5-Methyltetrahydrothiophene-2-carboxylic Acid 1-Dioxide (V). Into a stirred solution of 25 g of sodium hydroxide in 210 ml of water was poured 80.7 g of the above ester in a thin stream. Stirring was continued for 45 min; 60 ml of 96% sulfuric acid was added slowly with ice-bath cooling, and the acidic solution was saturated with sodium chloride. Continuous extraction of the solution with chloroform for 48 hr yielded after evaporation of solvent 68 g (99%) of V as a semisolid.

Racemate A of 5-Methyltetrahydrothiophene-2-carboxylic Acid 1-Dioxide (V). The mixture of racemates obtained above was dissolved in 300 ml of boiling chloroform, and hexane was added until the solution was nearly saturated at the boiling point of the mixture. The solution was allowed to cool open to the atmosphere, and a crop of white crystals separated which was recrystallized twice from chloroform, 26 g, mp 121–124°. The nmr spectrum of the recrystallized acid (V-A) contained only one doublet for the methyl group (τ 8.80, J = 6.5 cps), whereas the spectrum of the crude mixture of racemates contained a closely spaced double doublet (τ 8.80, J = 6.5 cps and τ 8.63, J = 6.0 cps). Attempts to resolve this material through its brucine salt were only partially successful.

(+)-5-Methyltetrahydrothiophene-2-carboxylic Acid 1-Dioxide of Racemate B ((+)-V-B). A solution of 42.7 g of V (composition: about 14.9 g of racemate A and 32.3 g of racemate B, nmr analysis) and 104 g of brucine in 236 ml of hot water was prepared. After standing at 25° for 12 days, a crystalline salt began to separate; an additional two weeks was required before separation of the salt ceased, 39.7 g (26.2%). The derived acid recovered after an additional crystallization of the salt from water displayed $[\alpha]^{26}_{546}$ +34.2° (*c* 5.1, chloroform). A third crystallization of the salt gave recovered acid of $[\alpha]^{28}_{546}$ +34.9° (*c* 4.9, chloroform); a fourth crystallization of the salt yielded acid of $[\alpha]^{26}_{546}$ +34.4° (*c* 4.9, chloroform). The salt thrice crystallized as above, 7.35 g, was dissolved in 100 ml of warm water and a solution of 7 g of potassium carbonate in 15 ml of water was added. Precipitation of brucine was complete within 15 min. The slurry was filtered, reduced in volume to 25 ml under vacuum, and filtered. The solution of the potassium salt of (+)-V-B was acidified with sulfuric acid and continuously extracted with chloroform for 48 hr. Recovered (+)-V-B, 1.356 g, $[\alpha]^{28}_{546}$ +34.9° (*c* 4.9, chloroform), mp 79–81°, was recrystallized from ether–pentane, 1.21 g, $[\alpha]^{26}_{546}$ +35.1° (*c* 4.9, chloroform), mp 79.5–81°. An additional crystallization of the substance did not change these properties. *Anal.* Calcd for $C_6H_{10}SO_4$: C, 40.46; H, 5.61; S, 17.96. Found: C, 40.53; H, 5.68; S, 17.67.

Decarboxylation of (+)-5-Methyltetrahydrothiophene-2-carboxylic Acid 1-Dioxide ((+)-V-B). A solution of 0.388 g of optically pure (+)-V-B, $[\alpha]^{25}_{546}$ +35.1° (*c* 4.9, chloroform), and 0.137 g of the ammonium salt of optically pure (+)-V-B, $[\alpha]^{25}_{546}$ +23.61° (*c* 0.66, water), was prepared in 10 ml of water. The solution was placed in an ampoule which had been thoroughly purged with nitrogen. The ampoule was sealed and placed in a constant-temperature bath at 164° for 72 hr. After this time, the ampoule was opened, and its contents were removed. Water was evaporated under reduced pressure, leaving a viscous oil which was taken up in 20 ml of methanol–ether. Ammonia gas was bubbled into the solution for 30 min to convert excess acid to the ammonium salt. The solvent was removed under reduced pressure, and the residue was extracted with two 30-ml portions of boiling ether. The solid ammonium salt remaining after extraction exhibited $[\alpha]^{25}_{546}$ +23.40° (*c* 0.64, water), 0.324 g. Decarboxylation thus proceeded to 43% of completion. Since only 25 mole % ammonium salt was employed as base, the decarboxylation reaction mixture was always acidic. Thus, the product could not have been partially racemized.

The ether extracts were evaporated yielding an oil which was chromatographed on a 1 × 30 cm column of silica gel with ethyl ether–pentane, 70:30, as eluent. The sulfone, optically pure (+)-IV, purified by chromatography, 0.120 g, exhibited $[\alpha]^{25}_{546}$ +11.80° (*c* 3.5, ethanol). The infrared and nmr spectra of this substance were identical with those of (+)-IV obtained by decarboxylation of 2-methyltetrahydrothiophene-2-carboxylic acid 1-dioxide and to those of racemic IV obtained *via* an independent synthesis reported above.[21a]

Electrophilic Substitution at Saturated Carbon. XXXIV. Isoinversion as a Mechanistic Component in Base-Catalyzed Hydrogen–Deuterium Exchange between Carbon Acids and Medium[1]

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Abstract: Analysis of the over-all stereochemical course of base-catalyzed hydrogen–deuterium exchange reactions of carbon acids in terms of mechanistic components is provided by a kinetic model. Rate constants for exchange with retention of configuration, exchange with inversion, and isoinversion (defined as inversion without exchange) have been determined for exchange of I-H_+ in methanol-O-*d* with potassium methoxide at 25° by two experimentally independent methods based on the model. One method used only kinetics, and the other used reresolution of partially racemized material. Exchange of I-D_+ in *t*-butyl alcohol with potassium phenoxide was also investigated by the latter method. Isoinversion is shown to be a contributing mechanistic component in both media. Primary substrate and solvent isotope effects on racemization of I are reported. The results are interpreted by a mechanism in which carbanions are tightly hydrogen bonded to just one solvent molecule at a time.

The stereochemical courses of hydrogen–deuterium exchange reactions of carbon acids have been divided into four categories on the basis of their k_e/k_α (rate constant for exchange over that for racemization) values: exchange with net retention ($k_e/k_\alpha > 1.0$), exchange with total racemization ($k_e/k_\alpha = 1.0$), exchange with net inversion ($0.5 \leq k_e/k_\alpha < 1.0$), and isoracemization (defined as racemization without exchange,

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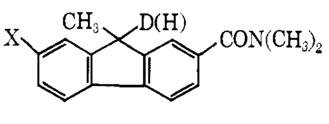
[1] (a) This research was sponsored by the U. S. Army Research Office, Durham, N. C. (b) Preliminary results of the work reported here have appeared in communication form: W. T. Ford, E. W. Graham, and D. J. Cram, *J. Am. Chem. Soc.*, **89**, 689, 690 (1967).

[2] National Science Foundation Trainee, 1965–1966.

