acetamide in the presence of perchloric acid[6] quantitatively yielded 9α-bromo-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-acetate (XII), (XII), m.p. 180–185° (dec.); $[\alpha]^{25}\text{D}$ +133° (chloroform); (*Anal.* Calcd. for $C_{23}H_{28}BrO_6$: C, 57.38; H, 6.07; Br, 16.60. Found: C, 57.26; H, 6.56; Br, 16.36). The 9β,11β-oxide (XIII), m.p. 192–195°; $[\alpha]_D$ +67° (chloroform), was obtained in 76% yield by treatment of XII with potassium acetate in acetone, (*Anal.* Calcd. for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 69.19; H, 7.29). Opening of the oxide (XIII) with hydrofluoric acid gave 9α-fluoro-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-acetate (XIV)[7] (44% yield), m.p. 235–238°; $[\alpha]^{25}\text{D}$ +101° (acetone); (*Anal.* Calcd. for $C_{23}H_{29}FO_6$: F, 4.52; Found: F, 4.63).

9α-Fluoro-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-acetate (XIV) in glycogen deposition potency is 50 times greater than hydrocortisone and in salt retaining potency is 4.6 times greater than desoxycorticosterone acetate (DOCA).[8]

The authors are indebted to A. Koning, R. W. Kratz and V. R. Shellman for technical assistance; to Dr. J. L. Johnson, J. E. Stafford and Mrs. G. S. Fonken for infrared and ultraviolet absorption studies; to Mr. W. A. Struck and associates for microanalyses and to Mr. L. M. Reineke and associates for paper chromatographic analyses.

---

[6] J. Fried and E. F. Sabo, THIS JOURNAL, **75**, 2273 (1953).

[7] R. F. Hirschmann, R. Miller, R. E. Beyler, L. H. Sarett and M. Tishler, *ibid.*, **77**, 3166 (1955).

[8] R. O. Stafford, B. J. Bowman, M. M. Meinzinger and L. E. Barnes, *Proc. Soc. Exp. Biol. Med.*, in press.

J. A. HOGG
F. H. LINCOLN
A. H. NATHAN
A. R. HANZE
W. P. SCHNEIDER
P. F. BEAL
J. KORMAN

RESEARCH LABORATORIES
THE UPJOHN COMPANY
KALAMAZOO, MICHIGAN

RECEIVED JULY 15, 1955

AN UNUSUAL ISOTOPE FRACTIONATION EFFECT

Sir:

We are investigating the exchange reaction $CNI + C^{14}N^- \rightleftarrows C^{14}NI + CN^-$ in water and various dioxane–water mixtures. The reaction is followed by precipitation and radioassay of the inorganic cyanide as silver cyanide. The equilibrium constant K is simply the ratio of the specific activities of cyanogen iodide to cyanide after equilibration, S_{CNI}/S_{CN}. A value of 1.05 has been predicted for this constant by statistical thermodynamics.[1] It can be determined experimentally by the relation

$$K = a/b(A_0 - A_e)/A_e$$

In this, a and b are the concentrations of cyanide and cyanogen iodide, A_6 and A_e are the specific activities of cyanide before and after exchange equilibrium, and it is assumed that no fractionation effects result from the separation process. On this basis, the following results have been obtained for K at 30.6° and with an a/b ratio of approximately unity:

% Dioxane in solvent	Number of samples taken	Apparent K (Av. + max. dev.)
0	12	1.08 ± 0.02
20	22	1.15 ± 0.02
28	22	1.18 ± 0.03
40	40	1.28 ± 0.02
60	22	1.29 ± 0.03

The surprising consequence of increased dioxane content of the solvent may be explained in terms of a combined equilibrium and precipitation isotope effect. In experiments in which a solution of labelled sodium cyanide was poured directly into a solution containing silver nitrate and cyanogen iodide, it was found that the precipitated cyanide had undergone complete exchange with the cyanogen iodide. Obviously, the rate of the equilibration reaction is much greater than the rates of the precipitation reactions between silver nitrate and sodium cyanide, labelled and unlabelled. Isotopic equilibrium is thus continuously maintained in the solution during the precipitation procedure.

Letting r be the ratio of the rates of the precipitation reactions and $a/b = f$, a mathematical analysis similar to that employed previously in problems of this type[2] yields the relation

$$S_{CNI}/S_{CN} = f\left(\frac{K}{K+f}\right)^r \Big/ 1 - \left(\frac{K}{K+f}\right)^r$$

If it is assumed that in pure water the precipitation is a rapid ionic process with negligible isotope effect, $r = 1$, and $K = 1.08$ is the true equilibrium constant. In solution of high dioxane content, the precipitation may, however, be a competitive process exhibiting isotope effect. Assigning the reasonable value of $r = 0.9$ under these conditions, the following predictions result, justifying the magnitude of the observed effect:

f	0.5	1.0	2.0	5.0	10.0
S_{CNI}/S_{CN}	1.23	1.25	1.28	1.35	1.42

A full report of this work, which is being supported by the U.S.A.E.C. under Contract No. AT(30-1)-1578, will appear subsequently.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF BUFFALO
BUFFALO 14, NEW YORK

FRANCIS E. JENKINS
GORDON M. HARRIS

RECEIVED JUNE 27, 1955

---

[1] D. R. Stranks and G. M. Harris, THIS JOURNAL, **75**, 2015 (1953).

[2] A. M. Downes and G. M. Harris, *J. Chem. Phys.*, **20**, 196 (1952); A. M. Downes, *Aust. J. Sci. Res.*, Series A, **5**, 521 (1952).