Electrophilic Substitution at Saturated Carbon. L. Isoinversion without an Available Conducted Tour Pathway for Proton Transfer[1]

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Abstract: The effect of using charge-delocalizing bases as catalysts on the stereochemical course of hydrogen-deuterium exchange reaction of fluorene carbon acids has been examined. Pentamethylguanidine (PMG) and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in *tert*-butyl alcohol have been used as media for determining k_e/k_α values (ratio of rate constants of hydrogen isotopic exchange to that of racemization) for (+)-9-deuterio-2-(*N*,*N*-dimethylcarboxamido)-9-methylfluorene ((+)-**1**-*d*), (+)-9-deuterio-3-(*N*,*N*-dimethylcarboxamido)-9-methylfluorene ((+)-**2**-*d*), (−)-9-deuterio-2,9-dimethylfluorene ((−)-**3**-*d*), and (−)-9-deuterio-2-iodo-9-methylfluorene ((−)-**4**-*d*). In all cases $k_e/k_\alpha < 1$, and in most runs < 0.5, pointing to isoinversion as the dominant mechanistic component. For (+)-**1**-*d* at 25° with PMG, $\Delta H^{\ddagger} = 9.2 \pm 0.5$ kcal mol^{-1} and $\Delta S^{\ddagger} = -47 \pm 2$ eu for isotopic exchange, whereas for racemization, $\Delta H^{\ddagger} = 15.6 \pm 0.4$ kcal mol^{-1} and $\Delta S^{\ddagger} = -23 \pm 1$ eu ($k_e/k_\alpha = 0.15$). For (+)-**2**-*d* with PMG, $\Delta H^{\ddagger} = 11.9 \pm 1.1$ kcal mol^{-1} and $\Delta S^{\ddagger} = -34 \pm 4$ eu for exchange, whereas for racemization $\Delta H^{\ddagger} = 16.0 \pm 0.3$ kcal mol^{-1} and $\Delta S^{\ddagger}\ -20 \pm 2$ eu ($k_e/k_\alpha = 0.39$). The isotope effect of k_α at 25° for (+)-**1** in *tert*-butyl alcohol–PMG was $k^{\mathrm{H}}/k^{\mathrm{D}} = 1.8$, but for (+)-**2** was $k^{\mathrm{H}}/k^{\mathrm{D}} = 6.6$. The reresolution technique applied to (+)-**1**-*d* racemization and exchange in *tert*-butyl alcohol–PMG indicated that 75% of the reaction went with isoinversion and 25% with racemization–exchange. Similarly, (+)-**2**-*d* went with about 45% isoinversion and 55% racemization with exchange. With (+)-**1**-*d*, (−)-**3**-*d*, and (−)-**4**-*d*, and charge-localizing tertiary bases such as triethylenediamine, exchange with racemization was the dominant result, although a net retention component was also present. The same was true with (−)-9-deuterio-3-iodo-9-methylfluorene ((−)-**5**-*d*) and (−)-9-deuterio-9-methyl-2-trimethylammonium iodide ((−)-**6**-*d*). When tripropylamine was used, traces of dipropylamine present changed this stereochemical course to exchange with high retention. With the charge-delocalizing bases, exchange is interpreted as occurring through solvent-separated ion pairs, and racemization through contact ion pairs with charge highly dispersed in both anion and cation. With charge dispersal in both members of an ion pair, a conducted tour pathway is not required for isoinversion.

Base-catalyzed proton or deuteron transfers from one to another site of optically active carbon acids have been found to occur without the proton or deuteron becoming drowned in the pool of deuterium or proton donors. In effect, these reactions are intramolecular, although mechanistically they involve ion pair reorganizations, followed by collapse to the covalent state.[2] All the carbon acids studied produced anions stabilized by substituents, some of which provided a conjugated π system along which the conjugate acid of the catalyst could migrate. The proton or deuteron then was donated to a new site. Proper manipulation of catalyst and substrate structure, of medium, and of pK_a relationships between carbon acid and the conjugate acid of the catalyst allowed high degrees of both stereospecificity and intramolecularity to be realized.[3]

With certain carbon acids, catalysts, and media, these base-catalyzed proton migrations took the form of an *isoinversion reaction.*[4] The mechanism was interpreted as involving an ion-pair reorganization in which the carbanion rotated with respect to the cation in a highly specific way. In the nonpolar media involved, the basic catalyst conducted the proton from the front to the back face of the carbanion through a series of hydrogen-bonded, contact ion pairs. One of these was achiral, and involved a planar carbanion, with the negative charge somewhat localized on a conjugating electronegative group. When no functional group was present that could provide a conducted tour pathway, isotopic exchange with retention was the observed result.[3h,i,4d]

Tertiary amines such as tripropylamine or triethylenediamine (TDA) have been reported to catalyze isotopic exchange with net retention,[4d] or isoinversion,[4d,e,i] depending on the absence or presence of a conducted tour pathway. The positive charge of the conjugate acids of these amines is localized, and they will be referred to as charge-localizing amines.

The present paper reports the results of a detailed study in *tert*-butyl alcohol of the rates of isotopic exchange (k_e) and racemization (k_α) of compounds **1–4** catalyzed by pentamethylguanidine (PMG) and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN). The conjugate

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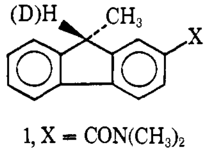
(1) The authors warmly thank the U. S. Army Research Office, Durham, N. C., for support of this work.

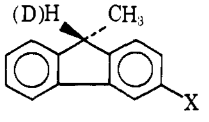
(2) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, pp 85–113, 175–184.

(3) (a) D. J. Cram and R. T. Uyeda, *J. Amer. Chem. Soc.*, **86**, 5466 (1964); (b) J. Almy, R. T. Uyeda, and D. J. Cram, *ibid.*, **89**, 6768 (1967); (c) J. Almy and D. J. Cram, *ibid.*, **91**, 4459 (1969); (d) D. J. Cram, F. Willey, H. P. Fischer, H. M. Relles, and D. A. Scott, *ibid.*, **88**, 2759 (1966); (e) R. Guthrie, W. Meister, and D. J. Cram, *ibid.*, **89**, 5288 (1967); (f) R. D. Guthrie, D. A. Jaeger, W. Meister, and D. J. Cram, *ibid.*, **93**, 5137 (1971); (g) D. A. Jaeger and D. J. Cram, *ibid.*, **93**, 5153 (1971); (h) D. J. Cram, C. A. Kingsbury, and B. Rickborn, *ibid.*, **83**, 3688 (1961); (i) W. D. Kollmeyer and D. J. Cram, *ibid.*, **90**, 1779 (1968).

(4) (a) D. J. Cram and L. Gosser, *ibid.*, **86**, 2950 (1964); (b) D. J. Cram and L. Gosser, *ibid.*, **86**, 5445, 5457 (1964); (c) W. T. Ford, E. W. Graham, and D. J. Cram, *ibid.*, **89**, 4661 (1967); (d) D. J. Cram, W. T. Ford, and L. Gosser, *ibid.*, **90**, 2598 (1968); (e) W. T. Ford and D. J. Cram, *ibid.*, **90**, 2606 (1968); (f) W. T. Ford and D. J. Cram, *ibid.*, **90**, 2612 (1968); (g) J. N. Roitman and D. J. Cram, *ibid.*, **93**, 2225 (1971); (h) Siu May Wong, H. P. Fischer, and D. J. Cram, *ibid.*, **93**, 2235 (1971); (i) J. Kovacs, H. Cortegiano, R. E. Cover, and G. L. Mayers, *ibid.*, **93**, 1541 (1971).

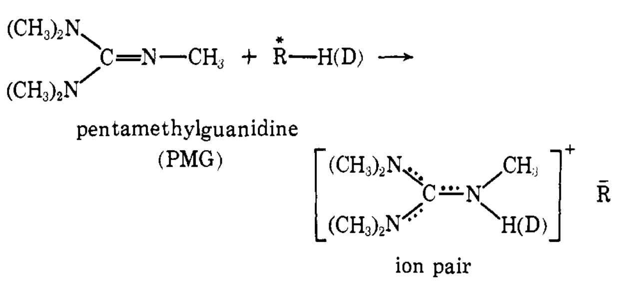


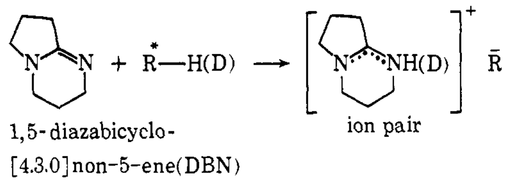
1, X = CON(CH$_3$)$_2$
3, X = CH$_3$
4, X = I
6, X = $\overset{+}{N}$(CH$_3$)$_3$$\overset{-}{I}$



2, X = CON(CH$_3$)$_2$
5, X = I

acids of these two bases have highly *delocalized* positive charge, and are referred to here as *charge delocalizing* amines. The effect of this charge delocalization in the cation on the ion-pair reorganization pathways has been examined. The results are contrasted with those obtained with tertiary, *charge-localizing amines* as catalysts with carbon acids **1–6**.





Results

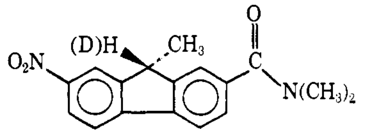
Starting Materials. Two pivotal compounds, 9-methylfluorene-2-carboxylic acid[4b] and 9-methylfluorene-3-carboxylic acid,[4d] served as starting materials for preparation by, conventional reactions of (+)-**1**-*d*,[4b] (+)-**1**-*h*,[4b] (−)-**1**-*d*,[4b] (+)-**2**-*d*,[4d] (−)-**2**-*d*,[4d] (+)-**2**-*h*,[4d] (−)-**3**-*d*, (−)-**3**-*h*, (−)-**4**-*d*, (−)-**5**-*h*, and (−)-**6**-*d*. Their rotations and deuterium contents are found in the footnotes of Table I.

Survey Experiments. Table I reports the results of a survey of the hydrogen isotope exchange (k_e) and racemization (k_α) reactions of compounds **1–6** in *tert*-butyl alcohol, catalyzed by both types of tertiary amine bases. Values of k_e/k_α were estimated from one-point, pseudo-first-order rate constants in each case. Many of the runs were made in the presence of amine hydriodide salts, which provided a reservoir of proton or deuteron donors of the same acidity as the conjugate acids of the basic catalysts employed. The solvent served as a larger reservoir of proton or deuteron donors for replenishing the salt reservoir by rapid exchange reactions. In each run, the proton or deuteron reservoir was less than 2% consumed at the time the reaction was interrupted. The k_e/k_α values of Table I are not strict measures of reaction rate ratios, but rather serve to characterize the reaction mechanism as having a particular dominant reaction component.

The generalizations visible in the data are as follows. (1) Isoinversion (inversion of configuration without isotopic exchange) is the dominant reaction course ($k_e/k_\alpha \lesssim 0.5$) whenever the charge-delocalizing bases were used as catalysts. (2) Exchange with racemization or slight retention is the dominant reaction course ($k_e/k_\alpha \sim 1.5 \pm 0.5$) whenever charge-localizing tertiary amines (free of secondary amine) served as catalysts. (3) When tripropylamine was contaminated with as much as ~0.1% dipropylamine, k_e/k_α values of >10 were observed.

