[g]	0.805	75.05	260	400

[a] Number of data points and per cent reaction followed are discussed in Results and Experimental Sections. [b] Base concentrations were determined at room temperature. No corrections were made for changes in concentration at higher temperatures. [c] ±0.05°. [d] Pseudo-first-order rate constants were calculated by methods described in the Experimental Section. All runs except 44 have an estimated accuracy of ±20%. [e] Third-order rate constants were calculated from k_{obsd} and [n-$C_3H_7NH_2$]. [f] Starting material contained 7.5% (−)-IV-*h*. [g] Starting material contained 9.2% (−)-IV-*h*.

The third-order constants for runs 42–46 are relatively independent of base concentration, demonstrating that racemization of (−)-IV-*d* was third order at amine concentrations from 0.6 to 1.4 *M*. The higher value of k_3 for run 47 was due probably to appearance of second-order racemization at low base concentration as observed for (+)-IV-*h* and isomeric (+)-I-*h*.

Activation Parameters. Enthalpies and entropies of activation calculated from kinetic data in Tables I–V are reported in Table VI. All calculations were made with pseudo-first-order rate constants from data at 25 and 50°, and from data at 50 and 75°. The values at 25 and 75° for isotopic exchange of I-*d* differ by values just outside of probable error. If the differences are real, they could be caused by changes in mechanism with temperature. Since none of the other reactions exhibited this behavior, experimental error is the preferred explanation. Proton tunneling may be responsible for the large differences in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ between racemization of (+)-IV-*h* and racemization of (−)-IV-*d* (see Discussion).

Relative Racemization and Exchange Rates. The exchange rate of IV-*d* in tetrahydrofuran with 0.8 *M* *n*-propylamine was 1.4 to 1.1 times faster than that of I-*d* at 25 to 75°. In contrast, the racemization rate of (+)-IV-*h* was 75 to 86 times faster than that of (+)-I-*h*. All of this difference in racemization rates lies in the entropy of activation (see Table VI). The differences in base order and activation energies for the racemization and exchange processes of I and IV are reflected in significant variance of k_e/k_α values with base concentration and temperature. Representative examples of these effects are reported in Table VII.

Table VI. Activation Parameters[a] for Isotopic Exchange and Racemization of I and IV in Tetrahydrofuran with 0.8 *M* *n*-Propylamine

Reaction	Run no. used in calcn	*T*, °C[a]	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
Exch I-*d*	7, 8, 9, 10	25	11.1 ± 0.5	−42 ± 2
Exch I-*d*	3, 4, 7, 8	75	9.4 ± 0.8	−48 ± 2
Rac (+)-I-*h*	18, 19, 20	25	4.6 ± 0.5	−69 ± 2
Rac (+)-I-*h*	13, 14, 18, 19	75	4.7 ± 0.5	−69 ± 2
Exch IV-*d*	23, 24, 26	25	10.2 ± 2.2	−45 ± 8
Exch IV-*d*	26, 27	75	8.9 ± 2.9	−49 ± 9
Rac (+)-IV-*h*	30, 31, 39	25	4.8 ± 0.8	−60 ± 3
Rac (+)-IV-*h*	39, 40	75	5.5 ± 0.8	−58 ± 3
Rac (−)-IV-*d*	44, 48, 49	25	11.4 ± 1.8	−42 ± 6
Rac (−)-IV-*d*	48, 49, 50	75	7.9 ± 3.0	−53 ± 10

[a] Values for 25° were calculated from data at 25 and 50°. Values for 75° were calculated from data at 50 and 75°.

Table VII. Change in Value of k_e/k_α with Change in Carbon Acid, Base Concentration, and Temperature

Run no. used in calcn	Amine concn, *M*	*T*, °C	k_e/k_α[a] 2-Amide I[b]	3-Amide IV[c]
1, 11	1.2	75.1	54 ± 4	...
3, 4, 13, 14; 27, 50	0.8	75.1	58 ± 5	1.7 ± 0.4
5, 6; 16	0.45	75.1	93 ± 10	...
7, 8, 18, 19; 26, 48, 49	0.8	49.9	33 ± 3	1.4 ± 0.3
21, 22; 42, 43	1.1	24.9	...	1.6 ± 0.4
9, 10, 20; 23, 24, 44	0.8	24.9	14 ± 1	1.8 ± 0.2
25, 46	0.58	24.9	...	2.5 ± 0.6

[a] Calculated from pseudo-first-order rate constants obtained in runs indicated. [b] Rate ratio for exchange of I-*d* and racemization of (+)-I-*h*. [c] Rate ratio for exchange of IV-*d* and racemization of (−)-IV-*d*.

From the dependence of k_e/k_α on base concentration it is apparent that the bimolecular reaction involving one molecule each of substrate and amine gave more stereospecific exchange with retention than the termolecular reaction. The k_e/k_α value of 54 for I at 75.1° is for the termolecular reaction at high amine concentration. For the corresponding bimolecular reaction $k_e/k_\alpha > 93$. There is a similar trend in the data for IV at 24.9°.

Second- and third-order rate constants, k_2 and k_3, for exchange of IV-*d* were obtained graphically from a plot of eq 1, which is shown in Figure 1. Because of

$$k_{obsd}/[\text{amine}] = k_2 + k_3[\text{amine}] \qquad (1)$$

scatter, no best fit of the data was attempted, but extreme values of the slope and intercept were determined. These extreme values were $k_2 = 2.1\text{–}3.3 \times 10^{-5}$ l. mol^{-1} sec^{-1} and $k_3 = 1.4\text{–}2.9 \times 10^{-5}$ l.^{2} mol^{-1} sec^{-1}. Comparison of these third-order rate constants to the average value of k_3 for racemization of (−)-IV-*d* (3.2×10^{-5} l.^{2} mol^{-2} sec^{-1}) gave values of $k_e/k_\alpha = 0.5\text{–}0.9$, net inversion with exchange, for the termolecular reaction. If ion-pair formation by one molecule of (−)-IV-*d* and two molecules of *n*-propylamine resulted

