

$$[H_+] = 1/2[e^{-\beta t} + e^{-\gamma t}] \quad (1)$$

$$[H_-] = 1/2[e^{-\beta t} - e^{-\gamma t}] \quad (2)$$

$$[D_+] = 1/2 \left[(1 - e^{-\beta t}) - \left(\frac{k_2 - k_1}{\gamma - 2k_4} \right) (e^{-2k_4 t} - e^{-\gamma t}) \right] \quad (3)$$

$$[D_-] = 1/2 \left[(1 - e^{-\beta t}) + \left(\frac{k_2 - k_1}{\gamma - 2k_4} \right) (e^{-2k_4 t} - e^{-\gamma t}) \right] \quad (4)$$

rotation α of a kinetic solution gives eq 5, where $\phi = k_4/(k_2 + k_3)$ (the reciprocal of the kinetic isotope effect, k_H/k_D for racemization), $\psi = (k_2 - k_1)/2(k_2 + k_3)$, $\theta = 2(k_2 + k_3)$ (the rate constant for racemization at zero time), and α_0 is the rotation at zero time. Only

$$\alpha = \alpha_0([H_+] + [D_+] - [H_-] - [D_-]) =$$

$$\left[\frac{\alpha_0}{(\phi - 1) + \psi} \right] [(\phi - 1)e^{-\theta(1-\psi)t} + \psi e^{-\theta\phi t}] \quad (5)$$

when $\phi = 1$ or $\psi = 0$ does α show simple first-order decay. Values of k_1 , k_2 , and k_3 may be calculated using eq 5, the experimentally determined dependence of α on time, and the independently measured rate constants k_4 and $k_e (= (k_1 + k_2))$ (rate constant for isotopic exchange).

We now report values of k_1 , k_2 , k_3 , and k_4 for treatment of I-H₊ with potassium methoxide in methanol-O-d. Kinetic experiments demonstrated that racemization of I is distinctly first order in potassium methoxide and first order in substrate in the concentration ranges studied. The racemization isotope effects and k_e/k_α values are shown in Table I.

Table I. Rate Ratios for Racemization and Exchange of I^a in Methanol with Potassium Methoxide^b at 24.9 ± 0.1 °

$(k_H^{CH_3OH}/k_D^{CH_3OH})^c$	$= 6.66 \pm 0.27^e$
$(k_H^{CH_3OD}/k_D^{CH_3OD})^c, d$	$= 6.50 \pm 0.22^e$
$\left(\frac{k_e}{k_\alpha} \right)^{I-H}$ CH ₃ OD	$= 0.92 \pm 0.05^e$
$\left(\frac{k_e}{k_\alpha} \right)^{I-D}$ CH ₃ OH	$= 0.82 \pm 0.05^e$

^a 0.060 M. ^b 0.07–0.08 M in KOCH₃. ^c Substrate isotope effect for racemization. ^d CH₃OD used contained greater than 0.99 atom of D per molecule by nmr. ^e All ratios are of second-order constants obtained by dividing base concentrations into least-squares first-order constants. We thank Dr. Paul Haake for use of a least-squares program. Errors reported are standard deviations.

Previous interpretation of the k_e/k_α value (0.82) for treatment of I-D₊ with potassium methoxide in methanol implied that, for racemization of I-H₊ in methanol-O-d, $k_2 > k_1$.^{2a} By eq 5, if $k_2 > k_1$ ($\psi > 0$) and $\phi < 1$ ($k_H/k_D > 1$), then experimentally the rotation of a kinetic solution of H₊ as starting material in methanol-O-d changes from (+) to (−) at some time during the run as the more reactive H₊ produces less reactive D_− by net exchange with inversion. In spite of the large isotope effect ($\phi = 0.15$), we observed no (−) rotation at any time. Calculations indicate that if the value of $k_2 - k_1$ was just 1% of the mean of k_1 and k_2 , a distinctly negative rotation ($\alpha_{obsd} - 0.003^\circ$ at the 436-m μ Hg line on a Perkin-Elmer Model 421 polarimeter) would have been observed during the

kinetic run, and that k_1 and k_2 most likely differ by less than 0.2% of their mean value. Therefore, $k_1 = k_2$, and the over-all net inversion with exchange indicated by the k_e/k_α value (0.92) for I-H₊ in methanol-O-d with potassium methoxide must be due to an *isoinversion* component (governed by k_3) in the mechanism for isotopic exchange and racemization. Second-order rate constants k_1 , k_2 , k_3 , and k_4 calculated from our data are given in Table II. The following