Control experiments demonstrated that in those runs conducted in the presence of added tripropylammonium iodide with tripropylamine as catalyst, trace amounts of dipropylamine were generated. Dipropylamine was not generated by prolonged heating of tripropylamine in the absence of the salt in *tert*-butyl alcohol at 175 and 200°. This fact was demonstrated by conducting kinetic runs with tripropylamine contaminated with ~0.1% dipropylamine. The rate constants, k_e and k_α, were determined for 2-amide (**1**) at these temperatures. Good pseudo-first-order behavior was observed, and no trends were visible in the kinetic points. Table II records the conditions, rate constants, activation parameters, and k_e/k_α values. These runs indicate that dipropylamine catalyzes the exchange reaction at rates many orders of magnitude faster than tripropylamine, and is responsible for most of the exchange reaction that occurs with retention. Had dipropylamine been continuously generated in runs 35 and 37, isotopic exchange would not have followed pseudo-first-order kinetics.

Kinetics of Isotopic Exchange and Racemization with Charge-Delocalizing Tertiary Amines as Catalysts. Table III records the conditions and results of the determinations of k_e and k_α in *tert*-butyl alcohol with PMG and DBN as catalysts. The reactions were assumed to be first order in tertiary amine, as was demonstrated for racemization and exchange of **7** with tripropylamine as catalyst.[4e] Pseudo-first-order rate constants were first determined, and second-order constants were calculated by dividing by the base concentration, which was about 0.04 ± 0.01 *M* in each run. The footnotes of Table III coupled with the Experimental Section identify the procedures.



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Rate Ratios and Activation Parameters. The data of Table I and III provide a means of determining the accuracy of one point, k_e/k_α values. Table IV records the values obtained from three sources: the single-point rate constants of Table I, the multipoint rate constants of Table II, and the values calculated from the curve-fitting procedure discussed in the next section. The difference between the multipoint and single-point k_e/k_α values varies between 10 and 100%. This comparison indicates that the one-point k_e/k_α values are useful for characterization of the dominant reaction path, but not for fine distinctions. The multipoint derived values and those obtained by the curve-fitting technique are in excellent agreement. The activation parameters derived from the kinetic data of Table III were calculated, and are found in Table V.

The conjugate acid of PMG delocalizes positive charge more thoroughly than that of DBN. This difference in charge-delocalizing abilities of the conjugate acids is reflected in the difference of pK_a values of these

Table I. Values of k_e/k_α for Substituted 9-Methylfluorene Carbon Acids' Hydrogen Isotopic Exchange with *tert*-Butyl Alcohol and Racemization Catalyzed by Tertiary Amines

Run	9-Methylfluorene				Base,[a]	Salt,[b]	T,	t,	%	%	
no.	Substituent	No.	Concn, M	Solvent	M	10^3M	°C	hr	exch	racem	k_e/k_α[c]
1	2-CON$(CH_3)_2$	(+)-**1**-*d*[d]	0.046	*tert*-BuOH	PMG, 0.045	PMGHI, 0.74	25	30.8	30	71	0.27
2	2-CON$(CH_3)_2$	(+)-**1**-*h*[e]	0.031	*tert*-BuOH	PMG, 0.098		25	3	7	24	0.30
3	2-CON$(CH_3)_2$	(+)-**1**-*h*[e]	0.060	*tert*-BuOD[f]	PMG, 0.078	PMGDI, 1.2	25	9	25	77	0.27
4	2-CON$(CH_3)_2$	(+)-**1**-*d*[d]	0.034	*tert*-BuOH	DBN, 0.18	DBNHI, 0.14	25	47.5	49	81	0.41
5	2-CON$(CH_3)_2$	(+)-**1**-*d*[d]	0.035	*tert*-BuOH	DBN, 0.10		25	15.4	9	20	0.42
6	2-CON$(CH_3)_2$	(+)-**1**-*h*[e]	0.053	*tert*-BuOD[f]	DBN, 0.17	DBNDI, 1.3	25	23.5	38	70	0.40
7	3-CON$(CH_3)_2$	(+)-**2**-*d*[g]	0.034	*tert*-BuOH	PMG, 0.008	PMGHI, 0.26	25	17.8	34	65	0.43
8	3-CON$(CH_3)_2$	(+)-**2**-*d*[g]	0.033	*tert*-BuOH	PMG, 0.037		25	7.0	16	56	0.21
9	3-CON$(CH_3)_2$	(+)-**2**-*h*[h]	0.037	*tert*-BuOD[f]	PMG, 0.025	PMGDI, 1.2	25	14.5	25	83	0.16
10	3-CON$(CH_3)_2$	(+)-**2**-*d*[g]	0.031	*tert*-BuOH	DBN, 0.066	DBNHI, 0.14	25	17.8	36	72	0.35
11	3-CON$(CH_3)_2$	(+)-**2**-*d*[g]	0.043	*tert*-BuOH	DBN, 0.116		25	10.5	44	75	0.42
12	3-CON$(CH_3)_2$	(+)-**2**-*h*[h]	0.059	*tert*-BuOD[f]	DBN, 0.117	DBNDI, 1.3	25	26.5	28	77	0.31
13	2-CH_3	(−)-**3**-*h*[i]	0.053	*tert*-BuOD[f]	PMG, 0.56	PMGDI, 4.6	50	12.5	26	61	0.32
14	2-CH_3	(−)-**3**-*h*[i]	0.068	*tert*-BuOD[f]	PMG, 0.59		50	6.5	14	31	0.41
15	2-CH_3	(−)-**3**-*d*[j]	0.051	*tert*-BuOH	PMG, 0.53	PMGHI, 2.1	50	20	43	83	0.32
16	2-CH_3	(−)-**3**-*h*[i]	0.056	*tert*-BuOD[f]	DBN, 0.76	DBNDI, 0.92	50	10.3	25	34	0.68
17	2-CH_3	(−)-**3**-*d*[j]	0.037	*tert*-BuOH	DBN, 0.61	DBNHI, 0.14	50	22.5	32	44	0.67
18	2-I	(−)-**4**-*d*[k]	0.016	*tert*-BuOH	PMG, 0.087	PMGHI, 0.26	25	12	23	85	0.14
19	2-I	(−)-**4**-*d*[k]	0.016	*tert*-BuOH	PMG, 0.11		25	4.3	9	60	0.10
20	2-I	(−)-**4**-*d*	0.029	*tert*-BuOH	DBN, 0.14	DBNHI, 0.14	25	27	34	72	0.33
21	2-I	(−)-**4**-*d*[k]	0.016	*tert*-BuOH	DBN, 0.12		25	12	20	56	0.37
22	2-CON$(CH_3)_2$	(−)-**1**-*d*[l]	0.048	*tert*-BuOH	TDA,[m] 0.15		175	12.3	31	26	1.2
23	2-CON$(CH_3)_2$	(−)-**1**-*d*[l]	0.043	*tert*-BuOH	Pr_3N,[n] 0.37	$Pr_3N^+HI^-$, 0.86	175	48	≥98	32	≥10
24	2-CON$(CH_3)_2$	(−)-**1**-*d*[l]	0.050	*tert*-BuOH	TDA,[m] 0.10	TDAHI, 0.10	175	21	72	71	1
25	3-CON$(CH_3)_2$	(−)-**2**-*d*[o]	0.033	*tert*-BuOH	TDA,[m] 0.10		177	20.8	87	98	~0.45[v]
26[p]	3-CON$(CH_3)_2$	(+)-**2**-*d*	0.046	*tert*-BuOH	Pr_3N,[q] 0.60		130	8	8	45	0.14
27	2-CH_3	(−)-**3**-*d*[j]	0.0428	*tert*-BuOH	TDA,[m] 0.15		175	43	25	13	2.1
28	2-CH_3	(−)-**3**-*d*[j]	0.055	*tert*-BuOH	TDA,[m] 0.062	TDAHI, 0.06	175	71	22	24	1
29	2-I	(−)-**4**-*d*[k]	0.025	*tert*-BuOH	TDA,[m] 0.15		175	24.3	52	27	2.3[v]
30	2-I	(−)-**4**-*d*[k]	0.020	*tert*-BuOH	Pr_3N,[q] 0.68		175	4	18	10	1.9
31	2-I	(−)-**4**-*d*[k]	0.016	*tert*-BuOH	Pr_3N,[n] 0.21	$Pr_3N^+HI^-$, 0.77	175	13	63	4	24
32	3-I	(−)-**5**-*h*[r]	0.037	*tert*-BuOD[f]	TDA,[m] 0.42		175	47	90	90	1[v]
33	2-$(CH_3)_3N^+I^-$	(−)-**6**-*d*[s]	0.044	*tert*-BuOH–DMSO[t]	Pr_3N,[n] 0.44		25	24	69[u]	69	1

[a] PMG is pentamethylguanidine (92 mol %), 8 mol % tetramethylurea except for run 2, whose PMG contained 30 mol % tetramethylurea; DBN is 1,5-diazabicyclo[4.3.0]non-5-ene; Pr_3N is tripropylamine; triethylenediamine is TDA. [b] Hydriodides or deuterioiodides of PMG, DBN, Pr_3N, or TDA. [c] k_e/k_α = log (1 − fraction exchanged)/log (1 − fraction racemized). [d] $[\alpha]^{25}_{546}$ +33.7° (*c* 1.1, dioxane), optically pure, mp 127–127.5°, 0.96 atom of excess deuterium per molecule. [e] $[\alpha]^{25}_{546}$ +33.4° (*c* 1.2, dioxane), optically pure, mp 126.5–127°. [f] 0.98 atom of excess deuterium per molecule. [g] $[\alpha]^{25}_{546}$ +8.7°, $[\alpha]^{25}_{546}$ +16.9° (*c* 1.0, dioxane), mp 88.0–89.5°, and 0.98 atom of excess deuterium per molecule. [h] $[\alpha]^{25}_{546}$ +5.8°, $[\alpha]^{25}_{436}$ +11.4° (*c* 1.2, dioxane), mp 86.5–89°. [i] $[\alpha]^{25}_{546}$ −11.8°, $[\alpha]^{25}_{436}$ −19.6° (*c* 1.1, dioxane), mp 42–44°. [j] $[\alpha]^{25}_{546}$ −13.5°, $[\alpha]^{25}_{436}$ −21.3° (*c* 1.2, dioxane), mp 43–44°, and 0.95 atom of excess deuterium per molecule. [k] $[\alpha]^{25}_{546}$ −31.7°, $[\alpha]^{25}_{436}$ −56.8° (*c* 1.0, dioxane), mp 55–56°, and 0.96 atom of excess deuterium per molecule. [l] $[\alpha]^{25}_{546}$ −32.7° (*c* 1.3, dioxane), 97% optically pure, with 0.96 atom of excess deuterium per molecule, mp 127–128°. [m] Triethylenediamine, mp 158–160°. [n] Contained ~0.1% dipropylamine. [o] $[\alpha]^{25}_{546}$ −6.0°, $[\alpha]^{25}_{436}$ −11.7° (*c* 1.0, dioxane), with 0.91 atom of excess deuterium per molecule, mp 83–86°. [p] Run 5, Table I, ref 4d. [q] Contained ~0.01% dipropylamine. [r] $[\alpha]^{25}_{546}$ −5.7°, $[\alpha]^{25}_{436}$ −11.2° (*c*, 1.2, dioxane), mp 90–93°. [s] $[\alpha]^{25}_{546}$ −44° (*c* 1.2 MeOH), mp 169.5–170°, with >0.90 atom of excess deuterium per molecule by nmr. [t] 75:25% by volume, *tert*-butyl alcohol–dimethyl sulfoxide. [u] 69 ± 10% atom of deuterium, determined by nmr. [v] The stereochemical course remained the same with the addition of triethylenediamine dihydroiodide.