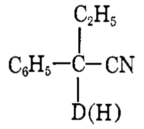
$k_e/k_\alpha < 0.5$). Examples in each category have been identified by relative values of one-point rate constants for exchange and racemization of carbon acids in a variety of solvent–base media.[3]

However, the mechanisms which produce the over-all stereochemical results of isotopic exchange are less well defined. Clearly, $k_e/k_\alpha > 1.0$ indicates that a mechanism of exchange with retention is important, but other mechanisms are competitive because the limiting k_e/k_α value of infinity has never been attained. Similarly, $k_e/k_\alpha < 0.5$ indicates that an isoinversion (inversion without exchange) mechanism is important, but the limiting k_e/k_α value of zero has never been attained. More ambiguous is $k_e/k_\alpha = 1.0$, a result that could be ascribed to a combination of retention and inversion mechanisms as well as a total racemization mechanism. The wealth of examples of $k_e/k_\alpha = 1.0$ now in the literature makes it unlikely that more than a small fraction of them are due to a fortuitous combination of mechanisms. Most ambiguous is $0.5 \leq k_e/k_\alpha < 1.0$, a result that could be due to any of several combinations of two or more mechanistic pathways. In all reported base-catalyzed hydrogen–deuterium exchange reactions that occurred with some stereospecificity, there were processes competing with the one which caused the net stereochemical result.[3]

The solvent and base employed have a profound influence on the course of isotopic exchange. Exchange of (−)-2-(N,N-dimethylcarboxamido)-9-methylfluorene-9-*d* (I-D₋) proceeded with net retention with amine and potassium alkoxide bases in the relatively nonpolar solvents *t*-butyl alcohol, benzene, phenol, and tetrahydrofuran.[4] Isoracemization of (+)-2-(N,N-dimethylcarboxamido)-7-nitro-9-methylfluorene-9-*d* (II-D₊) and of (+)-2-phenylbutyronitrile-2-*d* (III-D₊) occurred in *t*-butyl alcohol and in *t*-butyl alcohol–tetrahydrofuran mixtures with tri-*n*-propylamine as base.[5] The intermediate near-planar carbanions were said to exist in the form of ion pairs when amines were used as bases, or in the form of hydrogen-bonded anions when alkoxides were used as bases. In either case the mechanistic intermediates involved in isoracemization and exchange with retention were thought to be highly structured because of low solvent polarity. In contrast, exchange of I-D₋ with total racemization occurred in relatively polar solvents, ethylene glycol, methanol, and dimethyl sulfoxide, with alkoxides and ammonia as bases.[4] The total racemization was attributed to the ability of polar solvents to disperse charge and consequently promote destruction of asymmetrically solvated carbanionic species.[4]



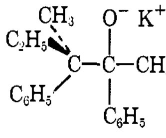
I, X=H
II, X=NO$_2$



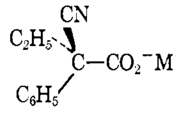
$C_6H_5-\overset{C_2H_5}{\underset{D(H)}{C}}-CN$

III

A mechanism of inversion with exchange was assigned to exchange of I-D₋ with tri-*n*-propylamine in methanol and with potassium methoxide in methanol.[4] The values of $k_e/k_\alpha \sim 0.7$ (one-point rate constants) were attributed to the ability of methanol to solvate charged species. Evidence for an inversion mechanism had previously been found in electrophilic substitutions with carbon leaving groups in polar solvents. For example, cleavage of the potassium salt of (+)-2,3-diphenyl-3-methyl-2-pentanol (IV) to 2-phenylbutane proceeded with 42% inversion of configuration in methanol,[6] and decarboxylation of salts of (−)-2-cyano-2-phenylbutyric acid (V) in ethylene glycol proceeded with 11% inversion.[7] The inversion-with-exchange mechanism for isotopic exchange was then formulated by analogy rather than with distinct experimental proof. In this paper we will show that the net inversion ($k_e/k_\alpha = 0.92$) in exchange of I-H₊ with potassium methoxide in methanol-O-*d* is due entirely to an intramolecular rather than an intermolecular inversion pathway in the mechanism for exchange.



IV



V

Kinetic Model for Hydrogen–Deuterium Exchange.[8] All processes which may occur during exchange of an optically active carbon acid (H₊) are defined in Chart I. In this scheme, the H or D refers to the isotope and the + or − to the sign of rotation of the carbon acid. The mechanism is identified by the rate constants: k_1 (exchange with retention), k_2 (exchange with inversion), k_3 (isoinversion), and k_4 (inversion of exchanged material). In this model, total *racemization with exchange* is composed of equal contributions from the processes governed by k_1 and k_2. The model assumes that material once deuterated never is reprotonated. If solvent contains more than 99% deuterium at its exchangeable positions, then the protons lost by substrate become drowned in the large deuterium pool. Equations 1–4 are the first-order rate expressions resulting from our definition of the model, where [H₊] represents the mole fraction of protio dextrorotatory material in the substrate. The simultaneous differential eq 1–4 are solved to give eq 5–8 which express the concentrations of each species in the substrate mixture in terms of rate constants and time, and where $\beta = k_1 + k_2$ and $\gamma = k_1 + k_2 + 2k_3 = \beta + 2k_3$.

Chart I. Processes Involved in Isotopic Exchange

$$\begin{array}{ll}
H_+ \xrightarrow{k_1} D_+ & H_- \xrightarrow{k_2} D_+ \\
H_+ \xrightarrow{k_2} D_- & H_- \xrightarrow{k_3} H_+ \\
H_+ \xrightarrow{k_3} H_- & D_+ \xrightarrow{k_4} D_- \\
H_- \xrightarrow{k_1} D_- & D_- \xrightarrow{k_4} D_+
\end{array}$$

$$d[H_+]/dt = -(k_1 + k_2 + k_3)[H_+] + k_3[H_-] \quad (1)$$

$$d[H_-]/dt = -(k_1 + k_2 + k_3)[H_-] + k_3[H_+] \quad (2)$$

$$d[D_+]/dt = k_1[H_+] + k_2[H_-] + k_4[D_-] - k_4[D_+] \quad (3)$$

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[3] For a review, see D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York, N. Y., 1965, Chapter 3.

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

[5] D. J. Cram and L. Gosser, *ibid.*, **86**, 2950, 5457 (1964).

[6] D. J. Cram, A. Langemann, and F. Hauck, *ibid.*, **81**, 5750 (1959).

[7] D. J. Cram and P. Haberfield, *ibid.*, **83**, 2354 (1961).

[8] Further details of the derivation are available from E. W. G.

Table I. Racemization and Exchange Kinetics of 0.060 *M* I-H(D)$_+$ in Methanol-O-*d*(*h*)[a] with Potassium Methoxide at 24.9 ± 0.1°

Run	Subst	Solv	[KOCH$_3$], *M*	Process	$k_1 \times 10^5$, sec^{-1} [b]	$k_2 \times 10^4$, l. mole^{-1} sec^{-1} [c]
1	H	H	0.0412	Racemization[d]	12.01 ± 0.01	29.2 ± 0.3
2	H	H	0.0730	Racemization[d]	21.2 ± 0.1	28.9 ± 0.3
3	H	H	0.0961	Racemization[d]	27.6 ± 0.1	28.7 ± 0.3
4	D	H	0.0794	Racemization[d]	3.44 ± 0.01	4.34 ± 0.13
5	D	D	0.0777	Racemization[d]	7.86 ± 0.01	10.12 ± 0.11
6	H	D	0.0739	Racemization[d]	48.5 ± 0.6	65.7 ± 1.5
7	H	D	0.0589	Exchange[e]	36.4 ± 0.8	61.8 ± 2.0
8	D	H	0.0726	Exchange[e]	2.59 ± 0.07	3.57 ± 0.13

[a] CH$_3$OD used contained greater than 0.99 atom of D per molecule. [b] First-order rate constants and their standard deviations were calculated by a least-squares computer program, for which we thank Dr. Paul Haake. [c] Second-order rate constants reported are first-order constants divided by base concentration. Estimated error was obtained by the method of total differentials assuming a 1% error in base concentration. [d] Racemizations were followed at 436 mμ; 25–50 points were taken in each run. [e] Deuterium analyses were carried out by infrared spectrophotometry; 6–8 points were taken in each run.

$$\mathrm{d}[\mathrm{D}_-]/\mathrm{d}t = k_1[\mathrm{H}_-] + k_2[\mathrm{H}_+] + k_4[\mathrm{D}_+] - k_4[\mathrm{D}_-] \quad (4)$$

$$[\mathrm{H}_+] = \frac{1}{2}[e^{-\beta t} + e^{-\gamma t}] \quad (5)$$

$$[\mathrm{H}_-] = \frac{1}{2}[e^{-\beta t} - e^{-\gamma t}] \quad (6)$$

$$[\mathrm{D}_+] = \frac{1}{2}\left[(1 - e^{-\beta t}) - \left(\frac{k_2 - k_1}{\gamma - 2k_4}\right)(e^{-2k_4 t} - e^{-\gamma t})\right] \quad (7)$$

$$[\mathrm{D}_-] = \frac{1}{2}\left[(1 - e^{-\beta t}) + \left(\frac{k_2 - k_1}{\gamma - 2k_4}\right)(e^{-2k_4 t} - e^{-\gamma t})\right] \quad (8)$$

