reflect the importance of X in product control rather than a change from a two-step to a concerted mechanism. Vibrationally excited neopentyl cations, *e.g.*, those formed from deamination and deoxidation, may undergo rearrangement faster than rotation about the $-\overset{+}{C}HD$ group with respect to X. Recent publications have focused attention on the importance of counter ion X and solvent in the competition between product formation and conformational changes of carbonium ions.[15]

Experimental

Synthesis of Labeled Compounds.—All compounds were prepared according to well established procedures. Trimethylacetic 1-^{13}C acid was the source of all the ^{13}C-labeled compounds. It was prepared in 91% yield (based on barium carbonate-^{13}C) from the carbonation, at −60°, of *t*-butyllithium with carbon-^{13}C dioxide generated from barium carbonate-^{13}C and 30% aqueous perchloric acid; carbonyl absorptions in the infrared: 5.97 (^{12}C=O), 6.05 μ (^{13}C=O); m.p. 35°. Reduction of the acid with lithium aluminum hydride gave neopentyl-1-^{13}C alcohol, m.p. 52°, in 92.8% yield. The alcohol was converted to the tosylate, m.p. 42–43°, in 92.3% yield by the pyridine method, and to neopentyl-1-^{13}C iodide[10] in 75% yield. Three-hour reflux of the acid with thionyl chloride (1:1.5 mole/mole) and addition of ammonium hydroxide gave the amide, m.p. 156–157°, in 90% yield. The amide was dehydrated to the nitrile with thionyl chloride in 27% yield; infrared absorptions of nitrile: 4.50 (^{11}C=N), 4.60 μ (^{13}C=N). Reduction of the nitrile with lithium aluminum hydride and treatment of the resulting amine with 70% aqueous perchloric acid gave neopentyl-1-^{13}C-ammonium perchlorate, m.p. 168–169°, in 75.6% yield after recrystallization from *n*-heptyl alcohol–*n*-pentane mixtures. The corresponding deuterated compounds were prepared by reduction with lithium aluminum deuteride. All liquid compounds were purified by gas chromatography.

Reactions of the Neopentyl Compounds.—Deamination of neopentylamines[18] gave *t*-amyl alcohol in 52.3% yield. Solvolysis of neopentyl tosylates in 50% aqueous acetic acid[9c] gave *t*-amyl alcohol in 9.5% yield. Solvolysis of neopentyl-1-^{13}C iodide in 14% aqueous silver nitrate[17] gave a 65.8% yield of *t*-amyl alcohol. Each alcohol was purified by gas chromatography.

Isotopic Analysis.—Mass spectra were measured with a Consolidated Model 21-103C mass spectrometer; n.m.r. spectra were determined at 60 Mc. on a Model A-60 spectrometer (Varian Associates, Palo Alto, Calif.), at a temperature of about 38°.

Acknowledgment.—We thank the United States Atomic Energy Commission (Grant AT(11-1)-1189) and the National Science Foundation (G-19243) for financial support of the work performed at Michigan State University.

(15) (a) D. J. Cram and M. R. V. Sahyun, *J. Am. Chem. Soc.*, **85**, 1257 (1963); (b) P. S. Skell and W. L. Hall, *ibid.*, **85**, 2851 (1963).

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Chemistry of Conjugate Anions and Enols. IV. The Kinetically Controlled Enolization of α,β-Unsaturated Ketones and the Nature of the Transition State[1,2]

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To establish the kinetically favored direction of enolization of α,β-unsaturated ketones the incorporation of deuterium into testosterone has been studied with weak acid, strong acid, and strong base catalysis. Isotope distribution, as determined by a combination of infrared and n.m.r. analysis, both before and after C-1(2) dehydrogenation with *Bacillus sphaericus*, demonstrated that strong acid led to preferential but not exclusive formation of the thermodynamically more stable $\Delta^{3,5}$-enol, while weak acid and strong base strongly favored formation of the $\Delta^{2,4}$-enol and -enolate. Comparison of enolization rates of the isomeric 6-methyltestosterone derivatives showed that with base the 6α-methyl compound formed the $\Delta^{3,5}$-conjugate anion more rapidly, while with strong acid the axial 6β-methyl isomer yielded the $\Delta^{3,5}$-enol fastest. It is concluded that in enolization with weak acid or strong base the transition state resembles the ketone form. The stereochemistry of enol protonation and the relationship of methylenic proton acidity to the transition state is discussed.

Steroidal Δ^4-3-ketones in common with other α,β-unsaturated ketones may undergo enol (enolate) dependent reaction at the α' (C-2) position *via* the homoannular $\Delta^{2,4}$-diene (Fig. 1, A,B) or at the α (C-4) or γ (C-6) positions *via* the $\Delta^{3,5}$-heteroannular diene (Fig. 1, C). While it is abundantly clear from a variety of reactions such as deconjugation,[3] alkylation,[4] enol ether, and enol acetate formation[5] that the thermodynamically more stable enol as well as enolate anion is the heteroannular $\Delta^{3,5}$-diene, the kinetically favored direction of enolization under acid and base catalysis has not been established with any degree of certainty. Wenkert and Jackson[6] found that the treatment of a tricyclic α,β-unsaturated ketone with sodium triphenylmethyl, followed by carbonation, led to essentially equal quantities of the α- and α'-carboxylic acids. This suggested equal rates of formation of the two possible anions assuming that no equilibration occurred during carbonation, which may be a doubtful assumption. Ringold and Turner[7] explained the dichlorodicyanoquinone-mediated C-1(2) dehydrogenation of Δ^4-3-keto steroids in the absence of strong acid as an attack on the kinetically determined $\Delta^{2,4}$-dienol, while Malhotra and Ringold[2] demonstrated in a qualitative manner the preferential formation of the $\Delta^{3,5}$-enol of cholest-4-en-3-one by treatment with deuterium chloride in diglyme.

Steric Course of Testosterone Enolization.—In view of the importance of chemical and enzymatic enolization reactions to the steroid field and in the hopes that such data would serve as a general model for

(1) Supported by grant T-185, American Cancer Society.

(2) Previous paper in this series: S. K. Malhotra and H. J. Ringold, *J. Am. Chem. Soc.*, **85**, 1538 (1963).

(3) H. J. Ringold and S. K. Malhotra, *Tetrahedron Letters*, 669 (1962).

(4) H. J. Ringold and S. K. Malhotra, *J. Am. Chem. Soc.*, **84**, 3402 (1962).

(5) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp. 310 and 311.

(6) E. Wenkert and B. G. Jackson, *J. Am. Chem. Soc.*, **81**, 5601 (1959).