Table II. Kinetics of Amine-Catalyzed[a] Racemization and Isotopic Exchange with *tert*-Butyl Alcohol of (−)-9-Deuterio-2-(*N*,*N*-dimethylcarboxamido)-9-methylfluorene ((−)-**1**-*d*)[b]

Run no.	[(−)-**1**-*d*], M	$[Pr_3N]$, M	T,[c] °C	Process	No. of points	% react followed	10^6k[d]		k_e/k_α
							sec⁻¹	l. mol⁻¹ sec⁻¹	
34	0.0286	0.644	175.0	Racem	7	51	3.19 ± 0.04	4.95 ± 0.16	11.1
35	0.0286	0.644	175.0	Exch	4	96	35.54 ± 0.92	55.19 ± 1.42	
36	0.0308	0.635	200.0	Racem	5	68	7.11 ± 0.07	11.20 ± 0.32	10.3
37	0.0308	0.635	200.0	Exch	5	84	73.34 ± 1.49	115.2 ± 4.6	
38	0.0298[e]	0.625	175.0	Racem	6	63	2.91 ± 0.23	4.65 ± 0.46	

[a] Tripropylamine contaminated with ~0.1% dipropylamine. [b] $[\alpha]^{25}_{546}$ −32.7° (*c* 1.3, dioxane), 97% optically pure, mp 127–128°, 0.96 atom of excess deuterium per molecule. [c] ±0.2°. [d] Second-order rate constants were determined by dividing the pseudo-first-order rate constants by the base concentration. The pseudo-first-order rate constants with errors for one standard deviation were obtained by a least-squares computer program. [e] (+)-**1**-*h* was used, $[\alpha]^{25}_{546}$ +33.4° (*c* 1.2, dioxane), optically pure, mp 126.5–127°.

conjugate acids[5] and in the difference in kinetic activities of the bases themselves. Changes in ratios of rate constants with changes in the charge-delocalizing bases from PMG to DBN range from 2.9 (3-amide, racemization, runs 55 and 51) to 8.2 (2-amide, racemization,

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(5) (a) K. B. Flynn and D. R. Nenortas, *J. Org. Chem.*, **28**, 3527 (1963); (b) R. G. Pearson and D. A. Vogelsong, *J. Amer. Chem. Soc.*, **80**, 1038, 1048 (1958); (c) S. J. Angyal and W. K. Warburton, *J. Chem. Soc.*, 2492 (1951); (d) comparison of rates of reactions catalyzed by PMG and DBN suggests the latter base to be the weaker by about 1 pK_b unit.

Table III. Rate Constants for Isotopic Exchange and Racemization of 2-(*N*,*N*-Dimethylcarboxamido)-9-methylfluorene (**1**) and of 3-(*N*,*N*-Dimethylcarboxamido)-9-methylfluorene (**2**) in *tert*-Butyl Alcohol

Run no.	Substrate, *M*	Base,[a] *M*	*T*,[b] °C	% react followed	No. points	Process	10^5k_1,[c] $\sec^{-1}$	10^5k_2,[d] $\sec^{-1}$ l. mol^{-1}
39	(+)-**1**-*d*,[e] 0.0486	DBN, 0.190 ± 0.002	25	69	19	Racem	0.875 ± 0.003	4.604 ± 0.067
40	(+)-**1**-*d*,[e] 0.0496	DBN, 0.121 ± 0.002	25	8	7	Racem	0.561 ± 0.004	4.636 ± 0.109
41	(+)-**1**-*h*,[f] 0.0524	DBN, 0.177 ± 0.003	25	35	16	Racem	0.106 ± 0.002	5.986 ± 0.117
42	(+)-**1**-*h*,[f] 0.0486	DBN, 0.086 ± 0.003	25	14	25	Racem	0.483 ± 0.005	5.632 ± 0.247
43	(±)-**1**-*d*,[h] 0.0308	DBN, 0.152 ± 0.002	25	55	7	Exch[g]	0.202 ± 0.004	1.331 ± 0.043
44	(+)-**1**-*d*,[e] 0.0516	PMG, 0.101 ± 0.001	25	19	10	Racem	2.761 ± 0.014	27.34 ± 0.41
45	(+)-**1**-*h*,[f] 0.0485	PMG, 0.082 ± 0.002	25	74	18	Racem	4.029 ± 0.007	49.02 ± 2.01
46	(+)-**1**-*h*,[f] 0.0401	PMG, 0.104 ± 0.005	25	55	8	Racem	5.676 ± 0.056	54.32 ± 3.41
47	(±)-**1**-*d*,[h] 0.0314	PMG, 0.111 ± 0.001	25	60	5	Exch[g]	0.441 ± 0.002	3.969 ± 0.076
48	(−)-**1**-*d*,[i] 0.0404	DBN, 0.156 ± 0.002	49.4	90	8	Racem	6.364 ± 0.025	40.80 ± 0.69
49	(−)-**1**-*d*,[i] 0.0424	PMG, 0.0303 ± 0.0006	49.4	81	7	Racem	6.480 ± 0.060	213.9 ± 5.7
50	(±)-**1**-*d*,[h] 0.0470	PMG, 0.0200 ± 0.0004	51.1	61	7	Exch[g]	0.302 ± 0.012	15.09 ± 0.50
51	(+)-**2**-*d*,[j] 0.0395	DBN, 0.124 ± 0.001	25	76	19	Racem	3.864 ± 0.007	31.16 ± 0.31
52	(+)-**2**-*h*,[k] 0.0496	DBN, 0.167 ± 0.001	25	81	11	Racem	21.65 ± 0.05	129.9 ± 0.8
53	(+)-**2**-*h*,[k] 0.0419	DBN, 0.078 ± 0.003	25	94	15	Racem	9.921 ± 0.58	127.0 ± 7.9
54	(±)-**2**-*d*,[l] 0.0296	DBN, 0.103 ± 0.001	25	69	6	Exch[g]	1.221 ± 0.088	11.85 ± 0.98
55	(+)-**2**-*d*,[j] 0.0329	PMG, 0.0366 ± 0.0003	25	65	18	Racem	3.321 ± 0.019	90.73 ± 1.28
56	(+)-**2**-*d*,[j] 0.0395	PMG, 0.113 ± 0.010	25	84	15	Racem	11.78 ± 0.04	104.3 ± 10.5
57	(+)-**2**-*h*,[k] 0.0496	PMG, 0.0118 ± 0.0003	25	70	25	Racem	7.073 ± 0.034	599.4 ± 18.6
58	(±)-**2**-*d*,[l] 0.0312	PMG, 0.0839 ± 0.0008	25	81	6	Exch[g]	2.946 ± 0.038	35.11 ± 0.80
59	(+)-**2**-*d*,[j] 0.0367	DBN, 0.0255 ± 0.0005	49.4	78	10	Racem	6.651 ± 0.024	260.8 ± 5.8
60	(+)-**2**-*d*,[j] 0.0438	PMG, 0.0119 ± 0.0003	50.9	82	10	Racem	9.549 ± 0.023	802.5 ± 12.4
61	(±)-**2**-*d*,[l] 0.0437	PMG, 0.0211 ± 0.0004	49.8	74	8	Exch[g]	3.806 ± 0.170	180.4 ± 12.1

[a] DBN stands for 1,5-diazabicyclo[4.3.0]non-5-ene, and PMG for pentamethylguanidine, 30 mol % in tetramethylurea. [b] ±0.1%. [c] First-order rate constants with errors of one standard deviation were calculated by a least-squares computer program. [d] Second-order rate constants are first-order rate constants divided by the base concentration. Estimated error was obtained by the method of total differentials. [e] $[\alpha]^{25}_{546}$ 33.7° (*c* 1.1, dioxane), optically pure, mp 127–128°, 0.96 atom of excess deuterium per molecule. [f] $[\alpha]^{25}_{546}$ 33.4° (*c* 1.2, dioxane), optically pure, mp 126.5–127°. [g] Deuterium analyses were carried out by mass spectrometry. [h] Mp 133–134°, 0.98 atom of excess deuterium per molecule. [i] $[\alpha]^{25}_{546}$ −32.7° (*c* 1.3, dioxane), 97% optically pure, mp 127–128°, 0.96 atom of excess deuterium per molecule. [j] $[\alpha]^{25}_{546}$ 8.7°, $[\alpha]^{25}_{436}$ 16.9° (*c* 1.0, dioxane), mp 88.0–89.5°, 0.98 atom of excess deuterium per molecule. [k] $[\alpha]^{25}_{546}$ 5.8°, $[\alpha]^{25}_{436}$ 11.4° (*c* 1.2, dioxane), mp 86.5–89°. [l] Mp 91–92°, 0.98 atom of excess deuterium per molecule.

Table IV. Comparison of k_e/k_α Values Derived from Single-Point Kinetic Data, Multipoint Kinetic Data, and Curve Fitting in *tert*-Butyl Alcohol at 25°

Derivative of 9-deuterio-9-methylfluorene	Base	Single-point data[a]		Multipoint data[b]		Curve fitting[c]	
		Runs used	k_e/k_α	Runs used	k_e/k_α	Runs used	k_e/k_α
2-Amide (**1**-*d*)	DBN	5	0.42	39, 43	0.29	62	0.29
2-Amide (**1**-*d*)	PMG	2	0.30	44, 47	0.15	63	0.15
3-Amide (**2**-*d*)	DBN	11	0.42	51, 54	0.38	64	0.38
3-Amide (**2**-*d*)	PMG	8	0.21	55, 58	0.39	65	0.39

[a] Table I. [b] Table II, second-order rate constants. [c] Table VII gives k_1, k_2, and k_3 values. $k_e/k_\alpha = (k_1 + k_2)/2(k_2 + k_3)$.

Table V. Activation Parameters for Isotopic Exchange and Racemization at 25°

Derivative of 9-deuterio-9-methylfluorene	Base	Process	Calcd from runs	$\Delta H^{\ddagger}$,[a] kcal/mol	$\Delta S^{\ddagger}$,[a] eu
(+)-**2**-Amido	PMG	Racem	44, 49	15.6 ± 0.4	−23 ± 1
(±)-**2**-Amido	PMG	Exch	47, 50	9.2 ± 0.5	−47 ± 2
(+)-**2**-Amido	DBN	Racem	39, 48	16.5 ± 0.3	−23 ± 1
(+)-**3**-Amido	PMG	Racem	55, 60	15.5 ± 0.5	−20 ± 2
(±)-**3**-Amido	PMG	Exch	58, 61	11.9 ± 1.1	−34 ± 4
(+)-**3**-Amido	DBN	Racem	51, 59	16.0 ± 0.3	−21 ± 1

[a] Errors were determined by the method of K. Wiberg, "Physical Organic Chemistry," Wiley, New York, N. Y., 1964, p 378.

runs 45 and 40). The rate ratios of 3-amide to 2-amide vary from values of 3.3 (PMG, racemization, runs 55 and 54) to 21 (DBN, racemization, runs 52 and 41).[5d]

Kinetic Components of the Isotopic Exchange–Racemization Reactions. In earlier work, *kinetic curve fitting* and *reresolution* methods were developed for breaking the exchange-racemization reactions into their component parts.[4c,f–h] These parts are denoted by k_1 (the rate constant for isotopic exchange of carbon acids with retention of configuration), by k_2 (isotopic exchange with inversion), and k_3 (inversion of a carbon acid without isotopic exchange, or *isoinversion*). In the present work, these three rate constants were estimated by the curve-fitting technique[4f] for both the 2- and 3-amides in *tert*-butyl alcohol at 25° with PMG and DBN as bases. The procedure for evaluating k_1, k_2, and k_3 involved finding the best fit of theoretical rotations to experimental data.