Equations 5–8 are used to solve for rate constants k_1, k_2, and k_3 in terms of reaction time t, an independently measured k_4, and the concentrations of the four components of a partially exchanged and racemized carbon acid. Combination of eq 5–6 gives eq 9. Solution of eq 5 gives eq 10 for β. Combination of eq 7–8 gives eq 11. Solutions for rate constants k_1 and k_2 are obtained by combination of eq 10–11 to give eq 12–13. Hence, one method of calculating the rate constants for the mechanistic components of isotopic exchange involves determination of the isotopic and enantiomeric composition of a partially exchanged and racemized carbon acid.

$$k_3 = \frac{1}{2t}\ln\left[\frac{([\mathrm{H}_+]/[\mathrm{H}_-]) + 1}{([\mathrm{H}_+]/[\mathrm{H}_-]) - 1}\right] \quad (9)$$

$$(k_1 + k_2) = \beta = \frac{1}{t}\ln\left[\frac{(1 + e^{-2k_3 t})}{2[\mathrm{H}_+]}\right] \quad (10)$$

$$(k_2 - k_1) = \frac{([\mathrm{D}_-] - [\mathrm{D}_+])(\gamma - 2k_4)}{(e^{-2k_4 t} - e^{-\gamma t})} \quad (11)$$

$$k_1 = \frac{1}{2}[\beta - (k_2 - k_1)] \quad (12)$$

$$k_2 = \frac{1}{2}[\beta + (k_2 - k_1)] \quad (13)$$

Another method of calculating k_1, k_2, and k_3 involves only kinetic measurements. Equation 14 expresses the rotation of a solution of an optically active carbon acid in terms of α_0 (its rotation at zero time) and the mole fractions of each component. Substitution of eq 5–8 into eq 14 gives eq 15, where $\phi = k_4/(k_2 + k_3)$ (the reciprocal of the kinetic isotope effect $k_\mathrm{H}/k_\mathrm{D}$ for racemization), $\psi = (k_2 - k_1)/2(k_2 + k_3)$, and $\theta = 2(k_2 + k_3)$ (the rate constant for racemization at zero time). Measurements of the exchange rate ($k_\mathrm{e} = \beta$), θ, and ψ permit evaluation of rate constants k_1, k_2, and k_3. Only when $\phi = 1$ (no isotope effect) or $\psi = 0$ ($k_2 = k_1$) does α exhibit simple first-order decay. For all cases where $\phi \neq 1$ and $\psi \neq 0$, ψ can be determined from eq 15 by a method of successive approximations if sufficiently accurate data on rotation as a function of time are available.

$$\alpha = \alpha_0([\mathrm{H}_+] + [\mathrm{D}_+] - [\mathrm{H}_-] - [\mathrm{D}_-]) \quad (14)$$

$$\alpha = \left[\frac{\alpha_0}{(\phi - 1) + \psi}\right][(\phi - 1)e^{-\theta(1-\psi)t} + \psi e^{-\theta\phi t}] \quad (15)$$

When $\phi < 1$ (normal isotope effect) and $\psi > 0$ (exchange with net inversion), a faster reacting protio compound is converted to a slower reacting deuterio compound of opposite rotation. As a result, the observed sign of rotation of a reacting solution should change at some time during the run as shown in Figure 1. If the isotope effect and the rate constant for racemization at zero time are known, the function ψ may be calculated from the time at which the observed rotation equals zero, t_x, or from the time at which the rotation reaches a minimum, t_m. As a result, the rate constants k_1, k_2, and k_3 may be calculated directly if $\phi < 1$ and $\psi \geq 0$.

Results

Kinetics of Racemization and Exchange of I-H(D) in Methanol-O-*d*(*h*). Racemization and hydrogen–deuterium exchange rate constants with all possible isotopic combinations for I-H(D) in methanol-O-*d*(*h*) with potassium methoxide at 24.9° are reported in Table I. The constant value obtained for second-order rate constants in runs 1–3 indicates that racemization is first order in potassium methoxide over the range of base concentrations employed. A large substrate isotope effect ($k_\mathrm{H}/k_\mathrm{D} = 6.6$) and a substantial solvent isotope effect ($k^{\mathrm{CH_3OD}}/k^{\mathrm{CH_3OH}} = 2.3$) were found for racemization. Although exchange occurred with net inversion with both combinations of solvent and substrate isotopes, the exchange of I-D$_+$ in methanol-O-*h* was the more stereospecific. These isotope effects are reported in Table II.

Rate Constants for Mechanistic Components. Kinetic Method. Application of the kinetic method of the

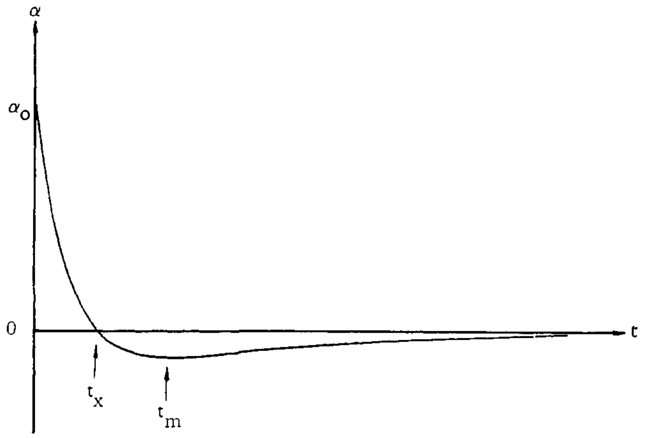

Figure 1. Observed rotation as a function of time for $\phi = 0.154$, $\psi = 0.18$, and $\theta = 4.85 \times 10^{-4}$ sec^{-1}.

model has enabled calculation of the rate constants for exchange with retention (k_1), exchange with inversion (k_2), and isoinversion (k_3) in the isotopic exchange of I-H$_+$ in methanol-O-*d*. Racemization was a simple first-order process, and no negative rotation was ever observed during run 6. Since there was a large hydrogen–deuterium isotope effect ($\phi = 0.15$), in terms of the model, $\psi = 0$. Calculated rate constants k_1, k_2, and k_3 are reported in Table III. Net inversion with exchange ($k_2 > k_1$) would cause the rotation during this kinetic run to become negative. If the rotation ever becomes negative, it must pass through zero at some time t_x (see Figure 1). This occurs when the exponential term of eq 15 equals zero. Solution of eq 15 for t_x gives eq 16, which was used to calculate values of t_x expected for hypothetical values of ψ. The time at which the rotation is a minimum, t_m of Figure 1, may be calculated from eq 17, which was obtained from eq 15 by equating the first derivative of α with respect to t to zero and solving for t. Substitution of t_m into eq 15 provided values for the minimum rotation, α_m, which could be observed for a given value of ψ under the experimental conditions used in run 6 ($\theta = 4.85 \times 10^{-4}$ sec^{-1}, $\phi = 0.154$, α_0 +0.904°). These calculations of t_x, t_m, and α_m are reported in Table IV. The calculated value of α_m −0.003° for $\psi = 0.01$ is greater than experimental error on the polarimeter used for kinetic runs. Assuming the polarimeter was accurate to 0.001°, a calculation of ψ was made by taking the time t_x to be that time during run 6 at which the polarimeter first read 0.000°. That calculation indicated a difference between k_1 and k_2 of only 0.2% of their mean value. Therefore, $k_1 = k_2$ within experimental error.

$$t_x = \left[\frac{1}{\theta(1 - \psi - \phi)}\right] \ln (1 - \phi)/\psi \qquad (16)$$

$$t_m = \left[\frac{1}{\theta(1 - \psi - \phi)}\right]\left[\frac{\ln (1 - \phi)(1 - \psi)}{\phi\psi}\right] \qquad (17)$$

Table II. Rate Ratios for Racemization and Exchange of 0.060 *M* I in Methanol with 0.07–0.08 *M* Potassium Methoxide at 24.9°

$(k_H^{CH_3OH}/k_D^{CH_3OH})^a$	6.66 ± 0.27^d
$(k_H^{CH_3OD}/k_D^{CH_3OD})^{a,b}$	6.50 ± 0.22^d
$(k_H^{CH_3OD}/k_H^{CH_3OH})^{b,c}$	2.27 ± 0.07^d
$(k_D^{CH_3OD}/k_D^{CH_3OH})^{b,c}$	2.33 ± 0.10^d
k_e/k_α (I-H in CH_3OD)^b	0.92 ± 0.05^e
k_e/k_α (I-D in CH_3OH)	0.82 ± 0.05^d

[a] Substrate kinetic isotope effect for racemization. [b] CH_3OD used contained greater than 0.99 atom of D per molecule. [c] Solvent isotope effect for racemization. [d] Ratios of second-order rate constants. Errors represent standard deviations. [e] A mean value from two experiments: ratio of second-order rate constants from Table I = 0.94 ± 0.05, and ratio of first-order rate constants from an independent run = 0.90 ± 0.05.

