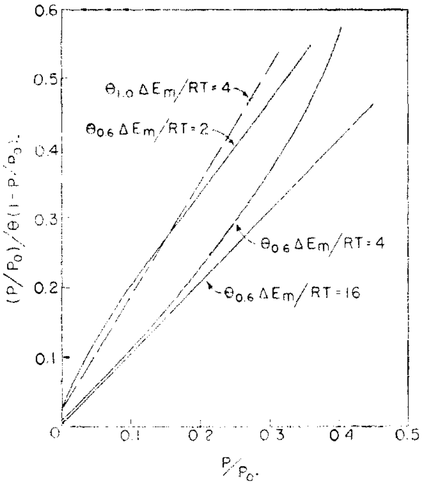

Fig. 6.—BET plots of $\theta_{0.6}$ and $\theta_{1.0}$.

slope of the BET plot will necessarily be correct. At low pressures, the BET function $p/p_0/\theta(1 - p/p_0)$ is approximately $p/p_0/\theta$. If θ is unity and varies slowly, the function in this range is $\sim p/p_0$ which is of course a linear plot of slope unity when plotted against itself.

If saturation of the first layer is not complete at low p/p_0, then the BET method may or may not succeed, as is evident from the examination of the various isotherms here.

Behavior in the Multilayer Region.—If eq. (2) is put in the doubly logarithmic form, all the isotherms here, from $\theta_{0.2}$ to θ_1 give effectively straight lines, above $\theta = 1$, with layer-by-layer fluctuations increasing as ΔE_0 increases (Fig. 7). The slope r is constant at 2.45–2.55 with no indication of changing to three below $\theta = 10$. The effect of $\Delta E_m/RT$ is merely that of a constant added to the doubly logarithmic pressure scale. (A change of the van der Waals force law constant to four changes r to 3.3.)

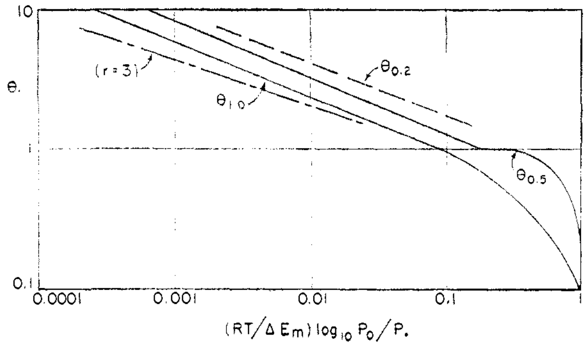

Fig. 7.—The isotherms plotted according to eq. 2. The periodic variations of $\theta_{0.2}$ are smoothed out in the broken line. A line of slope 3 is shown for comparison.

Aside from the scale factor for θ there is thus only one isotherm eq. (2) associated with $r = 2.5$. Since this scale factor can equally well be affected by surface area or a change in ΔE_0 or ΔE_m, there is no possibility of evaluating surface area from the plot in Fig. 7. Only when this plot breaks down, near $\theta = 1$, is it possible to make an unambiguous assignment of area on the basis of a temperature independent "Point B," whose existence must be demonstrated.

Acknowledgments.—I wish to thank Dr. P. H. Emmett and Dr. T. L. Hill for valuable discussions.

CAMBRIDGE, MASS. RECEIVED OCTOBER 16, 1950

[CONTRIBUTION FROM OAK RIDGE NATIONAL LABORATORY, CHEMICAL TECHNOLOGY DIVISION AND MEDICAL DIVISION OF THE OAK RIDGE INSTITUTE OF NUCLEAR STUDIES]

Preparation of Gallium Citrate by Ion Exchange

BY R. E. BLANCO AND J. D. PERKINSON, JR.

A general method is presented for the preparation of organic salts of gallium by ion exchange using experiments with citric acid as a guide. Gallium citrate was prepared by the elution of gallium from Dowex 50 resin (Nalcite HCR) with 0.5 *M* sodium citrate at *p*H 3.0. A solution 0.14 *M* in sodium citrate and 0.15 *M* in sodium chloride at *p*H 3.0 also proved to be an efficient elutriant. The highest mole ratio of gallium to citrate obtained was 0.24. Elution with sodium citrate at *p*H's 4, 7 and 8 proved to be inefficient for a mass transfer system as the result of hydrolysis and precipitation of gallium in the resin. Equilibrium studies of the distribution of gallium between Dowex 50 resin and sodium citrate in the *p*H range 2–7.5 showed the gallium citrate complex to be very strong at *p*H's 3.0 through 7.5.

Introduction

The preparation of the organic salts of gallium is of biochemical interest since it was shown by H. C. Dudley in distribution studies that gallium tends to concentrate in the skeletal tissue.[1] Thus the injection of radioactive gallium (half life 14.3 h.) might prove to be a treatment for bone cancer or a diagnostic aid in locating early bone cancer. Dudley has prepared radioactive gallium citrate by dissolution of irradiated gallium nitrate in hydrochloric and citric acids, and subsequent neutralization to a *p*H of about 7.0 with sodium hydroxide.