Table VI. Data for Application of Kinetic Curve-Fitting Technique for Calculation of Rate Constants for Exchange with Retention (k_1), Exchange with Inversion (k_2), and Isoinversion (k_3) for 2-Amide (**1**-*d*) and 3-Amide (**2**-*d*) in *tert*-Butyl Alcohol at 25.0 ± 0.1°[a]

Run no.	Substrate, *M*	Base, *M*	% react fol-lowed[a]	$10^5\theta$,[b] sec^{-1}	ϕ[c]	$10^5k_e^D$,[d] sec^{-1}	$10^5k_\alpha^H$,[e] sec^{-1}	ψ
62	(+)-**1**-*d*,[f] 0.0486	DBN, 0.190	69	0.875 ± 0.003	1.30 ± 0.10	0.253 ± 0.008	1.137 ± 0.034	0.025
63	(+)-**1**-*d*,[f] 0.0516	PMG,[g] 0.101	74	2.761 ± 0.014	1.79 ± 0.17	0.440 ± 0.012	5.812 ± 0.247	−0.011
64	(+)-**2**-*d*,[h] 0.0395	DBN, 0.124	76	3.864 ± 0.007	4.17 ± 0.20	1.470 ± 0.134	16.09 ± 1.09	0.049
65	(+)-**2**-*d*,[h] 0.0329	PMG,[g] 0.0366	65	3.321 ± 0.019	6.61 ± 0.22	1.285 ± 0.040	21.94 ± 0.89	0.038

[a] At least 18 points were taken in the calculation of ψ. [b] First-order rate constants for racemization of deuterated carbon acid at zero time with errors of one standard deviation. These constants were based on seven data points taken during the first 8% of reaction. [c] $(k^H/k^D)_\alpha$, Table VIII. [d] Calculated from first-order rate constants of runs 43, 47, 54, and 58, respectively, adjusted to the base concentration of runs 62–65, respectively. [e] Calculated from first-order rate constants of runs 41, 45, 52, and 57 adjusted to the base concentrations of runs 62–65, respectively. [f] $[\alpha]^{25}_{546}$ 33.7° (*c* 1.1, dioxane), optically pure, mp 127–128°, 0.96 atom of excess deuterium per molecule. [g] Pentamethylguanidine, 30 mol % in tetramethylurea. [h] $[\alpha]^{25}_{546}$ 8.7°, $[\alpha]^{25}_{436}$ 16.9° (*c* 1.0, dioxane), mp 88.0–89.5°, 0.98 atom of excess deuterium per molecule.

Table VII. Component Rate Constants[a] for Reactions of 2-Amide (**1**) and 3-Amide (**2**) in *tert*-Butyl Alcohol at 25°

Based on run	Carbon acid	Base	Technique	10^5k_1,[b] l. mol^{-1} sec^{-1}	10^5k_2,[c] l. mol^{-1} sec^{-1}	10^5k_3,[d] l. mol^{-1} sec^{-1}
62	(+)-**1**-*d*	DBN	Curve fitting	0.61 ± 0.06	0.72 ± 0.06	1.58 ± 0.33
63	(+)-**1**-*d*	PMG	Curve fitting	2.14 ± 0.21	1.83 ± 0.21	11.84 ± 2.88
66	(−)-**1**-*d*	PMG	Reresolution	2.87 ± 0.53	4.05 ± 0.81	10.60 ± 1.06
64	(+)-**2**-*d*	DBN	Curve fitting	5.16 ± 1.14	6.69 ± 1.14	8.89 ± 0.12
65	(+)-**2**-*d*	PMG	Curve fitting	15.84 ± 2.82	19.26 ± 2.82	26.10 ± 3.36

[a] Limits of error represent two standard deviations. [b] Isotopic exchange with retention. [c] Isotopic exchange with inversion. [d] Isoinversion.

Equation 1 expresses the rotational contribution,

$$\alpha_{\mathrm{exp}} = \alpha_{\mathrm{obsd}} - (f_{\mathrm{H}})(\alpha_0)e^{-k_\alpha^{\mathrm{H}}t} \tag{1}$$

α_{exp}, made by deuterated starting material to a reacting mixture at time t in terms of f_{H} (fraction of protonated material at time zero), α_0 (the observed rotation at time zero), and k_α^{H} (the first-order rate constant for racemization of the protiocarbon acid under the same conditions). In each run, values for α_{obsd} at time t were obtained with a recorder attached to a polarimeter. Values for k_α^{H} were calculated from appropriate runs of Table III by adjusting the values for the small changes in base concentration. The reactions were assumed to be first order in base, and the rotations of optically pure protio and deuterio substrates were assumed to be identical. In each run at least 18 points were taken, and α values calculated for each point.

Equation 2 expresses α in terms of the kinetic isotope

$$\alpha = \frac{\alpha_0}{(\phi - 1) + \psi}[(\phi - 1)e^{-\theta(1-\psi)t} + \psi e^{-\theta\phi t}] \tag{2}$$

effect for racemization, $\phi = (k^{\mathrm{H}}/k^{\mathrm{D}})_\alpha$, the first-order rate constant for racemization at zero time (θ), and a function ψ defined in eq 3. Typically, values of θ were

$$\psi = (k_2 - k_1)/2(k_2 + k_3) \tag{3}$$

determined from the first seven points taken during the first 8% of a particular run. No trends were visible in the data. Values of ϕ came from Table VI. Thus, all of the components of eq 2, except ψ, were available from direct experiments. Values of ψ were found with a computer program that estimated an initial value of ψ, and then calculated a set of theoretical rotations (α_{theor}) with eq 2. The sums of the squares of the differences between α_{exp} and α_{theor} were calculated. The computer program then continuously changed the values of ψ until the sums of the squares of the differences between α_{exp} and α_{theor} were minimized to present values. Table VI records the reaction conditions and the values of θ, ϕ, k_α^{H}, and ψ.

Once ψ was obtained by the above nonlinear least-squares method, the component rate constants (k_1, k_2, and k_3) were calculated with eq 4–6, and values of θ, ψ,

$$k_1 = (k_e^{\mathrm{D}} - \psi\theta)/2 \tag{4}$$

$$k_2 = (k_e^{\mathrm{D}} + \psi\theta)/2 \tag{5}$$

$$k_3 = (\theta/2) - k_2 \tag{6}$$

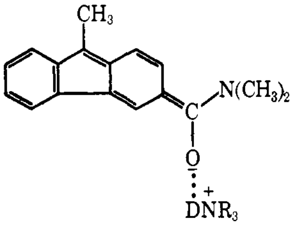
and k_e^{D}. Values of k_e^{D} were taken from appropriate runs of Table III adjusted to the base concentrations of runs 62-65 and are recorded in Table VI. The sensitivity of this curve-fitting technique is accentuated if α_{exp} follows a simple first-order decay. This condition applies if $\phi = 1$ (no isotope effect), or if $\psi = 0$ ($k_1 = k_2$), or if $\phi \gg \psi$. In runs 62–65, α_{exp} decay essentially was first order since $k_1 \sim k_2$ and $\phi > \psi$. Table VII gives the values of k_1, k_2, and k_3 obtained for runs 62–65.

The component rate constants (k_1, k_2, and k_3) also were obtained for the reactions in *tert*-butyl alcohol-PMG of the 2-amide (**1**) through use of the completely independent reresolution technique.[4c,f–h] In run 66, 97% optically pure (−)-**1**-*d* was partially racemized; the product was recovered and separated into racemate and enantiomer by fractional crystallization and manual separation of the crystals. The rotations of each were taken and the deuterium content was measured. From these data and the equations developed earlier,[6a] k_1, k_2, and k_3 were calculated, and Table VII records the results. The agreement between the two techniques is good for k_1 and k_3 (compare runs 63 and 66), but a little outside of probable error for k_2. Within error, for each technique, $k_1 \sim k_2$, and $k_3 > k_1$ or k_2. Thus, for runs

62–65, isoinversion dominates over retention or inversion with exchange, and the latter two components contribute about equally to the overall reaction. The overall agreement is good considering the large number of independently measured pieces of primary data that contribute to the final component rate constants.

Discussion

Correlation of Stereochemical Course of the Proton Transfer Reactions with Substituent Character and Position on Carbon Acids. Changes in the position and character of substituents in the fluorenyl system result in changes in the stereochemical reaction course of proton transfer reactions catalyzed by charge-localizing tertiary amines. Racemization with slight retention of configuration was observed for the 2-methyl, 3-iodo, 2-iodo, and 2-*N*,*N*-dimethylcarboxamido substituents, whereas the 2-cyano,[4d] 2-nitro,[4d] and 3-*N*,*N*-dimethylcarboxamido substituents gave isoinversion as the predominant reaction path. Thus, *substituents whose nature and (or) location provide good sites for delocalizing the charge of carbanions by conjugation are substituents that provide a path for isoinversion. In the absence of such a path, slight retention is observed.* This conclusion supports the conducted tour mechanism for isoinversion.[4d] This mechanism postulates achiral structures A, B, and C as part of the reaction coordinates for proton transfer with charge-localizing amines from the front to the back face of the carbanion.[6] Although structure D can be drawn for the 2-amido derivative, it seems to be too high energy to appear on the reaction coordinate.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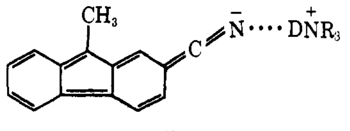
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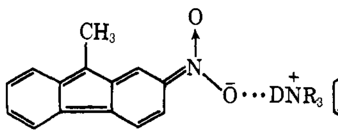
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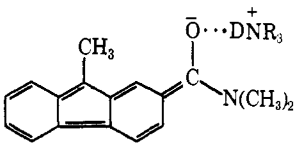
D

Isoinversion without a Conducted Tour Mechanism. When PMG or DBN were used as basic catalysts, isoinversion dominated the proton and deuteron transfer reactions. This result applied to compounds with the 2-amido, 3-amido, 2-methyl, and 2-iodo groups attached to the 9-methylfluorene ring system (**1**–**4**, respectively). Values of k_e/k_α for these compounds in *tert*-butyl alcohol were less than 0.5 for runs 1–9, 11–15, and 18–21 (Table I), and were less than 0.68 for all runs. No correlation of k_e/k_α values with the following factors is apparent: (1) the position or kind of substituent; (2) the absence or presence of common ion ammonium iodides; (3) the position of the isotopic label (carbon acid *vs.* *tert*-butyl alcohol). Particularly the 2-methyl substituent of compound **3** is incapable of distributing the negative charge of its derived carbanion. The 2-iodo substituent of compound **4** can only distribute negative charge through either involvement of d orbitals or σ bond polarization. These results demonstrate that when charge-delocalizing tertiary amines are employed, isoinversion is possible in carbon acids whose anions do not contain functional groups capable of distributing negative charge. Thus, a reaction path different from the conducted tour mechanism is required when *charges in both anion and cation of the ion pair intermediate are delocalized.* We will refer to this as the *nonstructured* isoinversion mechanism.

Characterization of the Nonstructured Isoinversion Mechanism. The detailed kinetic examination of the reactions of the 2-amide (**1**) and 3-amide (**2**) provides a means of characterizing the isoinversion reaction with the charge-delocalizing tertiary amine bases, PMG and DBN. The data of Table VII indicate that isoinversion (k_3) either dominates or is comparable to racemization with exchange ($k_1 + k_2$ when $k_1 \sim k_2$).

The activation parameters of Table V are quite different for racemization and for isotopic exchange. For example, at 25° with PMG and the 2-amide, $\Delta H_e^{\ddagger} - \Delta H_\alpha^{\ddagger} = -6.4$ kcal/mol and $\Delta S_e^{\ddagger} - \Delta S_\alpha^{\ddagger} = -24$ eu. With PMG and the 3-amide, $\Delta H_e^{\ddagger} - \Delta H_\alpha^{\ddagger} = -3.6$ kcal/mol and $\Delta S_e^{\ddagger} - \Delta S_\alpha^{\ddagger} = -14$ eu. Smid and coworkers[7] observed that at 24° the conversion of contact ion pairs of fluorenylsodium in tetrahydrofuran to solvent-separated ion pairs gave $\Delta H = -7.5$ kcal/mol and $\Delta S = -33$ eu. The similarity between our $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ values and the values of $\Delta\Delta H$ and $\Delta\Delta S$ for conversion of contact to solvent-separated ion pairs suggests that our transition state for racemization resembles a contact ion pair, and that for exchange a solvent-separated ion pair.

