

TABLE I

Preparation	Lactogenic activity I.U./mg.	"Growth hormone-like" activity	
		Total dose (mg.)	Net change in body weight (g.)
Starting material (3 components)	20	0.75	+ 4
Component I	30-35	0.75	+15
Components II and III	5-10	0.75	- 1

When the temperature was maintained at  $-20^{\circ}$  during the initial preparation of starting material from sheep pituitaries, our product contained a considerably greater proportion of component I than when the temperature was held at  $5^{\circ}$ . Also, highly purified component I can be converted easily into 3-component material upon standing in 2% aqueous  $\text{NH}_4\text{OH}$  at  $5^{\circ}$  for two hours.

The data obtained thus far indicate that component I is biologically highly active prolactin, whereas components II and III seem to be altered forms of this component.

**Acknowledgment.**—The authors wish to thank Dr. A. Segaloff for the crop-sac-stimulating assays, and Dr. D. E. Williams and Miss V. J. Powell for the physical chemical measurements.

(10) O. Riddle, R. W. Bates and S. W. Dykshorn, *Am. J. Physiol.*, **105**, 191 (1933).

MERCK SHARP & DOHME  
RESEARCH LABORATORIES

RALPH A. REISFELD  
GEORGE L. TONG  
EDWARD L. RICKES  
NORMAN G. BRINK

MERCK INSTITUTE FOR THERAPEUTIC RESEARCH  
RAHWAY, NEW JERSEY

SANFORD L. STEELMAN

RECEIVED JUNE 7, 1961

## FIRST OBSERVATION OF AQUEOUS TETRAVALENT CURIUM<sup>1</sup>

Sir:

We wish to report the first observation of *aqueous tetravalent curium*.

The measured  $\text{M}^{+3} = \text{M}^{+4} + e^-$  potentials of U, Np, Pu and Am become increasingly negative with atomic number.<sup>2,3</sup> The presently unknown value for the  $\text{Cm}^{+3} = \text{Cm}^{+4} + e^-$  potential is expected to be more negative than the  $\text{Am}^{+3} = \text{Am}^{+4} + e^-$  potential of  $-2.6$  to  $-2.9$  volts<sup>4</sup> and to lie considerably beyond the normal limiting value for stability in aqueous solution. Previous attempts to oxidize  $\text{Cm}^{+3}$  in aqueous systems produced no positive results, confirming the expected stability of the  $5f^7$  configuration.<sup>5-9</sup>

It was discovered recently that tetravalent americium (which has only a transient existence in usual

(1) This work was performed under the auspices of the U. S. Atomic Energy Commission.

(2) B. B. Cunningham, *Proc. Int'l. Conf. Peaceful Uses of Atomic Energy*, **7**, 225 (1956).

(3) B. B. Cunningham, *XVIIth Int'l. Congress of Pure and Applied Chemistry*, **1**, 64 (1960).

(4) R. A. Penneman, J. S. Coleman and T. K. Keenan, *J. Inorg. Nucl. Chem.*, **17**, 138 (1961).

(5) R. A. Penneman and L. B. Asprey, *Proc. Int'l. Conf. Peaceful Uses of Atomic Energy*, **7**, 355 (1956).

(6) J. J. Katz and G. T. Seaborg, "The Chemistry of the Actinide Elements," John Wiley and Sons, Inc., New York, N. Y., 1957, pp. 381-383.

(7) S. W. Rabideau, L. B. Asprey, T. K. Keenan and T. W. Newton, *Proc. Second Int'l. Conf. Peaceful Uses of Atomic Energy*, **28**, 361 (1958).

(8) T. K. Keenan, *J. Chem. Educ.*, **36**, 27 (1959).

(9) R. A. Penneman and T. K. Keenan, "The Radiochemistry of Americium and Curium," NAS-NS-3006 (1960).

aqueous media) exhibits remarkable stability in 15 M ammonium or alkali fluoride.<sup>10</sup> Such  $\text{Am(IV)}$  solutions show self-reduction at a rate of approximately 4%/hour due to the alpha activity of  $\text{Am}^{241}$ . It was hoped that tetravalent curium could be stabilized sufficiently by high fluoride concentrations to be observed in solution. A few milligrams of  $\text{Cm}^{244}$  had been brought to a high degree of purity from stocks made available to us by the Argonne National Laboratory. The specific activity of  $\text{Cm}^{244}$  is about 25 times that of  $\text{Am}^{241}$  and one would predict a self-reduction rate for  $\text{Cm(IV)}$  of 1-2%/minute. However, by using reasonably fast techniques, some 30-40 minutes should be available for spectral studies.

In the americium(IV) work, a compound containing americium *already in the tetravalent state* was used as a starting material, *i.e.*,  $\text{Am(OH)}_4$  was dissolved in 15 M ammonium fluoride. Attempts to make  $\text{Cm(OH)}_4$  by alkaline oxidation of  $\text{Cm(OH)}_3$  using hypochlorite or ozone were not successful. Therefore dissolution of  $\text{CmF}_4$  (prepared under anhydrous conditions) was attempted.