This communication reports the results of a study made to determine a general method for the production of the organic salts of gallium by ion exchange using experiments with citric acid as a guide. Ion exchange offers several advantages: (1) ease of remote control operation when handling radioactivity; (2) elimination of all anion impurities; (3) the possibility that in non-equilibrium systems, a different hydrolyzed form of gallium would be produced than in the case of straight neutralization. This effect could only be determined by distribution studies in animals.

A disadvantage of the ion exchange method, in the case of citric acid, is the low mole ratio of

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[1] H. C. Dudley and M. D. Levine, Naval Medical Research Institute, Project NM 011013, No. 3, 13 January 1949.

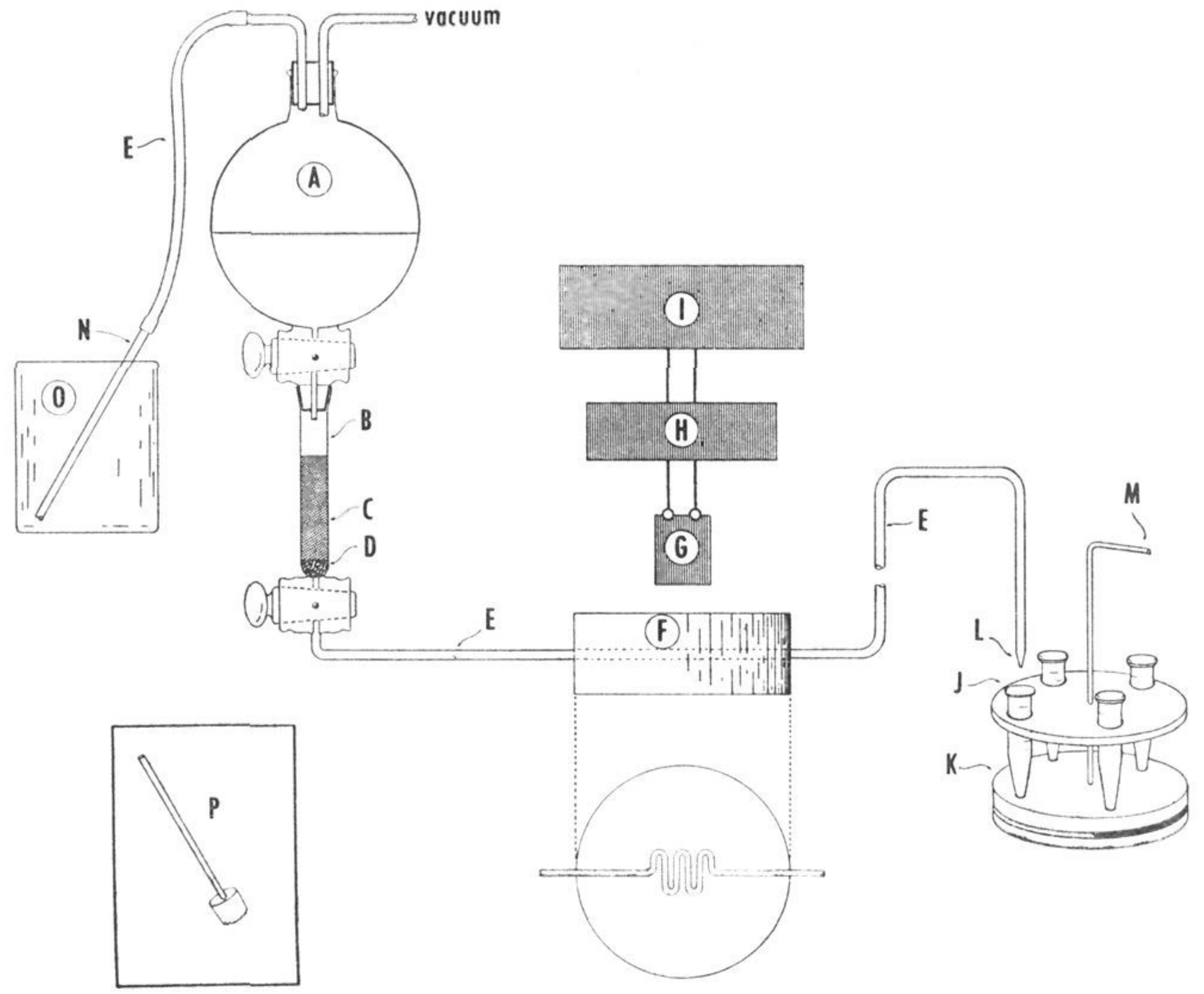

Fig. 1.—Ion exchange column and automatic effluent radio activity recorder: A, 250 ml. separatory funnel; B, 10 mm. i.d. × 7 cm. glass column; C, 1.9 ml. 100–200 mesh Dowex 50 resin; D, Pyrex glass wool plug; E, Tygon tube (3 mm. i.d.); F, polystyrene block containing tube maze; G, Geiger–Müller tube; H, count rate meter and scaler; I, Brown automatic recorder; J, 10-ml. centrifuge cones; K, receiver turn table; L, calibrated dropping tip; M, handle used to rotate turn table; N, 4 mm. glass tube; O, polystyrene beaker, $2^1/_2'' \times 3''$; P, S.S. plunger used to crush quartz capsule.

gallium to organic radical obtained as a product. In the following experiments, efforts were made to increase this ratio because of the adverse effect of citrate on intravenous injection.