Another comparison is informative. The isotopic exchange and racemization of nitroamide **7** in tetrahydrofuran-*tert*-butyl alcohol at 25° catalyzed by *tripropylamine* were studied earlier,[4e] and $\Delta\Delta H^{\ddagger} = -3.4$ kcal/mol and $\Delta\Delta S^{\ddagger} = -15$ eu. The striking similarity of $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ values for the three carbon acids (**1**, **2**, and **7**) suggests similar mechanisms for isoinversion for the three systems. Of these, **7** was by far the most acidic kinetically, since the charge of the anion could be delocalized into both a carboxamido and nitro group. With **7**, the charge-localizing tripropylamine was used, but with **1** and **2**, charge-delocalizing

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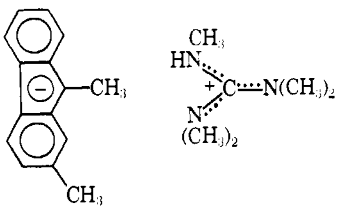
[6] Application of the method of L. A. Cohn and W. M. Jones [*J. Amer. Chem. Soc.*, **85**, 3397, 3402 (1963)] for breaking σ values into σ_R (through resonance) and σ_I (inductive effect) were applied to the pK_a data for 2-substituted fluorenes [K. Bowden, A. F. Cockerill, and J. R. Gilbert, *J. Chem. Soc. B*, 173, 179 (1970)]. The σ_2 values were calculated from a linear plot of ΔpK_a values against $\sigma_m + 0.5\sigma_p$ (Hammett σ values) and σ_3 values were assumed to correlate linearly with σ_p values. The σ_R values for the 2-methyl, 3-iodo, 2-iodo, and 2-carboxamido groups ranged from -0.09 to 0.18. The σ_R values for the 2-cyano, 2-nitro, and 3-carboxamido groups ranged from 0.33 to 0.42. The σ_I value for the 2-carboxamido substituent was 0.28, and that for the 3-carboxamido was 0.19, whereas those for the other substituents ranged between -0.07 and 0.71. The larger σ_R values correlate qualitatively with the ability of a substituent to provide an isoinversion result. Low σ_R values correlate with the inability of a substituent to provide an isoinversion result.

[7] T. E. Hogen-Esch and J. Smid, *J. Amer. Chem. Soc.*, **88**, 318 (1966).

amines were catalysts. Probably the pK_a differences between the carbon acids and the conjugate acids of the amine catalysts used were not far from one another, and this factor determined the lifetime and fate of the ion pair.

Isoinversion mechanisms at some point on their reaction coordinates involve a coplanar arrangement of the carbanion and ammonium ion. Although the ion pair could be hydrogen bonded at that point with **1**, **2**, or **7**, this would not have been possible with the 2-methyl system. The 2-methyl system **3** gave k_e/k_α values similar to those of the 2- and 3-amide systems. The coplanar ion pair for isoinversion of **3** cannot be hydrogen bonded, which fact suggests that hydrogen bonding in isoinversion of **1**, **2**, and **7** is not a *necessary condition for the isoinversion reaction.* However, these analogies do not explain the absence of an isoinversion component in the reactions of the 2-amide and the presence of one in those of the 3-amide when charge-localizing amines served as base. This contrast in result is best explained by the absence of a conducted tour path for the 2-amide and its availability for the 3-amide. The conducted tour mechanism invokes hydrogen bonding in the coplanar state, which automatically puts the two charges as close together as is structurally possible.



achiral contact ion pair

Correlation of Racemization Rates, Sizes of Isoinversion Components, and Kinetic Isotope Effects. Table VIII summarizes the data pertinent to this correlation. The racemization rates *increased* by an overall factor of 20 in the order, (2-amide, DBN) < (2-amide, PMG) < (3-amide, DBN) < (3-amide, PMG). The per cent contribution the isoinversion component made to the total racemization rate *decreased* by an overall factor of about 2 as the *rates increased.* Most striking is the *increase* in kinetic isotope effect by an *overall factor of 5* as the rates of racemization increased.

Table VIII. Relative Rates and Kinetic Isotope Effects for Racemization, and Sizes of Isoinversion Contributions to Racemization of Deuterated 2- and 3-Amides in *tert*-Butyl Alcohol at 25°

Carbon acid	Base	k_α^{rel}	% isoinversion component[a]	$(k^H/k^D)_\alpha$[b]
2-Amide, **1**-*d*	DBN[c]	1[d]	75	1.3[e]
2-Amide, **1**-*d*	PMG[f]	6[g]	54	1.8[h]
3-Amide, **2**-*d*	DBN[c]	7[i]	43	4.2[j]
3-Amide, **2**-*d*	PMG[f]	20[k]	43	6.6[l]

[a] 100 × $k_3/(k_1 + k_2 + k_3)$, Table VII. [b] Kinetic isotope effect for racemization. [c] 1,5-Diazabicyclo[4.3.0]non-5-ene, pK_a = ~13, ref 5d. [d] Runs 39 and 40, second-order rate constant set equal to unity. [e] Runs 39 and 41. [f] Pentamethylguanidine, pK_a = 13.8, ref 5c. [g] Run 44. [h] Runs 44 and 45. [i] Run 51. [j] Runs 51 and 52. [k] Run 55. [l] Runs 55 and 57.

Chart I. Mechanism for Isoinversion and Isotopic Exchange

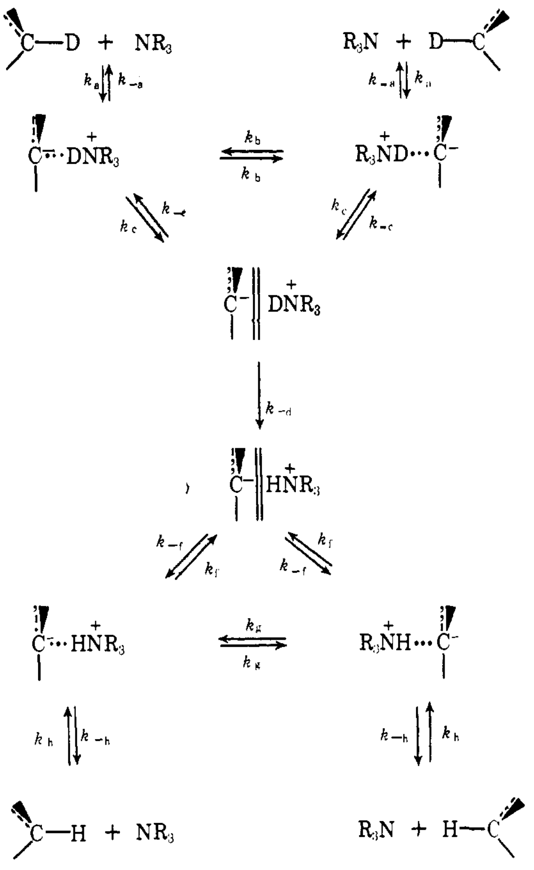


Chart I provides a mechanistic scheme developed previously for isoinversion of nitroamide **7** which satisfactorily accounts for this correlation. In this scheme, isoinversion involves a contact ion pair, and isotopic exchange goes through a solvent-separated ion pair (two bars between the ions). This picture is consistent with the more negative entropy of activation associated with isotopic exchange (see previous section) as compared to racemization. In Chart I, the ion pairs that exchange are formulated as symmetric. If hydrogen-deuterium exchange of a solvent-separated ion pair is much faster than its collapse to a contact ion pair, as is probable ($k_d \gg k_{-c}$), application of the steady-state approximation ($k_a \ll k_{-a}$, k_b, or k_c) gives eq 7 which expresses k_α

$$k_\alpha = \frac{k_a k_c}{k_{-a} + k_c} + \frac{2k_a k_{-a} k_b}{(k_{-a} + k_c)(k_{-a} + k_c + 2k_b)} \qquad (7)$$

in terms of k_a, k_{-a}, k_b, and k_c.

Two extreme conditions are envisioned. In the first $k_a \ll k_{-a}$, k_b, or k_c (steady-state approximation) and $k_{-a} \ll k_c$ or k_b. With this condition, $k_\alpha \cong k_a$ and a large kinetic isotope effect is possible. In the second, $k_a \ll k_{-a}$, k_b, or k_c (steady-state approximation), and $k_{-a} \gg k_b$ or k_c. With this condition, eq 7 reduces to 8,

$$k_\alpha = \frac{k_a}{k_{-a}}(2k_b + k_c) = K(2k_b + k_c) \qquad (8)$$

and a small isotope effect is possible.[8]

In Table VIII the ΔpK_a between the carbon acid and the conjugate acid of the basic catalyst undoubtedly decreases in the order listed. The observed increase in k_α^{rel} with the ΔpK_a decrease is expected. The larger the value of ΔpK_a, the larger the value of k_{-a} should be

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(8) D. J. Cram, D. A. Scott, and W. D. Nielsen, *ibid.*, **83**, 3696 (1961).

with respect to that for k_b or k_c, and the larger the value of k_b should be with respect to that for k_c. Thus, at the top of the table, the assumptions of eq 8 are the most applicable, the kinetic isotope effect is small (1.3), and the isoinversion component accounts for 75% of the total racemization rate ($k_b > k_c$). The smaller the ΔpK_a between carbon acid and the conjugate acid of the base, the smaller the value of k_{-a} should be with respect to that for k_b or k_c, and the smaller the value of k_b should be with respect to that for k_c. Thus, at the bottom of the table, k_α approaches k_a, the kinetic isotope effect is large (6.6), and the isoinversion component accounts for only about 43% of the racemization.

The results show that the kinetic isotope effect is much more sensitive to ΔpK_a change than is the relative size of k_b and k_c. In other words, k_{-a} changes much more than k_b or k_c. The binding energy between two ions of an ion pair is inversely proportional to the distance between the charges. The transition state defined by k_{-a} places the charges much closer together than those defined by k_b or k_c which are more comparable. Thus, k_{-a} should change more with changes in ΔpK_a than the relative values of k_b and k_c, as is observed.

Isotopic Exchange with High Retention of Configuration Catalyzed by Trace Amounts of Dipropylamine in Tripropylamine. All the runs of Table I that gave $k_e/k_\alpha > 10$ (23 and 31) were carried out with tripropylamine as base in the presence of about 10^{-3} *M* tripropylammonium iodide in *tert*-butyl alcohol at 175–200°. At the end of the runs, about 0.5% of the total amine present was dipropylamine. These runs involved compounds **1** and **4**. The high retention in these runs was demonstrated by the following experiments to have involved the dipropylamine as catalyst. Kinetic runs 36–38 (Table II) were carried out at 175 and 200° with 0.64 *M* tripropylamine contaminated with ~0.1% dipropylamine in the absence of salt. Values for k_e/k_α of about 10 were obtained. Runs 22, 24, 27, and 29 (carried out with triethylenediamine, free of secondary amine) on compounds **1**, **3**, and **4**, respectively, gave k_e/k_α values that ranged from 1.2 to 2.3. Clearly the traces of dipropylamine formed by decomposition of the salt (possibly by an S_N2 reaction) were the source of the high retention observed in runs 23 and 31. The value of $k_e/k_\alpha = 5.7$ reported previously (run 2, Table I)[4d] for the 2-amide ((−)-**1**-*d*) was possibly due to a trace of dipropylamine as well. Attempts to reduce the level of dipropylamine in tripropylamine to a level below 0.01% failed.