Table III. Comparison of Rate Constants for Mechanistic Components of Base-Catalyzed Hydrogen–Deuterium Exchange and Racemization of I at 24.9°

Constant	I-H$_+$ in CH_3OD with CH_3OK — 10^3k, l. mole^{-1} sec^{-1} — Kinetic^a	Resolution^b	I-D$_+$ in $(CH_3)_3COH$ with $C_6H_5OK^c$ 10^6k, sec^{-1}
k_1	3.02 ± 0.17^d	2.80 ± 0.46	12.1 ± 4.4
k_2	3.02 ± 0.17	2.99 ± 0.46	5.6 ± 4.4
k_3	0.26 ± 0.17	0.26 ± 0.05	0.46 ± 0.05
$k_4{}^e$	0.51 ± 0.01	0.51 ± 0.01	44.8 ± 0.8^f

[a] Second-order rate constants from kinetic data. [b] Second-order rate constants from reresolution data. A solution of 0.060 *M* I-H$_+$ and 0.069 *M* potassium methoxide in methanol-O-*d* (greater than 0.99 atom of D per molecule) was racemized to 44.2% of its original rotation before resolution. [c] First-order rate constants from the reresolution method. A solution of 0.13 *M* I-D$_+$ (0.97 atom of D per molecule), 0.081 *M* potassium phenoxide, and 0.014 *M* phenol in *t*-butyl alcohol was racemized to 49.0% of its original rotation before resolution. [d] Errors represent standard deviations. [e] Independently measured. [f] Calculated from a run containing 0.13 *M* I-H$_+$, 0.1074 *M* potassium phenoxide, and 0.0095 *M* phenol in *t*-butyl alcohol by assuming that racemization is first order in base, and that the rate is not affected by small changes in phenol concentration.

Table IV. Dependence of Rotation on ψ

ψ	$10^{-3}t_x$, sec	$10^{-4}t_m$, sec	α_m, deg
0.50	3.13	1.02	−0.425
0.18	4.8	1.00	−0.093
0.05	7.3	1.21	−0.019
0.01	11.0	1.56	−0.003

Reresolution Method. Rate constants k_1, k_2, and k_3 were calculated for exchange of I-H$_+$ in methanol-O-*d* with potassium methoxide and exchange of I-D$_+$ in *t*-butyl alcohol with potassium phenoxide using eq 9–13. The results are reported in Table III. The isotopic symbols of the model were switched when D$_+$ rather than H$_+$ served as starting material. Concentrations of the four species in partially exchanged and racemized I were determined from mass spectral deuterium analyses of the antipode and of the racemate obtained by fractional crystallization of the recovered material from acetone. This analytical method depends on the assumption that protio and deuterio compounds do not fractionate during recrystallization. An isotopic dilution experiment with another optically active carbon acid gave no isotopic fractionation,[9] indicating that this assumption is reasonable.

The rather large limits of error on k_1 and k_2 reported in Table III for the reresolution method are caused by possible errors in deuterium analyses (which were estimated to be accurate to ±0.003 atom D per molecule)

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(9) D. J. Cram and T. A. Whitney, *J. Am. Chem. Soc.*, **89**, 4651 (1967).

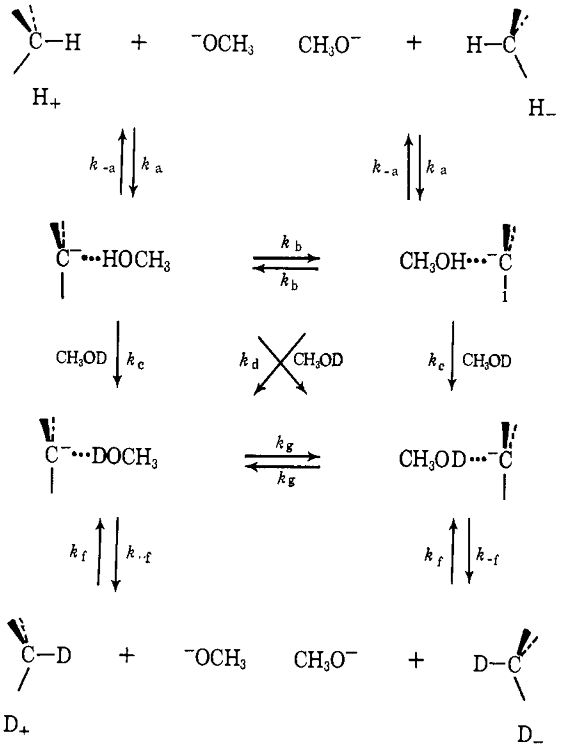
and in the rate constant k_4, and by the uncertainty in the time due to fluctuations in temperature for the first few minutes after mixing base and substrate.

The results in Table III show good agreement between the two experimentally independent methods of calculating rate constants for the mechanistic components. The kinetic method demonstrated conclusively that in methanol with potassium methoxide exchange of I-H$_+$ occurred with no net retention or inversion, and consequently that the over-all net inversion was due entirely to a small isoinversion component. The exchange and racemization of I-D$_+$ in *t*-butyl alcohol with potassium phenoxide also occurred with a small isoinversion component, even though the k_e/k_α value (1.00 ± 0.05) under these conditions indicated no net stereospecificity for the exchange. Racemization of I in *t*-butyl alcohol also had a large substrate isotope effect, $k_H/k_D = 5.9 \pm 0.4$. Since an isoinversion component contributed to the over-all result, the exchange in *t*-butyl alcohol must have taken place with low net retention in order to balance the isoinversion.

Discussion

Mechanism. Scheme I may be used to explain the stereochemical courses of isotopic exchange of I-H$_+$ in methanol-O-*d*. Mechanisms which involve carbanions hydrogen bonded to more than one solvent molecule have been discounted because of the intramolecularity observed in this and other proton transfers. Also discounted are mechanisms which involve nonhydrogen-bonded carbanions as discrete intermediates. A more detailed discussion of singly hydrogen-bonded carbanions appears later in this paper. In Scheme I, k_b and k_g are rate constants for intramolecular shifts of hydrogen bonds which interconvert enantiomeric hydrogen-bonded carbanions, while k_c and k_d are rate constants for exchanges of hydrogen-bonded carbanions with the solvent. When the new hydrogen bond forms on the side of the original covalent bond, k_c is the rate constant. When the new hydrogen bond forms on the opposite side, k_d is the rate constant. Processes by which deuterated material is reconverted to protonated material are neglected because the solvent always contained at least 99% deuterium at its exchangeable position.