Experimental

Materials.—The resin used in all experiments was Dowex 50 (Nalcite HCR), 100–200 mesh, supplied by National Aluminate Company. Since this resin has only one active group, nuclear sulfonic acid, its combining properties are not affected by *p*H. The resin was cleaned and converted to H^+ form by passing a large excess (40 bed volumes) of 6 *M* hydrochloric acid through a column of resin and washing with water. The amount of resin to be used was determined by weighing air-dry portions of resin on a gravimetric balance or by measuring the settled volume of H^+ form resin under water. The moisture content of the air dry resin was determined by weight loss after drying in a 110° oven.

The column used is shown in Fig. 1. The effluent from the column was conducted through a Tygon 3 mm. i.d. tube to a polystyrene tube maze located under a thin mica, end window, bell type, Geiger-Mueller counter tube and finally to the receiver centrifuge cones. The polystyrene tube maze was separated from the G.-M. tube by a 0.002 inch thick sheet of polystyrene. Both the maze and G.-M. tube were surrounded by 4″ of lead shielding. Any activity passing through the maze activated the G.-M. tube and was automatically recorded by the Brown recorder. This monitoring equipment is very similar to that described by Ketelle and Boyd.[2] The usefulness of a G.-M. tube, however, is limited to tracer level where the counting rate can be controlled by placing absorbers between the tube maze and the G.-M. tube. For high specific activities, the use of an ionization chamber is recommended.

The gallium prepared for physiological experiments was purified, as reported by H. C. Dudley,[3] by precipitation as the hydroxide by the addition of a slight excess of ammonia, ignition of the hydroxide to oxide at 1000°, partial dissolution of the oxide cake in 6 *M* nitric acid, and subsequent evaporation to gallium nitrate in the quartz irradiation ampoules. A spectrographic analysis of product obtained in this manner is shown in Table I.

TABLE I

SPECTROGRAPHIC ANALYSIS OF GALLIUM NITRATE PREPARED BY THE DUDLEY METHOD

V.S. = very strong, F.T. = faint trace, — = sought, not found

Ag— —
Al— —
As— —
Au— —
B— —
Ba— —
Be— —
Bi— —
Ca—F. T.
Nb— —
Cd— —
Co— —
Cu— —
Fe—F. T.
Ga—V. S.

Ge— —
Mg—F. T.
Mn— —
Mo— —
Na— —
Ni— —
Pb— —
Si— —
Sn— —
Sr— —
Ta— —

Ti— —
V— —
Zn— —

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[2] B. H. Ketelle and G. E. Boyd, THIS JOURNAL, **69**, 2800 (1947).

[3] H. C. Dudley, Naval Medical Research Institute, Project NM 011013, No. 6, 12, May 1949.

The gallium stock solution used in the ion exchange studies was prepared by dissolving the metal, as supplied by the Eagle–Pitcher Company (98.6% pure), in boiling 6 *M* hydrochloric acid with periodic additions of small amounts of 6 *M* nitric acid. Suitable amounts of radioactive, pure Ga tracer prepared as above, were added as needed.

Method–Equilibrium Experiments.—In these experiments, known masses of buffered resin were equilibrated with 25 ml. of solution which was 10^{-3} *M* in gallium chloride and 0.1 *M* or 0.5 *M* in citrate at *p*H's varying from 2 to 7.5. The resin was buffered by passing 0.1 *M* or 0.5 *M* sodium citrate of the proper *p*H through a column of clean H^+ resin until the *p*H of the effluent was the same as the feed, washed with water, and air dried. The moisture content of the resin was determined on separate samples by weight loss after drying in a 110° oven. The solutions were prepared by adjusting the *p*H of a solution of citric acid and gallium chloride (containing gallium tracer) with sodium hydroxide.

One-g. or 5-g. samples of resin were introduced into 25-ml. graduated, glass-stoppered cylinders, followed by 25 ml. of gallium citrate solution. The cylinders were shaken end over end at 84 r.p.m. for periods of 18 to 24 hours at 24 ± 1°. After the resin had settled, the supernate was sampled and its *p*H, gross beta, and gamma activity (millivolt) determined. The *p*H determinations were made with a Model G Beckman Meter equipped with semi micro, calomel-glass electrodes 270 and 290. The gross beta content was determined by evaporating known aliquots of solution to dryness on 26-mm. diameter watch glasses under a heat lamp and counting at known geometry under a thin mica, end window, bell type Geiger tube. The activity determinations were checked by counting 10-ml. aliquots of solution in a high pressure ionization chamber, gamma counter, connected to a vibrating reed electrometer. Errors in beta counting due to self absorption in the citrate crystals were found to be negligible since the relative millivolt (gamma) values checked very closely with the gross beta determinations.