Table II. Second-Order Kinetic Model Rate Constants for Racemization of I-H₊ in CH₃OD,^a 0.0739 M in CH₃OK at 24.9 ± 0.1 °

Constant	10 ³ k, l. mole ⁻¹ sec ⁻¹
k_1	3.02 ± 0.17 ^b
k_2	3.02 ± 0.17 ^b
k_3	0.26 ± 0.17 ^b
k_4	0.51 ± 0.01 ^b

^a CH₃OD used contained greater than 0.99 atom of D per molecule by nmr. ^b Errors reported represent standard deviations.

communication contains a more detailed discussion of the mechanism for hydrogen–deuterium exchange of I in hydroxylic solvents.⁴

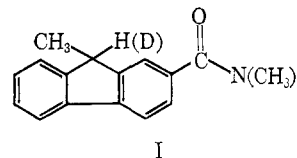
(5) National Science Foundation Trainee at UCLA, 1965–1966.

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Mechanistic Components in Base-Catalyzed Hydrogen–Deuterium Exchange between a Carbon Acid and Hydroxylic Solvents¹

Sir:

The preceding communication described a kinetic model for dissecting the mechanistic components in the base-catalyzed hydrogen–deuterium exchange reaction at asymmetric carbon between system I-H and methanol-O-d.² This communication describes an



experimentally independent method based on the kinetic equations which define the contributions to the over-all results of exchange with retention (rate constant k_1), of exchange with inversion (rate constant k_2), and of *isoinversion* (inversion without exchange, rate constant k_3). The method has been applied to reactions of I in two solvent–base systems.

The model assumes only that the substrate, once exchanged with isotopically labeled solvent, never regains its original isotope. Equations 1–5 provide solutions for rate constants k_1 , k_2 , and k_3 in terms of the isotopic and enantiomeric composition of the substrate at reaction time t and an independently measured²

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

(2) W. T. Ford, E. W. Graham, and D. J. Cram, *J. Am. Chem. Soc.*, **89**, 689 (1967).

rate constant for inversion of exchanged material (k_4). They are obtained from eq 1-4 of ref 2. By fractional crystallization of partially exchanged and racemized I and subsequent mass spectrometric deuterium analysis of the recovered enantiomer and racemate, we have determined $[H_+]$, $[H_-]$, $[D_+]$, and $[D_-]$ in mixtures of I. The bracketed symbols refer to mole fractions of the species of indicated isotope and enantiomer. Presumably, H_+ and D_+ as well as H_- and D_- do not fractionate during recrystallization.³ Rate constants k_1 , k_2 , and k_3 were calculated from the kinetic equations and isotopic and enantiomeric composition data gained from partially racemized and exchanged carbon acid. In the first experiment, H_+ in potassium methoxide and methanol-*O-d* was used. In a second experiment, D_+ was starting material and potassium phenoxide in *t*-butyl alcohol was the medium. Results are reported in Table I. When D_+ serves as

Table I. Rate Constants for Processes Involved in Base-Catalyzed Hydrogen-Deuterium Exchange and Racemization of I at $24.9 \pm 0.1^\circ$

Constant ^a	I- H_+ in CH_3OD and CH_3OK^b 10^3k , l. mole ⁻¹ sec ⁻¹ ^d	I- D_+ in $(CH_3)_3COD$ and $C_6H_5OK^c$ 10^6k , sec ⁻¹ ^e
k_1	2.80 ± 0.46^f	12.1 ± 4.4
k_2	2.99 ± 0.46	5.6 ± 4.4
k_3	0.26 ± 0.05	0.46 ± 0.05
k_4^g	0.51 ± 0.01	44.8 ± 0.8