Curium tetrafluoride was prepared by treating  $\text{CmF}_3$  with elemental fluorine using methods and apparatus previously described.<sup>11,12</sup> Addition of the resulting  $\text{CmF}_4$  to 15 M  $\text{NH}_4\text{F}$ , either at 25 or  $0^{\circ}$ , produced only vigorous bubbling accompanied by the immediate formation of white  $\text{CmF}_3$  from the yellow  $\text{CmF}_4$ . We believe that the  $\text{Cm(IV)}$  is oxidizing  $\text{NH}_4^+$  under these conditions.

However, upon addition of  $\text{CmF}_4$  to 15 M  $\text{CsF}$  at  $0^{\circ}$ , a solution of tetravalent curium as a fluoride complex is obtained. The light yellow solution shows an absorption spectrum similar to that previously obtained for solid  $\text{CmF}_4$ <sup>12</sup> (see Fig. 1).

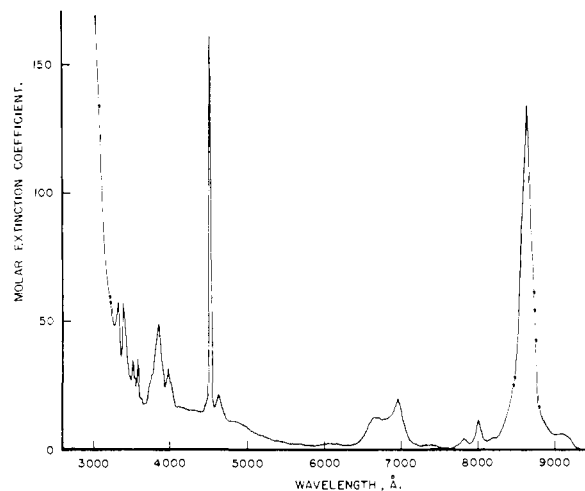


Fig. 1.—Absorption spectrum of  $\text{Cm(IV)}$  in 15 M  $\text{CsF}$  at  $10.5^{\circ}$  in 1 cm. quartz cell, 15 M  $\text{CsF}$  reference.

The 15 M  $\text{CsF}$  solution was pretreated with ozone (*ca.* 5%  $\text{O}_3$  in  $\text{O}_2$ ) for one hour to oxidize traces of impurities. The ozone stream was continued for about 10 minutes to stir and dissolve

(10) L. B. Asprey and R. A. Penneman, *J. Am. Chem. Soc.*, **83**, 2200 (1961).

(11) L. B. Asprey, *et al.*, *ibid.*, **79**, 5825 (1957).

(12) L. B. Asprey and T. K. Keenan, *J. Inorg. Nucl. Chem.*, **7**, 27 (1958).

the pellet of  $\text{CmF}_4$ . The solution was then centrifuged, the supernatant liquid was transferred to a quartz absorption cell and an aliquot taken for radiochemical assay. Care was taken to maintain the solution at  $\leq 10^\circ$  during these manipulations. The cell, containers, etc., all were prechilled in a refrigerator prior to use.

The spectrum was recorded immediately on a Model 14 Cary Spectrophotometer with sample and reference compartments held at  $10.5^\circ$ . Cesium fluoride ( $15 M$ ) was used as the reference solution.

Aqueous  $\text{Cm}^{244}(\text{IV})$  is not stable with time but disappears within *ca.* one hour as expected. The diminution of the two principal peaks was followed as a function of time with eleven different readings being obtained for each maximum. A zero-order rate constant of  $-1.3 \pm 0.2\%$ /minute was obtained at  $10.5^\circ$  which is consistent with the predicted alpha-induced reduction and curium half-life as described above. The reduction of  $\text{Cm}(\text{IV})$  is hastened by some other reaction at  $25^\circ$  as complete disappearance of the oxidized state was noted within 20 minutes at that temperature.

By extrapolation to the time of assay, estimates of the molar extinction coefficients for the two principal maxima were obtained. The location of the observable maxima ( $\pm 10 \text{ \AA.}$ ) in solution and the previously determined maxima for solid  $\text{CmF}_4$ <sup>12</sup> are compared in Table I.

TABLE I

Maxima of aqueous $\text{Cm}(\text{IV})$ in $15 M$ $\text{CsF}$ at $10.5^\circ$	Maxima of anhydrous $\text{CmF}_4$
3310 $\text{\AA.}$	
3380	
3506	
3565	
3830	3865 $\text{\AA.}$
	4010 } $\text{CmF}_3?$
	4118 }
4514 $\epsilon \cong 160$	4504
4620	4607
6650	6730
6960	6960
7820	7650
8000	7915
8640 $\epsilon = 130$	8560
9100	9100
	10975
	16120

Note that the molar extinction coefficients of  $\text{Cm}(\text{IV})$  are considerably greater than those of either aqueous  $\text{Cm}(\text{III})$  or  $\text{Am}(\text{IV})$ . In fact, the positions and magnitudes of the two principal peaks of  $\text{Cm}(\text{IV})$  are strongly reminiscent of aqueous  $\text{Am}(\text{III})$  with which it is isoelectronic.