(7) H. J. Ringold and A. Turner, *Chem. Ind.* (London), 211 (1962).

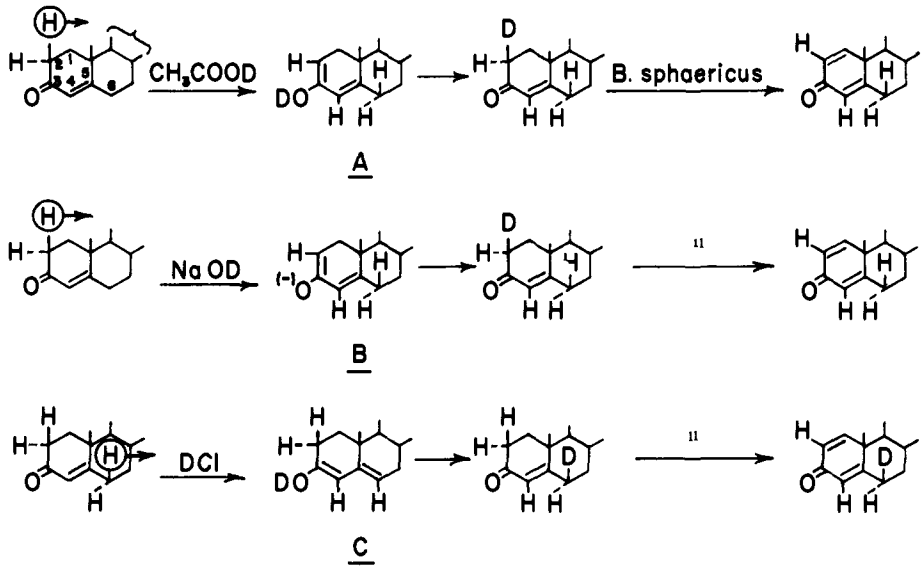

Fig. 1.—Favored paths of enolization, protonation, and dehydrogenation of testosterone.

the kinetic enolization behavior of α,β-unsaturated ketones, the deuterium incorporation pattern of testosterone has been studied under a variety of conditions (Fig. 1). Acid-catalyzed enolization was effected with deuterium chloride in deuterium oxide–diglyme solution at room temperature or with 50% deuterioacetic acid–deuterium oxide at elevated temperatures; base-catalyzed enolate anion formation was carried out with sodium deuteroxide in deuterium oxide–diglyme solution at room temperature. Following exchange, which was so regulated as to allow the incorporation on carbon of about 0.5 to 1.5 atoms of deuterium, the 17-hydroxyl group of the substrate was oxidized to remove deuterium on oxygen and the resulting deuterated androst-4-ene-3,17-dione analyzed for isotope at the exchangeable positions C-2, 4, and 6.

Total deuterium was determined by simple analysis[8] while the distribution of isotope was elucidated by a combination of biochemical and physical methods based on the following observations. Deuterium at C-4 could be readily detected by the characteristic[2] C–D stretching band at 2255 cm.$^{-1}$ in the infrared and by integration of the C-4 proton peak at 344 c.p.s. in the n.m.r. Anticipating the discussion to follow, no more than traces of C-4 deuterium were detected in our experiments and therefore this position may be ignored. Steroids of the 5α-androstan-3-one and androst-4-en-3-one series undergo C-1(2) dehydrogenation with whole cell or with sonically disrupted cell preparations of *Bacillus sphaericus* by the stereospecific loss of the 1α-proton and by the preferential and probably stereospecific loss of the 2β-proton (Fig. 1).[9] Furthermore, when 6β-deuterioandrost-4-ene-3,17-dione was microbiologically dehydrogenated at C-1(2) no loss of deuterium occurred. Therefore, when the deuterated substances produced by acid- or base-catalyzed enolization were dehydrogenated at C-1(2) all deuterium loss could be attributed to isotope originally present at C-2. These 1-dehydro derivatives could then be readily analyzed for remaining deuterium distribution by their n.m.r. spectra. Of the three vinylic protons present in the dehydrogenation product, androsta-1,4-diene-3,17-dione, the C-1 proton appears farthest downfield as a doublet at 420 and 430 c.p.s. (J = 10 c.p.s.) due to coupling with the C-2 proton. When deuterium is present at C-2, the C-1 proton appears as a singlet at 425 c.p.s. which is centered between the aforementioned doublet; integration of the respective areas provides a reasonable measure of the amount of deuterium remaining at C-2. A second analytical procedure depended upon integration of the C-2 and C-4 proton area in the 1,4-dienone. The C-2 proton appears as a pair of doublets ($J_{2,4}$ = 2, $J_{1,2}$ = 10 c.p.s.) centered at 380 and 370 c.p.s., while the C-4 proton overlaps the upfield portion of the C-2 proton. The total area under this region corresponds to two protons and since isotope incorporation at C-4 was minimal, any diminution of this area provided a direct measure of deuterium at C-2. In practice, the total area of the C-1 proton peak served as an internal standard for the area of one proton. Estimation of C-2 deuterium by the two methods agreed quite closely. Assignment of a number of carbon–deuterium stretching frequencies in the infrared (Table I) allowed qualitative corroboration of isotope distribution both before and after dehydrogenation.

TABLE I

PRINCIPAL INFRARED STRETCHING BANDS OF DEUTERATED TESTOSTERONE DERIVATIVES[21]

Derivative	Position of deuterium	Principal infrared bands (±5 cm.$^{-1}$)[a]
Δ^4-3-ketone	2β	2140
Δ^4-3-ketone	2,2	2140, 2220
Δ^4-3-ketone	6β	2140
Δ^4-3-ketone	6α	2190
Δ^4-3-ketone	4	2255
$\Delta^{1,4}$-3-ketone	2	2082 (w), 2225 (m), 2280 (st)
$\Delta^{1,4}$-3-ketone	6β	2155
$\Delta^{1,4}$-3-ketone	6α	2090 (sh), 2180 (sh), 2225 (st)
$\Delta^{1,4}$-3-ketone	4	2260

[a] w = weak, m = medium, st = strong, sh = shoulder.

Table II lists the isotope incorporation and distribution under the various enolization conditions. Two experiments with deuterium chloride, the first resulting in 0.6 atom incorporation and the second, 1.65 atoms,

(8) Deuterium analyses by Mr. Josef Nemeth, Urbana, Ill.

(9) H. J. Ringold, M. Hayano, and V. Stefanovic, *J. Biol. Chem.*, **238**, 1960 (1963).