^a Rate constants based solely on kinetic data and reported previously² are as follows: $k_1 = 3.02 \pm 0.17 \times 10^{-3}$ l. mole⁻¹ sec⁻¹; $k_2 = 3.02 \pm 0.17 \times 10^{-3}$ l. mole⁻¹ sec⁻¹; $k_3 = 0.26 \pm 0.17 \times 10^{-3}$ l. mole⁻¹ sec⁻¹. ^b Solution of 0.060 *M* I- H_+ and 0.069 *M* KOCH₃ in CH_3OD (greater than 0.99 atom of D/molecule by nmr) was racemized to 44.2% of its original rotation. ^c Solution of 0.13 *M* I- D_+ (0.97 atom of D/molecule), 0.081 *M* C₆H₅OK, and 0.014 *M* C₆H₅OH in $(CH_3)_3COH$ was racemized to 49.0% of its original rotation. ^d Second-order rate constants. ^e First-order rate constants. ^f Errors represent standard deviations. ^g Independently measured.

starting material, all of the H and D symbols in the kinetic model² must be interchanged.

$$k_3 = \frac{1}{2t} \ln \left| \frac{([H_+]/[H_-]) + 1}{([H_+]/[H_-]) - 1} \right| \quad (1)$$

$$k_1 + k_2 \equiv \beta = \frac{1}{t} \ln \left| \frac{(1 + e^{2k_4 t})}{2[H_+]} \right| \quad (2)$$

$$k_2 - k_1 = \frac{([D_-] - [D_+])(\beta + 2k_3 - 2k_4)}{(e^{-2k_4 t} - e^{-(\beta + 2k_3)t})} \quad (3)$$

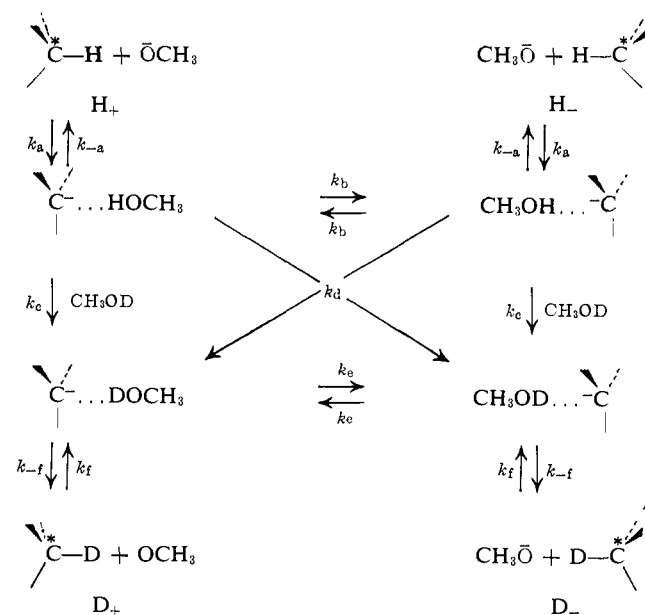
$$k_1 = \frac{1}{2}[\beta - (k_2 - k_1)] \quad (4)$$

$$k_2 = \frac{1}{2}[\beta + (k_2 - k_1)] \quad (5)$$

Rate constants k_1 , k_2 , and k_3 for reaction of I- H_+ in methanol-*O-d* found by this resolution method agree with those found by the purely kinetic method well within experimental error² (see Table I, footnote a). The kinetic method² clearly demonstrated that $k_1 = k_2$, and consequently that the observed over-all net inversion with exchange ($k_e/k_a = 0.92$) was due entirely to isoinversion. The following mechanism may be used to explain the stereochemical courses of isotopic exchange of I- H_+ in methanol-*O-d*. We have dis-

(3) D. J. Cram and T. A. Whitney (to be published) have demonstrated lack of fractionation in an analogous system.

counted mechanisms which involve carbanions hydrogen bonded to more than one solvent molecule because of the high intramolecularity observed in several 1,3- and 1,5-proton transfers⁴ (even in methanol) and the isoinversion component detected in the present work. The most likely energetic factors preventing formation of doubly hydrogen-bonded anions are the entropy required to form a trimer and the highly hydrogen-bonded structure of the solvent. Equally unlikely are mechanisms involving non-hydrogen-bonded carbanions as discrete intermediates.