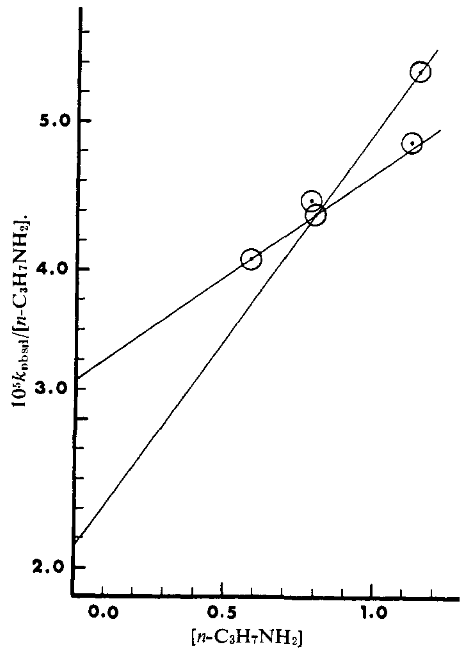

Figure 1. Plot used to evaluate second- and third-order rate constants for isotopic exchange of IV-*d* with *n*-propylamine in tetrahydrofuran.

in statistical distribution of four protiums and one deuterium in the cation and complete loss of configurational identity in the anion, a k_e/k_α value of 0.8 would result. The data for racemization of (−)-IV-*d* in Table V are insufficient for calculation of its second-order rate constant from eq 1. However, k_e/k_α for the bimolecular exchange must be greater than the value of 2.5 (Table VII) found at a base concentration where racemization was nearly third order.

Isotope Effects on Racemization of IV. Kinetic isotope effects for racemization of IV in tetrahydrofuran with *n*-propylamine are listed in Table VIII. The isotope effect was reduced considerably as temperature increased from 25 to 75° in accordance with the lower $\Delta H^{\ddagger}$ for (+)-IV-*h* compared to (−)-IV-*d*. Also recorded is a base isotope effect $(k^{RNH_2}/k^{RND_2})_\alpha$ based on racemization rates with *n*-propylamine and *n*-propylamine-N-d_2.

Table VIII. Isotope Effects for Racemization of 3-Amide IV with *n*-Propylamine in Tetrahydrofuran at Varied Temperatures

Runs used in calcn	*T*, °C	k_H/k_D[a]
30, 31, 44	24.9	6.3 ± 0.7
39, 48, 49	49.9	2.7 ± 0.5
40, 50	75.1	2.2 ± 0.5
30, 31, 41	24.9	0.56 ± 0.04[b]

[a] Calculated from third-order rate constants. [b] Amine isotope effect on racemization of (+)-IV-*h*, $(k^{RNH_2}/k^{RND_2})_\alpha$.

Mechanistic Components in Racemization of (−)-IV-*d*. A previous paper[5] described in detail two different experimental methods of determining rate constants for the mechanistic components of base-catalyzed hydrogen–deuterium exchange by means of a kinetic model. Another application of the model has been developed here to determine rate constants for exchange with retention (k_1), exchange with inversion (k_2), and isoinversion (k_3) in racemization of (−)-IV-*d* with *n*-propylamine in tetrahydrofuran. The procedure involved finding a best fit of theoretical rotation and time data to experimental data in run 44. Equation 2[5] indicates that the rotation of an exchanging and racemizing solution of (−)-IV-*d* at any time *t* is a function of its rotation at zero time (α_0), the substrate isotope effect for racemization ($\phi = k_H/k_D$), the rate of racemization of (—)-IV-*d* at time zero (θ), and a function Ψ defined in eq 3. All of the components of eq 2 except Ψ can be measured experimentally. Once Ψ has been determined, the rate constant for mechanistic processes can be calculated by solution of eq 4–6, in which k_e is the rate constant for isotopic exchange.

$$\alpha = \left[\frac{\alpha_0}{(\phi - 1) + \Psi}\right][(\phi - 1)e^{-\theta(1-\Psi)t} + \Psi e^{-\theta\phi t}] \quad (2)$$

$$\Psi = \frac{k_2 - k_1}{2(k_2 + k_3)} \quad (3)$$

$$k_2 - k_1 = \theta\Psi \quad (4)$$

$$k_1 + k_2 = k_e \quad (5)$$

$$\theta = 2(k_2 + k_3) \quad (6)$$

The data necessary for determination of k_1, k_2, and k_3 were collected from run 44. Continuous rotation and time data were obtained with a recorder attached to a polarimeter. The racemization rate constant of (−)-IV-*d* was taken to be the least-squares rate constant from eight data points collected in the first 6% observed racemization. Under these conditions random errors in the measurements were large enough to hide any trend in the data toward a faster rate, yet small enough to provide the $k_{obsd} = \theta = 2.09 \pm 0.05 \times 10^{-5}$ sec^{-1} of run 44. A value of $\Psi = -1.15$ was found to minimize the sum of deviations of eleven theoretical data points from corresponding experimental data points. Values of $\Psi = -1.10$ and $\Psi = -1.20$ gave larger deviations between theoretical and experimental data. These values of θ, Ψ, and $k_e = 3.70 \times 10^{-5}$ sec^{-1} (calculated from runs 23–24) provided the rate constants for mechanistic processes reported in Table IX.

Table IX. Rate Constants for Mechanistic Processes in Racemization of (−)-IV-*d* in Tetrahydrofuran with *n*-Propylamine

Process	Rate constant, sec^{-1}
Exchange with retention	$k_1 = 3.05 \times 10^{-5}$
Exchange with inversion	$k_2 = 0.65 \times 10^{-5}$
Isoinversion	$k_3 = 0.40 \times 10^{-5}$

Unfortunately, the curve-fitting technique used to find Ψ provided no way to set limits of error. While the errors involved in calculating Ψ were undoubtedly large, isoinversion was most likely a real contributor to the over-all mechanism. An assumed value of $k_3 = 0$ coupled with k_e and θ from runs 23, 24 and 44, gave $\Psi = -0.76 \pm 0.23$ in which the error represents one standard deviation. At the base concentration of 0.8 *M* used in run 44, racemization of (−)-IV-*d* was third order. If third-order racemization takes place