TABLE II

THE DISTRIBUTION OF DEUTERIUM INCORPORATED INTO TESTOSTERONE BY ENOLIZATION

	Catalyst					
	DCl		CH_3COOD		NaOD	
Experiment no.	1	2	3	4	5	6
Total atoms D incorpd.[a]	0.60	1.65	1.16	1.51	1.10	1.43
Atoms C-2 D lost by bacterial dehydrogenation[a]	0.15	0.55	0.72	0.84	0.94	0.89
Atoms D remaining at C-2 after 1,2-dehydrogenation[b]	None	0.1	0.38	0.57	0.25	0.52
Atoms D at C-2 (initial)	0.15	0.65	1.10	1.41	1.19	1.41
Atoms D at C-4 and C-6	0.45	1.0	0.06	0.10	None	None
Atoms D at C-4[c]	None	0.05	None	Trace	None	None
Atoms D at C-6	0.45	0.95	0.06	0.10	None	None
Init. D ratio, C_2/C_6	0.15/0.45	0.65/0.95	1.10/0.06	1.41/0.1	1.10/0	1.41/0

[a] Determined by direct analysis (see ref. 8). [b] Estimated by n.m.r.; accuracy about ± 0.05. [c] Estimated by n.m.r. and infrared.

are tabulated. In the first experiment the C-2:C-6 ratio was 0.15:0.45, demonstrating a preference but not an overwhelming preponderance for $\Delta^{3,5}$-enol over $\Delta^{2,4}$-enol formation while the ratio in the second experiment was 0.65:0.95. It should be noted that the experimental design based upon deuterium incorporation will tend to minimize in each case the actual extent that one enol is favored over the other since the favored enol will become increasingly subject to a primary deuterium isotope effect.

In the case of weak acid catalysis with deuterioacetic acid, two reactions were terminated after the incorporation of 1.16 and 1.51 atoms of deuterium, respectively, and led to only 0.06 and 0.10 atom at C-6. Formation of the $\Delta^{2,4}$-enol was therefore so markedly favored that both the first and second atom of deuterium were introduced at C-2.

The pattern in two experiments with sodium deuteroxide essentially paralleled that of deuterioacetic acid. When 1.1 and 1.43 atoms were incorporated, no deuterium could be detected at C-4 or at C-6 demonstrating a complete preference for $\Delta^{2,4}$-enolate anion formation.

Pertinent to the discussion to follow is the fact that deuterium loss at C-2 by dehydrogenation was considerably greater than deuterium retention in each case. Since dehydrogenation[9] has been shown to involve primarily 2β-proton loss, it is apparent that axial 2β-protonation of both the $\Delta^{2,4}$-enol and enolate anion was favored while protonation of the $\Delta^{3,5}$-enol in the deuterium chloride reaction was shown by infrared analysis to be exclusively 6β-axial. The latter observation confirms previous work[2] concerned with protonation of the $\Delta^{3,5}$-enol and -enol ether.

Nature of the Transition State.[10]—From our results it is clear that enolization of the Δ^4-3-ketone in the presence of strong acid leads to a moderate favoring of the more stable $\Delta^{3,5}$-enol as the kinetically determined product. With weak acid or with sodium deuteroxide, formation of the less stable $\Delta^{2,4}$-enol and -enolate anion are heavily favored. The strong acid results in aqueous medium are in general accord with the effect of anhydrous hydrogen chloride noted in the dichlorodicyanoquinone dehydrogenation of Δ^4-3-ketones where hydrogen chloride appeared to promote exclusive formation of the $\Delta^{3,5}$-enol.[7]

As a first approximation it may be stated that with strong acid catalysis and not with weak acid the transition state in the enolization of Δ^4-3-ketones bears sufficient resemblance to the enol to lead directly to the more stable enol. With deuteroxide as base the transition state does not approach anion sufficiently to lead to the more stable enolate anion. The results with deuteroxide paralleled experiments with the stronger base potassium *t*-butoxide in *t*-butyl alcohol which converted 2β-deuterioandrost-4-ene-3,17-dione into the $\Delta^{3,5}$-conjugate anion (trapped by 4,4-dimethylation), completely free of C-2 deuterium as was recovered starting material. Since formation of the conjugate anion has been shown to be rate determining[4] in the 4,4-dimethylation reaction, the $\Delta^{2,4}$-anion must have been kinetically favored. Further argument against a *strong* resemblance of the transition state to anion in the base catalysis case or even to enol in the strong acid case is the aforementioned fact that axial (β) protonation (deuteration) was favored both at C-2 and at C-6. Since the least hindered side is the α-side, and protonation at either 2β or 6β involves a strong diaxial interaction with the bulky angular methyl substituent, then, in accord with the arguments advanced by Zimmerman[11] and by Corey,[12] a transition state very close to enol or enolate should have led to α-protonation.

Striking confirmation of the greater general resemblance of the transition state to product in the case of acid- as contrasted to base-catalyzed enolization came from studies with derivatives of 6α- and 6β-methyltestosterone (Fig. 2). In the absence of a 6-methyl substituent and with acid catalysis the preference for C-6 axial protonation of the enol must, on the basis of a symmetrical transition state, be paralleled by an identical preference for axial proton loss, although we have not established this point experimentally. With potassium *t*-butoxide in *t*-butyl alcohol independent studies (to be published) have demonstrated that 6β-proton loss proceeds about eight times as fast as 6α-proton loss in the C-6-unsubstituted case. However, since 6β-methyltestosterone, due primarily to the diaxial 6β-methyl–10β-methyl interaction, must be unstable relative to 6α-methyltestosterone by about 4 kcal.,[13] even a moderate relief of this strain by development of some trigonal character in the transition state should lead to faster enolization of the 6β-methyl rather than the 6α-methyl

(10) In our considerations, the more fruitful approach appears to be treatment of the nature of the transition state in terms of the degree of stretching of the methylenic proton and the degree of development of trigonal character at the methylenic (C-2) or vinylogous (C-6) carbon atom, rather than in terms of the distance of movement along the reaction coordinate leading from starting material to product as in the Hammond postulate treatment; G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).

(11) See H. E. Zimmerman in "Molecular Rearrangements," ed. by P. de Mayo, Interscience Publishers, Inc., New York, N. Y., 1963, pp. 345–406, and references therein.

(12) E. J. Corey and R. A. Sneen, *J. Am. Chem. Soc.*, **78**, 6269 (1956).

(13) N. L. Allinger and M. A. Miller, *ibid.*, **83**, 2145 (1961).