When $k_1 = k_2$ as is observed, k_3 can contribute to the over-all mechanism by two distinct routes. (1) If $k_c = k_d$, then k_b and k_{-a} (or k_e and k_{-f}) must be high enough valued to make isoinversion competitive with exchange. (2) If $k_c \neq k_d$, k_b and k_{-a} (or k_e and k_{-f}) must be higher valued than k_c or k_d to account for the isoinversion and the lack of net retention or inversion in exchanged material. The relatively large primary isotope effect for racemization² (6.6) indicates that initial proton abstraction (k_a) is the slow step and that k_{-a} is small compared to k_c or k_d , whichever is greater.⁵ This conclusion is reasonable since the pK_a values of methanol and I differ by only 4 to 7 units. If k_{-a} is low valued, then k_b must be at least comparable to k_c or k_d (whichever is greater) in order to give measurable isoinversion. In other words, intramolecular reorganization occurs at least as fast as exchange of hydrogen-bonded donors of the solvent system. Since k_c and k_d describe processes distinctly different from one another, it seems likely that $k_c \neq k_d$.

In this mechanistic scheme, k_c and k_d describe processes in which hydrogen bonds to the carbanion are made and broken in the same transition state. Isoinversion processes described by k_b and k_e are also visualized as occurring without passing through a non-hydrogen-bonded carbanion as a discrete intermediate. Thus, the hydrogen-bonded methanol molecule could pass from one hydrogen-bonded site to another out around the electron pairs of the amide group and back

(4) (a) For a review see D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York, N.Y., 1965, Chapter 5; (b) D. J. Cram, F. Willey, H. P. Fischer, H. M. Relles, and D. A. Scott, *J. Am. Chem. Soc.*, **88**, 2759 (1966).

(5) D. J. Cram, C. A. Kingsbury, and B. Rickborn, *ibid.*, **83**, 3688 (1961).

to the 9 position on either face of I without ever becoming completely detached from the anion. A similar *conducted tour mechanism* was previously formulated for isoracemization of certain carbon acids by amines through ion-pair intermediates in nondissociating solvents.⁶

A k_e/k_a value of 1.00 ± 0.05 was found for the partial racemization and exchange of I-D₊ in *t*-butyl alcohol and potassium phenoxide under the conditions reported in Table I. Since isoinversion (k_3) is a contributor to the mechanism, exchange must have taken place with a small amount of net retention to balance fortuitously the isoinversion and give over-all lack of stereospecificity. In both solvent-base systems studied, only a small fraction of I may be said to react by distinctly stereospecific processes. Most of the reaction proceeds either by a delicate balance between exchange with retention and inversion or more likely by nonstereospecific processes of exchange with total racemization.

These results and the attendant hypotheses point to the possibility that in many cases of base-catalyzed hydrogen-deuterium exchange experiments of carbon acids, k_e/k_a values may reflect blends of isoracemization and exchange with retention, total racemization, or even inversion. The techniques described in these communications provide methods for differentiation. The present results leave undemonstrated an unambiguous case where inversion with exchange exceeds retention with exchange.

(6) D. J. Cram and L. Gosser, *J. Am. Chem. Soc.*, **86**, 2950, 5457 (1964).

(7) National Science Foundation Trainee at UCLA, 1965-1966.

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Acidity of Hydrocarbons. XXIII. Base-Catalyzed Proton Exchange of 1H-Undecafluorobicyclo[2.2.1]heptane and the Role of Carbon-Fluorine No-Bond Resonance

Sir:

The relatively large effect of perfluoroalkyl groups on chemical reactivity has long been appreciated by numerous workers. In addition to a normal electron-attracting inductive field effect, a conjugative interaction mechanism involving carbon-fluorine no-bond resonance (hyperconjugation) has been invoked frequently. Roberts¹ has suggested that I is an important contributing resonance structure of *p*-trifluoromethyl-aniline on the basis of dipole moment and pK data. Pauling² and Hine³ have used related concepts in interpreting various bond lengths and solvolytic reactivities of polyhalogenated compounds. Andreades⁴ obtained the relative rates in Table I for hydrogen-deuterium exchange of polyfluoroalkanes with sodium methoxide in methanol-*d*.