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

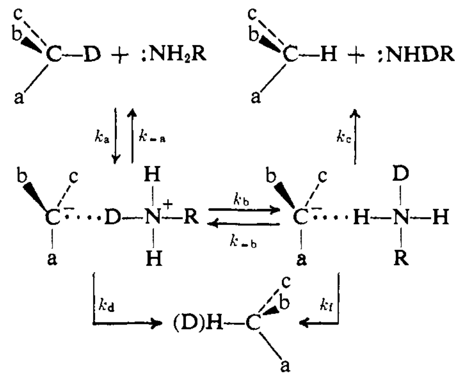
via ion pairs, and the ion pairs never exchange with the medium, statistical distribution of hydrogen and deuterium between inverted IV and two molecules of amine would give $4k_3 = k_2$. Application of $4k_3 = k_2$ to calculation of Ψ from eq 4–6 gave $\Psi = -0.97 \pm 0.21$. The value of $\Psi = -1.15$ obtained by fitting theoretical to experimental data and the theoretical value of $\Psi = -0.97$ from statistical distribution of hydrogen and deuterium between one substrate and two amine molecules are within experimental error of one another. The presence of a sizable isoinversion component in exchange of (−)-IV-*d* under conditions such that $k_e/k_\alpha = 1.8$ and the value for k_e/k_α of 0.45 to 0.89 for third-order exchange and racemization of (−)-IV-*d* provide strong evidence that deuterium was not exchanged into the medium. In fact, both the size of the isoinversion component and the k_e/k_α range imply that inverted IV is formed with greater than the statistical amount (20%) of deuterium which would result from total equilibration of five hydrogen atoms during inversion. However, the experimental errors are too large to allow a firm conclusion as to the exact balance between the isoinversion and inversion components. Besides, the isotope effect for proton *vs.* deuteron capture by the carbanion undoubtedly plays some role, and would provide a nonstatistical result even if the four hydrogens and one deuterium become completely shuffled.

Discussion

In order to formulate mechanisms for exchange and racemization of 2- and 3-(N,N-dimethylcarboxamido)-9-methylfluorene (I and IV) in tetrahydrofuran with *n*-propylamine, the following facts require explanation. (1) Over most of the range of base concentrations studied, (+)-I-*h*, (+)-IV-*h*, and (−)-IV-*d* racemized by third-order kinetics while I-*d* and IV-*d* exchanged by a mixture of second- and third-order kinetics. (2) Second-order isotopic exchange occurred with very high retention ($k_e/k_\alpha > 93$) for (+)-I-*d* and with at least moderate retention ($k_e/k_\alpha > 2.5$) for (−)-IV-*d*. (3) Third-order exchange occurred with high retention (k_e/k_α = 14–54) for (+)-I-*d*, but with net inversion (k_e/k_α = 0.45–0.89) for (−)-IV-*d*. (4) Third-order racemization of (−)-IV-*d* included a relatively large isoinversion component. (5) Isomer IV exchanged 1.1–1.4 times faster and racemized 75–86 times faster than isomer I; the entire racemization rate factor was due to a more negative entropy of activation for (+)-I-*h*. (6) The isotope effect for racemization of (+)-IV-*h* and (−)-IV-*d* decreased dramatically with increased temperature, and racemization of (+)-IV-*h* proceeded with significantly lower enthalpy and entropy of activation than did racemization of (−)-IV-*d*.

Mechanism for Second-Order Isotopic Exchange and Racemization. Both isomers exchanged with retention by second-order processes. The mechanism previously devised[4] to explain exchange of (−)-I-*d* with net retention in tetrahydrofuran with *n*-propylamine is shown in Chart I. The protonation of carbanion (rate constant k_c) is considered irreversible because of the large excess of protium in the solvent. In order to provide exchange with high retention, k_{-a}, k_b, k_{-b}, $k_c >> k_d$, k_f. No elaboration of the mechanism for inversion is presented because it was not carefully studied under second-order racemization conditions.

Chart I. Mechanism for Second-Order Isotopic Exchange and Racemization



Mechanism for Third-Order Isotopic Exchange and Racemization. Three distinct mechanisms for second-order dependence on *n*-propylamine in the exchange and racemization of (+)-I-*d* and (−)-IV-*d* in tetrahydrofuran will be considered.

Case I. The active base in deuteron abstraction from substrate might be the conjugate base of *n*-propylamine formed by the disproportionation of eq 7. The equilibrium constant K of eq 7 is about 10^{-25} (the pK_a of *n*-propylammonium ion is ~10.8, while that for ammonia is ~36[6]). If the rate of recombination of ions was diffusion controlled ($k \sim 10^{11}$ l. mol^{-1} sec^{-1}), the rate constant for ion formation could be only ~10^{-14} l. mol^{-1} sec^{-1}, which is smaller than observed rates of racemization and exchange of I and IV by 10^9. Clearly the anion formed in eq 7 cannot be the active catalyst.

$$2n\text{-}C_3H_7NH_2 \overset{K}{\rightleftharpoons} n\text{-}C_3H_7\bar{N}H + n\text{-}C_3H_7\overset{+}{N}H_3 \qquad (7)$$

Case II. Monomeric *n*-propylamine could be the base which abstracts a deuteron from carbon in a prerate-determining equilibrium step. Participation of a second amine molecule in the rate-determining steps for exchange and racemization would then give a third-order reaction. A prerate-determining equilibrium requires that a primary isotope effect on racemization rates be very low or even inverse.[5] The isotope effects on racemization of IV, k_H/k_D = 6.3 at 25° and 2.2 at 75°, are not low enough for a true prerate-determining equilibrium. Although part of these isotope effects will be attributed to proton tunneling in a later section of this discussion, that phenomenon should not qualitatively alter the evidence against prerate-determining equilibrium. Tunneling in proton abstraction from carbon would be balanced by tunneling in protonation of carbanion.

Case III. The active base in deuteron abstraction from (+)-I-*d* and (−)-IV-*d* is probably a dimer of *n*-propylamine. A mechanism incorporating third-order exchange and racemization processes is presented in Chart II. Protonation of carbanion (rate constant k_c) is considered irreversible because of the large excess of protium in the medium. In intermediates B and D, which possess hydrogen bonds between protium and carbanion, the deuterium atom may be in any of the other four possible positions. Two mechanisms for the process governed by k_b (and k_{-b}) are considered. The

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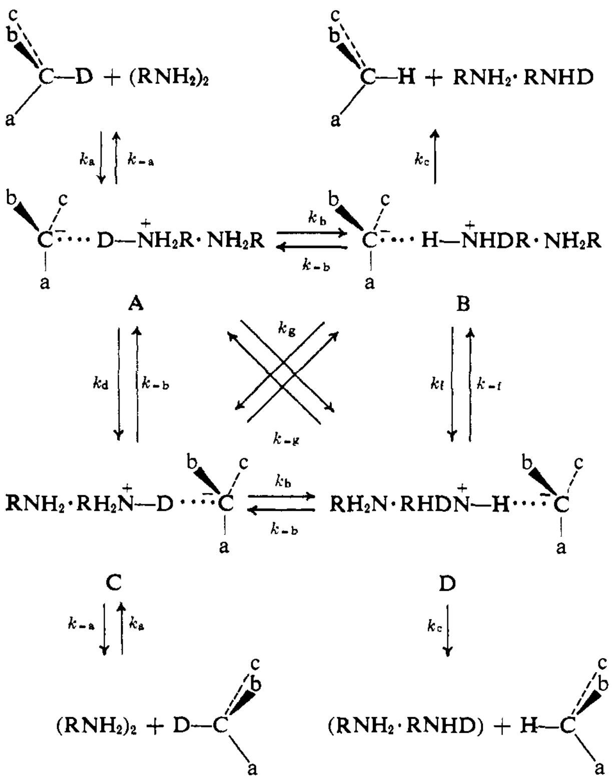
(6) N. S. Wooding and W. C. Higginson, *J. Chem. Soc.*, 774 (1952).