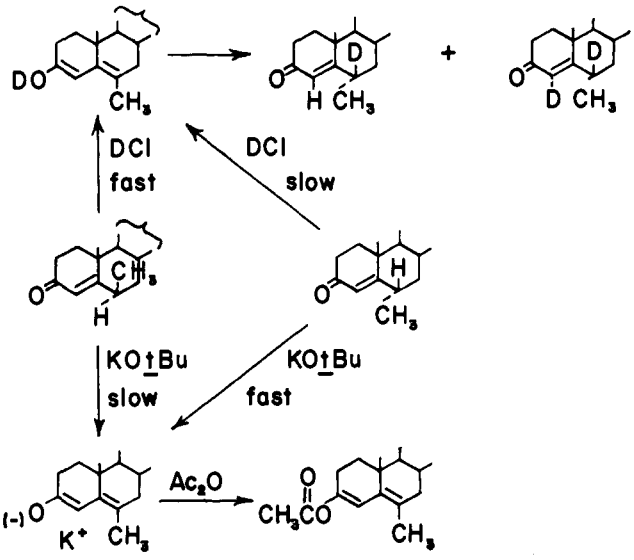

Fig. 2.—Enolization of isomeric 6-methyl-Δ^4-3-ketones with acid and with base.

isomer. Enolization studies carried out with potassium t-butoxide in t-butyl alcohol with trapping of the common $\Delta^{3,5}$-potassium enolate as the enol acetate[4] (Fig. 2) revealed that 6α-methylandrost-4-ene-3,17-dione formed the conjugate anion at least four times as rapidly as the 6β-methyl isomer, indicating very little enolate anion character in the transition state. In contrast, when enolization of the isomeric 6-methyltestosterones was carried out with deuterium chloride in diglyme–deuterium oxide the 6β-methyl isomer was shown to undergo inversion with concomitant incorporation of deuterium at C-6 much more rapidly than the 6α-methyl compound incorporated deuterium. After 4.5 hr., the 6β-methyl isomer had incorporated 1.7 atoms of deuterium and both the C-19 and C-6 methyl peaks in the n.m.r. spectrum indicated essentially complete inversion to the 6α-methyl isomer bearing deuterium at the 6β-position. The same period of exchange led to the incorporation of 0.87 atom of deuterium into the 6α-methyl isomer with only an estimated 0.45 atom of deuterium at 6β. Deuteration of the common 6-methyl enol also led to significantly more isotope incorporation at C-4[14] than did the C-6 unsubstituted[2] enol which provided a second measure of the relative rates at which the two isomers formed the $\Delta^{3,5}$-enol. Integration of the C-4 proton peak in the n.m.r. demonstrated 0.75 atom of C-4 deuterium proceeding from the 6β-methyl isomer and only 0.41 atom from the 6α-methyl substance. Since deuterium at C-4 could arise only *via* the $\Delta^{3,5}$-enol, it is apparent that, as with the 6-desmethyl substrate, deuterium chloride favored formation of this enol, and, since the least favored 6α-equatorial proton was lost preferentially, sufficient enolic (trigonal) character must have been developed in the transition state to relieve partially the 6β-methyl–10β-methyl interaction. However, a very strong resemblance of the transition state to enol in the case of both 6-methyl isomers would have necessitated a favoring of the 6β- over the 6α-methyl isomer by an order of about 3 to 4 kcal. or a minimum rate factor of 100-fold. It appears unlikely in fact that the actual rates differ by more than tenfold.

Our over-all results with this series of α,β-unsaturated ketones may best be summarized with the qualitative statements that: (A) enolization catalyzed by strong base or by weak acid leads to preferential loss of the C-2 proton and a transition state strongly resembling starting material,[15] while the preferential loss of the C-6 proton for deuterium chloride catalysis involves a transition state intermediate between protonated ketone and enol; (B) with the C-6 nonmethylated steroids, axial proton loss and gain at C-2 and C-6 is favored under all the experimental conditions described. The weak and strong acid results are in general agreement with the conclusions drawn by other workers,[12,16] but the results with strong base, where it has been assumed[16a,17] that the transition state resembles the enolate anion, are at variance. To rationalize our findings we have drawn from and unified certain of the numerous and at times bewildering array of postulated and general rules that have been advanced to explain and predict enolization reactions.

With respect to base catalysis, the simple relationship appears to apply that it is the most acidic proton which will be the one that is first removed and most rapidly replaced.[18] This predicts the loss of a C-2 proton before that of a C-6 proton since the former, being directly adjacent to the carbonyl group, is the proton most subject to the inductive effect of this function. The rule would also predict, in accord with our previous studies,[3,4] the much more rapid loss and replacement of a C-4 proton from the β,γ-unsaturated Δ^5-3-keto steroids due to the combined inductive effect of the carbonyl group and of the double bond. The enolization and reprotonation of the β,γ-unsaturated ketones will be fully treated in a subsequent paper.

Corey's concept[12] of the favoring (in the absence of overwhelming adverse steric factors) of axial over equatorial proton loss and gain due to more efficient $\sigma-\pi$ overlap in the transition state may also be incorporated within the same framework and an axial proton at C-2 or at C-6 can be considered to be more acidic than the corresponding equatorial proton. If continuous $\sigma-\pi$ overlap results in greater resonance stabilization when the leaving or entering proton is adjacent to the carbonyl group (C-2) rather than adjacent to a double bond (C-6), this would be another factor apart from the aforementioned inductive effect leading to more rapid loss of the C-2β proton relative to the C-6β proton. This surely must be an important factor in the relatively greater acidity of the C-4 proton of the Δ^5-3-ketones, whose central position allows overlap with both the carbonyl and the double bond.

The relationship of proton acidity to the nature of the transition state in this series of substances would appear to follow very simply and logically. *For catalysis*

(14) The greater degree of C-4 protonation of the enol in the presence of a 6-methyl substituent may be attributed to the relatively greater stability of the tetrasubstituted double bond in the resulting 6-methyl-β,γ-unsaturated ketone. This offers further evidence that even with strong acid the protonated ketone still makes a significant contribution to the transition state.

(15) Ketone in the case of base catalysis and protonated ketone in the case of weak acid.

(16) (a) C. G. Swain and E. R. Thornton, *J. Am. Chem. Soc.*, **84**, 817 (1962); (b) J. L. Kurz, *ibid.*, **85**, 987 (1963).

(17) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 232.