Scheme I



Treatment of Scheme I by the steady-state approximation gave eq 18–23 which express the experimental rate constants, k_1, k_2, k_3, and k_4, in terms of the rate constants of the scheme.[8]

$$k_1 = k_a\frac{m(k_{-f} + k_g) + nk_g}{(k_{-f} + 2k_g)(k_{-a} + k_c + k_d)(k_{-a} + k_c + k_d + 2k_b)} \tag{18}$$

$$k_2 = k_a\frac{n(k_{-f} + k_g) + mk_g}{(k_{-f} + 2k_g)(k_{-a} + k_c + k_d)(k_{-a} + k_c + k_d + 2k_b)} \tag{19}$$

$$m = k_c(k_{-a} + k_c + k_d + 2k_b) + k_b(k_d - k_c) \tag{20}$$

$$n = k_d(k_{-a} + k_c + k_d + 2k_b) - k_b(k_d - k_c) \tag{21}$$

$$k_3 = \frac{k_a k_{-a} k_b}{(k_{-a} + k_c + k_d)(k_{-a} + k_c + k_d + 2k_b)} \tag{22}$$

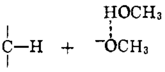
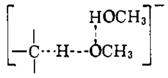
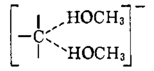
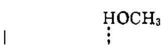
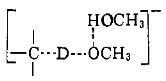
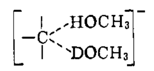
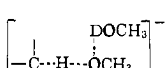
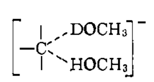
$$k_4 = \frac{k_g k_f}{(k_{-f} + 2k_g)} \tag{23}$$

When $k_1 = k_2$, as with I-H$_+$ in methanol-O-*d*, eq 18 and 19 require that either $k_c = k_d$ or $k_b \gg k_{-a}$, k_c, or k_d. These possibilities require examination.

If $k_c = k_d$, the carbanions exchange one tightly bound solvent molecule for another without regard for the face of the planar carbanion with which the original methanol molecule was associated. Experimentally, intramolecular shift of hydrogen bonds (k_b) must be competitive with intermolecular exchange of hydrogen bond donors (k_c and k_d) to account for the isoinversion component. One special case of $k_c = k_d$ involves $k_{-a} \gg k_b$, k_c, or k_d. In other words, the rate-determining steps for racemization are governed by k_b, k_c, and k_d. Simplification of eq 18–22 through use of $k_c = k_d$ and $k_{-a} \gg k_b$, k_c, or k_d gives $k_e/k_\alpha = k_c/(k_b + k_c) = 0.92$, or $k_c = 11.6k_b$. On the other hand, if $k_b \gg k_{-a}$, k_c, or k_d, simplification of eq 18–22 gives $k_\alpha = k_a$ and $k_e/k_\alpha = (k_c + k_d)/(k_{-a} + k_c + k_d) = 0.92$, or $(k_c + k_d) = 11.6k_{-a}$. Although this latter possibility appears intuitively less likely than the former, it can better explain the large substrate isotope effect on racemization of I in methanol with potassium methoxide.

Substrate Isotope Effect. In the model of Table V, the ground states and the rate-determining transition states for racemization of I in methanol are formulated for two cases: where k_b is very large; and where k_{-a} is very large. In the ground states of Table V, the methoxide ion is strongly hydrogen bonded to one methanol molecule. If $k_b \gg k_{-a}$, k_c, or k_d, the initial proton abstraction is rate determining, and the transition state contains no covalent bond, a partial C··· H··· O bond, and a partial O ··· H hydrogen bond. For loss of a covalent bond, a large primary isotope effect is expected. On the other hand, the model transition state for $k_{-a} \gg k_b$, k_c, and k_d contains two nearly

Table V

Substrate and solvent	Ground state	Transition states: $k_b \gg k_{-a}$, k_c, and k_d	Transition states: $k_{-a} \gg k_b$, k_c, and k_d
1-H in CH_3OH			
1-D in CH_3OH			
1-H in CH_3OD			

covalent O–H bonds and two partial O · · · H hydrogen bonds. Only a small primary isotope effect could be expected when there is little loss of stretching vibration in the transition state. In other words, the over-all isotope effect for large k_{-a} is the product of an equilibrium isotope effect and a kinetic isotope effect for exchange of hydrogen-bond donors expressed by eq 24.[10]

$$\frac{k_H}{k_D} = \frac{k_a{}^H k_{-a}{}^D k_c{}^H}{k_a{}^D k_{-a}{}^H k_c{}^D} = \frac{K_{eq}{}^H k_c{}^H}{K_{eq}{}^D k_c{}^D} \qquad (24)$$

Although the transition state for rate constant k_c is used in Table V, that for k_d would provide the same conclusions.

It is not clear what maximum primary isotope effects are. Two statistical mechanical models provide maximum isotope effects of $k_H/k_D = 6.9$ and $k_H/k_D = 13$ for abstraction of hydrogen from carbon at 25° in the absence of proton tunneling.[11] Streitwieser and coworkers have reported deuterium–tritium isotope effects as high as $k_D/k_T = 2.9$ for isotopic exchange of toluene and ethylbenzene in cyclohexylamine with lithium cyclohexylamide.[12] When converted to hydrogen–deuterium isotope effects by the equation of Swain and co-workers,[13] $k_D/k_T = 2.9$ becomes $k_H/k_D = 12$, the highest isotope effect for abstraction of hydrogen from carbon in the absence of tunneling of which we are aware. The authors concluded that in isotopic exchange of toluene, hydrogen abstraction was rate determining, and the carbanion, once formed, was never reconverted to starting material.

An alternative to the prerate-determining equilibrium explanation[10] for low primary hydrogen–deuterium isotope effects has been presented by Westheimer[14] and modified by Bell.[15] They contend that a maximum isotope effect is observed only when the hydrogen atom or ion being transferred is symmetrically located in the transition state between the atom to which it was covalently bonded and the atom to which a covalent bond is forming. In nonsymmetrical transition states, C · · · H · · · O stretching vibrations which involve motion of the hydrogen atom reduce the isotope effect. This approach has been used to explain the base strength dependence of isotope effects for hydrogen abstraction.[13,15] For example, the zero-order bromination of nitromethane catalyzed by water has $k_H/k_D = 3.8$, but catalyzed by hydroxide ion has $k_H/k_D = 9.6$.[15a] Isotope effects are maximized when the carbon acid and the conjugate acid of the basic catalyst have the same pK_a.[15b]

In previous work both the prerate-determining equilibrium approach[10,16] and the nonsymmetrical transition state approach[15,17] have been used to explain low primary isotope effects in carbanion-forming hydrogen abstractions. In the present work, both effects might reduce the isotope effect from a maximum value (attainable only if k_{-a} of Scheme I was negligibly valued, and the pK_a of the conjugate acid of the alkoxide catalyst was the same as that of the substrate) to the observed $k_H/k_D = 6.6$. The presence of an isoinversion component in the mechanism requires a contribution by the isotope effect for k_{-a} to the over-all isotope effect. A difference of 6–7 units in the pK_a values of I and methanol provides further reduction from the maximum. The isotope effects reported here agree well with previous values for sodium methoxide catalyzed exchange of fluorene in methanol ($k_D/k_T = 2.2$ or $k_H/k_D = 6$) from the Swain equation[13,18] and for exchange of fluorene in liquid ammonia ($k_D/k_T = 1.9$).[19]

The large isotope effect ($k_H/k_D = 6.6$) for racemization of I in methanol with potassium methoxide makes $k_{-a} \gg k_b$, k_c, or k_d in Scheme I very unlikely. On the other hand, it supports the possibility that $k_b \gg k_{-a}$, k_c, or k_d because only in that case is a covalent bond broken in the rate-determining transition state for racemization. Situations where $k_c = k_d$ but k_{-a} is of the same order of magnitude as k_b, k_c, and k_d are also consistent with a large isotope effect as long as the rate-determining transition states involve considerable loss of covalent bonding.

Singly Hydrogen-Bonded Carbanions.[20] Whatever the relative values of the rate constants of Scheme I, binding between the planar delocalized carbanion and the solvent molecule formed by hydrogen abstraction must be considerably stronger than binding between the carbanion and any other solvent molecule. Otherwise, isoinversion in racemization of I-H+ in methanol-O-*d* would not have been observed. A variety of intramolecular proton transfers support this "singly hydrogen-bonded carbanion" concept. Most striking is the 1,5 proton transfer converting triene VI to triarylmethane VII which occurred with 98% intramolecularity in nonpolar deuterated solvents with tertiary amine catalysts and 46% intramolecularity even in methanol-O-*d* with sodium methoxide catalyst.[21] Similar re-

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[10] (a) D. J. Cram, C. A. Kingsbury, and B. Rickborn, *J. Am. Chem. Soc.*, **83**, 3688 (1961); (b) D. J. Cram, D. A. Scott, and W. D. Nielsen, *ibid.*, **83**, 3696 (1961).