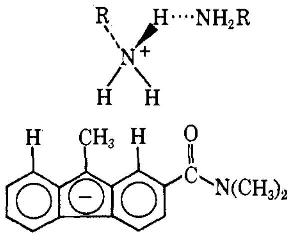
Chart II. Mechanism for Third-Order Exchange and Racemization



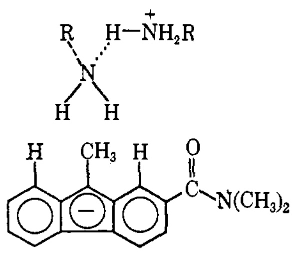
ammonium–amine cation may rotate to replace the C···D hydrogen bond by a C···H one involving a proton on the same nitrogen atom as the deuterium. Alternatively, rapid proton transfer from one nitrogen to the other may accompany breakage of the C···D hydrogen bond and formation of a C···H with a proton on the second nitrogen atom, leaving deuterium on the amine instead of the ammonium ion. Neither process would require much separation of charge. Proton transfers between amines and ammonium ions are nearly diffusion controlled.[7]

Third-order exchange of (+)-I-*d* occurred with relatively high retention, which requires k_{-a}, k_b, k_{-b}, k_c $>>$ k_d, k_f, k_g, k_{-g} in Chart II. Regardless of which mechanism is used to explain inversion of the ammonium carbanide ion pair (rate constants k_d, k_f, k_g, and k_{-g}), it must involve a more ordered transition state than isotopic exchange (rate constants k_b, k_{-b}), because of its more negative entropy of activation. If inversion involved breaking a hydrogen bond and rotating the carbanion with respect to the cation, in the transition state the ammonium ion would occupy the plane of the carbanion where association with the π-electron system is minimized. In this transition state (VI) at least one hydrogen atom of the aromatic ring would separate the cation from the π-electron system, an unlikely process. Inversion also might involve formation of an amine-separated ammonium–carbanide ion pair. However, on the way to inverted material, this ion pair would have to pass through a stage such as VII, which would involve even further separation of charge than in VI. Finally, inversion could take place by the *conducted-tour mechanism* which requires that negative charge be partially localized on oxygen and that an O···H hydrogen bond pass through the plane of the carbanion as in VIII and IX.

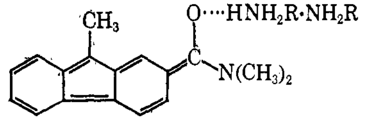
Third-order exchange of (−)-IV-*d* occurred with net inversion and nearly statistical distribution of hydrogen isotopes between nitrogen and carbon. This result requires that k_{-a} and k_c in Chart II be smaller than the fastest rate constant for inversion of ion pairs, k_d, k_f, k_g, or k_{-g}, and that shuffling of protons between the ammonium–amine molecules also be fast compared to processes described by k_{-a} and k_c. Rate constants k_{-a} and k_c probably are not affected much by a change of substrate from I to IV, whose kinetic acidities and pK_a values differ by very little.[3] Hence, the much greater rate of racemization of IV compared to I must be due to differences in rate constants k_b, k_{-b}, k_d, k_f, k_g, and k_{-g}. Reasonably, processes which occur after the initial ionization are much more sensitive to the nature of the anion than is the ionization itself. The dimethylcarboxamido substituent in the 3 position of IV can have negative charge localized on oxygen by destroying the aromaticity of one benzene ring (see IX), while the same substituent in the 2 position must destroy the aromaticity of two benzene rings to localize negative charge on oxygen (see VIII). The ease of localizing charge on the 3 substituent compared to the 2 substituent strongly supports the conducted tour mechanism for inversion. The accompanying shuffling of protons and deuterons between the two nitrogens could be done without destroying the contact ion pair or without completely breaking the hydrogen bond between the two ions.



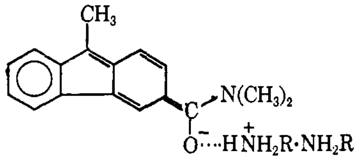
VI
(improbable transition state for isoinversion)



VII
(improbable transition state for isoinversion)



VIII
(planar ion pair of conducted-tour mechanism)



IX
(planar ion pair of conducted-tour mechanism)

Hückel molecular orbital calculations[8] indicate that in the unsubstituted fluorenide anion, charge is better distributed in the 3 than in the 2 position. Both the inductive and resonance effects of substituents would seriously perturb this charge distribution, but always

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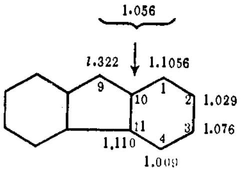
[7] E. Grunwald, *J. Phys. Chem.*, 71, 1846 (1967), and references cited therein.

[8] A. Streitwieser, Jr., and J. I. Brauman, "Supplemental Tables of Molecular Orbital Calculations," Vol. 1, Pergamon Press Inc., New York, N. Y., 1965, pp 247–250.



HMO π-electron densities in fluorenide anion

in a direction which would favor greater charge in the vicinity of a 3 substituent such as cyano, nitro, or amido than in the vicinity of similar 2 substituents. The conducted-tour mechanism could operate with a powerful enough electron-attracting and -distributing group from the 2 position, but should always be more facile with the same substituent in the 3 position. The results of a survey indicated that the cyano and nitro groups in the 2 position were powerful enough electron-attracting and -distributing groups to provide a conducted-tour pathway for inversion.[2] The N,N-dimethylamido group does not provide such a pathway when in the 2 position, but does when in the 3 position.