Column Experiments.—The resin (1.9 ml.) was placed in the column on a support of Pyrex glass wool and cleaned and converted to the hydrogen form by the passage of 200 ml. of 6 *M* hydrochloric acid followed by 50 ml. of water. In one experiment the resin was then converted to the sodium form by the passage of 1 *M* sodium hydroxide (until the effluent was alkaline) and washed with water. In all other experiments hydrogen form resin was used. The gallium was then adsorbed by passing a 0.1 *M* hydrochloric acid solution containing 75 mg. of gallium and radiogallium tracer through the column at a rate close to 0.7 ml./min./sq. cm. of column cross section. The rate was controlled by counting the drops from the calibrated dropping tip. After washing the column with 50 ml. of water the gallium was eluted by passing 0.5 *M* sodium citrate (prepared by neutralization of citric acid with sodium hydroxide) of the proper *p*H through the column and collecting suitable aliquots, as indicated by the automatically recorded elution curve, in the centrifuge cone receivers. The activity of each aliquot was determined by the counting techniques outlined above. The per cent. gallium contained in each sample was known since the total activity in the system had been determined by counting an aliquot of the feed solution. In cold runs, gallium determinations were made by spectrophotometric analyses.[4]

For use in physiological experiments where a high specific activity is desirable, 75 mg. of the purified gallium nitrate was irradiated in the Oak Ridge National Laboratory pile in quartz ampoules 12 mm. × 5 cm. or 18 mm. × 8 cm. When the former size was used the ampoule was crushed in a Lucite beaker (2.5″ diameter × 3″ high) and the gallium dissolved in 100 ml. of 0.1 *M* hydrochloric acid over a period of one hour with the aid of a heat lamp. When the latter size was used the gallium was dissolved in 1 ml. of 6 *M* HCl by heating one half hour with the heat lamp, transferred to the lucite beaker, and diluted to 60 ml. with water. The solutions were then transferred to the ion exchange column head tank by vacuum. When working with this level of radioactivity (10–30 millicuries of 0.64–3.15 m.e.v. beta and 0.84 to 2.51 m.e.v. gamma activity) it is necessary to have at least three inches of lead shielding.

Experimental Results

Equilibrium Experiments.—The equilibrium experiments were designed to determine the strength of the gallium citrate complex in the *p*H range 2 through 8. The *p*H at which the complex was the strongest was expected to be the most efficient condition for the elution of gallium from a resin column. The variation of the degree of complex formation for any given cation with *p*H can be determined by plotting the log of the distribution coefficient, K_d, as a function of the equilibrium *p*H where

$$K_d = \frac{\text{mg. Ga/g. oven dry H}^+\text{ form resin}}{\text{mg. Ga/ml. solution}}$$

K_d is known to be constant when the free cation concentration is of the order of 10^{-3} *M*.[5]

The results listed in Table II indicate that the gallium citrate complex is extremely strong in the *p*H range 3 through 7.5. Since essentially no gallium was adsorbed in this *p*H region, it was not possible to calculate the distribution coefficients. The K_d values of 32.6 and 492.0 indicate the weak character of the citrate complex at *p*H 2.0 in 0.5 *M* and 0.1 *M* sodium citrate, respectively. Although the adsorption characteristics of Dowex 50 do not change with *p*H, part of the change in K_d could possibly be the result of hydrolysis of the gallium at the higher *p*H's since the hydrolyzed gallium cations would have a lower valence and consequently be less strongly adsorbed. Calculations using the hydrolysis constant[6]

$$GaOH^{+2} \rightleftarrows Ga^{+3} + OH^- \quad K = 4 \times 10^{-12}$$

indicate that gallium is 50% hydrolyzed at *p*H 2.6. Ivanov and Rabovich[7] have shown that precipitation of the hydroxide starts at *p*H 3.4–3.45 with the formation of a basic gallium sulfate.

Table II

Determination of the Strength of the Gallium Citrate Complex as a Function of *p*H

Conditions—Set A: one g. air-dry, buffered, Dowex 50 resin equilibrated with 25 ml. of gallium citrate solution of the following composition: 0.5 *M* citrate; 10^{-3} *M*. gallium; adjusted to proper *p*H with sodium hydroxide; activity—7.3 × 10^3 beta cts./min./ml., 21.7 millivolts/10 ml. Set B: 5 g. resin, 25 ml. of 0.1 *M* citrate solution; activity, 1.75 × 10^4 beta cts./min./ml., 46.5 millivolts/10 ml. Other conditions as in Set A

Equilibrium analyses							
		Gross β cts./min./ml.					
*p*H		(× 10^3)	(× 10^4)	Millivolt gamma reading/10 ml.		Distribution coefficient	
A	B	A	B	A	B	A	B
2.1	1.6	4.0	0.0225	11.0	0.20	32.6	492
3.1	2.9	7.9	1.8	22.0	46.5	..	...
4.0	4.0	7.9	1.9	22.0	48.0	..	...
4.8	5.2	8.0	1.85	22.0	49.0	..	...
5.5	6.2	7.9	1.99	22.0	51.8	..	...
6.8	7.0	8.0	1.67	21.6	48.0	..	...
7.5	7.1	8.1	1.77	22.0	48.0	..	...