(18) It may be readily recognized that this statement is essentially an extrapolation of Ingold's rule that "when a proton is supplied by acids to the mesomeric anion of weakly ionizing tautomers of markedly unequal stability, then the tautomer which is most quickly formed is the thermodynamically less stable; it is also the tautomer from which the proton is lost most quickly to bases." C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 565.

with a given base, the more acidic the methylenic proton being removed, the smaller the degree of C–H bond stretching necessary to reach the transition state and therefore the lesser the development of anionic charge and the greater the resemblance of transition state to starting ketone. This predicts that the transition state for formation of the $\Delta^{2,4}$-anion (C-2 proton loss) will resemble ketone more than will the transition state for $\Delta^{3,5}$-anion formation (C-6 proton loss) while loss of a C-4 proton from the Δ^{5}-3-ketone to yield the $\Delta^{3,5}$-anion will lead to a transition state most resembling ketone. Since the rate of anion formation in these three cases parallels the acidity of the methylenic proton, the qualitative extrapolation follows that the lesser the development of anionic charge on the ketone at the transition state the lower the energy increment of the transition state above that of the starting ketone (*i.e.*, the lower the activation energy). In line with these arguments it should be noted also that in each case the loss of an axial rather than an equatorial proton will increase the resemblance of the transition state to ketone.

The last important factor playing a role in the nature of the transition state for base catalysis is the strength of the base removing a proton from the ketone, which has been the subject of extensive investigation by Swain and co-workers.[16,19] These investigators concluded[19] that in either acid- or base-catalyzed enolization the stronger the base the shorter the methylenic C–H bond at the transition state. In other terms, the stronger the base the less C–H bond stretching required and the closer the transition state to ketone. Acceptance of this reasonable argument indicates that only with a very weak base such as water can it be anticipated that the transition state for enolization of a Δ^{4}-3-keto steroid will bear a significant resemblance to the enolate anion.

With respect to acid catalysis and enol formation two opposing effects are operative. Protonation of the carbonyl leads to a lengthening of the carbonyl C–O bond (and a greater resemblance to enol) but also to a shortening of the methylenic C–H bond (and a greater resemblance to ketone). It should be noted that although the C–H bond has been shortened, the acidity of the methylenic proton has been increased by the development of partial carbonium ion character on the carbonyl carbon atom. Comparing reaction in aqueous medium of a weak acid, as for example acetic acid, to hydrochloric acid and assuming carbonyl protonation by hydronium ion in each case,[20] the transition-state determinant factor will be the strength of the base removing the methylenic proton. In the case of acetic acid the base will be the relatively strong one, acetate ion, which in accord with Swains'[16,19] argument will require relatively little C–H bond stretching and the transition state will therefore resemble protonated ketone more than enol. On the other hand, in dilute hydrochloric acid the strongest base present will be water which will require considerable C–H bond stretching and lead to a transition state with a greater resemblance to enol. In this latter case the acidity of the methylenic protons (C-2 *vs.* C-6) will assume little importance relative to the stability of the respective enols or relative to the relief of destabilizing interactions in the starting ketone such as the 6β-methyl–10β-methyl interaction in the 6-methyl derivative. Therefore, with weak acid as with strong base the most acidic proton (C-2β) should be lost first and the observed preferential formation of the least stable $\Delta^{2,4}$-enol with deuterated acetic acid was thus the expected reaction course. With deuterated hydrochloric acid catalysis, however, formation of the more stable $\Delta^{3,5}$-enol became the anticipated reaction course. It should be noted though that even with deuterium chloride the more acidic axial 6β-proton was preferentially lost rather than the equatorial 6α-proton. Only when the transition state very closely resembles enol may it be anticipitated that steric hindrance to approach from the β side will override loss or gain of the more acidic (*i.e.*, axial) proton from C-6.

(19) See C. G. Swain and A. S. Rosenberg, *J. Am. Chem. Soc.*, **83**, 2154 (1961), and earlier references therein.

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

Experimental[21]

Preparation of 6β-Deuterioandrost-4-ene-3,17-dione.—3-Ethoxy-androsta-3,5-dien-17β-ol[22] (100 mg.) was suspended in 20% deuterioacetic acid in deuterium oxide (2 ml.), the mixture was briefly warmed, and then stirred for 3 hr. at room temperature. Water was added and the resulting testosterone filtered, dried, and separated from polar by-products by chromatography on a thin-layer silica Gel plate utilizing ethyl acetate–benzene (1:3). Elution with acetone and oxidation at 0° with 8 *N* chromic acid in acetone (Jones[23] reagent) followed by precipitation in water and recrystallization from acetone–hexane gave 55 mg. of 6β-deuterioandrost-4-ene-3,17-dione, m.p. 172–173°. In the infrared,[11] the principal C–D stretching band appeared at 2140 cm.$^{-1}$ while the out-of-plane deformation band for the C-4 proton had shifted[2] from 869 to 854 cm.$^{-1}$. In the n.m.r. spectrum[21] the C-4 proton appeared as a sharp peak at 345 c.p.s. with a line-width at half-height of 2.4 c.p.s.[24] Found[8]: 0.91 atom of deuterium.

Dehydrogenation of 6β-Deuterioandrost-4-ene-3,17-dione with Cell-Free *Bacillus sphaericus* Preparation.[9,25]—Cells from 1.6 l. of a 42-hr. culture of *B. sphaericus* were sonically disrupted in 100 ml. of phosphate buffer (0.05 *M*, pH 7.3) for 10 min. and centrifuged at 3500 × *g* for 10 min. The supernatant was made up to 150 ml. with additional buffer, and menadione (5 mg.) and the 6β-deuterio steroid (40 mg.) in 2 ml. of ethanol–propylene glycol (1:1) were added, and the mixture shaken for 4 hr. at 30°. The steroid was recovered by extraction with ethyl acetate and the 6β-deuterioandrosta-1,4-diene-3,17-dione separated by silica gel thin-layer chromatography (ethyl acetate–benzene, 1:4); yield 31 mg., m.p. 138–140°; infrared: C–D stretching band at 2155 cm.$^{-1}$. Found[8]: 0.90 atom of deuterium.

Preparation of Deuterium Chloride Solution.—Gaseous hydrogen chloride was passed into 99.8% deuterium oxide to the saturation point; 5 ml. of this solution was diluted tenfold with deuterium oxide yielding approximately a 1 *N* solution which was titrated with standard alkali and then finally diluted further to yield a 0.5 *N* stock solution.