These experiments provide dramatic evidence that secondary amines induce rates of isotopic exchange many powers of ten faster than rates catalyzed by tertiary amines. That propylamine had this property was demonstrated in an earlier study.[4f] The explanations given for the retention in the earlier work with propylamine[4f] are equally applicable to the results of runs 23 and 31. The fact that tripropylamine probably catalyzed racemization confounds any further attempts at interpretation.

Experimental Section

General Procedures, Instrumentation, and Known Compounds. All melting points were taken on a Thomas-Hoover apparatus and were uncorrected. All optical rotations were measured on a Perkin-Elmer Model 141 polarimeter in a 1-dm cell thermostated at 25.0°. Deuterium analyses were performed by mass spectroscopy on an AEI MS 9 instrument at 9–12 eV. These analyses were accurate to ±0.02 atom of excess deuterium per molecule. Routine nuclear magnetic resonance (nmr) spectra were taken on the Varian AR-60 and A-60D machines, and infrared (ir) spectra were taken on the Beckman IR-5 spectrophotometer. The known compounds used here are referenced in the Results. Their physical properties and deuterium analyses are recorded in the footnotes of Tables I, II, III, and VI.

(−)-9-Deuterio-2-iodo-9-methylfluorene ((−)-**4**-*d*). To 0.5 g of the (+)-hydrochloride salt of (−)-2-amino-9-deuterio-9-methylfluorene,[4d] mp 240–244° dec, $[\alpha]^{25}{}_{546}$ +8.1° (*c* 0.4, acetone), was added 0.4 ml of concentrated hydrochloric acid. The solid was warmed to give a solution which was cooled to 0°. To the vigorously stirred solution was added dropwise a solution of 0.15 g of sodium nitrite in 1.0 ml of water until the reaction mixture gave a positive test for nitrous acid with iodine–starch paper. Then potassium iodide (0.38 g in 1.0 ml of water) was added by drops. The resulting solution was stirred at 25° and then heated at 100° for 5 hr. The reaction mixture was cooled and extracted with ether, and the ether solution was dried and evaporated. The residue was chromatographed on silica gel with pentane as eluent to give the desired product, (−)-**4**-*d:* wt 0.4 g (50%); mp 55–56°; $[\alpha]^{25}{}_{546}$ −31.7°; $[\alpha]^{25}{}_{436}$ −56.8° (*c* 1.0, dioxane); 0.96 atom of excess deuterium per molecule by mass spectrometry. *Anal.* Calcd for $C_{14}H_{10}DI$: C, 54.75; H and D, 3.88; I, 41.37. Found: C, 54.63; H and D, 3.88; I, 41.41.

By the same procedure, 0.5 g of racemic nondeuterated amine salt[4d] was converted to 0.35 g of (±)-**4**, mp 70–71°.

(−)-9-Deuterio-9-methyl-2-trimethylammoniumfluorene Iodide ((−)-**6**-*d*). A mixture of 0.30 g of (−)-2-amino-9-deuterio-9-methylfluorene,[4d] mp 62–64°, $[\alpha]^{25}{}_{546}$ −49° (*c* 1.2, dioxane), 1.5 g of methyl iodide, and 13 ml of absolute methanol was sealed in a heavy-walled glass tube and heated at 75° for 48 hr. The mixture was cooled, and diluted with copious amounts of ether. The precipitated salt was recrystallized from ether–ethanol to give a white solid: wt 0.45 g (80%); mp 169.5–170°; >0.90 atom of excess deuterium by nmr analysis; $[\alpha]^{25}{}_{546}$ −44° (*c* 1.2, dioxane). *Anal.* Calcd for $C_{17}H_{20}IN$: C, 55.75; H and D, 3.82; I, 34.65. Found: C, 55.75; H and D, 3.86; I, 34.33.

Nondeuterated (±)-**6** prepared by this procedure gave mp 153–154°.

(−)-2,9-Dimethylfluorene ((−)-**3**-*h*). A mixture of 1.00 g of (−)-2-carboxy-9-methylfluorene,[4d] mp 215–216°, $[\alpha]^{25}{}_{546}$ −39.5° (*c* 2.0, dioxane), 92% optically pure,[4d] and 2 ml of thionyl chloride was held at reflux for 1 hr. The excess thionyl chloride was removed by codistillation with added benzene portions. The residual yellow oil was diluted with 25 ml of dry xylene (molecular sieves), and mixed with 0.2 g of palladium–barium catalyst.[9] Hydrogen gas was passed into this mixture held at reflux for 24 hr. The mixture was filtered and concentrated and the residue chromatographed on silica gel with pentane as eluent. The product, (−)-**3**-*h*, gave: mp 42–44°; $[\alpha]^{25}{}_{546}$ −11.8°; $[\alpha]^{25}{}_{436}$ −19.6° (*c* 1.1, dioxane); 0.78 g (90%). *Anal.* Calcd for $C_{15}H_{14}$: C, 92.74; H, 7.26. Found: C, 92.67; H, 7.31.

(−)-9-Deuterio-2,9-dimethylfluorene ((−)-**3**-*d*). From 1.75 g of (−)-2-carboxy-9-deuterio-9-methylfluorene,[4d] mp 215–215.5°, $[\alpha]^{25}{}_{546}$ −38.7° (*c* 2.5, dioxane), 91% optically pure, 0.97 atom of excess deuterium per molecule, was prepared the corresponding acid chloride (see above procedure). Xylene, 25 ml dried over molecular sieves, 0.5 g of palladium–barium sulfate catalyst and 0.1 ml of sulfur–quinoline poison[10] were added to the acid chloride. The reaction mixture was stirred with hydrogen gas bubbling through it for 24 hr at 75°. The reaction mixture was filtered and concentrated and the residue chromatographed on silica gel with 10% ether–pentane as developer. The solid produced gave an nmr spectrum with a singlet at δ 10.6 (1 H) indicative of an aldehyde group. A mixture of 1.2 g of mossy zinc, 0.12 g of mercuric chloride, 0.1 ml of concentrated hydrochloric acid, and 1 ml of water was stirred for 5 min. The aqueous solution was decanted; the zinc amalgamate was covered with 1 ml of water, 0.2 ml of concentrated hydrochloric acid, 1 ml of toluene, and 1.0 g of the aldehyde. The solution was refluxed briskly for 9 hr, and every 3 hr 0.1 ml of concentrated hydrochloric acid was added. The product was extracted with ether and chromatographed on silica gel with pentane. The product, (−)-**3**-*d*, had: mp 43–44°; $[\alpha]^{25}{}_{546}$ −13.5°;

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(9) A. I. Vogel, "A Textbook of Practical Organic Chemistry," 3rd ed, Wiley, New York, N. Y., 1966, p 696.

(10) Reference 9, p 700.

$[\alpha]^{25}_{436}$ −21.3° (*c* 1.2, dioxane); 0.95 excess atom of deuterium per molecule (mass spectroscopy). *Anal.* Calcd for $C_{15}H_{13}D$: C, 92.27; H and D, 7.73. Found: C, 92.25; H and D, 7.68.

(−)-3-Iodo-9-methylfluorene ((−)-5). This synthesis resembled that used for (−)-**4**. Thus, 1.0 g of (−)-3-carboxy-9-methylfluorene,[4d] mp 180–181°, $[\alpha]^{25}_{546}$ −13.5°, $[\alpha]^{25}_{436}$ −27.3° (*c* 1.0, dioxane), was converted to 0.8 g (71%) of the carboxy azide (mp 71–73° dec, $[\alpha]^{25}_{546}$ −10.7°, *c* 1.1, dioxane). This material yielded 0.4 g (25% based on acid) of the hydrochloride salt of the amine (mp 260–265°, $[\alpha]^{25}_{546}$ −4°, *c* 0.1, methanol). This salt gave 0.14 g (10% based on acid) of (−)-**5**: mp 90–93°; $[\alpha]^{25}_{546}$ −5.7°, $[\alpha]^{25}_{436}$ −11.2° (*c* 1.2, dioxane). *Anal.* Calcd for $C_{14}H_{11}I$: C, 54.90; H, 3.60. Found: C, 54.78; H, 3.75.

General Procedures Used to Gather Data of Table I. All glassware used in this work, except the polarimeter cell, was cleaned with chromic acid, rinsed with water and dilute ammonium hydroxide solution, and dried in an oven at 120° for at least 12 hr. The polarimeter cell was thoroughly rinsed with solvent and dried with a stream of purified air before use. All optical rotations were measured on a Perkin-Elmer Model 141 polarimeter in a 1-dm cell thermostated at 25.0°. Rotations could be measured to $\alpha^{25}_{\text{obsd}}$ ±0.003°. Observed rotations were in the range of $\alpha^{25}_{\text{obsd}}$ 0.250–0.100° at 436 nm. A Lauda constant temperature bath Model NBS was used for temperature control. Absolute temperatures were determined by calibration with a National Bureau of Standards thermometer. The solvent, *tert*-butyl alcohol, was distilled from and stored over molecular sieves. The preparation of *tert*-butyl alcohol-*O-d* involved the formation of the *tert*-butyl orthoborate ester from boric acid and *tert*-butyl alcohol, and hydrolysis of the ester in deuterium oxide to give the deuterated alcohol.[11] It contained 0.98 atom of excess deuterium per molecule by nmr comparison of the hydroxyl protons and the ^{13}C satellite of the methyl groups. The DBN (Aldrich) was fractionally distilled from barium oxide; a center cut of constant boiling point 97–98° was collected. Pentamethylguanidine was prepared as before.[12] An nmr spectrum of the sample indicated that tetramethylurea was present also. Titration of a weighed sample of the base with standard aqueous hydrochloric acid showed 92 mol % pentamethylguanidine and 8 mol % tetramethylurea. Pentamethylguanidine hydriodide was prepared as previously reported.[4h] Tripropylamine was mixed with *p*-toluenesulfonyl chloride and molecular sieves, and was allowed to stand at 25° for 12 hr. The amine was flash distilled from the heterogeneous mixture, then fractionally distilled to give a constant boiling fraction at 156°. The infrared spectrum of the material indicated that less than 0.5% of propylamine and dipropylamine was present. Analysis by glc (F and M gas chromatograph machine using a 2-ft SE-30 on Chromosorb W column at 70° with a flow rate of 60 ml/min) coupled with comparisons with known mixtures demonstrated the presence of about 0.1% of dipropylamine. Triethylenediamine (TDA) was purified by sublimation at 35° *in vacuo*. The preparation of triethylenediamine dihydriodide was previously reported.[4h] Tripropylammonium iodide, prepared by conventional methods,[4h,e] contained within 1.5% the theoretical amount of iodide by Volhard titration. The hydriodide of DBN was prepared as follows. Hydriodic acid (Merck reagent, with preservatives) was added to 1 ml of DBN until the solution was acidic. The water was removed with an oil pump, while the last trace of it was removed by codistillation with benzene. The residue was evacuated for 12 hr. It was dissolved in absolute ethanol, dried over Drierite, allowed to stand for 1 hr, and filtered. The ethanol was concentrated under nitrogen to a volume of 2 ml. The ethanol solution was placed in a freezer, and the solid appeared. The solvent was decanted and the solid (very hygroscopic) was quickly washed with ice-cold ethanol and placed in an evacuated desiccator for 24 hr, mp 150–151°. *Anal.* Calcd for $C_7H_{13}N_2I$: C, 33.34; H, 5.19. Found: C, 33.48; H, 5.17.