As noted above, the rates of processes that occur after ionization are much more affected by substituents than is the ionization process itself. Charge is only partially developed in the transition state for ionization, whereas in the anions themselves a full charge must be accommodated.

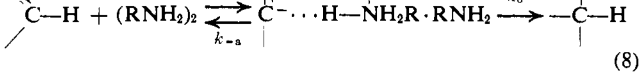
Structure of *n*-Propylamine in Tetrahydrofuran. Knowledge of the structure of *n*-propylamine in tetrahydrofuran would help our mechanistic interpretation. Although data are not available, a number of reports on self-association and solute–solvent association of amines in nonpolar solvents are relevant.[9,10] For example, for solutions of aniline in cyclohexane at 3 and 71°, dimerization constants ranged from 0.473 l. mol^{-1} to 0.258 l. mol^{-1}, respectively.[9c] In cyclohexane, di-*n*-butylamine has a dimerization constant of 0.13 l. mol^{-1} at 25°.[10] Association constants for aniline in tetrahydrofuran have been reported[9d] to range from 1.61 l. mol^{-1} at 3° to 0.704 l. mol^{-1} at 50.5°.

From the above information *n*-propylamine should be expected to have a dimerization constant in tetrahydrofuran at 25° greater than the 0.13 l. mol^{-1} reported for di-*n*-butylamine at 25° and less than the 0.389 l. mol^{-1} reported for aniline at 22°. The tetrahydrofuran–*n*-propylamine complex should have a lower valued formation constant because ethers are much weaker bases than amines. If monomeric and dimer *n*-propylamine were responsible for k_2 and k_3 in exchange of IV-*d*, and had equal base strengths in catalyzing exchange, the assumption $k_2 = k_3$ mol l.$^{-1}$ leads to an *n*-propylamine dimerization constant of 3 l. mol^{-1}. Similarly, the assumption $k_2 = 2k_3$ mol l.$^{-1}$ leads to a dimerization constant of 1.0 l. mol^{-1}. These values appear unreasonably high compared to the preceding estimates from data in the literature. Treatment of exchange rate data for I-*d* at 75° from Table I by this method would lead to the same conclusion. Therefore, if monomeric and dimeric *n*-propylamine are responsible for k_2 and k_3, the dimer must be a stronger base than the monomer. While no kinetic data are available, it is reasonable that X > XI > XII in kinetic base strength. The hydrogen bonds should be much stronger with a partial positive charge on nitrogen than in the neutral species. Probably X is the active species in our termolecular reactions, and XI in our (pseudo) bimolecular reactions.

$RNH_2 \cdot NH_2R$	$RNH_2 \cdot O(CH_2)_4$	RNH_2
X	XI	XII

Proton Tunneling. Results in Tables VI and VIII demonstrated that in racemization of (+)-IV-*h*, $\Delta H^{\ddagger}$ was 2.4 to 6.6 kcal/mol lower and $\Delta S^{\ddagger}$ was 5 to 18 eu more negative, than in racemization of (−)-IV-*d*. The isotope effect for racemization $(k_H/k_D)_\alpha$ varied from 6.3 at 25° to 2.2 at 75°. In the past, such data have been interpreted as evidence for proton tunneling.[11] From a statistical mechanical model, Bell[11a] made the following theoretical predictions for tunneling. (a) The isotope effect must be larger than it would be if tunneling did not occur. (b) The difference in activation energies for hydrogen and deuterium transfer, $E_a^D - E_a^H$, should be larger than the corresponding difference in zero-point energies of the C–D and C–H bonds. (c) Experimental values of the Arrhenius A factors should give $A_H/A_D < 0.5$. The isotope effects of 2.2 to 6.3 for racemization of IV are relatively low, but there is little basis for prediction of the isotope effect expected in the absence of tunneling. Although more accurate data would be desirable, our results ($E_a^D - E_a^H$ = 2.4–6.6 kcal/mol, $A_H/A_D = 10^{-4}$ to 0.06 for the 25–50° and 50–75° temperature intervals, respectively) conform to Bell's criteria b and c.

A possible objection to proton tunneling in racemization of IV may be raised. Proton abstraction was not the only contributor to the rate of racemization. In eq 8 attainment of stereospecificity in a hydrogen–deuterium exchange requires that k_{-a} be at least competitive with rate constants for steps leading to racemization and exchange (k_b in eq 8). In an extreme case proton abstraction could be part of a prerate-determining equilibrium ($K_{eq} = k_a/k_{-a}$) with k_b rate determining. The observed rate constant would then be $k_{obsd} = K_{eq}k_b$. This should lead to low or even inverse isotope effects because K_{eq} may have an inverse isotope effect and k_b, which involves making and breaking hydrogen bonds, should have at most a low isotope effect. The isotope effects for racemization of IV were not low enough for k_b to be rate determining. Since k_a also cannot be rate determining, the observed rate must follow eq 9 in which k_{-a} and k_b are of comparable value. To the extent that protonation of carbanion (k_{-a}) competes with exchange and racemization steps (k_b), the isotope effect will be lower than it would be if proton abstraction were rate determining ($k_{obsd} = k_a$). Tunneling should be important to both k_a



$$\text{C—H} + (\text{RNH}_2)_2 \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} \text{C}^- \cdots \text{H—}\overset{+}{\text{N}}\text{H}_2\text{R}\cdot\text{RNH}_2 \xrightarrow{k_b} \text{—C—H} \qquad (8)$$

$$k_{obsd} = k_ak_b/(k_{-a} + k_b) \qquad (9)$$

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[9] (a) J. H. Lady and K. B. Whetsel, *J. Phys. Chem.*, **68**, 1001 (1964); (b) K. B. Whetsel and J. H. Lady, *ibid.*, **69**, 1596 (1965); (c) K. B. Whetsel and J. H. Lady, *ibid.*, **68**, 1010 (1964); (d) J. H. Lady and K. B. Whetsel, *ibid.*, 71, 1421 (1967).

[10] S. Singh and C. N. R. Rao, *ibid.*, **71**, 1074 (1967).

[11] (a) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, pp 203–214; (b) R. P. Bell, *Trans. Faraday Soc.*, **55**, 1 (1959); (c) E. S. Lewis and L. H. Funderburk, *J. Am. Chem. Soc.*, **89**, 2322 (1967); (d) V. J. Shiner and M. L. Smith, *ibid.*, **83**, 593 (1961); (e) V. J. Shiner and B. Martin, *Pure Appl. Chem.*, **8**, 371 (1964); (f) E. F. Caldin and M. Kasparian, *Discussions Faraday Soc.*, **39**, 25 (1965).

and k_{-a}, which involve proton transfer, but not k_b, because it involves only shifting hydrogen bonds which should have a wide energy barrier.