[11] L. Melander, "Isotope Effects on Reaction Rates," The Ronald Press Co., New York, N. Y., 1960, p 22.

[12] (a) A. Streitwieser, Jr., W. C. Langworthy, and D. E. Van Sickle, *J. Am. Chem. Soc.*, **84**, 251 (1962); (b) A. Streitwieser, Jr., D. E. Van Sickle, and L. Reif, *ibid.*, **84**, 258 (1962).

[13] C. G. Swain, E. C. Stivers, J. F. Reuwer, Jr., and L. J. Schaad, *ibid.*, **80**, 5885 (1958).

[14] F. H. Westheimer, *Chem. Rev.*, **61**, 265 (1961).

[15] (a) R. P. Bell, *Discussions Faraday Soc.*, **39**, 16 (1965); (b) R. P. Bell and D. M. Goodall, *Proc. Roy. Soc.* (London), **A294**, 273 (1966).

[16] (a) D. J. Cram and R. T. Uyeda, *J. Am. Chem. Soc.*, **86**, 5466 (1964); (b) J. E. Hofmann, A. Schriesheim, and R. E. Nickols, *Tetrahedron Letters*, 1745 (1965).

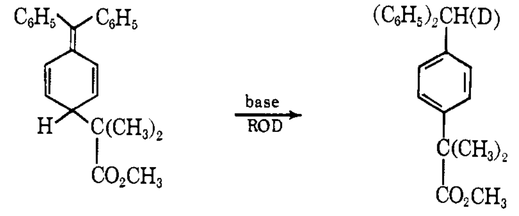
[17] S. Andreades, *J. Am. Chem. Soc.*, **86**, 2003 (1964).

[18] A. Streitwieser, Jr., and J. H. Hammons, *Progr. Phys. Org. Chem.*, **3**, 57 (1965).

[19] (a) F. S. Yakushin, Yu. G. Dubinskii, E. A. Yakovleva, and A. I. Shatenshtein, *Russ. J. Phys. Chem.*, **33**, 647 (1959); (b) F. S. Yakushin and A. I. Shatenshtein, *Kinetics Catalysis*, **1**, 457 (1960).

[20] Although we use the term "hydrogen bond," "ion-dipole interaction" or "partial bond" would serve as well.

[21] D. J. Cram, F. Willey, H. P. Fischer, H. M. Relles, and D. A. Scott, *J. Am. Chem. Soc.*, **88**, 2759 (1966).



VI VII

sults have been observed in base-catalyzed 1,3 proton transfers[22] and isoracemizations of carbon acids.[5,23] The energetic factors preventing strong association of the carbanion with more than one solvent molecule at a time are most likely the entropy required to form a trimeric species and the strongly hydrogen-bonded structure of the solvent.

The ability of delocalized carbanions to strongly bind to just one solvent molecule at a time implies that the negative charge in the anion may be concentrated at the carbon which is nearest that one molecule of solvent. Thus, the process defined by k_b in Scheme I might be a series of shifts of a hydrogen bond between sites in the carbanion which keeps a semilocalized negative charge at the site of hydrogen bonding. One hydrogen-bonded carbanion of I could be converted to its enantiomer by shifting the associated hydrogen from the π-electron system to a lone pair of electrons on the dimethylcarboxamido group and then to the opposite side of the planar hydrocarbon. Similar "conducted tour" mechanisms were previously formulated for isoracemization of carbon acids II and III by tri-*n*-propylamine in nondissociating protic solvents.[5,23]

Solvent Isotope Effect. The solvent isotope effect ($k^{CH_3OD}/k^{CH_3OH} = 2.3$) reported for racemization of I in methanol with potassium methoxide is similar to those observed in base-catalyzed allylic isomerizations[16a,24] and in isotopic exchange of monohydrofluorocarbons in methanol with sodium methoxide.[17] Regardless of which model in Table V is used for the transition state, there is an increase in the frequency of the O-H or O-D stretching vibration of the solvent molecule as hydrogen bonding to the methoxide ion is lost. This frequency increase is greater for O-H than for O-D, causing the solvent isotope effect. Our result supports the conclusions of Swain and co-workers that OD^- is a stronger base in D_2O than OH^- is in H_2O, and that a reaction which proceeds by distribution of charge in the transition state will exhibit rate enhancement in heavy water.[25]

In addition to the solvent isotope effect, greater stereospecificity of exchange was observed for I-D$_+$ in methanol-O-*h* than for I-H$_+$ in methanol-O-*d* (see Table II). In terms of Scheme I, this means that either k_b is larger with I-D than with I-H, or k_c and k_d are larger with methanol-O-*d* than with methanol-O-*h*. In connection with the latter possibility, the solvent isotope effect indicates that association of methoxide and methanol-O-*h* is stronger than association of methoxide and methanol-O-*d*. Thus, methanol-O-*d* should be more easily removed from solvent structure to bind with the carbanion.

Racemization in *t*-Butyl Alcohol. Scheme I may be applied to the isotopic exchange of I-D$_+$ in *t*-butyl alcohol with potassium phenoxide by interchanging the isotopic (H and D) symbols. The over-all lack of stereospecificity was due to a fortuitous combination of isoinversion, exchange with retention, and exchange with total racemization. Since exchange occurred with net retention, exchange of hydrogen-bond donors with the solvent must have taken place preferentially on one side of the carbanion such that $k_c > k_d$. Again, a large primary isotope effect ($k_H/k_D = 5.9$) indicates that k_{-a} cannot be very large relative to k_b and k_c. In order to produce the isoinversion component, k_b must be at least competitive with k_c, and $k_b \gg k_{-a}$, k_c, or k_d is a distinct possibility.

In nonpolar *t*-butyl alcohol, the mechanism probably involves ion pairs rather than solvated carbanions. The phenol molecule formed by proton abstraction probably associates with a solvated potassium ion, which rotates and returns another solvent molecule to the carbanion. Similar explanations have been invoked for other hydrogen–deuterium exchanges occurring with retention in nonpolar solvents.[4]

This paper has reported distinct experimental proof for isoinversion contributions to the over-all mechanisms of exchange of I-H$_+$ in methanol-O-*d* with potassium methoxide and I-D$_+$ in *t*-butyl alcohol with potassium phenoxide. However, in both media the predominant mechanistic course was total racemization with exchange indicated by large contributions from both k_1 and k_2 in our kinetic model. Experimental proof for net exchange with inversion has been found in a cyclic sulfone[9] but remains undiscovered in optically active 9-methylfluorene derivatives.

Experimental Section

Materials. Preparation of optically active and deuterated 2-(N,N-dimethylcarboxamido)-9-methylfluorene (I) has been described previously.[4] In this work, I-H$_+$ had mp 126.5–127°,[26] $[\alpha]^{25}_{546}$ +31.2°, $[\alpha]^{25}_{436}$ +60.3° (*c* 1.5, methanol), and $[\alpha]^{25}_{546}$ +33.4° (*c* 1.2, dioxane); while I-D$_+$ had mp 127–127.5°,[26] $[\alpha]^{25}_{546}$ +32.0°, $[\alpha]^{25}_{436}$ +61.8° (*c* 1.5, methanol), $[\alpha]^{25}_{546}$ +33.7° (*c* 1.1, dioxane), and contained 0.97 atom of excess D per molecule by combustion and falling drop analyses.[27] Rotations were accurate to ±0.4° under these conditions and were not concentration dependent.

Methanol was purified by the method of Fieser[28] and distilled onto molecular sieves. Methanol-O-*d* was prepared by hydrolysis of dimethyl carbonate in deuterium oxide according to Streitwieser and co-workers[29] and purified by the method of Fieser.[28] After distillation, it was stored in a dry nitrogen atmosphere. It contained 0.994 atom of excess D per molecule by falling drop analysis[27] and greater than 0.99 atom of excess D per molecule by nmr analysis of the hydroxyl protons and the ^{13}C satellite of the methyl group. Both methanol-O-*h* and methanol-O-*d* contained less than 0.03 wt % water by Karl Fischer titration. *t*-Butyl alcohol was distilled from and collected over molecular sieves. Phenol (Matheson reagent) was distilled at 0.1 mm. A small center cut with bp 42–43° was collected and stored under dry nitrogen.