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[4] H. C. Dudley, Naval Medical Research Institute, private communication.

[5] E. R. Tompkins and S. W. Mayer, This Journal, **69**, 2859 (1947); F. C. Nachod, "Ion Exchange," Academic Press, New York, N. Y., 1949, p. 181.

[6] W. M. Latimer, "Oxidation Potentials," Prentice-Hall, Inc., New York, N. Y., 1948.

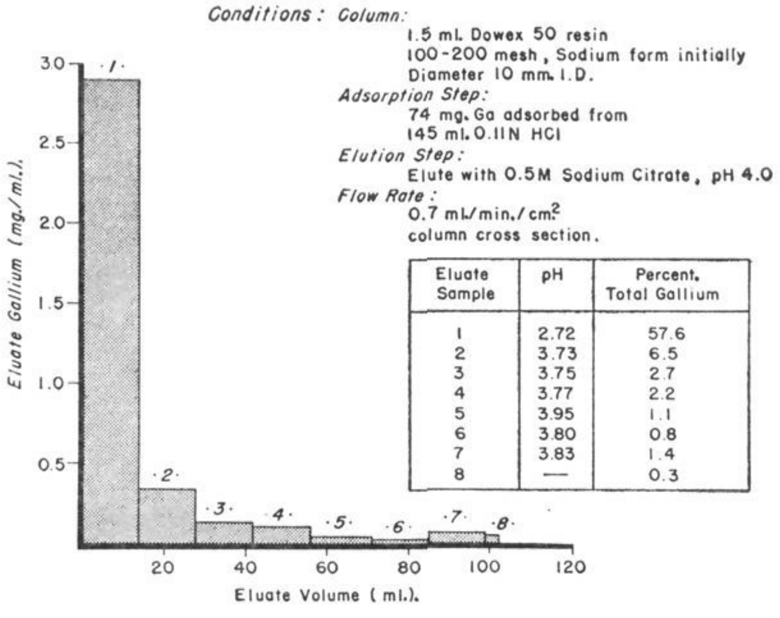
[7] Emin Ivanov and Ya. I. Rabovich, *J. Gen. Chem.*, **14**, 781 (1944).

Column Experiments

Adsorption.—The capacity of Dowex 50 resin for gallium was determined by passing an excess of 0.1 *M* hydrochloric acid containing 0.5 mg. gallium per ml. through the resin column and washing with 50 ml. of water. The average analyses of the effluent from two determinations showed that 56.1 mg. of gallium was adsorbed per ml. of resin. Since this value is very close to the theoretical capacity of 2.3 m.e.g./ml. for Dowex 50, it is indicated that gallium is strongly adsorbed at *p*H 1.0 and that the degree of hydrolysis is negligible. During the adsorption step all anions pass through the column and are effectively separated from the gallium.

Elution.—The equilibrium experiments indicated that efficient elution of gallium should be possible at any *p*H between 3.0 and 8.0. Since the product was to be used for physiological distribution studies, elution at the higher *p*H's seemed most practical.

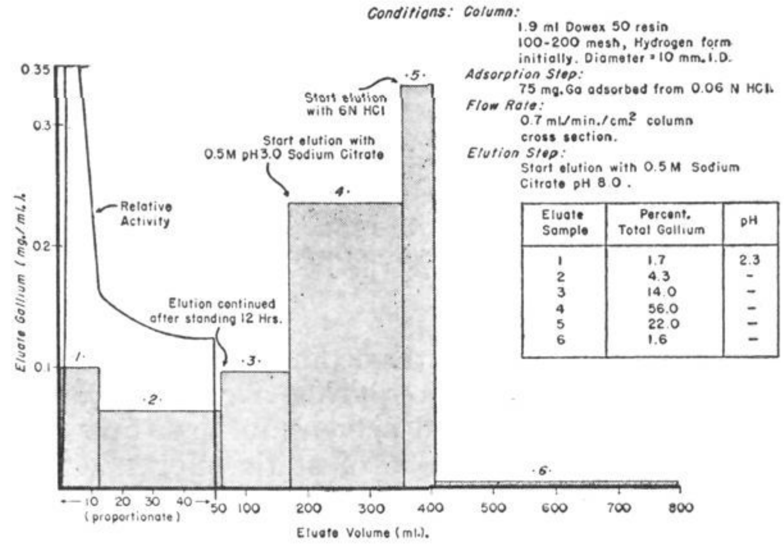
The quantitative results of elutions at *p*H's 4.0 and 8.0 are listed in Figs. 2 and 3, respectively.



Conditions: *Column:*
1.5 ml. Dowex 50 resin
100-200 mesh, Sodium form initially
Diameter 10 mm. I.D.
Adsorption Step:
74 mg. Ga adsorbed from
145 ml. 0.11N HCl
Elution Step:
Elute with 0.5M Sodium Citrate, pH 4.0
Flow Rate:
0.7 ml./min./cm.^{2}
column cross section.