Experimental Section

Materials and Equipment. All compounds used in kinetics were described previously,[2] as were the purifications of tetrahydrofuran and *n*-propylamine.[3] The *n*-propylammonium iodide used in run 17 was prepared by Mr. John Almy, and contained 1.97 atoms of excess deuterium per molecule by nmr.

All glassware, except the polarimeter cell, was cleaned with chromic acid, thoroughly rinsed with distilled water and dilute ammonium hydroxide, and dried in an oven at 120° for at least 12 hr. Exchange runs at 50 and 75° were carried out in sealed heavy-walled Pyrex tubes with 6-ml capacity. Exchange runs at 25° were carried out in tightly stoppered test tubes with a 10-ml capacity. Racemization runs at 50 and 75° were carried out in sealed heavy-walled tubes with a 2.5-ml capacity. Racemization runs at 25° were carried out in a 1-dm polarimeter cell with a 1-ml capacity. All rotations were measured on a Perkin-Elmer Model 141 polarimeter at 436 mμ.

Deuterium Analysis of I for Kinetic Runs. No attempts were made to determine the absolute deuterium content of isolated points. Analysis for % D in mixtures of I-*h* and I-*d* by infrared spectrophotometry has been described.[4]

A set of five standard mixtures of I-*h* and I-*d* was prepared by weighing amounts of solid totaling 9.9–10.1 mg into vials. Spectral grade chloroform (Merck) was added to each vial from a 300-μl pipet shortly before spectra were taken. A Perkin-Elmer Model 421 dual-grating spectrophotometer was used with the following adjustments: source current, 0.34 A; slit program, 2 × 990; suppression, 0; amplifier gain, 5; attenuator speed, 700; scale expansion, IX; scan rate, 30 cm^{-1}/min; and path length, 0.4 mm. The difference in absorbance (Δabs) between a peak at 1147 cm^{-1}, which appeared in V-*h* but not in V-*d*, and base line at 1155–1163 cm^{-1} was measured two to five times for each solution. Under these conditions a peak of 0.6 absorbance unit gave peak heights reproducible within a range of 0.007 absorbance unit. A plot of 100 × Δabs/weight of sample in milligrams against % H for these standards gave a calibration curve which deviated slightly from a straight line drawn between the points corresponding to 0% H and 100% H.

For each point in a kinetic run the 100 × Δabs/mg value was measured under the conditions described above. With each run measurements on one or two 100% H samples were made to serve as an infinity point. From the calibration curve each value of 100 × Δabs/mg was corrected by the deviation of the calibration curve from a straight line to make 100 × Δabs/mg proportional to protium content. In all runs analyzed by this procedure the 100 × Δabs/mg values for the infinity points were in the range 5.60–6.27. Because the calibration curve was so close to a straight line, results were not affected by these day-to-day fluctuations in instrument behavior.

Typical Isotopic Exchange Rate of I-*d*: Run 4. A solution of 171.8 mg of (+)-I-*d* in 20.00 ml of tetrahydrofuran was prepared in a tightly stoppered, 50-ml flask. The solution was stirred for 15 min at room temperature. With a graduated pipet, 1.43 ml of *n*-propylamine was added. The basic solution was stirred for another 5 min. A pipet was used to transfer about 2.6 ml of the solution into each of eight heavy-walled tubes. The tubes were immediately stoppered with septum caps. They were cooled to −78° and sealed at less than 1 mm. At time zero all eight tubes were submerged in a rate bath at 75.05°. Tubes were withdrawn at the times indicated in Table X, quenched at −78°, and opened. The contents were shaken with 1 *N* hydrochloric acid and ether. The ether solution was washed with 1 *N* hydrochloric acid and water, dried with magnesium sulfate, and evaporated to recover solid I. In the last two points the solution in the opened tube was allowed to warm to room temperature. An aliquot from each was withdrawn with a calibrated 0.5-ml Hamilton syringe fitted with Chaney adapter. The remainder of the solution was quenched in acid, and I was recovered as before. Each aliquot was titrated to the brom cresol green end point with standard hydrochloric acid. Both points had the same titer.

After drying at 1 mm overnight in a desiccator, about 10 mg of recovered I from each point was weighed into a vial. Deuterium analysis was carried out by the method above. A graphical plot of ln [$(100 \times \Delta\text{abs/mg})_\infty - (100 \times \Delta\text{abs/mg})_t$] *vs. t* for the data in Table X gave a rate constant of 3.43 × 10^{-4} sec^{-1} when the spurious sixth point was ignored. A least-squares computer program provided a rate constant with standard deviation of 3.53 ± 0.13 × 10^{-4} sec^{-1}. No deviation from first-order kinetics was observed.

Table X. Exchange of 0.032 *M* I-*d* in Tetrahydrofuran with 0.783 *M n*-Propylamine at 75.05°

Time, min	100 × Δabs/mg	Cor (calcd curve) 100 × Δabs/mg
3.1	0.68	0.75
11.3	1.60	1.73
19.4	2.43	2.58
27.6	3.00	3.17
37.9	3.59	3.75
47.9	3.65	3.81
60.7	4.57	4.69
73.6	4.78	4.90
∞	6.14	6.14

Typical Racemization Rate of (+)-I-*h* at 75°: Run 15. By the procedure described for exchange runs, a solution of 75.1 mg of (+)-I-*h* in 9.00 ml of tetrahydrofuran and 0.52 ml of *n*-propylamine was prepared. Eight heavy-walled tubes were filled with 1.1 ml of the solution. The tubes were sealed at −78°, placed in a bath at 75.14°, and quenched at −78°. Each tube was opened at −78° and allowed to warm to room temperature. The solution was transferred to a thermostated 1-dm polarimeter cell. The rotation of each solution was measured at 25° less than 15 min after the solution reached room temperature. Base concentration was determined by the method described for run 4. The data reported in Table XI provided a graphical rate constant of 4.18 × 10^{-6} sec^{-1} and a least-squares constant with standard deviation of 4.21 ± 0.02 × 10^{-6} sec^{-1}.