Deuterium Chloride-Catalyzed Enolization of Testosterone (Expt. 1).—A solution of testosterone (0.29 g.) in redistilled diglyme (10 ml.) and deuterium chloride solution (1 ml., 0.5 *N*) was stirred for 2 hr. at room temperature and then poured into excess ice–water. The precipitate was filtered, washed, and dried

(21) All infrared analyses were carried out in chloroform solution in a Beckman IR-7 with Bausch and Lomb replica grating; n.m.r. spectra were obtained with a Varian 4300 spectrometer at a frequency of 60 Mc./sec. The samples were dissolved in deuteriochloroform and the spectra were calibrated using the side-band technique. Peak positions are reported in c.p.s. downfield from tetramethylsilane (internal reference). We are grateful to Mr. T. A. Wittstruck for the n.m.r. and to Mr. N. Bacon for the infrared determinations.

(22) A. Serini and H. Koster, *Ber.*, **71**, 1766 (1938); A. Ercoli and P. de Ruggieri, *J. Am. Chem. Soc.*, **75**, 650 (1953).

(23) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *ibid.*, **75**, 2548 (1953).

(24) T. A. Wittstruck, S. K. Malhotra, and H. J. Ringold, *ibid.*, **85**, 1699 (1963).

(25) V. Stefanovic, M. Hayano, and R. I. Dorfman, *Biochim. Biophys. Acta*, **71**, 429 (1963).

in vacuo before being oxidized for 5 min. in acetone solution at 0° with 8 *N* chromic acid in sulfuric acid.[23] After precipitation in water and recrystallization from acetone–hexane, the product, androst-4-ene-3,17-dione, contained 0.60 atom of deuterium[8] and showed in the infrared a principal C–D stretching band centered at 2140 cm.$^{-1}$ (2β- and 6β-D) and a very weak band at 2220 cm.$^{-1}$. No 4-deuterio band at 2255 cm.$^{-1}$ was visible, while two bands for the C-4 proton (out-of-plane deformation) were seen at 869 and 854 cm.$^{-1}$, the latter corresponding to the shift already noted with a 6β-deuterio substituent.

Dehydrogenation of a 40-mg. sample with *B. sphaericus* was carried out as described above, and the product deuterioandrosta-1,4-diene-3,17-dione contained 0.45 atom of deuterium,[8] or a loss of 0.15 atom from C-2. In the infrared the principal deuterium band was at 2155 cm.$^{-1}$ (6β-D-$\Delta^{1,4}$) while a shoulder was present at 2227 cm.$^{-1}$. In the n.m.r. spectrum, the C-1 proton appeared as a clean doublet at 420 and 430 c.p.s. with no peak at 425 c.p.s. (see Discussion) while the integrated area of the C-2 and C-4 protons in the 370–380 c.p.s. region corresponded to 2.0 protons, demonstrating the absence of C-2 deuterium. The initial incorporation of deuterium at C-2 was therefore 0.15 atom.

Deuterium Chloride-Catalyzed Enolization of Testosterone (Expt. 2).—Extension of acid-exchange time to 8 hr. followed by Jones oxidation[23] gave androst-4-ene-3,17-dione containing 1.65 atoms of deuterium by analysis.[8] In the infrared, the principal C–D band was at 2140 cm.$^{-1}$ (2β,6β) while weak bands appeared at 2220 and 2255 cm.$^{-1}$ (4D-Δ^4). In the n.m.r. the C-4 proton peak at 345 c.p.s. exhibited a line-width at half-height of 2.5 c.p.s. Integration of the C-4 proton area in the n.m.r. and quantitation of the 2255 cm.$^{-1}$ peak in the infrared indicated a deuterium content at C-4 of about 0.05 atom.

Dehydrogenation at 1,2 with *B. sphaericus* was carried out as above and led to the loss of 0.55 atom of deuterium from C-2.[8] The 1,4-dienone exhibited its principal infrared deuterium band at 2155 cm.$^{-1}$ (6βD) and shoulders at 2220 and 2260 cm.$^{-1}$. The C-1 proton appeared in the n.m.r. as a triplet, the peaks at 420 and 430 c.p.s. being due to C-2 protonated material while the small peak at 425 c.p.s. was characteristic of C-2 deuterated compound. The C-2 and C-4 proton area in the 370-380 c.p.s. region was found, by integration, to be equivalent to 1.85 protons, thus demonstrating 0.15 atom of deuterium at C-2 and C-4. Since 0.05 atom had been found at C-4, the total initial incorporation of deuterium at C-2 corresponded to 0.65 atom.

Deuterioacetic Acid-Catalyzed Enolization of Testosterone (Expt. 3).—A solution of testosterone (100 mg.) in deuterioacetic acid–deuterium oxide (1 ml., 50%) was boiled for 40 min. Isolation of the product *via* precipitation in water, followed by Jones oxidation[23] and chromatography on thin layer, gave androst-4-ene-3,17-dione containing 1.16 atoms of deuterium.[8] The principal C–D infrared band was at 2140 cm.$^{-1}$ (2β-D) and a medium intensity band appeared at 2220 cm.$^{-1}$ (2,2-Di-D). The C-4 proton peak exhibited a width at half-height of 3.5 c.p.s. demonstrating the absence of deuterium at C-6β.[24] Microbiological dehydrogenation gave androsta-1,4-diene-3,17-dione containing 0.44 atom of deuterium.[8] The principal C–D infrared absorption peaks, in the order of increasing intensity, were at 2082, 2225, and 2280 cm.$^{-1}$ and are all attributed to the 2-deuterio-$\Delta^{1,4}$-diene. The C-1 proton appeared in the n.m.r. as a triplet at 420, 425, and 430 c.p.s. and integration of the 370–380 c.p.s. region showed 1.62 protons. The initial incorporation of C-2 deuterium therefore was about 1.1 atoms.

Deuterioacetic Acid-Catalyzed Enolization of Testosterone (Expt. 4).—Repetition of the above experiment but with extension of the boiling time to 1 hr. followed by 24 hr. additional reaction at room temperature afforded androst-4-ene-3,17-dione containing 1.51 atoms of deuterium.[8] The principal infrared bands were again at 2140 and 2220 cm.$^{-1}$ but a small shoulder at 2255 cm.$^{-1}$ indicated a trace of C-4 deuterium. Bacterial dehydrogenation gave the 1,4-dienone containing 0.67 atom of deuterium[8] and exhibiting the three characteristic C–D bands in the infrared for the 2-deuterio-$\Delta^{1,4}$-diene moiety, as well as a shoulder at 2155 cm.$^{-1}$ due to 6-deuterio-$\Delta^{1,4}$-diene. Integration of the C-2, C-4 proton area in the n.m.r. showed 1.4 protons, demonstrating the presence of about 0.6 atom of deuterium remaining at C-2, which was confirmed by the area of the 425 c.p.s. band. Deuterium incorporation therefore was essentially exclusive at C-2.