Eluate Sample	pH	Percent. Total Gallium
1	2.72	57.6
2	3.73	6.5
3	3.75	2.7
4	3.77	2.2
5	3.95	1.1
6	3.80	0.8
7	3.83	1.4
8	—	0.3

Fig. 2.—Elution of gallium with 0.5 *M* sodium citrate, *p*H 4.0.



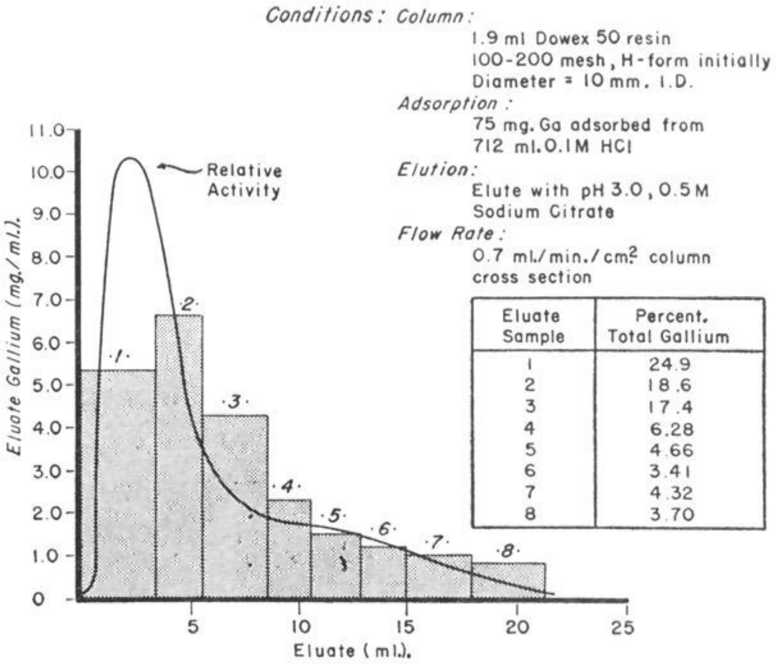
Conditions: *Column:*
1.9 ml Dowex 50 resin
100-200 mesh, Hydrogen form
initially. Diameter = 10 mm. I.D.
Adsorption Step:
75 mg. Ga adsorbed from 0.06 N HCl.
Flow Rate:
0.7 ml./min./cm.^{2} column
cross section.
Elution Step:
Start elution with 0.5 M Sodium
Citrate pH 8.0.

Eluate Sample	Percent. Total Gallium	pH
1	1.7	2.3
2	4.3	-
3	14.0	-
4	56.0	-
5	22.0	-
6	1.6	-

Fig. 3.—Elution of gallium with 0.5 *M* sodium citrate, *p*H 8.0

It should be noted that only the relative shape and abscissa of the automatically recorded elution curves are significant and not the ordinate since the amount of radioactive tracer was not the same in all of the experiments. In addition, the total elution time per experiment varied making the degree of radioactive decay a significant ordinate factor (Ga,^{70} half-life 20 min.; Ga,^{72} half-life 14.3 hr.). The results show that under these conditions of mass transfer the elution efficiency in this *p*H range is very low and that the gallium citrate product collected had a *p*H of the order of 2.3. The marked drop in *p*H and poor yield are attributed to hydrolysis of the gallium and precipitation of the hydrous oxide in the resin. Once precipitated, the gallium is only slowly redissolved by citrate at *p*H 8.0. However, when the *p*H of the elutriant citrate was subsequently changed to 3.0 an immediate increase in the concentration of gallium in the eluate was noted. The last traces of gallium were easily removed by elution with 6 *M* hydrochloric acid leaving the column clean and ready for the succeeding run (see Fig. 3).

Elution of gallium at *p*H 3.0 proved to be the most efficient. The results in Fig. 4 show the elution curve obtained by passing 0.5 *M* sodium citrate at *p*H 3.0 through 1.9 ml. of resin which contained 75 mg. of gallium plus gallium tracer.



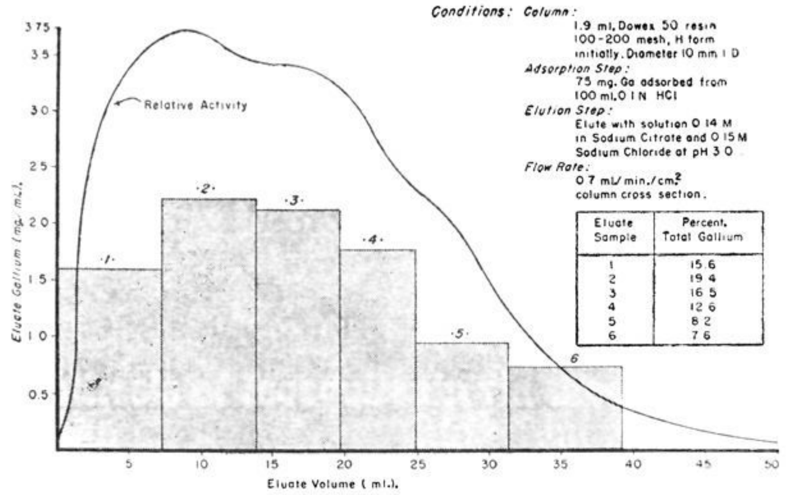
Conditions: *Column:*
1.9 ml Dowex 50 resin
100-200 mesh, H-form initially
Diameter = 10 mm. I.D.
Adsorption:
75 mg. Ga adsorbed from
712 ml. 0.1M HCl
Elution:
Elute with pH 3.0, 0.5M
Sodium Citrate
Flow Rate:
0.7 ml./min./cm.^{2} column
cross section