Deuterium Analyses of Compounds 1–5 by Mass Spectrometry. All quantitative measurements were performed on an AEI MS-9 instrument at 12 eV, 8 accelerating kV, 20-μA trap current, and 0.0-V ion repeller using the direct insertion technique with the source temperature below 100°. The data were obtained with potentiometers and a 1-mV Leeds and Northrup recorder. The following relative peak intensities were found for **3**-*h*: *m/e* 195, 0.164;[13] *m/e* 194, 1.00; *m/e* 193, 0.0. With (−)-**3**-*d* (0.95 atom of excess deuterium per molecule) as starting material, the deuterium content of recovered **3** was determined with the following equations, where (195) and (194) were the peak heights obtained from the L&N recorder: $\%\,H = (194)/[(195) - 0.164(194) + (194)]$; $\%\,D = 1.00 - \%\,H$; $\%\,\text{exch} = 1.00 - (\%\,D/0.95)$.

All intensities were medians of ratios obtained from at least seven scans. The error in these medians is ±2%. After each analysis the mass spectrometer was baked out at least 6 hr because the samples had a strong affinity for the walls of the source of the mass spectrometer. For **4**-*h* and **5**-*h*, *m/e* 307, 0.153[13]; *m/e* 306, 1.00; *m/e* 305, 0.0. The equations used for determination of the amount of isotopic exchange for **4**-*d* and **5**-*d* are as follows: $\%\,H = (306)/[(307) - 0.153(306) + (306)]$; $\%\,D = 1.00 - \%\,H$; $\%\,\text{exch} = 1.00 - (\%\,D/\text{fraction atom of excess deuterium per molecule in starting material})$. When **4**-*h* was subject to exchange, the last equation was modified to $\%\,\text{exch} = \%\,D$.

When amides **1** and **2** were analyzed for deuterium, an electron beam of 9 eV was employed. Under these conditions, **1**-*h* and **2**-*h* gave the following intensities: *m/e* 252, 0.190;[13] *m/e* 251, 1.00; *m/e* 250, 0.0. The per cent exchange was calculated as follows: $\%\,H = (251)/[(252) - 0.19(251) + (251)]$; $\%\,D = 1.00 - \%\,H$; $\%\,\text{exch} = 1.00 - (\%\,D/\text{fraction atom of excess deuterium per molecule in starting material})$.

The more refined deuterium analyses of **1** and **2** required for the kinetic data of Table III and for run 66 were made as described above. The source temperature range was 90–110° for **1** and 115–135° for **2**. Data were obtained with potentiometers and a 1-mV Leeds and Northrup recorder.

Control Runs on the Isolation Procedure of Exchange Samples for Deuterium Analysis. The isolation of 9-methylfluorene derivatives from the reaction mixture for deuterium analysis may cause the carbon acid to fractionate into racemate and antipode each with a different amount of deuterium incorporation. This effect would cause an inhomogeneous sampling for the deuterium analysis. Therefore, controls were run on **1** which was known to fractionate upon recrystallization from acetone. If any of the 9-methylfluorene derivatives did fractionate, then **1** would have the highest likelihood of this behavior. Synthetic mixtures of 30 mg of *ca.* 90, 50, and 20% optically pure (−)-**1**-*h* were dissolved in ether and concentrated in the same manner exchange points were isolated. Specific rotations were taken on different portions of each sample. In each case, the specific rotations agreed within experimental error. For the *ca.* 90% mixture, the specific rotations were $[\alpha]^{25}_{546}$ −30.4° (*c* 1.1, dioxane) and $[\alpha]^{25}_{546}$ −30.7° (*c* 1.0, dioxane). Since this sampling technique for optical rotations did not result in fractionation, the sampling technique for deuterium analyses was free of fractionation.

Procedures Illustrative of Runs of Table I. Run 18. In a 2-ml volumetric flask, 12.4 mg of (−)-**4**-*d* was dissolved in *tert*-butyl alcohol with 2.6 × 10^{-3} *M* pentamethylguanidine hydriodide. Then 0.03 ml of PMG was added by syringe and the solution was mixed thoroughly. The solution was placed in a 25.0° thermostated bath, and a portion of the solution was placed in a 1-dm polarimeter cell. The loss of optical activity was recorded on a 1-mV Leeds and Northrup recorder connected to the digital readout of the polarimeter. The observed initial rotations were −0.130, −0.150, and −0.268° at 578, 546, and 436 nm, respectively. After the required reaction time, the observed rotations of the solution were −0.017, −0.023, and −0.044° at 578, 546, and 436 nm, respectively. The base concentration was determined by titrating known amounts of the reaction solution with 0.0976 *N* hydrochloric acid to a phenolphthalein end point. The remainder of the reaction mixture was quenched in a mixture of ether and 2 *N* hydrochloric acid. The organic layer was washed with more acid and water, dried (Na_2SO_4), and concentrated to give recovered **4**. This sample was submitted for deuterium analysis.

Runs 19–21. These runs resembled run 18 except that the DBN base was titrated to a Bromocresol Green end point.

Runs 1–6. For example, in run 4, 17.6 mg of (+)-**1**-*d* was dissolved in 2 ml of *tert*-butyl alcohol containing 1.4 × 10^{-4} *M* DBN hydriodide. Then 0.048 ml of DBN was syringed into the solution which was mixed thoroughly. The rest of the procedure resembled that of run 18.

Runs 7–12. For example, in run 12, 30.1 mg of (+)-**2**-*h* was dissolved in *tert*-butyl alcohol-*O-d*, 1.3 × 10^{-3} *M* in DBN deuterio-

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(11) A. T. Young and R. D. Guthrie, *J. Org. Chem.*, **35**, 853 (1970).

(12) H. Eilingsfeld, G. Neubauer, M. Seefelder, and H. Weidinger, *Chem. Ber.*, 97, 1323 (1964).

(13) J. H. Beynon and A. E. Williams ("Mass and Abundance Tables for Use in Mass Spectrometry," Elsevier, New York, N. Y., 1963) report 0.164 for naturally occurring abundance of isotopes in $C_{15}H_{14}$, 0.153 in $C_{14}H_{11}I$, and 0.191 in $C_{17}H_{17}NO$.

iodide. Then 0.03 ml of DBN was syringed into the solution, which was mixed thoroughly. The rest of the procedure resembled that of run 18.

Runs 13–17. For example, in run 13, 21.9 mg of (−)-**3**-*h* and base (0.15 ml of PMG) were dissolved in 2 ml of *tert*-butyl alcohol-*O*-*d*, 4.6×10^{-3} *M* in PMG deuterioiodide. An aliquot of the solution was placed in a 1-dm polarimeter cell thermostated at 25.0°. The observed rotations of the solution were −0.122, −0.206, and −0.309° at 546, 436, and 365 nm, respectively. The total solution was transferred to a 5-ml flask, sealed with a ground glass stopper, and placed in a 50° constant temperature bath. After the required reaction time, the flask was cooled to room temperature, and an aliquot was placed in the 1-dm polarimeter cell. The observed rotations of the reaction solution were −0.048, −0.077, and −0.119° at 546, 436, and 365 nm, respectively. The base concentration was determined by titrating aliquots of the solution with standard hydrochloric acid to a phenolphthalein end point. The remainder of the solution was quenched in a mixture of ether and 2 *N* hydrochloric acid. The organic layer was washed with additional acid and water, dried (Na_2SO_4), and concentrated to give recovered **3**. The remainder of the procedure resembled that of run 18.

Run 31. This run is typical for those in which tripropylamine and high temperatures were used. Carbon acid (−)-**4**-*d* (16.6 mg), 0.6 ml of tripropylamine (∼0.01% dipropylamine), and salt (0.52 mg of tripropylammonium iodide) were dissolved in 2 ml of *tert*-butyl alcohol. An aliquot of the solution was placed in a 1-dm polarimeter cell thermostated at 25.0°. The observed rotations of the solution were −0.152, −0.175, and −0.308° at 578, 546, and 436 nm, respectively. Then the total solution was placed in a heavy-walled tube, frozen in a Dry Ice–acetone bath, degassed twice under nitrogen, sealed under vacuum, and submerged in a 175.0 ± 0.2° constant temperature bath. After the required reaction time, the tube was cooled and opened at 25°. The rotations of the solution were taken, again in a 1-dm polarimeter cell thermostated at 25.0°. The observed rotations of this reaction solution were −0.146, −0.169, and −0.290° at 578, 546, and 436 nm, respectively. The tripropylamine concentration was determined by titration of three aliquots of the kinetic solution to the Bromocresol Green end point with 0.00976 *M* hydrochloric acid to give concentrations in the range of 0.260–0.263 *M* with an average of 0.261 *M*. The remainder of the reaction mixture was quenched in a mixture of ether and 2 *N* hydrochloric acid. The organic layer was washed with more acid and water, dried (Na_2SO_4), and concentrated to give recovered **4**. This sample was submitted for deuterium analysis.

Run 32. In 1 ml of *tert*-butyl alcohol-*O*-*d* was dissolved the appropriate amount of triethylenediamine, the corresponding deuterioiodide salt, and 10.1 mg of (−)-**5**-*h*. The reaction was carried out and the product isolated and analyzed as in run 31.

Run 22. Carbon acid, 15.6 mg of (−)-**1**-*d*, $[\alpha]^{25}{}_{546}$ −32.7° (*c* 1.3, dioxane), was dissolved in 2.0 ml of *tert*-butyl alcohol containing 33 mg of TDA. The reaction mixture was placed in a heavy-walled tube, frozen, degassed twice, sealed under vacuum, and heated to 175°. The reaction was quenched at −78°, the tube was opened, and its contents were poured into 2 *N* hydrochloric acid. The substrate was extracted with two portions of ether. The combined organic layers were washed twice with water, dried, and concentrated. The recovered **1** was chromatographed on silica gel using 50% ether-pentane as eluent. The specific rotation of the material corresponded to 24% racemization.

Run 33. In a 5-ml volumetric flask, 80.8 mg of (−)-**6**-*d* was dissolved in 1.25 ml of dimethyl sulfoxide. A solution of tripropylamine (0.01% dipropylamine) in *tert*-butyl alcohol was added to the 5-ml mark. The solution was mixed thoroughly and placed in a 25° bath. A portion of the solution was placed in a polarimeter cell. The initial observed rotation was 0.625° at 546 nm. The loss of optical activity was recorded on an 1-mV Leeds and Northrup recorder attached to the polarimeter. After the appropriate reaction time, when the observed rotation of the solution was 0.200° at 546 nm, aliquots of the solution were titrated with standard hydrochloric acid to a Bromocresol Green end point. The remainder of the solution was added to copious amounts of ether, filtered, and dried under high vacuum. The solid was mixed thoroughly to ensure the homogeneity of the sample, and a portion of the recovered sample was used for deuterium analysis.

Deuterium Analysis of 6. In an nmr tube, 16.6 mg of **6** from run 33 was dissolved in deuterated dimethyl sulfoxide, and an HA-100 spectrum was taken at spectrum amplitude 10,000, sweep width 500, and offset 50 with lock on TMS. The protio quartet centered at δ 4.15 overlapped the shoulder of the trimethyl singlet for the ammonium moiety at δ 3.75, making integration meaningless. A base line was drawn maximizing the area of the quartet, and this area was compared to the C-9 methyl multiplet at δ 1.6 by the cut and weigh technique. The extent of exchange was 69 ± 10%.

A spectrum of 20 mg of the starting material, (−)-**6**-*d*, was taken on the HA-100 with spectrum amplitude 800, sweep width 500 with the lock on TMS, and no protio quartet was visible nor were there shoulders on the methyl singlet at δ 1.6. The estimated sensitivity is ±10% H; thus, the starting material was at least 90% D.