Inductive effects alone were considered to be insufficient to account for the large differences in re-

(1) J. D. Roberts, R. L. Webb, and E. A. McElhill, *J. Am. Chem. Soc.*, **72**, 408 (1950).

(2) L. Pauling, "The Nature of the Chemical Bond," 3rd ed, Cornell University Press, Ithaca, N. Y., 1960, pp 314-316.

(3) J. Hine and R. J. Rosscup, *J. Am. Chem. Soc.*, **82**, 6115 (1960).

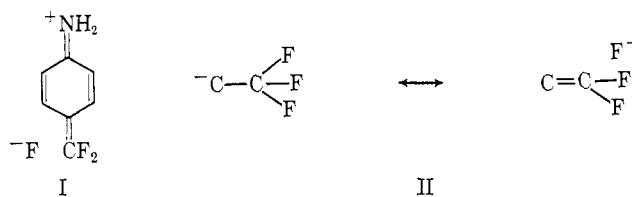
(4) S. Andreades, *ibid.*, **86**, 2003 (1964).

Table I. Relative Rates for Isotopic Exchange^a

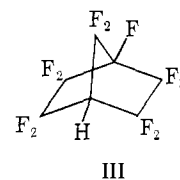
Substrate	Relative rate
CF ₃ H ^b	1
CF ₃ (CF ₂) ₆ H ^b	6
(CF ₃) ₂ CFH ^b	2 × 10 ³
(CF ₃) ₃ CH ^b	10 ⁹
1H-Undecafluorobicyclo[2.2.1]heptane (III)	5 × 10 ⁹

^a In sodium methoxide-methanol solution. ^b Reference 4.

activity; these differences were rationalized instead in terms of stabilization of the intermediate carbanion by a hyperconjugative effect, II.



One operational criterion for testing the presence of such hyperconjugation is the conformational requirement that the C-F bond overlap significantly with the orbital to which it is to be hyperconjugated. Andreades⁴ has suggested the use of a bridgehead system to test the importance of hyperconjugation; one useful molecule of this type, 1H-undecafluorobicyclo[2.2.1]heptane (III), has recently been synthesized.⁵ The carbanion intermediate in base-catalyzed exchange of the bridgehead proton is forced to remain pyramidal, and hyperconjugation of the type in II is greatly reduced by Bredt's rule. Consequently, the role of inductive effects is enhanced, and if such hyperconjugation is an *important* factor is stabilizing tris(trifluoromethyl)methyl anion, base-catalyzed proton exchange of tris(trifluoromethyl)methane should be orders of magnitude faster than that of III.⁶



The base-catalyzed exchange rates for the replacement of hydrogen for tritium in III were measured in methanol-*t* with sodium methoxide as catalyst in the temperature range -23 to -74° . Each kinetic point was a separate experiment performed in a 3-ml test tube by smashing a fragile bulb containing methanol-*t* into the temperature-equilibrated solution of III in methanolic sodium methoxide. At an appropriate time the kinetic point was quenched with a precooled solution of toluenesulfonic acid in methanol, worked up, and analyzed by normal liquid scintillation counting techniques. Usually four points plus two infinity determinations were made for each run. Rate con-

(5) S. F. Campbell, R. Stephens, and J. C. Tatlow, *Tetrahedron*, **21**, 2997 (1965). Note that these authors have shown that the bridgehead anion can be generated from III and used synthetically.

(6) The most serious weakness of this argument is that III may have enhanced acidity because of increased s character in the C-H bond derived from ring strain effects on the norbornane structure. A correlation between kinetic acidity and $J_{C^{13}-H}$ in this laboratory indicates that the bridgehead hydrogen of norbornane itself has enhanced reactivity by two orders of magnitude.