Sodium Deuteroxide-Catalyzed Enolization of Testosterone (Expt. 5).—Metallic sodium (50 mg.) was dissolved with stirring in a solution of 99.8% deuterium oxide (1 ml.) in diglyme (10 ml.). Testosterone (290 mg.) was added and the resulting solution stirred for 26 hr. at room temperature in an atmosphere of nitrogen. Conventional work-up and Jones oxidation gave androsta-1,4-diene-3,17-dione containing 1.1 atoms of deuterium[8] and whose infrared C–D bands were essentially the same as in expt. 3. Dehydrogenation with *B. sphaericus* gave 1,4-diene-3,17-dione containing 0.17 atom of deuterium, which were shown by infrared and n.m.r. to be present at C-2. Therefore, the initial incorporation of deuterium was specific for C-2.

Sodium Deuteroxide-Catalyzed Enolization of Testosterone (Expt. 6).—Repetition of experiment 5 with extension of the reaction time to 48 hr. and conventional work-up gave androsta-1,4-diene-3,17-dione containing 1.43 atoms of deuterium[8] (C–D bands at 2136 and 2220 cm.$^{-1}$). After bacterial dehydrogenation the 1,4-diene-3,17-dione contained 0.54 atom of deuterium[8] which were shown by infrared and n.m.r. to be present at C-2.

Demonstration of the Loss of C-2 Deuterium in the Formation of the $\Delta^{3,5}$-Anion with Potassium *t*-Butoxide.—A mixture of 2β-deuterioandrost-4-ene-3,17-dione[26] (50 mg.) and potassium *t*-butoxide (40 mg.) in *t*-butyl alcohol (2 ml.) was allowed to stir under nitrogen for 30 min. at room temperature to preform the $\Delta^{3,5}$-conjugate anion. Methyl iodide (0.5 ml.) was added and stirring continued for an additional 10 min. before the addition of dilute acetic acid and the isolation of steroids by ether extraction. Chromatography on silica gel (thin layer) led to the recovery of 10 mg. of 4,4-dimethylandrost-5-ene-3,17-dione, m.p. 165–167°, λ_{max}^{KBr} 5.78 and 5.85 μ, which was identical with a sample prepared by Jones oxidation of 3β,17β-dihydroxy-4,4-dimethylandrost-5-ene.[27]

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 79.89; H, 9.75.

Also, 27 mg. of starting material was recovered. By infrared analysis both the 4,4-dimethyl compound and the recovered starting material were completely free of deuterium, demonstrating that formation of the $\Delta^{2,4}$-anion was more rapid than $\Delta^{3,5}$-anion formation.

Deuterium Chloride-Catalyzed Enolization of 6α-Methyltestosterone.—A solution of 6α-methyltestosterone[28] (100 mg.) and deuterium chloride (0.5 ml., 0.5 *N*) in diglyme (5 ml.) was stirred for 4.5 hr. at 25° and then poured into water. The deuterated substance was shown to be free of 6β-methyl isomer by thin layer chromatography and by its n.m.r. spectrum. In the n.m.r., nondeuterated 6α-methyltestosterone exhibits the C-4 proton peak as a doublet at 345 and 347 c.p.s., the C-19 methyl group as a singlet at 72 c.p.s., and the 6α-methyl group as a doublet (due to coupling with the 6β-proton) at 61.5 and 67.5 c.p.s. Integration of the C-4 proton area (in the n.m.r.) of the deuterium-exchanged material demonstrated the incorporation of 0.41 atom of deuterium at C-4. Three peaks appeared for the 6α-methyl group, the doublet at 60.8 and 67.0 c.p.s. representing 6β-protonated material and a peak at 63.3 c.p.s. due to 6β-deuterated compound. The estimated deuterium content at C-6 was 0.45 atom. A sample of the exchanged material was oxidized to the 17-ketone with Jones reagent and analyzed for deuterium content by mass spectrum.[29] Found: 0.87 atom of deuterium (D_0, 47.0%; D_1, 20.3%; D_2, 31.0%; D_3, 1.7%).

Deuterium Chloride-Catalyzed Enolization of 6β-Methyltestosterone.—Treatment of the 6β-methyl isomer with deuterium chloride was carried out precisely as described above for the 6α-methyl steroid. 6β-Methyltestosterone[28] (nondeuterated) exhibits, in the n.m.r., the C-4 proton as a sharp singlet at 345 c.p.s., the C-19 methyl group as a singlet at 76.5 c.p.s., and the 6β-methyl as a doublet at 70 and 76.5 c.p.s. overlapping the C-19 methyl group. The exchanged material showed only a single 19-methyl peak at 72.8 c.p.s. demonstrating essentially complete inversion to the 6α-methyl isomer which was confirmed by the appearance of only a single 6-methyl peak at 63.8 c.p.s. (6α-methyl-6β-D). The area of the C-4 proton peak in the n.m.r. corresponded to the incorporation of 0.75 atom D at C-4. A sample of material oxidized to the 17-ketone was analyzed by mass spectrum.[29] Found: 1.68 atoms of deuterium (D_0, 9.6%; D_1, 25.7%; D_2, 51.8%; D_3, 12.9%).

3-Acetoxy-6-methylandrost-3,5-diene-17-one.—A solution of 6α-methylandrost-4-ene-3,17-dione[28] (300 mg.) and potassium *t*-

(26) Prepared by zinc–deuterioacetic acid dehalogenation of 2α-iodoandrost-4-ene-3,17-dione (see ref. 9) and containing 0.67 atom of deuterium, primarily 2β.

(27) H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, **22**, 602 (1957).

(28) H. J. Ringold, E. Batres, and G. Rosenkranz, *ibid.*, **22**, 99 (1957).

(29) Mass spectra by Dr. R. Ryhage, Karolinska Institutet, Stockholm.

butoxide (1.1 g.) in anhydrous *t*-butyl alcohol (5 ml.) was stirred at room temperature, under nitrogen, for 2 hr. Acetic anhydride (2 ml.) was added, the solution stirred for an additional 5 min., and poured into water. The precipitate was crystallized several times from aqueous methanol contained a drop of pyridine to yield an analytical specimen of enol acetate, m.p. 138–140°, λ_{max}^{KBr} 5.75 μ (17-keto and $\Delta^{3,5}$-enol acetate), λ_{max}^{EtOH} 245 mμ, ϵ 19,200.

Anal. Calcd. for $C_{22}H_{30}O_3 \cdot 0.5H_2O$: C, 75.21; H, 8.83. Found: C, 74.95; H, 8.93.