Control Run Demonstrating Generation of Dipropylamine When Tripropylammonium Iodide Is Heated in *tert*-Butyl Alcohol. An aliquot of a stock solution of 0.8 mg of tripropylammonium iodide (5.9×10^{-4} *M*) in 5 ml of *tert*-butyl alcohol with 227.4 mg of tripropylamine was placed in a heavy-walled tube. The solution was frozen in a Dry Ice–acetone bath, degassed twice under nitrogen, sealed *in vacuo* and submerged in a 175° constant temperature bath for 43 hr. Then the tube was cooled to 25° and opened. Analysis of the reaction mixture by glc (F and M gas chromatograph machine using a 2-ft SE-30 on Chromosorb W column at 70° with a flow rate of 60 ml/min) coupled with calibration runs with known mixtures demonstrated the presence of 0.1% dipropylamine, a tenfold increase in dipropylamine concentrations. As little as 0.005% dipropylamine in tripropylamine could be detected.

Procedures Illustrative of the Kinetic Runs of Table II. Runs 36 and 37. A solution of 196.1 mg of (−)-**1**-*d* in *tert*-butyl alcohol containing 0.635 *N* tripropylamine (0.01% dipropylamine) was prepared in a 25.0-ml volumetric flask. The observed rotation was −0.335 at 436 nm in a 1-dm polarimeter cell. A pipet was used to transfer 2-ml aliquots of solution into heavy-walled tubes. These tubes were stoppered with septum caps, frozen in a Dry Ice–acetone bath, sealed under high vacuum, and placed in a constant temperature bath held at 200.0 ± 0.2°. The tubes were removed at appropriate times, cooled to 25°, and opened, and rotations taken. The data gave a least-squares rate constant with standard deviation of $7.11 \pm 0.07 \times 10^{-6}$ for five points. For the exchange rate, additional tubes were removed at appropriate intervals. Each tube was cooled and opened at 25°. The contents of the tube were poured into a solution of 2 *N* hydrochloric acid and ether. The ethereal extract was washed with acid and water, dried, and concentrated to give solid **1**. Each point was analyzed for deuterium in the same manner as described previously for **1**. The data gave a least-squares rate constant for exchange with a standard deviation of $7.334 \pm 0.149 \times 10^{-5}$ for five points. The base concentration was determined at different intervals during the run by titrating a known amount of the reaction mixture with standard acid to a Bromocresol Green end point. In every case, the concentrations were the same within an experimental error of ±2%.

Procedures Illustrative of the Kinetic Runs of Table III. Run 39. A solution of the 19.9 mg of (+)-**1**-*d* was dissolved in 2 ml of *tert*-butyl alcohol. Then 0.03 ml of DBN was added, the mixture was shaken, and the solution transferred to a 1-dm polarimeter cell which was thermostated by water circulating from a bath held at 25.0°. A 1-mV Leeds and Northrup recorder connected to the polarimeter was used to collect data on which 1 in. of chart paper corresponded to 0.020°. The noise level of the polarimeter reproduced on the recorder was ±0.002°. The initial observed rotation of $\alpha^{25}{}_{\mathrm{obsd}}$ +0.294° was recorded, and it changed during reaction to a final rotation of $\alpha^{25}{}_{\mathrm{obsd}}$ +0.093 at 436 nm. After all the data were recorded, the DBN concentration was determined by titrating at least two aliquots to a Bromocresol Green end point with standard hydrochloric acid. A linear least-squares computer program provided a rate constant whose standard error is based on one standard deviation.

Run 47. A solution of 158.1 mg of (±)-**1**-*d* in 19.6 ml of *tert*-butyl alcohol was prepared in a tightly glass-stoppered 25-ml flask. With a graduated syringe, 0.4 ml of PMG was added. The mixture was immediately shaken until the solution was homogeneous, and the flask was placed in a thermostated 25.0° bath. Aliquots were withdrawn at appropriate times and shaken with 1 *N* hydrochloric acid and ether. The ethereal solution was washed with 1 *N* hydrochloric acid and water, dried with magnesium sulfate, and evaporated to recover the residue. Intermittently, aliquots were titrated with 0.0976 *N* hydrochloric acid to the phenolphthalein end point to determine the base concentration. Three aliquots were titrated during the run, and the base concentrations were the same within an experimental error of ±1%. After drying the residue at 1 mm, 12 hr, in a desiccator, the sample was submitted for mass spectroscopy to determine the amount of deuterium. A least-squares computer program provided a rate constant with standard error based on one standard deviation. In each case, at least six points were used to determine the pseudo-first-order rate constant, and no deviation from the first-order kinetics was observed.

Run 54. The general procedure of run 47 was utilized with 149.1 mg of (±)-**2**-*d*, 0.3 ml of DBN, and 19.7 ml of *tert*-butyl alcohol.

Run 55. The general procedure of run 39 was followed utilizing 16.6 mg of (+)-**2**-*d*, 0.015 ml of PMG, and 2 ml of *tert*-butyl alcohol. The initial observed rotation was $\alpha^{25}_{\text{obsd}}$ +0.195° and the final was $\alpha^{25}_{\text{obsd}}$ +0.071° at 436 nm.

Run 61. To a solution of 110 mg of (±)-**2** in 10 ml of *tert*-butyl alcohol was added 0.04 ml of PMG. The solution was mixed thoroughly and placed in a thermostated bath at 49.8°. Aliquots were withdrawn at appropriate times and shaken with 2 *N* hydrochloric acid, ether, and a trace of methanol. Subsequent procedures followed the pattern of run 47.

Run 60. To a solution of 22.1 mg of (+)-**2**-*d* in 2 ml of *tert*-butyl alcohol was added 0.003 ml of PMG. The solution was mixed thoroughly, and a portion was transferred to a 1-dm polarimeter cell which was thermostated by water circulating from a 51.1° bath. The temperature of the water was measured immediately after leaving the polarimeter cell at 50.9°. The initial observed rotation was $\alpha^{50.9}_{\text{obsd}}$ +0.198°, and the final observed rotation was $\alpha^{50.9}_{\text{obsd}}$ +0.029° at 436 nm. Subsequent procedures for recording data and determining base concentration were patterned after run 39.

Run 49. The procedure of run 60 was applied to 22.0 mg of (−)-**1**-*d* in 2 ml of *tert*-butyl alcohol followed by 0.012 ml of PMG. The initial observed rotation was $\alpha^{49.4}_{\text{obsd}}$ −0.490°, and the final observed rotation was $\alpha^{49.4}_{\text{obsd}}$ −0.092° at 436 nm.

Kinetic Components of Isotopic Exchange–Racemization Reactions by the Reresolution Technique. Run 66. The procedure as applied to (+)-**1**-*d* reactions in methanol–potassium methoxide has been detailed elsewhere.[4c] Only an outline is given here. A solution of 320.1 mg of (−)-**1**-*d* ($[\alpha]^{25}_{546}$ −32.7° (*c* 1.3, dioxane), containing 0.96 atom of excess deuterium per molecule) in 25 ml of *tert*-butyl alcohol was thermostated at 25.0°. By a graduated syringe, 0.4 ml of PMG was added and the solution was mixed thoroughly. A portion of the solution was transferred to a thermostated polarimeter cell. When the rotation decreased to $\alpha^{25}_{\text{obsd}}$ −0.292° from an initial rotation of $\alpha^{25}_{\text{obsd}}$ −0.579° at 546 nm the solution was quenched with hydrochloric acid. Aliquots from the polarimeter cell were titrated with standard hydrochloric acid to a phenolphthalein end point to give a base concentration of 0.105 *M*. The quenched mixture was extracted with ether. The combined ether solutions were washed with water, dried (Na_2SO_4), and concentrated to 275 mg of a dry, white solid A. An ir spectrum of solid A showed the typical absorption spectrum of **1** and no spurious absorptions. This material was subjected to fractional crystallizations in reagent grade acetone. Rotations were taken in dioxane at 546 nm and 25.0°. Recrystallization of solid A gave 50 mg of solid B having $[\alpha]^{25}_{546}$ +0.53° (*c* 1.1, dioxane), mp 132–133° (racemic **1**, lit.[4b] mp 133–134°). From the mother liquors of B, 150 mg of solid C was recovered. Solid C contained two distinct types of crystal structures. These structures were separated manually into prisms D having $[\alpha]^{25}_{546}$ − 16.1° (*c* 1.12, dioxane) and plates E having $[\alpha]^{25}_{546}$ −31.3° (*c* 1.6, dioxane). Recrystallization of the plates E gave solid F having $[\alpha]^{25}_{546}$ −31.4° (*c* 1.65, dioxane) (95% optically pure), mp 126–128° (optically pure **1**, lit.[4b] mp 127–128°, $[\alpha]^{25}_{546}$ +33.7°, *c* 1.1, dioxane). Solids B and F contained 0.76 and 0.88 atom of excess deuterium per molecule, respectively, by mass spectrometry using the direct insertion technique. The values of k_1, k_2, and k_3 were calculated from the above data with the method detailed previously,[4c] and they are recorded in Table VII.

Kinetic Runs of Table VI. Runs 62–65 were identical with runs 39, 44, 51, and 55, respectively, except the former runs involved many more data points.

Base-Catalyzed Nucleophilic Substitutions at Pentacoordinated Phosphorus

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Abstract: The alkoxy groups that occupy the equatorial positions in the trigonal-bipyramidal pentacoordinated phosphorus atom of four-membered cyclic tetraoxyalkylphosphoranes are replaced by the alkoxy groups of alcohols, under base catalysis. Analogous base-catalyzed nucleophilic substitutions are reported for five-membered cyclic unsaturated pentaoxyphosphoranes. The rings are preserved in these substitutions. The relative rates of (a) the substitution reactions and (b) the permutational isomerizations of the trigonal-bipyramidal oxyphosphoranes determine the course of the substitutions. The reactions of phosphonites, $RCH_2P(OCH_3)_2$, of phospinites, $(RCH_2)_2P(OCH_3)$, and of tertiary phosphines, $(RCH_2)_3P$, with highly electrophilic carbonyl compounds, *e.g.*, hexafluoroacetone, constitute a general synthesis of 1,2-oxaphosphetanes with pentacoordinated phosphorus.

This investigation is concerned with the mechanism of nucleophilic substitutions at the pentacoordinated phosphorus of the 1,2-oxaphosphetane ring system,[2] *e.g.*, **1** + R^{V}OH → **2** + R′′′OH; see Chart I.

We are also concerned with substitutions at the pentacoordinated phosphorus of the 1,3,2-dioxaphospholene ring system,[3] *e.g.*, **3** + R′′′OH → **4** + R′′OH; see Chart II.

The four-membered cyclic oxyphosphoranes required in this research have four or three oxygen atoms attached to the phosphorus, **1**, **2**, or **5**, respectively. Previous work from this laboratory[2] has shown that the reaction of tertiary phosphines, *e.g.*, **6** (Chart III), with hexafluoroacetone (**7**) gives derivatives of the 1,3,2-dioxaphospholane ring system, **8** (Chart IV), which can be transformed into oxaphosphetanes with two oxygen atoms attached to the phosphorus, **9** (Chart I). The overall reaction **6** + **7** → **8** → **9** proceeds in excellent yields, and the dioxyphosphetanes **9** are remarkably stable. The cyclic intermediates in the usual variation of the Wittig olefin synthesis[4] are

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[2] (a) F. Ramirez, C. P. Smith, J. F. Pilot, and A. S. Gulati, *J. Org. Chem.*, 33, 3787 (1968); (b) F. Ramirez, C. P. Smith, and J. F. Pilot, *J. Amer. Chem. Soc.*, 90, 6726 (1968).

[3] F. Ramirez, K. Tasaka, N. B. Desai, and C. P. Smith, *ibid.*, 90, 751 (1968).

[4] (a) G. Wittig and U. Schollkopff, *Chem. Ber.*, 87, 1318 (1954);