Typical Racemization Rate Determination (Run 5). All glassware except the polarimeter cell used in kinetic experiments was cleaned with chromic acid, rinsed with distilled water and dilute ammonia,

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(22) Reference 3, pp 175–193.

(23) Reference 3, pp 98–103.

(24) (a) D. H. Hunter and D. J. Cram, *J. Am. Chem. Soc.*, **86**, 5478 (1964); (b) S. W. Ela and D. J. Cram, *ibid.*, **88**, 5791 (1966).

(25) (a) C. G. Swain, A. D. Ketley, and R. F. W. Bader, *ibid.*, **81**, 2353 (1959); (b) C. G. Swain and R. F. W. Bader, *Tetrahedron*, **10**, 182 (1960).

(26) Melting points were taken with a Mel-Temp apparatus and are uncorrected.

(27) Performed by Josef Nemeth, Urbana, Ill.

(28) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, Mass., 1957, p 286.

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

dried in an oven for at least 12 hr at 120°, and stored in a desiccator over phosphorus pentoxide. The polarimeter cell was cleaned in the same manner and dried with a stream of purified nitrogen for 15 min.

Into a 2-ml volumetric flask was weighed 30.0 mg of I-D$_+$. Approximately 1.5 ml of methanol-O-*d* was added, and the solution was thermostated at 24.8°. After 30 min, 0.20 ml of a 0.64 *M* potassium methoxide in methanol-O-*d* solution and 0.3 ml of methanol-O-*d* were added to the 2.00-ml mark. The solution was thoroughly mixed and 1 ml was transferred to a 1-dm polarimeter cell thermostated at 24.8°. Change in rotation was observed at the 436-mμ Hg line on a Perkin-Elmer Model 141 polarimeter.

Potassium methoxide concentration was determined by titration of four aliquots of the kinetic solution to the phenolphthalein end point with 0.01234 *N* hydrochloric acid to give concentrations in the range 0.0772–0.0780 *M* with an average of 0.0777 *M*. Aliquots were measured by a calibrated 0.5-ml Hamilton syringe fitted with Chaney adapter. Graphical analysis of the polarimetric data gave a first-order rate constant of 7.92×10^{-5} sec^{-1}. Least-squares computer analysis[30] of 36 data points gave a first-order constant with standard deviation of $7.86 \pm 0.01 \times 10^{-5}$ sec^{-1} and a second-order constant of $1.012 \pm 0.011 \times 10^{-3}$ l. mole^{-1} sec^{-1} assuming an error of ±1.0% in base concentration.

Run 6. All procedures except the collection of data were the same as in run 5 Rotation data were recorded continuously by a recorder connected to the polarimeter No significant deviation from simple first-order kinetics was noticed. After 300 min, the rotation reached 0.000° and wavered over a range of only 0.001° for an additional 90 min. This precision was better than that claimed by the manufacturer of the polarimeter. Clearly, no negative rotation was observed. Representative points from the recorder chart were used to obtain the least-squares first-order rate constant. The recorder was used to collect part or all of the data in some of the other kinetic runs as well.

Typical Exchange Rate (Run 7). In a clean, dry, 25-ml flask were placed 224.8 mg of I-H$_+$ and 13.50 ml of methanol-O-*d*. After 30 min at 24.8°, 1.50 ml of 0.64 *N* potassium methoxide in methanol-O-*d* was added. The solution was mixed and stoppered with a septum cap. Aliquots of 1.6 ml each were withdrawn with a nitrogen-filled syringe and quenched in 5 ml of 2 *N* hydrochloric acid. The acidic solution was extracted with two small portions of ether. The ether solutions were washed with water, dried over magnesium sulfate, and evaporated to an oily solid which crystallized when pentane was evaporated from it. After further drying under vacuum the samples were analyzed for deuterium by quantitative infrared measurements of a band at 1147 cm^{-1}.[4] Deuterium content and time data are summarized in Table VI. Base concentration and rate constants were determined by the methods used for racemization rates.

Table VI

Time, min	% excess D	Time, min	% excess D
6.1	23	40.2	63
14.8	36	50.4	70
23.3	45	61.4	76
31.8	53	74.6	82

k_e/k_α for I-H$_+$ in Methanol-O-*d*. A flask containing 150 mg of I-H$_+$ and 6.5 ml of methanol-O-*d* was thermostated at 24.9°. After 30 min, 0.25 ml of 0.65 *M* potassium methoxide in methanol-O-*d* and more methanol-O-*d* were added to give a total of 7.00 ml. After mixing, 1.00 ml of the solution was pipetted into each of six septum-capped test tubes and held at 24.9°. Each aliquot was quenched by addition of 0.250 ml of 1 *N* hydrochloric acid in methanol–water. Rotations of the quenched solutions were measured at 436 mμ. Solid I was recovered from each aliquot and analyzed for deuterium by the method described for run 7.[4] The analytical data are summarized in Table VII. The α_{obsd} at time zero was calculated from the concentration and specific rotation of I-H$^+$ in methanol. Least-squares analysis of the data gave $k_e = 1.30 \pm 0.06 \times 10^{-4}$ sec^{-1} and $k_\alpha = 1.44 \pm 0.03 \times 10^{-4}$ sec^{-1}. Thus, $k_e/k_\alpha = 0.90 \pm 0.05$. The k_e/k_α value in Table **II** (0.92 ± 0.05) is the mean of this result and a ratio of second-order constants from Table I.

Table VII

Time, min	α_{obsd}, deg	% excess D
0.0	1.034	0
29.4	0.751	30
44.1	0.614	35
76.1	0.509	44
99.7	0.420	54
124.3	0.343	63
148.4	0.279	70

Partial Exchange of I-H$_+$ in Methanol-O-*d*. A solution containing 750 mg of I-H$_+$ in 40 ml of methanol-O-*d* was thermostated at 24.8°. After 15 min, 6.0 ml of a 0.65 *M* potassium methoxide solution and more methanol-O-*d* were added to the 50-ml mark. After thorough mixing, 1 ml of the solution was transferred to a thermostated polarimeter cell. When the rotation reached 0.400° at 436 mμ (compared to 0.904° for the same concentration of unracemized I-H$_+$ in methanol), the solution was quenched with 250 ml of 2 *N* hydrochloric acid. Two aliquots from the polarimeter cell were titrated as described in run 5 to give a potassium methoxide concentration of 0.069 *M*. The quenched mixture was extracted with three 150-ml portions of ether. The combined ether solutions were washed with water, dried over magnesium sulfate, and evaporated to 695 mg (95%) of dry, white solid A.

Reresolution of Partially Racemized I. All fractional crystallizations were carried out in reagent grade acetone Rotations were taken in dioxane at 546 mμ and 25°. Recrystallization of solid A gave 398 mg of solid B, having $[\alpha]$ +8.2° (*c* 1.1). From the mother liquors of B, 292 mg of solid C, having $[\alpha]$ +24.0° (*c* 1.05), was recovered. Solid B gave 257 mg of solid D, having $[\alpha]$ +1.8° (*c* 1.0). Solid D gave 149 mg of solid E, having $[\alpha]$ +0.4° (*c* 1.7). Solid C gave 153 mg of solid F, having $[\alpha]$ +30.3° (*c* 1.2). Solid F gave 85 mg of solid G, having $[\alpha]$ +32.3° (*c* 1.15). Solids E and G contained 0.642 and 0.361 atom excess D per molecule, respectively, by mass spectrometry.