Table XI. Racemization of 0.032 *M* (+)-I-*h* in Tetrahydrofuran with 0.647 *M n*-Propylamine at 75.14°

Time, hr	α_{436}, deg
2.6	+0.435
14.7	0.364
27.7	0.297
39.5	0.250
50.6	0.210
61.9	0.177
73.9	0.149
85.8	0.123

Kinetics of Racemization of (+)-IV-*h* at 25°. The procedure used to obtain the data at 25° in Table IV was identical with that used for racemization of (+)-I-*h* in run 20. Because the initial rotations in these runs were only 0.09–0.13°, the data were subject to greater instrumental error than data for (+)-I-*h*.

Kinetics of Racemization of (+)-IV-*h* at 50 and 75°. The procedure of run 15 for racemization of (+)-I-*h* was used with the following modifications. Heavy-walled tubes were filled by volumetric pipet with 1.00-ml aliquots. After quenching at −78°, each tube was opened, and 0.100 ml of acetic acid was added by micropipet. Rotations were taken when the acidic solutions warmed to 25°.

Kinetics of Racemization of (−)-IV-*d*. None of the runs in Table V were simple first-order racemizations. Two experimental approaches were used to obtain the reported rate constants.

Run 44. At 25° a solution of 8.0 mg of (−)-IV-*d* (0.908 atom excess deuterium per molecule) in 0.94 ml of tetrahydrofuran was prepared in a 1-ml volumetric flask. A timer was started and 0.065 ml of *n*-propylamine was added to the solution within 0.1 min. The basic solution was mixed by drawing it in and out of a capillary dropper several times and transferred to a 1-dm polarimeter cell which was thermostated by water circulation from a bath at 24.93°. A 1-mV Leeds and Northrup recorder connected to the polarimeter was used to collect the data. One inch of recorder chart corresponded to 0.020°.

Isotopic Exchange Rates of IV-*d*. The procedures used for preparation of solutions, sealing aliquots, and quenching points were identical with those described for I-*d*. Deuterium analyses were performed by the method used for one-point exchange determinations described before.[2] In kinetic runs all points were chromatographed, but only an infinity point was used for calibration. A control experiment illustrates the difficulties encountered in deuterium analyses. A solution of 63.6 mg of (−)-IV-*d* in 1.0 ml of *n*-propylamine and 7.0 ml of tetrahydrofuran was divided equally into three test tubes. The tubes were stoppered and held at 25° for 29 hr (over ten exchange half-lives). A gum of IV was recovered from each tube, purified, and analyzed. The 100 × Δabs/mg values for these three infinity points and two chromatographed samples of (+)-IV-*h* are listed in Table XII. One value was unreasonably low. The others gave an average value with standard deviation of 1.62 ± 0.05.

Table XII. Control Experiment on Infinity Points for Exchange Kinetics of (−)-IV-*d*

Source	100 × Δabs/mg	
(+)-IV-*h*	1.60	1.62 ± 0.05
	1.55	
Infinity point	1.64	
	1.68	
	1.38	

This variation in infinity point values had drastic effects on the least-squares observed rate constants, because the computer program calculated the least sum of squares of differences of ln (X_∞ − X_t) values between experimental data and points on the best straight line. Run 24 will serve as a specific example of this problem. The data listed in Table XIII, excluding the spurious point at 270 min, were used to obtain a least-squares, first-order rate constant of 3.47 ± 0.11 × 10^{-5} sec^{-1}. In order to provide for uncertainty in the infinity point, the least-squares computation was repeated using 1.60 (1.65 minus one standard deviation) as the infinity point. The resulting rate constant was 3.69 ± 0.13 × 10^{-5} sec^{-1}. The standard deviation reported for k_{obsd} in Table III is the sum of the standard deviation resulting from data scatter (±0.11) and the difference in rate constants obtained with the two different infinity points (±0.22). Hence, the reported k_{obsd} is 3.47 ± 0.33 × 10^{-5} sec^{-1}. The same procedure was used for all runs in Table III.

Table XIII. Exchange of 0.032 *M* IV-*d* in Tetrahydrofuran with 0.770 *M* *n*-Propylamine at 24.90°

Time, min	100 × Δabs/mg	
31	0.41	
71	0.50	
114	0.63	
168	0.68	
217	0.80	
270	0.80	
330	0.97	
394	1.08	
∞	1.63	1.65
∞	1.67	

Racemization Rate of (+)-I-*h* at 25°: Run 20. The procedure described previously for kinetic runs in methanol at 25° was used.[5] A solution of 8.0 mg of (+)-I-*h* and 0.065 ml of *n*-propylamine in tetrahydrofuran was prepared in a 1-ml volumetric flask and transferred to a thermostated 1-dm polarimeter cell. During rotation measurements the cell was thermostated by circulating water from a rate bath at 24.88°. At all other times the cell was kept in the same bath. After all the data were recorded, the *n*-propylamine concentration was determined by titration of two aliquots with standard acid as described for run 4. In no run of Table II did the base concentration change with time. No deviation from simple first-order substrate dependence was observed in any run. The noise level in the polarimeter, which was reproduced on the recorder chart, was about ±0.0005°. Change in rotation was followed until less than 25% of the initial activity remained. Base concentration was determined by the method of run 20.

Data for rotation and time were interpreted from the recorder chart at every 0.001° for nine points and every 0.005° thereafter. The mean time at which the recorder indicated a given rotation was chosen. In this way the relative values of time and rotation were determined much more accurately than they could have been without a recorder. An initial rotation of −0.130° was found by extrapolation of the recorder tracing to zero time. Contributions to the observed rotation from protio starting material at the time *t* of each data point were subtracted from observed rotations (α_{obsd}) by eq 10, in which α_D is the rotation due to deuterated starting material, f_H is the fraction of protonated starting material (0.092), α_0 is the observed rotation at zero time (−0.103°), and k_H^α is the rate constant for racemization of (+)-IV-*h* under the same conditions (runs 30, 31). It was assumed that the protium and deuterium fractions of the starting material had the same specific rotation. Table XIV records the data.