Eluate Sample	Percent. Total Gallium
1	24.9
2	18.6
3	17.4
4	6.28
5	4.66
6	3.41
7	4.32
8	3.70

Fig. 4.—Elution of gallium with 0.5 *M* sodium citrate, *p*H 3.0.

The highest mole ratio of gallium to citrate obtained in the eluate for a practical yield of gallium (60.9%), was 0.15. In an effort to increase the ratio of gallium to citrate, 216 mg. of gallium was adsorbed on 4 ml. of resin and eluted with 0.5 *M* sodium citrate at *p*H 3.0. In this case the mole ratio was 0.24 for a 49.6% yield of gallium (see Fig. 6). A further attempt was made to increase the mole ratio by decreasing the concentration of sodium citrate in the elutriant to 0.14 *M* at *p*H 3.0. In addition the elutriant was made 0.15 *M* in sodium chloride. Under these conditions the mole ratio in the eluate was 0.20 for a gallium yield of 62.7% (see Fig. 5). However, in this case the product volume was 24 ml. as compared to 8.5 ml. and 12.9 ml., respectively, for the two preceding elutions at *p*H 3.0 and in addition contained 0.15 *M* sodium chloride as a contaminant.

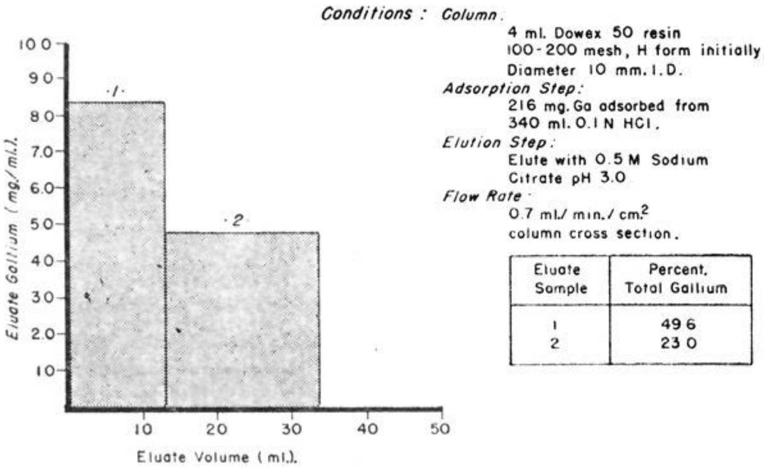
The effect of flow rate on the mole ratio was determined by repeating the elution at *p*H 3.0



Conditions: Column:
1.9 ml. Dowex 50 resin
100-200 mesh, H form initially. Diameter 10 mm. I.D.
Adsorption Step:
75 mg. Ga adsorbed from
100 ml. 0.1 N HCl
Elution Step:
Elute with solution 0.14 M
in Sodium Citrate and 0.15 M
Sodium Chloride at pH 3.0
Flow Rate:
0.7 ml./min./cm.^{2}
column cross section.

Eluate Sample	Percent. Total Gallium
1	15.6
2	19.4
3	16.5
4	12.6
5	8.2
6	7.6

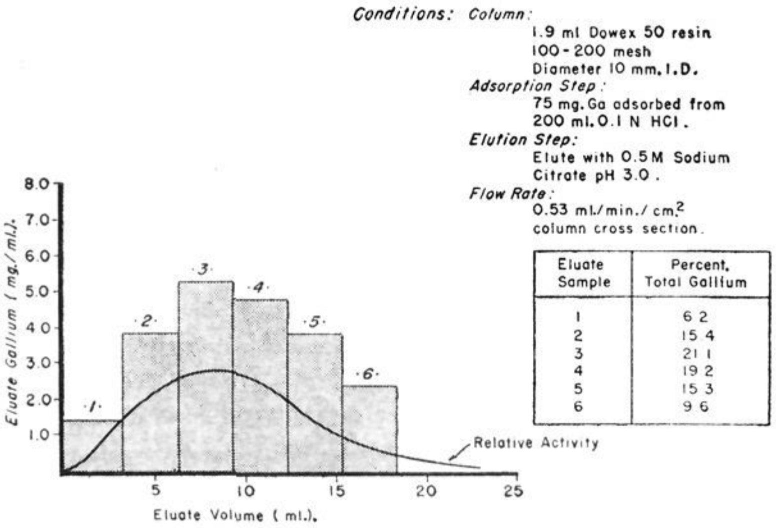
Fig. 5.—Elution of gallium with 0.14 *M* sodium citrate, 0.15 *M* sodium chloride at *p*H 3.0.