Partial Exchange of I-D$_+$ in *t*-Butyl Alcohol. Clean, freshly cut potassium, 79.3 mg, was dissolved in a solution of 0.21 mg of phenol in 17.0 ml of *t*-butyl alcohol. In another flask, 811 mg of I-D$_+$ was dissolved in 8.0 ml of *t*-butyl alcohol. After 15 min at 24.9°, the two solutions were combined to give a solution 0.13 *M* in I-D$_+$, 0.081 *M* in potassium phenoxide, and 0.014 *M* in phenol. After thorough mixing, 1 ml of the solution was transferred to a thermostated polarimeter cell. When the rotation reached 0.454° at 546 mμ (compared to 0.926° for the same concentration of I-D$_+$ in *t*-butyl alcohol) after 635 min, the solution was quenched with 200 ml of 2 *N* hydrochloric acid. The solid was recovered as previously described. A 30-g column of silica gel was prepared in 20% ether in pentane. The solid was placed on the column in a minimal amount of benzene and eluted with ether. Mass spectral analysis of the recovered solid J showed 0.469 atom excess D per molecule. The rotation and deuterium content of J provided a one-point k_e/k_α value of 1.00 ± 0.05. Fractional crystallizations starting with J were carried out by the method described above to give solid K, having $[\alpha]^{25}_{546}$ +33.6° (*c* 1.1, dioxane), and solid L, having $[\alpha]^{25}_{546}$ +1.6° (*c* 1.6, dioxane). Solids K and L contained 0.627 and 0.346 atom excess D per molecule, respectively, by mass spectral analysis.

Racemization Rate of I-H$_+$ in *t*-Butyl Alcohol with Potassium Phenoxide. In a 1-ml volumetric flask were placed 11.0 mg of phenol and 0.17 ml of 0.5 *M* potassium *t*-butoxide in *t*-butyl alcohol solution. In another flask, 32.4 mg of I-H$_+$ was dissolved in 0.5 ml of *t*-butyl alcohol. After 15 min at 24.9°, the substrate solution and more *t*-butyl alcohol were added to the base to give 1.00 ml of solution, which was thoroughly mixed and transferred to a polarimeter cell thermostated at 24.9°. Change of rotation was followed at 546 mμ. Titration of two aliquots to the brom cresol green end point with 0.01234 *N* hydrochloric acid determined the base concentration, 0.1074 *M*, and by difference the phenol concentration, 0.0095 *M*. The least-squares first-order rate constant of 14 data points was $1.32 \pm 0.01 \times 10^{-4}$ sec^{-1}.

Deuterium Analysis of I by Mass Spectrometry. All quantitative measurements were performed on an AEI MS 9 instrument at 20 ev, 8 accelerating kv, monitor 5-9 × 50, sample temperature 290°, inlet temperature 230°, source temperature 170°, source slit 30% open, and collector slit 40% open. Data were obtained with potentiometers and a recorder.[31]

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(30) We thank Dr. Paul Haake for use of a least-squares program.

(31) Devised by Mr. R. Gillespie.

The following relative intensities were found for I-H, measured (corrected): *m/e* 252, 0.1842 (0.1915[32]); *m/e* 251, 1.0000 (1.0000); and *m/e* 250, 0.207.

The corrected relative intensities were obtained by subtracting 0.207 times the measured 252 intensity from the measured 251 intensity. In subsequent deuterium determinations of mixtures of I-H and I-D, eq 25 and 26 were used to convert observed intensities [$(251)_{\text{obsd}}$ and $(252)_{\text{obsd}}$)] into corrected intensities [$(251)_{\text{cor}}$ and $(252)_{\text{cor}}$].

$$(252)_{\text{obsd}} = (252)_{\text{cor}} + 0.191(251)_{\text{cor}} \qquad (25)$$

$$(251)_{\text{obsd}} = (251)_{\text{cor}} + 0.207(252)_{\text{cor}} \qquad (26)$$

Table VIII

Known fraction D	$(252)_{\text{obsd}}/(251)_{\text{obsd}}$	Calcd fraction D	Deviation
0.295	0.556	0.292	−0.003
0.488	0.917	0.473	−0.015
0.681	1.474	0.649	−0.032

Because of the complexity of fragmentation, analyses were performed with a calibration curve. Standard mixtures were prepared by weighing amounts of $\text{I-H}_{\pm}$ and I-D_{+} totalling 100 mg into flasks, dissolving the solids in ether, evaporating the solvent, and thoroughly grinding the recovered solid in a mortar to ensure isotopic homogeneity. Analytical data for the standards are reported below. Results were reproducible to ±0.003 atom of D per molecule. A standard containing 0.488 atom of D per molecule was prepared from I-H_{+} and I-D_{+}. Its analysis was indistinguishable from that reported in the data below, demonstrating that racemate and antipode of I do not fractionate during vaporization into the heated inlet system of the mass spectrometer. All intensity ratios are medians of ratios obtained from three to five separate introductions of the sample into the instrument. Only samples of nearly equal deuterium content were analyzed at one time because amide I had a strong affinity for the walls of the inlet and source of the mass spectrometer, which gave a memory effect. Samples of racemate and antipode from both reresolutions described above and sample J from partial exchange of I-D_{+} in *t*-butyl alcohol were analyzed by this procedure. The calculated fraction of deuterium in each unknown sample was corrected by interpolation from the deviations reported for standards (Table VIII).

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[32] J. H. Beynon and A. E. Williams, "Mass and Abundance Tables for Use in Mass Spectrometry," Elsevier Publishing Co., New York, N. Y., 1963, report 0.1906 for naturally occurring isotopes in $C_{17}H_{17}NO$.

Studies on Electrolytic Substitution Reactions. III.[1] Isomer Distributions and Isotope Effects in Nuclear and Side-Chain Anodic Acetoxylation of Aromatic Compounds

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Lund, Sweden. *Received April 27, 1967*

Abstract: Using the determination of isomer distributions as an experimental tool, the anodic acetoxylation of representative aromatic compounds in acetic acid–acetate has been investigated with respect to a number of experimental variables, such as the influence of changing the anode potential, the nature of the cation, and the concentration of the acetate ion. As regards the nature of the anion, it has been found that the presence of acetate ion is essential for *nuclear* acetoxylation to occur. A concerted mechanism, involving a two-electron transfer from the π-electron system of the aromatic compound simultaneously with the formation of a C–O bond to an acetate ion, is proposed for this reaction. This type of mechanism is closely similar to that generally assumed to be valid for electrophilic aromatic substitution reactions. Results from isomer distribution studies for anodic nuclear acetoxylation of a number of simple aromatic compounds confirm the validity of this analogy, as do also isotope effect determinations. In sharp contrast to nuclear acetoxylation, it has been found that *side-chain* acetoxylation of alkylaromatic compounds can also be achieved in acetic acid containing salts of other anions, such as perchlorate and tosylate. For side-chain acetoxylation of ethylbenzene an isotope effect $k_H:k_D$ of 2.6 ± 0.3 was determined. The similarity between the product distributions of anodic and manganic acetate acetoxylation of *p*-methoxytoluene further supports the view that benzyl cations are intermediates in side-chain acetoxylation, although existing data do not allow a differentiation between different mechanisms for their formation.

On the basis of polarographic measurements and preparative electrolyses at controlled anode potential (cpe), it was recently proposed[2] that the anodic acetoxylation of aromatic compounds observed during electrolysis in glacial acetic acid–sodium acetate proceeds *via* an initial two-electron transfer from the π-electron system of the aromatic compound to the anode, followed by a nucleophilic attack of acetate ion on the intermediate dicationic species (eq 1).

$$\mathrm{ArH} \xrightarrow{-2e^-} \mathrm{ArH}^{2+} \xrightarrow{\mathrm{OAc}^-} \overset{+}{\mathrm{Ar}}{<}^{\mathrm{H}}_{\mathrm{OAc}} \xrightarrow{-\mathrm{H}^+} \mathrm{ArOAc} \qquad (1)$$

The simultaneously occurring acetoxylation of the α-carbon atom of a side chain of an alkylaromatic compound was accounted for by a similar mechanism,[2] involving an initial two-electron transfer to the anode and loss of a proton to form a benzyl cation which then re-

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[1] Part II: L. Eberson and K. Nyberg, *Tetrahedron Letters*, 2389 (1966).

[2] L. Eberson and K. Nyberg, *J. Am. Chem. Soc.*, **88**, 1686 (1966); *Acta Chem. Scand.*, **18**, 1568 (1964).