Relative Rates of Formation of the $\Delta^{3,5}$-Anion from the Isomeric 6-Methylandrost-4-ene-3,17-diones with Potassium *t*-Butoxide.—A solution of 6β-methylandrost-4-ene-3,17-dione[28] (25 mg.) in anhydrous *t*-butyl alcohol (1 ml.) was treated with potassium *t*-butoxide (50 mg., 5 equiv.) and stirred for 1 hr. at 25°. Acetic anhydride (0.2 ml.) was added and stirring continued for an additional 5 min. Water was added and the crystalline precipitate (24 mg.) filtered. Separation by silica gel thin layer chromatography (benzene–ethyl acetate, 7:3) established the presence of unreacted starting material and the enol acetate, 3-acetoxy-6-methyl-androst-3,5-diene-17-one, in a weight ratio of 5:4 (41% conversion). No 6β-methyl-Δ^4-3-ketone was detected. Identical treatment of 6α-methylandrost-4-ene-3,17-dione led to recovery of ketone and enol acetate in a weight ratio of 1:8 (87% conversion). Assuming quantitative formation of enol acetate from the $\Delta^{3,5}$-anion[4] and second-order kinetics, the 6α-methyl isomer underwent conjugate anion formation at about four times the rate of the 6β-methyl compound.

[CONTRIBUTION FROM THE CENTRAL RESEARCH DEPARTMENT, E. I. DU PONT DE NEMOURS AND CO., INC., WILMINGTON 98, DEL.]

Fluorocarbanions. Rates of Base-Catalyzed Hydrogen–Deuterium Exchange, Isotope Effects, and Acidity of Monohydrofluorocarbons[1]

BY S. ANDREADES

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The formation of perfluorocarbanions from monohydrofluorocarbons bearing hydrogen in primary, secondary, and tertiary positions has been demonstrated by isotopic exchange in sodium methoxide–methanol solution. The kinetics of exchange measured by F^{19} n.m.r., infrared, and mass spectral techniques give relative reactivities of 1.0, 6, 2×10^5, and 10^9 for fluoroform, 1-H-pentadecafluoroheptane, 2-H-heptafluoropropane, and tris(trifluoromethyl)methane, respectively. Heptafluoro-*n*-propyl and heptafluoroisopropyl carbanions, in the form of lithio derivatives generated from the corresponding monohydrofluorocarbons, have been trapped by reaction with propionaldehyde. The solvent isotope effect for labeled methanol, (k_{CH_3OD}/k_{CH_3OH}) = 1.5, was determined using rates of tritium exchange for the primary system. Activation parameters and solvent-corrected deuterium isotope effects are reported and used in a discussion of the mechanism of exchange and the acidity of monohydrofluorocarbons.

Introduction

Although fluorocarbanions are presumed intermediates in a variety of reactions, such as alkaline decarboxylation,[2] the attack of anions on fluorocarbonyl compounds,[3] and the attack of carbanions[4] or fluoride ion[5] on fluoroolefins, detailed mechanistic studies concerning the nature of perfluorocarbanions have not appeared.

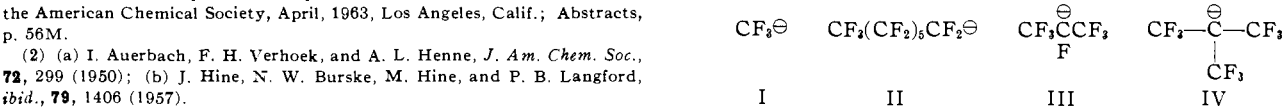
Monohydrofluorocarbons, in general, have been considered relatively inert[6] to common reagents, for example, concentrated potassium hydroxide at 100°.[6] In a series of extensive and definitive investigations of the mechanism of hydrolysis of mixed halomethanes,[2b,7] Hine and co-workers found the basic hydrolysis of fluoroform too slow to measure[7] ($<10^{-6}$ l. mole^{-1} sec.$^{-1}$ at 50°). Recently, reports have appeared that pentafluoroethane, 1-H-heptafluoropropane, and fluoroform undergo no deuterium or tritium exchange after 21–47 days in labeled, alkaline aqueous dioxane.[8] In the present paper, a detailed investigation of primary, secondary, and tertiary fluorocarbanions generated from monohydrofluorocarbons is described.

Method and Results

Monohydrofluorocarbons have been found to undergo readily base-catalyzed exchange in sodium methoxide–methanol solution according to eq. 1 in which R_f designates a perfluoroalkyl moiety. Four simple mono-

$$R_fH + CH_3OD \underset{(NaOCH_3)}{\overset{k_H}{\underset{k_D}{\rightleftharpoons}}} R_fD + CH_3OH \qquad (1)$$

hydrofluorocarbon systems (fluoroform, I_H; 1-H-perfluoroheptane, II_H; 2-H-heptafluoropropane, III_H; and tris(trifluoromethyl)methane, IV_H) were chosen as precursors to the primary, secondary, and tertiary fluorocarbanions I–IV. Compound II_H was included not only because of inherent interest in the $-CF_2H$



function but also because it is the only liquid (b.p. 95–96°) in the series and the homogeneity of its solutions[9] could conveniently be checked without vapor pressure measurements.

The rates of exchange (Table I) were measured in both the forward (k_H) and reverse (k_D) directions starting with the appropriate isotopically labeled substrate

(1) This work was presented in part at the 144th National Meeting of the American Chemical Society, April, 1963, Los Angeles, Calif.; Abstracts, p. 56M.

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(3) See, *e.g.*, E. T. McBee, O. R. Pierce, H. W. Kilbourne, and E. R. Wilson, *ibid.*, **75**, 3152 (1953).

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(5) W. T. Miller, Jr., W. Frass, and P. R. Resnick, *ibid.*, **83**, 1767 (1961), W. T. Miller, Jr., J. H. Fried, and H. Goldwhite, *ibid.*, **82**, 3091 (1960); J. H. Fried and W. T. Miller, Jr., *ibid.*, **81**, 2078 (1959).

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(7) J. Hine, A. M. Dowell, Jr., and J. E. Singley, Jr., *J. Am. Chem. Soc.*, **78**, 479 (1956); J. Hine and P. B. Langford, *ibid.*, **79**, 5497 (1957); and other related papers by Hine and co-workers.

(8) L. H. Slaugh and E. Bergman, *J. Org. Chem.*, **26**, 3158 (1961).

(9) The lack of detectable exchange reported by Slaugh and Bergman[8] was most likely due to extremely low solubilities of the substrates in aqueous dioxane.