Conditions: Column.
4 ml. Dowex 50 resin
100-200 mesh, H form initially,
Diameter 10 mm. I.D.
Adsorption Step:
216 mg. Ga adsorbed from
340 ml. 0.1 N HCl.
Elution Step:
Elute with 0.5 M Sodium
Citrate pH 3.0
Flow Rate:
0.7 ml./min./cm.^{2}
column cross section.

Eluate Sample	Percent. Total Gallium
1	49.6
2	23.0

Fig. 6.—Elution of gallium with 0.5 *M* sodium citrate *p*H 3.0.



Conditions: Column:
1.9 ml Dowex 50 resin
100-200 mesh
Diameter 10 mm. I.D.
Adsorption Step:
75 mg. Ga adsorbed from
200 ml. 0.1 N HCl.
Elution Step:
Elute with 0.5 M Sodium
Citrate pH 3.0.
Flow Rate:
0.53 ml./min./cm.^{2}
column cross section.

Eluate Sample	Percent. Total Gallium
1	6.2
2	15.4
3	21.1
4	19.2
5	15.3
6	9.6

Fig. 7.—Elution of gallium with 0.5 *M* sodium citrate, *p*H 3.0.

(Fig. 4) and reducing the elution flow rate from 0.7 to 0.53 ml./min./sq. cm. column cross section. Although the elution curve was more symmetrical indicating a closer approximation to equilibrium conditions, the gallium to citrate mole ratio was not changed appreciably (see Fig. 7). Further reductions in flow rate would be impractical as any increase in elution efficiency would be counterbalanced by decay loss of product gallium.

In all cases the *p*H of gallium citrate solution produced by the ion exchange method was approximately 2.3. Thus it was necessary to adjust the *p*H to 7.0 by the addition of 1.0 *M* sodium hydroxide. For highly radioactive solutions the use of the indicator brom cresol purple is effective.

OAK RIDGE, TENNESSEE RECEIVED DECEMBER 11, 1950

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA, LOS ANGELES, AND COLUMBIA UNIVERSITY]

The Correlation of Solvolysis Rates and the Classification of Solvolysis Reactions into Mechanistic Categories

BY S. WINSTEIN, ERNEST GRUNWALD[1] AND H. WALTER JONES[2]

The modes of classification of solvolysis reactions into mechanistic categories are discussed, and there are introduced the categories **N** (nucleophilic) involving a carbon–solvent interaction with covalent character in the transition state, and **Lim.** (limiting) involving an interaction without covalent character. The variation of solvolysis rate with solvent is scrutinized for a number of primary halides and benzenesulfonates, for a number of so-called borderline substances such as isopropyl bromide and benzyl chloride, and for *trans*-2-bromo- and *trans*-2-methoxycyclohexyl *p*-bromobenzenesulfonate with the aid of a linear free energy relationship. This linear relationship is quite successful when applied to nucleophilic solvents such as the aqueous alcohols, but solvolysis rates are lower than predicted by the relationship in acetic or formic acid except for the cases assigned to the **Lim.** category.

The attempt to describe the solvolysis of so-called borderline substances in a solvent in terms of two different simultaneous processes is not successful, and it is concluded that the description in terms of one process accounts for all known facts. The factors controlling rates of **N** and **Lim.** solvolyses, the conditions which convert solvolytic processes from the **N** to the **Lim.** category, and the assignment of cases to these categories are considered.

Most discussions of nucleophilic substitution on carbon are based on Hughes and Ingold's S_N1–S_N2 classification.[3]

In S_N1, a rapid product-controlling stage is thought to follow a slow rate-determining ionization of RX to a cationic intermediate, the rate determining ionization not requiring a covalent interaction[3e] between R and solvent in the transition state. The unimportance of steric effects in S_N1 substitution in contrast to their role in S_N2 reactions[3d,4,5] has perhaps been overemphasized.[6,7] We have reference not only to facilitation of S_N1

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[1] Jewett Fellow, Columbia University, 1948–1949; Department of Chemistry, Florida State University, Tallahassee, Fla.

[2] Some of the material reported in this article is from the Ph.D. Thesis of H. Walter Jones, U. C. L. A., 1948; Western Regional Laboratory, Dept. of Agriculture, Albany, Calif.

[3] (a) Gleave, Hughes and Ingold, *J. Chem. Soc.*, 236 (1935); (b) Hughes and Ingold, *ibid.*, 244 (1935); (c) Hughes, *Trans. Faraday Soc.*, **34**, 185 (1938); (d) Hughes, *ibid.*, **37**, 603 (1941); (e) Bateman, Church, Hughes, Ingold and Taher, *J. Chem. Soc.*, 979 (1940).

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