After the  $\text{Cm}(\text{IV})$  maxima had disappeared (within one hour), diminished  $\text{Cm}(\text{III})$  maxima were apparent at *ca.* 4000  $\text{\AA.}$  However, most of the  $\text{Cm}(\text{III})$  formed from the self-reduction is in the insoluble  $\text{CmF}_3$  state and floats on the surface of the sirupy solution.

In addition to the  $\text{Cm}(\text{III})$ , we noted a small amount of  $\text{Am}(\text{III})$  ( $\epsilon = 400$ ) at 5000  $\text{\AA.}$  present only after the  $\text{Cm}(\text{IV})$  had disappeared. The curium stock was known to contain some americium

impurity; therefore, the americium must have been present as  $\text{Am}(\text{IV})$  in solution (with  $\epsilon = 30$  for  $\text{Am}(\text{IV})$  at 4559  $\text{\AA.}$ , such a small concentration could not be detected spectrophotometrically) until after the  $\text{Cm}(\text{IV})$  had reduced.

Attempts were made to dissolve  $\text{CmF}_4$  in saturated potassium or rubidium fluoride solution but rapid reduction of the curium was observed. Further work is in progress to examine thoroughly the behavior of  $\text{Cm}(\text{IV})$  in fluoride media and to obtain a crystalline alkali  $\text{Cm}(\text{IV})$  fluoride for X-ray studies.

LOS ALAMOS SCIENTIFIC LABORATORY  
LOS ALAMOS, NEW MEXICO

THOMAS K. KEENAN

RECEIVED JULY 21, 1961

OPTICAL ROTATORY DISPERSION STUDIES. LVIII.<sup>1</sup>  
THE COMPLETE ABSOLUTE CONFIGURATIONS OF  
STEVIOI, KAURENE AND THE DITERPENE  
ALKALOIDS OF THE GARRYFOLINE AND ATISINE  
GROUPS<sup>2</sup>

Sir:

The recently announced<sup>3</sup> interconversion of steviol (I)<sup>4</sup> and the diterpene alkaloid garryfoline (II)<sup>5</sup> through  $(-)\text{-}\beta\text{-dihydrokaurene}$ <sup>6</sup> (dihydro derivative of III)—coupled with various rotatory dispersion measurements<sup>4,5a,7,8</sup> on ketonic degradation products of these diterpenoids—has resulted in mutually consistent, absolute configurational assignments at all asymmetric centers with the exception of C-9. Earlier summarized, circumstantial arguments<sup>3,5a,9</sup> led us to favor a 9,10-*anti* backbone in garryfoline (II); if this is correct, then our experimental interconversion<sup>3</sup> requires a similar stereochemical feature in steviol (I) and  $(-)\text{-kaurene}$  (III).<sup>6,8b</sup> We should now like to report rotatory dispersion measurements on some new steviol and kaurene derivatives, which settle this remaining stereochemical question for this entire group of naturally occurring diterpenoids. Incidental to these studies, it was observed that  $(+)\text{-mirene}$ <sup>6</sup> is actually a difficultly separable mixture of  $(+)\text{-kaurene}$  (antipode of III) and phyllocladene; its stereochemistry,<sup>8b</sup> therefore, is of no further concern.

Ozonolysis of steviol (I) methyl ester yields<sup>4</sup> the norketol V, whose positive Cotton effect (Fig. 1) is very similar to that<sup>10</sup> of ketonorepiallogibberic acid

(1) Paper LVII, C. Djerassi, E. J. Warawa, J. M. Berdahl and E. J. Eisenbraun, *J. Am. Chem. Soc.*, **83**, 3334 (1961).

(2) The work at Stanford University was supported by grant No. CRTY-5061 from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(3) E. Mosettig, P. Quitt, U. Beglinger, J. A. Waters, H. Vorbrueggen and C. Djerassi, *J. Am. Chem. Soc.*, **83**, 3163 (1961).

(4) F. Dolder, H. Lichti, E. Mosettig and P. Quitt, *ibid.*, **82**, 246 (1960).

(5) (a) H. Vorbrueggen and C. Djerassi, *Tetrahedron Letters*, 119 (1961); (b) C. Djerassi, C. R. Smith, A. E. Lippman, S. K. Figdor and J. Herran, *J. Am. Chem. Soc.*, **77**, 4801, 6633 (1955).

(6) L. H. Briggs, B. F. Cain, B. R. Davis and J. K. Wilmshurst, *Tetrahedron Letters*, No. 8, 8 (1959).

(7) C. Djerassi, R. Riniker and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6362 (1956).

(8) (a) L. H. Briggs, B. F. Cain, B. R. Davis and J. K. Wilmshurst, *Tetrahedron Letters*, No. 8, 13 (1959); (b) L. H. Briggs, B. F. Cain, R. C. Cambie and B. R. Davis, *ibid.*, no. 24, 18 (1960).

(9) A. J. Solo and S. W. Pelletier, *Chem. & Ind.*, 1108 (1960).

(10) See J. F. Grove and T. P. C. Mulholland, *J. Chem. Soc.*, 3007 (1960); J. F. Grove, J. MacMillan, T. P. C. Mulholland and W. B. Turner, *ibid.*, 3049 (1960).