$$\alpha_D = \alpha_{obsd} - f_H \alpha_0 e^{-k_H^\alpha t} \qquad (10)$$

Table XIV. Data from Run 44

Time, min	α_{obsd}, deg	α_D, deg	α_D(theory), deg
0.0	−0.130	−0.1180	−0.1180
3.9	−0.129	−0.1174	...
8.1	−0.128	−0.1169	...
13.0	−0.127	−0.1163	−0.116
16.0	−0.126	−0.1156	...
20.5	−0.125	−0.1150	...
25.7	−0.124	−0.1144	...
29.3	−0.123	−0.1137	...
34.0	−0.122	−0.1131	−0.112
58.0	−0.117	−0.110	...
80.0	−0.112	−0.106	−0.104
101.0	−0.107	−0.102	...
121.0	−0.102	−0.098	−0.096
140.0	−0.097	−0.093	...
161.0	−0.092	−0.089	−0.089
183.0	−0.087	−0.085	...
205.0	−0.082	−0.080	−0.080
234.0	−0.077	−0.075	...
258.0	−0.072	−0.071	−0.071
283.0	−0.067	−0.066	...
313.0	−0.062	−0.061	−0.062
346.0	−0.057	−0.056	...
376.0	−0.052	−0.052	−0.053
410.0	−0.047	−0.047	...
451.0	−0.042	−0.042	−0.044
491.0	−0.037	−0.037	...
542.0	−0.032	−0.032	...
602.0	−0.027	−0.027	−0.029

The theoretical rotations, α_D(theory), listed in Table XIV were calculated by the method discussed in the text using θ = 2.09 × 10^{-5} sec^{-1}, k_H/k_D = 6.3, α_0 = 0.1180°, and Ψ = −1.15. The value of θ, the racemization rate constant for (−)-IV-*d*, is the least-squares rate constant for the first nine points in Table XIV all of which lie in the first 6.2% loss of initial rotation. While these points in principle should not fit a straight line because of net exchange with retention, the scatter in the data was large enough to mask any trend away from a straight line, yet low enough to give a standard deviation of less than ±3% for the pseudo-first-order rate constant. The value of Ψ = −1.15 was found to fit eq 2 by trial and error. The sum of deviations of 11 theoretical points from their experimental points in Table XIV was 0.001°, and the standard deviation of theoretical points from experimental points was ±0.0014°. Values of Ψ = −1.10 and −1.20 produced significantly larger deviations between experiment and theory.

Runs 42–43 and 45–50. Experimental procedures used were identical with those described for (+)-I-*h*. The contributions to rotations from protio starting material were subtracted from α_{obsd} to give α_D by eq 10. Three or four data points from the first 30% loss of rotation were used to a ln (−α_D) *vs.* time plot. The rate constants were determined by estimating the slope of the tangent to the resulting curve at zero time. Such estimations are probably good only to ±20%, as indicated in Table V.

Calculation of Activation Parameters. All calculations of $\Delta H^\ddagger$ and $\Delta S^\ddagger$ in Table VI were made with pseudo-first-order rate constants from data at 25 and 50° and from data at 50 and 75°. When two runs were made with 0.8 M n-propylamine and the same temperature, the average of their rate constants was used. Observed rate constants were used for runs in which the base concentrations at two temperatures differed by less than 0.010 M; otherwise pseudo-first-order constants were calculated from base concentrations and second- or third-order rate constants, whichever was appropriate. Standard deviations were calculated by the method of total differentials.

Nonlinear Structure–Reactivity Correlations. The Reactivity of Nucleophilic Reagents toward Esters[1]

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Abstract: Rate constants are reported for the reactions of water and of nucleophiles of pK = 3.1–15.8 with a series of acetate esters with leaving groups of pK = 10–2. The reactions with oxygen anions exhibit a small sensitivity to the basicity of both the attacking group and the leaving group when the former is more basic than the latter and a large sensitivity to the basicity of both groups in the converse case. Logarithmic plots of rate constants against the pK of the attacking and leaving groups are nonlinear with limiting slopes, β, approaching 0.3 and 1.0 in both cases. The behavior of nucleophiles with "abnormal" reactivity in such plots is governed by their basicity rather than their absolute nucleophilic reactivity, so that inversions of relative reactivities may occur as the leaving group is varied. The reactions of "normal" nitrogen nucleophiles show β values for the nucleophile close to 0.8 over a range of 10^8 in reaction rate and then level off to a much smaller sensitivity to basicity in the reactions of strongly basic amines with the most reactive esters. Values of β for varying leaving groups are close to 1.0 for most reactions, indicating a large change in the charge on the leaving group in the transition state, and decrease to 0.4 for the rapid reactions. It is argued that no tetrahedral addition intermediate is formed before the transition state is reached in any of the aminolysis reactions. The similarity in the behavior of primary, secondary, and tertiary amines means that proton transfer is not required in these reactions and that amine attack and leaving-group expulsion can occur through transition state(s) of zero net charge. The results do not discriminate unequivocally between a concerted mechanism and one involving a metastable tetrahedral intermediate for these reactions.

The Bronsted slopes, β, of logarithmic plots of the rate constants for the reactions of nucleophilic reagents with phenyl acetates against the pK_a of the nucleophile are generally thought to be close to 0.8, indicating a large sensitivity of these reactions to the basicity of the nucleophile.[2–5] Hammett $\sigma\rho$ plots for reactions of substituted phenyl acetates with a given amine generally exhibit values of ρ near 2, indicating that these reactions also have a large sensitivity to the nature of the leaving group, while reactions with basic oxygen nucleophiles exhibit smaller ρ values.[6–9] A few exceptions to these generalizations are known. The reactions of strongly basic oxygen anions with p-nitrophenyl acetate exhibit very little sensitivity to the basicity of the nucleophile[10] and the reactions of thiol anions with p-nitrophenyl acetate[11] and of amino acids with acetic anhydride[12] and Leuchs anhydrides[1] exhibit Bronsted slopes of only approximately 0.4, 0.5, and 0.6, respectively. The rates of the nucleophilic reactions of imidazole with a series of acetate esters in which the pK of the leaving group varies from 16 to 4 exhibit a transition from a relatively small sensitivity to a large sensitivity with respect to the nature of the leaving group as the leaving ability of the alcohol is decreased.[14] This change was attributed to a change in the nature of the transition state from one resembling that expected for rate-determining attack of the amine on the ester to one resembling that expected for rate-determining breakdown of a tetrahedral addition intermediate; the results may be described equally well in terms of a tetrahedral intermediate or in terms of an asymmetrical energy barrier along the reaction coordinate with no addition intermediate. The change from a nucleophilic to a general base catalyzed mechanism as the leaving group becomes more basic in the reactions of esters with imidazole[14] and with acetate ion[15] may be interpreted in the same manner.

In spite of the large amount of experimental work on the problem, the mechanism of this class of reactions is

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